ARTICLE

Impact of a Pharmacist-Initiated Therapeutic Drug Monitoring Consult Service for Children Treated with Gentamicin

Ryan Murphy, Mirjana Chionglo, and L Lee Dupuis

ABSTRACT

Background: Starting in April 1988, the Pharmacy Department at The Hospital for Sick Children, Toronto, Ontario, provided a therapeutic drug monitoring (TDM) consult service for patients admitted to nursing units that did not have a clinical pharmacist as a member of the interdisciplinary team. This service was withdrawn on July 1, 2003.

Objective: To determine the appropriateness of clinicians' response to exceptional serum concentrations of gentamicin (peak concentration outside the range 5 to 10 mg/L or trough concentration outside the range 0.6 to 2 mg/L) and subsequent laboratory monitoring before and after termination of the pharmacist-initiated TDM consult service.

Methods: A chart review was conducted for the 6 months before and 6 months after removal of the pharmacist-initiated TDM consult service. All children admitted to general surgery units who received gentamicin therapy and who were reported to have exceptional serum concentrations of this drug were included. The ideal gentamicin dose assessment was determined for each concentration pair (peak and trough), and this ideal assessment was then compared with the dose assessment actually performed. Laboratory tests ordered (serum concentrations of gentamicin and creatinine) were compared with the institution's standard of care.

Results: Clinicians' action in response to exceptional serum gentamicin concentrations was appropriate in 99% (93/94) of cases before removal of the consult service and in 64% (64/100) of cases after removal of the service ($p < 0.001$). Furthermore, there were statistically significant differences in subsequent gentamicin monitoring with respect to ordering of repeat gentamicin concentration after dose adjustment, timeliness of dose adjustment, and ordering and drawing of samples for weekly determination of trough gentamicin concentrations and serum creatinine for patients whose therapy lasted longer than 7 days.

Conclusions: The appropriateness of assessment in cases of exceptional serum gentamicin concentration decreased significantly after withdrawal of a pharmacist-initiated TDM consult service.

ABSTRACT

Historique : En avril 1988, un service de consultation pour la surveillance pharmacocinétique des médicaments (SPM) a commencé à être offert par le service de pharmacie du Hospital for Sick Children, à Toronto en Ontario, pour les patients admis aux unités de soins qui n'avaient pas de pharmacien clinicien attitré au sein de leur équipe interdisciplinaire. Ce service a été aboli le 1er juillet 2003.

Objectif : Déterminer la pertinence de la réaction des cliniciens face à des concentrations plasmatiques de gentamicine exceptionnelles (concentration maximale en dehors de la marge de 5 à 10 mg/L ou concentration minimale en dehors de la marge de 0,6 à 2 mg/L) et de la surveillance subséquente des examens de laboratoire avant et après l'abolition de ce service de consultation pour la SPM assuré par le pharmacien.

Méthodes : Une analyse des dossiers médicaux a été menée dans les six mois précédant et suivant l'abolition du service de consultation pour la SPM assuré par le pharmacien. Tous les enfants admis à une unité de chirurgie générale, ayant reçu de la gentamicine et présentant des concentrations plasmatiques exceptionnelles de gentamicine ont été admis à l'étude. L'évaluation idéale de la dose de gentamicine a été déterminée pour chaque paire de concentrations (maximale et minimale), puis comparée à l'évaluation réelle de la dose. Les examens de laboratoire demandés (concentrations plasmatiques de gentamicine et de créatinine) ont été comparés aux normes de soins de l'établissement.

Résultats : La réaction des cliniciens face à des concentrations plasmatiques exceptionnelles de gentamicine était appropriée dans 99 % (93/94) des cas avant l'abolition du service de consultation, et dans 64 % (64/100) des cas après l'abolition de ce service ($p < 0{,}001$). De plus, on a observé des différences statistiquement significatives dans la surveillance subséquente relative à la gentamicine, notamment au chapitre de la revérification des concentrations de gentamicine après un ajustement de la dose, du moment de l'ajustement de la dose, ainsi que de la prescription et du prélèvement d'échantillons pour le dosage des concentrations minimales de gentamicine et des concentrations plasmatiques de créatinine pour les patients dont l'antibiothérapie dépassait sept jours.

Key words: gentamicin, therapeutic drug monitoring, pharmacist

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Conclusions : La pertinence de l'évaluation dans les cas de concentrations plasmatiques exceptionnelles de gentamicine a diminué significativement après l'abolition du service de consultation pour la SPM par le pharmacien.

