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British Columbia

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- Antipsychotic Agents for Elderly Inpatients (REPAIR Study)
- Analyse des modes de défaillance dans le circuit du médicament
- Safety Rounds
- Propofol-Induced Green Breast Milk

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The *CJHP* is an academic journal that focuses on how pharmacists in hospitals and other collaborative health care settings optimize safe and effective drug use for patients in Canada and throughout the world.

CJHP Vision

The aim of the *CJHP* is to be a respected international publication serving as a major venue for dissemination of information related to patient-centred pharmacy practice in hospitals and other collaborative health care settings in Canada and throughout the world.

Mission du *JCPH*

Le JCPH est une revue spécialisée qui traite principalement des moyens que prennent les pharmaciens pour optimiser l'utilisation sûre et efficace des médicaments dans les hôpitaux et les autres milieux de soins de santé misant sur la collaboration au Canada et ailleurs dans le monde

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The Value of Case Reports

Cynthia Jackevicius

In this issue of the *Canadian Journal of Hospital Pharmacy* (*CJHP*), we publish 2 unique papers, a case report on propofol-induced green breast milk, by Rainone and others,[1] and a case series on patients receiving ticagrelor and acetylsalicylic acid after placement of a Pipeline embolization device for cerebral aneurysm, by DeGrote and others.[2] Given that case reports and case series are found at the lower level of the "evidence hierarchy", one might question why the *CJHP* places value in publishing them.

Despite their subservience to randomized controlled trials in the evidence hierarchy, well-written case reports and case series play an important role in evidence generation and in clinical practice.[3] Case reports are categorized as patient-oriented research reports, which, by definition, include a description of some novel aspect related to a disease or therapy in one or more patient cases. In the absence of other evidence, case reports may thus provide valuable information to clinicians.[3]

Case reports may help with investigating new drug-related side effects, as does the report by Rainone and others[1] in this issue. A published case report may stimulate other clinicians to report similar cases, which may in turn prompt further investigations to more systematically evaluate a new hypothesis. By generating new hypotheses, case reports may also assist with the discovery of new diseases, therapeutic approaches, or indications for existing treatments. For certain special populations, case reports may initially constitute all of the available evidence, until postmarketing surveillance is conducted after completion of clinical trials or until larger observational cohorts are available, as for the case series described by DeGrote and others[2] in the setting of embolization procedures for cerebral aneurysm.

Case reports may also help us to understand how results from randomized clinical trials of typically healthier patients, with fewer comorbidities, translate to more diverse populations in real-world clinical practice. When we extrapolate research evidence beyond a clinical trial population, which often happens in our daily practice, unexpected results may occur. Case reports may be useful to help identify limitations in our extrapolations and raise awareness of potentially adverse consequences. They may also highlight the practical challenges of applying evidence to practice and may help to bridge the gap between evidence and practice, as did the case report on rivaroxaban use in a morbidly obese patient, previously published in this Journal.[4]

Who better than clinicians—who are the first to see how new therapies are being used and how patients respond to the new therapies—to share their valuable insights and experience in the medical literature through the use of case reports? Adverse reactions to new drugs may not be recognized until the postmarketing surveillance period, and it may be years before trends start appearing in the literature. It is vital for clinicians to contribute to the literature through case reports so that we can gain practical insights into the process of translating evidence to the real-world setting. Given that case reports can stimulate further research, we can acknowledge their contribution to the evidence base. Many professional organizations that develop guidelines, such as the American Heart Association, give case reports a lower ranking (e.g., level C evidence category), similar to that of clinical opinion. However, an objectively written, well-structured case report may actually constitute stronger evidence than subjective opinion.

Case reports may also provide an entry point into medical writing for junior clinicians. Therefore, it is important to also understand their limitations. By their nature, case reports have a small sample size, do not allow for blinding of participants and clinicians, and, because of their retrospective design, may be

missing relevant data that were not evaluated or documented in the medical record. Case reports cannot be used to infer causality or to calculate incidence or prevalence (because of lack of a denominator) and, most importantly, they have the potential to allow over- or mis-interpretation when the case is generalized to clinical practice.

A well-written case report should demonstrate critical thinking and logical reasoning, provide mechanistic insights, and tell a clear and compelling patient story. Many journals offer general information for authors on preparing case reports (including *CJHP*; see https://www.cjhp-online.ca/pages/files/AuthorInstructions.pdf), and some have published articles explaining how to write case reports. However, one study found that more than half of the 1316 emergency medicine case reports evaluated failed to provide essential information that would have increased transparency and replication, necessary attributes for research reports.[5] Given the inadequate quality of many published case reports, the CARE guidelines (which are similar to the CONSORT guidelines for reporting randomized controlled trials) have been developed to provide recommendations to standardize the publication of case reports.[6]

The CARE guidelines are based on a 13-item checklist for reporting cases, including a valuable visual timeline; they even encourage adding a patient perspective, where suitable.[6] The CARE guidelines are not specific for reporting cases of adverse drug reactions, nor do they recommend the inclusion of a causation algorithm (some journal-specific author guidelines for case reports do refer to causation algorithms). Although the Naranjo probability scale,[7] the most commonly used causation algorithm, represents an improvement over simple clinical judgment, its subjective nature limits its performance, and some questions have been raised about its reliability and validity.[8] No universally accepted method for assessing the causation of adverse drug reactions currently exists, and research is underway to develop new algorithms to assess the probability of adverse drug reactions, particularly in specialized settings.[9]

In recent years, publishing case reports has become a big business, with more than 150 journals now focusing on this area. A recent review showed that many of these are open-access journals with high acceptance rates, with about half having potentially questionable or predatory practices that raised concern among the investigators.[10] For a case report to become a valuable addition to the literature, it should be well written and published in a reputable, peer-reviewed journal. Therefore, authors considering publishing case reports must use due diligence in selecting the appropriate journal for their submission.

A fundamental tenet of evidence-based clinical practice is to use the best available clinical evidence, and at times, a case report or case series is the best available evidence to guide decision-making.[3] *CJHP* values case reports that contribute to the clinical evidence base and that may stimulate further investigations. Therefore, the Journal's editors welcome submission of high-quality case reports, which may represent important contributions to the literature.

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L'importance des observations cliniques

par Cynthia Jackevicius

Dans le présent numéro du *Journal canadien de la pharmacie hospitalière* (JCPH) sont publiés deux articles uniques : une observation clinique par Rainone et collab.[1] sur la coloration verte du lait maternel causée par le propofol et une série de cas par DeGrote et collab.[2] sur des patients ayant reçu du ticagrélor et de l'acide acétylsalicylique après la mise en place d'un dispositif d'embolisation Pipeline comme traitement pour un anévrisme cérébral. Comme les observations cliniques et les séries de cas se retrouvent au bas de l'échelle dans la hiérarchie des données probantes, l'on pourrait se demander pourquoi le JCPH trouve qu'il est important de les publier.

Bien qu'elles soient subordonnées aux essais cliniques contrôlés à répartition aléatoire dans la hiérarchie, les observations cliniques et les séries de cas bien rédigées jouent un rôle important dans la production de données probantes et dans la pratique clinique[3]. Les observations cliniques sont classées dans la catégorie des rapports de recherche axés sur le patient, ce qui, de par leur nature, inclut une description d'un aspect nouveau lié à une maladie ou à un traitement dans le cas d'un patient ou plus. En l'absence d'autres données probantes, les observations cliniques pourraient fournir de l'information importante aux cliniciens[3].

Les observations cliniques peuvent aider à l'étude de nouveaux effets indésirables des médicaments, comme le démontre l'article par Rainone et collab[1] dans le présent numéro. Une observation clinique publiée peut inciter les autres cliniciens à déclarer des cas semblables, ce qui peut alors mener à des recherches supplémentaires destinées à évaluer plus systématiquement une nouvelle hypothèse. En émettant de nouvelles hypothèses, les observations cliniques peuvent aussi faciliter la découverte de nouvelles maladies, de nouvelles approches thérapeutiques ou de nouvelles indications pour des traitements existants. Pour certaines populations spéciales, les observations cliniques peuvent, au départ, représenter l'ensemble des données probantes disponibles d'ici à ce que la pharmacovigilance ait lieu après la fin des essais cliniques ou d'ici à ce qu'une cohorte observationnelle de taille plus importante soit disponible, comme le décrivent DeGrote et collab[2] dans leur série de cas sur les procédures d'embolisation comme traitement pour l'anévrisme cérébral.

Les observations cliniques peuvent aussi nous aider à comprendre comment les résultats d'essais cliniques à répartition aléatoire de patients typiquement plus en santé, présentant moins de comorbidités, se traduisent chez des populations plus diverses dans la pratique clinique réelle. Lorsqu'on extrapole les données de recherches au-delà d'une population d'essai clinique, chose courante dans notre pratique quotidienne, des résultats inattendus peuvent apparaître. Les observations cliniques peuvent nous aider à distinguer les limites de nos extrapolations et nous sensibiliser aux conséquences indésirables potentielles. Elles peuvent aussi mettre en relief les difficultés concrètes de la mise en application de données probantes dans la pratique et elles peuvent aider à combler le fossé entre les données probantes et la pratique, comme le fit dans un précédent numéro l'observation clinique sur le rivaroxaban employé chez un patient atteint d'obésité morbide[4].

Qui de mieux placés que des cliniciens (qui sont les premiers à observer comment les nouveaux traitements sont employés et comment les patients réagissent à ceux-ci) pour faire part de leurs précieuses connaissances et expérience dans la littérature médicale par l'intermédiaire d'observations cliniques? Les réactions indésirables aux nouveaux médicaments pourraient ne pas être détectées avant la période de pharmacovigilance et il pourrait s'écouler des années avant de voir apparaître des tendances dans la littérature. Il est vital pour les cliniciens de contribuer à la littérature à l'aide d'observations cliniques pour que nous puissions ainsi acquérir des connaissances concrètes quant au processus nécessaire pour mettre en pratique des données probantes dans un contexte réel. Comme les observations cliniques peuvent stimuler la production de recherches ultérieures, nous pouvons admettre leur contribution au corpus de données probantes. Bon nombre d'organismes professionnels qui élaborent des lignes directrices, comme l'American Heart Association, accordent aux observations cliniques un score plus faible (par exemple, une catégorie de données probantes de niveau C), semblable à celui du jugement clinique. Cependant, une observation clinique bien structurée et rédigée objectivement pourrait en fait offrir des preuves plus fiables qu'un jugement subjectif.

Les observations cliniques peuvent aussi servir de premiers pas dans le monde de la rédaction médicale pour les cliniciens débutants. Or, il est important de connaître aussi leurs limites. De par leur nature, les observations cliniques s'appuient sur un échantillon de petite taille, elles ne permettent pas de garder les participants et cliniciens dans l'ignorance du traitement

administré et, en raison de leur plan rétrospectif, elles peuvent être privées de données pertinentes qui n'ont pas été évaluées ou consignées dans le dossier médical. Les observations cliniques ne permettent pas de déduire une causalité ou de calculer l'incidence ou la prévalence (en raison de l'absence d'un dénominateur) et, plus important encore, elles ont le potentiel de mener à des mésinterprétations ou à des surinterprétations lorsque le cas est généralisé à la pratique clinique.

Une observation clinique bien rédigée doit mettre en évidence un esprit critique et un raisonnement logique, offrir des connaissances mécanistes et raconter de façon claire et éloquente l'histoire du patient. Bon nombre de revues scientifiques donnent aux auteurs de l'information générale sur la préparation des observations cliniques (dont celle du JCPH consultable à https://www.cjhp-online.ca/pages/files/CJHPAuthorGuidelines_French.pdf) et certaines ont publié des articles précisant comment rédiger des observations cliniques. Or, une étude a permis de découvrir que plus de la moitié des 1316 observations cliniques en médecine d'urgence évaluées ne fournissaient pas les renseignements essentiels qui auraient accru la transparence et la possibilité de reproduction, des qualités nécessaires aux rapports de recherche[5]. Compte tenu de la qualité inadéquate de bon nombre d'observations cliniques, les lignes directrices CARE (semblables aux lignes directrices CONSORT pour la rédaction d'essais contrôlés à répartition aléatoire) ont été élaborées pour offrir des recommandations visant à normaliser la publication des observations cliniques[6].

Les lignes directrices CARE s'appuient sur une liste de contrôle comportant 13 éléments pour rendre compte de cas, dont une frise chronologique visuelle précieuse; elles encouragent même l'ajout de la perspective d'un patient, s'il y a lieu[6]. Les lignes directrices CARE ne sont pas spécifiques au compte rendu de cas de réactions indésirables aux médicaments; elles ne recommandent pas non plus l'ajout d'un algorithme pour l'évaluation de la causalité (cependant, certaines revues parlent d'algorithmes pour l'évaluation de la causalité dans leurs instructions aux auteurs concernant la rédaction d'observations cliniques). Bien que l'échelle de probabilité de Naranjo[7], l'algorithme pour l'évaluation de la causalité le plus souvent employé, soit préférable au simple jugement clinique, sa nature subjective limite sa performance. D'ailleurs, des questions ont été soulevées à propos de sa fiabilité et de sa validité[8]. Il n'y a actuellement aucune méthode universellement reconnue d'évaluation de la causalité des réactions indésirables aux médicaments et l'on cherche présentement à élaborer de nouveaux algorithmes permettant d'évaluer la probabilité d'apparition de réactions indésirables aux médicaments, particulièrement dans des contextes spécialisés[9].

Au cours des dernières années, la publication d'observations cliniques est devenue une affaire importante, avec plus de 150 revues scientifiques se concentrant sur ce domaine. Un examen récent a montré que bon nombre d'entre elles sont des revues en libre accès ayant des taux d'acceptation élevés et dont près de la moitié font preuve de pratiques potentiellement douteuses ou prédatrices qui ont soulevé des inquiétudes parmi les chercheurs[10]. Pour qu'une observation clinique puisse devenir un ajout précieux à la littérature, elle doit être bien rédigée et publiée dans une revue scientifique digne de confiance, révisée par les pairs. Ainsi, les auteurs qui désirent publier des observations cliniques doivent faire preuve de diligence raisonnable dans leur choix d'une revue appropriée pour leur manuscrit.

Un principe fondamental de la pratique clinique fondée sur des données probantes est l'utilisation des meilleures preuves disponibles et parfois une observation clinique ou une série de cas se révèlent les meilleures données probantes pour orienter la prise de décision[3]. Le JCPH accorde de la valeur aux observations cliniques qui enrichissent le corpus de données cliniques et qui peuvent pousser à mener d'autres recherches. Ainsi, les rédacteurs du Journal accueillent le dépôt d'observations cliniques de haut niveau qui peuvent représenter une contribution importante à la littérature.

[Traduction par l'éditeur]

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Ticagrelor and Acetylsalicylic Acid after Placement of Pipeline Embolization Device for Cerebral Aneurysm: A Case Series

Jodi R DeGrote, Elizabeth M Olafson, Alexander Drofa, Evgueni Kouznetzov, Michael Manchak, Nathan D Leedahl, and David D Leedahl

ABSTRACT

Background: Dual antiplatelet therapy with acetylsalicylic acid (ASA) and a P2Y12-receptor antagonist is often used to prevent thrombotic complications after placement of a Pipeline embolization device (PED) for cerebral aneurysm. Although clopidogrel is common in this setting, high rates of nonresponse to this drug have made ticagrelor a potentially attractive alternative.

Objective: To describe safety and efficacy outcomes for ticagrelor following PED placement, including measurement of platelet function.

Methods: A retrospective analysis of data was completed for patients who underwent PED placement for cerebral aneurysm at a single centre between November 2015 and March 2017, with subsequent prescription of ticagrelor and ASA as dual antiplatelet therapy. The primary end point was any ischemic stroke or death within 1 year after the procedure. Intracranial hemorrhage was a secondary end point. Additionally, measurement of and values for platelet reactivity units (PRUs) during receipt of ticagrelor and ASA were evaluated.

Results: A total of 29 patients were included in this retrospective study. One patient experienced ischemic stroke 226 days after placement of the PED. In addition, 3 patients died during the 1-year follow-up period for causes unrelated to stroke or bleeding complications. No cases of intracranial hemorrhage were observed. Samples for measurement of P2Y12 levels were drawn at the discretion of the neurointerventionalists, and the PRU value was measured at least once for 28 (97%) of the 29 patients. The mean number of PRU measurements per patient after initiation of ticagrelor was 2.1 (standard deviation [SD] 1). Mean PRU value after initiation of ticagrelor was 65 (SD 57).

Conclusions: In this case series describing the use of ticagrelor and ASA as dual antiplatelet therapy after PED placement for cerebral aneurysm, there was just one ischemic stroke, which occurred after the dual antiplatelet therapy had been discontinued. Further prospective trials are needed to describe the utility of ticagrelor use after PED placement, as well as its dosing and monitoring.

RÉSUMÉ

Contexte : Une bithérapie antiplaquettaire composée d'acide acétylsalicylique (AAS) et d'un inhibiteur du récepteur P2Y12 est fréquemment utilisée pour prévenir les complications thrombotiques après la mise en place d'un dispositif d'embolisation Pipeline pour traiter un anévrisme cérébral. Quoique le clopidogrel soit souvent utilisé dans ce contexte, des taux élevés d'absence de réponse à ce médicament ont fait du ticagrélor une solution de rechange potentiellement intéressante.

Objectif : Décrire les résultats relatifs à la sécurité et à l'efficacité du ticagrélor après la mise en place d'un dispositif d'embolisation, y compris l'analyse de la fonction plaquettaire.

Méthodes : Une analyse rétrospective de données a été réalisée dans un seul centre entre novembre 2015 et mars 2017 à l'aide des dossiers médicaux de patients chez qui a été posé un dispositif d'embolisation Pipeline comme traitement pour un anévrisme cérébral et à qui a ensuite été prescrite une bithérapie antiplaquettaire de ticagrélor et d'AAS. Le critère d'évaluation principal était les cas d'infarctus cérébral ou de décès durant l'année suivant l'opération. Les cas d'hémorragie intracrânienne ont servi de critère d'évaluation secondaire. De plus, l'analyse a porté sur l'évaluation de la réactivité plaquettaire et sa quantification en unités de réaction au P2Y12 pendant la prise de ticagrélor et d'AAS.

Résultats : Au total, 29 patients ont été admis à la présente étude rétrospective. Un patient a subi un infarctus cérébral 226 jours après la mise en place d'un dispositif d'embolisation Pipeline. De plus, 3 patients sont décédés au cours de la période de suivi d'un an en raison de causes sans lien avec des complications liées à un accident vasculaire cérébral ou à une hémorragie. Aucun cas d'hémorragie intracrânienne n'a été observé. Les échantillons destinés à la mesure des unités de réaction au P2Y12 ont été prélevés selon le jugement des neuro-intervenants et l'évaluation de la réactivité plaquettaire a été réalisée au moins une fois chez 28 (97 %) des 29 patients. Le nombre moyen de mesures des unités de réaction au P2Y12 par patient était de 2,1 (écart-type de 1). Après l'amorce d'un traitement par ticagrélor, le résultat moyen en unités de réaction au P2Y12 était de 65 (écart-type de 57).

Conclusions : Dans la présente série de cas décrivant l'utilisation d'une bithérapie antiplaquettaire composée de ticagrélor et d'AAS après la mise en place d'un dispositif d'embolisation Pipeline comme traitement pour

Keywords: ticagrelor, antiplatelet agent, neurointervention, Pipeline embolization device, flow diversion, dual antiplatelet therapy

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un anévrisme cérébral, seul un cas d'infarctus cérébral a été observé et il s'est produit après l'arrêt de la bithérapie antiplaquettaire. De plus amples études prospectives sont nécessaires pour décrire l'utilité et la posologie du ticagrélor ainsi que le suivi du traitement après la mise en place d'un dispositif d'embolisation Pipeline.

Mots clés : ticagrélor, antiplaquettaire, intervention neurologique, dispositif d'embolisation Pipeline, dérivation de flux, bithérapie antiplaquettaire

INTRODUCTION

The Pipeline embolization device (PED) (Medtronic, Minneapolis, Minnesota) is a flow diverter stent, which has offered substantial improvement in the management of complex aneurysms relative to conventional microsurgical and endovascular therapies. Flow diversion enhances aneurysmal occlusion and is associated with a lower rate of retreatment.[1] The benefits of this new type of stent are counterbalanced by the potential for severe thrombotic complications due to the increase in percentage of metal surface area. The decreased porosity of this flow diverter stent results in greater than 30% metal surface area (compared with < 10% for traditional intracranial stents) and may be responsible for the increased risk of in-stent thrombosis.[1]

Although the standard of care for patients receiving cardiac stents includes dual antiplatelet therapy, the best approach to antiplatelet therapy in the setting of neurovascular procedures remains unknown.[2] The combination of ticagrelor and acetylsalicylic acid (ASA) appears to be a safe and efficacious alternative to clopidogrel and ASA, most recently described by Moore and others.[3] To add to the growing body of knowledge in this area, we sought to complete a large case series, with 1-year follow-up, to describe ticagrelor use after PED placement for treatment of cerebral aneurysm. The objective was to describe safety and efficacy outcomes, including ischemic stroke, death, and intracranial hemorrhage. In addition, we described the measurement of and results for platelet reactivity units (PRUs) while patients were receiving ticagrelor and ASA.

METHODS

This retrospective, single-centre study was conducted at a 583-bed acute care facility located in North Dakota, USA, and included patients who received oral ticagrelor and ASA after PED placement in the setting of ruptured or unruptured cerebral aneurysm (November 2015 through March 2017). Patients were excluded if they had also received stent-assisted coiling or were less than 18 years of age. The investigation was approved by the Sanford Medical Center institutional review board, with a waiver of informed consent, and was performed in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments.

Potentially eligible patients were identified by querying the neurointerventional stent registry with the search terms "ticagrelor" and "Pipeline embolization device"; inclusion was validated by checking the ticagrelor prescription registry in the pharmacy department. The type of neurointerventional procedure and the administration of ticagrelor and ASA as dual antiplatelet therapy were confirmed using patient information collected via manual abstraction from the institution's medical records by 2 reviewers (J.R.D., E.M.O.).

Each PED had been placed by 1 of 2 neurointerventionalists (A.D., E.K.) at the institution, each of whom had endovascular neurosurgery fellowship training. The devices were placed in accordance with usual procedures, as outlined in neurointerventional radiology checklists. Given unpredictable platelet inhibition with clopidogrel,[4-6] ticagrelor (in combination with ASA) was the standard antiplatelet treatment at this institution. Patients who underwent elective PED placement generally received 5 days of combination therapy before the procedure, consisting of ticagrelor 90 mg twice daily and ASA 81 mg daily, followed by ticagrelor 90 mg twice daily and ASA 81 mg daily after the procedure. If stent placement was unplanned, single loading doses of ticagrelor 180 mg and ASA 325 mg were administered at the time of the procedure, followed by ticagrelor 90 mg twice daily and ASA 81 mg daily. Dual antiplatelet therapy with ticagrelor and ASA was continued until a follow-up appointment at 6 months after the intervention, when angiography was performed. If no complications (e.g., continued aneurysm filling or incomplete endothelialization) were identified, the ticagrelor was generally discontinued at that time.

