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EDITORIAL / ÉDITORIAL

ORIGINAL RESEARCH / RECHERCHE ORIGINALE

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Addressing Racism in Hospital Pharmacy Practice Research

Lauren Bresee

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It is clear that racism has long existed in the Canadian health care system and that racism is a public health crisis, particularly for Indigenous and Black people in Canada.[1-6] In addition to the known harms to patients that are due to racism in clinical practice, clinical research is also directly affected by racism.

When we conduct patient-based research, we want to ensure that the results of the study will be applicable to the broader patient population. We accomplish this aim by recruiting a representative study sample. However, important sociodemographic variables, including race and ethnicity, are often not reported in studies.[7,8] In addition, participants in randomized controlled trials are more likely to be white, wealthy, and male.[7] These factors limit both the ability to assess the relevance of the study results and the applicability of those results to nonwhite, non-male patients who are not wealthy.

To my knowledge, there is a paucity of research available that evaluates the impact of racism on patients in Canadian hospital pharmacy practice. As a result, it is unclear whether racism exists in hospital pharmacy practice, and if it does exist, how it affects patient outcomes. However, we do know that structural racism and health inequalities exist in other aspects of health care in Canada.[3,4] Given the lack of currently available evidence, important research questions include whether structural racism exists in hospital pharmacy practice, how it affects patients, and how it can be addressed to ensure that all patients receive equitable care.

How can we start to address the barriers of racism in hospital pharmacy practice research? Decisions about health research funding, including funding for hospital pharmacy research, need to include the principles of equity, diversity, and inclusion.[9] In addition, conducting and disseminating research about racism in Canadian hospital pharmacy is vital to addressing racism in our own individual practices. Also, information related to race and ethnicity should be reported in all research articles, both to identify whether there are barriers to participation in research for patients of certain races or ethnicities, and to determine the generalizability of the results beyond the study population.[4] This is certainly not an exhaustive list of ways to address barriers due to racism in hospital pharmacy research; rather, it only serves to emphasize the need to continue this discussion with our colleagues in the weeks and months to come.

Racism has no place in society, and it certainly has no place in hospital pharmacy research. As stated in the National Association of Pharmacy Regulatory Authorities' white paper on the culture of professionalism in pharmacy: "Pharmacy as a profession, as well as all individuals who contribute to the profession, are starting important conversations about these issues and are recognizing the responsibility we have, as individuals and as a profession, to acknowledge that racism and discrimination exist within our society, our workplaces, and our profession and the importance of working towards a profession that embraces inclusion, diversity, and equity."[10] We each need to take personal responsibility for preventing racism in hospital pharmacy practice and to continue those conversations to ensure that hospital pharmacy research also embraces inclusion, diversity, and equity.

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ON THE FRONT COVER

Darlings Island, New Brunswick

This photograph of Darlings Island, located northeast of Saint John, New Brunswick, was taken with a Nikon D5100 in the fall of 2012 by Joshua Bryant. Darlings Island is surrounded by several rivers, including Kennebecasis River and Hammond River. Many people enjoy kayaking and canoeing the rivers surrounding Darlings Island, and Hammond River is one of southern New Brunswick's best spots for Atlantic salmon. Josh works as a hospital telepharmacist for Northwest Telepharmacy Solutions. He enjoys hiking with his dog Hendrix, photography, playing guitar, and working out at the gym so that he can enjoy the occasional sweet.

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Aborder le racisme dans le domaine de la recherche pratique en pharmacie hospitalière

par Lauren Bresee

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Véritable crise sanitaire publique, le racisme existe depuis longtemps dans le système de soins de santé du Canada, en particulier à l'égard des populations autochtones et noires[1-6]. En plus des préjudices connus qu'il cause aux patients dans la pratique clinique, il affecte aussi directement la recherche clinique.

En menant des recherches basées sur le patient, nous voulons nous assurer que les résultats de l'étude soient applicables à la plus large population de patients possible. Pour ce faire, nous sélectionnons un échantillon d'études représentatif. Cependant, des variables sociodémographiques importantes, notamment la race et l'ethnicité, ne sont pas toujours rapportées dans les études[7,8]. De plus, les participants aux essais randomisés contrôlés ont plus tendance à être des hommes blancs et riches[7]. Ces facteurs limitent la capacité à évaluer la pertinence des résultats de l'étude et leur applicabilité à des patients non blancs, qui ne sont pas masculins ni riches.

À ma connaissance, les recherches disponibles qui évaluent l'impact du racisme sur les patients dans la pratique canadienne de la pharmacie hospitalière sont insuffisantes. Par conséquent, on ne sait pas si le racisme existe dans ce domaine et, le cas échéant, on ignore son impact sur les résultats des patients. Cependant, nous savons que le racisme structurel et les inégalités en matière de santé existent dans d'autres aspects des soins de santé au Canada[3,4]. Étant donné le manque de données probantes actuellement disponibles, d'importantes questions de recherche subsistent, à savoir si le racisme structurel existe dans la pratique de la pharmacie hospitalière, la manière dont il affecte les résultats pour les patients et la façon de l'aborder pour garantir que tous les patients reçoivent des soins équitables.

Comment pouvons-nous aborder les obstacles posés par le racisme dans la recherche pratique en pharmacie hospitalière? Les décisions portant sur le financement de la recherche dans le domaine de la santé, notamment de la pharmacie hospitalière, doivent comprendre les principes d'équité, de diversité et d'inclusion[9]. De plus, la réalisation et la diffusion d'études sur le racisme dans le domaine de la pharmacie hospitalière canadienne sont cruciales pour nous attaquer au problème dans nos pratiques individuelles. En outre, tous les articles de recherche doivent rapporter les informations concernant la race et l'ethnicité, à la fois pour établir s'il existe ou non des obstacles qui empêchent les patients de certaines races ou ethnicités d'y participer et pour déterminer la généralisation des résultats au-delà la population étudiée[4]. Il ne s'agit pas ici d'une liste complète des manières d'aborder les obstacles causés par le racisme dans la recherche en pharmacie hospitalière : elle ne sert qu'à souligner le besoin de poursuivre cette discussion avec nos collègues dans les semaines et les mois à venir.

Le racisme n'a pas sa place dans la société et certainement pas dans la recherche en pharmacie hospitalière. Comme l'indique le livre blanc de l'Association nationale des organismes de réglementation de la pharmacie sur la culture du professionnalisme en pharmacie : « La pharmacie, en tant que profession, ainsi que tous ceux qui y contribuent entament d'importantes discussions sur ces problèmes et reconnaissent la responsabilité qui leur incombe en tant que personnes et en tant que profession de reconnaître l'existence du racisme et de la discrimination au sein de notre société, sur nos lieux de travail et dans notre profession ainsi que l'importance de travailler pour une profession qui favorise l'inclusion, la diversité et l'équité[10]. » *[trad. libre]* Chacun doit assumer la responsabilité de prévenir le racisme dans la pratique de la pharmacie hospitalière et de poursuivre ces discussions pour veiller à ce que la recherche dans ce domaine soit ouverte à l'inclusion, à la diversité et à l'équité.

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Burnout among Hospital Pharmacists: Prevalence, Self-Awareness, and Preventive Programs in Pharmacy School Curricula

Colby Weichel, Joan S Lee, and Justin Y Lee

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ABSTRACT

Background: Clinician burnout is a work-related syndrome characterized by emotional exhaustion, depersonalization, and reduced personal accomplishment. It is associated with reduced quality of care, as well as the occurrence of medical errors and mental illness. Although burnout has been extensively studied in populations of physicians and nurses, there is limited research assessing burnout in pharmacists and their exposure to burnout-related education.

Objectives: To determine the prevalence of burnout and its associated risk factors among hospital pharmacists and to explore the status of preventive programs in pharmacy school curricula.

Methods: A cross-sectional online survey was conducted with hospital pharmacists working in the province of Ontario, Canada. Respondents completed the Maslach Burnout Inventory (MBI) and responded to questions about career characteristics and professional satisfaction. A multivariable regression analysis was used to determine factors independently associated with burnout. In addition, all pharmacy schools in Canada were surveyed electronically about their burnout-prevention curricula.

Results: Of 2465 hospital pharmacists in Ontario, 270 responded (11% response rate). Most respondents were women (77% [195/252]) and were working full-time (90% [227/252]), with a substantial proportion working in the acute care setting (39% [96/246]). The burnout rate was 61.1% (165/270; 95% confidence interval 55.5%–66.8%). Factors independently associated with burnout were dissatisfaction with work–life balance (odds ratio [OR] 2.62, $p = 0.005$) and feeling that contributions were unappreciated (OR 2.60, $p = 0.019$). Of those whose MBI score indicated burnout, 23% (36/158) were not aware of experiencing burnout. All 10 Canadian pharmacy schools responded to the survey, with 9 (90%) reporting that they did not have burnout-prevention curricula; however, 8 (80%) reported interest in incorporating such material.

Conclusions: The rate of burnout among hospital pharmacists in Ontario was high, and preventive action is needed. Opportunities exist to both improve pharmacists' resilience at the undergraduate level and reduce institutional stressors in the workplace.

Keywords: burnout, hospital, pharmacists, pharmacy education

RÉSUMÉ

Contexte : L'épuisement professionnel du clinicien est un syndrome lié au travail qui se caractérise par une fatigue émotionnelle, une dépersonnalisation et l'amoindrissement des réalisations personnelles. Il est associé à la réduction de la qualité des soins, à la survenance d'erreurs médicales et à la maladie mentale. Bien que ce sujet ait fait l'objet d'études approfondies dans les populations de médecins et d'infirmiers, les recherches qui se penchent sur l'épuisement des pharmaciens et la possibilité qui leur est offerte de bénéficier de formations relatives à l'épuisement sont limitées.

Objectifs : Déterminer la prévalence du surmenage professionnel et des facteurs de risque qui lui sont associés parmi les pharmaciens d'hôpitaux et examiner les programmes de prévention dans les formations en école de pharmacie.

Méthode : Une enquête transversale en ligne a été menée auprès des pharmaciens hospitaliers travaillant en Ontario, au Canada. Les répondants ont rempli le *Maslach Burnout Inventory* (MBI) *[Evaluation du syndrome de l'épuisement professionnel de Maslach]* et répondu à des questions portant sur les caractéristiques d'emploi et la satisfaction professionnelle. Une analyse de régression multivariable a permis de déterminer les facteurs indépendamment associés à l'épuisement. De plus, une enquête électronique portant sur le programme de prévention de l'épuisement a été menée dans toutes les écoles de pharmacie au Canada.

Résultats : Sur les 2465 pharmaciens d'hôpitaux en Ontario, 270 ont répondu (taux de réponse de 11 %). La plupart des répondants étaient des femmes (77 % [195/252]) travaillant à temps plein (90 % [227/252]); une part importante travaillait dans un environnement de soins aigus (39 % [96/246]). Le taux d'épuisement était de 61,1 % (165/270, intervalle de confiance 95 % 55,5 %-66,8 %). Les facteurs indépendamment associés à l'épuisement étaient l'insatisfaction liée à l'équilibre entre sa vie professionnelle et sa vie personnelle (rapport de cotes [RC] 2,62, $p = 0,005$) et l'impression d'un manque d'appréciation de sa contribution (RC 2,60, $p = 0,019$). Parmi les personnes dont le score MBI indiquait un épuisement professionnel, 23 % (36/158) ne savaient pas qu'elles en étaient victimes. Les dix écoles de pharmacie canadiennes ont répondu à l'enquête et neuf (90 %) ont rapporté ne pas avoir de programme axé sur la prévention de l'épuisement professionnel, cependant, huit (80 %) ont montré leur intérêt pour un tel programme.

Conclusions : Le taux d'épuisement professionnel parmi les pharmaciens d'hôpitaux en Ontario était élevé et des actions préventives sont nécessaires. Les possibilités existent pour améliorer la résilience des pharmaciens au niveau du premier cycle universitaire et réduire les facteurs de stress institutionnels sur le lieu de travail.

Mots-clés : épuisement, hôpital, pharmaciens, formation en pharmacie

INTRODUCTION

Burnout has been described as a work-related syndrome characterized by 3 elements: emotional exhaustion, depersonalization, and reduced feelings of personal accomplishment.[1] Among health care providers, this syndrome occurs when they begin to feel overwhelmed and frustrated by unforeseen circumstances, while attempting to have a positive impact on their patients' lives.[1] The occurrence of burnout has a significant impact on the health care system, as it is known to be associated with reduced quality of care, as well as with medical errors and mental illness.[2,3] Among physicians in the United States, burnout is estimated to cost the health care system US$4.6 billion per year through reduced working hours and physician turnover.[4] This amount is likely an underestimate, as it does not include the downstream effects and costs of burnout, such as medical errors, patient dissatisfaction, and increased malpractice lawsuits.[4]

Although burnout has been well characterized for physicians and nurses, study of burnout among pharmacists is still lacking. In 2016, a pilot survey of hospital pharmacists in the United States found a burnout rate of 61.2% that was largely driven by high emotional exhaustion.[5] To our knowledge, there are no previous studies in a Canadian context, and the current level of burnout among Canadian hospital pharmacists is unknown. It is unclear whether a high level of burnout is a regional phenomenon or whether burnout is more universal across jurisdictions, with rates similar to the United States.

Numerous strategies are currently being used to prevent and treat burnout, including mindfulness-based interventions, psychotherapy, and didactic education. Several health professional student groups have demonstrated the success of burnout-prevention strategies at the student level.[6-11] It is unknown whether pharmacy schools have implemented any courses or programs targeting the prevention of burnout in the workforce and if not, whether they would be interested in implementing such training.

To address these gaps, this study was undertaken to explore burnout in the Canadian pharmacy context. The primary objective was to determine the prevalence of burnout and its associated risk factors among hospital pharmacists in Ontario, which is the largest province in Canada (population 14.57 million in 2019). The secondary objective was to explore the current status of and interest in preventive programs in pharmacy school curricula.

METHODS

This study was based on 2 online surveys: a survey of Ontario hospital pharmacists and a survey of all 10 faculties and schools of pharmacy in Canada. The CHERRIES checklist was used to guide reporting of the methods and results of this study, as recommended by the EQUATOR (Enhancing the QUAlity and Transparency Of health Research) network.[12]

For both surveys, no personal identifiers were linked to survey results, and the data were stored on the password-protected computer of the primary investigator (C.W.). An informed consent form was attached to the email invitations for the surveys, and a link to the form was also provided in the introduction page to each survey. No incentives were offered for completing either of the surveys.

The study was approved by the Hamilton Integrated Research Ethics Board.

Survey of Ontario Hospital Pharmacists

Study Design

To determine the prevalence of burnout, a voluntary, cross-sectional open online survey was conducted using a convenience sample of Ontario hospital pharmacists. To recruit a broad and diverse geographic sample, an invitation to the survey was distributed to members of the Ontario Branch of the Canadian Society of Hospital Pharmacists via the branch e-Newsbrief, as well as to pharmacists at 33 hospital corporations representing more than 67 unique hospital sites across Ontario, through their staff pharmacist email distribution lists.

Before survey distribution, a pilot version was administered to 118 hospital pharmacists within a single hospital corporation (4 hospitals), to ensure that the questionnaire and consent forms were clearly understandable and appropriately worded to accurately investigate the intended research questions. All comments and feedback from the pilot respondents were taken into consideration, and the survey was modified accordingly. Responses from the pilot survey were also included in the province-wide data.

The pilot survey was administered in March 2019 and the province-wide survey in April and May 2019. For both surveys, an online survey platform, SurveyMonkey, was used to administer and collect responses through an automatic capture method. The questions were not randomized because the tool used for assessment of burnout, the Maslach Burnout Inventory (MBI), requires a standard order of questions. Adaptive questioning was used to minimize the complexity of the survey and to direct respondents to questions that were conditionally relevant according to their responses on other items. Respondents were not able to review or change their responses after proceeding to the next page of the survey.

All hospital pharmacists in Ontario were eligible to participate in the study. Pharmacy residents and students have different responsibilities and work environments than licensed pharmacists, with exposure to different stressors and risk factors. These groups were therefore deemed to represent a different population from pharmacists, and any responses from residents or students were excluded from the analysis. Respondents who did not complete the

full MBI were also excluded from the analysis because the level of burnout cannot be assessed from incomplete MBI information.

Survey Content

The survey questionnaire comprised 2 sections: the MBI itself and questions about personal and career characteristics and professional satisfaction. In total, there were 45 questions. All of the quantitative survey questions were mandatory, with a "prefer not to answer" option for questions about personal and work characteristics.

The first section used the standardized MBI Human Services Survey for Medical Personnel, which has been validated with various health care practitioners.[1,5] This inventory consists of 22 items that measure burnout in terms of emotional exhaustion, depersonalization, and personal accomplishment. Responses range from "never" (numeric value 0) to "every day" (6), according to the frequency at which the respondent experiences each item. Scores are tallied for each of the 3 components, and each score is assessed as high, moderate, or low, according to values validated in the MBI for health care professionals.[1] Burnout was defined on the basis of previously defined threshold values for health care providers, either as an emotional exhaustion score of 27 or higher or a depersonalization score of 10 or higher.[5]

The second section of the survey comprised questions about personal and work characteristics, as well as questions about professional satisfaction. Respondents were asked to rate satisfaction with various areas of their career from 0 to 5, where 0 = very dissatisfied and 5 = very satisfied. They were also asked to rate satisfaction with time spent in work-related activities or tasks from 0 to 2, where 0 = too little and 2 = too much.

Statistical Analysis

Descriptive statistics (medians with interquartile ranges and counts with percentages) were used to summarize the survey responses and demographic characteristics of respondents. Those with scores suggestive of burnout were compared with those whose scores were not suggestive of burnout. Descriptive statistics were also used to characterize differences in demographics and professional satisfaction between these groups.

To examine the relationship between professional dissatisfaction and burnout, univariable logistic regression analysis was conducted. To adjust for confounding baseline variables (e.g., age, sex, years in practice, working full-time, and primary area of practice), multivariable analysis was used to determine factors independently associated with burnout. All analyses used 2-tailed statistical tests, with statistical significance defined by a threshold p value of less than 0.05. A variance inflation factor greater than 10 was used as the threshold for determining the presence of significant multicollinearity.[13]

SPSS software (SPSS Statistics for Windows, version 25.0, IBM Corporation) was used to conduct the statistical analyses and logistic regression analyses.

The survey also included 3 qualitative questions. Those who felt burned out, based on their own self-assessment, were asked, "What do you feel are the biggest contributors to your feelings of burnout?" and "What do you feel is the most helpful to relieve and/or cope with your feelings of burnout?" Those who did not feel burned out were asked, "What do you feel has been most helpful to you in preventing burnout?" The responses to qualitative questions were analyzed using thematic content analysis, in which responses were grouped according to recurring themes, such as spending time with family or exercising.

Survey of Canadian Schools of Pharmacy

The second survey was a voluntary, self-administered, closed online survey of leadership faculty at each of the pharmacy schools in Canada. Potential respondents representing each school were chosen on the basis of job title (either the dean of pharmacy or a relevant faculty representative responsible for curricular development). The survey consisted of 4 questions about the current availability of and interest in incorporating preventive skill-building strategies against burnout syndrome. Descriptive statistics were used to summarize the survey responses.

RESULTS

Survey of Ontario Hospital Pharmacists

Of the 2475 hospital pharmacists licensed in Ontario at the time of the survey,[14] 388 completed at least a portion of the survey. Of these, 118 were excluded: 19 who were not staff hospital pharmacists (but rather were pharmacy students or residents) and 99 who quit the survey before completing the MBI. Therefore, the final analysis included 270 respondents who met the eligibility criteria, which corresponds to a response rate of 11%.

In the included cohort, most of the respondents were women (77% [195/252]), nearly half were between the ages of 35 and 44 years (43% [109/253]), and most were practising full-time (90% [227/252]). Median time in practice was 11 years, with a large proportion of respondents practising in the acute care setting (39% [96/246]). Full details of respondents' demographic and career-related characteristics are shown in Table 1. There were no statistically significant differences in any of the measured baseline characteristics between respondents with and without burnout (as determined from MBI scores).

The overall burnout rate was 61.1% (95% confidence interval [CI] 55.5%–66.8%; n = 165). This outcome was driven by the large proportions of respondents who had high emotional exhaustion (n = 144, 53%) and high depersonalization (n = 114, 42%) (Table 2). In the univariable regression

TABLE 1. Characteristics of Survey Respondents

Characteristic	Group[a]; No. (%) of Respondents[b]			*p* Value[c]
	Not Burned Out (*n* = 105)	Burned Out (*n* = 165)	All (*n* = 270)	
Age group (years)	*n* = 98	*n* = 155	*n* = 253	0.96
18–24	1 (1)	3 (2)	4 (2)	
25–34	6 (6)	9 (6)	15 (6)	
35–44	44 (45)	65 (42)	109 (43)	
45–54	26 (27)	47 (30)	73 (29)	
55–64	13 (13)	18 (12)	31 (12)	
Sex	*n* = 98	*n* = 154	*n* = 252	0.57
Female	74 (76)	121 (79)	195 (77)	
Time in practice (years) (median and IQR)	10 (5–20)	11 (6–20)	11 (5–20)	0.94
Work hours	*n* = 99	*n* = 153	*n* = 252	0.36
Full-time	88 (89)	139 (91)	227 (90)	
Primary area of practice	*n* = 96	*n* = 150	*n* = 246	0.30
Acute care	40 (42)	56 (37)	96 (39)	
Critical care	14 (15)	15 (10)	29 (12)	
Rehabilitation or long-term care	3 (3)	17 (11)	20 (8)	
Oncology	11 (11)	23 (15)	34 (14)	
Management	3 (3)	7 (5)	10 (4)	
Outpatient/ambulatory	14 (15)	15 (10)	29 (12)	
≥ 3 areas	5 (5)	9 (6)	14 (6)	
Other	6 (6)	8 (5)	14 (6)	

IQR = interquartile range.
[a]Burnout was assessed through analysis of responses to the Maslach Burnout Inventory.
[b]Except where indicated otherwise. Data were missing for some respondents for each variable; as such, the column heading shows the total number in each group and entries below indicate the number of respondents by variable.
[c]Comparison between respondents without and with burnout.

analysis, respondents who rated themselves as being very or somewhat dissatisfied with most of the work-related characteristics were also more likely to have burnout (Table 3). The only 2 characteristics not associated with burnout were dissatisfaction with time spent in clinical duties and dissatisfaction with time spent with students or teaching.

After adjustment for age, sex, years in practice, working full-time, and primary area of practice, multivariable logistic regression showed 2 factors to be independently associated with burnout: dissatisfaction with work–life balance (odds ratio [OR] 2.62, 95% CI 1.33–5.18, $p = 0.005$) and feeling that contributions were not appreciated (OR 2.60, 95% CI 1.17–5.78, $p = 0.019$). No significant multicollinearity was detected between independent variables used in the analysis.

In the qualitative portion of the survey, respondents were asked to identify the perceived contributors to their burnout. The most prominent themes to emerge were perceived high or unmanageable workload, lack of work–life balance, and lack of appreciation by colleagues and management. When respondents were asked about factors protective against burnout, the most common responses were taking time away from work, social interactions, and activities or exercise outside of work (Table 4).

When respondents were asked if they subjectively felt burned out, 23% (36/158) of those identified objectively as having burnout (based on the MBI) answered "No".

TABLE 2. Assessment of Burnout According to Maslach Burnout Inventory

Aspect of Burnout	Median Score (IQR)	No. (%) of Respondents (*n* = 270)
Emotional exhaustion	28 (20–36)	
Low score (≤ 18)		59 (22)
Moderate score		67 (25)
High score (≥ 27)		144 (53)
Depersonalization	8 (4–15)	
Low score (≤ 5)		91 (34)
Moderate score		65 (24)
High score (≥ 10)		114 (42)
Personal accomplishment	38 (31–42)	
Low score (≤ 33)		81 (30)
Moderate score		80 (30)
High score (≥ 40)		109 (40)

IQR = interquartile range.

This finding suggests that about 1 of every 4 respondents with burnout was not self-aware. Twelve percent (31/258) of respondents had exposure to some type of burnout-prevention training in their career, but less than 1% (2/258) had received training at the undergraduate level.

Survey of Canadian Schools of Pharmacy

The survey of Canadian pharmacy schools had a 100% response rate. Nine (90%) of the 10 schools did not currently have burnout-prevention curricula, but 8 (80%) expressed interest in incorporating such programs. Only one Canadian school reported current provision of burnout-prevention training. The training is limited and consists of a conference at the beginning of the pharmacy program, which includes a mindfulness workshop and a presentation by a psychologist.

DISCUSSION

This survey of hospital pharmacists in Ontario, Canada, found a burnout rate of 61.1%. This suggests that the burnout rate for pharmacists is as concerning as those previously reported for physicians (30%–54%) and nurses (35%–40%) in both Canada and the United States[3,15-17] (see Box 1). In the current survey, higher burnout rates were independently associated with a reduced work–life balance and decreased sense of worth in the workplace. These results correlated strongly with the qualitative responses, where the biggest contributors to pharmacist burnout were a lack of appreciation by colleagues and management and a lack of work–life balance.

The subscales for emotional exhaustion, depersonalization, and decreased personal accomplishment all had a substantial proportion of respondents scoring in the "high" range (Table 2). These results suggest that all of the subscales are contributing to burnout and that all 3 domains need to be addressed to combat burnout. There were also a large number of respondents who scored in the "moderate" range of the subscales, suggesting that even though they did not meet the predefined cut-offs for burnout, these respondents were likely at risk of developing burnout.

This high burnout rate is concerning. It is similar to that found by a pilot survey of US clinical hospital pharmacists, in which the burnout rate was 61.2%.[5] That US study also found an association between burnout and the feeling that contributions were underappreciated. Additional factors associated with burnout in that earlier study were inadequate administration and teaching time, uncertainty about health care reform, too many nonclinical duties, and "difficult" pharmacist colleagues. With the exception of uncertainty about health care reform, which we did not consider, these same factors also trended toward an association with burnout in our Canadian survey. However, we were unable to confirm whether these are important factors for Canadian pharmacists. This is likely because of a lack of statistical power.

The lack of burnout self-awareness demonstrated in this study is particularly concerning. The lack of self-awareness may stem from a lack of education regarding burnout or from a work culture where stress and busy-ness are accepted as normal. Regardless, such a gap in self-awareness is problematic. Affected pharmacists may continue to work through any feelings of emotional exhaustion and depersonalization. Over time, fatigue may accumulate and ultimately impair the quality of patient care. Other health care professional associations have recognized similar

TABLE 3. Univariable Regression Analysis for Relation between Professional Dissatisfaction and Burnout

Dissatisfaction Variable[a]	Odds Ratio (95% CI)		*p* Value
Overall career	6.93	(2.38–20.15)	< 0.001
Work–life balance	3.87	(2.20–6.80)	< 0.001
Interactions with RPh colleagues	4.73	(2.03–11.01)	< 0.001
Interactions with non-RPh colleagues	5.88	(1.72–20.08)	0.005
Intellectual challenge at work	3.13	(1.14–8.54)	0.026
Feeling contributions are appreciated	4.81	(2.63–8.82)	< 0.001
Time for professional growth	2.28	(1.20–4.32)	0.012
Time spent in clinical duties	1.60	(0.96–2.65)	0.07
Time for administrative tasks	1.68	(1.01–2.80)	0.047
Time spent with students/teaching	1.66	(0.99–2.78)	0.06

CI = confidence interval, RPh = registered pharmacist.
[a]Rated as very or somewhat dissatisfied.

TABLE 4. Self-Reported Influences on Burnout: Prominent Themes in Qualitative Questions

Protective Factors against Burnout	Contributors to Burnout
Time away from work (e.g., vacation, working part-time, taking full lunch hour)	Workload too high (e.g., understaffed, working through lunch, working late to keep up)
Social interactions (e.g., with colleagues, with family and friends outside of work)	Lack of work–life balance (e.g., energy to play with kids after work)
Activities/exercise outside of work	Lack of appreciation by colleagues and management

BOX 1. Key Points

Burnout among hospital pharmacists is high (61%) and comparable to burnout rates among physicians and nurses.

There is a gap in self-awareness among pharmacists who are burned out, an alarming phenomenon that can perpetuate burnout and could lead to suboptimal patient care.

Preventive burnout curricula are not widely implemented in pharmacy schools, but there exists an opportunity to develop such education to prepare students for the occurrence of burnout once they are in the workforce.

gaps in burnout awareness. For example, the Accreditation Council for Graduate Medical Education increased its efforts to support medical trainees and teachers in the United States to recognize the signs and symptoms of burnout; it also provided access to support and coaching in techniques to combat burnout.[18] In turn, pharmacists may also benefit from early education about burnout and the strategies available for early implementation against burnout in the workforce.

The data gathered in this study suggest 3 different platforms from which we can target burnout reduction among pharmacists: individual, system and management, and educational.

At the individual level, respondents identified several contributors to burnout, such as high workload, as well as protective factors, such as extracurricular hobbies and support from family and friends. A recurrent theme was to "leave work at work". Certainly, many options are available for following this advice, such as "taking vacation" or "exercising". Notably, if employees are to implement these strategies, they will need support from management. Placing the responsibility for preventing burnout solely on the individual might lead employees to seek out solutions that could be detrimental to the organization, such as reducing professional work effort.[19] Furthermore, although it makes sense to institute mindfulness training or create wellness programs to reduce employees' stress, it would be a mistake to overlook the system-level issues that intensify that stress.[20]

In the health care system at large, burnout among health care providers is associated with decreased quality of care and patient safety.[2,3] Health care providers may become disengaged, less committed, and possibly cynical. These attitudes may present challenges for organizational leaders as staff members, including pharmacists, reduce their collaborative efforts with colleagues and management, leading to suboptimal functioning of the health care system. Typically, accountability for addressing burnout and instituting change is placed on the individual. However, as with any systems-level thinking, tackling burnout should be a shared responsibility. The potential impact of management-led initiatives should not be underestimated. In a systematic review of burnout interventions among US physicians, Dyrbye and others[21] found that both individual and institutional interventions were needed to reduce burnout.

In our survey, pharmacists reported feeling underappreciated by their pharmacist colleagues, management, and colleagues from other professions. They also felt underacknowledged for working extra hours (e.g., working overtime, working through lunch) and for the high-quality patient care that they provide. Some of these factors can be addressed at the management level, where institutional initiatives to promote pharmacist achievements could help tackle such sentiments. Opportunities such as recognition during daily team huddles (i.e., brief meetings of health care staff that help to foster connections and alignment among staff through sharing of organizational goals, metrics, and individual achievements) or continuous quality improvement meetings represent "low-hanging fruit" that may be easier to incorporate than certain other initiatives. In a study of 14 hospitals with established recognition programs and 10 hospitals without such programs, meaningful recognition was found to be a significant predictor of decreased burnout among nurses.[22]

At the undergraduate level, education about burnout recognition and prevention strategies has commonly been implemented in faculties of nursing and medicine.[6-11] Among medical students, resiliency training programs, compassion fatigue programs, and self-relaxation programs have all been effective in improving burnout scores.[6-8] There is also a significant body of literature describing successful interventions to prevent burnout among nursing students. Strategies with some evidence for efficacy include acceptance and commitment training, a music integrative program, and a psychosocial training program.[9-11] Given this existing body of research, burnout education for pharmacy students could help them to identify symptoms and seek help earlier when experiencing symptoms of burnout in their professional careers. Currently, 9 of the 10 pharmacy schools in Canada do not offer any type of burnout-prevention education, but 8 out of these 9 schools would be open to including such content in the curriculum. Notably, McQuade and others[23] identified an increase in emotional exhaustion scores among US pharmacists before and after the year 2000, which correlated with a rise in clinical duties and responsibilities. It is reasonable to expect that with changes and expansion in pharmacists' professional scope will come a need to evaluate and update the means by which pharmacists are equipped with skills to combat burnout. Similar to curricula for other health care professions, the undergraduate pharmacy school curriculum may be an appropriate point to introduce strategies for recognition and prevention of burnout, in anticipation of burnout occurring once students graduate and join the workforce.

To the authors' knowledge, this is the first study to measure burnout and characterize associated risk factors in

a population of Canadian pharmacists. The survey reached a broad distribution of pharmacists and practice settings across Ontario, including 33 hospital corporations representing 67 hospital sites, CSHP Ontario Branch members, and both community and academic hospitals. The response rate was good and comparable to other similar studies involving health care professions.[3] To our knowledge, this was also the first study that surveyed faculties of pharmacy about burnout curricula to better understand the baseline level of relevant education. The validity of our results is strengthened by comparable burnout rates among US hospital pharmacists (61.1% versus 61.2%).[5]

This study had some limitations. Because the survey was voluntary, there was a risk of selection bias. It is possible that those who participated in the study were inherently different from those who did not participate. For example, pharmacists who were feeling burned out might have been more inclined to complete the survey because they identified with the survey topic. Alternatively, pharmacists who were feeling burned out might have been less inclined to spend their time on a voluntary survey with no incentives for participation. The prevalence of burnout may therefore be under- or over-represented by our findings.

The results of this study are also subject to the inherent limitations of the MBI. Although the MBI is the most widely used measure of burnout, with well-established reliability and validity, it treats burnout as a 1-dimensional, dichotomous state based on threshold cut-off scores within individual categories (e.g., emotional exhaustion). For some individuals, however, burnout may exist on a multifactorial continuum.[24] In addition, there may be individuals with burnout scores just below the cut-offs (i.e., in the moderate range) who may actually be experiencing burnout, but they would not be identified with the MBI. Although this study used the cut-off values most commonly used in the literature to determine burnout rates, some previous studies may have used other cut-offs, which may make comparisons more difficult.

Although the need for preventive strategies has been identified, as well as an interest in covering this topic in the undergraduate pharmacy curricula, further research is needed to determine which types of interventions will be most effective for both pharmacists and pharmacy students and what type of curricular interventions will be successful in the long-term, once students have graduated.

CONCLUSION

The rate of burnout among Canadian hospital pharmacists is high and is similar to that among US health-system pharmacists. Preventive action is needed across North America. Opportunities exist to both improve pharmacists' resilience at the undergraduate level and reduce institutional stressors in the workplace.

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Tacrolimus Dose-Conversion Ratios Based on Switching of Formulations for Patients with Solid Organ Transplants

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ABSTRACT

Background: Tacrolimus may be administered during hospitalization as an IV formulation or oral suspension. However, literature suggesting appropriate ratios for conversion from these formulations to capsules is limited.

Objective: To evaluate conversion ratios after a switch in formulation of tacrolimus for solid-organ transplant recipients.

Methods: This single-centre observational longitudinal study involved hospitalized patients who underwent a switch in formulation of tacrolimus according to 1 of 3 possible scenarios: IV to oral suspension, IV to capsule, or oral suspension to capsule. Data were collected from the earliest accessible electronic file (January 2009) to January 1, 2019. Conversion ratios were calculated for each of the 3 groups using data for blood concentrations and doses before and after the switch. The calculated ratios were then compared with recommended conversion ratios: 1:5 (i.e., 1 mg of IV tacrolimus is converted to 5 mg of oral tacrolimus, expressed as "5") for either of the switches involving an IV formulation and 1:1 (i.e., same amount, expressed as "1") for the switch from oral formulation to capsules.

Results: For the group who underwent switching from the IV formulation to oral suspension, the mean calculated conversion ratio was 3.04, which was significantly different from the recommended ratio of 5. For the group who underwent switching from the IV formulation to capsules, the calculated conversion ratio was 5.18, which was not significantly different from the recommended ratio of 5. For the group who underwent switching from oral suspension to capsules, the calculated conversion ratio was 1.17, which was not significantly different from the recommended ratio of 1.

Conclusion: In this small retrospective study of tacrolimus therapy, the calculated conversion ratio was significantly different from the recommended ratio for patients who were switched from IV administration to oral suspension, but not for those switched from IV administration or oral suspension to capsules. Therapeutic drug monitoring therefore appears indispensable, regardless of conversion ratios.

Keywords: conversion ratio, formulation, solid-organ transplant, tacrolimus, therapeutic drug monitoring

RÉSUMÉ

Contexte : Le tacrolimus peut être administré par IV ou sous forme de suspension orale pendant une hospitalisation. Cependant, il existe peu de documents qui proposent des ratios appropriés pour convertir ces formulations en capsules.

Objectif : Évaluer les ratios de conversion après un changement de formulation du tacrolimus pour les bénéficiaires de greffes d'organes solides.

Méthodes : Cette étude observationnelle longitudinale unicentrique impliquait des patients hospitalisés, pour qui la formulation de tacrolimus changeait en fonction de chacun des trois scénarios possibles : passage de l'administration par IV à la suspension orale, passage de l'administration par IV aux capsules ou passage de l'administration par suspension aux capsules. Le recueil des données a été effectué à partir du plus ancien dossier électronique accessible (janvier 2009) jusqu'au 1er janvier 2019. Les ratios de conversion ont été calculés pour chacun des trois groupes à l'aide de données pour les concentrations de sang et des doses avant et après le changement. Les ratios calculés ont ensuite été comparés avec les ratios de conversion recommandés : 1:5 (c.-à-d., 1 mg de tacrolimus administré par IV est converti en 5 mg de tacrolimus par voie orale, conversion exprimée par le nombre « 5 ») pour chacun des changements impliquant une formulation IV et 1:1 (c.-à-d. même quantité, conversion exprimée par le nombre « 1 ») pour le passage de la formulation orale aux capsules.

Résultats : Dans le groupe dont l'administration par IV est passée à une suspension orale, le ratio de conversion moyen calculé était de 3,04, ce qui était significativement différent par rapport au ratio recommandé de 5. Pour le groupe dont l'administration par IV est passée à des capsules, le ratio de conversion moyen calculé était de 5,18, ce qui n'était pas significativement différent par rapport au ratio recommandé de 5. Pour le groupe dont l'administration est passée de la suspension orale aux capsules, le ratio de conversion moyen calculé était de 1,17, ce qui n'était pas significativement différent par rapport au ratio recommandé de 1.

Conclusion : Dans cette petite étude rétrospective de la thérapie à l'aide du tacrolimus, le ratio de conversion calculé était significativement différent du ratio recommandé pour les patients qui passaient d'une administration IV à une suspension orale, mais pas pour ceux qui passaient d'une administration par IV ou d'une suspension orale à des capsules. La surveillance thérapeutique des médicaments semble donc indispensable, quels que soient les ratios de conversion.