Mots clés : gentamicine, surveillance pharmacocinétique des médicaments, pharmacien

INTRODUCTION

Therapeutic drug monitoring (TDM) of certain medications is essential to obtain the desired therapeutic effect and to reduce toxic effects. Aminoglycosides have a narrow therapeutic index and large interpatient pharmacokinetic variability. It is generally accepted that peak and trough serum aminoglycoside concentrations correlate with efficacy and toxic effects, respectively.[1] These factors make TDM a necessary component of safe and effective aminoglycoside therapy.

The pharmacist's knowledge of TDM facilitates individualized aminoglycoside dosing. Inappropriate ordering and interpretation of serum gentamicin concentration have justified the development of structured pharmacist-based pharmacokinetic services in other hospitals.[2]

The application of clinical pharmacokinetics is a common function of clinical pharmacy services. Pharmacist-based TDM services related to aminoglycosides have been shown to increase the likelihood of obtaining adequate peak concentrations, increase the frequency of clinical improvement, decrease the number of drug doses administered, decrease the mean total dose administered, and minimize changes in serum creatinine from baseline.[3-6] Furthermore, pharmacist-based TDM services have decreased morbidity and mortality, length of drug therapy, duration of hospital stay, and direct costs.[2-8]

From April 1, 1988, until July 1, 2003, a pharmacist-initiated TDM consult service was provided at The Hospital for Sick Children, an urban tertiary care centre located in Toronto, Ontario, for patients admitted to nursing units that did not have a clinical pharmacist as a member of the interdisciplinary team. For such patients, pharmacists automatically assessed all serum drug concentrations outside accepted therapeutic ranges and then designed individual dosing regimens and coordinated blood sampling for future monitoring of serum drug concentrations. The consult service was withdrawn on July 1, 2003, and the assessment of children with subtherapeutic or supratherapeutic serum drug concentrations became the physician's responsibility.

The purpose of this study was to determine the impact of removing the pharmacist-initiated TDM consult service on children treated with gentamicin. The primary outcome was the appropriateness of clinicians' actions (specifically dose adjustments) in response to exceptional serum gentamicin concentrations. The secondary outcome was the appropriateness of subsequent laboratory monitoring in relation to the hospital's standards of care.

METHODS

This study was approved by the Research Ethics Board at The Hospital for Sick Children.

A chart review was conducted for patients treated between January 2003 and January 2004, which represented the 6 months before and the 6 months after removal of the pharmacist-initiated TDM consult service (on July 1, 2003). All children admitted to general surgery units who received gentamicin therapy and who were reported to have exceptional serum gentamicin concentrations were included in the study. The following data were collected: age, sex, diagnosis, indication for gentamicin therapy, gentamicin dose, duration of gentamicin therapy, serum creatinine concentration, and serum gentamicin concentration.

Assessment of Serum Gentamicin Concentrations

All patients received traditional q8h gentamicin dosing. Exceptional serum concentrations of this drug were defined as peak value outside the range 5 to 10 mg/L and trough value outside the range 0.6 to 2 mg/L, as stated in the institution's standard of care.[9] For each point of assessment, the dose administration times recorded in the medication administration record and the peak and trough concentrations recorded in each

patient's chart were used to calculate the gentamicin elimination rate constant and half-life. The extrapolated maximal concentration and ideal dose adjustment were then calculated for each serum gentamicin concentration pair (peak and trough) using the Sawchuk–Zaske Method.[10,11] Measures of patient response were not included in the assessment of appropriateness.

Outcomes

The clinician's actual response in terms of dose adjustment was compared with the ideal calculated response to determine appropriateness. A clinician's response was considered appropriate if (1) a dose adjustment was unnecessary and no dose adjustment was initiated or (2) a dose adjustment was necessary and the revised regimen was correct. A clinician's response was considered inappropriate if (1) a dose adjustment was necessary but no dose adjustment was initiated, (2) a dose adjustment was necessary but the dose adjustment performed was incorrect, or (3) a dose adjustment was unnecessary but a dose adjustment was completed.

To determine the appropriateness of the clinician's plan for subsequent laboratory monitoring, the following data were collected: ordering of repeat determinations of serum gentamicin concentrations after dose adjustment, the appropriateness of timing of any dose adjustment, ordering of weekly determinations of trough gentamicin concentration and serum creatinine for courses of therapy longer than 7 days, and adjustment of antibiotics according to culture results.