The efficacy of antiplatelet therapy was assessed with the VerifyNow platelet inhibition assay (VerifyNow, San Diego, California). This assay was most commonly performed at 2 or 3 time points: 1–8 h after the 180-mg ticagrelor loading dose (for patients who received a loading dose), at the 6-month follow-up appointment, and at other times at the discretion of

the neurointerventionalist. If the PRU value measured at any of these time points was less than 70 and/or the patient was not appropriately tolerating dual antiplatelet therapy (as indicated by minor bleeding or other complications), the neurointerventionalist had the option to reduce the ticagrelor dosage to 60 mg twice daily.[7]

Demographic characteristics (age, sex, nature of procedure [elective or unplanned], size of aneurysm, location of aneurysm, number of stents placed, previous subarachnoid hemorrhage, smoking history) and results of platelet inhibition assays (measured in terms of PRUs) were collected for each patient.

The outcomes evaluated were ischemic stroke or death within 1 year after the procedure. Intracranial hemorrhage was a secondary end point. Ischemic stroke was defined as a documented focal neurological deficit, demonstrated by results of follow-up magnetic resonance imaging (MRI) that differed from imaging results before PED placement and associated with a change greater than 4 in scoring with the National Institutes of Health Stroke Scale that lasted for at least 24 h and was not attributable to delirium or encephalopathy.[8] Cerebral hemorrhagic complications were defined as new bleeding detected by computed tomography or MRI according to the same National Institutes of Health Stroke Scale score and time thresholds as the definition of ischemic stroke.[8] Two reviewers (J.R.D., E.M.O.) manually evaluated patients' electronic charts for documented complications. In addition, electronic medical records (EMRs) were queried with an electronic search function for the following keywords, to ensure full capture of data for stroke: "thrombus", "stroke", "infarct", "hemorrhagic", "hemorrhage", "bleed", and "blood".

Demographic data and results were analyzed using Microsoft Office Excel 2016 (Microsoft Corporation, Redmond, Washington), and descriptive statistics are reported here.

RESULTS

Between November 30, 2015, and March 20, 2017, a total of 34 patients met the initial inclusion criteria. Of these, 5 patients were excluded because they had undergone concomitant stent-assisted coiling, leaving a final sample of 29 patients. Of these patients, 10 (34%) were men, and the overall mean age was 61 years. Nine (31%) of the patients had a history of subarachnoid hemorrhage, and 19 (66%) had a history of smoking or were current smokers (Table 1).

All of the patients had undergone intracranial PED placement, and 18 (62%) of the procedures had been elective. For 25 of the 29 patients, 1 PED was placed, and for 4 patients, 2 PEDs were placed. The aneurysm size and location for each patient is described in Table 2.

One of the patients experienced an ischemic event during the 1-year follow-up period (Table 3). This event occurred on post-procedure day 226, after discontinuation of the dual antiplatelet therapy. More specifically, the ticagrelor had been stopped 196 days after PED placement, with continuation of ASA 81 mg daily; the patient confirmed adherence with the ASA therapy. In this patient, a single PED had been placed in the right internal carotid artery. MRI after the ischemic event showed complete occlusion of this artery, which resulted in small watershed infarcts in the right hemisphere.

Table 1. Demographic Characteristics of Patients Receiving Ticagrelor and ASA for PED

Characteristic	No. (%) of Patients* (*n* = 29)
Age, years (mean ± SD)	61 ± 13
Sex, male	10 (34)
Elective procedure	18 (62)
History of SAH	9 (31)
Smoker	19 (66)
No. of PEDs placed	
1	25 (86)
2	4 (14)

ASA = acetylsalicylic acid, PED = Pipeline embolization device, SAH = subarachnoid hemorrhage, SD = standard deviation.
*Except where indicated otherwise.

Three of the patients died (on post-procedure days 50, 70, and 313, respectively) for causes unrelated to neurologic or bleeding complication, specifically discontinuation of hemodialysis (with shift to palliative care), an unknown cause, and septic shock in an immunocompromised patient.

Overall, the patients continued ticagrelor therapy for a median of 196 days (interquartile range 184–215). The calculation of median ticagrelor duration was based on data for 27 of the 29 patients; for the other 2 patients, the discontinuation date could not be determined by chart review.

Samples for measurement of P2Y12 level were drawn at the discretion of the neurointerventionalists, and 28 (97%) of the 29 patients underwent at least one PRU measurement. The mean number of PRU measurements per patient was 2.1 (standard deviation [SD] 1). Among PRU values determined after initiation of ticagrelor, the mean was 65 (SD 57). Of the 28 patients for whom PRU level was measured, 21 had at least 1 PRU value less than 70. For 11 of the patients, the dosage of ticagrelor was reduced to 60 mg twice daily sometime during their therapy.

DISCUSSION

To the authors' knowledge, this is the largest case series, with the longest duration of follow-up, describing patients who received ticagrelor and ASA in the setting of PED placement for cerebral aneurysm. In this cohort of 29 patients, 1 patient experienced an ischemic event during the 12-month follow-up (after completing 6 months of post-procedure dual antiplatelet therapy). No cases of intracranial hemorrhage were observed.

Table 2 (Part 1 of 2). Detailed Information for Patients Receiving Ticagrelor and ASA for PED

Patient No.	Aneurysm Size	Location of Aneurysm	No. of PEDs Placed	Hemorrhagic or Thrombotic Complications	Death	PRU Value(s) Associated with Ticagrelor Administration	Ticagrelor Dosage Reduced to 60 mg BID
1	6.5 × 4.6 × 4.2 mm, with 3.93-mm neck	Left superior hypophyseal artery	1	None	Yes (time from procedure to death 70 days)	189	No
2	6 mm	Anterior communicating artery	1	None	No	9, 50, 7	No
3	8 × 5 × 5 mm with 6-mm neck	Right vertebral artery	1	None	No	85, 59, 91, 6	No
4	3.1 cm transverse × 2.8 cm	Basilar artery	1	None	Yes (time from procedure to death 50 days)	160	No
5	7.5-mm cavernous aneurysm and 1.3 × 3 mm blister-type aneurysm	Right internal carotid artery	2	None	No	9, 16, 6	Yes
6	9.5-mm fusiform aneurysm of carotid terminus, 4.1-mm fusiform aneurysm of the M1 segment	Left middle cerebral artery and terminus of left internal carotid artery	2	None	Yes (time from procedure to death 313 days)	118, 91	No
7	6 mm	Right posterior communicating artery	1	None	No	4, 8	Yes
8	2.87 × 1.7 mm blister type	Left internal carotid artery	1	None	No	235, 183, 69	Yes
9	7 mm × 10 mm	Right vertebral artery	1	None	No	31, 74	No
10	Previously treated aneurysm with increased filling of coil mass	Right superior cerebellar artery	1	None	No	185, 77, 61	No
11	5 mm	Anterior communicating artery	1	None	No	54, 14, 43	Yes
12	5.5 mm	Right internal carotid artery, cavernous	1	No hemorrhagic complications; one thrombotic complication (time from procedure to event 226 days)	No	7, 8	Yes
13	2 mm	Left internal carotid artery	1	None	No	80, 41	No
14	Previously treated aneurysm with recurrence	Left internal carotid artery	1	None	No	108, 19	No
15	14-mm aneurysm projecting from ophthalmic segment of right internal carotid artery; 1.6-mm carotid cave aneurysm; 2.1-mm dorsal wall blister aneurysm	Right internal carotid artery (multiple aneurysms)	2	None	No	68	No
16	3.3 × 3 mm, with 2.4-mm neck	Left ophthalmic artery	1	None	No	83, 52	No
17	2.2 mm, with 1.9-mm neck	Left internal carotid artery	1	None	No	71, 47, 75	Yes

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Table 2 (Part 2 of 2). Detailed Information for Patients Receiving Ticagrelor and ASA for PED

Patient No.	Aneurysm Size	Location of Aneurysm	No. of PEDs Placed	Hemorrhagic or Thrombotic Complications	Death	PRU Value(s) Associated with Ticagrelor Administration	Ticagrelor Dosage Reduced to 60 mg BID
18	7.7 × 9.1 mm	Left internal carotid artery	1	None	No	158, 110, 138	Yes
19	7.9 mm	Left internal carotid artery	1	None	No	15, 15, 24, 10	No
20	2.2-mm bilobular aneurysm	Left internal carotid artery	1	None	No	205, 20	No
21	4 mm	Right ophthalmic artery	1	None	No	79, 23	Yes
22	6.7 × 11 mm cavernous aneurysm, with 7-mm neck	Right internal carotid artery	1	None	No	124	No
23	8 mm, with 3.8-mm neck	Anterior communicating artery	2	None	No	79, 93	No
24	11 mm	Basilar artery	1	None	No	6, 28	No
25	6 mm	Posterior communicating artery	1	None	No	7, 8	Yes
26	6 × 4 mm	Right vertebral artery	1	None	No	No PRU values obtained	No
27	Wide neck (4.3 mm)	Left ventricular artery; across left posterior inferior cerebellar artery	1	None	No	4	No
28	1.5 mm	Right internal carotid artery (blister type)	1	None	No	20	Yes
29	3.8 mm	Right ophthalmic artery	1	None	No	73	Yes

ASA = acetylsalicylic acid, BID = twice daily, PED = Pipeline embolization device, PRU = platelet reactivity unit.

Table 3. Outcomes for Patients Receiving Ticagrelor and ASA after PED Placement

Outcome	No. (%) of Patients* (*n* = 29)
Ischemic stroke or death within 1 year	4 (14)
Intracerebral hemorrhagic complications within 1 year	0 (0)
Platelet function testing (after initiation of ticagrelor)	
Platelet function tested	28 (97)
No. of PRU measurements per patient (mean ± SD)	2.1 ± 1
PRU value (mean ± SD)	65 ± 57

ASA = acetylsalicylic acid, PED = Pipeline embolization device, PRU = platelet reactivity unit, SD = standard deviation.
*Except where indicated otherwise.

Overall, these findings are similar to those of another small, single-centre study. In their analysis comparing ticagrelor and clopidogrel therapy in 103 patients who underwent flow diverter placement for aneurysm, Moore and others[3] concluded that ticagrelor was safe and effective for prevention of thromboembolic complications. Similar to the study reported here, they did not observe any cases of intracranial hemorrhage during follow-up. Thrombotic complications occurred in 4.2% of patients in their ticagrelor cohort, similar to the observed thromboembolic complication rate of 3% in the current study. The average post-procedure follow-up period in the study by Moore and others[3] was 7.6 and 7.2 months in the clopidogrel and ticagrelor groups, respectively. Our study adds to knowledge about the utility of ticagrelor after PED placement by extending follow-up to 12 months after the procedure, by describing PRU data for all but one of the patients, and by including 11 patients whose dosage of ticagrelor was reduced to 60 mg twice daily (Table 2).

The interest in ticagrelor for patients who have undergone some form of neurointervention is largely attributed to the reported rate of nonresponse or hyporesponse to clopidogrel, which may be as high as 20% to 30%.[4-6] Furthermore, Adeeb and others[9] reported an alarming thrombotic complication rate in patients with nonresponse to clopidogrel, relative to those with response to clopidogrel, after PED placement (17.4% versus 5.6%; $p < 0.01$). At our institution, the use of ticagrelor after PED placement became the standard because of escalating concern about clopidogrel nonresponse and a desire to standardize care. Given the lack of robust clinical trials describing ticagrelor for this patient population, we continued to evaluate PRU levels in many of these patients, in an effort to assess bleeding risk and detect

opportunities to utilize a 60-mg twice daily dosing strategy (Table 2). This case series highlights a potential management strategy in the setting of highly variable practice in the United States, where it has been reported that up to 58% of facilities may not use ticagrelor, even for patients with nonresponse to clopidogrel.[10]

The PRU results for the patients in this case series prompt additional considerations for the clinician, since none of these patients would have met the criteria for "nonresponse".[11,12] Although a PRU range of 70 to 150 has been suggested as optimal to reduce hemorrhagic and thromboembolic complications,[7] the mean PRU value after ticagrelor administration was below this suggested range (65 [SD 57]). Indeed, the mean PRU value reported here implies that a portion of the values were below 60, a threshold that has been statistically associated with hemorrhagic complications after PED placement.[7] However, we did not observe any cases of intracranial hemorrhage in this patient population, despite some PRU values being less than this previously described target threshold. The absence of intracranial hemorrhage in this case series leads to additional consideration of whether PRU testing in these patients is valuable, and if so, what dosage of ticagrelor should be utilized at a defined PRU threshold. The neurointerventionalists at the study institution appreciated this risk and were able to reduce the dose of ticagrelor to 60 mg 2 times per day if the PRU was considered low and/or the patient was experiencing any minor bleeding.

This study had some limitations. Although we were able to describe patient scenarios that are common to hospitals where PED placement is performed, ours was a single-centre study with small sample size, which limits its generalizability. We cannot confirm any relation between our antiplatelet strategy and safety or efficacy outcomes. Data collection was performed retrospectively and depended on the accuracy and completeness of chart documentation. Although EMRs are integrated across 23 hospitals in our region of the United States, we cannot exclude the possibility that safety outcomes in some patients were managed by an outside facility. Finally, we did not assess certain common adverse effects of this medication combination, such as gastrointestinal bleeding.

CONCLUSION

In this case series describing the use of ticagrelor and ASA as dual antiplatelet therapy after PED placement for cerebral aneurysm, only one ischemic event was observed during the 1-year follow up, and this event occurred after dual antiplatelet therapy had been discontinued. No intracranial hemorrhage events were observed. Further prospective trials are needed to describe the utility of ticagrelor use after PED placement, as well as its dosing and monitoring.

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ON THE FRONT COVER

Garibaldi Provincial Park
British Columbia

The photograph on this issue's front cover was taken by Yvonne Huang while she was hiking up the rubble en route to the Black Tusk in Garibaldi Provincial Park. Yvonne is a Clinical Pharmacist at Surrey Memorial Hospital in Surrey, British Columbia. She used her iPhone to capture the image.

The *CJHP* would be pleased to consider photographs featuring Canadian scenery taken by CSHP members for use on the front cover of the Journal. If you would like to submit a photograph, please send an electronic copy (minimum resolution 300 dpi) to publications@cshp.ca.

ORIGINAL RESEARCH

Evaluation of Collaborative Medication Reviews for High-Risk Older Adults

Winnie W T Chan, Karen Dahri, Nilufar Partovi, Gregory Egan, and Vandad Yousefi

ABSTRACT

Background: Despite the widespread use of medication reviews, many older adults are still exposed to the risks of polypharmacy.

Objectives: To quantify and describe the drug therapy problems identified and interventions undertaken by pharmacists before and after implementation (on July 1, 2015) of collaborative medication review for high-risk older adult patients (> 80 years of age).

Methods: A retrospective single-centre pre–post cohort study was conducted between July 1, 2014, and July 31, 2016, to characterize the impact of collaborative medication reviews—consisting of a thorough medication review by a pharmacist and care conferences with the hospitalist and family physician—on prescribing patterns in an Acute Care for Elders unit. A standardized template was used to conduct medication reviews for the post-implementation group, whereas a chart review was conducted for the pre-implementation group. The primary outcomes were the number of drug therapy problems identified by the clinical pharmacists and the associated interventions by the pharmacists, which were categorized as clinical or compliance interventions. Secondary outcomes included the number of medications at discharge, the rate of hospital readmission within 30 days, and the length of hospital stay.

Results: A total of 137 patients were identified for inclusion in either the pre-implementation group (n = 70) or the post-implementation group (n = 67). After implementation of collaborative medication reviews, there were statistically significant increases in the mean number of drug therapy problems identified (p < 0.001), the mean number of interventions undertaken (p = 0.004), and the median length of hospital stay (p < 0.001). There was no difference between the 2 groups in the number of medications at discharge, the proportion of patients taking more than 5 medications at discharge, or readmission within 30 days.

Conclusion: At the study institution, implementation of a quality improvement program that included pharmacist-led medication reviews and collaborative care conferences involving community and hospital care providers helped to improve documentation by clinical pharmacists of potential medication-related problems and led to more interventions to optimize patients' medication regimens.

Keywords: geriatrics, senior or older adult, medication review, clinical pharmacists, intervention, polypharmacy

RÉSUMÉ

Contexte : Malgré l'utilisation répandue des revues des médicaments, bon nombre de personnes âgées sont encore exposées à des risques causés par la polypharmacie.

Objectif : Quantifier et décrire les problèmes pharmacothérapeutiques repérés et les interventions effectuées par les pharmaciens avant et après la mise en place (le 1er juillet 2015) d'une revue collaborative des médicaments chez les patients âgés (de plus de 80 ans) à haut risque.

Méthodes : Une étude de cohorte rétrospective avant-après menée dans un seul centre entre le 1er juillet 2014 et le 31 juillet 2016 dans le but d'offrir un portrait de l'influence des revues collaboratives des médicaments (qui se résument en une évaluation complète des médicaments par un pharmacien et des discussions sur les soins avec le médecin hospitalier et le médecin de famille) sur les habitudes de prescription dans une unité de soins de courte durée pour aînés. Un modèle standardisé a servi pour effectuer les revues des médicaments auprès du groupe d'après mise en place alors qu'une analyse des dossiers médicaux a été menée auprès du groupe d'avant mise en place. Les principaux critères d'évaluation étaient le nombre de problèmes pharmacothérapeutiques décelés par les pharmaciens cliniciens et les interventions connexes effectuées par les pharmaciens, qui ont été classées de type soit clinique soit conformité. Les critères d'évaluation secondaires comprenaient le nombre de médicaments au congé, les taux de réadmission dans les 30 jours suivant le congé et la durée du séjour à l'hôpital.

Résultats : Au total, 137 patients répondaient aux critères d'admissibilité pour le groupe d'avant mise en place (n = 70) ou pour le groupe d'après mise en place (n = 67). Après la mise en place des revues collaboratives des médicaments, on a observé une augmentation statistiquement significative dans le nombre moyen de problèmes pharmacothérapeutiques décelés (p < 0,001), le nombre moyen d'interventions effectuées (p = 0,004) et la durée médiane du séjour à l'hôpital (p < 0,001). Aucune différence n'a été remarquée entre les deux groupes quant au nombre de médicaments au congé, à la proportion de patients prenant plus de cinq médicaments au congé et au taux de réadmission dans les 30 jours suivant le congé.

Conclusion : À l'établissement où s'est déroulée l'étude, on a mis en place un programme d'amélioration de la qualité comprenant des revues des médicaments dirigées par des pharmaciens et des discussions sur les soins en collaboration avec des fournisseurs de soins communautaires et hospitaliers. Le programme a aidé à améliorer la consignation par les pharmaciens cliniciens de potentiels problèmes liés à la pharmacothérapie et a mené à un plus grand nombre d'interventions visant à optimiser la pharmacothérapie des patients.

Mots clés : gériatrie, aîné ou personne âgée, revue des médicaments, pharmaciens cliniciens, intervention, polypharmacie

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INTRODUCTION

In 2012, the American Board of Internal Medicine launched the Choosing Wisely Campaign to promote discussion between health care providers and patients to ensure that medical tests, treatments, and procedures were supported by evidence, were not duplicative, were free from harm, and were necessary.[1] To date, more than 70 medical specialty associations in the United States have joined the campaign to identify relevant tests and treatments in their areas of specialty that are overused and have limited clinical benefit.[1] The American Geriatrics Society, one partner in the Choosing Wisely campaign, has put forward the recommendation that providers should not "prescribe a medication without conducting a drug regimen review".[1]

Older adults tend to use more prescription and nonprescription medications than other age groups.[1] Polypharmacy, defined as the use of multiple medications, has been associated with increased inappropriate use of medications.[2] Older adults are also more prone to the adverse effects of medications, because of the pharmacokinetic and pharmacodynamic changes that occur with aging.[3] Medication reviews may help to identify unnecessary, ineffective, and unsafe medications, while uncovering the need for additional medications from which the patient might benefit. They can also help to identify the need for strategies to improve adherence, such as blister packaging or weekly dispensing. Medication reviews may be done differently at different institutions; however, they are typically carried out by pharmacists, who systematically review the medications that patients are taking to ensure that they are necessary, effective, and safe and that they are being taken correctly. Within the older adult population, a pharmacist's assessment of a patient's drug therapy during a medication review can help to identify medications on the Beers list, a list of potentially inappropriate medications to be avoided or used with caution in older adults in general or in those with certain comorbidities.[4] In addition to a medication review, a collaborative care conference involving the patient's family physician is thought to help improve continuity of care. In a cohort study of 105 patients who had at least one change in their drug regimen during a hospital stay, a clinical pharmacist followed up with each patient's general practitioner 4 to 5 months after discharge.[5] The study showed that 46.3% of the patients stopped a drug that had been started during their hospitalization, and 24.1% restarted a drug that had been discontinued during the hospital stay.[5] The reasons for these postdischarge changes were not documented, but the authors hypothesized that they were related to poor communication between hospital and community care providers.[5] Through the care conference, a patient's family physician can provide valuable input and can be informed of any medication changes, so that there will be appropriate postdischarge follow-up.

Despite the widespread use of medication reviews, the impact on clinical outcomes, such as hospital admissions and mortality, is unknown.[6] Medication reviews can be time-consuming, leaving many pharmacists unsure whether it is worthwhile to conduct them, given the apparent lack of benefit in terms of meaningful patient outcomes.[6] There is currently limited evidence concerning medication reviews and their effects on clinically important outcomes, with most studies being of short duration and underpowered for clinical outcomes. A systematic review of pharmacist-led medication reviews showed no significant effect on clinical outcomes, such as all-cause hospital admission or mortality, and only a slight reduction in the number of drugs prescribed.[6] However, the review authors included studies that took place in settings with limited multidisciplinary collaboration and younger patients, so the results may not be applicable to settings involving older adults where pharmacists work collaboratively with other members of the health care team. A Cochrane review evaluating the use of medication reviews for hospital inpatients showed that the type of medication review and the degree of pharmacist involvement did not affect outcomes such as all-cause mortality, all-cause hospital readmission, all-cause emergency department contact, and adverse drug events.[7] Given the limited evidence, the authors were unable to determine whether medication reviews were cost-effective, and given the short duration of follow-up, they could not identify any long-term effects on outcomes.[7] Other strategies that have been described to help improve prescribing for older adults include a collaborative team approach, as investigated in the study by Spinewine and others.[8] In that study, a clinical pharmacist conducted a medication review upon each patient's admission to the hospital's geriatric unit, collaborated with the multidisciplinary team to optimize pharmacotherapy, gave oral and written information on treatment changes for the patient, and provided written documentation for the patient's general practitioner at discharge. Significant reductions in overuse, misuse, and underuse of medications were observed, which could be attributed to the structured and collaborative approach.[8]

At the study institution, the Acute Care for Elders (ACE) units undertook an initiative in response to the Choosing Wisely recommendation concerning medication reviews. The objective of the current study was to quantify and describe the drug therapy problems identified and interventions undertaken by pharmacists before and after implementation of collaborative medication review for high-risk older adult patients. Various quality improvement outcomes were identified and compared between the pre- and post- implementation cohorts.