Mots-clés : ratio de conversion, formulation, greffe d'organe solide, tacrolimus, surveillance thérapeutique des médicaments

INTRODUCTION

Calcineurin inhibitors represent the cornerstone of immunosuppressive maintenance therapy in solid-organ transplantation.[1,2] Indeed, their introduction dramatically changed patients' outcomes, with an increase in 1-year post-transplant survival rate from 50% with azathioprine to 70%–80% with cyclosporine, the first calcineurin inhibitor on the market.[1,3] Despite their apparent benefits, these drugs are associated with multiple complications, most of which are concentration-dependent, such as nephrotoxicity, neurotoxicity, and hyperglycemia; as such, therapeutic drug monitoring is justified, to optimize efficacy and limit toxicity.[1,3,4]

Tacrolimus is one of the calcineurin inhibitors now in use. Because of its narrow therapeutic range and large inter- and intra-individual pharmacokinetic variability, therapeutic drug monitoring remains an important aspect of tacrolimus therapy. For example, various studies in patients with renal transplant have shown a strong correlation between low concentrations of drug and transplant rejection, and between high concentrations and nephrotoxicity.[5] The whole-blood concentration of tacrolimus varies widely among individuals, mainly because of its complex pharmacokinetic properties.[2] Indeed, the sources of pharmacokinetic variability can be numerous, whether external (such as drug–drug interactions) or internal (such as hepatic function and hematocrit).[2]

One source of pharmacokinetic variability is the formulation or route of administration.[2] Pharmacokinetic studies have shown that the bioavailability of oral tacrolimus is roughly 20% to 25%.[6-8] These results explain why the conversion ratio for IV to oral administration recommended by the International Society for Heart and Lung Transplantation (ISHLT) is 1:5 (i.e., 1 mg of IV tacrolimus converted to 5 mg of oral tacrolimus, expressed in this article as "5").[9] However, this recommended ratio does not seem to have been thoroughly validated through randomized controlled trials. An observational study involving patients who underwent stem-cell grafting reported a ratio of 5, but it remains questionable whether this conversion ratio is adequate for patients who have undergone solid organ transplants.[10] In addition, the question remains as to what conversion ratio would be adequate for a switch from oral suspension to capsules. In a phase 1 single-dose study, Undre and Dickinson[11] found that the bioavailability of prolonged-release tacrolimus suspension prepared from opened capsules seemed equivalent to that of the intact capsules. However, the conversion ratio recommended by the ISHLT might not be adequate for converting from IV doses to oral suspension doses. Moreover, the question remains as to whether a ratio of 1 is adequate for switching between the 2 oral formulations, even if their bioavailabilities seem equivalent.[11]

In the early post-transplant period, patients are usually in the intensive care unit and may be unable to take oral medications. Others may present months or years after the transplant with a complication that prevents oral administration of medication. These patients are started on tacrolimus by IV administration until the oral route is feasible. In addition, an oral suspension is often used as a bridge between the IV formulation and capsules or for patients who are unable to swallow capsules. The pharmacists in our transplant centre have long noticed that despite using the recommended conversion ratio of 5 when switching patients from IV to oral administration of tacrolimus, the trough concentration always seems to fluctuate greatly, and it is difficult to determine the proper dose adjustment. Therefore, the primary objective of this study was to calculate the conversion ratio for switches in tacrolimus formulation in solid organ transplant recipients.

METHODS

Study Design and Setting

We conducted a single-centre, observational, descriptive, cross-sectional, longitudinal study in a university-affiliated tertiary hospital. The design and conduct of this study were reviewed and approved by the Ethics Committee of the Institut universitaire de cardiologie et de pneumologie de Québec – Université Laval, which waived the need for written informed consent. Participant selection was performed retrospectively using pharmacy database software, from which we identified all patients who underwent a switch of tacrolimus formulation during the period from January 1, 2009 (earliest accessible electronic file) to January 1, 2019. Patients were included if they met the following inclusion criteria: at least one switch in formulation of tacrolimus during the hospital stay, specifically by 1 of 3 possible scenarios (IV to capsules [immediate release], IV to oral suspension, or oral suspension to capsules [immediate release]); age 18 years or older; and administration of each formulation for a minimum of 3 days. A given patient could be included multiples times if there were multiple switches of formulation during the same hospital stay.

Data Collection

Data were collected from electronic medical records and pharmacy database software.

Primary Outcome Measures

The main data collected were doses of tacrolimus received and trough concentrations of tacrolimus measured in the blood. At the study site, samples for determination of tacrolimus trough concentrations (measured by liquid chromatography coupled with tandem mass spectroscopy) were obtained at 0600, 60 minutes before the first dose of the day (at 0700), reflecting the daily dose received the previous day. We collected the trough concentrations associated with the 3 doses before the switch in formulation and the trough

concentrations associated with doses on days 3, 4, and 5 after the switch (Figure 1). For included patients, the dose of tacrolimus, but not the formulation, could have changed in the period from Day_{-3} to Day_{-1} or in the period from Day_{+3} to Day_{+5}; patients with a change in formulation during either of the data collection periods were excluded. The concentration of the drug at steady state referred to here was therefore a formulation-related, rather than a dose-related, steady state concentration. In this study, interindividual variability in metabolism and elimination was attenuated by using the concentration/dose (*C*/*D*) ratio (Figure 1), while intraindividual variability was attenuated by considering a 3-day average. Using ratios and averages allows drug monitoring without reliance on absolute doses and target concentrations. We also considered that collecting the concentration data at days 4 to 6 after the switch would yield values more likely to be at equilibrium, which would further reduce any remaining influence of the initial formulation.[6]

Secondary Outcome Measures

Other data collected were related to confounding variables: the transplanted organ, hematocrit, alanine aminotransferase (ALT), creatinine, estimated glomerular filtration rate, age, potentially interacting drugs (mainly inhibitors or inducers of cytochrome P450 3A4/5 [CYP3A4/5] isozymes and/or P-glycoprotein), and plasma albumin.[2,7,12-17]

Concerning potentially interacting medications, we considered only the presence of medications with a course of usage that overlapped with the observation period. The following medications were considered: any corticosteroids, any azole antifungals, nondihydropyridine calcium-channel blockers (verapamil, diltiazem), antibacterials (clarithromycin, erythromycin, rifampin), antiepileptic drugs (phenytoin, carbamazepine, primidone, phenobarbital), and protease inhibitors. For corticosteroids, we collected the doses received a week before the switch, on the day of the switch, and on day 5 after the switch, because it is known that the CYP3A4/5 induction effect of corticosteroids is dose-dependent.[18] To standardize any potential impact of corticosteroids, the dose data were all converted to equivalent prednisone doses. For the azoles, the starting date, dose, and ending date were collected, given that the degree of CYP3A4 inhibition seems to be dose-dependent for certain antifungals.[16,19] Clinical data, such as hematocrit and ALT, were collected before and after the switch.

The confounding variables were also used for subgroup analyses because of their potential effects on tacrolimus concentrations. To alleviate the effects of drug interactions, hematocrit fluctuations, and elevated ALT, we performed subgroup analyses in which patients were excluded if they had used azole antifungals, if they had a significant change in their corticosteroid dose, or if they had a change in ALT above 3 times the upper limit of normal. Other subgroup analyses were performed for patients with normalized hematocrit and for heart transplant recipients only.

Statistical Analysis

General demographic information was collected. Using the tacrolimus concentrations and doses from patients' medical records, we calculated *C*/*D* ratios, whereby tacrolimus trough concentrations were divided by the total daily dose received the previous day.[17] Mean *C*/*D* ratios were therefore calculated for the 3 days before the switch (denoted C/D_{pre}) and for days 4 to 6 after the switch (denoted C/D_{post}), as shown in Figure 1. The conversion ratio was defined as C/D_{pre} divided by C/D_{post}. For each of the 3 possible scenarios, a mean conversion ratio was then calculated across all patients. The Student *t* test was then performed to compare the mean calculated conversion ratio with the recommended ratio. For switching from IV to oral formulations (capsule or suspension), the recommended conversion ratio was 1:5 (i.e., oral dose 5 times higher than IV dose), and for switching from capsules to suspension, the recommended conversion ratio was 1:1. A *p* value of less than 0.05 was considered to represent a statistically significant difference between the recommended and calculated conversion ratios.

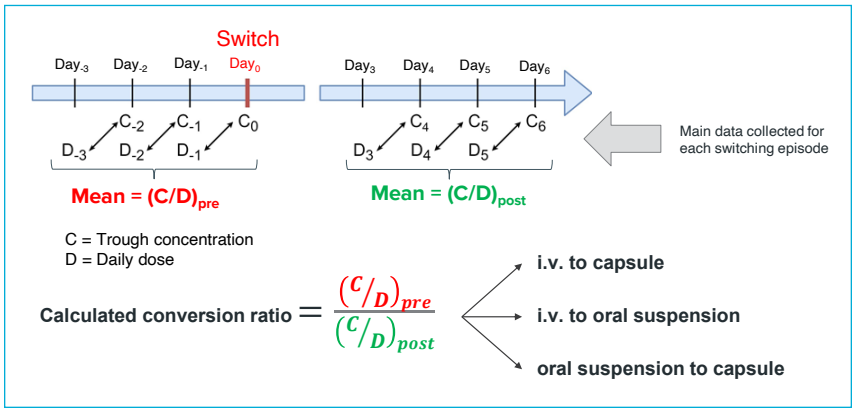

FIGURE 1. Calculation of the conversion ratio. For reporting purposes, the ratio is presented as a single value, according to the calculation shown.

For the subgroup analysis considering hematocrit, all *C*/*D* ratios were normalized to a hematocrit (Hct) value of 45% using the following equation: $(C/D) \times (\text{Hct}/0.45)$.[2,20] For the subgroup analysis considering the use of corticosteroids, we defined a relevant change in corticosteroid dose as being a modification of at least 25% from the previously recorded dose.

RESULTS

In total, 41 episodes of formulation switching were identified, distributed among 37 patients: 8 episodes (in 8 patients) of switching from IV to oral suspension, 14 episodes (in 14 patients) of switching from IV to capsules, and 19 episodes (in 15 patients) of switching from oral suspension to capsules. The mean age of the cohort was 52.5 (standard deviation [SD] 11.7) years, with women representing 13 (32%) of all episodes (Table 1). For most episodes (n = 36, 88%), the patients were heart transplant recipients. For most episodes, the patient was receiving enteral feeding on the day of the switch (n = 31, 76%), and none had any history of gastrointestinal disease. For most episodes (n = 26, 63%), the patients had undergone surgery (of any type) less then 30 days before the switch. Regarding the use of potentially interacting drugs, there were 38 episodes (93%) in which corticosteroids were used during the observation period. In contrast, there were only 5 episodes (12%) in which azoles were used during the observation period. No other interacting drugs from the prespecified list were used during the period of data collection. Mean hematocrit was 0.284 (SD 0.042) before the switch and 0.266 (SD 0.031) afterward.

For the patients who underwent switching from IV to oral suspension, we calculated a conversion ratio of 3.04 (SD 1.53), with a 95% confidence interval (CI) of 1.77–4.32

TABLE 1. Demographic and Clinical Variables of 3 Scenarios for Switching Tacrolimus Formulations

	Scenario; No. (%) of Episodes or Mean ± SD		
Variable	**IV to Oral Suspension (n = 8)**	**IV to Capsule (n = 14)**	**Oral Suspension to Capsule (n = 19)**
Sex, female	3 (38)	5 (36)	5 (26)
Age (years)	56.4 ± 9.0	54.5 ± 12.6	50.2 ± 12.0
Weight (kg)	77 ± 14.1	79.2 ± 15.6	78.25 ± 20.2
Time since transplant[a] (months)	39.4 ± 108.4	6.3 ± 8.2	22.9 ± 53.6
Enteral feeding	8 (100)	7 (50)	16 (84)
Recent surgery[b]	8 (100)	8 (57)	10 (53)
Type of transplanted organ			
Heart	7 (88)	12 (86)	17 (89)
Kidney	1 (12)	1 (7)	1 (5)
Lung	0 (0)	1 (7)	1 (5)
Interacting drugs			
Azoles	1 (12)	0 (0)	4 (21)
Corticosteroid	8 (100)	12 (86)	18 (95)
Dose 7 days before switch (mg)	53.8 ± 25.9	161.2 ± 335.7	39.7 ± 54.3
Dose on day of switch (mg)	42.2 ± 18.3	29.5 ± 20.5	22.1 ± 12.1
Dose 5 days after switch (mg)	37.7 ± 25.1	22.7 ± 15.1	20.9 ± 11.1
Clinical lab results before switch			
ALT (IU/L)	87.3 ± 101.6	63.3 ± 85.2	44 ± 57.7
eGFR (mL/min/1.73 m^2)	61.8 ± 31.4	59.1 ± 33.6	57.6 ± 35.1
Hematocrit	0.311 ± 0.053	0.272 ± 0.033	0.283 ± 0.044
Albumin (g/L)	33.8 ± 8.7	32.8 ± 4.4	30.9 ± 4.4
Clinical lab results after switch			
ALT (IU/L)	71.8 ± 89.4	40.1 ± 24.1	62.5 ± 112.3
eGFR (mL/min/1.73 m^2)	49.9 ± 36.5	53.4 ± 27.2	55.9 ± 35.8
Hematocrit	0.266 ± 0.014	0.273 ± 0.055	0.263 ± 0.021
Albumin (g/L)	28.7 ± 6.4	32.7 ± 3.8	29.8 ± 5.0

ALT = alanine aminotransferase, eGFR = estimated glomerular filtration rate, SD = standard deviation.
[a]Time since transplant at the moment of switch in formulation.
[b]Surgery of any type that occurred within 30 days of the switch in formulation.

(p = 0.008), which was significantly different from the recommended conversion ratio of 5 (oral dose 5 times higher than IV dose). For those who underwent switching from IV to capsules, the calculated conversion ratio was 5.18 (SD 3.17) (95% CI 3.35–7.00, p = 0.84) which was not significantly different from the recommended ratio of 5. For those who underwent switching from oral suspension to capsules, the calculated conversion ratio was 1.17 (SD 0.74) (95% CI 0.82–1.58, p = 0.32), which was not significantly different from the recommended ratio of 1. Figure 2 and Table 2 illustrate these findings.

We were also interested in evaluating, through subgroup analysis, switching episodes that were not biased by drug–drug interactions. In the group that switched from IV

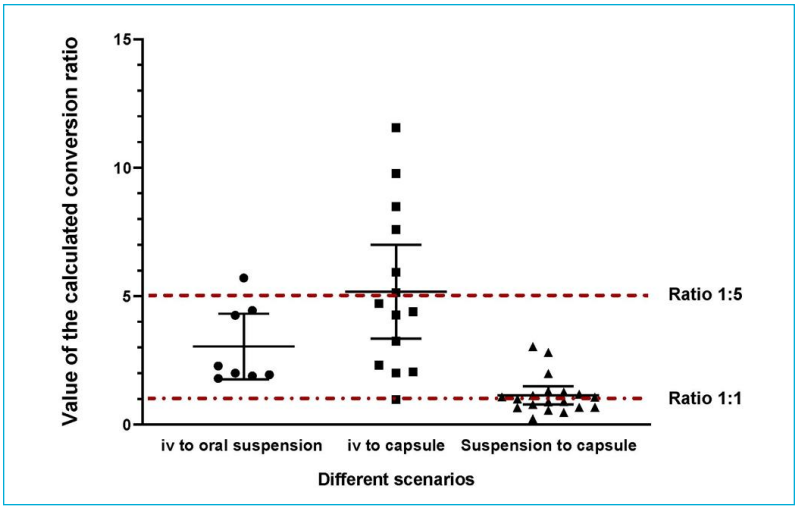

FIGURE 2. Calculated conversion ratios according to the various scenarios. Data points for individual patients are shown, along with the mean (longer horizontal line) and standard deviation (vertical line with shorter horizontal end lines) for each scenario.

TABLE 2. Calculated Conversion Ratios for Each Switching Scenario and Subsequent Subgroup Analyses

Scenario and Subgroup Analysis	Calculated Conversion Ratio (Mean ± SD)	*p* Value
IV to oral suspension	3.04 ± 1.53	0.008
(n = 8 switching episodes)	(95% CI 1.77–4.32)	
Excluding azoles (n = 7)	3.22 ± 1.56	0.023
Excluding significant CS dose change (n = 3)	3.30 ± 2.10	0.30
Hematocrit normalized (n = 7)	2.76 ± 1.24	0.003
Excluding 3 × ULN ALT (n = 7)	2.66 ± 1.17	0.002
Heart transplant only (n = 7)	3.20 ± 1.58	0.023
IV to capsule	5.18 ± 3.17	0.84
(n = 14 switching episodes)	(95% CI 3.35–7.00)	
Excluding azoles (n = 0)	NA	NA
Excluding significant CS dose change (n = 5)	6.10 ± 3.13	0.48
Hematocrit normalized (n = 14)	4.87 ± 2.65	0.85
Excluding 3 × ULN ALT (n = 9)	4.32 ± 2.89	0.50
Heart transplant only (n = 12)	5.06 ± 3.24	0.95
Oral suspension to capsule	1.17 ± 0.74	0.32
(n = 19 switching episodes)	(95% CI 0.82–1.58)	
Excluding azoles (n = 15)	1.10 ± 0.62	0.51
Excluding significant CS dose change (n = 13)	1.05 ± 0.61	0.79
Hematocrit normalized (n = 16)	1.11 ± 0.79	0.60
Excluding 3 × ULN ALT (n = 13)	1.20 ± 0.85	0.42
Heart transplant only (n = 17)	1.00 ± 0.56	0.97

ALT = alanine aminotransferase, CI = confidence interval, CS = corticosteroid, NA = not applicable, SD = standard deviation, ULN = upper limit of normal.

to oral suspension, excluding the single episode involving a patient who was using an azole did not affect the overall result: the calculated conversion ratio remained significantly different from the recommended ratio of 5. However, in the same group, excluding episodes for patients with relevant changes in corticosteroid doses (n = 5 episodes excluded) did affect the result, with the difference between calculated and recommended conversion ratios becoming nonsignificant; this may have been related to the small number of episodes in this subgroup analysis (n = 3). For the group with switching from IV to capsules, only utilization of corticosteroids was present; excluding episodes with relevant changes in corticosteroid doses (n = 9 episodes excluded) yielded a calculated conversion ratio that was nonsignificantly different from the recommended ratio of 5. In the group with switching from oral suspension to capsules, excluding the 4 episodes involving patients who were using an azole yielded a calculated conversion ratio that was nonsignificantly different from the recommended ratio of 1. In the same group, excluding episodes involving patients with relevant changes in corticosteroid dose (n = 6 episodes excluded) also yielded a nonsignificant difference between the calculated and recommended conversion ratios. In general, the results for these subgroup analyses were not substantially different from the results for the main analysis.

We also tried to alleviate the effect of abnormal physiological functions known to affect the pharmacokinetics of tacrolimus (low hematocrit or elevated ALT). To address hematocrit variation, we calculated normalized conversion ratios; the results for all 3 switching scenarios remained consistent with the results in the main analysis. Similarly, when we excluded episodes in which the ALT was elevated (at least 3 times the upper limit of normal), the results remained consistent with the main analysis. No significant changes in serum albumin were observed after the switch in formulation (relative to before the switch), with any of the 3 switching scenarios.

We were also interested in alleviating the potential impact of enteral feeding on the calculated conversion ratios. For the group switched from IV to oral suspension, all patients were receiving enteral feeding and it was therefore impossible to alleviate the impact of this factor. When patients with enteral feeding were eliminated from the group with switching from IV to capsules, the mean calculated conversion ratio was 5.93 (SD 2.96; p = 0.44), while for the group with switching from oral suspension to capsules, the ratio was 0.93 (SD 0.34; p = 0.74), both of which were not significantly different from the respective recommended ratios.

Given that the Institut universitaire de cardiologie et de pneumologie de Québec – Université Laval is a centre that specializes in heart transplants, there was a special interest in assessing results for this specific population. When patients with non-heart transplants were excluded from the analysis, the results for all 3 switching scenarios remained consistent with the original analysis, from a statistical standpoint (details shown in Table 2).

DISCUSSION

This study aimed to evaluate dose-conversion ratios for switches in formulation of tacrolimus in solid organ transplant recipients, in relation to the ISHLT's recommended ratios of 5 for conversion from IV to oral administration and 1 for conversion from oral suspension to capsules. For the conversion from IV to capsules, the calculated conversion ratio was 5.18 (SD 3.17), which is not significantly different from the recommended ratio of 5. This finding is in agreement with another study, which showed a similar ratio for allograft patients.[10] Moreover, in various subgroup analyses for the IV-to-capsule scenario, the calculated conversion ratios remained nonsignificantly different from the recommended ratios. Interestingly, for the conversion from IV to oral suspension, we found a conversion ratio of 3.04 (SD 1.53), which was significantly different from the recommended ratio of 5. In contrast, the conversion from oral suspension to capsules yielded a calculated conversion ratio that was not significantly different from the recommended ratio of 1.

From a pharmacokinetic standpoint, these results suggest that different formulations likely have different bioavailabilities.[2,6] Of note, a European phase 1 study involving 20 healthy men aimed to evaluate the relative bioavailability of tacrolimus administered orally or via nasogastric tube using either capsules or an oral suspension. In that study, when the drug was given orally, bioavailability was similar for the capsules and the oral suspension.[11] In fact, in the current study, the difference in results for conversion from IV administration to oral formulations (significantly different from recommended ratio for oral suspension, but not significantly different for oral capsules) was surprising. Indeed, given that the oral formulations did not yield any significant difference when compared with each other, these differing results for conversion from IV administration were unexpected. The statistically significant difference observed for the conversion from IV to oral suspension is intriguing yet convincing, given that it was observed with the smallest sample size of the 3 possible scenarios (n = 8 switching episodes).

This observed discrepancy in the ratio for conversion from IV to oral suspension might be due to administration of tacrolimus through the enteral feeding tube. In fact, we had no means to evaluate the adequacy and consistency of this method of administration.[21,22] Nevertheless, given that most of the switching episodes from IV to oral suspension occurred in patients with enteral feeding, this result could suggest, from a pharmacokinetic perspective, increased absorption of the drug. Indeed, enteral feeding might have allowed more tacrolimus to reach lower parts of

the intestine, where there are fewer CYP3A4 gut enzymes or efflux pumps such as P-glycoprotein, thus enabling greater absorption of the drug.[2] Of note, neither the duration or flow of enteral feeding nor the presence of diarrhea were evaluated in this study. Greater enteral feeding flow or presence of diarrhea would likely push the medication further into the digestive tract, thus increasing absorption.[2,23] Furthermore, the use of enteral feeding might suggest the possible presence of digestive tract and intestinal malfunction, which would affect tacrolimus absorption in the case of switching from IV to oral suspension.[24] Conversely, a switch from oral suspension to capsule would generally suggest clinical improvement, particularly in the gastrointestinal tract, possibly signifying more "normal" gut functions and absorption. This "normalization" might explain the similar pharmacokinetics of oral suspension and capsules and the ratio of 1 that we observed.

As for the subgroup analyses, although the calculated ratios varied a little, the observed tendencies between calculated and recommended ratios remained consistent with those of the main analysis. Concerning potential drug-drug interactions, the results remained consistent in all groups after exclusion of the few episodes involving use of azoles. However, it remains difficult to completely eliminate the possibility of drug interactions, given that only known major CYP3A4 inhibitors or inducers were considered.[2,15,17] There is also the possibility that substrate-substrate interactions occurred but were not accounted for.[2,15,17] Potential induction by corticosteroid is known to be a dose-dependent effect, but there does not seem to be a cut-off dose highlighted in the literature.[2,17,18] Thus, we empirically chose to exclude switching episodes associated with corticosteroid dose changes of 25% or more; however, the calculated conversion ratios cannot be taken at face value because the sample size was considerably reduced in these subgroup analyses. It was also difficult to evaluate whether a change of dose within such a short period of time could really affect the metabolism of tacrolimus. In a study by van Duijnhoven and others,[25] a 2-week tapering period followed by a single corticosteroid-free week led to an increase in tacrolimus exposure. In our case, the observation period was a little longer than a week. Nevertheless, the results remained consistent for all 3 scenarios relative to the main analysis.

The results also remained generally consistent in subgroup analyses accounting for physiological markers, such as hematocrit and ALT. Normalizing the hematocrit to 45% enabled us to alleviate the effect of variable red blood cell linkage to tacrolimus before and after the switch in formulation.[2,20] A reduction in hematocrit can potentially increase the unbound fraction of tacrolimus, thus increasing its hepatic clearance and lowering its total concentration.[2,13] For ALT, we considered 3 times the upper limit of normal as a sign of potential liver dysfunction, but excluding such episodes nonetheless yielded the same results. Because albumin is known to bind tacrolimus, we considered potential changes in serum albumin before and after the switches that might have accounted for variation in tacrolimus concentration in all 3 scenarios. No significant changes were observed.

When the raw data points (Figure 2) are examined, it is important to also notice the range of results (represented by SD). The calculated conversion ratios had large CIs for the IV to capsules scenario, but a much narrower range for the IV to oral suspension scenario, which yielded a statistically significant difference between the calculated and recommended ratios. The data points contributing to the calculated ratio clustered around 2 and 4, with a single higher value (5.71), which pulled the mean to a higher value (3.04). These data suggest that strong interindividual variability does exist, and can hardly be alleviated, despite attempts to reduce both external and internal confounding factors. There could also be one or more unidentified confounding variables not accounted for in the present study. Either way, these results further reinforce the importance of therapeutic drug monitoring, despite any recommended conversion ratio.

Other potential confounding factors that might have been considered for evaluation include sex, age, ethnicity, and genetic polymorphisms. It is still not clear whether sex has any significant effect on dose requirements for tacrolimus. Indeed, several pharmacokinetic studies have shown tacrolimus clearance and dose requirements to be higher in women,[17,20,26] whereas others have not.[27-29] Moreover, when midazolam was used as a drug probe, intestinal and hepatic CYP3A4 activity displayed only small differences between the 2 sexes.[30] In the current study, most of the patients were men (proportions ranging from 63% to 75% of each group). However, given the small sample sizes (including $n = 8$ in the IV to oral suspension group), any interpretation of the influence of sex would be risky.

Age is another potential modulator of tacrolimus dose requirements. It has well-characterized effects on the disposition of numerous drugs, especially relevant for geriatric (>75 years) and frail patients. For instance, it has been suggested, though not consistently proven, that as adults age, their tacrolimus dose requirement declines steadily.[2] Indeed, it was demonstrated more than 30 years ago that elderly patients have reduced total body water and lean body mass, and thus a relative increase in body fat,[31] providing a larger volume of distribution for hydrophobic drugs such as tacrolimus. Modulation of gastric pH and intestinal transit, as well as decreased liver volume and hepatic blood flow, have also been observed in elderly people.[32] Interestingly, no significant differences in either hepatic or combined hepatic and intestinal CYP3A activity have been demonstrated between young adults and elderly people (although the studies involved mostly healthy volunteers who had not undergone transplant).[33-35] Moreover, numerous population-based pharmacokinetic studies (with only

limited numbers of elderly patients) showed no significant effect of aging on tacrolimus disposition.[36-41] In contrast, a much larger study, analyzing 2205 patients included in the DeKAF study, showed lower dosing requirements in elderly people.[42] In the current study, mean age was similar across groups and fell within a narrow range of 50 to 56 years, with no geriatric patients, which prevented any analysis of the effect of age on tacrolimus dosing.

Other potential contributors to variability in tacrolimus dosing requirements are ethnicity and genetic polymorphisms, which are unequally distributed among different ethnic populations worldwide. For instance, African Americans were shown to require higher doses of tacrolimus than whites, which is mainly attributable to 20% to 50% lower bioavailability of the drug.[42-46] In today's era of pharmacogenetics, it is known that observed differences in the disposition of tacrolimus are mostly determined by ethnic variability in common polymorphisms for genes encoding drug-metabolizing enzymes and drug transporters. Of particular interest in the context of tacrolimus disposition is the CYP3A5*1 allele, found in 45% to 73% of African Americans, 5% to 15% of whites, 15% to 35% of Asians, and 25% of Mexicans.[2] Carrying a CYP3A5*1 allele was shown to produce an average 30% increase in the oral clearance of tacrolimus, resulting in a 50% higher dose requirement.[47] However, it is still unclear why African American noncarriers of the CYP3A5*1 allele had dose requirements similar to those of white noncarriers.[2]

Other genetic differences that could be involved in ethnicity-related variability in tacrolimus disposition are an increased frequency of inactivating alleles of CYP3A5*6 and CYP3A5*7 in African Americans, along with CYP3A4*1B and ABCB1 (Pgp) 3435CC variants, although the effect of these latter 2 on tacrolimus disposition appears to be of limited importance.[48-50] Again, in the present study, the small number of patients involved and the fact that all were white suggest limited impact of ethnicity and associated genetic polymorphisms on tacrolimus disposition. Moreover, as mentioned previously, the use of *C/D* ratios further attenuated interindividual variability.

This study had some limitations. One of our main concerns was not being able to ascertain the adequacy or consistency of drug administration through enteral feeding tubes. As such, adherence of drug molecules to the tube wall or interactions with food might have affected the absorption of tacrolimus,[21,22] especially for the scenario involving the oral suspension formulation. Furthermore, it was not possible to ascertain for all patients whether drugs were indeed administered through the tube, nor did we know the duration of feeding, the flow rate of enteral feeding, or the presence of diarrhea. As such, we cannot exclude the possibility of an effect of enteral feeding on tacrolimus administration, when dealing with the oral suspension, as it was shown to affect absorption of the drug.[51] Moreover, as with any retrospective study, complete detailed pathophysiological data were not available in the electronic patient records. In addition, the study sample consisted mostly of heart transplant recipients, so the generalizability of our results to the context of other solid-organ transplants is unknown.

This study was only a stepping stone to understanding the pharmacokinetic implications of switching formulations of tacrolimus. The sample sizes were quite small, and hence it is difficult to draw any firm conclusions. Larger studies are needed to determine consistent and adequate conversion ratios for switching between tacrolimus formulations. As it stands, our findings seem to suggest that switching from IV to oral suspension might require a different conversion ratio than the 1:5 recommended by the ISHLT, while the ratios currently used for the other 2 scenarios are likely adequate. Ultimately, however, considering the wide variability in trough concentrations of tacrolimus (as indicated by wide CIs and large SDs in our data), it is evident that therapeutic drug monitoring remains crucial, no matter which conversion ratio is being used.

CONCLUSION

In this small retrospective, cross-sectional, longitudinal study, a change in formulation of tacrolimus from IV to oral suspension yielded a conversion ratio different from the 1:5 ratio recommended by the ISHLT, whereas conversion ratios calculated for switches from IV to oral capsules and from oral suspension to capsules did not differ from the recommended ratios (5 and 1, respectively). Thorough therapeutic drug monitoring should remain the gold standard, no matter which conversion ratio is used.

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Stability of Extemporaneously Compounded Suspensions of Trimethoprim and Sulfamethoxazole in Amber Plastic Bottles and Amber Plastic Syringes

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ABSTRACT

Background: Trimethoprim (TMP) and sulfamethoxazole (SMX) are widely used, in combination, to treat or prevent various infections. Unfortunately, no liquid oral formulation is currently available in Canada for patients who are unable to swallow tablets.

Objective: To evaluate the stability of suspensions of TMP and SMX (8 and 40 mg/mL, respectively) prepared in Oral Mix or Oral Mix SF vehicle (Medisca Pharmaceutique Inc) and stored for up to 90 days in amber plastic bottles or amber plastic syringes at 5°C or 25°C.

Methods: Suspensions were prepared from bulk powder and from tablets in Oral Mix and Oral Mix SF vehicles, then transferred to amber plastic (polyethylene terephthalate glycol) bottles and plastic oral syringes and stored at 5°C and 25°C. Samples were collected on predetermined study days (0, 7, 14, 23, 45, 60, 75, and 90 days) and analyzed using a validated high-performance liquid chromatography – ultraviolet detection method. A suspension was considered stable if it maintained at least 90% of its initial concentration with 95% confidence. Observations of organoleptic characteristics such as colour and odour, as well as pH, were used to assess physical stability.

Results: Suspensions prepared from bulk powder maintained concentrations of TMP and SMX of at least 97% of the initial concentration over the 90-day study period. No obvious changes in colour, odour, or pH were observed. However, acceptable suspensions could not be prepared from the commercial tablets. A persistent foam that developed at the surface of all suspensions prepared from tablets could result in inconsistent dosing.

Conclusions: Extemporaneously compounded oral suspensions of TMP and SMX (8 and 40 mg/mL, respectively) prepared from bulk powder in Oral Mix and Oral Mix SF vehicles and stored in amber plastic bottles or syringes at 5°C or 25°C remained stable for at least 90 days. Suspensions made from tablets produced unacceptable formulations.

Keywords: trimethoprim, sulfamethoxazole, stability, compounded oral suspension, Oral Mix, Oral Mix SF

RÉSUMÉ

Contexte : Le triméthoprime (TMP) et le sulfaméthoxazole (SMX) sont largement utilisés conjointement pour traiter ou prévenir diverses infections. Malheureusement, aucune formulation liquide orale n'est actuellement disponible au Canada pour les patients incapables d'avaler des comprimés.

Objectif : Évaluer la stabilité des suspensions de TMP et de SMX (respectivement 8 et 40 mg/mL) préparées dans un véhicule Oral Mix ou Oral Mix SF (Medisca Pharmaceutique Inc.) et stockées pendant 90 jours dans des flacons ou des seringues en plastique ambré à 5 °C ou 25 °C.

Méthodes : Les suspensions ont été préparées à partir de poudre en vrac et de comprimés dans les véhicules Oral Mix et Oral Mix SF, puis transférées dans des flacons en plastique ambré (polyéthylène téréphtalate glycol) et dans des seringues orales en plastique et stockées à 5 °C et 25 °C. Des échantillons ont été recueillis à des jours prédéterminés (0, 7, 14, 23, 45, 60, 75 et 90 jours) et analysés à l'aide d'une méthode de détection par ultraviolet validée de chromatographie en phase liquide à haute performance. La suspension était jugée stable si elle préservait au moins 90 % de sa concentration initiale avec un seuil de confiance de 95 %. Les observations des caractéristiques organoleptiques, comme la couleur et l'odeur, ainsi que le pH, ont été faites pour évaluer la stabilité physique.

Résultats : Les suspensions préparées à partir de poudre en vrac préservaient au moins 97 % de la concentration initiale de TMP et de SMX pendant la période d'étude de 90 jours. Aucun changement manifeste de couleur, d'odeur ou de pH n'a été observé. Cependant, les suspensions acceptables n'ont pas pu être préparées à partir des comprimés commerciaux. Une mousse homogène se formait à la surface de ces suspensions, ce qui pourrait entraîner un dosage incohérent.

Conclusions : Les suspensions orales composées extemporanées de TMP et SMX (respectivement 8 et 40 mg/mL) préparées à partir de poudre en vrac dans des véhicules Oral Mix et Oral Mix SF et stockées dans des flacons ou des seringues en plastique ambré à 5 °C ou 25°C sont restées stables pendant au moins 90 jours. Les suspensions préparées à partir de comprimés ont donné des formulations inacceptables.

Mots-clés : triméthoprime, sulfaméthoxazole, stabilité, suspension orale composée, Oral Mix, Oral Mix SF

INTRODUCTION

Trimethoprim-sulfamethoxazole (TMP-SMX) is often used to treat various infections, including infections of the urinary tract, respiratory tract, and gastrointestinal system.[1] TMP-SMX is widely used as routine prophylaxis for *Pneumocystis jirovecii* (formerly known as *Pneumocystis carinii*) pneumonia in immunocompromised patients, including pediatric oncology patients, as well as patients with congenital and acquired severe immune deficiency.[2] Before the use of TMP-SMX prophylaxis, *P. jirovecii* pneumonia, a life-threatening infection, occurred in up to 43% of children with cancer.[3] TMP-SMX is the drug of choice for prophylaxis against this disease because of its high efficacy, as well as its tolerability, low cost, and broad antimicrobial spectrum.[4]

Oral suspensions of TMP-SMX are useful for patients who are unable to swallow tablets, which can occur because of conditions such as dysphagia and mucositis or simply young age. Unfortunately, the commercially available oral suspensions from Apotex[5] and Teva[6] have been in short supply in Canada since 2017, a situation expected to continue for an unknown period. To date, only one study concerning the stability of compounded TMP-SMX suspension has been published.[7] In that study, suspensions of TMP and SMX (8 and 40 mg/mL, respectively) in simple syrup were stable for only 20 days with storage at 4°C in amber plastic bottles. However, simple syrup has some disadvantages, particularly for pediatric formulations, because it does not properly mask the taste of the active ingredient and it does not contain an appropriate suspending agent for longer-term storage. Also, suspensions made from Apo-sulfatrim and Teva-trimel tablets in simple syrup, as described in the previous study,[7] were thick, with cakes formed at the surface, which led to difficulty in homogenizing the suspensions. Moreover, no data exist concerning the stability of suspensions of TMP-SMX (8 and 40 mg/mL, respectively) in dye-free Oral Mix and Oral Mix SF (sugar-free) vehicles (Medisca Pharmaceutique Inc).[8] These vehicles contain flavouring and preservatives that mask the taste of the medications and permit long-term stability.

The objective of this study was to determine the physical and chemical stability of oral suspensions of TMP and SMX (8 and 40 mg/mL, respectively) in Oral Mix and Oral Mix SF vehicles when stored at 5°C or 25°C in amber plastic bottles or oral plastic syringes for up to 90 days.

METHODS

Compounded Preparations from Bulk Powder and Tablets

Suspensions of TMP and SMX (8 and 40 mg/mL, respectively) were prepared from bulk powder and from tablets. For the bulk powder preparations, TMP USP micronized 98.6% powder (Medisca Pharmaceutique Inc, lot 611580/K) and SMX EP 99.9% powder (Medisca Pharmaceutique Inc, lot 610450/D) were first accurately weighed and then mixed together in a mortar using a pestle, before geometric incorporation of either Oral Mix (Medisca Pharmaceutique Inc, lot 611853/B) or Oral Mix SF (Medisca Pharmaceutique Inc, lot 611850/A) vehicle for a final volume of 150 mL. This operation was repeated 3 times to prepare 3 independent batches of suspension. Suspensions of the same total volume (150 mL) were similarly prepared from 15 pulverized tablets containing TMP and SMX (80 and 400 mg, respectively; Apo-sulfatrim, Apotex Inc, lot MX5200).

Design of Stability Study

Each 150-mL suspension was subdivided and packaged in 50-mL amber plastic (polyethylene terephthalate glycol) bottles (2 bottles of 50-mL fill volume per formulation per batch; Medisca Pharmaceutique Inc, lot 600990/A) and 3-mL amber plastic oral syringes (16 syringes of 2.5-mL fill volume per formulation per batch; PreciseDose Dispenser, Medisca Pharmaceutique Inc, lot 617025/B) and stored at 5°C or 25°C for up to 90 days. The remaining quantity of each suspension (10 mL) was discarded. For each formulation, 3 bottles (one per batch) were stored at each temperature; similarly, 3 syringes (one per batch) for each time point were stored at each temperature.

At each time point (0, 7, 14, 23, 45, 60, 75, and 90 days), a 2.5-mL aliquot from each bottle and 3 syringes per preparation were retrieved from each temperature condition. The bottles and syringes were vigorously shaken and vortex-mixed before sampling. For each test sample, odour and colour were inspected, the pH was measured, and samples were collected for later determination of the concentrations of TMP and SMX by high-performance liquid chromatography (HPLC) with ultraviolet (UV) detection (for practical reasons, the samples collected at each time point were frozen at –80°C, and all samples were analyzed on the same day). This design ensured that all stability conditions consisted of 3 separately prepared and stored formulations (experimental $n = 3$). Furthermore, each sample was analyzed twice by HPLC (technical $n = 2$).

Physical Properties

The physical properties of the suspensions prepared from bulk powder and from tablets were evaluated over the 90-day study period. At each time point, samples were examined for obvious changes in appearance and odour, and the pH was measured (model AP61 pH meter, Fisher Scientific). A difference in pH relative to initial measured value of not more than 1 unit was considered acceptable. The pH meter was calibrated at the beginning of each study day using commercially available standards.

Liquid Chromatography

HPLC-UV Method

The HPLC system (model Prominence UFLC, Shimadzu) was equipped with an LC-20AD binary pump operating at a flow rate of 1 mL/min, a DGU-20A5 solvent degasser, an SPD-M20A multiple-wavelength photodiode array detector set at 240 nm for TMP and 270 nm for SMX, an SIL-20AC HT refrigerated autosampler at 5°C, and a CTO-20AC column oven at 25°C. A Zorbax RX-C18 column (4.6 × 150 mm, 5 µm, Agilent Technologies Canada) was used for the study. Mobile phases consisted of 20 mmol/L aqueous monobasic potassium phosphate (JT Baker Inc, lot Y22465) adjusted to pH 2.5 using phosphoric acid and methanol (83:17; Fisher Scientific, lot 144689). The drugs were quantified using the area of the peak eluting at approximately 7.6 minutes for TMP and 11.2 minutes for SMX.

