Dose-Banding of Intravenous Piperacillin-Tazobactam in Pediatric Surgical Inpatients

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BACKGROUND Antimicrobial doses in children are often prescribed by using an individually calculated dose per weight (e.g., mg/kg) or based on body surface area. Dosing errors are the most commonly reported medication errors in children. A “dose-banding” strategy is frequently used for some over-the-counter drugs to prevent dosing errors. It could also lead to efficiencies by enabling batch preparation of intravenous (IV) medications in hospitals.

OBJECTIVES To evaluate whether use of dose-banding for IV piperacillin-tazobactam results in acceptable dose variation from standard practice of individualized prescription of 100 mg/kg in children.

METHODS We conducted a historically controlled intervention study comparing prescriptions of IV piperacillin-tazobactam before vs. after introduction of dose-banding prescribing guidance for surgical inpatients weighing >5 kg and <16 years of age at the tertiary referral pediatric hospital in Western Australia.

RESULTS Dose-banding of IV piperacillin-tazobactam (with a maximum of 15% departure from the recommended milligram-per-weight dose of 100 mg/kg) resulted in similar overall variation of prescribed dose in comparison to individualized milligram-per-weight (non-dose-banded) prescribing. There was a trend toward fewer prescriptions with large variance (>30% variation from the 100-mg/kg dose) in the dose-banded compared to the non-dose-banded group (1/140 vs. 5/105; $p = 0.09$).

CONCLUSIONS Our study showed dose-banding of IV piperacillin-tazobactam resulted in acceptable variation when compared to individualized milligram-per-weight dosing in children. Prospectively designed controlled trials are warranted to determine whether dose-banding could reduce medication errors and optimize use of hospital resources. Implications for future practice could include faster batch preparation, shorter checking and dispensing time, and reduction in drug wastage.

ABBREVIATIONS BSA, based on body surface area; IV, intravenous

KEYWORDS drug dose-banding; intravenous antibiotics; medication errors; pediatric surgical inpatients; prescribing errors

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Introduction

The ideal dose for a patient is the minimum dose to achieve maximum efficacy without side effects or with acceptable toxicity. Medication errors are one of the most common types of medical error.¹ Medication errors among children occur at every stage of the process from prescribing to administration,² although prescribing errors appear to be most common for antimicrobial agents.³ Unlike adults, for whom standard doses exist for most drugs regardless of patient size, most drugs in children are prescribed on the basis of drug mass per patient weight (e.g., mg/kg) or in some instances on the basis of drug mass per body surface area (BSA) as mg/m². This practice is unique to pediatrics and may partly explain why prescribing errors are more common among children than adults.^{4,5}

Medical incident reports are likely to underestimate

the true rate of medication errors.⁶ A systematic review suggested the prescribing error rate in children is between 5% and 27%,^{7–11} while prospective evaluation of drug charts placed the prescribing error rate in children as high as 13%.¹² In addition to the potential for error in calculating individual doses based on weight or BSA for children, age-based variability in absorption, metabolism, and excretion of drugs, as well as age-specific contraindications of certain medications, might make children more susceptible to complications arising from dosing errors as compared to adults.^{13,14} As many medications for children come in a range of liquid formulations and concentrations, the manual conversion of doses from drug weight (in mg) to volumes (in mL) may also contribute to dosing errors.^{15–17} Additionally, many drugs used in children are used for “off-label” indications, leading to less clear dosing guidance and greater potential for error.^{7–9}

“Dose-banding” is a strategy used frequently for self-administered “over-the-counter” medications to simplify patient administration and to help prevent medication errors. Dose-banding of some chemotherapeutic agents is also published widely.^{18–20} In dose-banding, the ranges (or bands) of body weight and corresponding rounded doses are predefined. The individual dose of a particular patient is calculated according to a single body weight value per band, usually the midpoint of the body weight band in which the actual body weight of the patient lies. The dose-banding strategy has several potential advantages over individualized milligram-per-weight or non-dose-banded dosing such as avoiding error through individualized dose calculations, enabling more cost-efficient batch preparation, reduced turnaround and patient waiting time, reduced medication wastage, and easier detection of prescription dose errors.^{18–21}