METHODS

This single-centre chart review involved patients admitted to either of 2 ACE units at a large urban tertiary care hospital between July 1, 2014, and July 31, 2016. The overall study population was subdivided according to the date when a new quality improvement program—collaborative medication review—was implemented (July 1, 2015): a pre-implementation group, for patients admitted between July 1, 2014, and June 30, 2015; and a post-implementation group, for patients admitted between July 1, 2015, and July 31, 2016.

The quality improvement program was based on a comprehensive medication review for each patient, within 48 h of admission, by the clinical pharmacist assigned to that patient's unit. The pharmacist reviewed the patient's preadmission medications, interviewed the patient or a caregiver, and determined whether any therapeutic issues existed with the patient's preadmission drug regimen. The pharmacist then contacted the patient's family physician by fax to notify the physician of the comprehensive medication review and to invite participation in a collaborative care conference with the clinical pharmacist and the hospitalist to discuss the patient's admission and drug therapy issues. If the family physician was unable to participate, documentation of the comprehensive medication review was shared with the physician by fax.

Patients eligible for collaborative medication review were older than 80 years of age and classified as being at high risk for readmission to hospital. At the study institution, high risk for readmission is assessed with the Readmission Risk Assessment Score (RRAS), a tool based on the LACE index (for length of stay, acuity of admission, Charlson comorbidity index, and number of emergency department visits in past 6 months).[9] A patient with a score of 10 or higher with the RRAS tool is considered to be at high risk for readmission to hospital. The age threshold was chosen on the basis of previous work by Hohl and others,[10] who showed that age over 80 years was associated with adverse drug events. In addition, before implementation of collaborative medication reviews, the previous monthly admission data for the units were reviewed to estimate the overall number of admissions that would meet the criteria for high risk of readmission. The age cutoff allowed for a reasonable number of patients to be systematically identified for collaborative medication review, without overburdening the clinical pharmacists. Patients were excluded if the medication review could not be completed within the first 48 h of admission. Possible reasons for a review not being completed included communication barrier with the patient and/or caregiver, transfer to another unit, anticipated discharge within 48 h, patient's request for a change to palliation, or patient's death. The same inclusion and exclusion criteria as described above were used to identify patients for the pre-implementation comparison group.

The primary outcomes were the number of drug therapy problems identified by the clinical pharmacists and the associated interventions by pharmacists, which were categorized as clinical or compliance interventions. The drug therapy problems were categorized according to the standardized definitions by Cipolle and others[11] (Table 1). Compliance interventions included preparation of a medication calendar detailing the prescribed medications, administration times, and instructions for the patient; initiation of a compliance aid such as blister packs or dosettes; counselling for the patient or caregiver; and medication management, which could include liaising with a community nurse or community pharmacist. The secondary outcomes were the number of medications at discharge, the proportion of patients taking more than 5 medications, and the number of medications on the Beers list of potentially inappropriate medications for older adults that patients were taking at the time of admission and discharge. Readmission to the same hospital within 30 days of discharge and length of hospital stay were also compared before and after implementation of collaborative medication review.

Baseline demographic characteristics collected for both groups included the following: age, sex, length of hospital admission, RRAS, living arrangements at home, medication compliance aids, number of comorbidities, and number of medications at the time of hospital admission. Comorbidity was defined as any chronic disease or condition identified by the physician in the course of obtaining the patient's medical history. For the post-implementation group, clinical pharmacists

Table 1. Standardized Definitions of Drug Therapy Problems*

Drug Therapy Problem	Definition
Drug without indication	Drug is being taken without clear indication
Indication without a drug	Patient has an indication for a drug but is not receiving it
Suboptimal dosing	Drug dose determined to be too high or too low
Wrong drug	Patient is receiving a drug, but it is not the most optimal drug for indication (e.g., calcium-channel blocker for hypertension instead of ACE inhibitor in a patient with diabetes mellitus)
Additional drug	Patient needs an additional drug for an indication
Adverse drug reaction	Patient is experiencing, or is at risk of experiencing, an adverse drug effect
Drug interaction	Medications are being taken together that have a clinically relevant interaction
Adherence issue	Patient is not adhering to medication (e.g., refusing, cannot swallow, forgetting to take)
Monitoring required	Drug therapy monitoring is required (e.g., renal function)
Duplicate therapy	Patient is receiving duplicate therapy for an indication

ACE = angiotensin-converting enzyme.
*Based on Cipolle and others.[11]

documented their assessments and interventions using a standardized medication review form (Appendix 1, available from https://www.cjhp-online.ca/index.php/cjhp/issue/view/187/showToc). On the form, the pharmacist can include a brief summary of the patient's reason for admission and any relevant medical history. The medication review and recommendation section of the template includes 4 columns for the following information: name of each drug, dose and frequency of the drug, indication for the drug, and the pharmacist's recommendation for the drug. For the post-implementation group, patients' health care records were reviewed for additional information not collected on the medication review form, such as discharge medications. For the pre-implementation group, no standardized documentation process was in place, so patients' medical charts were reviewed for pharmacists' entries about drug therapy problems and their recommendations. This information was then cross-referenced against the orders section of the medical chart to determine whether the recommendations had been carried out. Any verbal physician's orders that were recorded by the pharmacist were counted as a drug therapy problem and clinical intervention even if there was no accompanying chart note, on the assumption that there would have been a discussion with the physician before the verbal order was made. Interventions involving IV medications (e.g., vancomycin dose adjustment according to trough levels) were not counted, because the focus of this project was on home medications and the potential risks of polypharmacy. Any IV medications that a patient received in hospital would have been for an acute illness and would have been stopped or interchanged to an oral equivalent before discharge home. In addition, interventions such as adjustment of the dose or formulation of a medication to match manufacturer's availability (e.g., ciprofloxacin 400-mg tablet changed to ciprofloxacin 500-mg tablet) and therapeutic substitutions for equivalent hospital formulary medications (e.g., rabeprazole interchanged with pantoprazole) were not considered, because the pharmacist would have made such changes on the basis of product availability and hospital formulary to ensure continuity of care. Step-down from IV to oral antibiotic was considered an intervention because this change could facilitate a patient's discharge home.

For this retrospective study, only nonidentifiable information was obtained during the chart review, and patient consent was not required. Ethics approval for the study protocol was granted by the University of British Columbia Clinical Research Ethics Board, and operational approval was granted by Vancouver Coastal Health. All data were collected from the patients' medical charts by a single investigator (W.W.T.C.).

The data were entered into an Excel spreadsheet (Microsoft, Redmond, Washington) and analyzed using SPSS software, version 23.0 (IBM Corporation, Armonk, New York). Standard descriptive statistics were used to represent the baseline characteristics of both groups. Tests for normality were performed, and the mean or median was reported according to the distribution of the data. The independent-samples *t* test was used to compare the 2 groups in terms of mean numbers of drug therapy problems identified, interventions by pharmacists, medications at discharge, and medications from the Beers list at discharge. The χ^2 test was used to compare the proportions of patients receiving more than 5 medications at discharge and the rate of readmission to hospital within 30 days between the 2 groups. The Mann-Whitney *U* test was used to compare the median length of stay between the 2 groups. Two-tailed *p* values less than 0.05 were considered statistically significant for all comparisons.

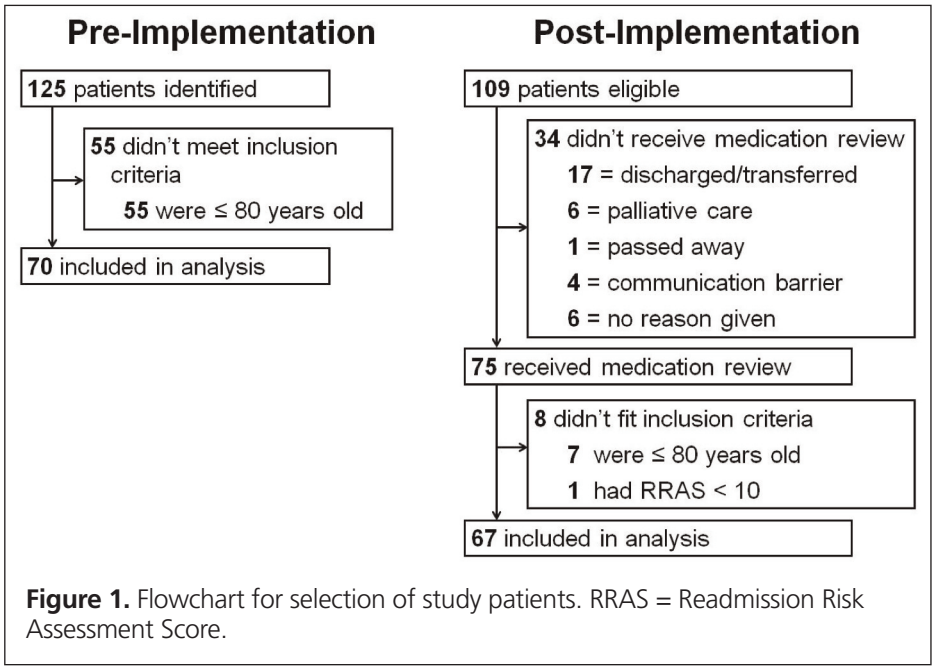

Figure 1. Flowchart for selection of study patients. RRAS = Readmission Risk Assessment Score.

Table 2. Baseline Characteristics

Characteristic	Study Group; No. (%) of Patients*		*p* Value
	Pre-implementation (*n* = 70)	Post-implementation (*n* = 67)	
Age (years) (mean ± SD)	88.1 ± 4.3	88.4 ± 5.1	0.75†
Sex, male	32 (46)	30 (45)	0.91§
RRAS (mean ± SD)	11.7 ± 1.4	11.5 ± 1.4	0.52†
No. of comorbidities (mean ± SD)	6.5 ± 2.7	6.5 ± 3.0	0.76†
Medications on admission			
No. of medications on admission (mean ± SD)	8.0 ± 3.5	8.3 ± 3.9	0.61†
No. of Beers list medications on admission (mean ± SD)	0.9 ± 1.0	1.0 ± 1.0	0.56†
No. (%) of patients taking > 5 medications	53 (76)	48 (72)	0.59§
Living arrangements before admission			
Home with family	26 (37)	21 (31)	0.47§
Home alone	10 (14)	17 (25)	0.10§
Care facility	17 (24)	10 (15)	0.17§
Home care	15 (21)	5 (7)	0.20§
Unknown	2 (3)	14 (21)	
Medication compliance aid			
Blister pack	13 (19)	33 (49)	< 0.001§
Vials	7 (10)	14 (21)	0.08§
Dosette	4 (6)	5 (7)	0.68§
Unknown	46 (66)	15 (22)	
Independence with medications			
Needs assistance	27 (39)	30 (45)	0.46§
Independent	19 (27)	27 (40)	0.10§
Unknown	24 (34)	10 (15)	

RRAS = Readmission Risk Assessment Score, SD = standard deviation.
*Except where indicated otherwise.
†By independent-samples *t* test.
§By χ^2 test.

RESULTS

A convenience sample of 137 patients was included in the study. During the pre-implementation period, 125 patients were admitted to the ACE units and were identified as being at high risk for readmission; 55 of these were excluded because their age was 80 years or younger, leaving a total of 70 patients in the pre-implementation group. During the post-implementation period, 109 patients were eligible, of whom 75 received a medication review; after exclusions based on age and RRAS score, 67 patients were included in the post-implementation group (Figure 1).

The mean age was 88.1 years (standard deviation [SD] 4.3 years) in the pre-implementation group and 88.4 years (SD 5.1 years) in the post-implementation group. Tests for significance were done for all baseline characteristics; blister packaging was the only characteristic with a statistically significant difference. The numbers of comorbidities, medications, and Beers list medications at the time of admission were similar (Table 2). In both groups, most patients had been living at home with their families. Patients' use of compliance aids and independence with medication administration (i.e., understands and can self-administer medications) were not well documented for the pre-implementation group and therefore could not be captured. About 49% of patients in the post-implementation group relied on blister packs, and 40% were independent with their medication administration.

In total, 67 drug therapy problems were identified in the pre-implementation group and 139 in the post-implementation group. There was a statistically significant increase in the mean number of drug therapy problems identified per patient after implementation of collaborative medication review (Table 3). The total number of documented pharmacist interventions increased from 58 (47 clinical, 11 compliance) for the pre-implementation group to 102 (64 clinical, 38 compliance) for the post-implementation group; however, considering the 2 categories of intervention, only the number of compliance interventions differed significantly between groups (Table 3). Among these compliance interventions, patient/caregiver counselling was the most common for the pre-implementation group and provision of a medication calendar was the most common for the post-implementation group (Table 4). The most common clinical intervention for both groups was discontinuation of a medication (Table 4).

In the post-implementation group, 20 of the 67 patients received a positive reply from their family physicians to participate

Table 3. Drug Therapy Problems and Pharmacist Interventions in Initial 48 h of Admission

Outcome	Study Group; Mean ± SD		*p* Value*
	Pre-implementation (*n* = 70)	Post-implementation (*n* = 67)	
No. of DTPs identified per patient	1.0 ± 1.3	2.1 ± 1.4	< 0.001
No. of pharmacist interventions per patient	0.9 ± 1.3	1.5 ± 1.5	0.004
Clinical interventions	0.7 ± 1.0	1.0 ± 1.1	0.12
Compliance interventions	0.2 ± 0.5	0.6 ± 0.8	0.001

*Independent *t* test; *p* values less than 0.05 were deemed significant.

Table 4. Interventions Performed by Pharmacists, in Relation to Study Group

Intervention	Study Group; No. (%) of Interventions*	
	Pre-implementation	Post-implementation
Clinical	*n* = 47	*n* = 64
Discontinue a medication	21 (45)	24 (38)
Add or restart a medication	10 (21)	8 (12)
Change medication or regimen	7 (15)	9 (14)
Dose titration	7 (15)	17 (27)
Monitor therapy	2 (4)	6 (9)
Compliance	*n* = 11	*n* = 38
Medication calendar	3 (27)	18 (47)
Initiation of blister packing	2 (18)	6 (16)
Initiation of PharmaCare special authority	1 (9)	1 (3)
Patient/caregiver counselling	4 (36)	9 (24)
Medication management (liasing with community nursing/pharmacy)	1 (9)	4 (11)

*The pre-implementation group had a total of 58 interventions; the post-implementation group had a total of 102 interventions.

in a care conference with the clinical pharmacist and hospitalist. However, the proposed care conference was conducted for only 15 of these patients, because of a last-minute cancellation by the family physician, the patient being discharged sooner than expected, or the patient being transferred to another facility.

There were no significant differences between the 2 groups in terms of number of medications or number of Beers list medications at discharge (Table 5). There was also no significant difference in terms of readmission to hospital within 30 days. Median length of stay was significantly longer for the post-implementation group than the pre-implementation group (14 versus 8 days).

DISCUSSION

This study showed that implementation of collaborative medication reviews and care conferences at the study institution led to a greater number of drug therapy problems being identified by the clinical pharmacists and a greater number of resulting interventions. However, no differences were seen in the number of medications (total and Beers list) at the time of discharge or the rate of hospital readmission within 30 days of discharge.

In a previous study, Spinewine and others[8] found that structured collaboration between the inpatient pharmacist and the interdisciplinary team reduced inappropriate medication use (misuse, underuse, and overuse of medications). The Choosing Wisely initiative introduced to the ACE units in this study attempted to go further by engaging each patient's community prescriber in a care conference to both gather collateral information about the patient's medical problems and ensure seamless care upon discharge from hospital. Kripalani and others[12] performed a systematic review to characterize types of communication and the prevalence of lack of communication between hospital and community care providers; they found infrequent communication between the 2 groups of care providers. For example, patients were often seen by their primary care physician before a detailed discharge summary had been transcribed and made available.[12] A care conference held during the patient's admission would ensure that community care providers are updated with the patient's progress. However, in the current study, it was difficult to engage family physicians to participate in the care conferences, with more than 70% opting to receive a faxed discharge summary. Unfortunately, the physicians did not provide reasons for declining to participate in care conferences, but time

Table 5. Secondary Outcomes, in Relation to Study Group

Outcome	Pre-implementation Group	Post-implementation Group	*p* Value
Medications at discharge	*n* = 60*	*n* = 57†	
No. of medications at discharge (mean ± SD)	8.7 ± 3.3	9.3 ± 3.7	0.30‡
No. of Beers list medications at discharge (mean ± SD)	0.8 ± 0.9	0.9 ± 0.9	0.31‡
No. (%) of patients taking > 5 medications	51 (85)	50 (88)	0.67§
	n = 62**	*n* = 58††	
No. (%) of patients with readmission within 30 days	10 (16)	5 (9)	0.33§
Median length of hospital stay (days)	8	14	< 0.001‡‡

SD = standard deviation.
*Does not include 8 patients who died before discharge and 2 whose documentation for discharge medication was missing.
†Does not include 8 patients who died before discharge, 1 whose documentation for discharge medication was missing, and 1 who was alive and still in hospital at the time of data analysis.
‡By independent-samples *t* test.
§By χ^2 test.
**Does not include 8 patients who died before discharge
††Does not include 8 patients who died before discharge and 1 who was alive and still in hospital at the time of data analysis.
‡‡By Mann-Whitney *U* test.

constraints are the most likely reason. It is the institution's goal to achieve a higher participation rate, and as such, we have been revising our communication tools to make it easier for family physicians to respond and indicate their availability.

Similar to what other researchers have found, this study showed that a collaborative medication review may be effective in identifying drug therapy problems. Although there was no difference in clinically important outcomes such as hospital readmission, the study was not powered sufficiently to evaluate this outcome. A comprehensive medication review would detect omission of necessary medications, which might have prompted prescribers to add a medication and may explain the lack of difference in the number of medications at discharge. This supposition is supported by the finding that the most common interventions were discontinuation of a medication and adding or restarting a medication. In a study in a nursing home setting, which involved a pharmacist-led medication review, Furniss and others[13] determined the number of interventions made by the pharmacist, finding that the most common pharmacist recommendation was to discontinue a medication. Their intervention resulted in a reduction in the number of medications prescribed, but there was minimal impact on morbidity and mortality.[13]

In the current study, the number of drug therapy problems identified was higher than the number of interventions by pharmacists in both the pre- and post-implementation groups. This result does not necessarily mean that pharmacists' recommendations were not accepted. Hanlon and others[14] noted significantly lower inappropriate prescribing scores when a clinical pharmacist was involved in seeing patients and working closely with the physician at an ambulatory care clinic. Physicians were also receptive to pharmacists' recommendations and made more medication changes than when they were working independently.[14] These findings contrast with those of the current study, likely because of the different study setting (ambulatory care versus acute care) and consequently different patient characteristics. Some drug therapy problems are less urgent than others, and an intervention may be made by the community care provider once the patient is medically stable. Some interventions may also be more suitable for the community setting because of the need for longer follow-up. This could also explain why there was no significant reduction in the number of Beers list medications upon discharge: a patient might be reluctant to stop taking a sedative for insomnia while acutely ill with pneumonia, with tapering by the family physician required at a later date.

This study had several limitations. Given its retrospective nature, the quality of data extracted relied on the documentation available in the hospital record and the clinical pharmacists' chart notes. The documentation was of better quality in the post-implementation phase, because standardized forms were completed during the pharmacists' medication review of each patient (Appendix 1). For the pre-implementation group, only about half of the patients had a clinical pharmacist note documenting the assessment and pharmaceutical care plan. It was particularly difficult to identify compliance interventions, as these were not routinely documented and (according to anecdotal information) were often made in the course of verbal interactions with the patient (e.g., patient/caregiver counselling). This situation contrasts with the post-implementation group, for whom compliance interventions were documented alongside the clinical interventions. Additionally, only one investigator conducted the data collection, so the collected data could not be assessed for authenticity. The analysis was also not adjusted for confounding

factors. For evaluating 30-day hospital readmission, the data were limited to one health authority site, and readmissions to other health jurisdictions might have been missed. The low frequency of care conferences might also have been a limitation, in that medication changes might not have been relayed to community care providers in a timely manner.

The increase in drug therapy problems identified by the pharmacist and in pharmacists' compliance interventions for the post-implementation group could simply be due to introduction of a standardized medication review form, which allowed for more consistent documentation. Before implementation of this quality improvement program, pharmacists independently determined whether a patient needed a medication review. If such a medication review was conducted and recommendations were made to the physician, it was up to the pharmacist's discretion whether any of this information was documented in the patient chart. The implementation of collaborative medication reviews did not require additional staffing on the ACE units. There were in-service sessions to inform the staff of this new program, and additional training was provided to pharmacists to assist them in using the standardized medication review form. Templates were also provided for conducting the care conference in a systematic way (including introduction of all participants, brief background on the patient, review of medications, and review of recommendations).

CONCLUSION

The implementation of collaborative medication reviews resulted in more drug therapy problems being identified and more interventions being undertaken by pharmacists. However, there is insufficient evidence to say whether the collaborative medication reviews benefited patients in terms of clinically important outcomes, such as hospital readmission and mortality. The results of this study indicate that the implementation of a structured medication review allowed for more consistent documentation by pharmacists, making it easier to identify their interventions. This documentation could be beneficial because it provides clear information for other health care professionals about the rationale for medication changes. With the eventual implementation of computerized documentation and order entry programs in institutions within our health care authority, the standardization of communication will become a forced function. In the interim, use of standardized documentation tools can help with communication between health professionals and can improve the ability to identify and solve drug-therapy problems.

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ORIGINAL RESEARCH

Safety of Rectal Administration of Acetaminophen in Neonates

Lori Chen, Monica Zhang, Jason Yung, Jennifer Chen, Carol McNair, and Kyong-Soon Lee

ABSTRACT

Background: On the basis of pharmacokinetic modelling, high-dose acetaminophen by rectal administration has been recommended for neonates needing antipyretic or analgesic therapy, but the safety and efficacy of this approach have not been established in vivo.

Objectives: The primary objective was to assess the safety of rectal acetaminophen administration for neonates, as indicated by changes in the results of hepatic and renal function tests. The secondary objective was to assess the efficacy of rectal acetaminophen administration in terms of the Premature Infant Pain Profile-Revised (PIPP-R) score.

Methods: This single-centre retrospective chart analysis was conducted in the neonatal intensive care unit at a quaternary care children's hospital. Neonates who received all prescribed doses of acetaminophen by continuous rectal administration for 24 h or more, from January 1, 2011, to December 31, 2012, were included. For the primary objective, hepatotoxicity was assessed in terms of changes in liver enzyme levels, and nephrotoxicity was assessed in terms of changes from baseline serum creatinine values.

Results: Twenty-five patients, who received a total of 27 courses of acetaminophen by rectal administration, met the inclusion criteria. Median gestational age at initiation of acetaminophen was 37.0 weeks (interquartile range 35.0–39.8 weeks). Values of alanine aminotransferase remained within normal limits during acetaminophen therapy for all but 3 patients, for whom the changes were attributable to confounding factors. Renal function remained unchanged. The secondary outcome of efficacy (based on PIPP-R score) could not be evaluated because of concurrent use of opioids for most patients.

Conclusions: Continuous rectal administration of acetaminophen over a short period (< 48 h) appeared to be well tolerated. The conclusions that can be drawn from these results are limited because of small sample size, the prescribing of doses lower than those recommended by the hospital's formulary, and limited blood sampling. Further studies are required.