Assay Validation

The assay was validated by evaluating the accuracy and reproducibility of the standard curves on 3 different days. On each validation day, suspensions of TMP 9.6 mg/mL and SMX 48 mg/mL were prepared from Medisca bulk powders in Oral Mix and Oral Mix SF vehicles. Medisca powders were chosen over reference standards to produce the calibration standards because of their lower cost. The stock solutions were then diluted with each vehicle to obtain solutions of 6.4, 7.2, 8.0, 8.8, and 9.6 mg/mL for TMP and 32, 36, 40, 44, and 48 mg/mL for SMX. Samples (100 µL) of these solutions were diluted with methanol (10 mL) in 15-mL centrifuge tubes. Each mixture was vortex-mixed (20 seconds) and then centrifuged (3400 rpm, 15 minutes). Supernatant (300 µL) was diluted with water (600 µL) to yield standards of 21.33, 24.00, 26.66, 29.33, and 32.00 µg/mL for TMP and 106.67, 120.00, 133.33, 146.67, and 160.00 µg/mL for SMX. These standards were analyzed by HPLC in triplicate to create the standard curve.

Intraday variability was evaluated by injecting standard samples in triplicate within the same day, and interday variability was evaluated by injecting standard samples on 3 different days. Finally, intraday and interday errors were assessed from the coefficients of variation of the peak areas of each standard.

Standard Curve and Sample Preparation for HPLC Injection

For the HPLC analysis on the assay day, fresh standard curves and test samples were prepared and diluted as described in the assay validation section. These solutions for injection, with nominal concentrations of 26.67 µg/mL for TMP and 133.33 µg/mL for SMX, were analyzed in duplicate by HPLC immediately after preparation.

Forced Degradation of TMP and SMX

Suspensions of TMP and SMX (8 and 40 mg/mL, respectively) were prepared from bulk powder in Oral Mix and Oral Mix SF vehicles, as described above. Forced degradation was performed by mixing 0.5 mL of each suspension with either 0.5 mL of water, 0.5 mL of aqueous hydrochloric acid 1 mol/L, 0.5 mL of aqueous sodium hydroxide 1 mol/L, or 0.5 mL of aqueous hydrogen peroxide 30%. The solutions were stored for 3 hours at 60°C, except for a second solution in water stored for 3 hours at 4°C, then treated as previously described and analyzed by HPLC. The chromatograms obtained from these degradation analyses were compared with chromatograms obtained from TMP-SMX in Oral Mix and Oral Mix SF (10 mg/mL) diluted 1:1 with water and analyzed by HPLC to look for any changes in concentration, retention time, and peak shape. Finally, the chromatograms were inspected for additional peaks.

Statistical Analysis

For each combination of suspension type, container, and storage temperature, the mean was calculated for the 3 samples, each assayed in duplicate. The percent remaining was analyzed by linear regression, and a 95% confidence interval (CI) was constructed around the slope of percent remaining versus study days. The time to achieve 90% of the initial concentration (T-90) with 95% confidence (expressed as "$T\text{-}90_{95\%CI}$") was calculated from the time (in days) for the lower limit of the 95% CI to reach 90%. Analysis of variance and multiple linear regression were used to test differences in concentration on different study days, with different suspending agents, containers, and temperatures for both TMP and SMX. The 5% level was used as the a priori cut-off for significance.

Concentrations of TMP and SMX were considered "acceptable" or "within acceptable limits" if the lower limit of the 95% CI of concentration remaining ($T\text{-}90_{95\%CI}$) was greater than 90% of the initial (day 0) concentration.

RESULTS

Physical Study

The suspensions prepared from bulk powder had a uniform appearance and good "pourability" and were easily redispersed after settling. No notable changes in colour (white) or odour (sweet cherry) were observed after storage under different conditions for 90 days. Moreover, the difference in pH relative to initial pH was not more than 0.2 unit for these preparations under all tested conditions. Taste was not evaluated during this study.

However, the suspensions prepared from tablets were not acceptable. Indeed, the suspension prepared with Oral Mix SF vehicle was highly viscous, and this formulation was therefore not included in the study. The suspension prepared with Oral Mix vehicle was less thick, but a persistent layer

of foam developed at the surface of the suspension, which made redispersion difficult after settling and resulted in inconsistent sampling and high variability in measured concentrations. Apo-sulfatrim tablets include methylcellulose, a surfactant that might have caused the foam. Other commercial tablets, such as Teva-trimel tablets, contain sodium lauryl sulfate, a surfactant that could also lead to foaming.[1] However, the latter tablets were not tested in our study.

Overall, the results obtained with suspensions prepared from tablets were not consistent and are not reported.

Assay Validation

Regression analysis of the peak area of TMP and SMX versus the concentration of each TMP and SMX standard demonstrated linearity over the range of concentrations tested, with coefficients of determination (r^2) of at least 0.99993 for TMP and 0.9998 for SMX. As described above, all test samples were first frozen at –80°C during the study and then analyzed on the same assay day. On the assay day, the coefficients of determination were at least 0.99996 for TMP and 0.9998 for SMX.

During validation, the highest intraday coefficients of variation for the standards, calculated for triplicate injection samples, were 0.46% for TMP and 0.35% for SMX, and the highest interday coefficients of variation over 3 days were 3% for TMP and 2% for SMX. On the assay day, the highest intraday coefficients of variation for triplicate injection samples of the standards were 0.39% for TMP and 0.35% for SMX. Moreover, a combined standard of TMP 26.66 µg/mL and SMX 133.33 µg/mL was analyzed every 24 injections. For this standard, the highest intraday coefficient of variation, calculated for 7 injections, was 0.20% for TMP and 0.35% for SMX.

Forced Degradation

No peak overlap of TMP and SMX with excipients, impurities, or degradation products was observed during forced degradation. Similarity of the UV spectra from all sampling points on the peak was compared using the HPLC system software (LabSolution v. 5.54, Shimadzu) to compute a similarity index and determine the presence of multiple components within the peak. The similarity index ranges between –1 (dissimilar) and +1 (identical).[9] The peak purity index calculated between 250 and 310 nm was not less than 0.9999 in all cases.

In Oral Mix vehicle, the peak for TMP was not reduced in water, HCl, or NaOH and was reduced by 14% in H_2O_2; in Oral Mix SF vehicle, the peak for TMP was reduced by 2% in water, 5% in HCl, 10% in NaOH, and 22% in H_2O_2 (Figure 1). In Oral Mix vehicle, the peak for SMX was not reduced in water or NaOH and was reduced by 11% in HCl and 6% in H_2O_2; in Oral Mix SF vehicle, the peak for SMX was not reduced in water, HCl, or NaOH and was reduced by 9% in H_2O_2 (Figure 1). Furthermore, no interference from vehicles was observed, as shown in the chromatogram with water at 4°C in Figure 1. The HPLC method was therefore considered stability-indicating.

Chemical Stability and Statistical Analysis

The concentrations of TMP and SMX in Oral Mix or Oral Mix SF vehicle, prepared from bulk powder, were not less than 97% of the initial concentration after storage in amber plastic bottles or amber plastic syringes at 5°C or 25°C for up to 90 days (Tables 1 and 2).

The 95% confidence limits constructed around the concentrations on the last study day exceeded 90% for TMP and 93% for SMX for all combinations of container, suspension vehicle, and storage temperature. Analysis of variance detected differences in the percent remaining for both TMP and SMX due to study day ($p < 0.001$), suspending agent ($p < 0.001$), temperature ($p < 0.001$ for TMP, $p = 0.031$ for SMX), and container ($p = 0.037$ for TMP, $p = 0.90$ for SMX). Multiple linear regression also detected differences in the percent remaining due to suspending agent ($p < 0.001$) and temperature ($p = 0.004$ for TMP, $p < 0.001$ for SMX). There was no significant relation with container ($p = 0.10$ for TMP, $p = 0.92$ for SMX). The study method was able to detect differences in concentration of 2% or more for both TMP and SMX.

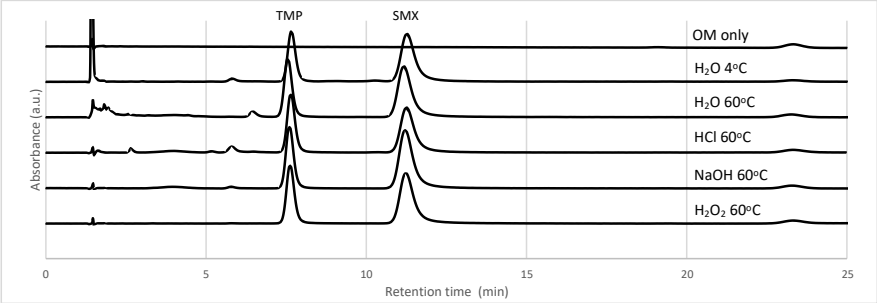
Analysis of the concentration results support a before-use date (BUD) of 90 days at both temperatures and with all combinations of container and suspending agent.

DISCUSSION

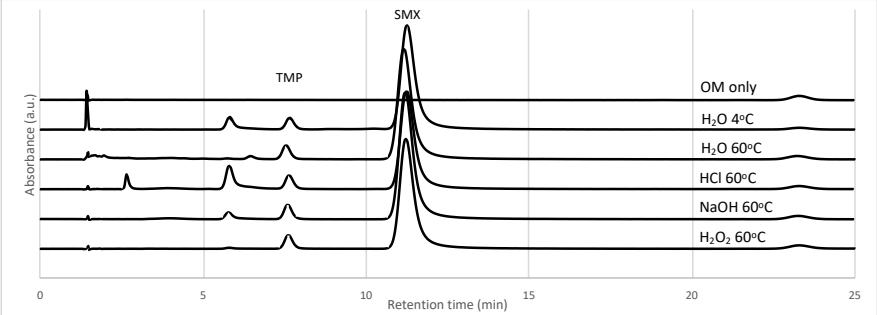
The results of the HPLC analysis showed that suspensions of TMP and SMX (8 and 40 mg/mL, respectively) prepared from bulk powder in Oral Mix and Oral Mix SF maintained at least 97% of their original concentrations for the entire 90-day study period with storage at 5°C or 25°C in amber plastic bottles or amber plastic syringes. Analysis of the concentration results supports a BUD of 90 days at both temperatures and with all combinations of container and suspending agent. This indicates that there is less than a 2.5% chance that after 90 days of storage the concentration of either TMP or SMX will be less than 90% of the initial concentration.

Inspection of Table 1 reveals some positive degradation rates. Positive (as well as negative) degradation rates have been reported from previous studies in which the study drug degraded very slowly. This is the result of an interaction between analytical variability and slow degradation rate, such that random error results in the appearance of a positive degradation rate. It is for this reason that confidence intervals are required for analyzing stability data, because they combine the average degradation rate and the analytical variability, providing BUDs that are useful to pharmacists (i.e., there is less than a 2.5% chance that concentrations identified in Table 1 as the lowest concentrations would ever be observed in clinical practice on the 90th day of storage).

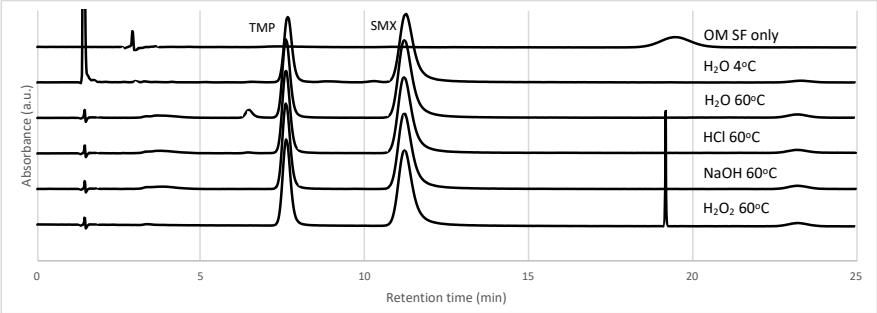
A- TMP and SMX in Oral Mix at 240 nm



B- TMP and SMX in Oral Mix at 270 nm



C- TMP and SMX in Oral Mix SF at 240 nm



D- TMP and SMX in Oral Mix SF at 270 nm

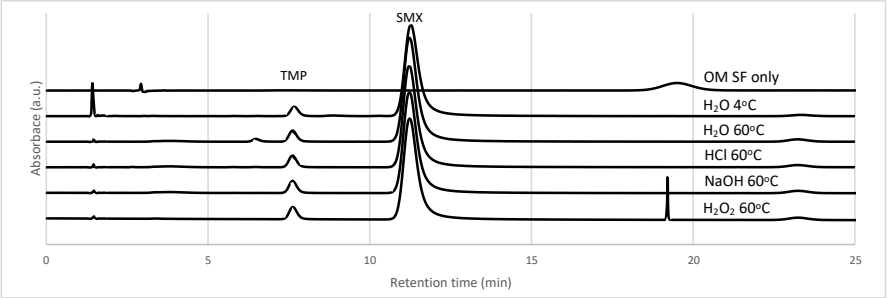


FIGURE 1. Panels A and B: Representative chromatograms of Oral Mix (OM) only, as well as trimethoprim (TMP; retention time 7.6 minutes) and sulfamethoxazole (SMX; retention time 11.3 minutes) in Oral Mix, analyzed at 240 and 270 nm (for TMP and SMX quantification, respectively), in water at 4°C and after forced degradation in water, hydrochloric acid 1 mol/L, sodium hydroxide 1 mol/L, and hydrogen peroxide 30% at 60°C. Panels C and D: Representative chromatograms of Oral Mix SF (OM SF) only and TMP and SMX in Oral Mix SF at 240 and 270 nm in water at 4°C and after forced degradation in water, HCl 1 mol/L, NaOH 1 mol/L, and H_2O_2 30% at 60°C.

TABLE 1. Proportion of Initial Concentration of Trimethoprim Remaining (as Mean % ± Relative Standard Deviation) on Each Study Day, after Preparation from Bulk Powder in Oral Mix and Oral Mix SF Vehicles and Storage in Amber Plastic Bottles and Amber Plastic Syringes at 5°C and 25°C

	Oral Mix				Oral Mix SF			
	5°C		25°C		5°C		25°C	
Study Day	Bottles	Syringes	Bottles	Syringes	Bottles	Syringes	Bottles	Syringes
0	100.00		100.00		100.00		100.00	
7	98.4 ± 1.6	99.2 ± 2.7	101.2 ± 2.9	104.7 ± 3.5	102.3 ± 0.6	104.0 ± 1.3	105.6 ± 1.6	104.7 ± 3.3
14	98.7 ± 3.8	102.9 ± 4.5	101.0 ± 3.6	103.2 ± 2.7	104.1 ± 3.5	101.6 ± 1.3	105.9 ± 1.6	107.4 ± 1.9
23	102.9 ± 3.7	100.0 ± 2.3	106.7 ± 4.6	108.1 ± 5.1	108.5 ± 2.6	106.9 ± 2.2	109.7 ± 1.7	109.2 ± 1.0
45	101.1 ± 3.1	99.5 ± 3.5	101.7 ± 2.9	99.3 ± 2.2	104.6 ± 3.0	101.1 ± 1.1	105.8 ± 1.7	102.9 ± 2.4
60	101.4 ± 4.2	99.8 ± 2.9	102.1 ± 3.9	103.4 ± 3.6	106.7 ± 3.1	104.4 ± 0.7	105.4 ± 1.4	105.9 ± 1.8
75	104.2 ± 3.9	102.3 ± 3.7	98.4 ± 2.3	102.6 ± 3.2	107.0 ± 2.2	107.5 ± 1.6	103.8 ± 1.2	106.0 ± 1.1
90	97.0 ± 5.7	102.7 ± 2.9	100.5 ± 2.6	102.5 ± 2.9	102.4 ± 1.5	106.6 ± 1.1	104.2 ± 1.4	109.1 ± 1.4
Degradation rate (%/day)	0.00980	0.02111	−0.01966	−0.00991	0.01598	0.05384	0.00098	0.04140
T-90[a] (95% confidence)	161.8	485.0	111.6	110.7	191.0	774.4	125.9	236.7
Lowest concentration (95% confidence) on day 90	94.4	97.8	90.4	90.5	94.4	98.6	91.0	95.4
Coefficient of correlation (*r*)	0.1354	0.4510	−0.2703	−0.1221	0.2274	0.6274	0.0122	0.4432

SF = sugar-free.

[a]The T-90 is the time for the concentration to decline by 10%, i.e., to reach 90% of the initial concentration. The shortest T-90 with 95% confidence ($T\text{-}90_{95\%CI}$) uses the fastest degradation rate, determined from the 95% confidence limit of the slope.

No previous study has demonstrated the physical and chemical stability of extemporaneously prepared TMP-SMX suspensions for this period of time under these conditions. These results are important as they will allow pharmacists to compound this suspension with a BUD longer than 20 days. The only previously published study of this drug combination[7] evaluated the stability of TMP and SMX in suspensions stored for 20 days, with the compounded formulations prepared using simple syrup as the suspending vehicle. The suspending agents included in the composition of the vehicles used in the current study made them suitable for the compounding of suspensions from pure drug powders. These vehicles are dye-free and have a light cherry flavour that may have a positive impact on the taste of the formulation and patients' adherence with treatment.

As demonstrated in this study, suspensions of TMP and SMX should not be compounded from tablets because of physical incompatibility between these vehicles and (probably) the excipients in the tablets. Indeed, the suspension prepared from tablets in Oral Mix vehicle created excessive foam at the surface after shaking, which could lead to inconsistent dosing. In addition, although not observed in our study, solid caking at the bottom of bottles is hard to disperse and would lead to difficulty in resuspension by patients and inaccuracy in dosage.

Unfortunately, many public drug insurance plans (e.g., Régie de l'assurance maladie du Québec, Ontario Drug Benefit) do not reimburse preparations compounded from bulk drug powders because a Drug Identification Number (DIN) is required to submit a claim; as such, patients are limited to using only approved tablets or capsules. Nonetheless, we strongly recommend preparation of suspensions from bulk drug powder, given the unacceptable quality of preparations made from tablets. We also strongly believe it would be in the best public interest if TMP-SMX suspensions compounded from bulk powders were to be covered by public drug insurance plans in all provinces, as preparations from tablets result in unacceptable suspensions that can lead to dose inaccuracies and treatment failure.

CONCLUSION

Extemporaneous compounding of a liquid formulation of TMP-SMX is necessary for administration to patients incapable of swallowing tablets, including young children. This study has shown that compounding oral suspensions from bulk powder results in the only acceptable formulation, given that compounding from tablets produced unacceptable suspensions.

TABLE 2. Proportion of Initial Concentration of Sulfamethoxazole Remaining (as Mean % ± Relative Standard Deviation) on Each Study Day, after Preparation from Bulk Powder in Oral Mix and Oral Mix SF Vehicles and Storage in Amber Plastic Bottles and Amber Plastic Syringes at 5°C and 25°C

	Oral Mix				Oral Mix SF			
	5°C		25°C		5°C		25°C	
Study Day	Bottles	Syringes	Bottles	Syringes	Bottles	Syringes	Bottles	Syringes
0	100.00		100.00		100.00		100.00	
7	101.7 ± 0.7	103.5 ± 3.4	104.0 ± 3.7	100.8 ± 6.2	103.7 ± 1.8	105.7 ± 2.1	107.2 ± 1.5	105.7 ± 3.6
14	102.4 ± 4.2	101.2 ± 1.5	103.8 ± 3.6	101.3 ± 5.0	105.3 ± 6.0	101.4 ± 2.9	107.2 ± 2.3	109.5 ± 2.4
23	103.5 ± 1.6	101.5 ± 2.0	103.7 ± 4.7	99.8 ± 2.4	105.2 ± 2.8	99.9 ± 1.0	101.4 ± 1.1	104.5 ± 7.7
45	103.9 ± 5.1	101.8 ± 5.0	105.0 ± 5.0	104.1 ± 1.8	102.8 ± 3.5	105.2 ± 1.1	106.8 ± 5.0	105.4 ± 3.2
60	102.6 ± 2.4	105.3 ± 1.3	103.4 ± 0.9	102.5 ± 4.5	102.8 ± 1.5	107.9 ± 1.7	107.7 ± 5.1	108.6 ± 1.2
75	101.8 ± 2.7	101.0 ± 3.7	101.0 ± 2.6	102.0 ± 5.8	107.0 ± 5.1	108.0 ± 4.3	104.6 ± 2.8	107.8 ± 2.9
90	100.2 ± 6.4	101.2 ± 6.1	103.6 ± 4.2	103.7 ± 4.8	102.4 ± 1.9	105.1 ± 2.6	105.1 ± 1.4	104.2 ± 6.7
Degradation rate (%/day)	−0.00305	0.00609	0.00399	0.03544	0.01420	0.06398	0.02413	0.02621
T-90[a] (95% confidence)	224.2	227.9	215.09	2716.9	205.8	1425.3	169.6	167.5
Lowest concentration (95% confidence) on day 90	96.0	95.5	95.1	100.4	94.8	99.2	93.2	93.3
Coefficient of correlation (*r*)	−0.0731	0.1209	0.0787	0.7444	0.2203	0.6691	0.2787	0.2916

SF = sugar-free.
[a]The T-90 is the time for the concentration to decline by 10%, i.e., to reach 90% of the initial concentration. The shortest T-90 with 95% confidence ($T\text{-}90_{95\%CI}$) uses the fastest degradation rate, determined from the 95% confidence limit of the slope.

Suspensions of TMP and SMX (8 and 40 mg/mL, respectively) prepared from pure powder in Oral Mix or Oral Mix SF vehicle and stored in amber plastic bottles or amber syringes at 5°C or 25°C remained stable for 90 days.

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Therapeutic Drug Monitoring of Vancomycin in Adult Patients with Methicillin-Resistant *Staphylococcus aureus* Bacteremia or Pneumonia

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ABSTRACT

Background: Vancomycin remains widely used for methicillin-resistant *Staphylococcus aureus* (MRSA) infections; however, treatment failure rates up to 50% have been reported. At the authors' institution, monitoring of trough concentration is the standard of care for therapeutic drug monitoring of vancomycin. New guidelines support use of the ratio of 24-hour area under the concentration–time curve to minimum inhibitory concentration (AUC_{24}/MIC) as the pharmacodynamic index most likely to predict outcomes in patients with MRSA-associated infections.

Objectives: To determine the discordance rate between trough levels and AUC_{24}/MIC values and how treatment failure and nephrotoxicity outcomes compare between those achieving and not achieving their pharmacodynamic targets.

Methods: This retrospective cohort study involved patients with MRSA bacteremia or pneumonia admitted to the study hospital between March 1, 2014, and December 31, 2018, and treated with vancomycin. Data for trough concentrations were collected, and minimum concentrations (C_{min}) were extrapolated. The AUC_{24}/MIC values were determined using validated population pharmacokinetic models. The C_{min} and AUC_{24}/MIC values were characterized as below, within, or above pharmacodynamic targets (15–20 mg/L and 400–600, respectively). Discordance was defined as any instance where a patient's paired C_{min} and AUC_{24}/MIC values fell in different ranges (i.e., below, within, or above) relative to the target ranges. Predictors of treatment failure and nephrotoxicity were determined using logistic regression.

Results: A total of 128 patients were included in the analyses. Of these, 73 (57%) received an initial vancomycin dose less than 15 mg/kg. The discordance rate between C_{min} and AUC_{24}/MIC values was 21% (27/128). Rates of treatment failure and nephrotoxicity were 34% (43/128) and 18% (23/128), respectively. No clinical variables were found to predict discordance. Logistic regression identified initiation of vancomycin after a positive culture result (odds ratio [OR] 4.41, 95% confidence interval [CI] 1.36–14.3) and achievement of target AUC_{24}/MIC after 4 days (OR 3.48, 95% CI 1.39–8.70) as modifiable predictors of treatment failure.

Conclusions: The relationship between vancomycin monitoring and outcome is likely confounded by inadequate empiric or initial dosing. Before any modification of practice with respect to vancomycin monitoring, empiric vancomycin dosing should be optimized.

Keywords: vancomycin, therapeutic drug monitoring, area under the concentration–time curve, trough, methicillin-resistant *Staphylococcus aureus*

Note: This article contains supplementary material, available at https://www.cjhp-online.ca/index.php/cjhp/issue/view/206

RÉSUMÉ

Contexte : La vancomycine reste largement utilisée contre les infections dues au *Staphylococcus aureus* méthicillinorésistant (SAMR); cependant, on rapporte des taux d'échec de traitement allant jusqu'à 50 %. Dans l'institution où travaillent les auteurs, la surveillance de la concentration minimale constitue la norme de soins du suivi thérapeutique pharmacologique de la vancomycine. De nouvelles lignes directrices soutiennent l'utilisation du ratio de 24 h de l'aire sous la courbe de concentration-temps à concentration minimale inhibitrice (AUC_{24}/MIC) en tant qu'indice pharmacodynamique, vraisemblablement pour prédire certains résultats concernant les patients présentant des infections associées au SAMR.

Objectifs : Déterminer le taux de discordance entre la concentration minimale et les valeurs de l'AUC_{24}/MIC et la manière dont les échecs de traitement et les résultats de néphrotoxicité se comparent entre les personnes atteignant leurs cibles pharmacodynamiques et celles qui ne l'atteignent pas.

Méthodes : Cette étude de cohorte rétrospective impliquait des patients atteints d'une bactériémie au SAMR ou d'une pneumonie au SAMR, admis à l'hôpital où se déroulait l'étude entre le 1er mars 2014 et le 31 décembre 2018 et traités à l'aide de vancomycine. Les données relatives aux concentrations minimales ont été recueillies, et les concentrations minimales (C_{min}) extrapolées. Les valeurs de l'AUC_{24}/MIC ont été déterminées à l'aide de modèles de population pharmacocinétiques validés. La caractérisation des valeurs de la C_{min} et des valeurs de l'AUC_{24}/MIC se décrit comme suit : « en dessous », « à l'intérieur » ou « au-dessus » des cibles pharmacodynamiques (respectivement 15-20 mg/L et 400-600). La discordance était définie comme une situation où les valeurs associées de la C_{min} et de l'AUC_{24}/MIC tombaient dans des plages différentes (c.-à-d., en dessous, à l'intérieur ou au-dessus) par rapport aux plages cibles. Une régression logistique a permis de déterminer les prédicteurs d'échecs de traitement et de néphrotoxicité.

Résultats : Au total, 128 patients ont été inclus dans les analyses. De ceux-ci, 73 (57 %) ont reçu une dose initiale de vancomycine de moins de 15 mg/kg. Le taux de discordance entre les valeurs de la C_{min} et de l'AUC_{24}/MIC était de 21 % (27/128). Les taux d'échec de traitement et de néphrotoxicité se montaient respectivement à 34 % (43/128) et 18 % (23/128). Aucune variable clinique n'a pu prédire la discordance. La régression logistique a permis de déterminer le début de l'administration de la vancomycine après un résultat de culture positif (rapport de cotes [RC] 4,41, 95 % intervalle de confiance [IC] 1,36–14,3) et l'atteinte de la cible de l'AUC_{24}/MIC après quatre jours (RC 3,48, 95 % IC 1,39-8,70) en tant que prédicteurs modifiables de l'échec du traitement.

Conclusions : Il existe probablement une confusion relative à la relation entre la surveillance de la vancomycine et le résultat à cause d'un dosage empirique ou initial inadéquat. Avant de modifier la pratique relative à la surveillance de la vancomycine, le pharmacien doit optimiser son dosage empirique.

Mots-clés : vancomycine, suivi thérapeutique pharmacologique, aire sous la courbe concentration-temps, minimal, *Staphylococcus aureus* méthicillinorésistant

INTRODUCTION

Methicillin-resistant *Staphylococcus aureus* (MRSA) is an important pathogen causing a wide variety of clinically significant and often life-threatening infections.[1,2] MRSA infections are associated with significant morbidity and mortality, increased length of stay in hospital, and increased cost of care.[3] Vancomycin by IV administration remains the drug of choice for MRSA[4]; however, the incidence of vancomycin treatment failure is reportedly as high as 50%.[3] Given the burden of MRSA infections, the paucity of alternative anti-MRSA agents, and the wide pharmacokinetic variability of vancomycin, there is a need to better understand vancomycin therapeutic monitoring to improve its effectiveness and safety while also minimizing the emergence of resistant pathogenic organisms.[5]

Although vancomycin is one of the oldest and most studied antibiotics, the correlation between monitoring of serum levels of the drug and clinical efficacy continues to be controversial. The latest (2020) consensus guidelines for therapeutic drug monitoring of vancomycin identified the ratio of 24-hour area under the concentration–time curve to minimum inhibitory concentration (AUC_{24}/MIC) as the pharmacodynamic parameter most likely to predict clinical efficacy, with bactericidal activity being achieved with AUC_{24}/MIC values of 400 or above and an upper limit of 600 to minimize the risk of nephrotoxicity.[6] However, because of the logistic challenges associated with calculating AUC in practice, attaining trough levels of 15 to 20 mg/L has historically been recommended as a surrogate for the AUC_{24}/MIC in cases of serious MRSA infections. Despite these past recommendations, retrospective and simulation studies have shown that targeting trough levels of 15 to 20 mg/L is not always associated with attainment of the AUC_{24}/MIC target of at least 400. Conversely, using Monte Carlo simulations, Patel and others[7] demonstrated that trough levels over 15 mg/L were not always required to achieve AUC_{24}/MIC values of 400 when the MIC was 1 mg/L or lower, whereas targeting trough levels of 15 to 20 mg/L did not consistently result in AUC_{24}/MIC values of 400 or above for MIC values of at least 2 mg/L. These results have led to updated guidelines favouring AUC_{24}/MIC monitoring.[6-10] Furthermore, although both trough levels of at least 15 mg/L and AUC_{24}/MIC above 600 are associated with an increased risk of nephrotoxicity,[6,11,12] the trough target of 15 to 20 mg/L does not correlate with clinical efficacy.[7,9,13,14]

As evidence supporting AUC_{24}/MIC monitoring grows and new tools emerge to aid with AUC estimation,[15] institutions are engaging in practice shifts away from monitoring trough levels to align with proposed AUC_{24}/MIC targets.[16-18] The primary objective of this study was to explore discordance rates between vancomycin trough level and AUC_{24}/MIC monitoring in a cohort of patients with MRSA bacteremia or pneumonia. Given the limited clinical data regarding the significance of trough level and AUC_{24}/MIC exposure in terms of clinical outcomes, our secondary objectives were to determine how proportions of efficacy and safety outcomes compare between those achieving and those not achieving the pharmacodynamic targets defined by trough and AUC_{24}/MIC monitoring.

METHODS

Study Design and Setting

This retrospective observational study was conducted at 2 campuses of The Ottawa Hospital, a public, university-affiliated teaching institution with approximately 1100 beds. Ethics approval for this study was obtained, before initiation, from the Ottawa Hospital Research Ethics Board (REB CRRF 1154/protocol 20190031-01H).

Patient Selection

Consecutive patients admitted to either campus of The Ottawa Hospital between March 1, 2014, and December 31, 2018, who had blood or respiratory cultures that grew MRSA were identified from the local microbiology database and assessed for study eligibility.

Patients were included if they were at least 18 years of age and had MRSA bacteremia or MRSA pneumonia. MRSA bacteremia was defined by at least one blood culture that was positive for MRSA. MRSA pneumonia was defined as MRSA growth in respiratory cultures and consistent clinical presentation of pneumonia, defined as the presence of infiltrate on chest radiography and at least one of the following criteria: purulent tracheal secretions documented in nursing notes, documented temperature of 38°C or above, or leukocyte count of 10 000/μL (10×10^9/L) or higher. Patients with MRSA-positive results for both blood and respiratory cultures were included in the MRSA pneumonia group. Additional inclusion criteria were treatment with vancomycin for at least 3 days and at least 1 serum vancomycin level reported at steady state (i.e., before the third dose or later). Patients were excluded from the study if they had infective endocarditis; had received concomitant therapy for MRSA with linezolid, daptomycin, sulfamethoxazole-trimethoprim, or tigecycline; or required dialysis within the first 3 days of vancomycin therapy.

Data Collection

Data were manually collected from electronic medical records by 3 of the investigators (R.M., J.H., and V.N.). A standardized and piloted case report form was used to collect patients' demographic information, comorbidities, sequential organ failure assessment (SOFA) scores, blood and respiratory culture results, concomitant antibiotic use during vancomycin therapy, vancomycin doses and serum levels, timing of doses and serum levels, patient weight, serum creatinine throughout the course of vancomycin therapy, and concomitant use

of nephrotoxic drugs during vancomycin therapy (limited to IV contrast, amphotericin B, aminoglycosides, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, nonsteroidal anti-inflammatory drugs, and IV acyclovir and ganciclovir).

Treatment failure was defined as one or more of the following: death from any cause within 30 days of the index MRSA culture; microbiologic failure, defined as a blood or sputum sample growing MRSA that was obtained 7 or more days after the initiation of vancomycin therapy; or recurrence of MRSA bacteremia within 60 days after discontinuation of vancomycin therapy.[19,20]

Nephrotoxicity was defined as an increase in serum creatinine by 50% across any 2 consecutive time points from day 3 of vancomycin initiation up to 5 days after the end of vancomycin therapy.[21] Nephrotoxicity was also assessed using the RIFLE criteria at the time of discharge from the intensive care unit (ICU) (if applicable) and hospital discharge.[22]

Identification of Bacterial Strains and Determination of MIC

For the purpose of this study, MRSA clinical isolates were recovered from frozen stocks when available. The MICs for vancomycin were further determined by an agar dilution method. Mueller Hinton agar (MHA) plates containing vancomycin concentrations of 0.0625 to 128 μg/mL were prepared. Select colonies from 18- to 24-hour overnight incubation on a blood agar plate were each suspended in 1 mL sterile saline, and the turbidity was adjusted to 0.5 McFarland standard. These suspensions were then diluted 1:10 in sterile saline to give an inoculum concentration of 10^7 colony-forming units (CFU)/mL. Bacterial suspensions were then inoculated onto the MHA-containing vancomycin plates with the help of multipoint inoculators with 37 points (3 mm in diameter), each pin being able to deposit approximately 1 to 2 μL on the agar surface (equivalent to 10^4 CFU in a spot 5–8 mm in diameter). *Staphylococcus aureus* ATCC 25923 and ATCC 29213 were included on all test plates as control organisms. The plates were incubated at 35°C to 37°C for 24 hours. Results were read as the presence or absence of growth, where the MIC of a strain was considered as the lowest concentration of the antibiotic at which there was no visible growth.

Pharmacokinetic Analysis

Only single serum vancomycin levels were expected to be available for most patients within each dosing interval. Therefore, validated 2-compartment population pharmacokinetic models of vancomycin for critically ill and non–critically ill patients were used to obtain pharmacokinetic parameters, including clearance, volume of distribution, and the elimination rate constant (k_e) (see Supplement 1, available at https://www.cjhp-online.ca/index.php/cjhp/issue/view/206).[23,24] First-order elimination equations were then used to determine C_{max} and C_{min} values for each dosing interval.

Discordance analysis was conducted using only the first trough level measured at steady state for each patient. The extrapolated C_{min} value was then used in place of C_{trough} to avoid variability related to timing of sampling. Paired C_{min} and model-predicted AUC_{24}/MIC values were categorized as falling below, within, or above their pharmacodynamic targets (15–20 mg/L and 400–600, respectively). Concordance was defined as both estimates falling within the same range relative to the respective pharmacodynamic targets (i.e., both below, both within, or both above target). Discordance was defined as paired estimates falling in different ranges relative to the respective pharmacodynamic targets (e.g., C_{min} was within the therapeutic range, but the AUC_{24}/MIC ratio was above or below the therapeutic range). This approach was thought to be clinically relevant, because discordance would result in different actions depending upon the method of monitoring used by the clinician.

Given that utilization of 2 vancomycin levels is considered the most accurate method of AUC determination, we identified cases in which 2 levels within a single dosing interval were available at any point during the course of therapy. In these cases, the AUC_{24}/MIC was calculated using both the 2-point method and population pharmacokinetic models (Supplement 1).[15,23,24] The AUC_{24}/MIC values obtained using each method were then plotted, and the agreement between the 2 methods was determined using correlation statistics.

Predictors of treatment failure, nephrotoxicity, and discordance were determined using logistic regression analysis. Modifiable covariates included in the model for treatment failure were time to a therapeutic C_{trough} level (≥ 15 mg/L), time to therapeutic AUC_{24}/MIC (≥ 400), vancomycin dose (mg/kg), and initiation of vancomycin after the first positive culture result. Covariates included in the model for nephrotoxicity were the proportions of patients with C_{min} values greater than 20 mg/L or AUC_{24}/MIC greater than 600. Covariates included in the model for discordance were use of a vasopressor, serum creatinine at or above 100 μmol/L, and site of infection (bacteremia versus pneumonia). We employed a 10:1 rule for covariate inclusion, whereby 1 covariate could be included for every 10 events.

RESULTS

We identified 299 patients who had blood and/or respiratory cultures positive for MRSA between March 1, 2014, and December 31, 2018. A total of 128 patients met the inclusion criteria (Figure 1). Baseline and vancomycin treatment characteristics of these patients are summarized in Table 1. Of these 128 patients, 51 (40%) had MRSA bacteremia, whereas 77 (60%) had MRSA pneumonia. Rates of bacteremia and pneumonia were similar between the

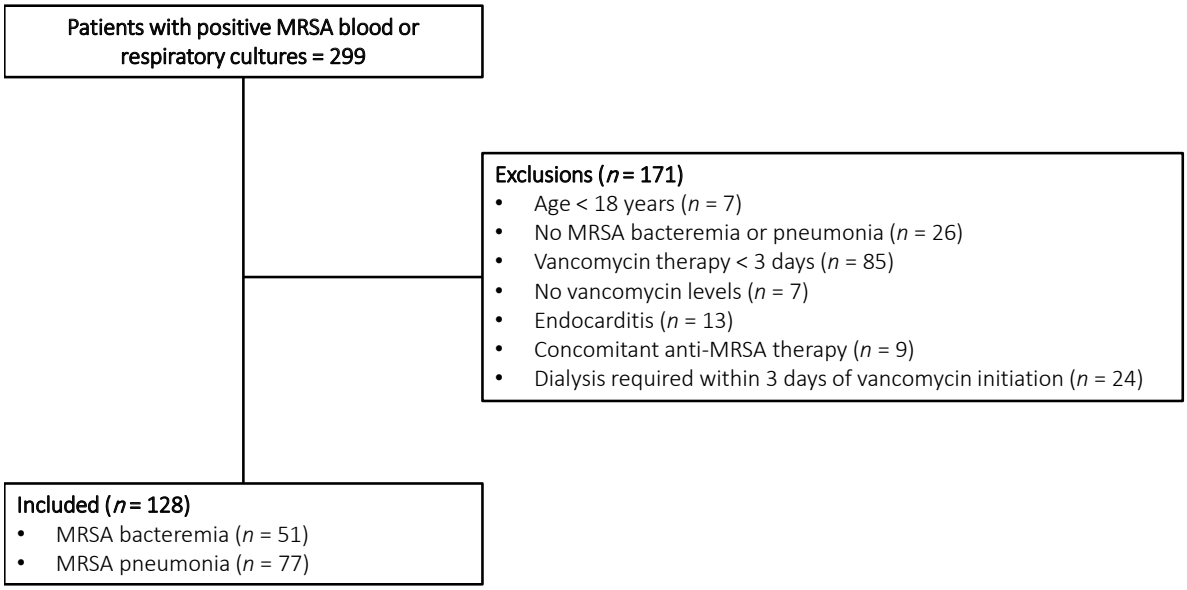

FIGURE 1. Flow diagram for patient inclusion. MRSA = methicillin-resistant *Staphylococcus aureus*.

