Review Article

Precision of Pharmacokinetic Parameters in Children: A Systematic Review

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Abstract

The purpose of paediatric pharmacokinetic studies is to provide precise estimates of the true value of pharmacokinetic parameters to inform dosing. We evaluated age-specific estimates of pharmacokinetic parameters in peer-reviewed studies. Systematic reviews of 10 drugs included publications describing >1 pharmacokinetic study in patients <18 years. A pharmacokinetic study was defined as peer-reviewed primary data used to estimate one or more of Volume of distribution (Vd) or Clearance (CL). We defined uncertainty as the width of the 95% confidence interval divided by the population estimate of the study mean. Acceptable uncertainty as uncertainty was defined as <20%. Review of 21594 abstracts identified 137 eligible manuscripts containing 203 pharmacokinetic studies that included 176 Vd and 178 CL parameter estimates. Pharmacokinetic parameter estimates were derived from 2 or more age groups in 227 (64%) estimates. Acceptable uncertainty was found in 59 (34%) Vd and 35 (20%) CL, estimates. Heterogeneity was found with wide prediction intervals reported by drug and parameter. There was limited literature to support allometric dosing in the ten commonly used drugs we studied. There are multiple factors that may contribute to variability. We explore the importance of precise pharmacokinetic data, utility of parameter estimate ranges and the feasibility and extrapolation of pharmacokinetic parameter estimates. Factors contributing to observed uncertainty included modest sample sizes, within sample heterogeneity and dosing that accounts for patient factors in addition to age. These present opportunities to improve the quality and utility of pharmacokinetic data that underpins paediatric dosing.

Introduction

The success of drug therapy is contingent upon administration of the optimal dose at the optimal dosing interval. Dose and frequency recommendations are based on pharmacokinetic parameter estimates derived from pharmacokinetic studies from relevant populations [1-3]. Systematic error in dosing may occur if recommendations are based on estimates that are significantly different from the true population mean. In turn, routine sub-therapeutic or supra-therapeutic dosing will lead to biased estimates of drug effectiveness and toxicity, and undermine the value of paediatric drug therapy.

As with other estimates of 'true' population values, the precision with which population pharmacokinetic parameters are known can be assessed by the 95% confidence interval of the mean [4]. This interval includes the most plausible values of the mean for the population represented by the sample.

Confidence intervals for population values can be calculated in individual pharmacokinetic studies, or, if studies are sufficiently homogeneous, by combining similar pharmacokinetic studies using meta-analysis. Parameters known with greater precision will have narrower 95% confidence intervals and thus can more precisely inform dosing recommendations. Presently there is no recommended size for a confidence interval of pharmacokinetic parameter. By proxy, industry standards for pharmacotherapeutic precision suggest that variations of less than 10% are acceptable for preparation and administration [5].

The objectives of this study were to estimate average values of pharmacokinetic parameters in children reported in peer-reviewed publications, to assess the degree of heterogeneity between studies of similar populations and report ranges of pharmacokinetic parameters for the 10 most commonly used drugs in the ICU.

Materials and Methods

We performed a systematic review and meta-analysis of paediatric pharmacokinetic studies of ten drugs commonly given to children: acetaminophen, dopamine, fentanyl, furosemide, gentamicin, lorazepam, midazolam, morphine, ranitidine and vancomycin, were selected as they are commonly administered to critically ill children [6]. The main outcome was the precision of the population estimates of the pharmacokinetic parameters for volume of distribution and clearance. Precision was operationalized as the uncertainty of each estimate, based on our previous work [7-9] and USP standards for intravenous preparations [5]. Acceptable uncertainty was defined as where the margins of the 95% confidence interval for the population mean were within 10% of the study mean. Greater uncertainty was quantified by use of >10-50% and >50% categories.