Keywords: pharmacodynamics, neonatal intensive care unit, hepatotoxicity, nephrotoxicity, pain control

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RÉSUMÉ

Contexte : Selon une modélisation pharmacocinétique, des doses élevées d'acétaminophène administré par voie rectale ont été recommandées comme traitement antipyrétique ou analgésique chez le nouveau-né, mais l'innocuité et l'efficacité de cette modalité d'administration n'ont pas été établies in vivo.

Objectifs : L'objectif principal était d'évaluer l'innocuité de l'acétaminophène administré par voie rectale chez le nouveau-né en observant les changements dans les résultats des bilans hépatique et rénal. L'objectif secondaire était d'évaluer l'efficacité de l'acétaminophène administré par voie rectale à l'aide du score obtenu dans le *Premature Infant Pain Profile-Revised* (PIPP-R).

Méthodes : La présente étude rétrospective menée dans un seul centre comportait une analyse des dossiers médicaux de patients admis à l'unité de soins intensifs néonatals d'un établissement de soins quaternaires pour enfants. Les nouveau-nés ayant reçu toutes les doses prescrites d'acétaminophène par administration rectale ininterrompue pendant 24 heures ou plus, entre le 1er janvier 2011 et le 31 décembre 2012, étaient admissibles à l'étude. Pour l'objectif principal, l'hépatotoxicité a été évaluée en fonction des variations observées dans les taux d'enzymes hépatiques et la néphrotoxicité a été évaluée en fonction des changements observés dans la créatininémie par rapport aux valeurs de départ.

Résultats : Vingt-cinq patients qui ont reçu un total de 27 traitements par acétaminophène administré par voie rectale répondaient aux critères d'inclusion. L'âge gestationnel médian lors de l'amorce du traitement par acétaminophène était de 37,0 semaines (écart interquartile de 35,0 semaines à 39,8 semaines). Les valeurs d'alanine-aminotransférase demeuraient à l'intérieur des limites normales pendant le traitement par acétaminophène pour tous les patients à l'exception de trois pour lesquels les changements étaient attribués à des facteurs de confusion. La fonction rénale demeurait inchangée. Le critère d'évaluation secondaire quant à l'efficacité (s'appuyant sur le score obtenu dans le PIPP-R) n'a pu être évalué en raison de la prise concomitante d'opioïdes chez la plupart des patients.

Conclusions : L'administration rectale ininterrompue d'acétaminophène pendant une courte période (moins de 48 heures) semblait être bien tolérée. Cependant, les conclusions qui peuvent être tirées de ces résultats sont limitées en raison de la petite taille de l'échantillon, de la prescription de doses plus faibles que celles recommandées dans la liste des médicaments de l'hôpital et de l'insuffisance des échantillons sanguins. De plus amples études sont nécessaires.

Mots clés : pharmacodynamique, unité de soins intensifs néonatals, hépatotoxicité, néphrotoxicité, contrôle de la douleur

INTRODUCTION

Acetaminophen is a commonly used antipyretic and analgesic agent for neonates. Although the drug is relatively safe, its well-documented toxicity can lead to hepatotoxicity and death. Relative to adults, neonates and infants have lower activity levels of the cytochrome P450 2E1 isozyme, which means they have lower ability to form the toxic metabolites of acetaminophen and greater ability to form glutathione.[1] Nevertheless, these young patients are still able to form hepatotoxic metabolites to some degree, and the variable metabolism and clearance of acetaminophen in this population can still cause adverse effects.[2,3] Case reports exist of hepatotoxicity occurring in neonates and infants who received high doses of acetaminophen, although the problem resolved after treatment with *N*-acetylcysteine.[4,5]

Rectal administration of acetaminophen is used when enteral administration is not possible or when IV administration is unavailable. Rectal administration of acetaminophen in neonates is poorly studied, and appropriate dosing is unclear because of high variability in absorption and clearance, along with poor absorption overall, in neonates.[2,6,7]

Two efficacy studies have suggested that rectal administration of acetaminophen at daily doses of 40–80 mg/kg is insufficient to achieve an analgesic effect,[8,9] and some evidence suggests that higher-than-usual doses of acetaminophen (e.g., loading dose of 30–45 mg/kg and maintenance doses of 20–30 mg/kg) are required when the drug is administered rectally.[2,10]

In addition, several different formulations for rectal administration have been studied, including a diluted oral solution (to be administered rectally) and various types of suppositories, with widely differing pharmacokinetic parameters.[10] Most previous studies of this drug in neonates have been pharmacokinetic in nature and have not focused on adverse effects.

Dosing references list a wide range of possible doses for neonates. The optimal dosage of acetaminophen for rectal administration is unknown because of the limited number of studies and the significant variation in dosing and other practices that these studies describe.[2,10] At the authors' institution, the defined formulary approach to rectal dosing for neonates,[11] instituted in 2010, is based upon a pharmacokinetic paper by Anderson and others.[10] According to that paper, the maximum daily dose for rectal solution for term neonates (120 mg/kg) is substantially higher than that for infants and older children (80 mg/kg); this suggested maximum is based upon a single-dose study involving 5 preterm neonates. Furthermore, the dosing suggested by Anderson and others[10] has not been prospectively validated in neonates, and those authors stated that "these regimens may cause hepatotoxicity in some individuals if used for longer than 2-3 days."

The primary objective of this study was to assess the safety of rectal administration of acetaminophen in neonates at dosages of up to 120 mg/kg daily. The secondary objective was to assess efficacy.

METHODS

Study Design, Setting, and Patient Population

A retrospective chart analysis was conducted in the neonatal intensive care unit (NICU) at The Hospital for Sick Children (Toronto, Ontario), a level 4 nursery in a quaternary care children's hospital. No deliveries occur on site, and 40% of admissions involve a surgical condition. The study was approved by the SickKids Research Ethics Board.

All neonates who were admitted to the NICU from January 1, 2011, to December 31, 2012, and who had received acetaminophen were screened for inclusion in the study. Neonates (postmenstrual age ≤ 44 weeks) who received all prescribed doses of acetaminophen by continuous rectal administration for at least 24 h in the NICU were included in the study. Patients were excluded if their medication administration records were not available in the electronic chart, if they had not received acetaminophen by rectal administration, or if the route of administration was uncertain. At the study site, usual practice is to avoid excessive use of acetaminophen for patients with pre-existing hepatic or renal dysfunction, although limited doses may be used, with close surveillance, in select cases; hence, pre-existing hepatic or renal dysfunction were not considered as exclusion criteria.

Acetaminophen Doses for Rectal Administration

Acetaminophen was ordered for neonates according to recommended doses by gestational age (GA), based on the pharmacokinetic paper by Anderson and others[10]:

- GA < 30 weeks: not recommended for use
- GA 30–33 weeks: 20 mg/kg per dose q12h (40 mg/kg per day)
- GA 34–39 weeks: 25 mg/kg per dose q8h (75 mg/kg per day)
- GA ≥ 40 weeks: 30 mg/kg per dose q6h (120 mg/kg per day)

Data Collection

Eligible patients were identified using drug utilization reports in the pharmacy medication management system (BDM Pharmacy, BDM IT Solutions, Saskatoon, Saskatchewan). Specifically, a list of patients in the NICU for whom acetaminophen had been prescribed was generated by the BDM Pharmacy system. Data from study participants were collected from the electronic medical records.

Data were collected for the following characteristics:

- admission diagnosis
- patient age (GA at birth, postmenstrual age at acetaminophen initiation)
- weight (at birth, upon acetaminophen initiation)
- indication for acetaminophen (pain, fever, or both)
- surgical status (surgery performed within 7 days before acetaminophen administration)

- total number of acetaminophen doses
- doses, frequency, route, and duration of acetaminophen therapy
- daily and weekly data for liver enzymes (alanine aminotransferase [ALT], alkaline phosphatase, γ-glutamyl transferase, bilirubin) and renal function markers (serum creatinine, urea) at baseline, during acetaminophen therapy, and up to 3 weeks after the last day of acetaminophen administration
- pain, measured with the Premature Infant Pain Profile-Revised (PIPP-R) score,[12] at 12 h before and during acetaminophen administration
- name and duration of concurrent opioids, at 24 h before and during acetaminophen administration
- name and duration of concurrent nephrotoxic drugs received during acetaminophen use and hepatotoxic drugs received during and up to 3 weeks after acetaminophen use, with dosages of these medications being reviewed for any outliers

Study Outcomes

The primary outcome was the safety of rectal administration of acetaminophen, in terms of hepatotoxicity and nephrotoxicity. Hepatotoxicity was defined as the result of any liver enzyme test (ALT, alkaline phosphatase, γ-glutamyl transferase, conjugated bilirubin, or unconjugated bilirubin) exceeding the upper limit of normal, as defined by Chang and others.[13] Nephrotoxicity was defined as a relative increase in serum creatinine of 1.5 times or more from baseline.[14]

The secondary outcome was level of pain as measured by the PIPP-R score.

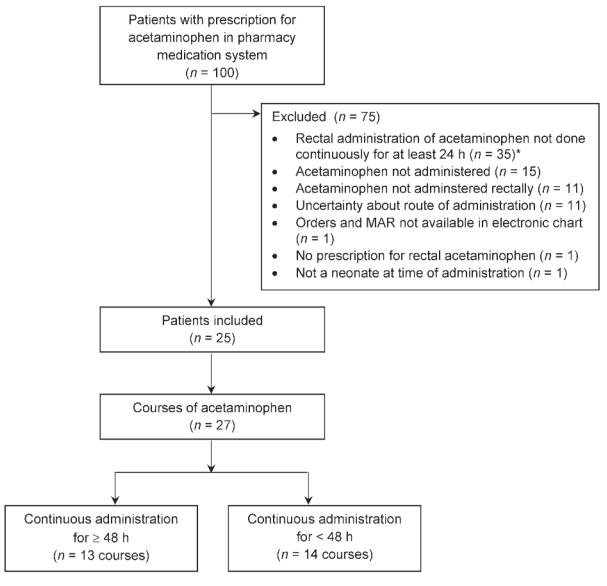

Figure 1. Patient enrolment. *Patients with acetaminophen therapy for less than 24 h were excluded because safety was the main end point, and patients receiving high doses for more than 24 h are thought to be at higher risk for toxic effects. MAR = medication administration record.

Statistical Analysis

Descriptive statistics were used to analyze the data for baseline characteristics and study outcomes. Available laboratory values at baseline and at 24 and 48 h after acetaminophen administration were analyzed. Descriptive statistics (minimum, maximum, median, interquartile range [25th to 75th percentiles], mean, standard deviation) are presented for all parameters with more than one value. Microsoft Excel (version 2007; Microsoft Corporation, Redmond, Washington) was used for the analyses.

RESULTS

A total of 100 patients received acetaminophen during the study period; however, only a total of 27 courses of acetaminophen, administered to 25 patients, met the inclusion criteria and were evaluated in the analysis (Figure 1). Most of the patients were girls, most were between 34 and 39 weeks GA at acetaminophen initiation, and 60% of the patients had a surgical admission diagnosis (Table 1).

Among the 27 acetaminophen courses, 26 (96%) were for pain, and 21 (78%) involved concurrent opioids. Total parenteral nutrition (TPN) was the most common potentially hepatotoxic treatment, and aminoglycosides were the most common potentially nephrotoxic medication. Overall, 16 (59%) and 1 (4%) of the 27 courses used a lower-than-recommended or higher-than-recommended dose, respectively (Table 2). Six courses involved a higher frequency of lower doses or higher frequency of recommended doses (relative to the formulary).

For the most part, mean ALT values across all courses of therapy remained below the upper limit of normal (Figure 2A). More specifically, individual ALT values were below the upper limit of normal during the evaluation period, with the exception of 3 patients, whose ALT values increased substantially from baseline while they were taking acetaminophen or within 2 weeks of discontinuing this drug. Each of these patients had confounding factors that have been described as causing elevated ALT. One of the patients had moderate to severe hypoxic ischemic encephalopathy with elevated results on liver function testing since birth.[15] The second patient received isoniazid 5 days after acetaminophen initiation and was also receiving concurrent TPN, both of which are known to cause hepatotoxicity and elevated liver function results[13,16]; this patient's liver values began increasing sometime between 4 and 8 days after initiation of isoniazid. The third patient's increase in ALT was attributed to TPN cholestasis by the clinical team, on the basis of clinical assessment and other

Table 1. Baseline Characteristics of Neonates Receiving Rectal Administration of Acetaminophen

Characteristic	No. (%) of Patients* (*n* = 25)†
Sex, male	9 (36)
Admission diagnosis	
Surgical	15 (60)
Medical	10 (40)
Underwent surgical procedure within 7 days before acetaminophen initiation	17 (68)
Gestational age (GA) at birth, by category	
GA < 30 weeks	5 (20)
GA 30–33 weeks	4 (16)
GA 34–39 weeks	14 (56)
GA ≥ 40 weeks	2 (8)
Overall median GA (weeks) (minimum, maximum)	34.6 (24.7, 40.4)
Overall IQR (25th–75th percentile)	31.6–36.9
Birth weight (kg), by GA category (mean ± SD)	
GA < 30 weeks	1.08 ± 0.40
GA 30–33 weeks	1.27 ± 0.39
GA 34–39 weeks	2.44 ± 0.94
GA ≥ 40 weeks	3.72 ± 0.07
Overall median birth weight (kg) (minimum, maximum)	1.90 (0.63, 4.23)
Overall IQR (25th–75th percentile)	1.32–2.59
Postmenstrual age (PMA) at acetaminophen initiation, by category	*n* = 27 courses
PMA < 30 weeks	0 (0)
PMA 30–33 weeks	4 (15)
PMA 34–39 weeks	16 (59)
PMA ≥ 40 weeks	7 (26)
Overall median PMA (weeks) (minimum, maximum)	37.0 (31.6, 43.1)
Overall IQR (25th–75th percentile)	35.0–39.8
Weight (kg) at acetaminophen initiation, by PMA category (mean ± SD)	*n* = 27 courses
PMA < 30 weeks	NA
PMA 30–33 weeks	1.57 ± 0.46
PMA 34–39 weeks	2.47 ± 1.00
PMA ≥ 40 weeks	3.24 ± 0.87
Overall median weight (kg) (minimum, maximum)	2.23 (1.09, 4.89)
Overall IQR (25th–75th percentile)	1.78–3.47

IQR = interquartile range, NA = not applicable, SD = standard deviation.
*Except where indicated otherwise.
†The 25 patients received a total of 27 courses of acetaminophen.

Table 2. Acetaminophen Dosage Characteristics and Concurrent Toxic Medications

Characteristic*	No. (%) of Courses† (*n* = 27)
Indication for acetaminophen	
Pain	26 (96)
Fever	0 (0)
Both pain and fever	1 (4)
Dose (mg/kg) of rectal acetaminophen, by PMA category (mean ± SD)	
PMA < 30 weeks (*n* = 0)	NA
PMA 30–33 weeks (*n* = 4)	18.6 ± 2.9
PMA 34–39 weeks (*n* = 16)	20.7 ± 5.6
PMA ≥ 40 weeks (*n* = 7)	23.2 ± 6.4
Overall median dose (mg/kg) (minimum, maximum)	21.9 (9.5, 29.4)
Overall IQR (25th–75th percentile)	19.7–25.0
No. (%) of courses with lower-than-recommended dose, by PMA category	
PMA < 30 weeks (*n* = 0)	NA
PMA 30–33 weeks (*n* = 4)	1 (25)
PMA 34–39 weeks (*n* = 16)	9 (56)
PMA ≥ 40 weeks (*n* = 7)	6 (86)
No. (%) of courses with higher-than-recommended dose, by PMA category	
PMA < 30 weeks (*n* = 0)	NA
PMA 30–33 weeks (*n* = 4)	NA
PMA 34–39 weeks (*n* = 16)	1 (6)
PMA ≥ 40 weeks (*n* = 7)	NA
Duration of rectal administration of acetaminophen (days)	
Median (minimum, maximum)	2.0 (1.0, 8.0)
IQR (25th–75th percentile)	1.0–3.0
Rectal acetaminophen administered > 3 days	9 (33)
Switched from rectal to oral/nasogastric acetaminophen	6 (22)
Concurrent use of opioids	
Morphine alone	17 (63)
Fentanyl alone	1 (4)
Morphine + fentanyl	3 (11)
None	6 (22)
Concurrent use of potentially nephrotoxic medications	
Acyclovir	0 (0)
Aminoglycosides alone	11 (41)
Amphotericin	0 (0)
Furosemide	0 (0)
Vancomycin alone	2 (7)
Both aminoglycosides and vancomycin	5 (19)
None	9 (33)
Concurrent use of potentially hepatotoxic medications	
Lipids (with or without total parenteral nutrition)	23 (85)
Anticonvulsants	0 (0)
Other	1 (4)
None	3 (11)

IQR = interquartile range, NA = not applicable, PMA = postmenstrual age, SD = standard deviation.
*PMA categories refer to time of initiation of acetaminophen therapy.
†Except where indicated otherwise.

laboratory findings.[16] The prescribed acetaminophen doses for these 3 patients were 20 mg/kg q6h, 22 mg/kg q8h, and 24 mg/kg q8h, respectively. When results for these 3 patients were omitted from the analysis, all mean ALT values remained below the upper limit of normal (Figure 2B). For all patients, serum creatinine remained the same or declined from baseline, thus showing no evidence of nephrotoxicity.

The secondary outcome of efficacy (based on PIPP-R score) could not be evaluated because most patients were receiving opioids concurrently.

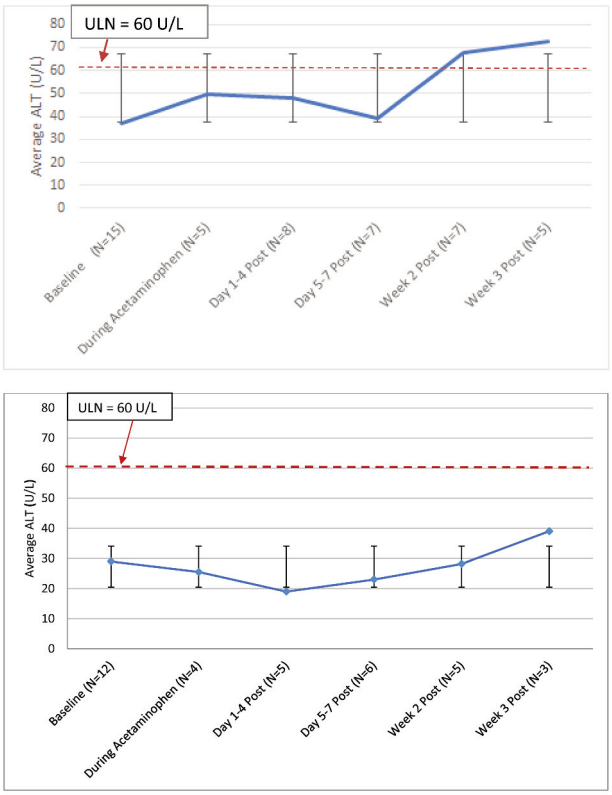

Figure 2. Top: Mean alanine aminotransferase (ALT) levels for all neonates who received rectal administration of acetaminophen, from baseline to 3 weeks after the last acetaminophen dose. A total of 15 acetaminophen courses were included; however, data were not available at all time points for all patients. Bottom: Mean ALT levels for neonates without confounding factors (n = 12 courses). Error bars indicate standard deviations, and the dashed red line in each graph indicates 60 U/L (units per litre), which is the upper limit of normal (ULN).

DISCUSSION

In this single-centre retrospective chart analysis, we attempted to evaluate the safety and efficacy of acetaminophen administered rectally to neonates in the NICU. In terms of safety, we found no evidence of hepatotoxicity or nephrotoxicity among neonates included in the study. However, the doses given were often discordant with the institution's formulary guidelines, which were based on a study by Anderson and others.[10] The doses administered were most often lower than recommended or were provided at higher frequency than recommended. This usage pattern may suggest that prescribers lack familiarity with dosing guidelines for rectal acetaminophen by GA; at least some of the dosage deviations may be due to use of dosing ranges appropriate for oral administration, with which most prescribers are familiar.

It proved impossible to evaluate the secondary objective of efficacy directly attributable to acetaminophen (according to PIPP-R scores), because the study centre commonly uses acetaminophen as an opioid-sparing agent; as such, most patients were also receiving some form of opioid therapy. The opioid doses were not consistently available or recorded, and the opioid-sparing effects of acetaminophen could therefore not be assessed. Conversely, patients receiving opioids were not excluded from the analysis, because doing so would have further reduced the already limited sample size.

The major limitations of this study were its small sample size and the short duration of rectal administration of acetaminophen. Use of acetaminophen beyond 2 or 3 days is more likely to increase the risk of toxicity,[10] but only about half of this cohort (n = 13 courses) received rectal acetaminophen therapy for 2 days (48 h) or more. This limitation might be difficult to address even with larger sample sizes, given that the usual clinical indications for rectal administration of acetaminophen do not support prolonged or continuous use. The small number of patients included in this study may reflect the infrequent use of rectal acetaminophen for NICU patients in general. For instance, only 25% of patients receiving acetaminophen at the study institution were eligible for inclusion in the data analysis, even though the study setting was a high-volume surgical NICU and the recruitment period lasted for 2 years. This infrequent use may be due to lack of awareness of the availability and potential efficacy of this form of therapy. We were unable to find other studies reporting on the frequency of rectal administration of acetaminophen in NICUs. Another limitation was the relatively low number of results of hepatic and renal function tests available for review; ethical considerations would preclude more frequent monitoring even with a prospective study design.

We found substantial variation in dosing and other practices for acetaminophen administration in neonates. The extent of variation at other sites must be determined to evaluate whether our findings are generalizable to other sites.

CONCLUSION

Continuous rectal administration of acetaminophen in a surgical NICU setting was infrequent, and even when this form of therapy was used, it was often not prescribed according to formulary guidelines. We found no evidence of toxicity of rectally administered acetaminophen in these circumstances. The need for increased awareness of proper dosing was identified, and educational strategies are now being implemented in the NICU where this study was performed. Further studies are required to evaluate the safety and efficacy of rectal acetaminophen administration when utilized according to guideline recommendations.

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ORIGINAL RESEARCH

Risk Evaluation for Antipsychotic Agents Used in Elderly Inpatients (REPAIR)

Flora Yu, Reza Rafizadeh, Vincent H Mabasa, and Nirmal Kang

ABSTRACT

Background: Antipsychotics have been approved for the treatment of certain psychiatric illnesses. However, these medications are also frequently used off label, and recent studies have suggested a concerning potential increase in the risk of death when used by elderly patients with dementia. Most of the available literature focusing on off-label use of antipsychotics comes from long-term care facilities; there is a lack of quantitative data for elderly patients in the acute care setting. This study was designed to examine this scenario and to identify potential quality improvement opportunities to minimize harm.

Objectives: The primary objectives were to determine the prevalence of hospital-initiated off-label use of antipsychotics for elderly inpatients and to determine the plan for these drugs upon discharge. The secondary objectives included identifying the most common diagnosis and the most common agent used.