2 participating sites. A higher proportion of patients in the pneumonia group than the bacteremia group were admitted to the ICU (43/77 [56%] versus 3/51 [6%]). The requirement for vasopressors was 31/77 (40%) among patients with pneumonia and 5/51 (10%) among those with bacteremia. Only 5 (4%) of the 128 patients received a loading dose of at least 25 mg/kg.

Table 2 summarizes therapeutic drug monitoring parameters for vancomycin. For all patients, the mean first steady-state value for C_{min} was 15.0 (standard deviation [SD] 7.1) mg/L, and the corresponding mean AUC_{24}/MIC value was 432 (SD 205). There were no instances in which 2 levels were available for AUC_{24}/MIC determination for the first steady-state levels; therefore AUC_{24}/MIC values were

TABLE 1. Demographic and Vancomycin Treatment Characteristics

Characteristic	Study Group; Mean ± SD or No. (%) of Patients		
	Bacteremia (*n* = 51)	Pneumonia (*n* = 77)	All (*n* = 128)
Age (years)	60 ± 17	64 ± 16	62 ± 16
Sex, female	24 (47)	33 (43)	57 (45)
Admitted to ICU	3 (6)	43 (56)	46 (36)
Admitted to ward	48 (94)	34 (44)	82 (64)
Weight (kg)	81.0 ± 27	81.4 ± 24	81.2 ± 25
Baseline SCr (µmol/L)	89 ± 48	101 ± 70	96 ± 62
Initial vancomycin dose (mg/kg)	14.8 ± 4	14.7 ± 4	14.7 ± 4
Initial dose < 15 mg/kg	32 (63)	41 (53)	73 (57)
Use of loading dose	3 (6)	2 (3)	5 (4)
Use of vasopressors	5 (10)	31 (40)	36 (28)
SOFA score	1.9 ± 2.7	5.1 ± 4.8	3.8 ± 4.4
Received IV contrast agent	18 (35)	12 (16)	30 (23)
Received any nephrotoxic drug[a]	27 (53)	28 (36)	55 (43)

ICU = intensive care unit, SCr = serum creatinine, SD = standard deviation, SOFA = sequential organ failure assessment.
[a]Amphotericin, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, nonsteroidal anti-inflammatory drugs, aminoglycosides, or acyclovir/ganciclovir (by IV route).

TABLE 2. Parameters for Therapeutic Drug Monitoring of Vancomycin

Vancomycin Parameter	Study Group; Mean ± SD or No. (%) of Patients		
	Bacteremia (*n* = 51)	Pneumonia (*n* = 77)	All (*n* = 128)
Trough (mg/L)[a]	14.2 ± 7.7	16.0 ± 6.7	15.3 ± 7.1
C_{min} (mg/L)[a]	13.9 ± 7.6	15.6 ± 6.8	15.0 ± 7.1
AUC_{24}/MIC[a]	400 ± 216	453 ± 195	432 ± 205
Attainment of C_{min} target (≥ 15 mg/L)[a]	22 (43)	40 (52)	62 (48)
Attainment of AUC_{24}/MIC target (≥ 400)[a]	23 (45)	48 (62)	71 (55)
Time to attainment of C_{min} target[b] (days)	4.7 ± 2.4	4.0 ± 2.3	4.4 ± 2.4
Time to attainment of AUC_{24}/MIC target[c] (days)	4.8 ± 2.5	3.8 ± 2.1	4.2 ± 2.3
MIC = 1 µg/mL	49 (96)	70 (91)	119 (93)
No. of dose changes during therapy	3 ± 2	2 ± 2	2 ± 2

AUC_{24} = 24-hour area under the concentration–time curve, C_{min} = minimum vancomycin concentration, MIC = minimum inhibitory concentration, SD = standard deviation.
[a]Values reflect the first measurement during vancomycin course (before the third dose or later).
[b]Based on 110 patients who achieved target during course of therapy.
[c]Based on 115 patients who achieved target during course of therapy.

determined using only the population pharmacokinetic models for either critically ill patients (*n* = 42) or non–critically ill patients (*n* = 86). Of the 128 patients, 19 had multiple samples drawn for steady-state levels within a single dosing interval later during their course of therapy. For these patients, AUC_{24}/MIC values calculated using both the 2-level method and the population pharmacokinetic models showed good correlation (r^2 = 0.84; Figure 2).

The mean times to therapeutic C_{min} (≥ 15 mg/L) and attainment of target AUC_{24}/MIC (≥ 400) for the overall cohort were 4.4 (SD 2.4) and 4.2 (SD 2.3) days, respectively. Among the 128 initial MRSA-positive blood or respiratory cultures, 119 (93%) had an MIC of 1 µg/mL, whereas 8 (6%) and 1 (1%) had MIC values of 0.5 µg/mL and 2 µg/mL, respectively.

Results of the discordance analysis are presented in Figure 3. Among the 128 measured first steady-state trough levels, 27 (21%) exhibited discordance between C_{min} and AUC_{24}/MIC values. Of the 101 (79%) cases in which C_{min} and AUC_{24}/MIC values were found to be concordant, 72 (71%) were outside the therapeutic range. Figure 4 depicts good correlation between C_{min} and AUC_{24}/MIC values (r^2 = 0.749).

Clinical outcomes are summarized in Table 3. Treatment failure occurred in 43 (34%) of the 128 patients. Treatment failure was more common in the group with pneumonia (35/77 [45%]) than the group with bacteremia (8/51 [16%]). Table 4 summarizes univariate analyses of treatment outcomes. Both initiation of vancomycin after the first positive culture result (odds ratio [OR] 4.41, 95% confidence interval [CI] 1.36–14.3) and time to attainment of target AUC_{24}/MIC longer than 4 days (OR 3.48, 95% CI 1.39–8.70) were predictive of treatment failure according to logistic regression. Empiric dosing below 15 mg/kg (OR 1.06, 95% CI 0.46–2.42) and time to attainment of target C_{min} longer than 4 days (OR 1.12, 95% CI 0.27–4.70) were not predictive of treatment failure.

Nephrotoxicity was observed in 23 (18%) of the 128 patients, with similar frequency between the pneumonia and bacteremia groups. In a logistic regression model to determine predictors of nephrotoxicity, the proportions of patients with C_{min} values greater than 20 mg/L (OR 0.74, 95% CI 0.20–2.69) or AUC_{24}/MIC greater than 600 (OR 2.45, 95% CI 0.60–12.46) were included as covariates. Neither was found to be predictive of nephrotoxicity. Logistic regression did not identify any predictors of discordance associated with vasopressor usage (OR 0.81, 95% CI 0.29–2.21), serum creatinine at or above 100 µmol/L (OR 0.66, 95% CI 0.26–1.62), or infection site (bacteremia versus pneumonia) (OR 1.15, 95% CI 0.45–2.92) as covariates.

DISCUSSION

In this study, first steady-state trough levels were discordant with their corresponding AUC_{24}/MIC values in 21% of cases. In the study cohort, treatment failure and nephrotoxicity rates were 34% and 18%, respectively. Although no clinical variables were found to predict discordance, we found that initiation of vancomycin after the first positive culture result and time to AUC_{24}/MIC target attainment longer than 4 days were predictive of treatment failure. Notably, the average initial vancomycin dose was only 14.7 (SD 4) mg/kg, with only 4% of patients receiving a loading

dose and 55% of patients reaching their AUC_{24}/MIC target at the time of the first sample drawn for determination of steady-state vancomycin level. Collectively, the modifiable predictors of treatment failure described above highlight an opportunity to improve empiric dosing strategies by ensuring the timely initiation of appropriate therapy at adequate initial doses. These fundamental (and achievable) antimicrobial stewardship endeavours should precede any change in practice with respect to therapeutic drug monitoring of vancomycin. Whether it be the use of AUC_{24}/MIC or the use of trough levels, the approach to drug monitoring will be hard pressed to improve patient outcomes without first optimizing the way in which vancomycin is prescribed.

Vancomycin trough levels have long been touted as an acceptable surrogate for the AUC_{24}/MIC.[21] However, published clinical studies describing the correlation between measured first steady-state trough levels and the corresponding calculated AUC_{24}/MIC are limited, and the data that are available show variable degrees of correlation. Monte Carlo simulation studies by Patel and others[7] demonstrated

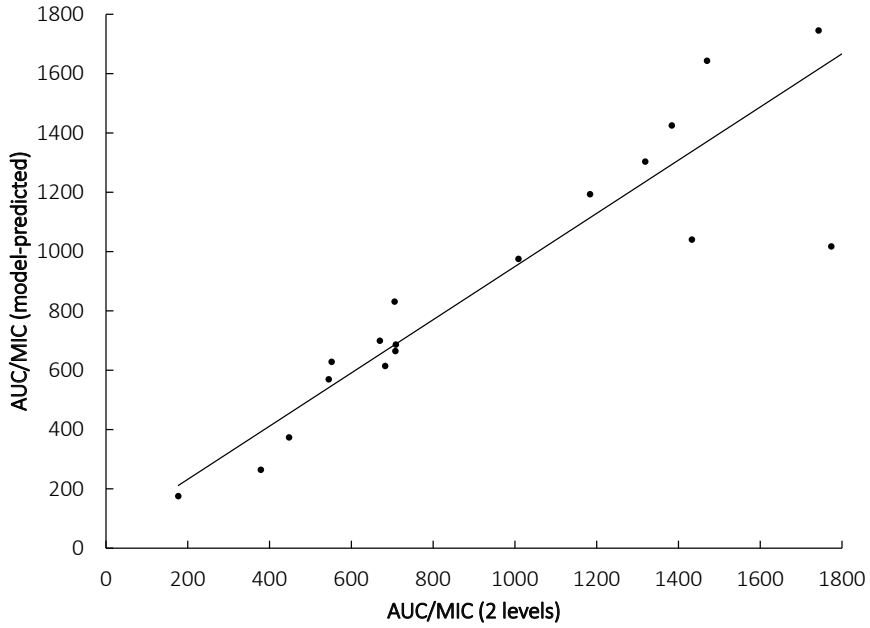

FIGURE 2. Comparison of values for the ratio of area under the concentration–time curve to minimum inhibitory concentration (AUC/MIC), calculated using population pharmacokinetic models or using 2 vancomycin levels obtained during a single dosing interval ($r^2 = 0.84$). For AUC/MIC values obtained using 2 levels, individual values for the elimination rate constant (k_e) were calculated using first-order elimination kinetics (as described in the Methods). Once values for k_e, maximum vancomycin concentration (C_{max}), and minimum vancomycin concentration (C_{min}) were determined, the corresponding AUC/MIC was calculated as described in the Methods. The plotted AUC/MIC values reflect exposures over various time intervals.

AUC_{24}/MIC	C_{min} (mg/L)		
	Below 15	15-20	Above 20
Below 400	56 (44)	1 (1)	0 (0)
400-600	8 (6)	29 (23)	11 (9)
Above 600	2 (2)	5 (4)	16 (13)

Concordance	101 (79)
AUC_{24}/MIC overestimates C_{min}	15 (12)
C_{min} overestimates AUC_{24}/MIC	12 (9)

FIGURE 3. Discordance analysis. Data are represented as number (%) of 128 patients. AUC_{24}/MIC = ratio of 24-hour area under the concentration–time curve to minimum inhibitory concentration, C_{min} = minimum vancomycin concentration.

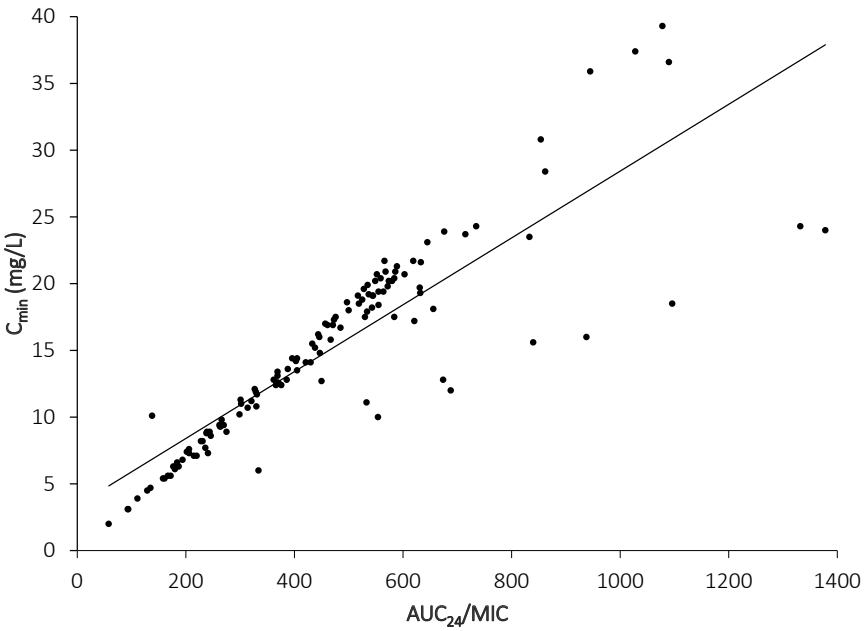

FIGURE 4. Discordance analysis (r^2 = 0.749). AUC_{24}/MIC = ratio of 24-hour area under the concentration–time curve to minimum inhibitory concentration, C_{min} = minimum vancomycin concentration.

that trough values above 15 mg/L achieved through various dosing strategies are not required to consistently achieve AUC_{24}/MIC values above 400. Similarly, simulation studies by Pai and others[15] suggested poor correlation between trough levels and AUC_{24}/MIC values, with an r^2 value of 0.409, which may be partly explained by MRSA isolates with MIC values greater than 1 mg/L. Jin and others[25] compared AUC_{24}/MIC values calculated using either creatinine clearance (as a surrogate for vancomycin clearance) or individual pharmacokinetic parameters with steady-state trough levels. These authors found that the AUC_{24}/MIC values calculated using patient-specific pharmacokinetic parameters and commercial software showed a stronger correlation with trough levels (r^2 = 0.964) than AUC_{24}/MIC values calculated using creatinine clearance (r^2 = 0.694). In a 2017 study exploring the relationship between the incidence of acute kidney injury and Bayesian-derived AUC_{24}/MIC in MRSA bacteremia, Chavada and others[26] found that 26.7% of patients with trough concentrations below 15 mg/L achieved AUC_{24}/MIC values above 400. In that study, trough levels and AUC_{24}/MIC values were found to be highly correlated (r^2 = 0.88).[26] In a retrospective study of 95 elderly patients receiving vancomycin, the correlation between Bayesian-derived AUC_{24} and extrapolated C_{min} levels was modest (r^2 = 0.51).[9] More than 30% of cases in which C_{min} was below 15 mg/L actually achieved the AUC_{24} target of 400.[9]

TABLE 3. Treatment Outcomes

Outcome	Study Group; No. (%) of Patients		
	Bacteremia (*n* = 51)	Pneumonia (*n* = 77)	All (*n* = 128)
Treatment failure	8 (16)	35 (45)	43 (34)
Death within 30 days	2 (4)	18 (23)	20 (16)
Microbiologic failure	6 (12)	21 (27)	27 (21)
Bacteremia recurrence	3 (6)	0 (0)	3 (2)
Nephrotoxicity[a]	9 (18)	14 (18)	23 (18)

[a]Nephrotoxicity was defined as a 50% increase in serum creatinine over any 2 consecutive time points from day 3 of vancomycin initiation up to 5 days after the end of vancomycin therapy.

In the current study, C_{min} and AUC_{24}/MIC values were highly correlated, which suggests that using trough-based versus AUC_{24}/MIC monitoring would have led to similar clinical decisions (i.e., dose adjustments) in the majority of cases. However, the observed rates of discordance were lower than anticipated, with a high proportion of vancomycin trough levels (44%; 56/128) falling below both C_{min} and AUC_{24}/MIC targets. The difference in the degrees of correlation between C_{min} and AUC_{24}/MIC values in our study compared with those described in the literature may be in part attributable to differences in methods for calculating AUC_{24}/MIC. A higher degree of correlation might also be expected if there were a lower degree of variability in the distribution of MIC values. However, the proportion of isolates with MIC = 1 mg/L (93%) in the current study was consistent with other centres, and current guidelines advise that MIC of 1 mg/L be assumed in the event that the exact MIC value is not known.[6] Considering that the average vancomycin dose was just below the recommended 15 mg/kg, these results suggest that our discordance analysis, and any subsequent relationship between target attainment and

TABLE 4. Univariate Analysis of Treatment Outcomes

Factor	Outcome; No. (%) of Patients or Mean ± SD		*p* Value
	Treatment Failure (*n* = 43)	Treatment Success (*n* = 85)	
ICU (versus ward)	26 (60)	20 (24)	< 0.001[a]
Pneumonia (versus bacteremia)	35 (81)	42 (49)	< 0.001[a]
Age (years)	64.3 ± 15.0	60.8 ± 16.9	0.26[b]
Baseline SCr (μmol/L)	119 ± 72	84 ± 54	0.002[b]
Minimum vancomycin concentration (C_{min})			
Measured value (mg/L)	16.1 ± 6.5	14.4 ± 7.4	0.21[b]
Attainment of target	22 (51)	40 (47)	0.66[a]
Time to attainment of target (days)	4.6 ± 2.5	3.6 ± 1.9	0.020[b]
AUC_{24}/MIC			
Calculated value	466 ± 182	455 ± 274	0.79[b]
Attainment of target	30 (70)	41 (48)	0.021[a]
Time to attainment of target (days)	4.6 ± 2.6	3.5 ± 1.5	0.004[b]
Initial vancomycin dose			
As mg/kg	14.3 ± 3.6	15.0 ± 4.5	0.42[b]
< 15 mg/kg	25 (58)	48 (56)	0.86[a]
Time from positive culture result to vancomycin initiation (days)	−0.02 ± 3.2	−1.0 ± 2.0	0.13[b]
Vancomycin started after positive culture result (versus before)	9 (21)	7 (8)	0.040[a]

AUC_{24}/MIC = ratio of 24-hour area under the concentration–time curve to minimum inhibitory concentration, ICU = intensive care unit, SCr = serum creatinine, SD = standard deviation.
[a]χ^2 test.
[b]*t* test.

clinical outcomes, may be confounded by inadequate initial vancomycin dosing. We hypothesize that this is a consequence of the standard (one-size-fits-all) dosing strategies for vancomycin (and potentially dose rounding) that are commonly employed in our institution, rather than weight-based dosing.

The current accepted threshold for efficacy is AUC_{24}/MIC above 400, with clinical data supporting this value limited primarily to single-centre retrospective analyses. In a recent meta-analysis, Dalton and others[27] assessed the performance of the AUC_{24}/MIC in predicting efficacy outcomes for MRSA infections. In addition to highlighting considerable heterogeneity in the study populations and methodologies of the included studies, the authors found that the sensitivity and specificity of the AUC_{24}/MIC was suboptimal with respect to predicting efficacy outcomes. Furthermore, vancomycin efficacy thresholds in outcome assessment studies ranged from 211 to 667.[27] When compared with our current study, in which we defined AUC_{24}/MIC = 400 as the efficacy threshold, the variability in the literature suggests that optimal therapeutic efficacy thresholds are incompletely understood and depend on the type of MRSA infection and methods of both AUC_{24} calculation and MIC determination. It is also important to consider that the median time to target attainment in our study was 4 days and that a time to attainment of target AUC_{24}/MIC longer than 4 days was predictive of treatment failure. AUC_{24}/MIC target attainment and its relationship with efficacy outcomes are reportedly dependent on achieving pharmacodynamic targets early (i.e., within days 1–2) in the course of therapy.[20,28] In contrast, time to attainment of the C_{min} target longer than 4 days did not predict treatment failure. Since C_{min} and trough levels have been used as surrogates for the AUC_{24}/MIC and have not been shown to be predictive of efficacy outcomes on their own, this result is not surprising. Our univariate analysis additionally showed that patients with treatment failure were more likely to have significantly higher baseline serum creatinine. It is possible that this is a marker of severity of illness, given that ICU admission was associated with treatment failure; however, it is also conceivable that clinicians take a more conservative approach to vancomycin dosing in patients with compromised renal function, though we note that patients with treatment failure were not more likely to have starting doses below 15 mg/kg relative to those with treatment success.

The main limitation of our study was that we were only able to determine the AUC_{24}/MIC using one vancomycin

level, while relying on previously published population-based pharmacokinetic models to estimate pharmacokinetic parameters such as the elimination rate constant and vancomycin clearance. Although the primary objective of our study was to determine discordance between first steady-state trough levels and AUC_{24}/MIC values, we collected all vancomycin trough levels measured during each patient's course of therapy and identified 19 instances in which multiple samples for postdistributional vancomycin levels were drawn within a single dosing interval, which allowed for comparison of AUC_{24}/MIC values calculated using 2 levels and via population pharmacokinetic models, as described in the Methods. Although calculation of the AUC using 2 vancomycin levels allows determination of patient-specific pharmacokinetic parameters, the high degree of correlation between the 2 methods in our study supports our use of population pharmacokinetic models in the absence of multiple vancomycin levels. Additionally, the methods of AUC determination in our study have precedents in the literature[29] and likely provide a more accurate estimation than simply calculating the AUC based on dividing the vancomycin dose by clearance, as has been used in numerous outcome studies that have informed the current AUC_{24}/MIC therapeutic thresholds.[30-32]

CONCLUSION

Although the latest vancomycin guidelines for therapeutic drug monitoring recommend AUC_{24}/MIC above 400 as the pharmacodynamic target for efficacy in cases of serious MRSA infection, the association between achievement of this threshold and improvement in patient outcomes depends on ensuring both appropriate selection of the empiric antibiotic and adequate initial dosing. Our findings suggest that the relationship between vancomycin monitoring and outcome is confounded by inadequate empiric dosing, which highlights an opportunity to improve vancomycin dosing strategies to ensure that therapeutic targets are achieved as soon as possible. In light of the new vancomycin drug monitoring guidelines, it is imperative to ensure that the approach to empirical dosing is optimized before any attempt to modify practice with respect to vancomycin monitoring.

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Stability of *N*-Acetylcysteine 60 mg/mL in Extemporaneously Compounded Injectable Solutions

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ABSTRACT

Background: *N*-Acetylcysteine (NAC) administered by the IV route is the current treatment of choice for acetaminophen overdose. However, the protocol approved by health authorities in most countries has a complex dosing regimen, which leads to dosage errors in one-third of cases. Therefore, the Canadian Antidote Guide in Acute Care Toxicology and individual poison centres have begun to recommend a simplified regimen using continuous IV infusion. Unfortunately, no study has demonstrated the stability of IV solutions of NAC at concentrations above 30 mg/mL or in solutions other than 5% dextrose.

Objective: To evaluate the stability of solutions of NAC 60 mg/mL in 0.9% sodium chloride, 0.45% sodium chloride, or 5% dextrose, stored for up to 72 hours in polyvinyl chloride (PVC) bags at 25°C.

Methods: Solutions of the desired concentration were prepared from a commercial solution of NAC 200 mg/mL, with dilution in 0.9% sodium chloride, 0.45% sodium chloride, or 5% dextrose, and were then stored at room temperature in PVC bags for up to 72 hours. At predetermined time points (0, 16, 24, 40, 48 and 72 h), samples were collected and analyzed using a stability-indicating high-performance liquid chromatography method. A solution was considered stable if it maintained at least 90.0% of its initial concentration. Particulate matter count was also evaluated to confirm chemical stability. Finally, organoleptic properties, such as odour and colour, were evaluated to assess the stability of the solutions.

Results: All solutions maintained at least 98.7% of their initial concentration. No obvious changes in odour or colour were observed. Moreover, particle counts remained acceptable throughout the study, according to the criteria specified in United States Pharmacopeia (USP) General Chapter <788>.

Conclusions: NAC 60 mg/mL, diluted in 0.9% sodium chloride, 0.45% sodium chloride, or 5% dextrose and stored in PVC bags at 25°C, was chemically and physically stable for a period of at least 72 hours.

Keywords: *N*-acetylcysteine, stability, antidote, acetaminophen overdose

RÉSUMÉ

Contexte : La N-acétylcystéine (NAC) administrée par IV est actuellement le traitement de choix en cas de surdose d'acétaminophène. Cependant, le protocole approuvé par les autorités sanitaires de la plupart des pays s'accompagne d'un schéma posologique complexe qui entraîne des erreurs de dosage dans un tiers des cas. C'est pourquoi, le *Guide canadien des antidotes en toxicologie d'urgence* et les centres antipoison ont commencé à recommander un schéma simplifié utilisant des perfusions IV. Malheureusement, aucune étude n'a permis de démontrer la stabilité des solutions IV de NAC à des concentrations supérieures à 30 mg/mL ou dans des solutions autres que 5 % de dextrose.

Objectif : Évaluer la stabilité des solutions de 60 mg/mL de NAC dans 0,9 % de chlorure de sodium, 0,45 % de chlorure de sodium ou 5 % de dextrose, stockées jusqu'à 72 heures dans des pochettes de chlorure de polyvinyle (PVC) à 25 °C.

Méthodes : Les solutions ont été préparées à partir d'une solution commerciale de 200 mg/mL de NAC, avec une dilution dans 0,9 % de chlorure de sodium, dans 0,45 % de chlorure de sodium ou dans 5 % de dextrose. Elles ont ensuite été stockées à température ambiante dans des pochettes en PVC pendant une période allant jusqu'à 72 h. À des instants prédéterminés (0, 16, 24, 40, 48 et 72 h), des échantillons étaient recueillis et analysés à l'aide d'une méthode de chromatographie en phase liquide à haute performance indiquant la stabilité. Si la solution préservait au moins 90 % de sa concentration initiale, elle était jugée stable. Un comptage de particules a aussi permis de confirmer la stabilité chimique. Finalement, les propriétés organoleptiques, comme l'odeur et la couleur, ont été examinées pour évaluer la stabilité des solutions de NAC.

Résultats : Toutes les solutions préservaient au moins 98,7 % de leur concentration initiale. Aucun changement manifeste d'odeur ou de couleur n'a été observé. De plus, le nombre de particules est resté acceptable pendant toute la durée de l'étude selon les critères indiqués dans le chapitre général de la *Pharmacopée américaine* (USP) <788>.

Conclusions : La solution de 60 mg/mL de NAC, diluée dans 0,9 % de chlorure de sodium, dans 0,45 % de chlorure de sodium ou dans 5 % de dextrose et stockée dans des pochettes en PVC à 25 °C était chimiquement et physiquement stable pendant au moins 72 h.

Mots-clés : N-acétylcystéine, stabilité, antidote, surdose d'acétaminophène

INTRODUCTION

For more than 40 years, *N*-acetylcysteine (NAC) administered by the IV route has been used as the treatment of choice for acetaminophen (paracetamol) overdose. However, the 21-hour protocol approved by the health authorities of most countries has a complex dosing regimen: 150 mg/kg (maximum 15 g) of NAC in 3 mL/kg (up to 200 mL) of 5% dextrose in water (D5W) over 1 hour, 50 mg/kg (maximum 5 g) of NAC in 7 mL/kg (up to 500 mL) of D5W over 4 hours, and then 100 mg/kg (maximum 10 g) of NAC in 7 mL/kg (up to 1000 mL) of D5W over 16 hours.[1] This means that nurses must administer 3 bags, each with a different concentration, to each patient. In a study by Hayes and others,[2] one-third of patients experienced medication errors related to the 3-bag protocol. Recently, many poison centres and toxicologists have begun to recommend a 1-bag or 2-bag regimen to simplify the prescription and administration of the antidote and to minimize the potential for medication errors.[3-5]

The Canadian Antidote Guide in Acute Care Toxicology, which brings together the recommendations of Canada's 5 poison centres, states that continuous IV infusions of NAC should be administered using a volumetric pump.[6] In 2016, the US Food and Drug Administration contracted the American Society of Health-System Pharmacists to develop and implement national standardized concentrations for IV medications, in an effort called the Standardize 4 Safety Initiative.[7] Antidotes are high-risk medications used to treat medication errors and are typically administered to critically ill patients. Thus, antidotes should be considered in the development of standardized concentrations.

Little stability data are available in the literature concerning IV solutions of NAC. Dribben and others[8] showed that NAC at a concentration of 30 mg/mL in polyvinyl chloride (PVC) bags containing 5% dextrose is physically and chemically stable at room temperature (25°C) for a 60-hour period. In that study, less than 10% of the NAC was lost over 60 hours, and 10% to 15% was lost over 72 hours. The US manufacturer's package insert states that NAC (concentration unspecified) is physically and chemically stable for 24 hours at room temperature in 0.45% sodium chloride (container unspecified).[9] This information is not provided in the monographs approved by Health Canada.[10] The results of other published studies have not been specific to IV solutions and therefore cannot be extrapolated.[11,12]

When a patient is poisoned, clinicians always aim to give the most concentrated solutions of any required antidotes. The rationale is to limit the volume administered, given that patients in this situation are often intoxicated with multiple agents, and fluid overload must be avoided (e.g., to prevent accumulation of fluid in the lungs).[13,14] The objective of the current study was to evaluate the physical and chemical stability of NAC 60 mg/mL in various diluents with storage in PVC bags at 25°C; as such, we tested twice the maximum concentration that is known to be stable in diluents that are currently used in clinical practice but for which data are not yet available. The results of this analysis could be used by pharmacists and toxicologists to establish a standard NAC concentration for IV administration according to established procedures in their hospitals.

METHODS

Extemporaneous Preparations

Multiple solutions of NAC 60 mg/mL were prepared from a 200 mg/mL commercial solution (Teligent OÜ; lot 185061, expiry May 2020). Sixty-millilitre samples of the commercial solution (equivalent to 12 000 mg of NAC) were transferred into 200-mL volumetric flasks using a 100-mL graduated cylinder and brought to volume with either 0.9% sodium chloride (Baxter; lot W8K16M0, expiry May 2020), 0.45% sodium chloride (Baxter; lot W8J31A1, expiry April 2020), or 5% dextrose (Baxter; lot W8F26A1, expiry December 2019). The solutions all had a final concentration of 60 mg/mL.

Design of Stability Study

Each 60 mg/mL solution of NAC was packaged into three 150-mL PVC bags (Baxter; lot DR18I20066), such that each bag contained 60 mL of solution. The remaining quantity of each solution (20 mL) was discarded. All of the bags were incubated at 25°C ± 2°C and 60% ± 5% relative humidity for up to 72 hours. At each time point (0, 16, 24, 40, 48, and 72 hours), the bags were shaken for 10 seconds, and a 1-mL aliquot was then retrieved from each bag using a 1-mL sterile syringe. From this 1-mL aliquot, only 20 µL was precisely measured for further analyses. For each test sample, the organoleptic properties (odour and colour) were inspected, and the NAC concentration was assayed by high-performance liquid chromatography with ultraviolet detection (HPLC-UV). Finally, at 0 and 72 hours, the particle count was evaluated by light obscuration using 25 mL from each bag.

Liquid Chromatography

HPLC-UV Method

The HPLC system (Prominence UFLC, Shimadzu) was equipped with an LC-20AD binary pump operating at a flow rate of 0.6 mL/min, a DGU-20A5 solvent degasser, an SPD-M20A multiple-wavelength photodiode array detector set at 220 nm for NAC, an SIL-20AC HT refrigerated autosampler at 5°C, and a CTO-20AC column oven at 25°C. A C18 with polar end capping Hydro-RP Synergi 4 column (3.0 × 100 mm, 3 µm, Phenomenex) was used for this study. The isocratic mobile phases consisted of 97% aqueous solution of o-phosphoric acid 14.6 mmol/L (solution

from 85% o-phosphoric acid, Fisher Scientific; lot 173953) and 3% methanol (Fisher Scientific; lot 144689). The total run time for each injection was 15 minutes. Quantification was performed using the area under the peak eluting at approximately 3.1 minutes.

Preparation of Stocks and Standard Curve Solutions

A stock solution of NAC 10 mg/mL was prepared from bulk powder (Sigma Aldrich; lot WXBC7926V) by dissolving 67.9 mg of NAC in 6.79 mL of a 10% methanol aqueous solution. Five standards with nominal concentrations of 0.25, 0.50, 0.75, 1.0, and 1.5 mg/mL were prepared by diluting the stock solution with the 10% methanol aqueous solution to create a calibration curve. These standards were analyzed in triplicate using HPLC. The precision of this method was assessed by evaluating the intraday coefficients of variation of each standard's peak area. The acceptable limit for the coefficient of variation was defined as less than 1%.

Sample Preparation for HPLC Injection

For the HPLC analysis, 20 µL of each test sample was first diluted with 1 mL of 10% methanol aqueous solution in a 1.5-mL centrifuge tube, vortex-mixed for 10 seconds, and then transferred to a sealed 96-well plate (VWR; lot 25114129). These injection solutions had a nominal concentration of 1.176 mg/mL and were analyzed in duplicate immediately after preparation.

Forced Degradation of N-*Acetylcysteine*

A stock solution of NAC 10 mg/mL was prepared from bulk powder by dissolving 67.9 mg of NAC in 6.79 mL of a 10% methanol aqueous solution. A 0.5-mL volume of this solution was mixed with either 0.5 mL of water, 0.5 mL of aqueous hydrochloric acid 0.1 mol/L, 0.5 mL of aqueous sodium hydroxide 0.1 mol/L, or 0.5 mL of 3% aqueous hydrogen peroxide. These 4 solutions were then stored at 60°C for 3 hours. A 100-µL volume of the acidic solution was neutralized using 50 µL of aqueous sodium hydroxide 1 mol/L and then diluted with 850 µL of 10% methanol aqueous solution. Similarly, 100 µL of the alkaline solution was neutralized using 50 µL of aqueous hydrochloric acid 1 mol/L and diluted with 850 µL of 10% methanol aqueous solution. The water and peroxide solutions were directly diluted with 900 µL of 10% methanol aqueous solution. Finally, all of the solutions were prepared as described above and analyzed by HPLC. The chromatograms obtained from these analyses were compared with the chromatograms obtained from the NAC standard solutions and from a 1 mg/mL solution of NAC in 3% aqueous hydrogen peroxide that was not subjected to heat (because NAC in 3% aqueous hydrogen peroxide subjected to heating was completely degraded).

Particle Count by Light Obscuration

Particle count was evaluated in 25 mL of each bag of NAC 60 mg/mL (n = 9) at 0 and 72 hours using a light obscuration particle counter (LS-20 particle counter, Lighthouse Worldwide Solutions). Each sample was run through the instrument 3 times, in accordance with United States Pharmacopeia (USP) General Chapter <788>,[15] which recommends using a sample with a minimum volume of 20 mL spread across four 5-mL aliquots, with the results for the first aliquot being discarded. To ensure that the preparation meets the USP criteria, the average number of particles present in each test unit should not exceed 25 per millilitre for particles equal to or greater than 10 µm in diameter and should not exceed 3 per millilitre for particles equal to or greater than 25 µm in diameter.[15]

RESULTS

No notable changes in odour (sulphur smell) or colour (transparent) were observed in any of the solutions after 72 hours of storage under various conditions.

Regression analysis of the peak area of NAC versus concentration of the NAC standard demonstrated linearity over the range of concentrations tested, with a coefficient of determination (R^2) of 1.00. The coefficient of determination is used to evaluate the linearity of the method within a specific concentration range. The closer this value is to 1, the better the linear model is able to predict the concentration of a sample. The intraday coefficients of variation calculated for the triplicate injection samples were considered acceptable (no greater than 1.0%), falling between 0.05% and 0.18% for all standards of the calibration curve.

No peak overlap of NAC with excipients, impurities, or degradation products was observed. The NAC peak impurity index calculated between 190 and 250 nm was not less than 0.9999 in any case. The impurity index is considered valid when it is close to 1. Therefore, in this case, the impurity index was acceptable. The following recoveries were observed after degradation: 88% in 3% aqueous hydrogen peroxide at 25°C, 100% in water, 83% in aqueous hydrochloric acid 0.1 mol/L, 91% in aqueous sodium hydroxide 0.1 mol/L, and 5% in 3% aqueous hydrogen peroxide at 60°C (Figure 1).

Moreover, the concentration of NAC was at least 90.0% of the initial concentration in all preparations stored in PVC infusion bags at 25°C for up to 72 hours (Table 1).

Finally, the results obtained in the evaluation of particulate matter fell within the criteria for particulate matter in injection solutions specified by UPS General Chapter <788> Test 1A for all samples, both at the initial time point and after 72 hours of storage at 25°C and 60% relative humidity (Table 2).

DISCUSSION

According to the HPLC analyses, solutions of NAC 60 mg/mL prepared in 0.9% sodium chloride, 0.45% sodium chloride, and 5% dextrose maintained at least 98.7% of their initial

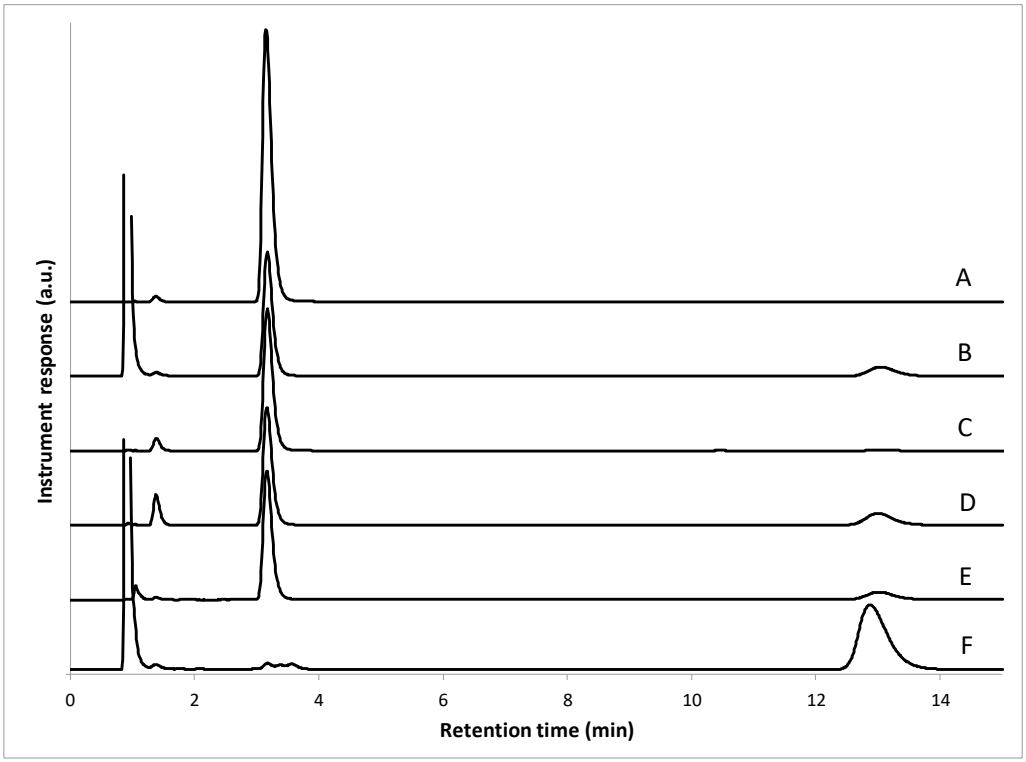

FIGURE 1. Representative chromatograms of *N*-acetylcysteine, at nominal concentration of 1 mg/mL, in various diluents with various storage conditions. A: In 10% methanol aqueous solution. B: In 3% aqueous hydrogen peroxide not subjected to heating. C: In water, at 60°C for 3 hours. D: In hydrogen chloride 0.1 mol/L, at 60°C for 3 hours. E: In sodium hydroxide 0.1 mol/L, at 60°C for 3 hours. F: In 3.0% aqueous hydrogen peroxide, at 60°C for 3 hours.

concentrations for up to 72 hours when stored at 25°C in PVC infusion bags. In addition, the particulate matter counts demonstrated that these NAC solutions fell within USP specifications for particulate matter in solutions for injection, with fewer than 25 particles of diameter 10 µm or larger per millilitre and fewer than 3 particles of diameter 25 µm or larger per millilitre. The results also indicated that no physical or chemical changes occurred under the defined storage conditions.