Search Strategy

Searches were constructed and performed by an academic librarian (EU), using MEDLINE (1966 – December 2018) and EMBASE (1980 – December 2018) databases. A three-tier strategy was used. First, alternate generic, brand and alternative names for each drug were identified using MEDLINE (scope notes), EMBASE (CAS registry number), e-CPS, and STAT! Ref. These comprehensive lists of drug name alternatives were used as keywords. Second, the selection was restricted to paediatric pharmacokinetic studies using the "limit" function in search criteria (18 years or less) and keywords including "neonate, infant, child, adolescent, and pediatric". Third, the literature search was narrowed to pharmacokinetic studies using keywords including "pharmacokinetics, kinetics, volume of distribution, clearance".

Study identification, eligibility and data abstraction

Eligible publications described at least one pharmacokinetic study in patients aged 18 years and younger. An eligible pharmacokinetic study was defined as the use of primary data from intravenous drug administration, to a group of paediatric patients to estimate one or more of the pharmacokinetic parameters - clearance, and volume of distribution. Pharmacokinetic parameter estimates had to be reported in a way that was amenable to statistical analysis and not normalized to adult weight. One publication could include more than one pharmacokinetic study.

Within each pharmacokinetic study we abstracted 5 main items. First, the age group or age groups of the patients evaluated. We predefined 6 specific age groups; Neonatal unspecified (birth - 28 days post-natal age), premature neonates (<36 weeks gestational age), term neonates (36 weeks gestational age -28 days post-natal age), infant (age >28 days – 2 years), child (age 2 years – 12 years) and adolescent (age >12 years – 18 years) similar to previous recommendations for paediatric drug studies [10]. To describe studies where age was incompletely specified we included a generic group for studies with an unspecified paediatric (age <18 years). Second, pharmacokinetic parameter estimates were abstracted and converted into common units for each of volume of distribution (L/kg) and clearance (L/kg/hr). Third, the standard deviation of the estimate was abstracted or calculated from either raw data or the standard error in the report [4]. Finally, the number of age groups studied and the sample size of each age group was recorded. The sample size of a pharmacokinetic study was defined as the sample size of the parameter with the greatest number of subjects.

An academic librarian (EU) conducted the searches, and exported results into Mendeley (Elsevier, Amsterdam, Netherlands). Two members of the study team (MG, BY), independently reviewed titles and abstracts to identify ineligible studies and then reviewed the remaining publications in full to identify eligible studies and abstract data. Inconsistent data were reviewed by a third person (CP) and differences resolved by consensus. The percentage agreement was calculated for study inclusion and the abstracted parameter estimates.

Data management and analysis

There were two types of studies: (1) those estimating parameters on each individual and reporting the mean and standard deviation across individuals; and (2) those using a single hierarchical model that included all individuals to estimate population parameters and between-individual heterogeneity. These studies both estimate the same underlying quantities, but by different means, so to pool them, we used the following approaches: In the first type of study, the sample mean, standard deviation and

number of individuals in the sample were abstracted. In the second type of study, the population estimate and the estimated between-individual standard deviation (as reported directly or estimated from the coefficient of variation) and number of individuals were abstracted.

For each study, using the published sample size and the published or calculated between individual standard deviation of the parameter value, and, assuming a normal distribution for each estimate around its mean with standard error equal to SD/sqrt(n), we calculated the 95% confidence interval for the mean value of each pharmacokinetic parameter, For each parameter, we calculated the uncertainty of the estimate by relating the width of the 95% confidence interval to the point estimate using the following formula:

Uncertainty of estimate =

$$100 \times \frac{\text{upper 95\% confidence limit} - \text{lower 95\% confidence limit}}{\text{estimated mean}}$$

Standardizing the imprecision by the estimated population mean reflects the effect of potential variations in the true value of the mean on dosing recommendations. For example, if the true value of the volume of distribution for a drug was 30% more than the population estimate from a given study, then dosing recommendation may result in routine under-dosing by 30% and a conclusion that therapy is less effective than when it is optimally dosed. Acceptable uncertainty was defined as variation of 20%; this corresponds to the ends of the confidence interval being 10% higher and 10% lower than the estimated mean.