Methods: A retrospective cohort study was performed with a convenience sample. Patients included in the analysis were elderly adults (≥ 65 years) who had been admitted to either of 2 medical units at a community hospital between September 1 and November 8, 2014. Descriptive statistics were used to examine prevalence patterns for the off-label use of antipsychotics.

Results: A total of 250 patients were included in the analysis. Forty-five patients (18%, 95% confidence interval [CI] 13.7%–23.2%) received a hospital-initiated antipsychotic for off-label use during the admission. For 27 (60%, 95% CI 45.5%–73.0%) of these 45 patients, the off-label therapy was discontinued upon discharge or death, and for 13 (29%, 95% CI 17.7%–43.4%), the agent was continued upon discharge without a plan in place. The most frequent diagnosis was delirium, and the agent most frequently used was haloperidol.

Conclusions: Off-label antipsychotic therapy was initiated for almost 1 in every 5 elderly patients receiving care in 2 medical units at a community hospital. These findings suggest a need to monitor and reassess the off-label use of these agents, especially at the time of discharge.

Keywords: antipsychotic, off-label use, elderly patients, atypical antipsychotic, conventional antipsychotic

RÉSUMÉ

Contexte : Les antipsychotiques ont été approuvés pour le traitement de certains troubles psychiatriques. Or, ces médicaments sont aussi fréquemment utilisés en dérogation des directives de l'étiquette et des études récentes ont supposé une potentielle augmentation préoccupante du risque de décès lorsqu'ils sont employés pour traiter des patients âgés atteints de démence. La majeure partie de la littérature portant sur l'emploi non conforme d'antipsychotiques provient de centres d'hébergement et de soins de longue durée. Or, on constate un manque de données quantitatives sur les patients âgés dans les milieux de soins de courte durée. La présente étude a été conçue pour examiner ce scénario et découvrir de potentielles occasions d'amélioration de la qualité en vue de réduire au minimum les risques de préjudice.

Objectifs : Les objectifs principaux étaient de déterminer la prévalence de l'emploi non conforme d'antipsychotiques amorcé à l'hôpital chez les patients aînés et de déterminer le plan relatif à la prescription de ces médicaments au moment du congé. Les objectifs secondaires incluaient de déterminer quels étaient le diagnostic le plus fréquent et le médicament le plus utilisé.

Méthodes : Une étude de cohorte rétrospective a été menée à l'aide d'un échantillon de commodité. Les patients retenus pour l'analyse étaient des personnes âgées (de 65 ans et plus) ayant été admises à l'une des deux unités médicales dans un hôpital communautaire entre le 1er septembre et le 8 novembre 2014. Des statistiques descriptives ont été employées pour analyser les modèles de prévalence en ce qui concerne l'emploi non conforme d'antipsychotiques.

Résultats : Au total, 250 patients ont été retenus pour l'analyse. Pendant l'hospitalisation, un antipsychotique a été amorcé hors conformité chez 45 patients (18 %, intervalle de confiance [IC] de 95 % de 13,7 % à 23,2 %). Pour 27 (60 %, IC de 95 % de 45,5 % à 73,0 %) de ces 45 patients, le traitement non conforme a été arrêté au moment du congé et, pour 13 autres (29 %, IC de 95 % de 17,7 %–43,4 %), le traitement a été poursuivi au congé sans mise en place d'un plan. Le diagnostic motivant le plus souvent l'emploi non conforme de ces médicaments était le délire et le médicament le plus employé était l'halopéridol.

Conclusions : Le traitement non conforme par antipsychotique a été amorcé pendant le séjour à l'hôpital pour près d'un patient âgé sur cinq qui recevait des soins dans l'une des deux unités médicales d'un hôpital communautaire. Ces résultats laissent croire qu'une surveillance de l'emploi non conforme de ces médicaments et qu'une réévaluation d'un tel traitement sont nécessaires, particulièrement au moment du congé.

Mots clés : antipsychotique, emploi non conforme, patients âgés, antipsychotique atypique, antipsychotique classique

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INTRODUCTION

Antipsychotic agents, both conventional and atypical, are indicated for the treatment of certain psychiatric illnesses, such as schizophrenia, bipolar disorder, and refractory depression.[1,2] Conventional agents have been available since the mid-1900s, but use of the "newer" atypical agents has been on the rise, because these agents are described as having similar benefits with fewer adverse effects.[3]

Antipsychotic agents are frequently used off label, especially in elderly patients, for various conditions, including behavioural and neuropsychiatric symptoms in dementia, delirium, anxiety, obsessive–compulsive disorder, eating disorders, depression, and substance abuse.[1,4] For treatment of behavioural and neuropsychiatric symptoms in dementia (e.g., agitation, aggression, delusions, hallucinations, repetitive vocalization, and wandering), nonpharmacological measures are generally recommended as first-line management.[5] However, in cases of severe aggression or psychosis, antipsychotics are often administered, given the ease of use in clinical practice, as well as the absence of other effective agents.[3,6]

In 2008, the US Food and Drug Administration issued a warning[7] about the use of all antipsychotics, both conventional and atypical agents, based on 2 cohort studies that showed an increased risk of death among elderly patients being treated for dementia-related psychosis.[6,8] In one of these cohort studies, Gill and others[6] found that use of a new atypical antipsychotic was associated with an increased risk of death at 30 days, relative to non-use, with adjusted hazard ratios (HRs) of 1.31 (95% confidence interval [CI] 1.02–1.70) for the community-dwelling cohort and 1.55 (95% CI 1.15–2.07) for the long-term care cohort. When conventional and atypical antipsychotics were compared, there was higher risk of death at 30 days in the conventional antipsychotic group, with adjusted HRs of 1.55 (95% CI 1.19–2.02) for the community-dwelling cohort and 1.26 (95% CI 1.04–1.53) for the long-term care cohort.[6] In addition, Schneider and others[9] suggested an increase in the risk of death with use of atypical antipsychotics, relative to placebo, for brief periods of use (less than 8 to 12 weeks). In terms of adverse effects, use of antipsychotics in elderly patients has also been described as contributing to the risk of stroke and falls.[10,11] In terms of efficacy in the treatment of behavioural and neuropsychiatric symptoms of dementia, there is no clear evidence of benefit for the use of antipsychotics.[1,12,13] Given the mounting evidence that suggests risk of harm and the controversial evidence of benefit, the American Geriatrics Society has recommended the avoidance of all antipsychotics for "behavioral problems of dementia unless non-pharmacological methods have failed and the patient is a threat to self or others".[14] Health Canada[15] and the Canadian Geriatrics Society[16] have issued similar advisories and recommendations.

Despite the aforementioned health concerns, it appears that off-label use of antipsychotics is still quite common. For example, in a cross-sectional analysis published in 2008, Kamble and others[17] reported the prevalence of and factors associated with antipsychotic drug use among elderly nursing home residents in the United States. The authors found that nearly 1 in 4 elderly nursing home residents received antipsychotic agents for off-label diagnoses, with the majority of use occurring in patients with dementia (70%), depression (41%), and anxiety (18%). This study was restricted to nursing home residents. The focus of the study reported here was to investigate the prevalence of off-label use of antipsychotics for elderly patients admitted to hospital and to identify any potential quality improvement opportunities to minimize harm.

METHODS

This retrospective cohort study involved patients at a 300-bed community hospital. The study received ethics approval from the local research ethics board.

The primary objectives of the study were to determine the extent of hospital-initiated off-label use of antipsychotics and to determine whether a postdischarge treatment plan was in place at the time of discharge. Hospital-initiated use of an antipsychotic was defined as use of an antipsychotic for a patient who had not been taking antipsychotic medications just before admission (i.e., all agents of this class were newly initiated in hospital). Off-label use was defined as use of a drug for an indication not reported in the Health Canada drug product monograph for that particular agent. Secondary objectives were to determine the percentage of patients with dementia for whom off-label antipsychotic use was initiated in hospital, and to characterize the most common diagnosis and the most common agent used for these off-label purposes.

Patients eligible for inclusion were elderly adults (at least 65 years of age) admitted to either of 2 designated medical units for elderly patients at a community hospital between September 1 and November 8, 2014. Eligible patients were identified from a patient list generated by the hospital's health and business analytics department according to the study's inclusion criteria. In cases of readmission of the same patient, the first admission was included in the analysis; subsequent admissions were excluded.

All data were collected from electronic and scanned health records (i.e., admission, consultation, progress, nursing, and discharge notes) within the hospital's database. The following data were collected for each patient: demographic and clinical characteristics (age, sex, and relevant comorbidities); use of antipsychotics just before admission, during admission, and upon discharge (drug name, type of antipsychotic, indication, and dosing regimen); and plan at discharge for hospital-initiated antipsychotics with off-label use (discontinuation by prescriber, discontinuation because of patient death, continuation with no plan, or continuation with a plan). Having a plan was defined as any mention in the discharge summary of follow-up for the hospital-initiated antipsychotic with off-label use.

A convenience sample size of 250 patients was chosen by consensus among the investigators. All data were analyzed with descriptive statistics.

RESULTS

A total of 260 patient encounters from the 2 medical units met the inclusion criteria. Of these, 10 were readmissions; for these patients, only the initial admission was included in the analysis, and subsequent admissions were excluded, leaving the desired sample size of 250. Overall, 164 (66%) of the 250 patients were women, and patient age ranged from 65 to 98 years (median 83.5 years, interquartile range 70.5–96.5 years) (Table 1). Sixteen (6%) of the patients had been receiving an antipsychotic for off-label use before admission.

Off-label use of an antipsychotic was initiated during the hospital admission for 45 (18%, 95% CI 13.7%–23.2%) of the patients. For 27 (60%, 95% CI 45.5%–73.0%) of these patients, off-label therapy was discontinued upon discharge or death. Upon discharge, 18 patients (40%, 95% CI 27.0%–54.6%) had these agents continued (Figure 1). Notably, for 13 patients (29%, 95% CI 17.7%–43.4%), the drug was continued at discharge with no reported plan in place for further assessment or discontinuation in the community.

In terms of the secondary outcomes (Table 2), we found that hospital-initiated off-label use of an antipsychotic was ordered for 26 (32%) of the 82 patients with a history of dementia. For all patients with off-label use of antipsychotics, the diagnoses were recorded, and these are reported in Table 2. The most common antipsychotics used were haloperidol and loxapine (Table 2).

Sixteen (6%) of patients in this study had off-label use of an antipsychotic before admission. We found that these patients were still receiving antipsychotic therapy upon discharge. Compared with the time of admission, 9 of these 16 patients had the same antipsychotic regimen and 7 had a change in regimen (a dosing change or addition of another agent) at the time of discharge. Interestingly, none of these patients were free of off-label antipsychotic use at discharge.

Table 1. Baseline Characteristics

Characteristic	No. (%) of Patients* (*n* = 250)
Age (years), median (IQR)	83.5 (70.5–96.5)
Sex, female	164 (66)
Medical comorbidity	
Psychiatric illness†	58 (23)
For which antipsychotic use is indicated	13 (5)
For which antipsychotic use is not indicated	45 (18)
Dementia	82 (33)
Diabetes mellitus	71 (28)
History of ischemic or hemorrhagic stroke	71 (28)
History of myocardial infarction	46 (18)
Antipsychotics before admission	28 (11)
Off label	16 (6)
On label	7 (3)
Unknown purpose	5 (2)

IQR = interquartile range.
*Except where indicated otherwise.
†Includes mood disorders (e.g., depression, bipolar disorder), schizophrenia, anxiety disorders, eating disorders, addictive behaviours, and personality disorders.

DISCUSSION

The objective of this study was to characterize hospital-initiated off-label use of antipsychotics in the elderly population.

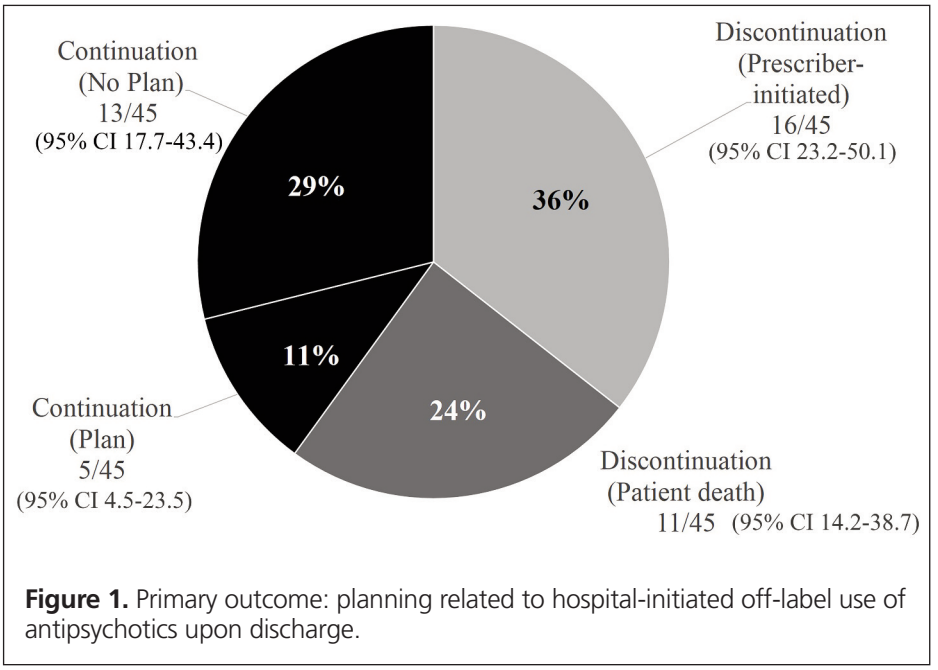

Figure 1. Primary outcome: planning related to hospital-initiated off-label use of antipsychotics upon discharge.

Table 2. Secondary Outcomes

Outcome	No. (%) of Patients
Hospital-initiated off-label antipsychotic use for patient with dementia	26/82 (32)
Regimen for hospital-initiated off-label antipsychotic use	*n* = 45 patients
Regular basis only	2 (4)
As-needed basis only (prn)	23 (51)
Both regular and as needed	20 (44)
Diagnosis relevant to hospital-initiated off-label antipsychotic use†	
Delirium	34
Agitation	29
Nausea	6
Behavioural and neuropsychiatric symptoms in dementia	5
Insomnia	3
End of life	1
Anxiety	1
Antipsychotic ordered†	
Haloperidol	27
Loxapine	25
Quetiapine	18
Olanzapine	1
Risperidone	1

*Except where indicated otherwise.
†These data relate to a total of 45 patients with hospital-initiated off-label use of an antipsychotic. Data are presented as numbers of patients, without percentages, and the sum of data values is greater than 45 because some patients had more than one diagnosis or more than one antipsychotic ordered.

In this study, 18% of patients were newly initiated on an antipsychotic (off-label use) at some point during their hospital admission. Importantly, none of these patients had been taking an antipsychotic before admission; however, an additional 6% of patients were already receiving off-label antipsychotic therapy before admission, which means a higher overall number of patients receiving this type of therapy while in hospital.

During the writing of this article, 2 additional studies were published addressing the off-label use of antipsychotics in the hospital setting.[18,19] In a retrospective cohort study of 17 775 patients (age 18 years or older), Herzig and others[18] examined the use of antipsychotics for delirium in a hospital setting. These authors found that 9% of patients were taking an antipsychotic while in hospital, with such therapy being newly initiated for 5%; these rates are much lower than observed in our study. One factor may have been a difference in age between the patient populations: about half (50.4%) of their patients were between the ages of 18 and 64 years, whereas the patients in our study were 65 years or older. In fact, Herzig and others[18] reported age 75 years or older as a characteristic associated with a higher rate of antipsychotic initiation (relative risk 1.4, 95% CI 1.2–1.7). This could explain the lower rate in their study compared with ours. The other study, a research letter, examined the use of antipsychotics in hospitalized elderly patients (age 65 years or older).[19] The authors of that study similarly found that 9% of patients were receiving an antipsychotic while in hospital; however, they did not specify whether the drug therapy was newly initiated in patients who had not been taking antipsychotic medications before admission.[19]

In our study, even though most hospital-initiated agents were discontinued upon discharge, either at the prescriber's direction or because of patient death, we were mainly interested in the 18 patients whose antipsychotic medications were continued after discharge (representing 40% of the 45 patients with antipsychotics newly initiated during the hospital stay). Interestingly, Herzig and others[18] reported a much lower rate (26%) for continuation of antipsychotics at discharge; however, they excluded patients who died during hospitalization or who left against medical advice. For an interesting comparison, if we were to exclude the 11 patients in our study who died, the percentage would increase to 53% (18 of 34 patients) whose hospital-initiated agents were continued on discharge. Once again, this finding may have been influenced by the age of our patient population. Loh and others[19] reported a more comparable rate (48%) for elderly patients whose antipsychotics were continued at discharge.

Of concern in our study, hospital-initiated off-label use of antipsychotics was continued at discharge without any plan for 29% of patients. Among the 11% of patients for whom there was a plan, common discharge plans included follow-up with a family physician, mental health clinic, or geriatric psychiatrist (e.g., monitor QTc, taper or discontinue the antipsychotic). Kamble and others[17] found that 24.82% of elderly nursing home residents received an antipsychotic at some point over the course of a year. In clinical practice, a hospital stay preceding transfer to a nursing home facility is common, especially for elderly patients. Although our study was not designed to specifically characterize a direct association between hospital-initiated off-label use of antipsychotics and an influx of these agents into nursing homes, such an association remains a possibility. Medications are easy to initiate at times of immediate need, but opportunities to re-evaluate and deprescribe are often missed.[20] A future study focusing on the downstream effects of hospital-initiated off-label use of antipsychotics on patients transferred back to the community would be of great importance.

In this study, the most common diagnoses for hospital-initiated off-label use of antipsychotics were delirium and agitation. Herzig and others[18] and Loh and others[19] also reported delirium as the most common indication. As defined by the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders*,[21] delirium is a disturbance in attention and awareness, which develops over a short period of time, represents a change from baseline, and fluctuates during the course of the day. In the context of this diagnosis, off-label use of antipsychotics may be helpful in situations where a patient is a threat to self or others,[14] but these agents need to be regularly

assessed for appropriateness and effectiveness. The Confusion Assessment Method (CAM) is a simple tool that is frequently used by clinicians to assess delirium (sensitivity 94%–100%, specificity 90%–95%).[22] At our community hospital, CAM scores are recorded daily in the nursing notes; however, given the retrospective design of our study, ambiguity arose regarding the interpretation of documented CAM scores.

The results presented here suggest a preference for conventional agents at our site, although the literature suggests popularity of atypical agents, given similar efficacy and fewer adverse effects. Herzig and others[18] and Loh and others[19] both reported more frequent use of atypical antipsychotics. Our community hospital has a preprinted order for geriatric delirium. For severe agitation or psychosis, quetiapine 6.25–12.5 mg PO q2h prn (maximum 50 mg in 24 h) and/or loxapine 2.5 mg PO q4h prn (maximum 10 mg in 24 h) is recommended. For severe agitation when an oral agent cannot be used, haloperidol 0.25 mg IM or SC q1h prn (maximum 1.5 mg in 24 h) is recommended. For all of these agents, the preprinted order specifies an automatic stop date of 3 days, which encourages reassessment. In the study reported here, the agents most commonly used were haloperidol, loxapine, and quetiapine (in descending order), which is consistent with the agents recommended in the preprinted order. However, most of the orders analyzed in the study were free-text handwritten orders; preprinted orders were not used. We did not specifically look at the appropriateness of dosing regimens; nonetheless, better education about and awareness among staff physicians regarding the use of preprinted orders would ensure greater dosing consistency and would encourage more frequent reassessment of the need for ongoing off-label use of antipsychotics.

This study had several limitations that could affect interpretation of the results. Given the retrospective design, data were collected by reviewing scanned charts in the electronic database, but these records may have been incomplete and inconsistent. More specifically, the study relied heavily on dictated discharge summaries to identify the plan for hospital-initiated off-label use of antipsychotics upon discharge. In addition, data on antipsychotics were obtained from electronic medication records, which indicate what has been prescribed but not necessarily actual administration of the drug. For our study, documentation of actual administration was unnecessary, because we did not assess hard end points associated with harm (e.g., death, stroke). If a future study assessing such end points were to be conducted, use of medication administration records would be preferable. Furthermore, the study results were drawn from a small convenience sample at a single centre, and therefore may not be generalizable to other sites.

CONCLUSION

In this study, about 1 in every 5 patients was newly initiated on an antipsychotic for off-label use during hospital admission, with the most common diagnosis being delirium. Nearly a third (29%) of patients were receiving a hospital-initiated agent at discharge with no documented plan for reassessment or discontinuation in the community. These findings were presented to hospitalists and nurses at the study site. These discussions led to improved awareness about this issue and development of an action plan to assist in improving current practices.

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ARTICLE DE SYNTHÈSE

Analyse des modes de défaillance, de leurs effets et de leur criticité dans le circuit du médicament : revue de littérature

Émile Demers, Laurence Collin-Lévesque, Marianne Boulé, Sophie Lachapelle, Christina Nguyen, Denis Lebel et Jean-François Bussières

RESUMÉ

Contexte : L'analyse des modes de défaillance, de leurs effets et de leur criticité (AMDEC) est une méthode d'analyse systématique et proactive des risques permettant de déterminer les défaillances majeures de processus complexes.

Objectif : Recenser tous les articles concernant l'utilisation de l'analyse des modes de défaillance et de leurs effets (AMDE), de l'AMDEC et de l'AMDEC en santé (AMDECS) dans le cadre du circuit du médicament.

Sources des données, sélection des études et extraction des données : La base de données MEDLINE a été interrogée pour la période de janvier 1990 à janvier 2017. La stratégie de recherche a inclus les études appliquant intégralement ou partiellement la méthode AMDEC et traitant d'un ou de plusieurs volets du circuit du médicament. Une recherche manuelle complémentaire a permis d'inclure les références pertinentes des articles consultés.

Synthèse des données : Les chercheurs ont trouvé 171 articles. Ils en ont retenu 39, soit 32 décrivant l'utilisation de l'approche AMDE ou AMDEC et sept décrivant l'utilisation de l'approche AMDECS. Ils ont répertorié de quatre à 378 modes de défaillance, selon les études publiées. Dix des 39 articles font état d'une analyse avant et après la mise en vigueur de mesures correctives. Dans quatre de ces 10 articles, l'analyse a été réalisée de façon théorique, soit avant la mise en vigueur réelle des mesures. À partir des articles retenus, un tableau-synthèse a été élaboré avec les éléments suivants : année de publication, premier auteur, pays, objectif principal, objectifs secondaires, description de la méthode, description des résultats, commentaires. Le tableau-synthèse a permis de commenter l'état d'utilisation des analyses de type AMDEC dans le cadre du circuit du médicament.

Conclusions : Cette revue de la littérature a retenu 39 articles publiés ayant utilisé l'approche AMDE, AMDEC ou AMDECS dans le cadre du circuit du médicament. La plupart des études ont utilisé l'approche AMDE ou AMDEC, tandis que l'AMDECS n'était que rarement employée. Seule une minorité des études ont évalué les effets de mesures correctives mises en œuvre. Cette approche permet la cartographie d'un processus de soins, la détermination des modes de défaillance et la priorisation des actions correctives. Il faudrait encourager son usage pour l'évaluation du circuit du médicament.