There are several published guidelines for pediatric rounding for antimicrobial drugs and some of these have been incorporated into electronic prescribing systems.^{22–24} Dose-banding has been shown to be a viable and efficient method for intravenous (IV) antibiotic treatment in neonates.²⁵ However, there is only 1 study that has measured the impact of dose-banding of antimicrobial drugs in children on prescribing errors rate.²⁶ Our study aimed to assess whether introduction of a simple dose-banding algorithm for IV piperacillin-tazobactam would result in greater variation of prescribed doses from the ideal mg/kg dose, compared to that observed historically for individualized milligram-per-weight dosing, and to study its effects on prescribing errors in pediatric surgical inpatients weighing over 5 kg and <16 years of age at our hospital.

Materials and Methods

Setting, Participants, and Comparison. This study was conducted in the surgical unit of our tertiary pediatric referral center. We retrospectively reviewed 105 consecutive pediatric patients who received IV piperacillin-tazobactam (preintervention group) between July and October 2014 among surgical inpatients ≥ 5 kg and <16 years of age at Princess Margaret Hospital and compared them with 140 consecutive patients receiving IV piperacillin-tazobactam immediately post implementation of dose-banding (postintervention group) in June 2015 in the same unit (Figure). The 105 patients in the preimplementation group received 488 prescriptions usually as a course over an average of 4.6 days. The 140 patients from the postimplementation group received 628 prescriptions as a course over 4.5 days. Duplicate prescriptions in both the groups were excluded as they were repeats for the same patient at exactly same doses. General surgical patients were selected to be included as they usually get admitted to a single ward and generally receive IV piperacillin-tazobactam postoperatively before step down to oral

Figure. Patient selection process and study methodology.

antibiotics. The most frequent diagnoses among the patients were appendicitis, burns, abscess in various body sites, infected wound, trauma wound repair, dog bite wound repair, and stoma site infection.

Intervention. In keeping with Australian guidelines, 100 mg/kg (piperacillin component) was considered the “recommended milligram-per-weight dose” for IV piperacillin-tazobactam. A validated set of published guidelines for IV piperacillin-tazobactam considered 15% as a safe rounding range for children.²⁷ Hence, we decided to round the doses to maximum 15% departure from the 100-mg/kg dose. Body weight categories and their corresponding rounded doses were defined such that the maximum departure from the 100-mg/kg dose was 15% (Table 1). Children ≥ 40 kg received the maximum IV dose of 4 g (piperacillin component) 3 times a day for non-severe infection. An educational in-service was provided for staff surgeons and their junior staff in their clinical meeting, and summary lanyard cards (Table 1) were distributed. The lanyard cards gave contact details for our study team for any queries. Education and distribution of lanyard cards also occurred for nurses at 2 in-service sessions, one each for morning and evening shift staff. Hospital pharmacists were educated about the program in 2 clinical meetings; ward pharmacists were asked to notify the project team where dose-banding recommendations were not being adhered to. Preparation of the medication involved the following steps: 1) order charted as per-dose bands; 2) dose checked to ensure it complied with the dose

Table 1. Lanyard Depicting Weight-Based Dose Bands for IV Piperacillin-Tazobactam Used in the Intervention

Weight Band, kg	Recommended Piperacillin-Tazobactam Dose*
5–6	500 mg
>6–7	600 mg
>7–8.5	800 mg
>8.5–11	1000 mg
>11–14	1300 mg
>14–17.5	1600 mg
>17.5–22.5	2 g
>22.5–27	2.5 g
>27–32.5	3 g
>32.5–37.5	3.5 g
>37.5	4 g

IV, intravenous

* Standard dose: 100 mg/kg (piperacillin component) every 8 hours; severe infections: 100 mg/kg (piperacillin component) every 6 hours.

bands; 3) order sent to central IV admixture service for preparation; 4) medication dispensed through the dispensing software (to create a label); and 5) 24 hours of the medication prepared for each patient, making a 100-mg/mL solution into individual, patient-labeled syringes and delivered to the ward via pneumatic tube or pharmacy round as required.