Next, we evaluated heterogeneity between study-specific estimates of parameters. Using a random effects meta-analysis model, with weights equal to the reciprocals of the variance of each estimate (i.e., the reciprocal of the standard error squared), we calculated the pooled population estimate and its 95% confidence interval for each parameter, first within each age group, and following exploration of the data, across age groups. Graphical presentation shows point-estimates for the pooled values of PK parameters and the 95% confidence intervals for the mean for meta-analyses of studies of the same drug in similar populations. The I^2 value was used to summarize the extent of heterogeneity and a 95% prediction interval was added to the figure to facilitate interpretation of between-study variation in the estimated values of PK parameters. In this study the prediction interval covers the range of likely values for the PK value in a new study with characteristics similar to the pre-existing studies [11]. Research Ethics Board approval was not required.

Results

Review of 21594 publications identified from the MEDLINE and EMBASE searches resulted in review of 641 full publications,

and inclusion of 138 eligible publications [12-150], of 11,154 patients that described 203 pharmacokinetic studies, and described estimates for mean values of 178 clearances and 176 volume of distribution parameter estimates (Figure 1).
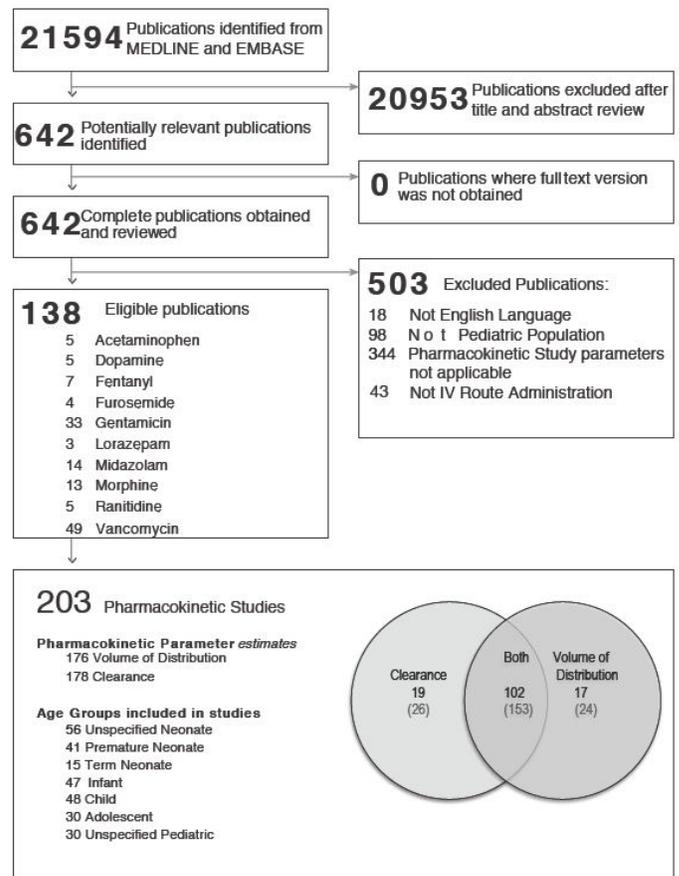

Figure 1: Systematic review process of peer reviewed publications. The process of systematic review is depicted above. A total of 138 publications were included which identified 203 pharmacokinetic studies across the 2 parameters. Studies were excluded if not in the English language, not within the paediatric age group (<18 years), if the reported pharmacokinetic parameters were not amenable to data analysis, or the medications was administered intravenously.

There were 26 (19%) manuscripts published in the 1980s, 41 (30%) in the 1990s, 17 (12%) were published in the 2000s and 54 (39%) were published after 2010. All 10 preselected drugs had been evaluated. Each drug had a median (IQR) of 6 (5-14) pharmacokinetic studies, ranging from 3 (2%) studies for lorazepam to 49 (36%) studies for vancomycin. Parameter estimates using age-specific data were reported for 5 drugs in premature neonates, 5 drugs in term neonates, 3 drugs in infants, 3 drugs in children and 2 drugs in adolescents. Of 354 parameter estimates 220 (62%) were for gentamicin or vancomycin (Table 1).