Mots-clés : analyse des modes de défaillance et de leurs effets; analyse des modes de défaillance, de leurs effets et de leur criticité; analyse des modes de défaillance, de leurs effets et de leur criticité en santé; médicament; mode de défaillance; criticité; risques

ABSTRACT

Background: Failure mode, effects, and criticality analysis (FMECA) is a systematic and proactive risk analysis method to determine major failures in complex processes.

Objective: To identify all articles involving the use of failure mode and effects analysis (FMEA), FMECA, or FMECA in health care within the medication use system.

Data Sources, Study Selection, and Data Extraction: The MEDLINE database was searched, for the period January 1990 to January 2017. The search included studies using the FMECA method, in part or in full, and dealing with one or several components of the medication use system. The reference lists of articles identified in the initial search were checked manually for additional pertinent references.

Data Synthesis: The researchers identified 171 articles, and retained 39 for analysis: 32 describing use of the FMEA or FMECA approach and 7 describing use of the FMECA in health care approach. They identified between 4 to 378 failure modes, according to the published studies. Among the 39 articles, 10 reported a pre- and post-implementation analysis of corrective measures. In 4 of those 10 articles, the analysis was conducted on a theoretical basis, that is, before the corrective measures were actually implemented. Using the articles retained for analysis, a summary table was developed with the following elements: publication year, main author, country, primary objective, secondary objectives, descriptions of both method and results, and comments. The summary table gave the opportunity to comment on the use of the FMECA-type analysis within the medication use system.

Conclusions: This literature review included 39 published articles using an FMEA, FMECA, or FMECA in health care approach within the medication use system. Most studies used either the FMEA or the FMECA approach, whereas the FMECA in health care approach was used only rarely. Only a minority of studies assessed the effects of corrective measures that were implemented. This overall approach allows for mapping of a care process, determination of failure modes, and prioritization of corrective measures. Its use for the assessment of the medication use system should be promoted.

Keywords: failure mode and effects analysis; failure mode, effects, and criticality analysis; failure mode, effects, and criticality analysis in health care; drug; failure mode; criticality; risks

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CONTEXTE

L'analyse des modes de défaillance, de leurs effets et de leur criticité (AMDEC) est une méthode d'analyse systématique et proactive des risques permettant de déceler les défaillances majeures de processus complexes[1-3]. L'AMDEC pose comme axiome que l'organisation même d'un système, et non les individus qui le composent, doit être au cœur de toute démarche de réduction des risques[3]. De là, l'idée d'une erreur associée à un individu est remplacée par l'idée d'un mode de défaillance associé à un système.

Une AMDEC est un processus multidisciplinaire qui permet de coter trois indices et d'en calculer le produit par mode de défaillance ainsi que la somme de ces produits[3]. De façon générale, une échelle de cotation numérique sert à calculer chaque indice, soit un indice de fréquence de survenue de chaque mode de défaillance, un indice de sévérité des conséquences de la survenue du mode de défaillance et un indice de capacité de détection du mode de défaillance. Ainsi, pour un mode de défaillance donné et coté à l'aide d'échelles de 1 à 10, le risque le moins élevé donne une valeur de 1 (1 × 1 × 1) alors que le risque le plus élevé donne un produit de 1000 (10 × 10 × 10), ce risque est nommé l'indice de criticité (IC) dans la littérature. À noter que l'analyse des modes de défaillance et de leurs effets (AMDE) est une analyse similaire sans évaluation de la criticité.

L'AMDEC a été créée par l'armée américaine dans les années 1950 et a par la suite été popularisée par la NASA, les constructeurs aéronautiques et l'industrie automobile[4-6]. L'AMDEC a fait son apparition dans le domaine de la santé dans les années 1990[7].

Aux États-Unis, The Joint Commission a publié des principes méthodologiques directeurs relatifs à l'AMDEC[8,9]. La démarche proposée consiste en la sélection d'un processus comportant un risque élevé, la constitution d'une équipe multidisciplinaire d'experts, la schématisation exhaustive des étapes du processus à l'étude, la détermination par remue-méninges de tous les modes de défaillance possibles, la détection des causes et des effets de chaque mode de défaillance, la hiérarchisation des modes de défaillances, l'implantation de mesures correctives, l'analyse du nouveau processus et l'évaluation des changements accomplis.

Au début des années 2000, le Veterans Administration National Center for Patient Safety a développé une variante de l'AMDEC, soit l'AMDEC en santé (AMDECS aussi appelé *Healthcare failure mode effect analysis*)[10]. The Joint Commission estime que l'AMDECS est plus facile à appliquer en santé en raison de la simplification et de l'amélioration de la démarche. L'AMDECS comprend notamment des échelles de cotations simplifiées (p. ex. score de 1 à 4 plutôt que de 1 à 10) et exige une prise de décision relative à chaque mode de défaillance détecté : « accepter », « contrôler » ou « éliminer ». Une personne responsable est nommée pour assurer le suivi de chaque mode de défaillance à contrôler et à éliminer. Néanmoins, la méthode d'analyse des risques demeure identique à celle de l'AMDE / AMDEC.

Pour les professionnels travaillant en établissement de santé, les AMDE / AMDEC / AMDECS représentent des approches utiles qui peuvent contribuer à améliorer les pratiques et qui satisfont à au moins une pratique organisationnelle requise d'Agrément Canada (c.-à-d. la tenue d'analyses prospectives liées à la sécurité des usagers)[11]. Nous ignorons dans quelle mesure ils connaissent l'approche AMDEC et s'ils ont accès aux articles ayant recours à cette approche.

Recenser tous les articles concernant l'utilisation de l'approche AMDE / AMDEC / AMDECS dans le cadre du circuit du médicament.

SOURCES DES DONNÉES, SÉLECTION DES ÉTUDES ET EXTRACTION DES DONNÉES

La méthodologie repose sur l'interrogation de la base de données MEDLINE pour la période de janvier 1990 à janvier 2017 à l'aide de la stratégie suivante : « "*Healthcare Failure Mode and Effect Analysis*"[mh] OR "*Healthcare Failure Mode and Effect Analysis*"[all] OR "*Failure Mode and Effect Analysis*"[all] OR "*FMEA*"[all] OR "*FMECA*"[all]) AND ("*Drugs*"[all] OR "*Medication*"[all] OR "*Hospital*"[all]) AND ("1990/01/01"[pdat] : "2017/01/27"[pdat] ». Les investigateurs ont en outre effectué une recherche manuelle complémentaire portant sur les références des articles consultés.

L'un des auteurs (E.D.) a effectué une première sélection des articles à partir du titre. Puis, à partir du résumé structuré, il a procédé à l'inclusion des articles correspondant aux critères d'inclusion suivants : études appliquant intégralement ou partiellement la méthode AMDEC et traitant d'un ou de plusieurs volets du circuit du médicament. Un autre auteur (J.F.B.) a vérifié les raisons de sélection et de refus des résumés structurés. La consultation des autres auteurs a permis de résoudre les divergences. Les AMDEC portant sur d'autres processus, comme la communication entre professionnels de la santé ou l'admission aux urgences, étaient incluses dans la mesure où le circuit du médicament occupait une place prépondérante dans l'énumération des étapes et des modes de défaillance. Les articles traitant uniquement des procédés industriels de fabrication des médicaments ont été exclus, de même que les articles publiés dans une langue autre que l'anglais ou le français.

À partir des articles retenus, nous avons élaboré un tableau synthèse comportant les éléments suivants : année de publication, premier auteur, pays, objectif principal, objectifs secondaires, description de la méthode, description des résultats, commentaires. À partir du tableau synthèse, nous avons commenté l'état de l'utilisation des analyses de type AMDE / AMDEC / AMDECS dans le cadre du circuit du médicament. Nous avons procédé uniquement aux analyses des statistiques descriptives.

RÉSULTATS

Les chercheurs ont trouvé 171 articles. Ils en ont retenu 39, soit 32 décrivant l'utilisation de l'approche AMDE ou

AMDEC[5,12-42] et sept décrivant l'utilisation de l'approche AMDECS[43-49]. Plusieurs articles retenus utilisent les termes « AMDE » et « AMDEC » sans distinction, peu importe la présence ou l'absence d'un calcul de criticité dans leur méthodologie; les résultats présentés ici combinent donc l'ensemble de ces articles. La figure 1 illustre le processus de sélection des articles.

Des 39 études prises en compte, 11 proviennent des États-Unis, cinq du Canada, cinq d'Espagne, quatre de Suisse et 14 d'autres pays. Presque toutes les études (n = 37) portent sur des processus dans les unités de soins ou des cliniques externes, contre 22 dans les départements de pharmacie. Les équipes multidisciplinaires engagées dans la tenue de l'AMDE / AMDEC / AMDECS sont formées de professionnels exerçant entre deux et huit professions, selon les études. Les plus concernés étaient les médecins, les infirmières, les pharmaciens et les gestionnaires. Les participants à ces analyses ont décelé de quatre à 378 modes de défaillance, selon les études publiées.

En ce qui concerne le dépistage des modes de défaillance, il était généralement réalisé par consensus lors d'une rencontre de l'équipe de recherche. La cotation des différents modes de défaillance s'est faite de façon consensuelle (n = 32), mais elle correspondait parfois à la moyenne des cotations individuelles des participants (n = 3). Pour leur part, Kunac et Reith[26] ont opté pour une cotation des modes de défaillances par la médiane. Hosoya et collab.[24] ont utilisé des cotations obtenues par sondage de patients et non par consensus d'experts. Ashley et Armitage[43] ont eu recours à deux modes de cotation, soit celle par consensus et celle par moyenne. Les résultats obtenus indiquent que les IC obtenus par consensus sont plus élevés que ceux obtenus par moyenne en général. De façon générale, la plupart des IC sont calculés pour chacun des modes de défaillances détectés et pour chacune des étapes du processus. Plusieurs auteurs ont aussi calculé l'IC global du processus à l'étude. Certains auteurs ont modifié légèrement la méthodologie conventionnelle. Par exemple, Apkon et collab.[13] ont calculé des IC associés à des processus et non aux modes de défaillance ni aux sous-étapes constituant le processus. Armitage et collab.[14] ont coté indépendamment chacune des causes associées à chaque mode de défaillance, au lieu de coter directement chacun des modes de défaillance.

Enfin, les valeurs des indices de criticité recensées variaient de sept à 729 (c.-à-d. administration du mauvais médicament ou de la mauvaise dose) tandis que dans les AMDECS, les valeurs recensées variaient de huit à 16. Le tableau 1 présente un profil synthèse des AMDE / AMDEC utilisés dans le circuit du médicament.

Des 39 études prises en compte, 10 d'entre elles sont des analyses de type pré et postimplantation de mesures correctives. Quatre de ces analyses pré et postimplantation se sont déroulées en fait avant l'implantation réelle des mesures correctives; les panélistes étaient invités à évaluer les effets potentiels des mesures correctives avant qu'elles aient été implantées[18,19,31,36]. Par ailleurs, une autre de ces analyses est une sorte d'évaluation pré et postimplantation *a posteriori* : Bonnabry et collab.[17] ont réalisé une AMDEC sur un processus avant et après des mesures correctives déjà implantées au moment des séances de remue-méninges. Lorsqu'elles sont explicitées, les mesures correctives varient d'un article à l'autre. Lago et collab.[27] énoncent une série de mesures entreprises à la suite de leur analyse, entre autres en ce qui a trait à la double vérification, à la création de nouvelles feuilles d'ordonnances prérédigées, à l'implantation du bilan comparatif des médicaments au transfert des patients, à la diminution du nombre de formats multidoses disponibles et à l'utilisation d'étiquettes de couleur pour repérer les dossiers et les préparations de chimiothérapie.

Le tableau 2 présente un profil synthèse des AMDECS utilisés dans le circuit du médicament. Aucune de ces AMDECS ne présentait d'analyse de type pré et postimplantation.

DISCUSSION

À notre connaissance, il s'agit de la première revue de littérature recensant tous les articles ayant utilisé l'approche AMDE / AMDEC / AMDECS dans le cadre du circuit du médicament de 1990 à 2017. Il s'agit d'une approche utilisée surtout dans les pays anglo-saxons (c.-à-d. États-Unis, Royaume-Uni, Canada, Nouvelle-Zélande) mais également dans la francophonie (France, Suisse, Canada).

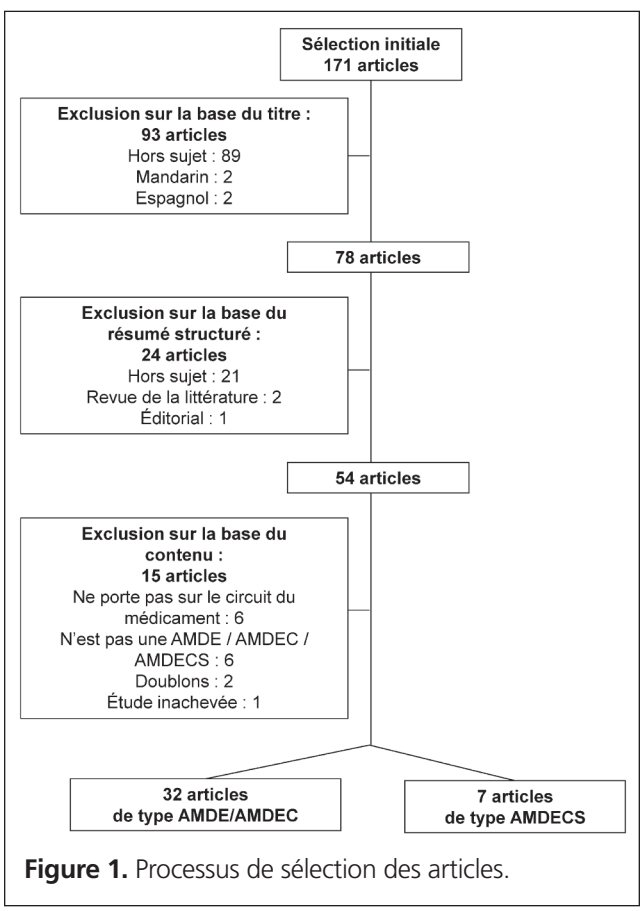

Figure 1. Processus de sélection des articles.

Tableau 1 (partie 1 de 2). Profil synthèse des AMDE et des AMDEC utilisées dans le circuit du médicament

Référence	Pays	Processus en pharmacie (PH) ou en unités de soins, de cliniques externes (UC)	Nombre de professions représentées dans l'équipe de recherche	Nombre de modes de défaillance décelés	Interventions (protocole avec AMDE ou AMDEC pré-post seulement) et évaluation post-implantation (implantation réelle ou simulée)	Mode de défaillance comportant IC le plus élevé (valeur de l'IC rapportée dans l'étude)
Adachi et Lodolce (2005)[12]	États-Unis	PH + UC	4	5	NA	« Programmer la pompe » (246)
Apkon et al. (2004)[13]	États-Unis	PH + UC	5	6	Mesures correctives diverses (réel)	« Programmer la pompe » (269 pré, 99 post)
Armitage et al. (2011)[14]	Swaziland	PH	2	11	NA	« Mauvais médicament / dose car personnel non formé » (729)
Baker et al. (2008)[15]	États-Unis	UC	6	ND	NA	« Prescriptions identifiées au mauvais patient » (420)
Berruyer et al. (2014)[16]	Canada	PH + UC	4	49	NA	« Non-vérification de l'identité du patient » (600)
Bonnabry et al. (2005)[17]	Suisse	PH	2	18	Informatisation du circuit du médicament (réel *a posteriori*)	« Erreur de dosage » (512 pré, 64 post)
Bonnabry et al. (2006)[18]	Suisse	PH + UC	3	27	Informatisation du circuit du médicament (simulé)	« Erreur de dose dans la production des protocoles » (432 pré, 9 post)
Bonnabry et al. (2008)[19]	Suisse	UC	5	27	Optimisation de la prescription électronique (simulée)	« Prescription ambiguë, illisible ou incomplète » (392 pré, 148 post)
Coles et al. (2005)[20]	États-Unis	PH + UC	ND	ND	NA	ND
de la Riva et al. (2015)[21]	Espagne	PH + UC	2	6	NA	« Mauvais médicament : emballage similaire » (300)
Delage et al. (2015)[22]	Canada	UC	4	11 pré, 16 post	Changement des pompes intelligentes (réel)	« Erreurs de débit » (280 pré, 70 post)
Dräger (2016)[23]	Allemagne	UC	ND	20	NA	ND
Hosoya et al. (2015)[24]	Japon	UC	ND	4	NA	« Oubli par distraction » (7 ± 1)
Kaestli et al. (2014)[25]	Suisse	PH + UC	5	23	NA	« Mauvaise dose de morphine prescrite » (441)
Kunac and Reith (2005)[26]	Nouvelle-Zélande	PH + UC	6	72	NA	« Manque de formation sur l'innocuité des médicaments » (273)
Lago et al. (2012)[27]	Italie	PH + UC	6	204	Mesures correctives diverses (réel)	« Prescription aux SIP » (IC sommatif de l'étape : 420 pré, 140 post)
Manrique-Rodríguez et al. (2014)[28]	Espagne	UC	3	19	Automatisation des procédures de pompes intelligentes (réel)	« Non-respect des concentrations et des heures d'administration standardisées en infusions intermittentes » (210 pré, 70 post)
Nguyen et al. (2013)[29]	Canada	UC	5	53	NA	« Pas de conseils aux patients » « Absence de mention écrite du conseil » (551)

suite à la page 380

Tableau 1 (partie 2 de 2). Profil synthèse des AMDE et des AMDEC utilisées dans le circuit du médicament

Référence	Pays	Processus en pharmacie (PH) ou en unités de soins, de cliniques externes (UC)	Nombre de professions représentées dans l'équipe de recherche	Nombre de modes de défaillance décelés	Interventions (protocole avec AMDE ou AMDEC pré-post seulement) et évaluation post-implantation (implantation réelle ou simulée)	Mode de défaillance comportant IC le plus élevé (valeur de l'IC rapportée dans l'étude)
Nickerson et al. (2008)[5]	Canada	PH + UC	4	78	NA	ND
Ofek et al. (2016)[30]	Israël	UC	5	13	NA	« Solution prédiluée contre-indiquée » (600)
Ponzetti et al. (2016)[31]	Italie	PH + UC	ND	35 pré, 12 post	Passage de protocole IV vers SC (simulé)	ND
Robinson et al. (2006)[32]	États-Unis	PH + UC	4	ND	NA	ND
Rodriguez-Gonzalez et al. (2015)[33]	Espagne	UC	4	40	Mesures correctives diverses (réel)	« Dose incorrecte » (320 pré, 224 post)
Saizy-Callaert et al. (2001)[34]	France	UC	6	11	NA	« Modification de la prescription non détectée » (36)
Shebl et al. (2012)[35]	Royaume-Uni	PH + UC	4	50	NA	« Médicament non donné à l'heure prévue » « Médicament administré incorrectement » (576)
Silva and Cassiani (2013)[36]	Brésil	UC	5	52	Mesures correctives diverses (simulé)	ND
Arenas Villafranca et al. (2014)[37]	Espagne	PH + UC	2	82	NA	« Identification erronée de la prescription » (479)
Walsh et al. (2013)[38]	États-Unis	UC	ND	69	NA	« Erreur de communication pour changements de dose »
Weingart et al. (2011)[39]	États-Unis	PH + UC	6	199	NA	« Non-respect de la posologie par le patient »
Wetterneck et al. (2009)[40]	États-Unis	UC	8	Plus de 200	NA	ND
Williams and Talley (1994)[41]	États-Unis	PH + UC	6	26	NA	« Disponibilités de doses létales » (576)
Yousefinezhadi et al. (2016)[42]	Iran	UC	6	378	NA	« Mauvaise dose administrée et durée d'administration » (245)
Profil synthèse						
32 études	14 pays	PH (*n* = 18) UC (*n* = 30)	Min. : 2 Max. : 8	Min. : 4 Max. : 378	Interventions (*n* = 10)	Min. : 7 Max. : 729

AMDE = analyse des modes de défaillance et de leurs effets; AMDEC = analyse des modes de défaillance, de leurs effets et de leur criticité; IC = indice de criticité; Max. = maximum; Min. = minimum; NA = non applicable; ND = non déterminé; SIP = soins intensifs pédiatriques.

Le circuit du médicament en établissement de santé est complexe et comporte au moins 54 étapes[50], de la sélection des médicaments à leur élimination, en passant notamment par la prescription, la validation pharmaceutique, la préparation, l'administration et la consignation des renseignements au dossier du patient ou d'autres registres. Bien que des investissements importants aient été effectués dans ce circuit au cours de la dernière décennie, avec une informatisation de plusieurs processus et une robotisation de plusieurs de ces étapes (p. ex. ensacheuse, robot, pompe de remplissage, armoire automatisée, lecteur code-barres), force est de constater les nombreux modes de défaillance et les risques inhérents à cette complexité. À titre d'exemple, le rapport 2016-2017 sur les incidents et les accidents survenus lors de la prestation de soins de santé et de services sociaux au Québec révèle un total de 503 447 incidents et accidents rapportés au cours de la dernière année. De ce nombre, ceux liés à la médication représentent 26,6 % (*n* = 133 850) tandis que ceux liés à des équipements représentent 1,4 % (*n* = 7220)[51].

Tableau 2. Profil synthèse des AMDE et des AMDEC utilisées dans le circuit du médicament

Référence	Pays	Processus en pharmacie (PH) ou en unités de soins, cliniques externes (UC)	Nombre de professions représentées dans l'équipe de recherche	Nombre de modes de défaillance détectés	Interventions (protocole avec AMDE ou AMDEC pré-post seulement)	Mode de défaillance comportant IC le plus élevé (valeur de l'IC rapportée dans l'étude)
Ashley and Armitage (2010)[43]	Royaume-Uni	PH + UC	3	30	NA	« Réaction allergique » (16)
Day et al. (2006)[44]	États-Unis	UC	Au moins 3	21	NA	« Prescription d'hémodialyse » (16)
Esmail et al. (2005)[45]	Canada	UC	5	13	NA	« L'infirmière prend le mauvais médicament » (12)
Li et al. (2017) [46]	Chine	PH + UC	6	5	NA	« Erreur de prescription (dose, soluté, fréquence, horaire) » (16)
Ouellette-Piazzo et al. (2007)[47]	États-Unis	UC	ND	20	NA	Non spécifié
van Tilburg et al. (2006)[48]	Pays-Bas	PH + UC	7	61	NA	« Changement de la prescription pas relevé par la pharmacie » « Ancienne dose servie par la pharmacie après un changement de la prescription » (8)
Vélez-Díaz-Pallarés et al. (2013)[49]	Espagne	PH + UC	5	11	NA	« Erreurs de prescription » (16)
Profil synthèse						
7 études	Six pays	PH (*n* = 4) UC (*n* = 7)	Min. : 3 Max. : 7	Min. : 5 Max. : 61	Aucune intervention	Min. : 8 Max. : 16

AMDE = analyse des modes de défaillance et de leurs effets; AMDEC = analyse des modes de défaillance, de leurs effets et de leur criticité; IC = indice de criticité; Max. = maximum; Min. = minimum; NA = non applicable; ND = non déterminé.