The institution's standards of care with respect to gentamicin dosing and monitoring were published in the formulary, which was freely available to all medical, nursing, and pharmacy staff during the study period.[9]

Statistical Analysis

The sample size was calculated on the basis of assumptions that 90% of the exceptional serum gentamicin concentrations monitored by a pharmacist-initiated TDM consult service would be assessed appropriately but only 75% of those monitored by physicians (after removal of the TDM consult service) would be assessed appropriately. A minimum sample size of 112 pairs of serum gentamicin determinations per group was deemed necessary to allow for a type I error rate of 0.05 and a type II error rate of 0.20 (power of 80%). Data collection was stopped before the calculated sample size was reached because an overwhelmingly significant difference was observed between the groups.

Differences observed before and after removal of the pharmacist-initiated TDM consult service were analyzed with either the χ^2 test or Fisher's exact test (for sample size less than 30). Statistical analyses were performed using Statistical Package for Social Sciences for Windows (version 10.1; SPSS Inc, Chicago, Illinois).

RESULTS

One hundred and forty-six children, for whom a total of 194 pairs of gentamicin results were available, were included in this study: 72 children (with 94 pairs of results) before discontinuation of the pharmacist-initiated TDM consult service and 74 children (with 100 pairs of results) after discontinuation of the TDM consult service (Table 1).

The actions taken in response to exceptional serum concentrations of gentamicin were appropriate in 93 (99%) of 94 instances with the TDM service in place and in 64 (64%) of 100 instances after the TDM service was terminated ($p < 0.001$) (relative risk 21.92, 95% confidence interval 3.16–152.23). Of the 93 instances in which the clinician's action was appropriate while the TDM service was in place, 72 (77%) required no dose adjustment, and 21 (23%) required an adjustment. Of the 64 instances in which the clinician's action was appropriate after discontinuation of the TDM service, 56 (88%) required no dose adjustment, and 8 (12%) required an adjustment. Of the 36 instances in which the clinician's action was inappropriate after discontinuation of the TDM service, 20 (56%) involved a dose adjustment that was necessary but not made or made incorrectly, and 16 (44%) involved modification of the drug regimen when no dose adjustment was necessary. Of instances when a dose adjustment was required, the adjustment was made before the next scheduled dose in all 21 cases when the TDM service was in place but in only 1 of 8 cases after the TDM service was discontinued ($p < 0.001$).

The sample sizes for assessment of the secondary outcome were smaller because no dose adjustment was required in most cases (Table 2). Before discontinuation of the TDM service, repeat determination of serum gentamicin concentration was ordered appropriately in all 21 cases after dose adjustment. After discontinuation of the service, repeat determination of serum gentamicin concentration was ordered appropriately in only 5 of 8 cases after dose adjustment ($p = 0.006$).

Table 1. Characteristics of Children Receiving Gentamicin Before and After Discontinuation of a Therapeutic Drug Monitoring (TDM) Service

Characteristic	No. (%) of Patients*	
	With TDM Service (*n* = 72)	Without TDM Service (*n* = 74)
Median age (years)	8.5	5.8
Age range	110 days–17.5 years	7 days–15.6 years
Male	46 (64)	47 (64)
Female	26 (36)	27 (36)
No. of gentamicin concentration pairs	94	100
Median length of gentamicin treatment and range (days)	5 (1–30)	6 (1–20)
No. of positive culture results	15	16
Underlying condition		
Appendicitis	29 (40)	32 (43)
Malignancy	9 (12)	11 (15)
Pelvic abscess	5 (7)	2 (3)
Bowel obstruction	2 (3)	5 (7)
Other†	27 (38)	24 (32)
Indication for gentamicin		
Surgical prophylaxis	61 (85)	63 (85)
Febrile neutropenia	5 (7)	6 (8)
Documented infection	2 (3)	4 (5)
Urinary tract infection	2 (3)	0
Other	2 (3)	1 (1)

*Except where indicated otherwise.
†Includes esophageal obstruction, Crohn's disease, ulcerative colitis, gastroesophageal reflux, gastroenteritis, abdominal abscess, pelvic abscess, perianal abscess, peritonitis, jejunal perforation, biliary atresia, splenic laceration, cholangitis, lung resection, pancreatic transection, spina bifida, necrotizing fasciitis, chronic osteomyelitis, and Hirshsprung's disease.

For 42 patients, 14 in the period before discontinuation of the TDM service and 28 after discontinuation, gentamicin therapy continued beyond 7 days. A weekly trough gentamicin concentration was appropriately requested for all 14 patients before discontinuation and for 4 of the 28 patients after ($p < 0.001$). Interestingly, the requested trough concentration was actually drawn for only 5 of the 14 patients before discontinuation and for 4 of the 28 patients (i.e., all of those for whom it was requested) after discontinuation ($p < 0.001$). Similar patterns of ordering and drawing of samples emerged for serum creatinine (Table 2).