To date, the only study that has evaluated the stability of NAC in PVC infusion bags showed that 30 mg/mL solutions in 5% dextrose were stable at 25°C for a maximum of 60 hours.[8] In addition, the US manufacturer's package insert states that NAC is physically and chemically stable

TABLE 1. Concentration of *N*-Acetylcysteine and Percent of Initial Concentration Remaining at Each Time Point after Preparation in Various Diluents and Storage in Polyvinyl Chloride Bags at 25˚C

	Diluent; Data Type; Mean ± SD					
	0.9% Sodium Chloride		0.45% Sodium Chloride		5% Dextrose	
Time	Assay (mg/mL)	% of Initial Conc'n	Assay (mg/mL)	% of Initial Conc'n	Assay (mg/mL)	% of Initial Conc'n
0 h	58.8 ± 0.003	–	58.7 ± 0.001	–	59.0 ± 0.002	–
16 h	58.7 ± 0.004	100.0 ± 0.3	58.8 ± 0.006	100.1 ± 0.5	59.0 ± 0.003	99.9 ± 0.3
24 h	58.8 ± 0.006	100.0 ± 0.5	58.6 ± 0.001	99.8 ± 0.1	59.0 ± 0.003	99.9 ± 0.2
40 h	58.7 ± 0.003	99.8 ± 0.2	58.4 ± 0.004	99.5 ± 0.3	58.7 ± 0.006	99.4 ± 0.5
48 h	58.5 ± 0.001	99.7 ± 0.1	58.4 ± 0.004	99.5 ± 0.4	58.5 ± 0.004	99.2 ± 0.3
72 h	58.3 ± 0.007	99.3 ± 0.6	58.2 ± 0.004	99.1 ± 0.4	58.2 ± 0.006	98.7 ± 0.5

Conc'n = concentration, SD = standard deviation.

TABLE 2. Particulate Matter in *N*-Acetylcysteine 60 mg/mL Solutions Stored in Polyvinyl Chloride Bags at 25°C for 72 Hours

	Storage Time; No. of Particles/mL (Mean ± SD)[a]	
Diluent and Particle Size	**0 hours**	**72 hours**
In 0.9% sodium chloride		
Particles ≥ 10 µm	5.5 ± 5.3	3.4 ± 1.4
Particles ≥ 25 µm	0.3 ± 0.2	0.2 ± 0.1
In 0.45% sodium chloride		
Particles ≥ 10 µm	3.8 ± 0.3	1.8 ± 0.5
Particles ≥ 25 µm	0.2 ± 0.1	0.2 ± 0.1
In 5% dextrose		
Particles ≥ 10 µm	2.7 ± 0.6	2.1 ± 1.8
Particles ≥ 25 µm	0.1 ± 0.1	0.2 ± 0.2

SD = standard deviation.
[a]Data are based on samples analyzed in triplicate (n = 9).

for a maximum of 24 hours at 25°C in 0.45% sodium chloride and 5% dextrose.[9] However, this information is not provided in the monographs approved by Health Canada.[10] Therefore, to our knowledge, the current study is the first to demonstrate the stability of NAC 60 mg/mL diluted in 0.9% sodium chloride, 0.45% sodium chloride, and 5% dextrose solutions and stored in PVC infusion bags for up to 72 hours at room temperature.

When determining the most suitable standardized solution of NAC for IV administration, clinicians should consider the physical and chemical stability of the admixture (as demonstrated in this study), as well as the most concentrated solution (for critically ill patients needing fluid restriction) suitable for peripheral IV administration, given that most acetaminophen-intoxicated patients will not have central line access.

Table 3 summarizes the calculated osmolarities of final admixtures, considering the limits of commercially available products. The osmolarities of the diluents used

TABLE 3. Calculated Osmolarity of *N*-Acetylcysteine in IV Infusion Bags at Different Concentrations, Based on Commercial Solution of NAC 200 mg/mL for IV Administration

	Diluent; Calculated Osmolarity of Final Admixture (mOsm/L)		
Final Concentration in Infusion Bags	**5% Dextrose**	**0.45% Sodium Chloride**	**0.9% Sodium Chloride**
30 mg/mL	603	521	654
40 mg/mL	720	643	768
50 mg/mL	838	766	883
60 mg/mL	955	889	997

to prepare these admixtures were 250 mOsm/L for 5% dextrose, 154 mOsm/L for 0.45% sodium chloride, and 310 mOsm/L for 0.9% sodium chloride,[16-18] whereas the osmolarity of the 200 mg/mL solution of NAC was 2600 mOsm/L.[9] Calculation of osmolarity for NAC 60 mg/mL in 5% dextrose is given as an example:

NAC fraction = 60 mg/mL × 1/200 mg/mL = 0.3

Dextrose fraction = 1 – NAC fraction = 1 – 0.3 = 0.7

Final osmolarity = (NAC osmolarity × NAC fraction) + (dextrose osmolarity × dextrose fraction) = (2600 mOsm/L × 0.3) + (250 mOsm/L × 0.7) = 955 mOsm/L

Caution should be applied with NAC 60 mg/mL solutions in 5% dextrose and 0.9% sodium chloride, because the osmolarity may be above the maximum osmolarity tolerated for peripheral IV administration. In addition, there is no firm consensus within the scientific community concerning maximum osmolarity. However, the latest guidelines published by the American Society for Parenteral and Enteral Nutrition state that "an osmolarity up to 900 mOsm/L can be safely infused peripherally".[19]

Multiple adverse events and safety issues have been reported with the standard 3-bag IV regimen, consisting of a loading dose of 150 mg/kg (maximum 15 g) of NAC in 3 mL/kg (up to 200 mL) of D5W infused over 60 minutes, followed by 50 mg/kg (maximum 5 g) of NAC in 7 mL/kg (up to 500 mL) of D5W infused over 4 hours, followed by 100 mg/kg (maximum 10 g) of NAC in 7 mL/kg (up to 1000 mL) of D5W infused over 16 hours.[1] For example, Ferner and others[20] prospectively analyzed 186 NAC infusion bags prepared on site and found that only one-third of the bags contained within about 10% of the anticipated dose of NAC. In addition, about one-tenth of the bags contained 50% more NAC than expected. Smart infusion pumps are now widely used in hospitals for safety reasons.[21] In its latest guidelines for optimizing safe implementation and use of smart infusion pumps (published in 2020), the US Institute for Safe Medication Practices recommended, among other things, to standardize and limit the number of drug concentrations for continuous and intermittent infusions and to use commercially prepared solutions when available.[22] The standard IV regimen for NAC cannot be programmed into smart infusion pumps, as there may be too many different concentrations required. With many hospitals and poison control centres seeking to use simpler alternative IV regimens for NAC,[3-5,23,24] this study provides health care professionals and the pharmaceutical industry with data previously not available concerning the stability of concentrated NAC.

CONCLUSION

Solutions of NAC 60 mg/mL prepared with 0.9% sodium chloride, 0.45% sodium chloride, or 5% dextrose and stored

in PVC bags at 25°C were stable for up to 72 hours. All of the solutions, which were prepared from a commercial 200 mg/mL solution, maintained at least 90.0% of their initial concentration under all tested storage conditions.

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Pharmacist Intervention to Improve Medication Adherence in Patients with Acute Coronary Syndrome: The PRIMA-ACS Study

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ABSTRACT

Background: Despite ample evidence of benefit, adherence to secondary prevention medication therapy after acute coronary syndrome (ACS) is often suboptimal. Hospital pharmacists are uniquely positioned to improve adherence by providing medication education at discharge.

Objective: To determine whether a standardized counselling intervention at hospital discharge significantly improved patients' adherence to cardiovascular medications following ACS.

Methods: This single-centre, prospective, nonrandomized comparative study enrolled patients with a primary diagnosis of ACS (January 2014 to July 2015). Patients who received standardized discharge counselling from a clinical pharmacist were compared with patients who did not receive counselling. At 30 days and 1 year after discharge, follow-up patient surveys were conducted and community pharmacy refill data were obtained. Adherence was assessed using pharmacy refill data and patient self-reporting for 5 targeted medications: acetylsalicylic acid, P2Y purinoceptor 12 (P2Y12) inhibitors, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, β-blockers, and statins. Thirty-day and 1-year medication utilization, cardiovascular readmission rates, and all-cause mortality were also assessed.

Results: Of the 259 patients enrolled, 88 (34.0%) received discharge counselling. Medication data were obtained for 253 patients (97.7%) at 30 days and 242 patients (93.4%) at 1 year. At 1 year after discharge, there were no statistically significant differences between patients who did and did not receive counselling in terms of rates of nonadherence (11.9% versus 18.4%, $p = 0.19$), cardiovascular readmission (17.6% versus 22.3%, $p = 0.42$), and all-cause mortality (3.4% versus 4.2%, $p > 0.99$). Overall medication nonadherence was 2.8% (7/253) at 30 days and 16.1% (39/242) at 1 year.

Conclusions: Discharge medication counselling provided by hospital pharmacists after ACS was not associated with significantly better medication adherence at 1 year. Higher-quality evidence is needed to determine the most effective and practical interventions to ensure that patients adhere to their medication regimens and achieve positive outcomes after ACS.

Keywords: acute coronary syndromes, medication adherence, hospital pharmacist, discharge counselling, patient education

RÉSUMÉ

Contexte : Malgré l'abondance de preuves démontrant ses avantages, l'adhésion à la pharmacothérapie de prévention secondaire après les syndromes coronariens aigus (SCA) est souvent « sous-optimale ». Les pharmaciens d'hôpitaux occupent une place unique pour améliorer l'adhésion en expliquant au patient l'usage des médicaments au moment du congé hospitalier.

Objectif : Déterminer si une consultation standardisée au moment du congé hospitalier améliore significativement ou non l'adhésion à la pharmacothérapie cardiovasculaire après les SCA.

Méthodes : Des patients ayant reçu un diagnostic primaire de SCA (de janvier 2014 à juillet 2015) ont été inscrits pour participer à cette étude comparative unicentrique prospective et non randomisée. Ceux ayant bénéficié d'une consultation standardisée par un pharmacien clinicien au moment du congé ont été comparés aux patients qui n'en n'avaient pas reçu. Trente jours et un an après le congé, des enquêtes de suivi du patient ont été menées et les données de renouvellement d'ordonnance des pharmacies communautaires ont été recueillies. L'adhésion a été évaluée à l'aide des données de renouvellement d'ordonnance et celles rapportées par le patient pour cinq médicaments ciblés : l'acide acétylsalicylique, les inhibiteurs P2Y purinoceptor 12 (P2Y12), les inhibiteurs de l'enzyme de conversion de l'angiotensine ou les antagonistes des récepteurs de l'angiotensine II, les antagonistes β et les statines. L'utilisation des médicaments à 30 jours et à un an, le taux de réadmission en raison d'un trouble cardiovasculaire et le taux de mortalité toutes causes confondues ont également fait l'objet d'une évaluation.

Résultats : Sur les 259 patients inscrits, 88 (34 %) ont bénéficié d'une consultation au moment du congé. Des données concernant la médication de 253 patients ont été obtenues (97,7 %) à 30 jours et pour 242 patients (93,4 %) à un an. Un an après le congé, aucune différence statistique significative n'a été observée entre les patients ayant reçu ou non une consultation concernant la non-adhésion (11,9 % contre 18,4 %, $p = 0,19$), la réadmission en raison d'un trouble cardiovasculaire (17,6 % contre 22,3 %, $p = 0,42$), et le taux de mortalité toutes causes confondues (3,4 % contre 4,2 %, $p > 0,99$). La non-adhésion aux médicaments de manière générale se montait à 2,8 % (7/253) à 30 jours et à 16,1 % (39/242) à un an.

Conclusions : La consultation concernant la médication donnée par les pharmaciens d'hôpitaux au moment du congé après les SCA n'était pas associée à un meilleur suivi de la médication un an plus tard. Des données probantes de meilleure qualité sont nécessaires pour déterminer les interventions les plus efficaces et pratiques pour que les patients adhèrent à leur régime médicamenteux et qu'ils obtiennent des résultats positifs après les SCA.

Mots-clés : syndromes coronariens aigus, suivi de la médication, pharmaciens d'hôpitaux, consultation au moment du congé, éducation du patient

INTRODUCTION

Cardiovascular disease is the leading cause of death worldwide and the second leading cause of death among Canadians.[1,2] Acute coronary syndrome (ACS) results from an acute reduction in blood flow to the heart and manifests as unstable angina, non-ST elevation myocardial infarction (NSTEMI), or ST elevation myocardial infarction (STEMI).[3] After the initial coronary event, secondary prevention with pharmacologic therapy can reduce the risk of recurrent events and death.[4] These evidence-based therapies include acetylsalicylic acid (ASA), lipid-lowering agents (statins), β-blockers, and angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs).[5-8] P2Y purinoceptor 12 (P2Y12) inhibitors (e.g., clopidogrel), in combination with ASA, are also recommended after ACS with or without percutaneous coronary intervention.[5-8]

Despite the documented benefits of secondary prevention therapies, there is evidence that adherence to long-term medical therapy is suboptimal and that nonadherence is associated with increased risk of recurrent cardiovascular events and death.[4,9-12] Medication adherence has been defined as the extent to which patients take drug therapy as recommended by their health care providers, and for chronic diseases it can be as low as 50%.[13] A meta-analysis published in 2013 found that good (≥ 80%) adherence to cardiovascular medication therapy was associated with a 20% reduction in the risk of cardiovascular disease and a 35% lower risk of death.[12] These consequences highlight the critical need for interventions to improve medication adherence after ACS.

Hospital pharmacists provide pharmaceutical care and disease management to patients with various conditions. The 8 clinical pharmacy key performance indicators described by Fernandes and others[14] are important activities that hospital pharmacists can perform to improve patient outcomes. One of these indicators is the provision of patient education at discharge, whereby hospital pharmacists can inform patients of the importance of drug therapy and encourage medication adherence. This key performance indicator, in combination with other clinical services, has been shown to improve medication adherence and medication knowledge, while decreasing morbidity such as hospital readmissions.[15-17] The effect of discharge counselling on patients with ACS is not as certain, with recent systematic reviews finding only small numbers of trials, with variable quality and high heterogeneity, for analysis.[18,19] The purpose of the current study was to better understand whether a discharge counselling intervention provided by hospital pharmacists to patients with a diagnosis of ACS would significantly improve medication adherence after discharge.

The primary objective was to determine whether patients' adherence to secondary prevention medications at 30 days and 1 year after discharge was higher for patients who were counselled before discharge by a hospital pharmacist, relative to those who were not counselled. Secondary objectives were to determine the proportion of ACS patients counselled by a pharmacist, the utilization rates of each secondary prevention drug class, and the rates of cardiovascular readmissions and death.

METHODS

Design and Setting

This prospective, observational, nonrandomized controlled study assessed the effectiveness of discharge counselling delivered by clinical cardiology pharmacists to hospital patients with a diagnosis of ACS. The study was conducted at the Queen Elizabeth II Health Sciences Centre, a tertiary adult academic health centre in Halifax, Nova Scotia, which is part of Nova Scotia Health. The Queen Elizabeth II Health Sciences Centre provides acute care services to Nova Scotians and specialized cardiac care to Atlantic Canadians.[20] This research was approved by the institutional research ethics board on July 5, 2013.

Population

Patients admitted to the health centre's cardiology service with a primary diagnosis of ACS, confirmed by a physician, were included in the study. Patients were excluded if they died while in hospital, had a history of ACS but were admitted for another reason, declined to participate, resided in a long-term care facility, had a life expectancy of less than 30 days, were previously enrolled in the study or were participating in another ACS study, had dementia, were unable to communicate with study personnel, or did not have any secondary prevention medications prescribed at discharge.

All patients received usual care, which consisted of management by a multidisciplinary team that included a cardiologist, medical residents, nurses, pharmacist, dietician, physiotherapist, and occupational therapist; management provided to individual patients differed according to patients' specific needs, staff availability, and other factors. Patients whose ACS was managed with coronary artery bypass graft were transferred postoperatively to the cardiovascular surgery unit. Patients received counselling from the multidisciplinary team about cardiac risk factors, which covered topics such as smoking cessation, nutrition, and diabetes management. At discharge, all patients were referred to the cardiac rehabilitation clinic for additional outpatient management of their coronary artery disease.

Data Collection

Research assistants, who were trained in study procedures by the principal investigator (M.C.), identified potential patients according to the study's inclusion and exclusion criteria. Eligible patients were asked to provide consent for study participation in the evenings, when the clinical

pharmacists were not present. The patients were made aware of the study objectives and of the fact that they might not receive counselling from a pharmacist during their hospital admission. Once written consent was obtained, patients were interviewed and their charts were reviewed, with data recorded on a standardized data collection sheet.

The research assistants also surveyed each patient, or a family member (if the patient was unavailable), at 30 days and 1 year after discharge to collect data on medication use, readmission to hospital, and death. These outcomes were based on self-reporting by patients or family members and were not confirmed with other databases. Before each follow-up interview, the research assistants obtained 30-day and 1-year pharmacy refill data from the patient's community pharmacy. Telephone calls to the patients were placed between 28 and 35 days after discharge for the 30-day follow-up and between 51 and 53 weeks after discharge for the 1-year follow-up. At least 3 attempts were made to contact the patient. If nonadherence was discovered, a standardized letter was sent to the patient's family physician, recommending follow-up with the patient. The research assistants recorded the data on paper forms and then entered them into an Access database (Microsoft Corporation) for analysis.

Intervention

Pharmacists provided usual care to ACS patients, which consisted of some or all of the following activities: admission and discharge medication reconciliation, development of a pharmaceutical care plan to identify and resolve drug therapy problems, attendance at patient rounds, and discharge patient counselling. One or 2 pharmacists, out of 5 trained pharmacists, were responsible for the health centre's 2 cardiology units during the weekday hours. Patients who received the standardized discharge counselling intervention were given a medication calendar and an information sheet explaining why secondary prevention medications after ACS are important (Appendix 1, available at https://www.cjhp-online.ca/index.php/cjhp/issue/view/206). P2Y12 inhibitors were not listed on the information sheet because they had a defined duration of therapy (1–12 months).

Variability in patient counselling was minimized by using a standardized patient education checklist, which outlined the information to be covered: the rationale for use and benefits of secondary prevention medications; the risk reduction associated with each medication; medication strength; how and when to take the medications; drug interactions; transient and serious adverse effects; monitoring (e.g., blood pressure, electrolytes); and when to contact a health care provider. Pharmacists counselled as many patients with ACS as possible within the limits of time available, balanced with their other clinical responsibilities. Pharmacists also prioritized patients according to clinical judgment of patient need and upon request of the health care team. All clinical pharmacists, including the principal investigator, were blinded as to whether particular patients had consented to the study and would be receiving follow-up after discharge. Pharmacists documented, on a dedicated study form, the patients who received discharge counselling during the study period; the research assistants used this list, in conjunction with patient consent information, to determine the makeup of the 2 study groups (i.e., consenting patients who did and did not receive counselling).

Outcome Measures

The primary outcome of nonadherence at 30 days and 1 year was determined from prescription data obtained from each patient's community pharmacy and confirmed with the patient during the telephone interview. Patients were considered adherent if, at each time point, they were taking all secondary prevention medications that had been prescribed at discharge. Patients were considered nonadherent if they discontinued one or more drugs that had been prescribed at discharge, unless the medication was stopped by the physician or the planned duration of therapy was completed (e.g., for P2Y12 inhibitor). Switching from one drug to another within the same therapeutic class did not constitute nonadherence. Specific adherence measures, such as proportion of days covered or taking the correct dose and schedule, were not assessed. In cases of discrepancy between pharmacy refill data and patients' self-reported information, the latter was used.

Medications targeted for assessment of adherence were ASA, P2Y12 inhibitors, β-blockers, ACE inhibitors/ARBs, and statins. If a patient could not be reached by telephone, adherence for β-blockers, ACE inhibitors/ARBs, and statins was determined from pharmacy refill data. Adherence for ASA and P2Y12 inhibitors was determined from patient self-report only, because ASA is available without a prescription and was not consistently reported in pharmacy refill data, and P2Y12 inhibitors were prescribed for a specific duration that had be confirmed with the patient. Secondary outcomes were medication utilization, readmission for cardiovascular reasons, and all-cause mortality, at 30 days and 1 year after discharge. Secondary outcomes were calculated using data for only those participants who completed telephone follow-up. Rates of medication use were calculated as the total number of patients taking the targeted medications at each time point.

Statistical Analysis

A sample size calculation was initially performed with the assumption that equal numbers of patients would be in the groups who did and did not receive counselling. Adherence to therapy for all targeted ACS medications combined at 1 year was estimated to be 50% for those without counselling and 70% for those with counselling.[13] Therefore, it was calculated that 103 patients would be needed in each group,

with 80% power and a significance level of 0.05. After 150 patients had been enrolled, the research assistants noted an imbalance between the groups, so the sample size was recalculated. The revised sample size calculation indicated that 78 patients were required in the group with counselling and 156 patients in the group without counselling, to reflect a 1:2 enrolment ratio, with 80% power and a significance level of 0.05, for a total of 234 patients.

Patient characteristics were compared for significant differences using the χ^2 and Student t tests for categorical and continuous variables, respectively. Variables that affected adherence at 1 year were tested in univariate analysis, and those with a p value less than or equal to 0.10 were to be included in the multivariate logistic regression model. All tests were considered significant at a p value less than 0.05. Analyses were conducted using SAS STAT software 12.3, version 9.1 (SAS Institute).

RESULTS

Patients were assessed for study eligibility from January 2014 to July 2015, and 259 patients provided consent and met the inclusion criteria (Figure 1). Eighty-eight patients (34.0%) were counselled by a pharmacist, and 171 patients (66.0%) were not counselled by a pharmacist. Most patients (n = 52, 59.1%) received 15–29 minutes of counselling, and about a quarter (n = 23, 26.1%) received less than 15 minutes. Baseline demographic characteristics indicated a few significant differences between the patient groups (Table 1). Among those who received counselling, there was a higher rate of percutaneous coronary intervention and a lower rate of coronary artery bypass grafting ($p < 0.001$) to manage the ACS, relative to those who did not receive counselling. Patients counselled by a pharmacist had a diagnosis of STEMI more often than those without counselling, whereas the reverse was true for diagnoses of NSTEMI and unstable angina (p = 0.047). A family history of cardiac disease and a diagnosis of diabetes (as both a comorbidity and a risk factor) were also different between the groups.

Patients' use of targeted medications on admission ranged from 38 (14.7%) for P2Y12 inhibitors to 134 (51.7%) for statins and increased at discharge for all types of medications (Figure 2). Use of ASA and statins was high at discharge and remained at similar levels throughout follow-up, whereas use of ACE inhibitors/ARBs remained at approximately 60% in the follow-up period. The proportion of patients who were taking 3 or 4 targeted medications (excluding P2Y12 inhibitors) increased at discharge (n = 246/259, 95.0%) and decreased slightly at 1 year (n = 176/207, 85.0%) (Figure 3).

Nonadherence to any targeted medication was 2.8% at 30 days and 16.1% at 1 year (Table 2). For individual therapeutic classes, nonadherence at 1 year was highest for β-blockers (7.5%), followed by P2Y12 inhibitors (6.8%).

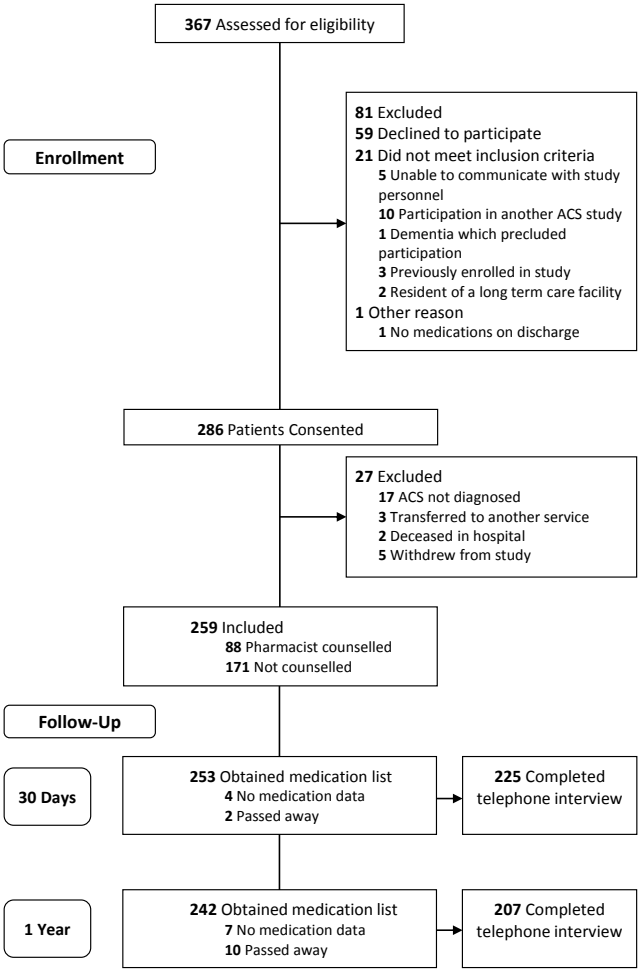

FIGURE 1. Flow chart of the study population from enrolment through to follow-up 1 year after discharge. ACS = acute coronary syndrome.

At 1 year after discharge, there were no statistically significant differences between patients who did and did not receive standardized counselling, for rates of nonadherence, cardiovascular readmission, and all-cause mortality (Table 3). No patient characteristics were significantly associated with medication nonadherence (Table 4); therefore, a multivariate logistic regression analysis was not performed.

At 1 year, the top reason that patients gave for intentional discontinuation of a medication was receiving a request from the prescriber (128 [75.3%] of total 170 medications stopped), followed by experiencing an adverse drug reaction (18/170 [10.6%]). Few patients indicated cost as a factor (2/170 [1.2%]). The research assistants sent letters to the family physicians of 5 patients to advise them of their patients' medication nonadherence.

DISCUSSION

Medication nonadherence after a hospital admission for ACS was not significantly different between patients who did and did not receive counselling by a hospital

TABLE 1. Patient Characteristics at Baseline, by Pharmacist Counselling Group

Characteristic	Group; No. (%) of Patients[a]						*p* Value
	Overall (*n* = 259)		Without Counselling (*n* = 171)		With Counselling (*n* = 88)		
Age (years) (mean ± SD)	63.3 ± 10.8		63.8 ± 10.7		62.2 ± 10.9		0.42
Sex, male	198	(76.4)	134	(78.4)	64	(72.7)	0.31
No. of medications (mean ± SD)							
On admission	6.0 ± 4.7		6.4 ± 4.8		5.3 ± 4.5		0.07
On discharge	9.8 ± 3.8		10.0 ± 3.8		9.5 ± 3.6		0.29
Drug plan (yes)	220	(84.9)	144	(84.2)	76	(86.4)	0.62
Compliance packaging (yes)	23	(8.9)	15	(8.8)	8	(9.1)	0.95
Education							
Grade 9 or less	57	(22.0)	41	(24.0)	16	(18.2)	0.44
High school (grades 10–12)	94	(36.3)	63	(36.8)	31	(35.2)	
Postsecondary	100	(38.6)	62	(36.3)	38	(43.2)	
No response	8	(3.1)	5	(2.9)	3	(3.4)	
Annual income							
< $20 000	53	(20.5)	37	(21.6)	16	(18.2)	0.78
$20 000–$40 000	72	(27.8)	46	(26.9)	26	(29.5)	
> $40 000	100	(38.6)	67	(39.2)	33	(37.5)	
No response	34	(13.1)	21	(12.3)	13	(14.8)	
Diagnosis							
STEMI	67	(25.9)	36	(21.1)	31	(35.2)	0.047
NSTEMI	154	(59.5)	108	(63.2)	46	(52.3)	
Unstable angina	38	(14.7)	27	(15.8)	11	(12.5)	
ACS management							
PCI	111	(42.9)	55	(32.2)	56	(63.6)	< 0.001
CABG	77	(29.7)	72	(42.1)	5	(5.7)	
Medical	71	(27.4)	44	(25.7)	27	(30.7)	
Cardiac risk factors							
Hypertension	174	(67.2)	117	(68.4)	57	(64.8)	0.55
Diabetes	97	(37.5)	72	(42.1)	25	(28.4)	0.031
Dyslipidemia	184	(71.0)	122	(71.3)	62	(70.5)	0.89
Family history[b]	134	(51.7)	96	(56.1)	38	(43.2)	0.048
Smoking	70	(27.0)	41	(24.0)	29	(33.0)	0.12
None	11	(4.2)	6	(3.5)	5	(5.7)	0.41
Comorbidities							
Coronary artery disease[c]	94	(36.3)	67	(39.2)	27	(30.7)	0.18
Cerebrovascular disease	11	(4.2)	9	(5.3)	2	(2.3)	0.26
Hypertension	174	(67.2)	117	(68.4)	57	(64.8)	0.55
Arrhythmia	11	(4.2)	9	(5.3)	2	(2.3)	0.26
Chronic renal failure[d]	7	(2.7)	5	(2.9)	2	(2.3)	0.76
Heart failure	18	(6.9)	14	(8.2)	4	(4.5)	0.28
Dyslipidemia	184	(71.0)	123	(71.9)	61	(69.3)	0.66
Diabetes	95	(36.7)	71	(41.5)	24	(27.3)	0.024
Peripheral vascular disease	9	(3.5)	7	(4.1)	2	(2.3)	0.45
None	35	(13.5)	19	(11.1)	16	(18.2)	0.11
No. of comorbidities (mean ± SD)	2.3 ± 1.5		2.5 ± 1.5		2.1 ± 1.5		0.054

ACS = acute coronary syndrome, CABG = coronary artery bypass graft, NSTEMI = non-ST segment elevation myocardial infarction, PCI = percutaneous coronary intervention, SD = standard deviation, STEMI = ST segment elevation myocardial infarction.

[a]Except where indicated otherwise.

[b]Family history was documented by the physician in the patient's chart.

[c]Coronary artery disease was defined as previous myocardial infarction, CABG, or PCI.

[d]Chronic renal failure was defined as estimated glomerular filtration rate less than 30 mL/min.

pharmacist. The rate of nonadherence to secondary prevention medications was low at 30 days after discharge (2.8%) and increased at 1 year after discharge (16.1%). In comparison, nonadherence to cardiovascular medications reported in the literature has ranged from 72% for β-blockers to 35% for ARBs.[13] In our study, nonadherence to therapy for individual drug classes was highest for β-blockers (7.5%), followed by P2Y12 inhibitors (6.8%). Outcomes of importance to patients, such as readmission and death, did not differ between the groups who did and did not receive counselling. Failure to detect any differences may be related to the overall high rates of adherence, along with the smaller-than-expected number of patients who were counselled by pharmacists. In addition, our study did not detect any patient characteristics significantly associated with better medication adherence.

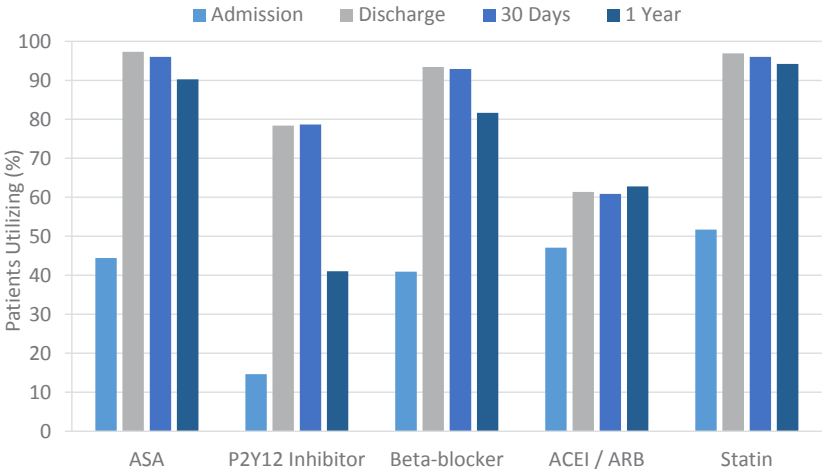

FIGURE 2. Proportions of patients taking each secondary prevention medication after acute coronary syndrome. The number of patients with evaluable data at each time point was as follows: 259 at admission, 259 at discharge, 225 at 30 days, 207 at 1 year (except 205 for acetylsalicylic acid [ASA]). ACEI = angiotensin-converting enzyme inhibitor, ARB = angiotensin II receptor blocker, P2Y12 = P2Y purinoceptor 12.

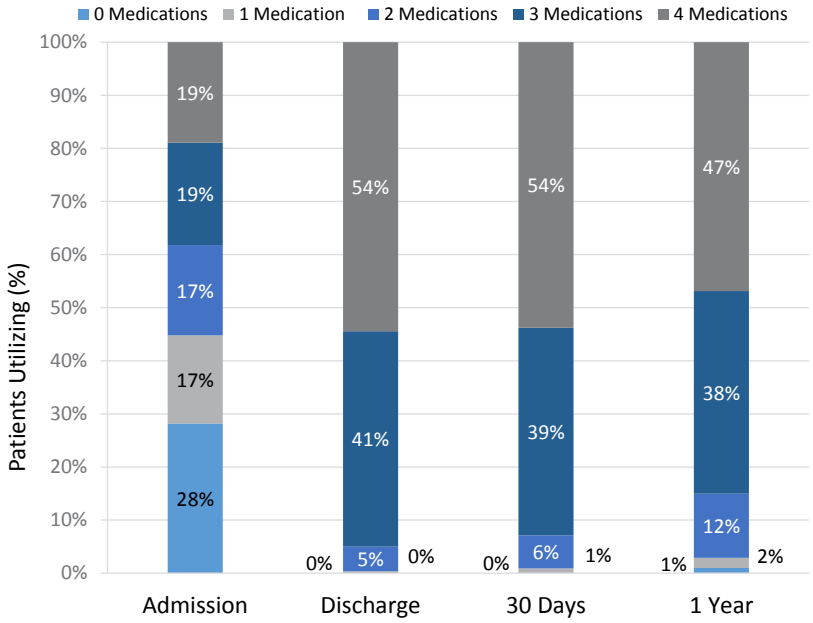

FIGURE 3. Proportions of patients taking up to 4 secondary prevention medications (acetylsalicylic acid, angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker, β-blocker, statin) after acute coronary syndrome. The number of patients with evaluable data at each time point was as follows: 259 at admission, 259 at discharge, 225 at 30 days, and 207 at 1 year. P2Y purinoceptor 12 inhibitors were excluded from this figure because of variable duration of use.

TABLE 2. Medication Nonadherence Rates[a] for All Patients Following Discharge after Acute Coronary Syndrome

	Time Frame; No. (%) of Evaluable Patients	
Medication	**30 Days**	**1 Year**
ASA	1/218 (0.5)	3/199 (1.5)
P2Y12 inhibitors	0/178 (0.0)	11/161 (6.8)
Clopidogrel	0/162 (0.0)	10/145 (6.9)
Ticagrelor	0/16 (0.0)	1/16 (6.3)
β-Blocker	3/236 (1.3)	17/227 (7.5)
ACE inhibitor/ARB	3/155 (1.9)	9/145 (6.2)
Statin	5/245 (2.0)	9/235 (3.8)
Overall[b]	7/253 (2.8)	39/242 (16.1)

ACE = angiotensin-converting enzyme, ARB = angiotensin II receptor blocker, ASA = acetylsalicylic acid, P2Y12 = P2Y purinoceptor 12.
[a]Determined as the number of patients who were taking the specified medication at each time point, divided by the number of patients for whom the medication was prescribed at discharge, with subtraction of those who were lost to follow-up or who died.
[b]Total number (%) of patients who were nonadherent to any secondary prevention medication.

Systematic reviews have found the benefit of pharmacist-led interventions for post-ACS medication adherence to be variable and/or uncertain.[12,18,21,22] In a systematic review of the effect of pharmacist care on medication adherence for patients with ACS, the interventions were usually multifaceted and were provided in both the hospital and the community.[18] Multifaceted interventions are challenging to evaluate because the effectiveness and intensity of individual components is unknown or difficult to measure. Only 4 of the 12 studies in that systematic review showed improved medication adherence in the ACS patient population, and they were characterized by small sample sizes and/or interventions that extended beyond the hospital setting.[18] Zhao and others[23] randomly assigned 90 patients to either a multifaceted intervention by the hospital pharmacist (individualized drug regimen, patient education, and monthly follow-up telephone calls) or usual care with no pharmacist interventions. At 6 months, medication adherence was significantly higher in the intervention group.[23] Jalal and others[24] enrolled 71 patients in a randomized controlled pilot study that compared postdischarge counselling provided by community pharmacists with usual care; they found that medication adherence among those who received counselling was significantly higher at 3- and 6-month follow-up. Ho and others[25] randomly assigned 253 patients to a multifaceted intervention (medication reconciliation, patient education, collaboration with primary care providers, and refill reminders) or usual care. Adherence to therapy with 4 secondary prevention medications was significantly better in the intervention group at 1 year. Budiman and others[26] enrolled 136 patients in a nonrandomized prospective trial with a multifaceted intervention (medication reconciliation, patient education, postdischarge telephone call) for comparison with historical controls. A combination score for medication adherence and literacy was significantly higher in the intervention group than the control group.[26] In contrast, our study enrolled a large patient cohort and was designed to evaluate a single practical intervention provided by pharmacists while the patients were still in the hospital.

Interventions to improve adherence to therapy with multiple medications in patients with coronary disease, although not specific to interventions delivered by pharmacists, have also been systematically reviewed.[22] The pooled analysis indicated significantly improved adherence with an intervention (odds ratio 1.52, 95% confidence interval [CI] 1.25–1.86), regardless of intervention type (simple or complex), category (patient education, counselling, or intensified patient care), or method of measuring adherence. The

TABLE 3. Patient Outcomes at 30 Days and 1 Year after Hospital Discharge with Acute Coronary Syndrome

	Time Frame and Group; No. (%) of Evaluable Patients					
	30 Days			**1 Year**		
Variable	**With Counselling**	**Without Counselling**	***p***	**With Counselling**	**Without Counselling**	***p***
Medication nonadherence[a,b]	2/88 (2.3)	5/165 (3.0)	>0.99	10/84 (11.9)	29/158 (18.4)	0.19
Attended cardiac rehabilitation[c]	18/83 (21.7)	22/142 (15.5)	0.24	32/68 (47.1)	54/139 (38.8)	0.30
Cardiovascular readmission[c]	3/83 (3.6)	7/142 (4.9)	0.75	12/68 (17.6)	31/139 (22.3)	0.42
Death[b]	0/88 (0.0)	2/165 (1.2)	>0.99	3/87 (3.4)	7/165 (4.2)	>0.99

[a]Nonadherence to any secondary prevention medication.
[b]All patients with medication lists were assessed for overall nonadherence and death.
[c]All patients with follow-up telephone interviews were assessed for attending cardiac rehabilitation and cardiovascular readmission.