Ainsi, au moins 28 % des incidents et accidents rapportés en établissement de santé au Québec sont liés au circuit du médicament. En tenant compte de la classification proposée par le National Coordinating Council for Medication Error Reporting and Prevention (NCCMERP), on compte parmi les événements indésirables liés à la médication, huit de catégorie I (associés à un décès), 11 de catégorie H (associés à des interventions de maintien de la vie), sept de catégories G (associés à des conséquences permanentes pour le patient) et 99 de catégories F (associés à des conséquences temporaires pour le patient). L'utilisation d'AMDE / AMDEC / AMDECS peut contribuer à l'analyse du processus et des étapes du circuit du médicament et mener ainsi à des interventions plus ciblées concernant le circuit du médicament. Ces analyses devraient être plus largement utilisées dans le réseau de la santé canadien.

Les AMDE / AMDEC / AMDECS incluses dans notre revue documentaire atteignent généralement les objectifs fixés, soit d'établir un inventaire des modes de défaillance potentiels associés à un processus et d'évaluer les conséquences potentielles de la survenue de ces défaillances. Seule 10 des 39 analyses retenues décrivent une démarche de type pré et postimplantation. En fait, quatre de ces 10 analyses présentent une méthode où l'équipe multidisciplinaire a été invitée à déterminer et à coter théoriquement des mesures correctives pré et postimplantation avant leur application éventuelle : les modes de défaillance, leurs effets et leur criticité. En apportant des changements à une pratique, on peut introduire de nouveaux modes de défaillance, ce qui rend la somme des IC difficilement interprétable. Une analyse pré et postimplantation revêt de l'intérêt surtout si l'on compare les indices de criticité avant et après le changement, plutôt que la seule comparaison de la somme des indices.

Même si les analyses AMDE / AMDEC / AMDECS n'atteignent leur plein potentiel de réduction des risques qu'en étant réalisées de façon pré et postimplantation, les analyses ponctuelles demeurent les plus fréquentes. Ce compromis en soi révèle combien la réalisation des AMDE / AMDEC / AMDECS est un exercice qui peut être exigeant. La réalisation de ce type d'analyse requiert des travaux préliminaires afin de sélectionner le processus et les étapes ciblées, de cartographier ces derniers et de revoir la littérature. De plus, l'analyse exige la mobilisation de divers professionnels durant plusieurs rencontres afin d'expliquer la méthode, de présenter la cartographie préliminaire des processus et des étapes, de déterminer les modes de défaillance et de procéder à la cotation de chacun des modes. La réalisation d'un AMDE /

AMDEC / AMDECS peut s'échelonner sur plusieurs semaines et ne donne de bons résultats que lorsque tous les intervenants sont présents à toutes les rencontres. En outre, la nature de l'exercice demeure qualitative. La méthode permet de structurer des rencontres et d'encourager les échanges entre les membres d'une équipe multidisciplinaire sur la nature des modes de défaillance. Un tel effort d'analyse n'est pas forcément facile à répéter après un changement de pratique ou après l'implantation de mesures correctives au sein d'un établissement. Compte tenu de l'investissement personnel des participants dans la démarche, toute évaluation postérieure devrait préférablement reposer sur les mêmes panélistes. Toutefois, il est probablement plus judicieux de faire une étude observationnelle avec un protocole spécifique à la détermination de l'impact des changements mis en place. Par conséquent, la méthode AMDE ne peut pas avoir d'impact direct, car elle n'est conçue que pour déterminer les situations problématiques.

Même dans les publications médicales plus récentes, les articles retenus employant la méthode AMDECS demeurent minoritaires par rapport à ceux portant sur l'AMDE et l'AMDEC, malgré le fait que l'AMDECS relève directement du domaine de la santé. Rah et collab.[52] ont comparé l'AMDEC et l'AMDECS pour déceler les processus associés à un risque élevé en chirurgie. Bien que les résultats concordent à 85 % entre les deux approches, les auteurs soulignent l'importance d'essayer différentes approches et d'utiliser celle qui correspond davantage à ses besoins[52].

La consultation des 39 études met en évidence une grande hétérogénéité, tant pour les processus et les étapes ciblés que pour les modes de défaillance détectés et les cotes attribuées à chacun. Cette hétérogénéité est une conséquence de l'application de la méthode AMDE / AMDEC / AMDECS. Chaque établissement, chaque équipe multidisciplinaire, chaque processus comporte ses particularités. Il faut très souvent ajuster les échelles de cotation afin d'obtenir un degré suffisant de résolution pour commenter le processus étudié. Par exemple, si on analyse une étape qui se produit 1000 fois par jour avec un taux d'erreur de 1 %, il faut probablement faire ajuster la cote de fréquence de survenue d'un mode de défaillance par une échelle utilisant des heures et des jours plutôt qu'une échelle type utilisant davantage des jours-mois-années. En outre, la cotation des modes de défaillance dépend de la connaissance fine des processus et des étapes qu'ont les panélistes, mais également des données locales et de la littérature qui aident à baliser la fréquence, la sévérité et la capacité de détection des modes de défaillance.

En somme, les résultats d'une AMDE / AMDEC / AMDECS sont avant tout utiles pour un établissement donné. Ils lui servent à prendre conscience des modes de défaillance, de leur hiérarchie et à encourager la mise en place de mesures correctives. Si l'on envisage de répéter cette méthode dans le temps, afin de se comparer à soi-même, la comparaison doit se faire à l'aide d'un échantillon comparable de modes de défaillance ou en étant conscient de l'introduction de nouveaux modes. S'il est peu utile de comparer les indices globaux de criticité entre les études ou entre des établissements, il est intéressant de consulter les différents modes de défaillance d'un autre établissement et la magnitude du risque associée à chacun, peu importe si on réalise ou non de telles analyses localement.

Cette revue documentaire comporte des limites. Tout d'abord, notre étude n'a eu recours qu'à une seule base de données. D'autres sources de données pourraient donc être envisagées (p. ex. Embase, Google Scholar) afin de découvrir des études supplémentaires. Ensuite, notre étude présente uniquement un profil descriptif général. Enfin, une analyse qualitative détaillée de chacune des études pourrait permettre de déterminer les difficultés rencontrées, les meilleures échelles de cotations et les approches de rencontres optimales.

CONCLUSION

Cette revue de littérature porte sur 39 articles publiés ayant utilisé l'approche AMDE / AMDEC / AMDECS dans le cadre du circuit du médicament. La plupart des études utilisent l'approche AMDE / AMDEC, tandis que l'AMDECS n'est que rarement employée. Il existe en outre une grande hétérogénéité entre les différentes analyses sur le plan des processus ciblés et des méthodes employées. Seule une minorité des études font état d'analyses réalisées avant et après l'implantation de mesures correctives. L'AMDE / AMDEC / AMDECS est une approche multidisciplinaire très utile pour cartographier un processus de soins, déterminer les modes de défaillance et prioriser les actions correctives. Il faudrait encourager son usage pour l'optimisation du circuit du médicament.

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Safety Rounds: A Patient Safety Initiative

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INTRODUCTION

The reporting of medication safety incidents is an important responsibility of hospital pharmacists. The authors had the impression that within the Department of Pharmacy at their institution, medication safety incidents, including near misses, were not being reported or were being reported reluctantly. Computerized prescriber order entry (CPOE) and electronic medication administration records (eMARs) were soon to be implemented at this hospital. With the planned changes in pharmacy and medication workflows, it was expected that additional safety concerns would arise. We used an established safety program, the Comprehensive Unit-based Safety Program (CUSP),[1] to identify, implement, and measure a safety initiative to see whether we could improve the culture of safety within the department.

DESCRIPTION OF PROGRAM

St Michael's Hospital is a university-affiliated tertiary care hospital with 463 inpatient beds in Toronto, Canada. The CUSP was chosen as the model for the Department of Pharmacy's safety initiative, because it calls for front-line staff to identify the safety issue that will be addressed and its possible solutions; in addition, CUSP requires that the impact of the intervention be measured. The CUSP model is a 6-step quality improvement program, as described in Table 1. This implementation and evaluation project involved both inpatient and hospital-affiliated clinic pharmacists; however, pharmacists working in the outpatient community pharmacy of the hospital were excluded.

Step 1 of CUSP involved conducting a baseline assessment (in May 2011) to allow subsequent measurement of the impact of the intervention. The Hospital Survey on Patient Safety Culture,[2] a validated survey instrument, was used to assess 7 unit-level and 3 hospital-level aspects of safety culture and to determine an overall safety grade. For each statement in the survey, the number of responses of "agree" and "strongly agree" was used to calculate the positive response rate. To determine the overall safety grade, respondents were asked to choose 1 of 5 responses, ranging from "excellent" to "failing". The survey was disseminated electronically through the SurveyMonkey online survey tool at 2 time points: baseline (step 1 of CUSP) and 1 month after completion of CUSP (step 6). The timing of the second survey, at a point when the intervention had been in place for 4 months, was chosen because we did not wish concurrent medication system changes to affect the results. All pharmacists who had worked in the department both before and after CUSP implementation were invited to complete the surveys. Completion of the survey implied consent to participate in the study. The protocol was approved by the St Michael's Hospital Research Ethics Board.

As step 2 of CUSP, the institution's medical director of quality and safety provided 2 educational sessions to pharmacists on the topic of the culture of safety and the institution's safety initiatives. After these sessions, pharmacists were asked to complete another online survey (SurveyMonkey) to identify their top 3 safety concerns and their preferred methods of disseminating any safety information (step 3). Responses were collated by themes. The top safety concern identified in this survey was the possibility that new types of errors might be introduced by implementation of the CPOE/eMAR system. The preferred method of communicating information about the occurrence of errors related to the new CPOE/eMAR system was a group session that would provide an open forum for discussion of the errors and their potential resolution. Hence, "safety rounds" became the intervention identified for implementation and measurement. The initiative was endorsed by the director of pharmacy (step 4).

The safety rounds were modelled after "Pharmacy Improving Patient Safety" rounds at the London Health Sciences Centre (London, Ontario),[3] although the structure and follow-up differed. Our safety rounds were hour-long sessions held every 2 weeks (step 5). All pharmacists were encouraged to attend during the first 4 months of the program. To best foster safety improvement, ground rules were established and agreed upon by participants with regard to confidentiality, shared learning, and

Table 1. Steps in the Comprehensive Unit-Based Safety Program[1]

Step	Activity	Site-Specific Details
1: Measurement	Conduct cultural survey	Collected baseline data using the Hospital Survey on Patient Safety Culture.
2: Education	Provide training in the science of safety	Medical director of quality and safety delivered 2 lectures on the culture and science of safety to pharmacy staff.
3: Engagement	Identify safety concerns and interventions	Pharmacists were asked to identify the top 3 patient safety concerns within the Department of Pharmacy and to identify methods by which department members could work together to resolve safety issues. The project team compiled results and identified safety rounds as the intervention.
4: Endorsement	Garner senior executive support	Proposed safety rounds were introduced at the monthly pharmacist meeting. The proposed intervention received support from the director of pharmacy.
5: Intervention	Deliver program	Safety rounds were held every 2 weeks for 4 months (total of 8 rounds, 1 h each). Meeting minutes taken during each session were shared with participants.
6: Measurement	Document outcome of intervention	Program was evaluated, using the Hospital Survey on Patient Safety Culture, 1 month after completion of step 5, and results were compared with baseline data.

the nonpunitive nature of the rounds. The safety rounds were facilitated by the Department of Pharmacy's professional practice leader (E.T.). Before rounds, actual or near misses and associated safety concerns were identified by pharmacists by means of the hospital's incident tracker or were reported directly to the professional practice leader. During rounds, each case or incident was presented, along with a root-cause analysis, if applicable. Participants then discussed the case, to validate the findings of the root-cause analysis and to explore potential process and practice changes that could prevent or minimize recurrence. A total of 8 safety rounds were conducted over 4 months. On average, 2 to 4 incidents or topics were discussed at each session. The average attendance was 21 pharmacists (range 8 to 29).

FINDINGS

Before the intervention, 33 (72%) of 46 eligible pharmacists completed the Hospital Survey on Patient Safety Culture; after the intervention, 14 (50%) of 28 eligible pharmacists did so. The lower number of eligible respondents for the post-intervention survey was due to staff turnover; all responses submitted for each survey were included in the analysis. The demographic characteristics for the 2 groups were similar with respect to age, experience, and training (data not reported). There was no change in rating for the domain for "overall perception of safety" (46% before the intervention versus 44% after the intervention). Several domains showed a substantial increase in positive rating (e.g., teamwork within the unit and feedback about errors), while for others there was a decrease in positive rating (e.g., hospital management support for patient safety, teamwork across units, and handoffs and transitions) (Figure 1). All respondents rated the overall safety grade for the department as excellent, very good, or acceptable both before and after the intervention (before the intervention: excellent 9%, very good 47%, acceptable 44%; after the intervention: very good 53%, acceptable 47%).

DISCUSSION

The lack of an increase in the overall perception of a safety culture, as measured by the surveys, may be attributed to the responses for specific safety domains. In particular, positive responses decreased for the 2 domains of hospital management support and hospital handoffs and transitions, with the latter domain being one of the lowest-ranking domains both before and after CUSP.

The decrease in positive perception of hospital management support reflects the perceived delay in implementation of system-wide changes that were discussed during the safety rounds. Hence, one lesson learned is the need to educate pharmacists that changes at the corporate level may take time, because other departments, disciplines, and stakeholders may have to be involved. The need for involvement of other stakeholders may also explain the post-implementation decrease in perception of the domain of teamwork across units. In other words, we can influence our own practice sooner and more effectively than we can influence the practice of other disciplines.

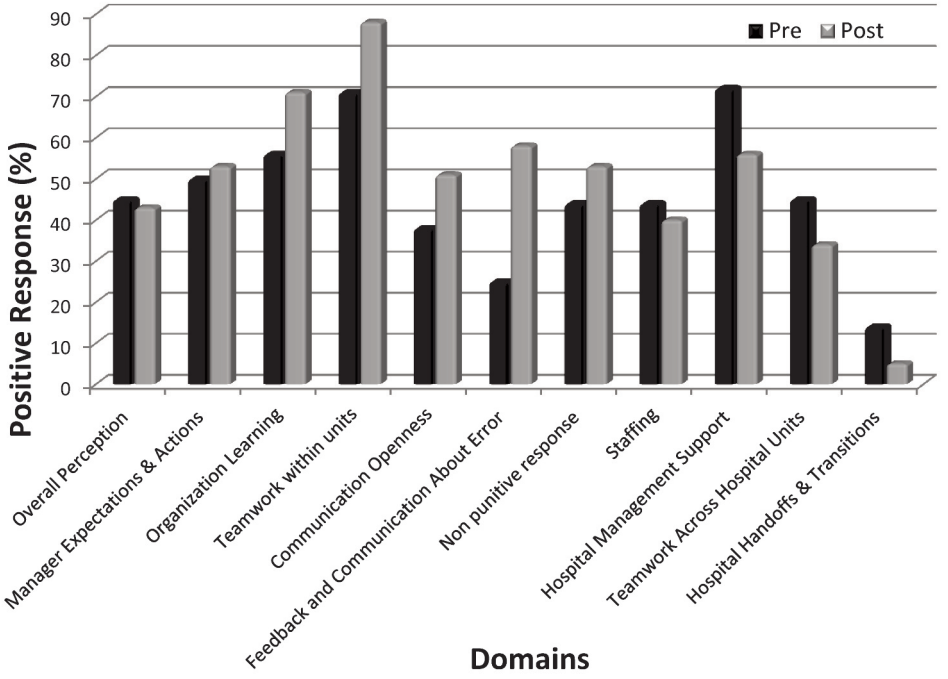

Figure 1. Results of the Hospital Survey on Patient Safety Culture, subdivided by safety domain, before (pre) and after (post) implementation of the Comprehensive Unit-based Safety Program. The data indicate percentages of respondents at each time point who "agreed" or "strongly agreed" with the statements contributing to that domain.

The decrease in positive responses for the perception of hospital handoffs and transitions may be related to the hybrid paper and electronic medication ordering system that was in place as CPOE was implemented over a period of 12 months. Transitions of patients between units with different systems resulted in a large number of errors. Although this transfer-related problem could not be resolved during the safety rounds, discussion increased awareness of the problem and alerted pharmacists to the high potential for errors during patient transfers within the dual system while it was in place.

With the collaborative, interdepartmental discussions initiated through this project, safety rounds brought about increases in positive perceptions for the domains of organizational learning, teamwork within the unit (e.g., within the Department of Pharmacy), and feedback about errors. All of these domains were directly addressed by the safety rounds.

IMPLICATIONS

Safety rounds were thought by the pharmacists to be valuable and hence were continued beyond the CUSP project period. Since implementation of CPOE throughout the entire hospital, the type of errors discussed during safety rounds has changed from errors and incidents related to CPOE transitions of care to medication-specific issues (e.g., tapering doses for steroids). One of the lessons learned was the need to create a pharmacist work group to further evaluate and assess the feasibility of ideas proposed during safety rounds. Recommendations from this work group are discussed during monthly pharmacists' meetings and then implemented. This work group has also been able to create a mechanism for communication of information to other disciplines to address multidisciplinary medication issues.

Although for the purposes of this project, the safety rounds were initially limited to pharmacists, monthly safety rounds have since been implemented for pharmacy technicians. Joint pharmacist and technician safety rounds have also been piloted, with the aim of holding these sessions quarterly, to discuss errors and concerns that affect both groups.

LIMITATIONS

The project, which led to significant changes in pharmacists' day-to-day activities, was carried out during the summer months, at a time when the department had a large number of staffing changes. This turnover occasionally affected attendance at the safety rounds and may also have affected the response rate for the second survey. Existing practices, policies, and culture at other institutions may limit the generalizability of these results.

SIGNIFICANCE FOR PRACTICE

In an increasingly complex medication system, it is important for pharmacists to have a safe venue to discuss and resolve identified safety concerns. At St Michael's Hospital, safety rounds have proven to be an effective mechanism to engage staff, creating a forum where staff can discuss errors and possible solutions to avoid recurrence. Although the measured perception of a culture of safety did not increase during this program, the actions of the pharmacists have improved. Whereas initially errors were reluctantly reported, now both errors and near misses are routinely reported. With pharmacists' ongoing participation in error reporting and the continuation of these safety rounds, we hope that future surveys will reveal an enhanced culture of safety in the Department of Pharmacy of St Michael's Hospital.

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Propofol-Induced Green Breast Milk: A Case Report

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INTRODUCTION

Propofol is indicated for the induction and maintenance of general anesthesia, for sedation during intensive care, and for conscious sedation during surgical and diagnostic procedures.[1] Propofol undergoes extensive metabolism in the liver to form water-soluble metabolites that are renally excreted.[1] Some of the metabolites have been associated, in a multitude of case reports, with green discoloration of the patient's urine.[2-9] Propofol is also highly lipophilic.[1] It has been reported that propofol passes minimally into maternal breast milk.[10] One previous publication reported the occurrence of green breast milk after propofol administration, although the authors were unable to confirm the presence of propofol in the breast milk by laboratory analysis.[11] Here, we present another case report of green breast milk following propofol administration and discuss the pharmacokinetic characteristics of this drug that could explain its possible excretion into breast milk. We also suggest a diligent approach to analysis and care for future cases.

CASE REPORT

A 27-year-old woman presented to the emergency department with a 4-day history of increasing right lower quadrant, periumbilical pain, and decreased appetite.* She reported no oral intake since 2 days before presentation. The patient's obstetric history consisted of 5 pregnancies and 5 full-term births, her last child having been born 8 months before the presentation. She was actively breastfeeding at a frequency of 6 to 8 times daily without any reported complications.

The patient's prior medical history included bicornuate uterus, insertion of an intrauterine device 2 months after the most recent birth, and abdominal hernia repair 2 years before the current presentation. She reported daily use of a multivitamin and an omega-3 supplement, as well as occasional intake of acetaminophen, but no use of prescribed medications. She had no allergies and denied using recreational drugs, smoking tobacco, or consuming alcohol.

The results of hematological and biochemical laboratory tests showed no abnormalities. All microbiological tests yielded negative results, including blood and urine culture. The attending staff diagnosed acute appendicitis, and the patient underwent appendectomy under general anesthesia. Intraoperative findings included an extremely fibrotic appendix and meso-appendix, both of which were removed.

During the procedure, the patient received cefazolin, granisetron, ketorolac, propofol, rocuronium, succinylcholine, and sufentanil. The patient also received 2 induction boluses of propofol (IV), with the first dose of 150 mg being followed shortly after by the second dose of 50 mg. The surgery was successful, with no complications and minimal blood loss.

Twenty-two hours after the procedure, the patient extracted her breast milk for the first time since surgery. The collected breast milk had a light green colour. However, no discoloration of the urine was noted. Her active medications at that time were regular acetaminophen, cefazolin, ibuprofen, and pantoprazole, as well as as-needed doses of oxycodone and dimenhydrinate. A sample of the extracted green breast milk was analyzed by gas chromatography–mass spectrometry for the presence of propofol.[12] However, this technique yielded negative results. The patient refrained from breastfeeding but continued extracting her milk. She experienced no postoperative complications and was discharged home from the hospital in stable condition on postoperative day 2. The patient reported that her breast milk spontaneously and progressively returned to its usual colour and was completely free from any green discoloration by postoperative day 4, at which point breastfeeding was resumed with no issues.

*The patient provided verbal consent for publication of this case report. Approval was also granted by the local institutional research ethics board.

DISCUSSION

Few studies have demonstrated the passage of propofol into breast milk.[10,11] However, many of propofol's pharmacokinetic properties favour this transfer. After its administration, propofol rapidly distributes from the blood to surrounding tissues in a 3-compartment model.[1] Propofol is highly lipophilic and non–water soluble, with a volume of distribution of 2.85 to 6.07 L/kg.[1] Therefore, even after a single bolus dose, propofol is widely distributed and has a terminal half-life of up to 480 min.[1] This significant lipophilicity favours its diffusion through the mammary alveoli and its solubility and accumulation in the lipid fraction of breast milk.[13] Furthermore, any medication with a molecular mass less than 500 daltons may easily diffuse into breast milk.[13] Propofol's low molecular mass of 178.3 daltons[1] therefore favours its passage into breast milk. Conversely, propofol is highly protein-bound (up to 99%), and molecules that are more than 95% protein-bound are less likely to diffuse into the breast milk.[13]

Propofol undergoes extensive metabolism in the liver to form water-soluble inactive metabolites that are renally excreted.[4,6,14,15] Less than 1% of propofol is excreted unchanged in the urine.[16] The main metabolic pathway of propofol includes oxidation by the cytochrome P450 2B6 isozyme, and to a lesser extent cytochrome P450 2C9 isozyme, as well as phase II metabolism to form the drug's main metabolites: propofol glucuronide, quinol-1-glucuronide, quinol-4-glucuronide, and quinol-4-sulphate conjugates.[4,6,12,16] Other minor metabolites have also been identified.[12,14]

The pharmacokinetic properties of propofol metabolites have not been thoroughly investigated. However, Bleeker and others[17] found that propofol and its glucuronide metabolites were detectable in the plasma up to 15 h after surgery, with the glucuronide metabolites being excreted in the urine for more than 60 h after surgery, following continuous infusion of propofol in 9 patients who underwent lung surgery. Therefore, in the case reported here, it is possible that propofol metabolites were present in the patient's breast milk when it was extracted 22 h after surgery.