We calculated the “variation” of the prescribed dose from “recommended milligram-per-weight” dose, defined as the percentage difference from 100 mg/kg to a maximum of 4000 mg, for both preintervention and postintervention groups. We categorized patients in both groups by degree of variation ranging from 0% to >30% departure from the recommended milligram-per-weight dose (larger or smaller). For the evaluation, we considered >30% variation as “prescribing error.” This was based on the assumption that such degree of variation is double of the acceptable dose-rounding margins in the published guidelines and should capture most potentially unsafe prescriptions for IV piperacillin-tazobactam.²⁶ Based on the assumption to reduce the prescription error by one-fourth from the baseline value (5% in our hospital data), with a value of 0.05 and β value of 80%, the minimum sample size was 73 in each group. We included more patients in the study to account for any loss of data and for further strengthening of the study. We used the Fischer exact test to compare the proportion of children in each category across the preintervention and postintervention groups. The *p* value of 0.05 was considered as significant.

This evaluation was approved and conducted in accordance with the Hospital Pharmacy Committee of Governance Evidence Knowledge Outcome as a Qual-

Table 2. Distribution of Weight and Sex Among Preintervention (*n* = 105) and Postintervention (*n* = 140) Groups

	Preintervention No. (%)	Postintervention No. (%)
Age Range, yr		
≤1	12 (11.4)	24 (17.1)
>1–3	15 (14.3)	13 (9.2)
>3–5	16 (15.2)	29 (20.7)
>5–10	29 (27.6)	41 (29.2)
>10–16	33 (31.4)	33 (23.6)
Weight range, kg		
5–10	12 (11.4)	28 (20)
11–20	33 (31.4)	43 (30.7)
21–30	17 (16.2)	28 (20)
31–40	22 (20.9)	13 (9.3)
>40	21 (20)	28 (20)
Sex		
Male	57 (54.3)	95 (67.8)
Female	48 (45.7)	45 (32.1)

ity Improvement Activity. De-identified information was collected from hospital prescriptions.

Results

Before introducing a dose-banding intervention, we retrospectively identified 488 consecutive prescriptions of IV piperacillin-tazobactam between July and October 2014 among surgical inpatients. A total of 105 preintervention prescriptions (1 prescription per patient) were selected for final review after removing the duplicates (Figure). These patients were referred to as “preintervention group” or “historical controls.” We then studied a comparable number of consecutive prescriptions immediately after introduction of dose-banding intervention; 140 prescriptions were chosen for review in the “postintervention group” after removal of duplicate prescriptions. The baseline characteristics of the preintervention and postintervention groups were similar (Table 2).

Overall, there was no statistically significant difference in the proportion of children in the postintervention and preintervention groups across each category of departure from recommended milligram-per-weight dose (Table 3, *p* = 0.22), although there was a trend toward fewer prescriptions with >30% variation from the recommended milligram-per-weight dose in the dose-banding group (1/140 vs. 5/105; *p* = 0.09). The prescription errors in the preintervention group ranged from 37.5% to 55% variation from the recommended milligram-per-weight dose.

Table 3. Comparison of Variation of Prescribed Dose From Recommended Milligram-per-Weight Dose of IV Piperacillin-Tazobactam in the Preintervention (n = 105) and Postintervention (n = 140) Groups

Variation of Prescribed Dose From RMW Dose (100 mg/kg), %	Preintervention, No. (%)	Postintervention, No. (%)	p value
0	44 (41.9)	53 (37.8)	0.52
>0–2.5	37 (35.2)	47 (33.5)	0.79
>2.5–5	11 (10.5)	26 (18.5)	0.08
>5–10	5 (4.8)	7 (5)	0.93
>10–20	3 (2.8)	4 (2.8)	1.0
>20–30	0 (0)	2 (1.4)	*
>30	5 (4.7)	1 (0.7)	0.089

IV, intravenous; RMW, recommended milligram-per-weight

* Undefined.