There were 15 positive blood culture results before and 16 positive results after discontinuation of the TDM service. The appropriateness of adjustment of antibiotics on the basis of culture results could not be compared because there were no requirements for changes in antibiotic therapy.

DISCUSSION

In this study, pharmacists made appropriate gentamicin dose adjustments in response to serum concentrations of the drug more frequently than physicians (99% and 64%, respectively; $p < 0.001$). Other similarly designed studies have shown benefit from a pharmacist-initiated TDM consult service. Bollish and others[2] evaluated a pharmacist-based aminoglycoside pharmacokinetic service by assessing the appropriateness of determinations of serum gentamicin concentration before and after a 6-month pilot service was implemented. Their chart review included 43 serum gentamicin determinations (for 20 patients) before and 243 determinations (for 39 patients) after implementation of the service. Before implementation of the TDM service, 6 (14%) of the serum gentamicin concentrations were assessed appropriately, whereas after implementation of the service, 231 (95%) of the results were assessed appropriately.

Anderson and others[12] analyzed the appropriateness of ordering and interpretation of serum gentamicin concentrations by physicians over a 10-month period. Definite indications for obtaining serum gentamicin level determinations were present for 189 (89.2%) of 212 samples. In total, 110 (51.9%) of 212 samples were improperly drawn, and 85 (40.1%) of the 212 results were ignored (no action taken). Furthermore, only 26 (42%) of the 62 correctly drawn (and not ignored) samples for determination of serum gentamicin were acted on appropriately. In the opinion of the

Table 2. Results for Secondary Outcome (Appropriateness of Response)

Question and Response	With TDM Service	Without TDM Service	*p* value
Were gentamicin concentrations ordered appropriately after dose adjustments?	(*n* = 21)	(*n* = 8)	0.006
Yes	21	5	
No	0	3	
Was the gentamicin dose adjusted before the scheduled next dose?	(*n* = 21)	(*n* = 8)	<0.001
Yes	21	1	
No	0	7	
For therapy > 7 days, was a weekly determination of trough concentration ordered?	(*n* = 14)	(*n* = 28)	<0.001
Yes	14	4	
No	0	24	
For therapy > 7 days, was a weekly sample drawn for determination of trough concentration?	(*n* = 14)	(*n* = 28)	<0.001
Yes	5	4	
No	9	24	
For therapy > 7 days, was a weekly determination of serum creatinine ordered?	(*n* = 14)	(*n* = 28)	<0.001
Yes	14	9	
No	0	19	
For therapy > 7 days, was a weekly sample drawn for serum creatinine determination?	(*n* = 14)	(*n* = 28)	0.005
Yes	11	9	
No	3	19	

TDM = therapeutic drug monitoring.

study's authors, at most 42 (19.8%) of 212 serum gentamicin results were used appropriately in making patient care decisions. Flynn and others[13] assessed the frequency and appropriateness of determination of serum gentamicin concentration over a 9-week period and found that only 10 (22%) of 45 results were used to make appropriate therapeutic decisions.

In the chart review reported here, most of the cases required no dose adjustment (77% before and 88% after discontinuation of the TDM service). The latter finding, coupled with a lack of documentation about serum gentamicin concentrations for patients treated after discontinuation of the service, made it difficult to determine whether or not serum gentamicin concentrations were actually assessed. However, in this situation, it was assumed that the clinician made a conscious decision to continue with the initial dosing regimen. Furthermore, as previously mentioned, the pattern of clinicians' inappropriate assessments after discontinuation of the TDM service was inconsistent. Therefore, the reasoning behind these patient care decisions is unknown.

After discontinuation of the TDM service, the clinicians appeared to assume that determination of serum gentamicin concentration was appropriately timed with respect to dose administration. Thus, gentamicin dose adjustments were made in 12 instances in this patient group when an appreciation of the impact of the timing of the samples relative to the time of dose administration would have suggested no dose adjustment.