TABLE 4. Patient Characteristics According to Adherence with Any Secondary Prevention Medication at 1 Year after Discharge

Characteristic	Group; No. (%) of Patients[a]				*p* Value
	Nonadherent (*n* = 39)		Adherent (*n* = 203)		
Age (years) (mean ± SD)	64.2 ± 9.2		62.6 ± 10.9		0.38
Sex, male	27	(69.2)	157	(77.3)	0.28
No. of medications on discharge (mean ± SD)	9.5 ± 3.0		9.6 ± 3.7		0.46
Drug plan (yes)	32	(82.1)	174	(85.7)	0.56
Compliance packaging (yes)	1	(2.6)	18	(8.9)	0.18
Pharmacist counselling (yes)	10	(25.6)	74	(36.5)	0.19
Education					
Grade 9 or less	8	(20.5)	40	(19.7)	0.32
High school (grades 10–12)	11	(28.2)	78	(38.4)	
Postsecondary	20	(51.3)	77	(37.9)	
No response	0	(0.0)	8	(3.9)	
Annual income					
< $20 000	9	(23.1)	38	(18.7)	0.73
$20 000–$40 000	8	(20.5)	59	(29.1)	
> $40 000	18	(46.2)	77	(37.9)	
No response	4	(10.3)	29	(14.3)	
Diagnosis					
STEMI	9	(23.1)	57	(28.1)	0.78
NSTEMI	25	(64.1)	115	(56.7)	
Unstable angina	5	(12.8)	31	(15.3)	
ACS management					
PCI	13	(33.3)	93	(45.8)	0.11
CABG	17	(43.6)	55	(27.1)	
Medical	9	(23.1)	55	(27.1)	
Cardiac risk factors					
Hypertension	25	(64.1)	136	(67.0)	0.73
Diabetes	13	(33.3)	71	(35.0)	0.84
Dyslipidemia	29	(74.4)	143	(70.4)	0.62
Family history[b]	22	(56.4)	104	(51.2)	0.55
Smoking	9	(23.1)	56	(27.6)	0.56
None	2	(5.1)	9	(4.4)	0.85
Comorbidities					
Coronary artery disease[c]	12	(30.8)	75	(36.9)	0.46
Cerebrovascular disease	0	(0.0)	9	(4.4)	0.36
Hypertension	25	(64.1)	136	(67.0)	0.73
Arrhythmia	0	(0.0)	9	(4.4)	0.18
Chronic renal failure[d]	1	(2.6)	2	(1.0)	0.42
Heart failure	1	(2.6)	12	(5.9)	0.40
Dyslipidemia	29	(74.4)	142	(70.0)	0.58
Diabetes	13	(33.3)	69	(34.0)	0.94
Peripheral vascular disease	1	(2.6)	6	(3.0)	0.89
None	4	(10.3)	31	(15.3)	0.42
No. of comorbidities (mean ± SD)	2.1 ± 4.4		2.3 ± 1.5		0.46

ACS = acute coronary syndrome, CABG = coronary artery bypass graft, NSTEMI = non-ST segment elevation myocardial infarction, PCI = percutaneous coronary intervention, SD = standard deviation, STEMI = ST segment elevation myocardial infarction.

[a]Except where indicated otherwise.

[b]Family history was documented by the physician in the patient's chart.

[c]Coronary artery disease was defined as previous myocardial infarction, CABG, or PCI.

[d]Chronic renal failure was defined as estimated glomerular filtration rate less than 30 mL/min.

interventions delivered by pharmacists in 7 of the 16 studies were all complex in nature and included patient education, counselling, intensified patient care, medication aids, reminders, and collaborative care.[22] Finally, a systematic review by Bonetti and others[19] focused on the impact of pharmacist-led discharge counselling on clinical outcomes, rather than medication adherence. Hospital readmissions were found to be reduced with discharge counselling relative to usual care (risk ratio 0.86, 95% CI 0.76–0.997), as were emergency department visits (risk ratio 0.70, 95% CI 0.54–0.91). However, because of heterogeneity and the small number of trials, the authors were unable to draw conclusions about the effectiveness of pharmacist-led discharge counselling.[19] Higher-quality evidence, with more consistent reporting and measurement methods, is needed to better understand the impact of pharmacists' interventions on medication adherence. In our study, patient outcomes constituted a secondary end point and were not significantly different between patients who did and did not receive discharge counselling from a pharmacist.

Pharmacists provided discharge counselling to 34% of patients with ACS who enrolled in the study, lower than the estimated 50%. Pharmacists counselled fewer patients who underwent coronary artery bypass grafting (relative to those who received other forms of ACS management), likely because these patients were transferred to the cardiovascular surgery unit. Other differences between patients who did and did not receive counselling (specifically NSTEMI diagnosis, cardiac history, and diabetes) may also be related to the patient subgroup who underwent revascularization surgery. It is unknown what impact these differences might have had on medication adherence. Nonetheless, these findings can be used to help the cardiology team and pharmacy department to review and prioritize the patient care activities to be provided by cardiology pharmacists and the specific populations in greatest need of pharmacist intervention. Such prioritization is especially vital given that no differences were found in medication adherence after pharmacist counselling. The lack of clinical pharmacy services for patients undergoing cardiovascular surgery was identified at the time of the study. Since then, the hospital's pharmacy department has introduced a new practice model, which has resulted in greater pharmacist coverage and cross-training for cardiovascular surgery.

This study also identified possible gaps in care among ACS patients. Optimal secondary prevention therapy for this patient population was informed by Canadian and US guidelines that were current at the time of the study.[5-8] ASA and statins were recommended universally except for patients with contraindications, and prescription rates for ASA and statins were correspondingly very high (> 90%) at discharge and at 1 year. In contrast, P2Y12 inhibitors were recommended for patients with percutaneous coronary intervention or fibrinolysis for a period of 12 months. Our study indicated that 78.0% (n = 202/259) of patients were taking a P2Y12 inhibitor at discharge, with the proportion dropping to 41.1% (n = 85/207) by 1 year after discharge. ACE inhibitors were suggested for patients with heart failure, left ventricular dysfunction, post-anterior myocardial infarction, hypertension, or diabetes, with ARBs being recommended for patients intolerant of ACE inhibitors. The guidelines also suggested that ACE inhibitors were a reasonable option for all patients after ACS, although this was based on lower-quality evidence. In our study, only 60% of patients were taking an ACE inhibitor or ARB at discharge and during follow-up. Finally, β-blockers were recommended for most patients with ACS, except those with contraindications.[5-8] In our population, β-blocker utilization was high (> 90%) at discharge but decreased to 82.1% (n = 170/207) at 1 year. Overall, there was good adherence to prescribing guidelines for ASA and statins, but the use of β-blockers, ACE inhibitors/ARBs, and P2Y12 inhibitors had fallen or these drugs were potentially underutilized during the 1-year follow-up period, which may reflect areas needing attention.

The strengths of our study included the large sample size and the long study duration, relative to other published studies.[23,24,26-28] Our study had minimal loss to follow-up for patients alive at 30 days and 1 year. Medication lists were obtained for 97%– 98% of possible patients, and telephone interviews were completed for 83%–88% of possible patients. The pragmatic design also provided advantages for evaluating the intervention in a real-world setting. The simple intervention is practical, quickly implemented, and scalable, and hospital pharmacists are capable of providing it within their usual scope of practice. There are several methods to measure medication adherence,[13] but by combining patient self-reporting with pharmacy refill records, we were able to exclude intentional nonadherence due to justifiable patient- and provider-related factors. Finally, medication adherence was assessed for multiple medications, instead of focusing on only one.

There were several limitations associated with the study, particularly the observational, nonrandomized study design, which can be subject to selection and information bias, as well as confounding.[29] Selection bias could have occurred if the group that received the intervention (counselling) was different in some respect from the group that received no intervention, because patients were not randomly assigned to the study groups. In our study, patients who underwent coronary artery bypass grafting were less likely to receive counselling because they were transferred to the cardiovascular surgery unit and were unavailable to receive counselling before discharge. Patients with a diagnosis of NSTEMI, a history of cardiac problems, and diabetes comorbidity might have been more likely to require bypass grafting, which may explain why these groups also were less likely to receive counselling. Confounding

introduces bias when an uncontrolled or unknown factor is associated with both the intervention and the outcome. Although data were collected on several disease and medication adherence characteristics, other relevant factors may have gone unmeasured. Another potential source of bias is misclassification of intervention status, because the research assistants relied on lists prepared by the hospital pharmacists to identify patients who received counselling. Despite the high rates of follow-up, patients with missing information at 30 days and 1 year were excluded from the analysis, which may have led to biased estimates of medication adherence.

Randomization of patients to an intervention or control arm was not feasible because discharge counselling was a current service provided by pharmacists to ACS patients. We attempted to blind the pharmacists to patient participation, to limit the chance that pharmacists would treat study patients differently or provide additional counselling to them. As well, the cardiology pharmacists did not collect patient data or conduct follow-up telephone interviews, which helped to limit bias in determining adherence outcomes. Usual care was not controlled for in the study, and patients could have received additional services from pharmacists or counselling from other health care providers. Our study had unexpectedly low rates of nonadherence, which reduced the power to determine a difference between patient groups (e.g., at 1 year, 11.9% in the group with counselling versus 18.4% in the group without counselling; $p = 0.19$). High medication adherence, good participation in cardiac rehabilitation (39%–47% at 1 year), and high follow-up rates may suggest that the patient cohort was very motivated. Ho and others[25] proposed that the high adherence reported in their study was because patients who volunteer to participate in research were more likely to be adherent. However, low nonadherence rates in our study may also suggest poor ascertainment of medication adherence. The method of calculating adherence—which was based on self-reporting and refill records together, to exclude intentional nonadherence—may have artificially increased rates relative to those found in the literature. Finally, our study took place from 2014 to 2016 and may not represent current practice.

CONCLUSION

A discharge medication counselling intervention by hospital pharmacists was not associated with better medication adherence in a patient cohort that demonstrated high medication adherence at 1 year. Our study revealed high utilization rates for ASA and statins on discharge from hospital, which were sustained at 1 year. Potential suboptimal utilization of β-blockers, P2Y12 inhibitors, and ACE inhibitors or ARBs may indicate gaps in care. Given that there was no difference in outcomes and given that only one-third of ACS patients enrolled in the study were counselled by a hospital pharmacist before discharge, the patient care activities provided by cardiology pharmacists and the populations in greatest need of pharmacist intervention should be reviewed and prioritized. While it is important that hospital pharmacists continue to care for patients with high rates of recurrent events and death, higher-quality evidence is needed to determine the most effective and practical interventions to ensure that patients adhere to their medication regimens and achieve good outcomes after ACS.

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Optimizing Thiopurine Therapy with a Xanthine Oxidase Inhibitor in Patients with Systemic Autoimmune Diseases: A Single-Centre Experience

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ABSTRACT

Background: Thiopurines are a mainstay of therapy for autoimmune diseases. However, up to 20% to 30% of patients experience overproduction of the methylated metabolites, known as 6-MMP, to the detriment of the active metabolite, 6-thioguanine nucleotide (6-TGN). These patients, commonly referred to as "shunters", are predisposed to thiopurine resistance and hepatotoxicity. In patients with inflammatory bowel diseases, the combination of thiopurine with a xanthine oxidase inhibitor (XOI) is used to reverse this skewed metabolism and to prevent treatment failure or hepatotoxicity. Data on the use of this strategy for patients with other diseases are limited.

Objectives: To investigate and describe the use of thiopurine–XOI combination therapy in shunters with systemic autoimmune diseases.

Methods: Shunters treated in the study hospital between January 1, 2005, and December 31, 2015, were identified using the hospital's laboratory database, and clinical data were collected retrospectively. For each patient with optimization of thiopurine therapy, clinical and laboratory data were assessed over a 6-month period.

Results: Thirty-four patients were identified as shunters; for 14 of these patients, thiopurine therapy was optimized with an XOI. In these 14 patients, the median dose of azathioprine was reduced from 1.95 to 0.78 mg/kg with combination therapy. In addition, median 6-TGN level increased from 135 to 385 pmol/8 × 10^8 erythrocytes ($p = 0.001$); furthermore, 6-TGN levels rose to above 235 pmol/8 ×10^8 erythrocytes for 11 of the 14 patients. Conversely, the median 6-MMP level decreased from 6267 to 271 pmol/8 × 10^8 erythrocytes ($p = 0.001$). Except for a 12% increase in mean corpuscular volume, no clinically significant changes in blood count were recorded. Notable infections were reported in 3 patients, and 1 patient had to discontinue treatment because of cytopenia. After 6 months, median prednisone daily dose was reduced by 74%, from 16.7 mg to 4.4 mg ($p = 0.005$), and 4 patients had been weaned off corticosteroids. Of the 14 patients, 11 (79%) were in full remission, and 2 (14%) were in partial remission.

Conclusion: Optimizing thiopurine therapy with an XOI may be a safe and effective strategy for patients with systemic autoimmune diseases.

Keywords: 6-mercaptopurine, allopurinol, azathioprine, febuxostat, thiopurines, xanthine oxidase inhibitors

RÉSUMÉ

Contexte : Les thiopurines sont des piliers de l'intervention thérapeutique contre les maladies auto-immunes. Cependant, 20 % à 30 % des patients surproduisent des métabolites méthylés (connus sous le nom 6-MMP), au détriment du métabolite actif, le nucléotide 6-thioguanine (6-TGN). Ces patients, communément appelés « courts-circuiteurs » sont prédisposés à résister à la thiopurine et à l'hépatotoxicité. Pour les patients ayant des maladies inflammatoires intestinales, on utilise la combinaison de thiopurine avec une xanthine oxydase inhibitrice (XOI) afin d'inverser ce métabolisme anormal et prévenir l'échec du traitement ou l'hépatotoxicité. Les données concernant l'adoption de cette stratégie pour les patients atteints d'autres maladies sont limitées.

Objectifs : Étudier et décrire l'utilisation de la thérapie combinée de thiopurine et de XOI pour les « courts-circuiteurs » ayant des maladies auto-immunes systémiques.

Méthodes : Les « courts-circuiteurs » traités dans l'hôpital où s'est déroulée l'étude entre le 1er janvier 2005 et le 31 décembre 2015 ont été identifiés à l'aide de la base de données du laboratoire de l'hôpital et les données cliniques ont été recueillies de manière rétrospective. L'évaluation des données cliniques et de laboratoire de chaque patient bénéficiant d'une optimisation de la thérapie par la thiopurine a porté sur six mois de traitement.

Résultats : Trente-quatre patients ont été identifiés comme « courts-circuiteurs » et 14 d'entre eux ont bénéficié d'une optimisation de la thérapie par la thiopurine à l'aide d'une XOI. Ces derniers ont subi une thérapie de combinaison qui a fait passer la dose moyenne d'azathioprine de 1,95 à 0,78 mg/kg. De plus, le niveau moyen de 6-TGN est passé de 135 à 385 pmol/8 × 10^8 érythrocytes ($p = 0,001$). En outre, 11 des 14 patients ont vu le niveau de 6-TGN passer à plus de 235 pmol/8 ×10^8 érythrocytes. Inversement, le niveau moyen de 6-MMP est passé de 6267 à 271 pmol/8 × 10^8 érythrocytes ($p = 0,001$). À l'exception d'une augmentation de 12 % du volume corpusculaire moyen, aucun changement clinique important dans la numération globulaire n'a été noté. Trois patients ont développé des infections notables et l'un d'eux a dû arrêter le traitement à cause d'une cytopénie. Après six mois, la dose moyenne quotidienne de prednisone a été réduite de 74 %, pour passer de 16,7 mg à 4,4 mg ($p = 0,005$), et quatre patients ont été sevrés des corticostéroïdes. Sur les 14 patients, 11 (79 %) ont été déclarés en rémission totale et 2 (14 %) en rémission partielle.

Conclusion : L'optimisation de la thérapie par la thiopurine associée à une XOI pourrait être sécuritaire et constituer une stratégie efficace pour les patients ayant une maladie auto-immune systémique.

Mots-clés : 6-mercaptopurine, allopurinol, azathioprine, febuxostat, thiopurines, xanthine oxydase inhibitrice

INTRODUCTION

The thiopurines azathioprine and 6-mercaptopurine have been the mainstay of therapy for an array of chronic systemic inflammatory and autoimmune diseases. Because of their ease of use and low cost relative to newer molecules, thiopurines remain useful. However, up to 50% of patients will experience treatment failure or an adverse event while receiving thiopurine therapy.[1]

Both azathioprine and 6-mercaptopurine are prodrugs that are metabolized to 6-thioguanine nucleotide (6-TGN), the main active metabolite (Figure 1).[2-7] In patients receiving azathioprine, the prodrug undergoes nonenzymatic splitting in the liver, which leads to formation of 6-mercaptopurine. The 6-mercaptopurine is further converted to 6-TGN through a series of metabolic transformations.[2-7] Phosphorylated 6-TGN subsequently interferes with DNA synthesis, which alters the proliferation of B and T lymphocytes.[4,5] Up to 85% of 6-mercaptopurine is transformed by xanthine oxidase to inactive 6-thiouric acid through the intermediates thioxanthine and 8-hydroxymercaptopurine.[5,6] Thiopurine methyltransferase (TPMT) is a key enzyme involved in the metabolism of thiopurines, which leads to the formation of 6-methyl-mercaptopurine and 6-methyl-mercaptopurine ribonucleotides.[4,5,7,8] These 2 methylated metabolites are unstable and cannot be distinguished by laboratory assays; they are therefore reported jointly as "6-MMP". The presence of 6-MMP is associated with hepatotoxicity.[4,7,8]

TPMT is known to exhibit genetic polymorphism regarding its activity level in the erythrocytes through autosomal codominance.[8] Low TPMT in patients receiving azathioprine or 6-mercaptopurine is correlated with possibly fatal myelosuppression due to significant formation of 6-TGN, while intermediate phenotypes necessitate reduction of the initial dose.[7,8] Nudix hydrolase dephosphorylates the active 6-TGN metabolites, thus preventing their incorporation into DNA.[9] Genetic variants of Nudix hydrolase that decrease its activity are also associated with myelosuppression.[9] For these reasons, it is recommended that TPMT phenotyping or genotyping, as well as Nudix hydrolase genotyping, be performed before initiation of thiopurine therapy.[9]

In patients with inflammatory bowel disease (IBD), 6-TGN levels between 235 and 450 pmol/8 × 10^8 erythrocytes have been associated with a 3- to 5-fold increase in the odds ratio for a therapeutic response.[4,10] However, higher levels of 6-TGN do not lead to greater rates of remission and are associated with an increased risk of adverse effects, such as neutropenia.[10] A 6-MMP level above 5700 pmol/8 × 10^8 erythrocytes correlates with transaminase elevation and a 3-fold increase in the risk of hepatotoxicity, whereas levels above 11 450 pmol/8 × 10^8 erythrocytes correlate with myelotoxicity.[4,10,11]

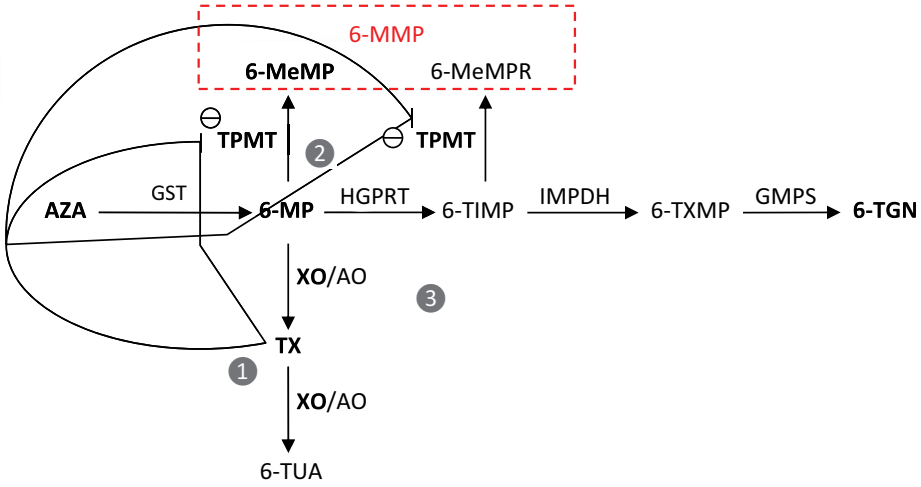

FIGURE 1. After intestinal absorption, azathioprine (AZA) is transformed into 6-mercaptopurine (6-MP) through a spontaneous reaction with sulfhydryl-containing compounds, including reduced glutathione; the presence of glutathione-*S*-transferase (GST) accelerates the process. The 6-MP is then converted by 3 competing pathways: transformation by xanthine oxidase (XO) to the inactive molecule 6-thiouric acid (6-TUA); formation of 6-methyl-mercaptopurine (6-MeMP) and 6-methyl-mercaptopurine ribonucleotides (6-MeMPR) by thiopurine methyltransferase (TPMT), which are measured indistinctively by laboratory assays and are reported as 6-MMP, a hepatotoxic methylated metabolite; and formation of 6-thioguanine nucleotide (6-TGN) through a series of enzymatic alterations, first by hypoxanthine-guanine phosphoribosyl transferase (HGPRT), followed by inosine monophosphate dehydrogenase (IMPDH) and then guanosine monophosphate synthetase (GMPS). AO = aldehyde oxidase, 6-TIMP = 6-thioinosine monophosphate, 6-TXMP = 6-thioxanthosine monophosphate, TX = thioxanthine.

A subset of patients have skewed thiopurine metabolism, which can be explained by a hypermethylation phenomenon; these patients are commonly referred to as "shunters".[12] This term implies a metabolic shift toward preferential production of 6-MMP, which results in high levels of these metabolites (> 5700 pmol/8 × 10^8 erythrocytes) associated with a low level of 6-TGN. Shunters may also be identified by a ratio of 6-MMP to 6-TGN greater than 20, regardless of the specific levels of 6-TGN and 6-MMP.[13] High TPMT activity is not the major reason for preferential 6-MMP production.[13] Furthermore, in most patients, dose escalation does not appear to resolve the issue, as excessively low 6-TGN levels tend to persist while 6-MMP reaches toxic concentrations.[14] Up to 20% of patients with IBD who are treated with thiopurines appear to be shunters.[13] In one recent study, [4] 31% of patients with various systemic autoimmune diseases who were treated with thiopurines were identified as shunters. Overall, the preferential 6-MMP metabolism observed in shunters leads to a higher risk of hepatic cytolysis and frequent treatment failure.

The addition of a xanthine oxidase inhibitor (XOI), such as low-dose allopurinol, will correct the metabolic profile by reducing 6-MMP and increasing 6-TGN concentration. XOIs are thought to optimize the metabolism of thiopurines by increasing levels of thioxanthine, which is a TPMT inhibitor.[6,13] This strategy has been used with success in patients with IBD and has been the subject of numerous publications.[2-6,15-17] More recently, this strategy was shown to be beneficial and safe for a small number of patients with autoimmune liver disease.[18] However, data on the use of this strategy in the context of diseases other than IBD are limited.

The objectives of this study were to describe and evaluate the use of thiopurine–XOI combination therapy in patients with systemic autoimmune diseases and skewed thiopurine metabolism and to describe their clinical progression.

METHODS

Study Design

We conducted a retrospective, descriptive single-centre study of the management and progression of patients with non-IBD autoimmune diseases who were identified as shunters, with emphasis on those whose thiopurine therapy was optimized with thiopurine–XOI combination therapy. The study was conducted at the Hôpital du Sacré-Coeur de Montréal, a tertiary care hospital in Canada. The institutional research ethics board approved the study protocol.

Patient Selection

Patients treated in the hospital between January 1, 2005, and December 31, 2015, and characterized as "shunters" (defined on the basis of 6-MMP to 6-TGN ratio > 20 and/or 6-MMP > 5700 pmol/8 × 10^8 erythrocytes) were identified through the hospital laboratory database. Patients receiving immunosuppressive therapy in the context of IBD, chemotherapy, or organ transplant were excluded. Patients who were not receiving a thiopurine at the time of metabolite monitoring, those with follow-up outside the study hospital and its affiliated clinics, and those whose medical records were unavailable were also excluded.

Measurements and Data Collection

One of the authors (M.B.; a senior resident in general internal medicine [PGY5]) collected the data retrospectively from the medical charts using a standardized form. Selected patients were divided into 2 groups based on whether or not optimization with concurrent XOI therapy was performed. Data for demographic, clinical, and biological characteristics were collected for both groups.

Extensive clinical and biochemical follow-up data were collected for the patients with optimization of thiopurine therapy before and up to 6 months after the addition of an XOI. These data included adjuvant immunosuppressive agents used; relevant laboratory values, such as liver function tests, complete blood count, inflammatory markers, and 6-TGN and 6-MMP levels; thiopurine dose variations; and adverse drug events (e.g., serious infections, cytopenia, disturbance of liver function tests, nausea or vomiting, fatigue, myalgia).

Outcome Assessment

For patients with optimization, response to therapy was assessed 6 months after initiation of the XOI. Given the broad spectrum of diseases, reliance upon a single disease activity scale was not feasible. Remission was therefore appraised on the basis of clinical and biochemical data from the medical records. These data comprised the attending physician's global evaluation, successful tapering of steroids or IV immunoglobulin, sufficiency of ongoing treatment without recourse to new immunomodulatory agents, and resolution of hepatotoxicity, if applicable (defined as serum alanine aminotransferase and/or aspartate aminotransferase ≤ 1.5 times the upper limit of normal). Each patient's outcome was categorized as full remission, partial remission, or non-remission. In cases of uncertainty about the assessment of a patient's outcome, another investigating physician or the attending physician was consulted.

Laboratory Assays

TPMT phenotype screening was conducted by high-performance liquid chromatography with fluorimetric detection, as described by Ford and Berg.[19] The laboratory reference values defined normal TPMT enzyme activity as greater than 50 nmol 6-methylthioguanine per gram of hemoglobin per hour (nmol 6-MTG/g Hb/h), heterozygote intermediate enzyme activity as 15 to 50 nmol 6-MTG/g Hb/h, and homozygote low enzyme activity as

less than 15 nmol 6-MTG/g Hb/h. 6-TGN and 6-MMP levels were quantified by reverse-phase high-performance liquid chromatography, as described by Lennard and Singleton.[20] The analyses were performed in the laboratory of CHU Sainte-Justine, Montréal, Quebec.

Statistical Analysis

Given the small sample size, all statistical analyses were performed using nonparametric statistics. Descriptive data are reported as proportions or medians with interquartile ranges (IQRs). The Mann–Whitney *U* test was used to compare differences between medians, whereas the Fischer exact test and the χ^2 test were used to compare differences between proportions. The Wilcoxon signed-rank test was used to compare paired variables. Two-tailed testing was performed for all statistical analyses, with a significance threshold of 0.05. The statistical analyses were performed with SPSS software, version 24.0 (IBM Corporation).

RESULTS

Patient Characteristics

In total, 254 patients had thiopurine measured between January 1, 2005, and December 31, 2015, of whom 151 were excluded (Figure 2). Of the 103 patients remaining, 34 (33%) were identified as "shunters", of whom 14 had thiopurine treatment optimized with the addition of an XOI. One of these patients was not formally considered to be a shunter at the time of therapy optimization but was included in the analysis because she displayed early evidence of skewed metabolism. Her 6-MMP to 6-TGN ratio was 12, despite a low dose of azathioprine (1.33 mg/kg). She was experiencing gastrointestinal side effects, which prevented further dose increments while the thiopurine was being used as a third-line immunosuppressant.

Characteristics of the 14 patients with optimization of thiopurine therapy are shown in Table 1. Most patients were female and white. The most common indications for immunosuppressant therapy were vasculitis and connective tissue diseases (n = 6 each); the other indications were eosinophilic fasciitis (n = 1) and myasthenia gravis (n = 1). Most patients had a normal TPMT phenotype. Nudix hydrolase genotyping was not performed for any of these patients, because this analysis was not standard practice at the time; indeed, Nudix hydrolase genotyping is still not readily available. Other than the skewed metabolism itself, reasons for treatment failure leading to optimization of thiopurine therapy included hepatotoxicity (n = 3), corticosteroid dependence (n = 6), nonresponsive or relapsing illness (n = 6), and/or unfavourable metabolite profile (n = 3). Split-dose administration was attempted in 7 patients before optimization, but it was inefficient. When started on optimized therapy (time 0), 12 patients were receiving oral corticosteroids and 5 were being treated with IV immunoglobulin. Six patients (43%) were receiving at least 1 immunosuppressant in addition to prednisone and hydroxychloroquine. Methotrexate was the most common add-on therapy, followed by biologics.

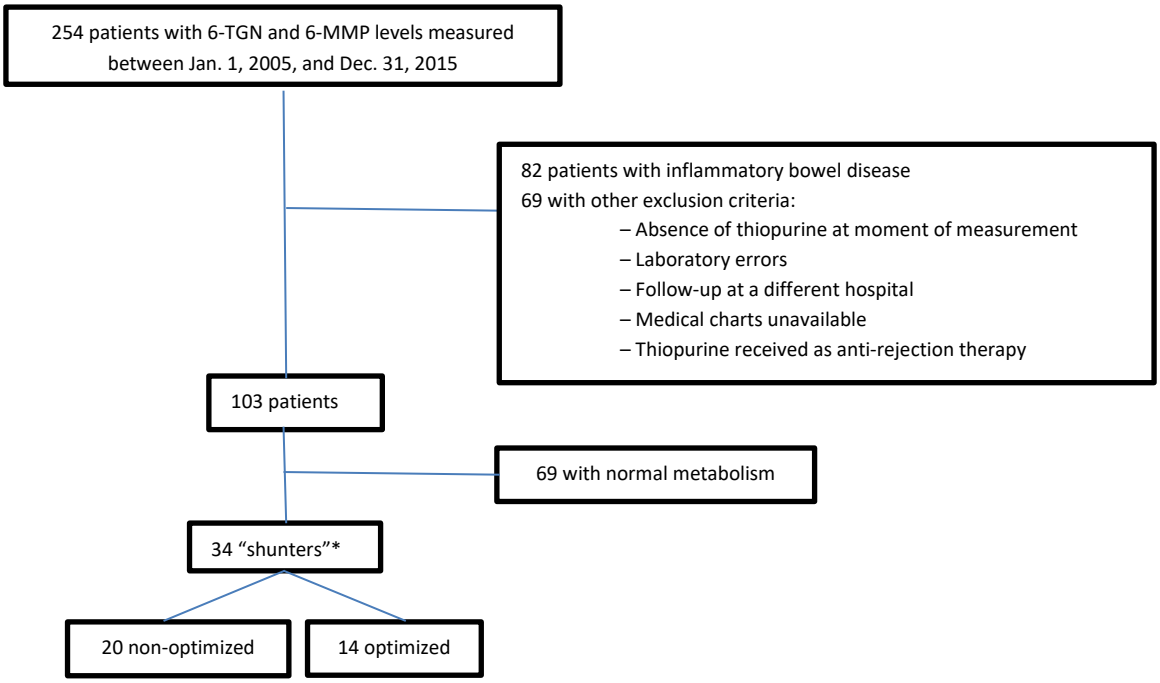

FIGURE 2. Flow diagram of the screening and patient selection process. *"Shunters" are defined as patients with ratio of methylated metabolite (6-MMP) to 6-thioguanine (6-TGN) greater than 20 and/or 6-MMP greater than 5700 pmol/8 × 10^8 erythrocytes.

TABLE 1. Demographic, Clinical, and Laboratory Characteristics of Patients with Optimized Thiopurine Metabolism

Characteristic	No. (%) of Patients[a] (*n* = 14)	
Demographic data		
Age (years) (median and IQR)	61	(50–64)
Sex		
Female	10	(71)
Male	4	(29)
Ethnicity		
White	9	(64)
Non-white	5	(36)
Clinical data		
Disease		
Vasculitis	6	(43)
Connective tissue disease	6	(43)
Other	2	(14)
Concurrent therapy		
Corticosteroids (prednisone equivalent)	12	(86)
Methotrexate	4	(29)
Cyclophosphamide	1	(7)
IVIG	5	(36)
Rituximab	2	(14)
Infliximab	1	(7)
Hydroxychloroquine	2	(14)
Colchicine	1	(7)
Laboratory data		
TPMT phenotype[b]		
> 50 nmol 6-MTG/g Hb/h	10	(71)
15–50 nmol 6-MTG/g Hb/h	3	(21)
< 15 nmol 6-MTG/g Hb/h	0	
Unavailable	1	(7)
GFR (mL/min/1.73 m^2) (median and IQR)	97.0	(64.5–106.8)

GFR = glomerular filtration rate, Hb = hemoglobin, IQR = interquartile range, IVIG = IV immunoglobulin, TPMT = thiopurine methyltransferase, 6-MTG = 6-methylthioguanine.
[a]Except where indicated otherwise.
[b]Normal phenotype was defined as > 50 nmol 6-MTG/g Hb/h.

Dynamics of Metabolite Levels

Follow-up after optimization of therapy was conducted over a period of 6 months. Before optimization, the weight-based dose of thiopurine was 1.95 mg/kg (IQR 1.69–2.64 mg/kg), which was reduced to 0.78 mg/kg (IQR 0.67–1.01 mg/kg) when combined with an XOI, a 60% decrease ($p = 0.003$). Patients also received allopurinol 100 mg daily ($n = 12$), allopurinol 50 mg daily ($n = 1$), or febuxostat 40 mg daily ($n = 1$). Progression of maximal 6-TGN levels, maximal 6-MMP levels, and 6-MMP to 6-TGN ratios by 6 months after optimization with an XOI is shown in Figure 3. Maximal 6-TGN levels increased by 185% ($p = 0.001$), and 6-TGN levels rose to over 235 pmol/8 × 10^8 erythrocytes for 11 (79%) of the 14 patients. Maximal 6-MMP levels decreased by 96% ($p = 0.001$), and all patients achieved a normal 6-MMP to 6-TGN ratio (≤ 20) by 6 months after XOI initiation, which represented a 98% decrease ($p = 0.001$).

Impact on Blood Count

Changes in complete blood count by 6 months after optimization are shown in Table 2. There was a slight decrease in median hemoglobin, from 129 to 124 g/L. The mean corpuscular volume increased significantly, by 12%. Although the platelet count remained within the normal range, there was a statistically significant decrease (by 17%). The median neutrophil count decreased by 21% ($p = 0.07$), and no significant neutropenia was identified. A 24% decrease in leukocytes was observed ($p = 0.038$). Three patients experienced clinically relevant leukopenia, defined as leukocyte count at or below 3.5 × 10^9/L, and the dose of azathioprine was promptly adjusted accordingly. Despite dose adjustments, one individual had to discontinue the treatment regimen after 3 months, because of concerns about myelotoxicity (leukocyte count fell to 2.6 × 10^9/L and hemoglobin to 91 × 10 g/L). This patient's 6-TGN level was 522 pmol/8 × 10^8 erythrocytes, above the recommended threshold of 450. He was the only patient receiving febuxostat, and he had a much higher dose of azathioprine after initiation of XOI than the other patients (1.7 mg/kg versus median of 0.78 mg/kg). Another patient had to cease therapy 1 month after the last outcome assessment (at month 7), because of a hypersensitivity drug reaction with eosinophilia and systemic symptoms (i.e., DRESS), first thought to be caused by the allopurinol.[21] Febuxostat was subsequently tried, but the symptoms returned.[21] All 3 patients with development of leukopenia had concomitant 6-TGN levels above 450 pmol/8 × 10^8 erythrocytes. Lymphopenia (lymphocyte count < 1 × 10^9/L) was frequent, occurring in 9 of the 14 patients. Serious infectious events were observed in 3 patients. One case of shingles (leukocytes 6.3 × 10^9/L; lymphocytes 0.8 × 10^9/L) and one case of perforated diverticulitis (leukocytes 9.1 × 10^9/L; lymphocytes 0.3 × 10^9/L) were reported. An HIV-positive patient presented with *Shigella* gastroenteritis, as well as recurrent hidradenitis suppurativa (leukocytes 5.0 × 10^9/L; lymphocytes 0.7 × 10^9/L).

Impact on Liver Function Tests

Before optimization of thiopurine therapy, 7 of the 14 patients had 6-MMP levels above 5700 pmol/8 × 10^8 erythrocytes. For all 7 patients, 6-MMP returned to normal after optimization. Hepatic cytolysis occurred in 2 of these patients and also in a third patient whose 6-MMP level was 5359 pmol/8 × 10^8 erythrocytes. Among the 3 patients with hepatotoxicity, resolution was observed in 2 patients within 1 month after optimization of therapy.

Clinical Progression

Six months after optimization of thiopurine therapy, 11 (79%) of the 14 patients were in remission, 2 were in partial

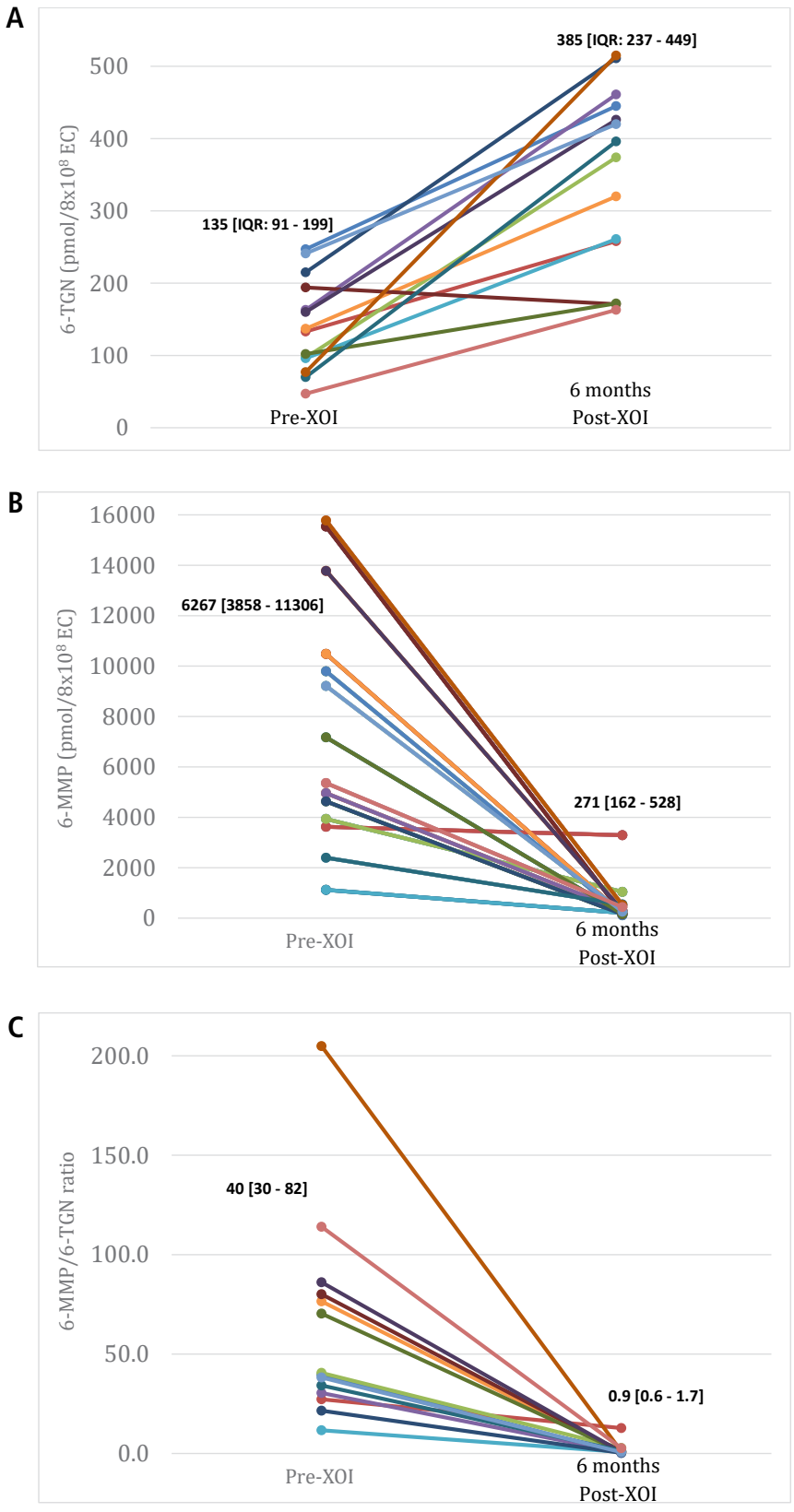

FIGURE 3. Outcomes before and 6 months after initiation of xanthine oxidase inhibitor (XOI) for patients with optimization of thiopurine therapy (n = 14; each coloured line represents 1 patient), with medians and interquartile ranges (IQRs) shown for each time point. A: Maximal levels of 6-thioguanine (6-TGN). B: Maximal levels of methylated metabolites (6-MMP). C: Maximal ratio of 6-MMP to 6-TGN. EC = erythrocytes.