Discussion

Dose-banding appears to be a promising strategy for reducing antimicrobial prescription errors in children. Johnson et al²² proposed and validated a set of rounding ranges (in percentage) and assigned 120 of the most commonly prescribed pediatric medications to a rounding category. The Royal Brompton and Harefield have also proposed guidelines for multiple antibiotic dose bands (e.g., Aztreonam, Cefazidime, Meropenem, Metronidazole, Colistin, piperacillin-tazobactam).²³ An automated dose rounding algorithm has been proposed as a feasible mechanism for providing dose guidance via electronic prescribing systems,²³ and a pharmacokinetic simulation suggested that weight-based dose-banding of nevirapine for human immunodeficiency virus would be a simple and effective dosing strategy in resource-limited settings.²⁴ In our setting, implementation of dose-banded prescribing for IV piperacillin-tazobactam in children resulted in no greater overall variation from the recommended milligram-per-weight dose than individualized milligram-per-weight or non-dose-banded dosing. This suggests dose-banding could be a feasible strategy for pediatric IV antibiotic dose guidance.

Dose-banding has been shown to be a viable and efficient method for IV antibiotic treatment in neonates, reducing the need for babies to receive treatment within the special care neonatal unit by simplifying administration of antibiotics on the postnatal wards.²⁵ A 2-week prospective study at Royal London Hospital that evaluated 590 medication (analgesics and antibiotics) orders found that the implementation of a dose-banding strategy reduced prescribing errors rate in children significantly, from 9.4% for non-dose-banded drugs to 0% for dose-banded drugs.²⁶ In our center the proportion of prescribing errors (>30% variation from recommended milligram-per-weight dose) for IV piperacillin-tazobactam in children decreased from 4.7% to 0.7% after implementation of dose-banding (p

= 0.09). Rather than increase the overall variation from the recommended milligram-per-weight dose, our experience suggests dose-banding might be effective for reducing the incidence of significant prescribing errors. Given the small numbers and the way the pharmacy department prepared the medications for the trial it did not really alter dispensing and checking time, as it was only with a single patient group. However, if it were to be implemented hospital wide, there would be the potential to streamline batch production, which could reduce the pharmacy time required. For nursing staff on the ward preparing doses, there are the benefits of all the dilutions and draw ups being standard, which could increase safety and reduce the nursing time.

It is difficult to be certain whether the observed reduction in prescribing error is attributable to chance, the dose-banding intervention, or perhaps just an increased attention to prescribing recommendations generated by the education sessions. It was beyond the scope of our evaluation to assess any pharmacokinetic or clinical impact of underdosing or overdosing. Although we did not specifically look for drug side effects, there was no increased reporting of any severe adverse drug reaction or worse patient outcome found in the postintervention group. Our experience to date has been confined to surgical patients and where the recommended milligram-per-weight is consistent across indications. Formal evaluation of dose-banding for antibiotics used across many indications and with varying indication-specific recommended milligram-per-weight dose recommendations is warranted. Further, our experience should not be automatically generalized to other therapeutic classes like anticonvulsants with narrow therapeutic index. We did not formally elicit feedback on prescriber and nurse preferences for dose-banding over conventional dosing, although we note that adherence to the dose-banding guidelines was high.

In conclusion, our results indicate that dose-banding is a feasible strategy for prescribing IV piperacillin-tazobactam in children, and it may reduce prescribing

errors. We recommend larger prospective studies of dose-banding across a broader range of drugs and drug classes, including an assessment of any impact on pharmacokinetic parameters, clinical effectiveness, and laboratory and clinical adverse events.

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