Many case reports have described the effect of propofol on the colour of urine. Most of the published cases have reported the occurrence of green discoloration after continuous infusion of propofol. There have also been a few cases in which green urine was observed shortly after a single bolus induction dose of propofol.

In 3 cases, propofol induction doses (100 to 200 mg), administered for endotracheal intubation or preoperative sedation, were associated with green discoloration of the urine within just a few hours after administration or as little as 1 h after surgery.[9,18,19] In the first case, the green colour resolved by the end of the 2.5-h surgery.[9] In the 2 other cases, urine colour returned to normal 24 h after administration[18] and 48 h after surgery.[19]

Lee and others[3] reported 3 cases of green discoloration of the urine after continuous infusion of propofol. Sedation was maintained with propofol infusion rates of 3 to 4 mg/kg per hour.[3] In 2 of these cases, the green urine appeared after 6 h of infusion, whereas in the third case the discoloration was observed after 64 h. In all cases, urine colour returned to normal 3 to 6 h after propofol discontinuation.[3] No concomitant use of medication known to cause green urine discoloration was reported.

The green colour of urine following propofol administration is believed to be caused by the inactive phenolic metabolites of this drug (1-glucuronide, 4-glucuronide, and 4-sulphate conjugates).[1,4] In the current case, the gas chromatography–mass spectrometry analysis did not detect propofol or its metabolites in the green breast milk. However, the sensitivity of the technique to detect these molecules in breast milk had not been determined in the laboratory at that time. Therefore, it is possible that propofol and its metabolites were present in the breast milk sample, but were below the limits of detection. We suggest validating the sensitivity of a gas chromatography–mass spectrometry analysis for the detection of propofol and its metabolites in future cases.[12]

Only 2 previous reports of green breast milk have been published, with inconclusive results as to the cause of the green colour. In the first report, Birkholz and others[11] hypothesized that the green breast milk was due to propofol administration. However, these authors also reported that they were unable to identify propofol and its conjugated metabolites in the expressed breast milk.[11] The breast milk discoloration was first seen 8 h after surgery and had resolved by 48 h after surgery.[11] In the current case, the discoloration resolved on postoperative day 4, much later than in the previous case. Nevertheless, divergent timing of green urine discoloration secondary to propofol has also been reported, and this variation may be due to interpatient pharmacokinetic differences. In the second prior report of green breast milk, Yazgan and others[20] hypothesized that the green discoloration was due to the iron content of the reddish-brown multivitamin that the mother had been taking daily since delivery. In the current case, the patient also had postpartum exposure to a multivitamin, which might have contained iron. However, the timing of the appearance and disappearance of the green discoloration of the breast milk, combined with the fact that the mother had been taking the multivitamin for months before this observation, led us to believe that the propofol used for anesthesia was a more likely cause than the multivitamin. Furthermore, given the common use of iron-containing multivitamins by women who are breast-feeding, green breast milk would be observed more frequently if iron supplementation was the cause. We calculated a Naranjo score of 4, indicating propofol as a possible cause of the adverse drug reaction of green breast milk in this case.[21]

CONCLUSION

Propofol metabolites may discolour biological fluids other than urine. We have described a second case of green breast milk following administration of propofol. Health care professionals and patients should remain vigilant for this possible, though rare, adverse event. Given the uncertainty about trace amounts of propofol in the green breast milk, breastfeeding in this situation might expose the infant to uncertain effects; therefore, we recommend caution in the continuation of breastfeeding until the colour returns to normal. If breastfeeding is pursued, we recommend that the infant be closely monitored.

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Should Emergency Pharmacists Focus on Providing Care to Admitted Patients Rather than Non-admitted Patients?

THE "PRO" SIDE

Emergency pharmacists (EPhs) should give priority to patients requiring admission, both to improve patient outcomes and to reduce health care costs.[1,2] I am making this argument with recognition that prioritization will always be required, as there are many other valuable activities to which EPhs can devote their time. The prioritization of inpatients is paramount during the provision of pharmaceutical care in the emergency department (ED), to address the factors contributing to high risk for adverse drug events (ADEs) and medication errors, such as ED overcrowding, diversity of clinical presentations, use of high-risk medications, and high patient–health care provider ratios.[3]

ED overcrowding has reached epidemic proportions, as a result of an imbalance between public demand and hospital capacity.[4] It is associated with an increased risk for medication errors, which can be alleviated by the services that EPh provide.[5] In Canada, about 11% of all ED visits result in inpatient admission.[6] To put this statistic into perspective, about 60% of all hospital inpatients are admitted from the ED.[6] Admitted patients' length of stay in the ED has been increasing steadily through the years, and patients can spend upward of 34 h in the ED awaiting a bed or transfer to another hospital.[6] The American Society of Health-System Pharmacists[7] endorses the concept that inpatient ward pharmacists be accountable for admitted patients, but adherence with this recommendation may not be feasible, depending on the location and acuity of individual patients. ED crowding with inpatients is often a direct result of overcapacity within the hospital, and inpatient ward pharmacists may not be able to provide timely pharmaceutical care because of their high existing workload. Brown and others[8] were able to reduce medication errors involving ED patients with prospective pharmacy review by EPhs, which included dosage calculations; identification of inappropriate drugs, routes, or schedules; order clarifications; and drug allergy clarifications.[8] Focusing the efforts of EPhs on patients who are being referred for admission is crucial, as these patients often have critical illnesses or urgent needs, and they represent high-risk populations. Through early, proactive involvement, EPhs can reduce the risk of medication errors.

The ED is characterized by a diversity of clinical presentations, and previous studies have supported the use of EPhs for timely administration of high-risk medications or procedures in acute phases of illness, such as cardiopulmonary resuscitation, pain management, sepsis management, procedural sedation, intubation, and antifibrinolytic therapy.[9] Patients in need of such high-risk medications and procedures are often in critical, complex situations, have high pharmacotherapeutic needs, and are likely to be admitted. As such, EPhs should give them priority and be proactive in their management to improve patient outcomes. For example, rather than reactively identifying ADEs after admission orders have been processed, EPhs can proactively support the admission team at the time admission orders are prepared. This crucial role was apparent in a study showing that admitted patients seen by EPhs received more appropriate initial medication regimens, as reflected by a 75% reduction in interventions by ward pharmacists.[10] Therefore, the ED is a good location for pharmacists to effectively identify and resolve preventable ADEs for patients who will be admitted with a diversity of presentations.

ADEs account for about 28% of all ED visits and 24% of hospital admissions.[11] Furthermore, more than one-third of drug-related ED presentations identified by pharmacists have been missed by emergency physicians.[12] These cases are associated with longer hospital stays, greater mortality, and higher costs to the health care system.[13] Most preventable ADEs that happen in the ED are attributed to improper medication reconciliation or to inappropriate medication orders.[14] Therefore, Accreditation Canada has identified medication reconciliation as a priority for Canadian hospitals, which are expected to complete this process for all ED patients with a decision to admit.[15] Pharmacist-led management of ADEs and preparation of admission drug histories have been associated with lower mortality rates.[1] Importantly, EPhs are able to provide more accurate best possible medication histories (BPMHs) than other health professionals, and are associated with fewer medication errors.[16] Thus, timely medication histories and identification of ADEs in the medication reconciliation process may result in admitted patients having an accurate medication regimen early in their hospital stay and early identification of medication-related events. Barriers to practice, such as insufficient time to perform medication reconciliation activities, may be overcome with adequate pharmacy staffing in the ED. This was made evident by a Canadian survey, in which only 23% of ED pharmacy teams surveyed reported that their

EDs had adequate staffing, and 81% of ED managers expressed the need for additional staffing in the ED to allow proper completion of BPMHs.[17]

The issues described above—overcrowding of the ED, driven by high numbers of admitted patients, who have diverse, clinically complex problems (including ADEs) and who are taking high-risk medications while awaiting transfer to the ward (with further potential for ADEs)—mean that the volume of patients frequently exceeds the capacity of the health care practitioners caring for them. ED nurses must frequently administer potentially dangerous medications, and medication orders may be given verbally in critical patient situations.[18] Medication errors can occur because of the high patient–nurse ratios, nurses' inability to properly check medicines being administered, nurses' fatigue secondary to high patient volume, and therefore the possibility of nurses forgetting to administer medications. One study showed that ED nurses administered medications in a less timely manner than ward nurses for boarded (admitted) patients,[18] the most common reason being "insufficient time". In that study, medication reviews and intervention by EPhs ensured that medication administration complied with the orders prescribed.[18] In addition, the provision of education about time-sensitive medications to other health professionals, such as timely administration of antibiotics for patients with sepsis, can improve patient outcomes.

In conclusion, as the volume of patients admitted from the ED increases with ED overcrowding, prioritization of these patients by the EPh is important for the safe and prompt treatment of these patients. EPhs are integral to ED medical teams, and ideally they should provide pharmaceutical care to all patients, regardless of admission status. However, because of funding constraints, only 39% of Canadian hospitals had at least 0.5 full-time equivalent clinical pharmacy services personnel in the ED.[19] Therefore, until adequate pharmacy staffing is available in the ED, prioritization of those at highest risk of medication errors—who are often inpatients awaiting transfer to the ward—is crucial in the provision of care.

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THE "CON" SIDE

For most pharmacists, stepping into the emergency department (ED) can feel like stepping into the jungle: scary, unpredictable, and chaotic. These feelings are justified. The ED is a fast-paced, complex environment with a diverse population (ambulatory to critical care, pediatrics to geriatrics, medical to surgical, and involving resuscitations and traumas).[1] The ED is particularly prone to medication errors given the high volume of patients, frequent interruptions, high frequency of verbal orders, and common use of high-risk medications.[2] To enhance the quality of care and the safety of drug delivery in the ED, an emergency pharmacist (EPh) must fulfill a unique role that is different from those of both ambulatory and inpatient pharmacists. To optimize this role, the EPh should prioritize

the care of non-admitted patients (i.e., ambulatory patients not requiring admission and patients who are ill enough to require admission but have not yet been formally admitted to a hospital service).

Other countries have recognized the ED as a unique clinical environment and have developed guidelines for EPh roles. The American Society of Health-System Pharmacists (ASHP) lists medication order review, drug information, and patient care involving high-risk medications and procedures as priorities for the EPh, placing lower importance on medication reconciliation and care of admitted patients.[3] When EPh staffing is insufficient (e.g., when only a single EPh is present in the ED, as is the case for most of Canadian hospitals[4]), the ASHP recommends that the ward pharmacist, not the EPh, be accountable for admitted patients remaining within the ED.[3] Similarly, the practice standards of the Society of Hospital Pharmacists of Australia advocate for the prioritization of patients at greatest risk of adverse drug reactions, with lower priority being given to admitted patients provided they can be assessed by the ward pharmacist within 24 h.[5]

In Canada, the role of the EPh is still relatively new. The Canadian Society of Hospital Pharmacists has not developed any guidelines for the EPh role, and standardization is lacking. A recent survey of Canadian EPhs revealed a wide range of activities performed, with heavy emphasis on medication reconciliation and care of admitted patients.[4] The lack of ED specialty residencies and role models, and a paucity of emergency medicine training in Canadian pharmacy curricula may limit pharmacists' confidence to care for non-admitted patients. The reported activities may reflect pharmacists' familiarity and comfort, rather than what's in the best interest of the ED and its patients.

By prioritizing the care of admitted patients, EPhs miss the opportunity to intervene with the assessment, prescribing, administration, and monitoring of all mediations administered by the ED team. The literature suggests that both the quality and safety of care of ED patients are improved when EPhs are involved as early as possible in the ED visit (Box 1).[6-13] The EPh improves outcomes through involvement in traumas, resuscitations, and the care of patients requiring time-sensitive medications before the decision to admit. These patients often have multiple non–drug-related issues requiring physician and nursing care, such that without involvement of an EPh focusing on the optimization of medications, drug therapy issues may be overlooked by the rest of the team. The clinically significant end points in Box 1 can be achieved only when the EPh is available throughout the assessment and care of these critically ill patients before their admission.

EPhs can also facilitate positive outcomes through their care of less acutely ill patients who are likely to be discharged home. For example, more than 1 in 9 ED visits are drug-related, but only one-third of the affected patients are admitted to hospital[14]; the remaining two-thirds would benefit from assessment by an EPh. As another example, in the absence of interaction with an EPh, the drug therapy of non-admitted patients may not be assessed until a later visit to a community pharmacist, who will not have access to the hospital medical record and laboratory results. When EPhs review ED discharge prescriptions, they may intervene in up to 10% of cases.[15] Outcomes are also improved when EPhs provide discharge education targeting high-risk medications such as opioids[16] and anticoagulants.[17]

Box 1. Quality and Safety Outcomes of Selected Emergency Pharmacist Activities

Trauma
- Decreased time to postintubation sedation (by 19 min) and analgesia (by 23 min)[6]
- Improved appropriateness of antibiotics for type 3 open fractures (74% versus 29%)[7]

Resuscitation
- Higher survival to hospital admission (25% versus 17.8%)[8]
- 13-fold reduction in errors during trauma and resuscitation[9]

Stroke
- 20-min reduction in time to thrombolysis[10]
- Lower stroke disability scores at 24 h[11]

Sepsis
- 20% improvement in appropriateness of empiric antibiotics[12]
- 44-min reduction in time to first antibiotics[13]

When EPhs are freed from caring for admitted patients, a door opens upon new opportunities. Many innovative EPh-led programs have been described in which an EPh takes on nontraditional roles as a value-added service to the health care system. EPh-driven programs have led to a 50% decrease in time to administration of prothrombin complex concentrate in patients with warfarin-associated hemorrhage[18] and to discontinuation of antibiotics for 55% of patients without a urinary tract infection (as determined by post-discharge culture review).[19] Safe and effective patient outcomes have also been demonstrated when EPhs managed phenytoin dosing[20] and influenza vaccinations[21] or led a venous thromboembolism clinic.[22]

In summary, EPhs are not simply inpatient pharmacists located in the ED. Medication reconciliation and assessment of admitted patients can be done by other members of the pharmacy team, and prioritizing admitted patients impedes the EPh's ability to perform value-added activities. Each ED is unique, and EPhs should work with physician, nursing, and pharmacy leaders to identify departmental priorities and determine how they can best improve the quality and safety of ED care. It is time to expand our conceptions of the EPh role. Together, let's lace up our boots and bravely go deeper into that jungle.

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L'erreur est humaine…

par Douglas Doucette

Dernièrement, la question des erreurs de médicaments a reçu beaucoup d'attention. Lors d'un récent congrès en pharmacie, Melissa Sheldrick a raconté l'histoire déchirante du décès de son fils par surdose involontaire de baclofène impliquant la pharmacie de la famille. Depuis, Melissa est devenue l'une des plus ferventes militantes pour la sécurité des patients, et je vous encourage à prendre connaissance de ses efforts courageux visant la prévention des erreurs de médicaments (https://pharmacyconnection.ca/interview-melissa-sheldrick-winter-2018/). L'été dernier, les médias canadiens ont fait état d'un incident de sous-dosage potentiel attribuable aux procédures d'administration par voie intraveineuse de trois antinéoplasiques (https://www.theglobeandmail.com/canada/article-hundreds-of-cancer-patients-received-partial-doses-of-medication/). De nombreux hôpitaux et centres de cancérologie ont détecté l'erreur et entrepris d'informer autant de patients et de leur famille que possible, de répondre à leurs inquiétudes concernant les risques potentiels et de les assurer que le problème avait été corrigé pour les patients subséquents (https://www.theglobeandmail.com/canada/article-manitoba-will-now-inform-cancer-patients-of-partial-doses-as-quebec/).

Des études montrent que les erreurs de médicaments et les réactions indésirables graves aux médicaments constituent une des principales causes de préjudices dans le monde. L'Institut canadien d'information sur la santé indiquait récemment qu'une hospitalisation sur dix-huit occasionnait un préjudice, et que bon nombre de ces incidents étaient liés aux médicaments (https://www.cihi.ca/sites/default/files/document/cihi_cpsi_hospital_harm_fr.pdf). Pour remédier à cette tendance, la Société canadienne des pharmaciens d'hôpitaux (SCPH) s'engage à faire évoluer les pratiques en matière de sécurité des médicaments, comme le démontrent ses fréquentes collaborations avec d'autres organisations et organismes. Par exemple, les *Lignes directrices : Déclaration et prévention des incidents médicamenteux* (consultable au https://www.cshp.ca/medication-incidents), élaborées par la SCPH conjointement avec l'Institut pour l'utilisation sécuritaire des médicaments du Canada, détaillent l'information sur les meilleures pratiques pour la déclaration et la prévention des incidents liés aux médicaments à l'intention des programmes organisationnels afin d'améliorer la qualité des soins aux patients. Dans le même ordre d'idées, la SCPH a collaboré avec l'Institut canadien pour la sécurité des patients et avec d'autres organismes afin de mettre au point l'outil *Cinq questions à poser au sujet de vos médicaments* dans le but d'aider patients et soignants à parler de médicaments et d'améliorer la communication auprès des fournisseurs de soins de santé (http://www.patientsafetyinstitute.ca/fr/toolsresources/5-questions-to-ask-about-your-medications/pages/default.aspx).

Un récent sondage de la SCPH, réalisé dans le cadre de son programme Excellence (consultable au https://www.cshp.ca/what-we-heard), montre que 68 % des répondants occupant des postes de direction ont eu à participer à l'évaluation de l'efficacité des stratégies de réduction des risques au sein du système d'utilisation des médicaments de leur organisation. Même si ce résultat indique la mise en pratique des connaissances, le tiers des répondants peut encore faire mieux. En ce qui concerne les soins directs aux patients, les stratégies à adopter peuvent comprendre une attention accrue aux décisions prises lors du transfert des soins et la promotion d'initiatives comme la déprescription et la gestion responsable des antimicrobiens, des opioïdes et d'autres classes de médicaments. Toujours selon ce sondage, les patients souhaiteraient en apprendre davantage au sujet de l'utilisation, des bienfaits et des effets indésirables de leurs médicaments. Les cliniciens de première ligne peuvent contribuer à réduire le risque d'erreurs de médicaments et des préjudices qui en découlent grâce à des consultations avec les patients afin de comprendre leurs croyances et leurs comportements vis-à-vis de leurs médicaments et de leur état de santé, de leur prodiguer des conseils et de faire part de leurs plans et objectifs aux autres fournisseurs de soins de santé.

Au fil des ans, la SCPH s'est mobilisée pour promouvoir la sécurité des patients et la diminution des préjudices liés aux médicaments qui peuvent être évités. Parallèlement, en tant que praticien, vous assumez un rôle vital dans la détection et la déclaration des erreurs. Demandez-vous dans quelle mesure vous êtes conscient de la détection d'erreurs et des stratégies de déclaration et de prévention d'erreurs liées aux médicaments en place dans votre service ou votre établissement. Quelle serait votre réaction ou celle de votre équipe à une erreur de médicament touchant l'un de vos patients, que le préjudice subi soit apparent ou non? Quel soutien offririez-vous à ce patient et à sa famille ainsi qu'aux fournisseurs de soins de santé impliqués? En réfléchissant à ces questions à l'avance, vous contribuerez à prévenir et à affronter les erreurs de médicaments.

[Traduction par l'éditeur]

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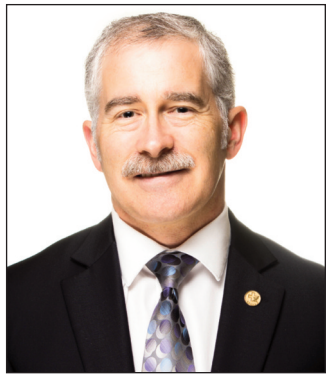
To Err Is Human, …

Douglas Doucette

The issue of medication errors has been receiving much attention lately. At a recent pharmacy conference, Melissa Sheldrick shared the heartbreaking story of her son's death from an unintended overdose of baclofen involving the family's pharmacy. Melissa has become a leading advocate for patient safety, and I encourage you to read about her courageous efforts to prevent medication errors (https://pharmacyconnection.ca/interview-melissa-sheldrick-winter-2018/). This past summer, Canadian media reported on a medication error involving 3 oncology drugs that were potentially underdosed as a result of IV administration procedures (https://www.theglobeandmail.com/canada/article-hundreds-of-cancer-patients-received-partial-doses-of-medication/). Numerous hospitals and cancer centres detected the error, undertaking widespread notification of patients and families, responding to their concerns about the potential risks, and providing assurances that the issue had been resolved for future patients (https://www.theglobeandmail.com/canada/article-manitoba-will-now-inform-cancer-patients-of-partial-doses-as-quebec/).

Research shows that medication errors and serious adverse drug reactions are a leading cause of harm worldwide. The Canadian Institute for Health Information recently reported that harm occurred for 1 of every 18 hospitalizations in Canada, with many of these incidents involving medications (https://www.cihi.ca/sites/default/files/document/cihi_cpsi_hospital_harm_en.pdf). To counter this statistic, the Canadian Society of Hospital Pharmacists (CSHP) is committed to advancing medication safety practices, as evidenced by frequent collaborations with other organizations and agencies. For example, developed in conjunction with the Institute for Safe Medication Practices Canada, the CSHP's *Medication Incidents: Guidelines on Reporting and Prevention* (available through https://www.cshp.ca/medication-incidents) provide best-practice information for organizational programs to report and help prevent medication incidents, and enhance quality of patient care. Similarly, CSHP collaborated with the Canadian Patient Safety Institute and others to develop *5 Questions to Ask About Your Medications*, a tool to help patients and caregivers talk about medications and improve communications with healthcare providers (http://www.patientsafetyinstitute.ca/en/toolsResources/5-Questions-to-Ask-about-your-Medications/Pages/default.aspx).



The CSHP's recent survey of its Excellence program (available from https://www.cshp.ca/what-we-heard) showed that 68% of management level respondents were involved in evaluating the impact of risk reduction strategies for the medication system within their organization. This finding indicates that knowledge is being translated into practice, but one-third of respondents still have room to improve. In direct patient care, such strategies may involve paying more attention to decisions at transitions of care and promoting initiatives such as deprescribing and stewardship of antimicrobials, opioids, and other medication classes. The same survey showed that patients want to learn more about the uses, benefits, and side effects of their medications. Front-line clinicians can help to reduce the risk of medication errors and related harm through patient encounters, seeking to understand patients' beliefs and behaviours about medications and health conditions, providing education, and sharing goals and plans with other healthcare providers.

Over the years, CSHP has shown strong advocacy for patient safety and the reduction of preventable medication harm. At the same time, you, as individual practitioners, have a vital role in detecting and reporting errors. Reflect on your own level of awareness for error detection and the strategies available in your department or institution for reporting or preventing medication errors. How would you and your team respond to a medication error involving your patient, whether or not harm was evident? How would you support the patient and family, and those healthcare providers involved? Thinking about these issues ahead of time will help in efforts to prevent and address medication errors.

Douglas Doucette, BSc(Pharm), PharmD, FCSHP, is President and External Liaison for the Canadian Society of Hospital Pharmacists.

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