TABLE 2. Change in Complete Blood Count (CBC) before and 6 Months after Optimization of Thiopurine Therapy with Xanthine Oxidase Inhibitor (n = 14)

	Time Point; Median Value (IQR)				
Element of CBC	Before Optimization		6 Months after Optimization		p Value
Leukocytes (× 10^9/L)	6.8	(5.3–10.7)	5.2	(3.7–7.0)	0.038
Neutrophils (× 10^9/L)	4.7	(3.7–8.2)	3.7	(2.5–4.4)	0.07
Hemoglobin (g/L)	129	(115–136)	124	(110–130)	0.12
Mean corpuscular volume (fL)	91.5	(87.9–94.6)	102.6	(93.7–106.4)	0.001
Platelets (× 10^9/L)	300	(266–389)	248	(196–329)	0.002

IQR = interquartile range.

remission, and 1 had stopped treatment (at 3 months). Of the 11 patients in remission, 8 had 6-TGN levels above 235 pmol/8 × 10^8 erythrocytes. Prednisone was successfully reduced by 74% (p = 0.005), from a median daily dose of 16.7 mg (IQR 5.0–41.0 mg) to 4.4 mg (IQR 0–8.1), and 4 patients were weaned off corticosteroids. No significant reductions were observed in the number of immunosuppressive medications received (25% decrease; p = 0.16) or the cumulative monthly dose of IV immunoglobulin (29% decrease; p = 0.69).

Overview of Patients without Optimization of Therapy

Except for ethnicity (95% white), the characteristics of the 20 patients who did not undergo optimization of thiopurine therapy, including age (62 [IQR 53–74] years), sex (55% female), diseases (20% vasculitis, 40% connective tissue disease, 40% other diseases), and TPMT (65% > 50 nmol 6-MTG/g Hb/h, 35% unavailable), were similar to those of patients with therapy optimization. Median 6-MMP levels were 3155 (IQR 1559–6206) pmol/8 × 10^8 erythrocytes, and 5 of the patients had levels above 5700 pmol/8 ×10^8 erythrocytes. Four of these patients experienced hepatic cytolysis, which eventually led to drug discontinuation in all cases. Median 6-TGN levels were 112 (IQR 70–200) pmol/8 × 10^8 erythrocytes, and 17 patients (85%) had levels below 235 pmol/8 × 10^8 erythrocytes. The reasons for non-optimization were adverse reaction to azathioprine (n = 4), option unacknowledged by physician (n = 4), patient's record of nonadherence or unreliability (n = 3), need for chemotherapy (n = 2), unspecified strategy (n = 2), patient not recognized as a shunter by the attending physician (n = 1), advanced age (n = 1), other option preferred (n = 1), loss to follow-up (n = 1), and death (n = 1). Overall, thiopurine failure occurred in 17 (85%) of the 20 patients in this group. Five of these patients were transitioned to biological agents.

DISCUSSION

The strategy of adding XOI to optimize thiopurine therapy and reverse an unfavourable metabolite profile has been extensively studied in patients with IBD.[15,22] To our knowledge, however, this study is the first to investigate this approach in the setting of systemic autoimmune diseases. A 6-MMP to 6-TGN ratio above 20 has been associated with therapy resistance, whereas 6-MMP levels greater than 5700 pmol/8 × 10^8 erythrocytes increase the risk of hepatotoxicity.[16,23] The metabolite profile improved in all 14 study patients (100%) receiving combination therapy, which is consistent with the IBD literature.[16,17,22,23] This result suggests that optimization therapy may be beneficial for other conditions beyond IBD.

Whether higher 6-TGN levels are linked to positive clinical outcomes in this specific context is debatable. Several IBD studies concluded that there was an association between intracellular 6-TGN levels above 235 pmol/8 × 10^8 erythrocytes and remission (odds ratio 3.0 to 5.0).[10,24] In addition, in IBD studies, remission rates with combination therapy have generally fallen within the range of 50% to 80%.[2,15,22,25,26] One small study in patients with systemic lupus erythematosus found that lower 6-TGN targets than those used in IBD (159 versus 235 pmol/8 × 10^8 erythrocytes) were associated with efficacy, which indicates that the ideal range of metabolites may vary between clinical indications.[27] This is of importance considering that the most common reasons for thiopurine failure are inadequate dosage regimens and hypermethylation, both characterized by low 6-TGN levels.[28] In our study, all 14 patients had low 6-TGN levels (relative to IBD targets) at initiation of optimization. Six months after initiation of optimization therapy, 79% had reached an appropriate 6-TGN range (according to IBD targets). Optimization therapy appears to be an effective way to correct the detrimental metabolic shift observed in shunters and may be helpful in inducing remission. In this study, 79% of patients had entered full remission by 6 months. In contrast, the failure rate was 85% among shunters without therapy optimization.

Concurrent therapy with allopurinol has proven to be an effective strategy in IBD to increase 6-TGN and reduce 6-MMP levels. It can overcome adverse effects encountered

with thiopurine monotherapy, such as gastrointestinal intolerance, myelotoxicity, and hepatotoxicity, in up to 80% to 90% of patients,[15,25,26] presumably through the ability of allopurinol to reduce the required doses of thiopurine and inhibit 6-MMP production.[26,29] In this study, 6-MMP levels decreased to 4% of their original value, consistent with previously published data.[16] Hepatotoxicity resolved with optimized therapy in two-thirds of the patients, and all 7 patients with 6-MMP levels above 5700 pmol/8 $\times 10^8$ erythrocytes achieved normal concentrations, preventing further manifestation of liver damage. Despite achieving normal 6-MMP levels, hepatic cytolysis persisted in 1 patient, which is consistent with other studies.[25,30] By the end of the study, no new cases of hepatotoxicity had been reported, which could presumably be a result of the combination therapy. Split-dose administration of thiopurines represents another strategy to overcome preferential 6-MMP production, although this approach is often insufficient,[31] as was seen in the current study.

Leukopenia was observed in 21% of the patients after the addition of an XOI, all of whom had 6-TGN levels above 450 pmol/8 $\times$ 10^8 erythrocytes. In previous studies, leukopenia occurred in 10% to 30% of patients with optimized therapy.[22,30] Serious infections were documented in 3 patients (21%) in the current study, one of whom had an HIV infection with a history of recurrent infections. No clinically significant changes in hemoglobin or platelet levels were observed. In this study, the overt steroid-sparing properties of the optimized therapy, with a 74% decrease in corticosteroid dose, may offer a potential advantage in reducing infectious risk and may prevent other adverse events related to corticosteroid use.

Remission was achieved in most patients, indicating that this approach is a safe and efficient way to bypass hypermethylation and hepatotoxicity with adequate metabolites and laboratory monitoring. Also, 25% of patients without therapy optimization were eventually switched to biologics. Whether optimized therapy could limit the use of biologics or other more expensive therapies remains unknown. Data from IBD studies suggest that up to 66% of patients with initial failure of thiopurine monotherapy may attain remission through coprescription of an XOI, without further recourse to biologics.[15]

This study had several limitations. The retrospective design using medical chart review may have led to misinterpretation of data or missing information. However, data collection was performed by a single researcher, which conferred a standardized process. The small sample size, the impossibility of using a single clinical scale to evaluate remission, and the absence of a control group prevented comprehensive evaluation of the optimized therapy. Another study limitation is potential selection bias. The analysis included all patients whose thiopurine metabolism was optimized during the study period, but optimization was not attempted for several other shunters from the same period. The choice to optimize thiopurine therapy with an XOI depends on several factors that could influence decision-making by the attending physician and the patient. Given that thiopurine optimization is a potentially risky strategy, patients for whom optimization is planned must be carefully selected, with a view to reliability and adherence. This selection bias may have influenced the results of this study. Lastly, some patients needed multiple disease-modifying agents, which might have been a confounding factor, especially in contexts where optimal 6-TGN targets for diseases other than IBD have not yet been defined.

The main strength of this study was the heterogeneous study population with severe diseases, which was representative of real-world clinical practice in systemic autoimmune diseases.

CONCLUSION

This retrospective study has shown that optimizing thiopurine therapy with the addition of an XOI may be a safe and effective strategy for patients with systemic autoimmune diseases. More research is needed to confirm the clinical benefit and to determine the optimal 6-TGN targets in diseases other than IBD.

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Assessment of Canadian Hospital Pharmacists' Job Satisfaction and Impact of Clinical Pharmacy Key Performance Indicators

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ABSTRACT

Background: The clinical pharmacy key performance indicators (cpKPIs) are quantifiable measures of quality to advance clinical pharmacy practice and improve patient care. Although when delivered in combination they have been linked to important patient outcomes, no data are available relating to their impact on hospital pharmacists' job satisfaction.

Objectives: To determine the level of job satisfaction among Canadian hospital pharmacists and whether participation in cpKPI activities contributes to hospital pharmacists' job satisfaction.

Methods: A mixed-methods study was conducted. An electronic survey, consisting of 36 questions, was developed using a validated pharmacist job satisfaction tool and was then distributed nationally to hospital pharmacists between January 30 and March 14, 2019. Focus groups were conducted with pharmacists at Horizon Health Network in New Brunswick to further explore activities that contribute to their job satisfaction.

Results: Overall, 284 pharmacists from 9 provinces completed the electronic survey. The mean job satisfaction score among hospital pharmacists was 3.93 (standard deviation 0.85) out of 5. Job satisfaction scores increased with increases in self-identified time spent performing cpKPI activities ($r = 0.148$, $p = 0.014$). Pharmacist satisfaction increased with time spent performing medication reconciliation on admission ($\beta = 0.140$, $p = 0.032$) and decreased with time spent identifying and resolving drug therapy problems ($\beta = –0.153$, $p = 0.030$). Three focus groups, comprising a total of 13 pharmacists, were conducted; during these sessions, some cpKPIs were highlighted favourably, although pharmacists described some ambivalence toward patient education. The importance of having an impact and receiving appreciation was highlighted.

Conclusions: Canadian hospital pharmacists are generally satisfied with their jobs, and participation in cpKPI activities was found to be positively associated with hospital pharmacists' job satisfaction.

Keywords: clinical pharmacy key performance indicators, job satisfaction, medication reconciliation, patient education, drug therapy problems

RÉSUMÉ

Contexte : Les indicateurs clés de performance de la pharmacie clinique (ICPpc) sont des mesures quantifiables de la qualité qui permettent de faire avancer la pratique en pharmacie et d'améliorer les soins du patient. Bien qu'ils aient été associés à des résultats importants pour les patients lorsqu'ils sont utilisés conjointement, aucune donnée concernant leur impact sur la satisfaction professionnelle des pharmaciens d'hôpitaux n'est disponible.

Objectifs : Déterminer le degré de satisfaction professionnelle des pharmaciens d'hôpitaux canadiens et noter si la participation aux activités liées aux ICPpc y contribue.

Méthodes : Une étude à méthodologie mixte a été menée. À l'aide d'un outil validé mesurant la satisfaction professionnelle du pharmacien, les investigateurs ont préparé une enquête électronique comprenant 36 questions, qui a été distribuée à l'échelle nationale aux pharmaciens d'hôpitaux entre le 30 janvier et le 14 mars 2019. Des groupes de travail comprenant des pharmaciens au Réseau de santé Horizon au Nouveau-Brunswick ont exploré plus en profondeur les activités qui contribuaient à leur satisfaction professionnelle.

Résultats : Globalement, 284 pharmaciens de neuf provinces ont répondu à l'enquête électronique. Le score moyen de satisfaction des pharmaciens d'hôpitaux était de 3,93 (écart type 0,85) sur 5. Les scores relatifs à la satisfaction professionnelle augmentaient lorsque le temps passé à faire des activités liées aux ICPpc augmentait ($r = 0,148$, $p = 0,014$). La satisfaction du pharmacien augmentait quand il passait du temps à faire le bilan comparatif des médicaments au moment de l'admission ($\beta = 0,140$, $p = 0,032$) et diminuait quand il devait déterminer et résoudre des problèmes de pharmacothérapie ($\beta = –0,153$, $p = 0,030$). Trois groupes de discussion comprenant 13 pharmaciens au total se sont penchés sur la question. Pendant leurs séances, ils ont mis en valeur certains ICPpc, bien que les pharmaciens aient décrit des ambivalences concernant les instructions données au patient. Ils ont aussi souligné l'importance d'avoir un effet positif et d'être apprécié.

Conclusions : Les pharmaciens d'hôpitaux canadiens sont généralement satisfaits de leur travail et la participation à des activités liées aux ICPpc est associée à leur satisfaction professionnelle.

Mots-clés : indicateurs de performance clés de la pharmacie hospitalière, satisfaction professionnelle, bilan comparatif des médicaments, éducation des patients, problèmes de pharmacothérapie

INTRODUCTION

Low job satisfaction among employees has been associated with lower overall life satisfaction, lower mental well-being, and poorer physical health.[1,2] In addition, job satisfaction of health care workers has been linked to their patients' satisfaction with care provided.[3] Poor job satisfaction has also been linked with employee absenteeism[4] and, among pharmacists, intentions to quit the profession.[5] Factors associated with increased job satisfaction of hospital pharmacists, as reported in the literature, include perceived importance of their job to patients, perceived skill utilization, personal allocation of time, increased time spent interacting with patients, female sex, and older age.[5-9] The extent of involvement in clinical activities—such as drug therapy monitoring, consulting with prescribers, and participation in medical team rounds—has also been positively linked to hospital pharmacists' job satisfaction in several studies in both the United States and Asia.[8,10-12] Job satisfaction is considered an important contributing factor to employee engagement.[13]

Key performance indicators are used in various industries as quantifiable measures of success.[14,15] The clinical pharmacy key performance indicators (cpKPIs) were developed in 2013 by a Canadian working group,[15] with the intent of having clinical pharmacists focus their patient care efforts on processes of care that have been demonstrated to affect important patient outcomes, such as hospital readmissions.[16] The 8 cpKPI activities are performing medication reconciliation on admission (including best possible medication history), participating in interprofessional patient care rounds, delivering pharmaceutical care, identifying and resolving drug therapy problems (DTPs), providing patient medication education during the hospital stay, providing patient medication education at discharge, performing medication reconciliation at discharge, and delivering all activities as a bundle of proactive direct patient care.[15] The cpKPIs have been endorsed by the Canadian Society of Hospital Pharmacists (CSHP),[17] and the extent of their implementation into practice has been studied.[18,19]

Despite the link of cpKPIs with relevant patient outcomes,[15] it remains to be determined how they are related to pharmacists' job satisfaction. The current study aimed to examine the level of job satisfaction among Canadian hospital pharmacists, to determine whether increased time spent performing cpKPI activities positively or negatively contributes to Canadian hospital pharmacists' job satisfaction, and to gather Canadian hospital pharmacists' perspectives on activities that contribute to their job satisfaction and whether this includes the cpKPI activities. Secondary objectives of this study were to determine whether Canadian hospital pharmacists' job satisfaction and cpKPI participation are further linked with gender, age, highest academic degree held, or number of hospital beds.

METHODS

An English-language survey, consisting of 36 questions, was developed using Opinio survey software (ObjectPlanet Inc) and distributed to licensed Canadian hospital pharmacists between January 30 and March 14, 2019. A survey invitation with link to the online survey was sent by email by the principal investigator (M.L.) to all pharmacists within Horizon Health Network, which is the largest of 2 health authorities in New Brunswick and the second-largest in Atlantic Canada. The survey invitation was also distributed through CSHP (specifically through the organization's provincial branches, e-newsletter, and Pharmacy Specialty Networks). Members of the CSHP cpKPI Collaborative were invited to distribute the email invitation to pharmacists within their respective health care institutions, in order to reach non-CSHP members. Survey questions covering demographic characteristics were used to ensure that potential participants met the inclusion criteria.

Job satisfaction was measured using a validated pharmacist job satisfaction tool originally developed by Barnett and Kimberlin.[20] This general pharmacist job satisfaction tool consists of 4 facet-free statements, 2 with positive wording and 2 with negative wording, with responses on a 5-point Likert scale.[20] Facet-free items measure an individual's global satisfaction with his or her job without referring to any particular aspect of the work; responses to this type of question may be used to draw conclusions about overall job satisfaction.[20] For questions relating to cpKPIs, the definition of each cpKPI was provided within the survey, using descriptions from the CSHP's cpKPI *Knowledge Mobilization Guide*.[17] For each cpKPI, participants were asked to report the proportion of patients under their care for whom they provided care related to the cpKPI, as well as the percentage of time spent performing that care in a typical week. Questions were adapted in part from a CSHP member survey conducted in fall 2017,[18] to allow comparisons with this survey.

Focus groups were conducted with licensed pharmacists at 3 sites within Horizon Health Network. All staff pharmacists were eligible to participate. Practice leader pharmacists, pharmacy managers, and pharmacy supervisors were excluded from participation to avoid perceived differences in authority and status. An email invitation was sent to eligible pharmacists at each site. Given the potentially sensitive topic of discussion (i.e., job satisfaction), the focus groups were conducted at a location outside the pharmacy department, to improve the likelihood that participants would contribute freely. The sessions were approximately 60 minutes in length and were facilitated by the principal investigator, who at the time of data collection was a pharmacy resident. The research objectives were reviewed with the participants at the start of each focus group. Field notes were completed by the principal investigator after each focus group to record any additional

thoughts regarding the session. Given the confidential nature of this research, focus group transcripts were not returned to participants for review.

Several measures were taken to maintain the trustworthiness of the research findings. To test the focus group guide, a pilot focus group was completed with a group of ineligible pharmacists (i.e., pharmacists in leadership roles). An employee of Horizon Health Network's Research Services Department was in attendance for both the pilot focus group and the first focus group, to provide further feedback and insight. The principal investigator had established relationships with some of the participants at the site where they were completing their residency; therefore, it was important to discuss observations with a neutral party (the Research Services employee) for the focus group conducted at that site.

This study was conducted in accordance with ethical standards and received approval from Horizon Health Network's Research Ethics Board (2018-2695). Survey participants were asked to confirm their consent before survey initiation. Focus group participants provided written informed consent to participate.

Data Analysis

Descriptive statistics were used to summarize all study variables. Job satisfaction was calculated as the average of the 4 items after reverse scoring of the negatively worded items, with any score above 3 indicating satisfaction. A bivariate correlation analysis was conducted to measure the association between total time spent performing cpKPI activities and pharmacists' job satisfaction. Lastly, linear hierarchical regression analysis was used to determine which cpKPI activities best predicted job satisfaction. Variance associated with demographic (i.e., gender, age, education) and site (i.e., number of hospital beds as a proxy for hospital size) characteristics was controlled in step 1 of the regression analysis, and time spent performing each of the 7 cpKPI activities was then entered in step 2. The proactive direct patient care bundle was not included in the regression analysis because, by definition, it encompasses all other cpKPIs. The required sample size for the study was estimated to be 104 using the medium Cohen f^2 effect size of 0.15, α of 0.05, power of 80%, 7 tested predictors, and 11 total predictors.

Qualitative data were explored by means of thematic analysis. All focus groups were recorded and transcribed verbatim by the principal investigator. Transcripts were then analyzed independently by 3 members of the research team (M.L., S.M., H.N.) through application of a systematic analytic process of coding for theme development, with the help of Microsoft Word 2011 (Microsoft Corporation) and NVivo 12 for Windows (QSR International). Relationships between codes were identified, which led to generation of common themes illustrating the participants' experiences. Field notes were also analyzed as supporting data for the transcriptions.

RESULTS

Quantitative Results

In total, 284 pharmacists from across Canada completed the survey. Most respondents were female (76.4%, 217/284), and the mean age was 40 years (standard deviation [SD] 10.4 years). Respondents consisted mainly of staff pharmacists (i.e., pharmacists not in a leadership role) (74.6%, 212/284). Approximately half (52.5%, 149/284) of the respondents had completed either an Accredited Canadian Pharmacy Residency (ACPR) or a postgraduate PharmD, in addition to their entry-to-practice degree. The demographic characteristics of participants are fully reported in Table 1.

TABLE 1. Characteristics of Survey Participants

Characteristic	No. (%) of Participants[a] (*n* = 284)
Age (years) (mean ± SD)	40.0 ± 10.4
Gender	
Female	217 (76.4)
Male	65 (22.9)
Other	2 (0.7)
Highest level of education achieved	
Bachelor of Science in Pharmacy or entry-level PharmD	135 (47.5)
Accredited Canadian Pharmacy Residency program or postgraduate PharmD	149 (52.5)
Time in practice (years) (mean ± SD)	15.2 ± 10.9
Size of institution (no. of beds) (mean ± SD)	345 ± 238
Hospital type (*n* = 282)	
Teaching	192 (68.1)
Nonteaching	77 (27.3)
Pediatric	13 (4.6)
Province of pharmacy licensure	
Alberta	27 (9.5)
British Columbia	27 (9.5)
Manitoba	20 (7.0)
New Brunswick	35 (12.3)
Newfoundland and Labrador	15 (5.3)
Nova Scotia	44 (15.5)
Ontario	102 (35.9)
Prince Edward Island	4 (1.4)
Saskatchewan	10 (3.5)
Primary role	
Pharmacy resident	7 (2.5)
Staff pharmacist	212 (74.6)
Practice leader/coordinator	38 (13.4)
Pharmacy supervisor/coordinator	8 (2.8)
Pharmacy manager	19 (6.7)

SD = standard deviation.
[a]Except where indicated otherwise.

Mean job satisfaction was 3.93 (SD 0.85) out of 5, which indicates that pharmacists were generally satisfied in their jobs.

Correlation analysis revealed a significant relationship between pharmacists' job satisfaction and total self-reported time spent performing cpKPI activities, with job satisfaction increasing as the time spent performing these activities increased ($r = 0.148$, $p = 0.014$). Two of the cpKPIs were found to have statistically significant relationships with job satisfaction in the regression analysis, which controlled for various demographic and site characteristics. Pharmacists' job satisfaction increased with time spent performing medication reconciliation on admission ($\beta = 0.140$, $p = 0.032$) (Table 2). However, pharmacists' job satisfaction decreased as the time spent identifying and resolving DTPs increased ($\beta = -0.153$, $p = 0.030$) (Table 2). On average, respondents reported spending the largest proportion of their time identifying and resolving DTPs (Table 3). The average percentage of time spent performing each of the cpKPI activities and the percentage of patients under the pharmacists' care who received each type of care are reported in Table 3.

Male gender ($\beta = 0.150$, $p = 0.014$) and larger hospital size ($\beta = 0.151$, $p = 0.019$) were significant predictors of job satisfaction. No significant relationships were found between hospital pharmacists' job satisfaction and completion of a higher academic degree or age.

Qualitative Results

Three focus groups were conducted between January and March 2019. A total of 13 pharmacists participated, giving a response rate of 22% (13/59). Each focus group contained between 3 and 6 participants. Seven major themes were identified from the data: enjoyment of cpKPI activities, having an impact, supportive interprofessional team, ambivalence, sources of job dissatisfaction, pharmacists as medication experts, and community versus hospital pharmacy practice.

Enjoyment of cpKPI Activities

Pharmacists in all of the focus group discussions mentioned several cpKPI activities in a favourable manner, including medication reconciliation, participation in interprofessional patient care rounds, and development of pharmaceutical care plans. One pharmacist described interprofessional patient care rounds favourably by stating they enjoyed "influencing patient care from the start so at the bedside … being part of the medical team" (Participant A5). Another highlighted some benefits of medication reconciliation, saying that this activity "gives you that doorway to introduce yourself and to review their [i.e., the patient's] medications and explain what your role is and then that way, even if you're not going to be actively following the patient the whole time, they also know that there is a pharmacist available and it can open that opportunity for them to also reach out or to ask or seek the pharmacist if required" (Participant B2).

Having an Impact

Participants highlighted the importance of feeling like they are having an impact through their work: "I really like it when I feel like I've actually done something that is helpful" (Participant C3).

TABLE 2. Regression Analysis Predicting Job Satisfaction from Demographic Characteristics, Hospital Size (as Number of Beds), and Time Spent Performing Clinical Pharmacy Key Performance Indicator Activities

Model	Variable	Standardized β Coefficient	*p* Value
Step 1: $n = 262$ $R = 0.226$ $R^2 = 0.051$ Adjusted $R^2 = 0.036$ $F(4,257) = 3.5$, $p = 0.009$	Gender (female = 1, male = 2)	0.134	0.030
	Age	0.021	0.74
	Education	0.014	0.83
	No. of hospital beds	0.183	0.004
Step 2: $n = 262$ $R = 0.351$ $R^2 = 0.123$ Adjusted $R^2 = 0.085$ $F(11,250) = 3.2$, $p < 0.001$	Gender (female = 1, male = 2)	0.150	0.014
	Age	0.043	0.48
	Education	−0.011	0.87
	No. of hospital beds	0.151	0.019
	Medication reconciliation on admission	0.140	0.032
	Participation in interprofessional patient care rounds	0.124	0.08
	Completion of pharmaceutical care plan	0.078	0.29
	Identification and resolution of drug therapy problems	−0.153	0.030
	Patient education during hospital stay	0.111	0.17
	Patient education at discharge	−0.011	0.90
	Medication reconciliation at discharge	0.044	0.56

TABLE 3. Breakdown of Responses Relating to Clinical Pharmacy Key Performance Indicators (cpKPIs)

cpKPI Activity	Mean Time Spent (%)	Proportion of Patients Receiving cpKPI Care; % of Respondents[a]				
		None	1%–25%	26%–50%	51%–75%	76%–100%
Medication reconciliation on admission	17.5	19.1	23.0	11.7	9.9	36.4
Participation in interprofessional patient care rounds	18.6	20.5	17.3	12.7	11.3	38.2
Completion of pharmaceutical care plan	25.5	13.8	25.4	15.5	16.6	28.6
Identification and resolution of drug therapy problems	32.0	3.5	13.1	19.1	23.0	41.3
Patient education during hospital stay	10.1	13.5	58.0	14.9	8.2	5.3
Patient education at discharge	7.1	28.6	50.2	9.5	5.3	6.4
Medication reconciliation at discharge	7.2	35.0	31.1	8.1	12.7	13.1
Patient care bundle	NA	34.2	24.9	12.1	11.4	17.4

NA = not applicable.
[a]Data are shown as percentage of all respondents who reported provision of care related to each cpKPI to various proportions of patients under their responsibility. As such, under this spanner heading, the 5 values in each row sum to 100%.

Supportive Interprofessional Team

Participants described the importance of being supported within their work environment. In particular, they highlighted the importance of being part of an interprofessional team and having their input valued within this team: "It's always a good feeling when one of your recommendations is accepted" (Participant B2). Receiving appreciation for their work both from patients and from other colleagues was also highlighted: "And I think there's a real appreciation here for pharmacy too from other disciplines … and that helps with the satisfaction" (Participant A4).

Participants also described patient interactions favourably: "The patient relationships that you form … you get to know the patients really well and they ask about your family and you know their family and those kind of things and just the relationship you make with them" (Participant A4).

Participants stressed the importance of a supportive pharmacy team, which included pharmacy colleagues with whom to collaborate in different specialty areas, as well as supportive management. The expanded scope of pharmacy technicians was also discussed favourably, as it allowed pharmacists to further focus their patient care efforts.

Ambivalence

Participants shared contradictory opinions toward both patient education and documentation activities. Some pharmacists described enjoying patient education for reasons that included increasing patient understanding: "I think counselling on discharge is a big one for us because often there's a lot of medications involved and a lot of changes and if you're able to provide clarity for them then, it's not confusing when they're going home" (Participant A5). Pharmacists also valued the appreciation they received from patients when providing education: "I think patients … especially if there are multiple changes … they appreciate the overview because so much happens in hospital" (Participant B2).

However, other participants described education less favourably, for example, because they were unsure of the impact that the education was having: "You get that glazed look where you don't know if what you're trying to share is having any impact" (Participant C2). One pharmacist admitted feeling guilty about saying that patient education was not the favourite part of their job: "I know the education part should be what I should be saying [for most enjoyed patient care activity] but it's not that I don't enjoy it, it's just maybe not my top thing" (Participant C1).

Contradictory opinions also existed about documentation. Participants described a large time commitment required for proper documentation; however, some pharmacists did highlight the usefulness of good documentation.

Sources of Job Dissatisfaction

Participants described several work activities that they did not enjoy doing or felt were not a good use of their time or skill set, including dealing with medication coverage issues. Such issues often had associated paperwork. Pharmacists also described dispensary and order entry tasks less favourably. Other negative job factors described in the focus groups included duplication of work (e.g., redoing work that has been done improperly), technical and clerical tasks (e.g., triaging phone calls), and lack of time in the workplace to complete all the desired patient care activities.

Pharmacists as Medication Experts

The concept of pharmacists as medication experts was well described within the focus groups. Participants described the medication expertise of pharmacists and their

ability to answer drug information questions as strengths of hospital pharmacists.

Community versus Hospital Pharmacy Practice

A common theme arising within focus group discussions was the perception that hospital pharmacy practice had many benefits over community pharmacy practice. Pharmacists described feeling fortunate for their careers in the hospital, which allowed them to practise to their full scope: "I will say making the transition for me from community to hospital has made a difference in my job satisfaction and like the fulfilment that I get from work. Not to say that I didn't enjoy community because there's pros and cons of course to every avenue. I just feel like I'm able to use my skill set and my training more effectively in the hospital setting than I felt like I was in [the] community" (Participant B2).

DISCUSSION

Pharmacists in this study reported higher job satisfaction (3.93 out of 5) than hospital pharmacists in previously published international studies, in which job satisfaction scores, calculated with the same validated job satisfaction tool, ranged from 2.9 to 3.62 (specifically, 2.9 in a Japanese study published in 1998; 3.0 in a Hong Kong study published in 2011; 3.43 in a US study published in 1996; and 3.62 in an Australian study published in 2011).[8,10,11,21] In our study, job satisfaction increased with more self-reported time spent performing cpKPI activities, which aligns with previous literature showing similar associations between time spent performing clinical pharmacy activities and job satisfaction.[8,12] Of note, the previous job satisfaction studies were published between 1996 and 2011. The role of the hospital pharmacist has progressed significantly since the first of these studies was published, with advanced pharmacy practice roles leading to more time spent on clinical activities and less time performing traditional drug distribution activities.[22] We hypothesize that this shift may explain the increased job satisfaction rate reported by Canadian hospital pharmacists in our study.

Job satisfaction was found to increase with increasing time spent performing medication reconciliation on admission. In the focus group discussions, participants described this activity favourably, as it was the doorway to establishing a relationship with the patient. Previous literature has also shown an association between patient interaction activities and increased pharmacist job satisfaction,[5] which offers a potential explanation for the association that we found between time spent performing medication reconciliation and job satisfaction.

The finding of decreased job satisfaction with increased time spent identifying and resolving DTPs was surprising. Pharmacists who spend more time identifying and resolving DTPs may spend less time interacting with patients, which might account for this negative correlation with job satisfaction. A possible explanation for decreased patient contact could be that these responses reflect pharmacists who work primarily in the dispensary setting, where a negative association with job satisfaction has been previously reported in the literature,[21] or in non–direct patient care, where patient interaction would be more limited. Given that pharmacists reported spending the largest proportion of their time identifying and resolving DTPs, the negative association found in this study certainly warrants further investigation, and there may be some benefit to exploring further advances in automation to reduce time spent on this activity.

The ambivalence toward patient education described during the focus group discussions was also surprising. Despite providing an opportunity for patient interaction, patient education was not found to have a significant relationship with job satisfaction in the regression analysis. Previous literature has also presented conflicting findings regarding pharmacist involvement in patient education and its relation with job satisfaction.[10,11] Implementation of patient education remains low, with few respondents reporting the provision of education for 76%–100% of their patients, both during the hospital stay (5.3%) and at discharge (6.4%), a finding echoed in previous cpKPI implementation surveys.[18,19] Although ambivalence in focus groups may not necessarily be associated with job dissatisfaction, patient education represents 2 of the 8 cpKPIs, and this ambivalence coupled with low implementation cannot be overlooked. Facilitators of cpKPI implementation that have been reported in the literature include learning about the cpKPI initiative and seeing the benefit of the cpKPIs.[23] Although it is well documented that patients benefit from education provided by a pharmacist,[16] pharmacists in the focus group discussions identified uncertainties about the true impact of their educational efforts. Given that perceived job importance to patients is an important contributor to job satisfaction,[5] further education for pharmacists describing the benefits of patient education may therefore aid with both implementation and pharmacist job satisfaction in the provision of patient education.

The strengths of this study included it being the first to explore job satisfaction among Canadian hospital pharmacists and the first to explore the impact of participation in cpKPI activities on hospital pharmacists' job satisfaction. A validated pharmacist job satisfaction tool was used, which allowed for comparisons with previously published studies. The survey was distributed nationally, and responses were collected from across the country. The distribution of responses by province was similar to that seen in the 2017 CSHP member survey and included a higher proportion of staff pharmacists than did the 2017 survey,[18] suggesting

that our study encompassed a representative sample of front-line hospital pharmacists. Finally, this study's mixed methodology allowed for a more complete picture of hospital pharmacists' job satisfaction in relation to participation in cpKPI activities.

The limitations of this survey included the risk of response-related bias. Given the potential overlap between the primary research institution and the various CSHP distribution channels, as well as the unknown number of non-CSHP members reached, a denominator could not be determined and a response rate was therefore not calculated. However, using the total number of hospital pharmacists in Canada when this survey was distributed, the response rate might have been as low at 5% (284/6297).[24] As well, although an effort was made to reach pharmacists not belonging to CSHP, it is likely that most respondents were CSHP members (because the CSHP was one of the primary distribution channels), and levels of job satisfaction among members may not be representative of job satisfaction among nonmembers. The specifics of participants' job descriptions (percentage of dispensary versus clinical time) were also not explored. Survey and focus group responses may also have been limited because the survey tool and discussion guide were available only in English, and hospital pharmacists whose preferred language is not English may have been excluded. In addition, focus group responses may not have fully captured the perspectives of hospital pharmacists at smaller sites, given that the focus groups were completed at the 3 largest sites within Horizon Health Network (which were the most convenient sites for participant recruitment).

CONCLUSION

This study provides valuable insight into hospital pharmacists' job satisfaction, showing that Canadian hospital pharmacists were generally satisfied with their jobs. Job satisfaction was found to increase with total time spent performing cpKPI activities. A statistically significant increase in job satisfaction was seen with increasing time spent performing medication reconciliation on admission. However, satisfaction decreased with increasing time spent identifying and resolving DTPs. This information may be useful for hospital pharmacy management in the further implementation of cpKPI initiatives, as well as with recruitment and retention strategies. Areas for future research include further investigation of the negative association found between the identification and resolution of DTPs and hospital pharmacists' job satisfaction. As well, further study is warranted to explore the potential ambivalence of pharmacists toward patient education.

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Les médicaments qui interfèrent avec les bilans biologiques : revue de la littérature

par Imene Ben Jdidia, Kaouther Zribi, Meriam Boubaker, Amira Brahem, Mouna Sayadi, Marwa Tlijani, Zahra Saidani et Amani Cherif

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RÉSUMÉ

Contexte : Le bilan biologique fait partie intégrante du processus de diagnostic qui oriente les décisions de prise en charge thérapeutique. Cependant, ces analyses restent sujettes à des interférences endogènes ou exogènes qui altèrent le résultat.

Objectif : L'objectif de notre travail était de fournir un aperçu actualisé et complet des interférences les plus documentées dues aux médicaments, afin que l'interprétation des résultats soit fiable et la prise en charge du patient, meilleure.

Sources des données : Il s'agit d'une revue systématique exhaustive de la littérature réalisée en 2018. La recherche bibliographique a été réalisée dans différentes bases de données en ligne, à savoir Pubmed, ScienceDirect et Google Scholar.

Sélections des études : Seules les publications en français ou en anglais concernant les médicaments à usage humain ont été retenues. Les interférences avec les examens biologiques, dues aux médicaments, que les investigateurs ont étudiées, concernaient uniquement le dosage sanguin (sérum / plasma).

Extraction des données : Un tableur Excel a servi à exploiter les résultats. Au total, 82 articles ont été retenus. Les interférences étudiées touchaient 47 paramètres biologiques correspondant à différents bilans : bilan hormonal, bilan hépatique, bilan rénal.

Synthèse des données : Les mécanismes rapportés dans notre littérature étaient à 56,9 % d'ordre analytique, à 17,82 % d'ordre physiologique et à 20,11 % d'ordre pharmacologique. Le reste des mécanismes (5,17 %) n'étaient pas définis.

Conclusions : Les cliniciens devraient être vigilants lors de la validation et de l'interprétation des résultats d'un examen biologique pour les patients recevant ces types de médicaments. Enfin le dialogue clinico-biologiste est la meilleure garantie pour éviter des explorations complémentaires inutiles, souvent lourdes et coûteuses.

Mots-clés : médicaments; bilans biologiques; interférence avec les examens biologiques, due aux médicaments (*drug-related laboratory test interference* [DLTI])

Nota : Cet article comprend un document supplémentaire, disponibles à https://www.cjhp-online.ca/index.php/cjhp/issue/view/206

ABSTRACT

Background: Biological assessment is an integral part of the diagnostic process that guides therapeutic management decisions. However, these analyses remain subject to interference from endogenous or exogenous factors, which may alter the results.

Objective: To provide an up-to-date and comprehensive overview of the most commonly documented types of interference attributable to medications, to ensure reliable interpretation of test results and better management of patients.

Data Sources: This comprehensive systematic review of the literature was carried out in 2018. The bibliographic search was carried out in various online databases, specifically PubMed, ScienceDirect and Google Scholar.

Study Selection: Only publications in French or English concerning medicinal products for human use were retained. The investigators' examination of drug-related interference with laboratory tests was limited to blood assays (serum or plasma).

Data Extraction: An Excel spreadsheet was used to analyze the results. A total of 82 articles were selected. The interferences studied affected 47 biological parameters corresponding to various types of assessment: hormonal, hepatic, and renal.

Data Synthesis: The mechanisms reported in the literature identified were analytical (56.9%), physiological (17.82%), and pharmacological (20.11%). The remainder of the mechanisms (5.17%) were not defined.

Conclusions: Clinicians should be vigilant in validating and interpreting laboratory test results for patients receiving these types of drugs. Dialogue between clinicians and biological scientists is the best way to avoid unnecessary additional testing, which is often cumbersome and costly.

Keywords: drugs, biological assessments, drug-related laboratory test interference (DLTI)

INTRODUCTION

Les décisions de prise en charge thérapeutique en médecine humaine sont toutes orientées par une démarche diagnostique qui comprend plusieurs examens parmi lesquels le bilan biologique.

Soixante-dix pour cent des décisions médicales sont basées sur les résultats des examens biologiques du laboratoire et jouent un rôle de plus en plus important dans le parcours de soins[1].

À ce jour, environ 4000 tests biologiques différents ont été mis au point, dont des tests en hématologie, en biochimie, en bactériologie etc.[2]. L'amélioration de leurs performances, sensibilités, spécificités et reproductibilités se poursuit continuellement. Cependant, ces analyses restent sujettes à des interférences endogènes ou exogènes qui peuvent altérer le résultat, ce qui conduit à d'autres tests inappropriés, à des diagnostics erronés et à des traitements potentiellement défavorables pour le patient[3]. Les médicaments font partie des principales sources de ces interférences. La Food and Drug Administration a introduit aussi la notion de *Drug-related laboratory test interference* (DLTI) ou « interférence avec les examens biologiques, due aux médicaments »[2]. Malgré l'influence significative de plusieurs médicaments sur les résultats de certains paramètres biologiques, de nombreux cliniciens accordent peu d'importance à ces effets, puisqu'ils se concentrent uniquement sur l'intention thérapeutique du médicament[4].