The appropriateness of timing of dose adjustments differed between the 2 groups. Before discontinuation of the TDM service, all dose adjustments were made before the next scheduled dose. However, after discontinuation of the service, most dose adjustments were not made before the next scheduled dose, which would have increased the potential for suboptimal therapy or toxic effects. With prolonged gentamicin therapy, weekly monitoring of trough gentamicin concentration or serum creatinine was always suggested, although not always implemented, for patients treated before discontinuation of the TDM service. Pharmacists were able to suggest monitoring parameters through the hospital ordering system, but these orders required authorization by a physician before they could be implemented. After discontinuation of the TDM service, weekly monitoring of trough gentamicin concentration and serum creatinine was rarely ordered or carried out. This suggests a lack of understanding about the increased risk of nephrotoxicity with prolonged

gentamicin therapy on the part of both physicians and nurses. Clearly, education regarding nurses' compliance with orders for laboratory tests is also required.

This study was limited by its retrospective nature. The data extracted were not always complete. Exact dose times were not always available and, when necessary, standard dose times were assumed when calculating pharmacokinetic parameters. Also, documentation regarding the assessment of serum gentamicin concentrations was not always adequate for patients treated after discontinuation of the TDM service; therefore, explanations for decisions with respect to dose adjustment or lack thereof were not always available. Conclusions about secondary outcomes are limited by the small number of data points available for analysis.

After elimination of the pharmacist-initiated TDM consult service, a TDM algorithm was put in place to allow continued triaging of responses to TDM questions (as in Table 2). Physicians were directed to call the Drug Information Service or the dispensary when pharmacist support was required for specific patients; if a full clinical consult was necessary, a TDM-certified pharmacist was available. Through this mechanism, 4 pairs of serum gentamicin determinations, included in the results for the second patient group, had full pharmacist consultation with documentation. Informal assistance by pharmacists in the Drug Information Service or the dispensary was not adequately documented, and it is therefore impossible to accurately determine the degree of pharmacy involvement in the decision-making process for patients treated after discontinuation of the formal TDM service. Furthermore, 17 pairs of serum gentamicin determinations in this group involved children with febrile neutropenia who were followed by the Haematology/Oncology Service. Physicians in this service have greater exposure to TDM, as well as limited TDM education as part of their orientation. In addition, the Haematology/Oncology team includes pharmacists who are often consulted informally regarding the care of children who are receiving care on other units (off-service). In previous studies, the impact of pharmacist-based TDM services has been evaluated after implementation of such services, but not after withdrawal of the service, as was done here. It is possible that the care provided by physicians and nurses after withdrawal of the pharmacist-initiated TDM service in this study was influenced by prior interaction with pharmacists. Continued pharmacy involvement after removal of the TDM service, as well as the education provided during the period when the pharmacist-initiated TDM service was available, may explain why the results in this investigation were not as dramatic as reported by other investigators.

Finally, the impact of a pharmacist-based TDM service on direct patient outcomes was beyond the scope of this retrospective study. However, pharmacist-based TDM services involving aminoglycosides have led to positive patient outcomes in other hospitals, including decreases in morbidity and mortality, length of drug therapy, and duration of hospital stay.[4-8]

In conclusion, the appropriate assessment of exceptional serum gentamicin concentrations decreased significantly after discontinuation of a pharmacist-initiated TDM consult service. Potential consequences may include increased potential for toxic effects, increased potential for suboptimal therapy, decreased quality of life, increased workload, and increased overall costs. Given these results, the Pharmacy Department will review strategies to improve TDM in nursing units without clinical pharmacy services by focusing on physician education and expanding clinical pharmacy services to all areas of the hospital.

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Ryan Murphy, BScPharm, ACPR, was, at the time this study was conducted, a pharmacy resident at The Hospital for Sick Children, in Toronto, Ontario. He is now the Health Programs Manager at Murphy's Health Education Centre, Charlottetown, Prince Edward Island.

Mirjana Chionglo, BScPhm, ACPR, is the Haematology/Oncology Pharmacist in the Department of Pharmacy and the Division of Haematology/ Oncology at The Hospital for Sick Children, Toronto, Ontario.

L Lee Dupuis, MScPhm, ACPR, FCSHP, is a Clinical Coordinator in the Department of Pharmacy and a member of the Division of Haematology/Oncology and of Child Health Evaluative Sciences, Research Institute, at The Hospital for Sick Children, and is a member of the Faculty of Pharmacy, University of Toronto, Toronto, Ontario. She is also an Associate Editor with *CJHP*.

Address correspondence to:
Ryan Murphy
Health Programs Manager
Murphy's Health Education Centre
20 Linden Avenue
Charlottetown PE
C1A 3Y8

e-mail: rmurphy@murphyspharmacies.com

Correction

For all scientific research articles in the February and April issues of CJHP, the bibliographic citation line at the end of the abstract (giving the year, volume, and page range of the article) had an incorrect date. The year should be 2007.