Jusqu'à présent, la littérature rapporte plus de 40 000 DLTI. Néanmoins, peu d'études ont tenté de fournir un résumé global sur les données portant sur ce sujet.

Des revues systématiques de la littérature présentant une analyse des données seraient indispensables.

Dans ce cadre, l'objectif de notre étude est de fournir un aperçu actualisé et complet des interférences les plus documentées dues aux médicaments, pouvant servir de guide pratique pour les biologistes et les cliniciens afin qu'ils soient en mesure de faire une interprétation fiable des résultats et d'améliorer la prise en charge du patient.

MÉTHODES

Type de l'étude

Il s'agit d'une revue systématique exhaustive de la littérature, réalisée en 2018.

Recherche bibliographique

Les références bibliographiques présentant l'interférence des médicaments avec les bilans biologiques ont été répertoriées. La recherche bibliographique a été réalisée dans différentes bases de données en ligne, à savoir PubMed, ScienceDirect et Google Scholar. Seules les publications en français et en anglais concernant les médicaments à usage humain ont été retenues. Les DLTI étudiées concernaient uniquement le dosage sanguin (sérum / plasma). Les autres échantillons, tels que l'urine, ont donc été exclus de cette étude.

La stratégie de recherche suivante a été utilisée : les mots clés utilisés seuls ou combinés : *interference*, *interfering*, *interfere*, *drug*, *drugs*, médicaments, *drugs effects*, *laboratory tests*, *laboratory assays*, *renal function tests*, *thyroïd function test*, *analytical interferences*, *physiological interferences*.

La recherche électronique a été complétée par une sélection des articles trouvés.

Collecte et analyse des données

Dans un premier temps, l'utilisation d'un tableur Excel a permis l'exploitation de toute l'information pertinente décrite dans chacun des documents retenus. Les paramètres suivants de chaque médicament figurant dans le tableau ont été recueillis : dénomination commune internationale (DCI), le paramètre biologique dont le dosage est affecté, l'effet spécifique sur le dosage ou encore le sens de la variation (si disponible), le mécanisme de l'interférence ainsi que la méthode concernée et enfin la référence de cette information. La classe pharmacologique a été désignée selon l'usage thérapeutique du médicament.

Dans un deuxième temps, nous avons sélectionné les interférences qui ont été citées au moins trois fois, c'est-à-dire dans trois article différents.

RÉSULTATS

Au total, 82 articles ont été retenus, dont 56 % dataient de moins de cinq ans au moment de la revue. L'article le plus ancien datait de 1972 et le plus récent de 2018.

La littérature met à notre disposition de nombreuses références concernant les DLTI. Le nombre de publications consultées dans cette étude s'accroît de plus en plus au fil des ans, en particulier ces dernières années, comme le montre la figure 1 « Évolution du nombre des publications sur les interférences des médicaments avec les examens biologiques en fonction du temps ».

Soixante-neuf interférences ont été collectées et saisies sur le tableur Excel. Les DLTI étudiées touchaient 47 paramètres biologiques correspondant à différents bilans : bilan hormonal, bilan hépatique, bilan rénal, etc.

Les résultats sont exprimés dans le tableau 1 récapitulatif des DLTI analytiques les plus citées[1,2,5-84].

Les mécanismes les plus fréquemment impliqués

D'après notre étude, les médicaments peuvent avoir un impact sur les résultats des tests de laboratoire selon différents mécanismes. Ainsi, cet impact peut être d'ordre pharmacologique (ADME : absorption, distribution, métabolisme et excrétion). En effet, l'absorption de certains médicaments peut modifier les paramètres à analyser à travers le bilan biologique. À titre d'exemple, nous citons les inhibiteurs de l'enzyme de conversion qui modifient

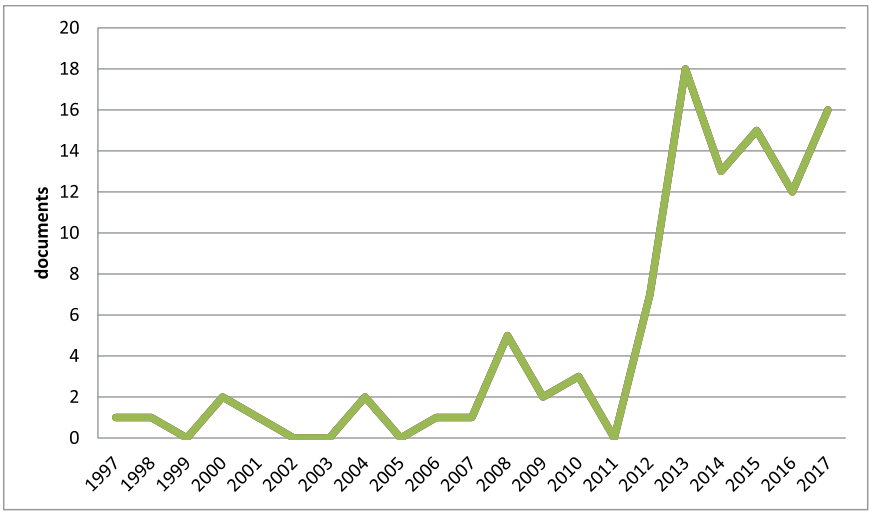

FIGURE 1. Évolution du nombre des publications sur les interférences des médicaments avec les examens biologiques en fonction du temps.

la glycémie, l'aldostéronémie, etc. Cette interférence est atténuée après l'excrétion du médicament en cause[8,10,83]. Un autre mécanisme consiste à modifier l'échantillon biologique testé (par exemple l'hémolyse dans le sang) : interférence physiologique. Certains médicaments interfèrent également directement avec le test lui-même en réagissant avec les réactifs du test : interférence analytique.

Les mécanismes rapportés dans notre littérature étaient les suivants : 56,9 % d'ordre analytique, 17,82 % d'ordre physiologique et 20,11 % d'ordre pharmacologique. Le reste des mécanismes (5,17 %) n'étaient pas définis.

Les médicaments qui risquent le plus d'interférer avec les tests biologiques

Les mécanismes des interférences des différentes classes médicamenteuses avec les bilans biologiques ont été rapportés dans le document supplémentaire (disponible au https://www.cjhp-online.ca/index.php/cjhp/issue/view/206)[1,2,5-12,14-43,45-84].

Les résultats des études bibliographiques relatives à ces interférences ont montré que les émulsions lipidiques administrées par voie intraveineuse (IV) sont la classe de médicaments qui risque le plus d'interférer avec les tests de laboratoire par des mécanismes essentiellement d'ordre analytique, à savoir : interaction des particules de lipoprotéines avec les réactifs de dosage et présence d'excipients causant une réactivité croisée sur les méthodes de dosage de triglycérides lipases[6].

Les médicaments anti-infectieux se trouvent au deuxième rang des agents qui risquent le plus d'interférer avec les tests de laboratoire, les céphalosporines en tête de liste et particulièrement céfoxitine, céfuroxime, céfazoline et céfixime. Les tests qui risquent le plus d'être affectés par ces interférences sont les dosages de créatininémie et de glycémie[2].

Les médicaments du système nerveux (SN) figurent aussi parmi les principaux xénobiotiques impliqués dans les DLTI. Les agents antidépresseurs, anti-parkinsoniens et antipsychotiques étaient tous inclus dans la catégorie des médicaments du SN, car ils entraînent des changements dans le fonctionnement cérébral et entraînent des altérations de la perception, de l'humeur et/ou de la conscience. La détermination du fait qu'un patient réagit positivement à un médicament, tel que la phencyclidine, l'amphétamine ou les benzodiazépines, peut être influencée par d'autres médicaments du SN que prend le patient. Cette interférence s'explique par la similarité entre la structure des médicaments à base de phencyclidine, d'amphétamine et de benzodiazépines et les autres médicaments du SN ou de leurs métabolites. Le personnel de laboratoire et les cliniciens doivent garder à l'esprit cette possibilité d'interférence, car cela peut conduire à des conclusions incorrectes concernant la conformité.

Les produits de contraste sont une autre classe importante de médicaments qui interfèrent avec les tests de laboratoire. Un produit de contraste médical est une substance utilisée pour améliorer le contraste des structures ou des fluides dans le corps pendant l'imagerie médicale[1]. Les agents de contraste au gadolinium sont généralement utilisés en imagerie par résonance magnétique, tandis que les molécules d'iode organique sont les produits de contraste le plus couramment utilisés pour l'amélioration des méthodes d'imagerie à base de rayons X. Ces derniers, à cause de leur haute densité, peuvent augmenter la densité du plasma ou du sérum à tel point qu'elle dépasse celle des séparateurs de gel. Ils provoquent ainsi la formation d'une barrière de gel inappropriée dans les tubes sanguins, ce qui affecte la détermination des taux de protéines dans le sang quand on recourt à certaines méthodes[5].

L'impact des interférences médicamenteuses avec les bilans biologiques

Les interférences étudiées montrent l'existence d'un impact clinique des DLTI. L'acide ascorbique qui interfère

TABLEAU 1 : Tableau récapitulatif des interférence avec les examens biologiques, due aux médicaments (*drug-related laboratory test interference* [DLTI]) analytiques les plus citées[a]

Paramètres biologiques \ Médicaments	Emulsion lipidique I.V.	Aspirine	glucocorticoïde	acétaminophène	PCG	PCI	Triméthoprime	Céphalosporines	pénicillines	flucytosine	Rifampicine	Streptomycine	Spironolactone	Héparine	Méthyldopa	Chlorpromazine	Dopamine	Ac monoclonaux	Biotine	Acide ascorbique	hydroxycobalamine	Vitamine A	*N*-Acétylcystéine	mannitol
glucose		ND																						
créatinine																								
urée																								
acide urique																								
Protéines sériques	ND					ND								ND										
albumine																								
Cholestérol																								
LDL																		ND						
bilirubine																								
transaminases															ND									
FT4, FT3																								
TSH																								
FSH, LH																								
Stéroïdes sexuels																								
Cortisol																								
prolactine																								
phosphate																								
magnésium																								
potassium																								
calcium																								
fer																								
Gaz du sang																								
hémogramme																								
Tests de coagulation																								

FSH : hormone folliculo-stimulante ; FT3 : *free triiodothyronine* ou tri-iodothyronine libre ; FT4 : *free thyroxine* ou thyroxine libre ; LDL : lipoprotéine de basse densité ; LH : hormone lutéinisante ; ND : sens de variation non défini ; PCG : produits de contraste gadolinés ; PCI : produits de contraste iodés ; TSH : *thyroid-stimulating hormone* ou thyréostimuline.

[a]Case rouge : interférence positive ; case verte : interférence négative ; case rouge et verte : interférence positive et/ou négative ; case vide : pas d'interférence.

positivement avec la mesure de la glycémie par la plupart des dispositifs d'autosurveillance basés sur l'enzyme glucose oxydase ou glucose déshydrogénase en est un exemple. Kim et collab.[74] rapportent qu'à la suite de cette interférence, l'injection d'une dose élevée d'insuline a entrainé une hypoglycémie. Leur étude a montré également que les DLTI masquant une hypo/hyperglycémie sont menaçantes pour la vie et surtout quand il s'agit d'une fausse hyperglycémie.

Outre les conséquences cliniques, les DLTI sont capables d'engendrer un coût supplémentaire considérable en raison du traitement inapproprié des patients ou des investigations complémentaires. À titre d'exemple, le coût des réactifs consommés pour les essais répétés du dosage de la calcémie à la suite d'une suspicion d'interférence par le gadoversamide pour un seul échantillon est de 0,76 $, ce qui engendre un surcoût en terme de réactif estimé à 481 $ (633 × 0,76 $: 633 étant le nombre de fois où le test a été répété). Ainsi, le coût total des analyses supplémentaires de cette interférence était de 3 132 $ pour tous les échantillons traités pendant toute la période de l'étude[85].

DISCUSSION

L'évolution du nombre d'articles reflète l'intérêt de la recherche scientifique pour les DLTI et l'importance de cette problématique.

En effet, les interférences que produisent les médicaments sur les tests biologiques signifient que les résultats de laboratoire peuvent être faussés par un médicament qui interfère avec le test (par exemple, un résultat faussement positif ou négatif ne reflète pas précisément la quantité, la présence ou l'absence de la substance analysée).

Les interférences des examens biologiques en général engendrent un taux d'erreurs pouvant atteindre 40 %[62]. Lorsque des approches pour éliminer les substances qui produisent des interférences sont incorporées dans la méthodologie d'essai, le taux d'erreurs peut baisser jusqu'à 0,1 %[62]. Cependant, il n'est pas toujours facile de prévoir une interférence. On la découvre souvent fortuitement, comme dans le cas où les résultats se révèlent discordants par rapport au tableau clinique du patient.

La majorité des études publiées sur les DLTI mentionnent que la polymédication augmente le risque des interférences médicamenteuses. Une étude datant de 1998 a évalué l'interférence de divers médicaments sur des tests de laboratoire; le pourcentage de tests affectés par l'interférence était de 7 % lorsque le patient prenait un médicament, de 16,7 % lorsque le patient prenait deux médicaments, de 66,7 % lorsque le patient prenait trois ou quatre médicaments et de 100 % lorsque le patient prenait cinq médicaments[86].

Si une interférence n'est pas démasquée, les conséquences de résultats erronés peuvent être d'ordre clinique (l'impact varie d'un risque minime jusqu'à la perte de la possibilité de traiter ou à une thérapie inappropriée qui pourrait conduire à la morbidité ou à la mort), économique et même fausser les résultats de recherches cliniques (par la publication de conclusions erronées dans la littérature scientifique).

Les fabricants d'instruments et de réactifs et les développeurs de méthodes représentent la « première ligne » idéale permettant de détecter les DLTI potentiels. En effet, ils ont une connaissance approfondie des réactifs utilisés ainsi que des informations appartenant au fabricant, qui ne sont pas mises à la disposition des utilisateurs, mais qui pourraient aider à prévoir les interactions.

De plus, il serait possible de mettre en œuvre des évaluations standardisées des DLTI potentiels lors des essais cliniques.

Par ailleurs, on peut remédier à ces DLTI en mettant en place des protocoles particuliers pour certaines interférences connues et bien décrites. On cite l'exemple des produits de contraste qui peuvent interférer avec le dosage colorimétrique du zinc et de l'enzyme de conversion de l'angiotensine. Ce même produit peut aussi interférer avec la détermination de la créatinine par la réaction de Jaffe[39]. Etant donné que la demi-vie d'élimination des produits de contraste est habituellement inférieure à deux heures, les prélèvements sanguins devraient avoir lieu après cette période pour les patients ayant reçu ces composés à des fins diagnostiques. Il est également préférable d'opter pour des méthodes de dosage qui ne sont pas affectées par ce type d'interférences, du moins pour ces patients[36].

Il est aussi possible d'avoir recours à de nombreuses procédures pour réduire l'effet de l'interférence des émulsions lipidiques intraveineuses avec les bilans biologiques, à savoir : centrifugation à haute vitesse, utilisation d'agents clarifiants ou de solvants organiques et mesures spectrales à plusieurs longueurs d'ondes et emploi d'un réactif destiné à la clarification des échantillons riches en triglycérides en se liant aux chylomicrons et/ou VLDL qui est une lipoprotéine de très basse densité[18,26].

Il en est de même pour la classe des anti-infectieux, car ils peuvent interférer avec le dosage de la glycémie par la méthode réductimétrique. Cependant, cette méthode est de moins en moins courante dans les laboratoires d'analyses, en raison des interférences documentées ; ainsi, la quasi-totalité des études recommandent le dosage du glucose par des réactions enzymatiques à l'enzyme glucose oxydase ou à l'hexokinase[2,8].

En milieu clinique, l'enregistrement des DLTI nécessitera la prise en compte de l'historique détaillée et précise, ainsi qu'une amélioration du transfert des dossiers médicaux entre les établissements.

Il faut souligner auprès des patients l'importance de connaître et de fournir des informations complètes et précises sur leur médication. De même, le personnel de laboratoire doit s'assurer que ces informations ont été obtenues auprès de tous les patients, ce qui aiderait à prévoir les interférences potentielles.

CONCLUSION

Cette étude a montré que les émulsions lipidiques administrées par voie IV, les médicaments anti-infectieux, les médicaments du SN et les produits de contrastes tendent davantage à provoquer des DLTI. Ces médicaments représentent également la majorité des traitements utilisés dans les hôpitaux et les cliniques.

Par conséquent, la communication entre les différents acteurs, prescripteurs, pharmaciens, préleveurs et biologistes permet la transmission de renseignements pouvant améliorer le jugement de la cohérence clinico-biologique du résultat de l'examen prescrit. Dans ce contexte, un dialogue clinico-biologique bien conduit permettrait de suspecter une interférence possible.

Comme il est impossible de se souvenir de toutes les interférences *in vitro, in vivo* pour chaque paramètre biologique, une base de données en ligne, la notification automatisée des résultats de laboratoire et le dossier médical électronique sont des stratégies nécessaires qui devraient être mises en œuvre dès que possible pour limiter l'impact clinique des DLTI.

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Hyponatremia Secondary to Decreased Oral Intake and SIADH and Possibly Exacerbated by Horsetail (*Equisetum arvense*)

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INTRODUCTION

Hyponatremia is defined as serum sodium less than 135 mmol/L and is the most frequent electrolyte abnormality in hospitalized and ambulatory patients.[1] Geriatric patients are especially vulnerable to hyponatremia, which occurs in 4% to 11% of these patients.[1] In up 14% of patients with hyponatremia, the problem may be drug-induced,[1,2] with thiazide diuretics being the most common cause of drug-induced hyponatremia.[1,2] Thiazide-associated hyponatremia most commonly occurs within the first few weeks of therapy but may develop months to years after initiation.[3] Several risk factors are associated with diuretic-induced hyponatremia, such as age, female sex, low body mass, and a low-sodium diet.[4]

The mechanism of drug-induced hyponatremia involves changes in the homeostasis of sodium and water. Drugs can affect water homeostasis by increasing the pituitary secretion of arginine vasopressin, thus potentiating the effect of endogenous hormone at the renal medulla and resetting the osmostat.[1,2] This results in a lower threshold for secretion of arginine vasopressin.[1,2]

Horsetail (*Equisetum*) is a plant native to Europe, North America, western Asia, and northwest Africa.[5,6] There are several different species of horsetail, including *E. arvense*, *E. bogotense, E. giganteum, E. hyemale*, *E. myriochaetum*, and *E. telmateia*.[5,6] Horsetail has traditionally been used in Europe as an oral diuretic for the treatment of edema.[5,6] The German Commission E expert panel has approved one specific species of horsetail (*E. arvense*) for this indication.[6] A small, double-blind, randomized placebo-controlled trial involving healthy male volunteers suggested that *E. arvense* has diuretic properties similar to those of hydrochlorothiazide.[7] The mechanism of action for diuresis is not entirely clear, but this effect may be attributable to flavonoids, phenolic compounds, and mineral constituents.[5,6] There is little clinical research evaluating the efficacy and safety of horsetail. When taken orally, horsetail has been reported to cause mild gastrointestinal side effects: abdominal distention, increased frequency of bowel movements, and nausea.[5] Horsetail has also been associated with seborrheic dermatitis, pancreatitis, liver failure, headache, and thiamine deficiency.[5,6]

We report a case of hyponatremia attributed to decreased oral intake and syndrome of inappropriate secretion of antidiuretic hormone (SIADH; due to nausea), possibly exacerbated by the diuretic effect of horsetail (*E. arvense*).

CASE REPORT

A 70-year-old woman presented to the emergency department with nausea and fatigue.* The patient had had decreased oral intake for 2 days before presentation. Her medical history included hypertension, hypertrophic cardiomyopathy, anxiety, and compression fractures of the thoracic spine. The patient's home medications included olmesartan 40 mg PO daily, zopiclone 7.5 mg PO at bedtime, amlodipine 10 mg PO daily, fluocinonide 0.05% cream daily as needed, and lorazepam 0.5 mg PO daily as needed. The only recent change in medication was an increase in the dosage of amlodipine, from 5 mg daily to 10 mg daily, which occurred 30 days before presentation. The patient stated that she had been taking natural supplements for approximately 10 years (Table 1). The patient reported that she did not drink alcohol or use recreational drugs and that she was a current smoker of approximately 40 years' duration. Six months before presentation, the serum sodium was 132 mmol/L.

The patient was 163 cm tall and weighed 56 kg. Her vital signs upon presentation were as follows: blood pressure 142/78 mmHg, heart rate 73/min, temperature 36.9°C, respiratory rate 18/min, and oxygen saturation 96% on room air. The physical examination showed very mild pitting edema to the ankles bilaterally. Other physical findings

*The patient gave informed consent to publish the case report.

TABLE 1. Natural Supplements before Admission

Product	Dose and Route
Apple cider vinegar 500 mg/chromium 2.2 µg	1 tablet PO daily
Vitamin K_2 120 µg/cholecalciferol 1000 units	1 tablet PO daily
Vitamin C 500 mg	1 tablet PO daily
Horsetail (*Equisetum arvense*) 15 mg	1 tablet PO daily
Multivitamin	1 tablet PO daily
Cholecalciferol 1000 units	1 tablet PO daily
Vitamin B_{12} 1000 µg	1 tablet PO daily
Kelp (iodide 553 µg)	1 tablet PO daily
Calcium carbonate 230 mg/magnesium 70 mg/vitamin D 200 units	2 tablets PO twice daily
Flax seed 1000 mg/α-linoleic acid 530 mg/oleic acid 137 mg/linoleic acid 120 mg	1 tablet PO daily

TABLE 2. Summary of Laboratory Values on Admission

Laboratory Parameter	Measured Value	Reference Range
Serum		
Sodium	113 mmol/L	133–145 mmol/L
Potassium	3.8 mmol/L	3.5–5 mmol/L
Chloride	82 mmol/L	98–111 mmol/L
Creatinine	47 µmol/L	40–100 µmol/L
Osmolality	236 mmol/kg	280–300 mmol/kg
Urine		
Osmolality	293 mmol/kg	> 100 mmol/kg[a]
Sodium	81 mmol/L	> 30 mmol/L[a]
Morning cortisol	598 nmol/L	170–500 nmol/L
TSH	5.46 mIU/L	0.2–4 mIU/L
Free T4	16.5 pmol/L	10–25 pmol/L

TSH = thyroid-stimulating hormone.
[a]Suggests a diagnosis of syndrome of inappropriate antidiuretic hormone.

were unremarkable. The patient appeared euvolemic and did not have signs or symptoms of heart failure. The results of laboratory tests at the time of admission are presented in Table 2. The complete blood count and liver enzymes were normal. While in the emergency department, the patient received 0.9% sodium chloride at 75 mL/h for 7 hours.

The patient's herbal medications and amlodipine were held upon admission to hospital, and the olmesartan and zopiclone were continued. On day 1 of the admission, the patient received 2 doses of metoclopramide 10 mg IV for nausea. Her fluid intake was restricted to 1000 mL/day. On day 2, the patient felt much improved, as the nausea and fatigue had resolved. On day 3, sodium chloride was started (1 g PO twice daily). On day 5, the fluid restriction was discontinued. On day 6, the patient was discharged, at which time the serum sodium was 130 mmol/L (Figure 1).

The patient was instructed to discontinue the following medications: apple cider vinegar/chromium (this medication may cause hypokalemia and hyperreninemia), *E. arvense* (because this medication contributed to hyponatremia), and amlodipine (because of peripheral edema). The patient was instructed to continue sodium chloride at a reduced dose of 1000 mg PO daily. The patient's intake of fluid was not restricted at the time of hospital discharge. The patient was instructed to continue olmesartan 40 mg PO daily, zopiclone 7.5 mg PO at bedtime, and lorazepam 0.5 mg PO daily as needed. Approximately 30 days after discharge, the patient restarted the following products and medications: vitamin K_2 120 µg/cholecalciferol 1000 units 1 tablet PO daily; vitamin C 500 mg 1 tablet PO daily; multivitamin 1 tablet PO daily; cholecalciferol 1000 units 1 tablet PO daily; vitamin B_{12} 1000 µg 1 tablet PO daily; kelp (iodide 553 µg) 1 tablet PO daily; calcium carbonate 230 mg/magnesium 70 mg/vitamin D 200 units, 2 tablets PO twice daily; and flax seed 1000 mg/α-linoleic acid 530 mg/oleic acid 137 mg/linoleic acid 120 mg 1 tablet PO daily.

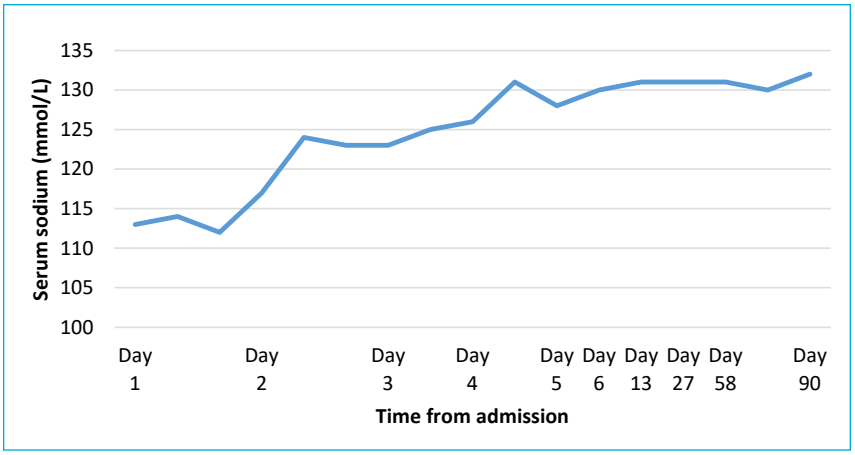

FIGURE 1. Summary of serum sodium. Note: The *y* axis is not linear.

DISCUSSION

The patient described here was euvolemic. The diagnosis of SIADH was suggested by the laboratory results, which showed serum osmolality less than 270 mmol/kg, urine osmolality greater than 100 mmol/kg, and urine sodium concentration greater than 30 mmol/L.[4] The patient was not hypothyroid and did not have adrenal insufficiency. It was thought that her low sodium was likely due to decreased oral intake and SIADH (the latter potentially triggered by nausea) and may have been exacerbated by *E. arvense*. The patient did not have so-called "tea and toast" induced hyponatremia, which may occur in elderly patients with low glomerular filtration rate, who follow a diet that is low in salt and protein combined with drinking large amounts of water.[8] Our patient had an estimated glomerular filtration rate of 55 mL/min and stated that she had been eating regular meals, except for the 2 days before admission, with no change in her fluid intake. In addition, the nausea had been present for only 2 days, which suggested that *E. arvense* may have contributed to the hyponatremia.

A literature search of PubMed, Google Scholar, Embase, and Reactions Weekly from inception to March 2020 using the search terms "horsetail", "hyponatremia", and the scientific names of several species of horsetail (*E. arvense*, *E. bogotense*, *E. giganteum*, *E. hyemale*, *E. myriochaetum*, and *E. telmateia*) yielded 3 citations[9-11] (Table 3). The dose, frequency, and duration of *E. telmateia* and *E. arvense* were not reported. In 1 case, hyponatremia developed after acute ingestion of an unknown species of homemade horsetail juice. Our patient had taken *E. arvense* 15 mg daily for 10 years and had lower serum sodium than 2 of the previously reported cases and higher serum potassium than all 3 of the previous cases. We suggest it may be possible for hyponatremia from *E. arvense* to

TABLE 3. Summary of Cases of *Equisetum* spp. Causing Hyponatremia

Ref	Age (yr)/ Sex	Medical History	Concomitant Medications	*Equisetum* Species	Presenting Symptoms	Laboratory Values	Treatment	Duration of Admission	Follow-Up
9	84/F	Hypertension	None	*E. telmateia*, dose and frequency not reported, duration 6 months	Falls, muscle weakness, lack of energy	SNa 120 mmol/L SK 2.3 mmol/L SCr 124 µmol/L UNa 34 mmol/L UK 11 mmol/L ADH 1.9 pmol/L UO and SO not reported	Management of hyponatremia and hypokalemia not reported; repeat SNa and SK not reported	Not reported	At 6 months, patient was asymptomatic with no electrolyte abnormalities
10	32/F	Not reported	Not reported	Unknown amount of homemade horsetail juice, species not reported Presentation 6 h after ingestion	Headache, lethargy, abnormal behaviour, tonic clonic seizure[a]	SNa 118 mmol/L SK 2.6 mmol/L SCl 85 mmol/L Glucose 10 mmol/L[b] SCr 43 µmol/L UO 702 mmol/kg UNa 68 mmol/L UK 84 mmol/L SO 240 mmol/kg TSH 1.4 mIU/L Free T4 20 pmol/L	Initially treated with 500 mL 0.9% NaCl and 14 mmol KCl After 28 h and 900 mL 2.5% NaCl, SNa was 134 mmol/L	5 days	At 12 days, patient had fully recovered
11	38/F	Not reported	Not reported	*E. arvense*, dose, frequency, and duration unknown	Presented with cardiopulmonary arrest[c] and generalized twitching	SNa not reported SK 2.8 mmol/L Low thiamine level (actual level not reported) Toxicology screen negative (details not reported)	Electrolyte and thiamine replacement (details not reported)	Not reported	Patient died

ADH = antidiuretic hormone, F = female, SCl = serum chloride, SCr = serum creatinine, SK = serum potassium, SNa = serum sodium, SO = serum osmolality, TSH = thyroid-stimulating hormone, UK = urinary potassium, UNa = urinary sodium, UO = urine osmolality.

[a]Computed tomography (CT) of the head showed diffuse cerebral edema, and the patient was transferred to the intensive care unit.

[b]Reference range for serum glucose 3.5–9 mmol/L.

[c]Cardiac catheterization performed for suspected cardiac cause showed that coronary arteries were normal. CT and magnetic resonance imaging/magnetic resonance angiography of the head excluded acute findings. CT angiography of the chest excluded pulmonary embolism, and the results of echocardiography were unremarkable.

develop after years of therapy, as may occur with thiazide diuretics.[3] Horsetail (species not reported) has been associated with serum sodium less than 116 mmol/L (n = 1) and less than 122 mmol/L (n = 3); however, details of these cases were not reported.[12] Two of the cases identified in our literature review involved young women[10,11] and one an elderly woman.[9] The patient in the current case report was a 70-year-old woman.

We have provided a more comprehensive case report than those identified by our literature search, with more information about the patient's past medical history; medication use; dose, frequency, and duration of the *E. arvense*; and hyponatremia treatment and 90-day follow-up. The hyponatremia was considered to be a possible adverse drug reaction to *E. arvense*, as assessed by the Naranjo adverse drug reaction probability scale (score of 4).[13]

CONCLUSION

We have reported a case of hyponatremia secondary to decreased oral intake and SIADH triggered by nausea, possibly exacerbated by the diuretic effect of *E. arvense*. However, the patient had decreased oral intake and nausea for only 2 days. Other causes of hyponatremia were excluded. It may be prudent for health care providers to monitor serum sodium levels within the first few weeks of starting *E. arvense* therapy and then at regular intervals, especially in elderly female patients with low body weight. More research is needed to assess the efficacy and safety of *E. arvense*.

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Se dresser contre l'injustice et travailler à la réconciliation dans le domaine des soins de santé

par Jody Ciufo, Zack Dumont, Tania Mysak, Shirin Abadi et Tamar Koleba

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Les récentes découvertes de tombes anonymes contenant des restes d'enfants sur le site d'anciens pensionnats autochtones ont profondément ébranlé les Canadiens et bien d'autres dans le monde. En tant que personnes, nous devons faire face à la violence et à l'injustice du colonialisme qui sévit dans ce pays et reconnaître le traumatisme intergénérationnel vécu par les survivants de ces pensionnats. Nous devons nous tenir aux côtés des peuples autochtones et prendre des mesures pour mettre un terme à la discrimination et à l'exploitation qui perdurent.

En tant qu'association professionnelle, comment la Société canadienne des pharmaciens d'hôpitaux (SCPH) peut-elle se dresser contre l'injustice et travailler en vue de la réconciliation dans le domaine des soins de santé? Ce travail commence par une reconnaissance de la complicité historique des systèmes de soins de santé canadiens, qui ont soumis des communautés autochtones, y compris des enfants dans les pensionnats, à des expériences et des tests médicaux contraires à la déontologie (https://academic.oup.com/pch/article/19/2/64/2647158) en matière d'interventions chirurgicales, d'administration de médicaments et de vaccins (https://www.cmaj.ca/content/193/11/E381).

Dans chaque province, l'horrible héritage du colonialisme se transmet aujourd'hui sous forme de racisme institutionnel dans notre système de soins de santé. En Saskatchewan, des femmes autochtones rapportent avoir été stérilisées de force pas plus tard qu'en 2019 (https://globalnews.ca/news/7920118/indigenous-women-sterilization-senate-report/). En 2020, Joyce Echaquan est décédée dans un hôpital du Québec après avoir filmé les maltraitances à caractère raciste de la part du personnel. En Colombie-Britannique, le rapport *In Plain Sight* de 2020 dévoile que 84 % des 9000 Autochtones participant à l'enquête avaient subi de la discrimination en accédant à des services de santé (https://engage.gov.bc.ca/app/uploads/sites/613/2021/02/In-Plain-Sight-Data-Report_Dec2020.pdf1_.pdf). Le racisme dans les soins de santé est omniprésent et mortel.

En tant que corps de professionnels de la santé, la SCPH se rend compte des graves préjudices qu'a causé – et que continue de causer – le système de soins de santé canadien aux peuples autochtones et aux personnes de couleur. Nous reconnaissons que la responsabilité de changer les systèmes et les institutions dans lesquels nous travaillons nous incombe. Le racisme qui sévit sur nos lieux de travail est inacceptable : les traumatismes, les maltraitances et les offenses doivent cesser.

Le conseil appelle les membres de la SCPH à se joindre à lui pour combattre le racisme systémique là où nous le rencontrons, qu'il se manifeste sous forme de traitement inéquitable des patients ou d'obstacles auxquels sont confrontés les pharmaciens membres des communautés de PANDC (personnes autochtones, noires et de couleur) pour faire progresser leur carrière. Ce travail revêtira un aspect différent pour chacun : suivre un programme de formation sur l'antiracisme, rapporter les discriminations que l'on observe et défendre la sécurité culturelle autochtone au moyen de l'humilité culturelle. Voilà des mesures importantes permettant de faire une différence significative (https://www.fnha.ca/wellness/wellness-and-the-first-nations-health-authority/cultural-safety-and-humility). Les appels à l'action de la Commission de vérité et réconciliation du Canada proposent d'autres voies pour améliorer la qualité des services de santé pour les Autochtones. Notons une meilleure reconnaissance des pratiques de guérison des communautés autochtones et une meilleure représentation des Autochtones au sein de la profession (https://ehprnh2mwo3.exactdn.com/wp-content/uploads/2021/04/4-Appels_a_l-Action_French.pdf).

Qu'elle soit modeste ou importante, chaque mesure prise contre le racisme systémique est importante. Au cours des mois à venir, la SCPH cessera d'utiliser le terme raciste « Syndrome de l'homme rouge » et rédigera des directives pertinentes portant sur la reconnaissance des termes destinées à la Société. Avec ces efforts apparemment modestes, nous nous engageons à amplifier et à placer la voix des membres des communautés autochtones au centre des débats. Simultanément, nous reconnaissons que les partenaires qui n'appartiennent pas à ces communautés doivent être des instigateurs du changement dans le cadre de leur travail. Nous espérons que vous ferez entendre votre voix et votre expertise auprès de notre communauté. Les membres qui souhaitent contribuer au travail de la SCPH pour lutter

contre le racisme sont invités à nous contacter à info@cshp.ca. Nous encourageons particulièrement les personnes ayant vécu une telle expérience à nous contacter si elles se sentent à l'aise de le faire.

En tant que professionnels de la pharmacie, les membres de la SCPH ont l'habitude de faire face à des problèmes complexes, de rechercher des données probantes rigoureuses et de défendre des personnes vulnérabilisées par notre culture. En travaillant ensemble, notre communauté est bien outillée pour lutter pour l'équité, et chacun de nous a un rôle à jouer pour que le racisme dans le système de soins de santé ne soit plus qu'un souvenir.

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Standing Against Injustice and Working Towards Reconciliation in Health Care

Jody Ciufo, Zack Dumont, Tania Mysak, Shirin Abadi, and Tamar Koleba

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The recent discoveries of unmarked graves with children's remains at former residential schools have shaken Canadians, and others around the world, to the core. As individuals, we must face the violence and injustice of colonialism in this country and recognize the intergenerational trauma of residential school survivors. We must stand with Indigenous peoples and act to end the ongoing discrimination and abuse.

As a professional association, how can the Canadian Society of Hospital Pharmacists (CSHP) stand up against injustice and work towards reconciliation in health care? This work begins with acknowledging the historic complicity of Canadian health care systems, which subjected Indigenous communities, including children in residential schools, to unethical medical experiments and testing (https://academic.oup.com/pch/article/19/2/64/2647158) for surgeries, drugs, and vaccines (https://www.cmaj.ca/content/193/11/E381).

In every province, the horrific legacy of colonialism continues in the institutional racism of our health care system today. In Saskatchewan, Indigenous women have reported experiencing coerced sterilizations as recently as 2019 (https://globalnews.ca/news/7920118/indigenous-women-sterilization-senate-report/). In 2020, Joyce Echaquan died in a Quebec hospital after filming staff's racist abuse. In British Columbia, the 2020 "In Plain Sight" report found that 84% of the 9,000 Indigenous people taking part in the investigation had experienced discrimination while accessing health services (https://engage.gov.bc.ca/app/uploads/sites/613/2021/02/In-Plain-Sight-Data-Report_Dec2020.pdf1_.pdf). Racism in health care is ubiquitous and deadly.

As a body of health care professionals, CSHP sees the grave harms the Canadian health care system has caused and continues to cause Indigenous peoples and people of colour. We recognize that we are accountable for changing the systems and institutions in which we work. The racism in our workplaces is unacceptable—the trauma, abuse, and indignity must stop.

The Board calls on CSHP members to join us in committing to fight systemic racism wherever we encounter it, whether it surfaces in the inequitable treatment of patients or in the barriers Black, Indigenous, or people of colour (BIPOC) pharmacists face in career advancement. This work will look different for each individual: completing an anti-racism training program, reporting discrimination when we see it, and advocating for Indigenous cultural safety through cultural humility are all important steps in making a meaningful difference (https://www.fnha.ca/wellness/wellness-and-the-first-nations-health-authority/cultural-safety-and-humility). The Truth and Reconciliation Commission's Calls to Action offers further ways we can work towards improving the quality of Indigenous health services, such as advocating for greater recognition of Indigenous healing practices and increasing Indigenous representation within the profession (https://ehprnh2mwo3.exactdn.com/wp-content/uploads/2021/01/Calls_to_Action_English2.pdf).

Large or small, every action against systemic racism matters. In the coming months, CSHP's next steps include working to eliminate from use the racist term "Red Man Syndrome," and creating meaningful land acknowledgement guidelines for the Society. In these modest efforts, we commit to amplifying and centring the voices of Indigenous members. At the same time, we recognize that non-Indigenous allies must be accountable for the work of creating change. We hope you will share your voice and expertise with our community. Members who wish to help shape CSHP's anti-racism work are invited to contact us at info@cshp.ca. Those with lived experience are especially encouraged to reach out if they feel safe and comfortable in doing so.

As pharmacy professionals, CSHP members are no strangers to facing complex challenges, seeking rigorous evidence, and advocating for and with those whom our culture makes vulnerable. Together, our community is well-equipped to fight for equity, and each one of us has a role to play in making racism in health care a relic of the past.

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