Drug name	Pharmacokinetic Studies		Pharmacokinetic parameter estimates					
			Number calculated exclusively from children from single age group					Total evaluated
	All N(col. %)	Single age group N(col. %)	Preterm	Term	Infant	Child	Adol.	
Acetaminophen	6	3	3	2	0	0	0	11
Dopamine	6	3	0	0	0	0	0	7
Fentanyl	9	5	0	0	0	0	0	17
Furosemide	5	4	2	0	0	2	0	9
Gentamicin	56	43	22	10	2	7	4	93
Lorazepam	4	2	0	0	0	0	4	7
Midazolam	19	8	0	0	0	6	0	36
Morphine	24	21	20	7	3	0	0	38
Ranitidine	5	3	0	4	0	0	0	9
Vancomycin	69	35	18	4	11	8	2	127
Total	203	127	65	27	16	23	10	354

Table 1: Pharmacokinetic Parameter studies reviewed by drug. We describe the studies included in this systematic review of peer reviewed articles by drug. The 138 articles identified provided 203 individual pharmacokinetic studies for a total of 354 parameter estimates. 141 (40%) of pharmacokinetic parameter estimates were from a single age group studied. Studies that included unspecified neonatal or paediatric age groups were not considered a single age group. 'Adol' represents the adolescent age group.

Pharmacokinetic Study Characteristics

The ages of children studied and corresponding sample sizes were reported in all 203 (100%) pharmacokinetic studies. Diagnoses and baseline medical conditions among patients from all studies were common and expected given age groups, clinical setting and administered medications. Pharmacokinetic parameter estimates were derived from a single age group in 141 (40%) estimates from patients from 2 age groups in 43 (12%) parameter estimates, and from 3 or more age groups in 40 (11%) estimates. Fifty-five (16%) parameter estimates described their population as being from all 'paediatric' age ranges and in 75 (21%) estimates included patients classified only as 'neonatal' without specification of gestational age. The median (IQR) sample size was 19 (10-39). Ten (5%) studies had fewer than 5 participants, 112 (55%) studies had 20 or fewer, and 28 (10%) had 100 or more participants (Figure 2).
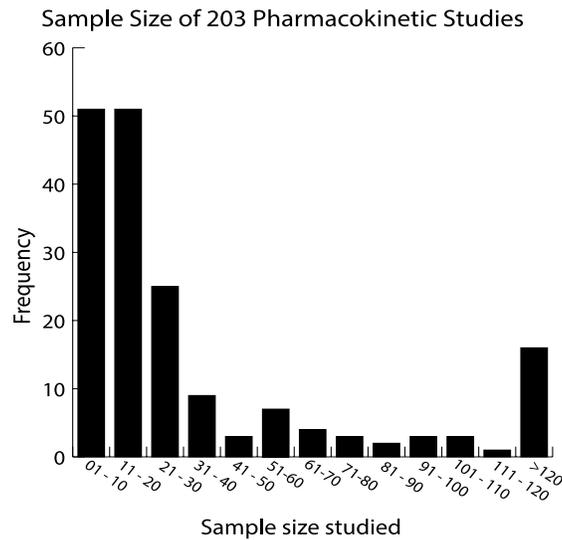
Figure 2: Sample size of Pharmacokinetic studies. Sample sizes from the 203 pharmacokinetic studies evaluated. The median (IQR) sample size was 19 (10-39). Ten (5%) studies had fewer than 5 participants, 112 (55%) studies had 20 or fewer, and 28 (10%) had 100 or more participants.

Pharmacokinetic parameter estimates of population value

Volume of distribution was reported in 176 (87%) studies. There was a median (IQR) uncertainty of 28 (16-48)% and greater than 20% uncertainty was present in 117 (66%) estimates. Clearance was reported in 178 (88%) studies. The median (IQR) uncertainty was 43 (25-72)% and greater than 20% uncertainty was found in 143 (80%) studies. There was significant heterogeneity found across all drugs in both volumes of distribution and clearance estimates (Figure 3).
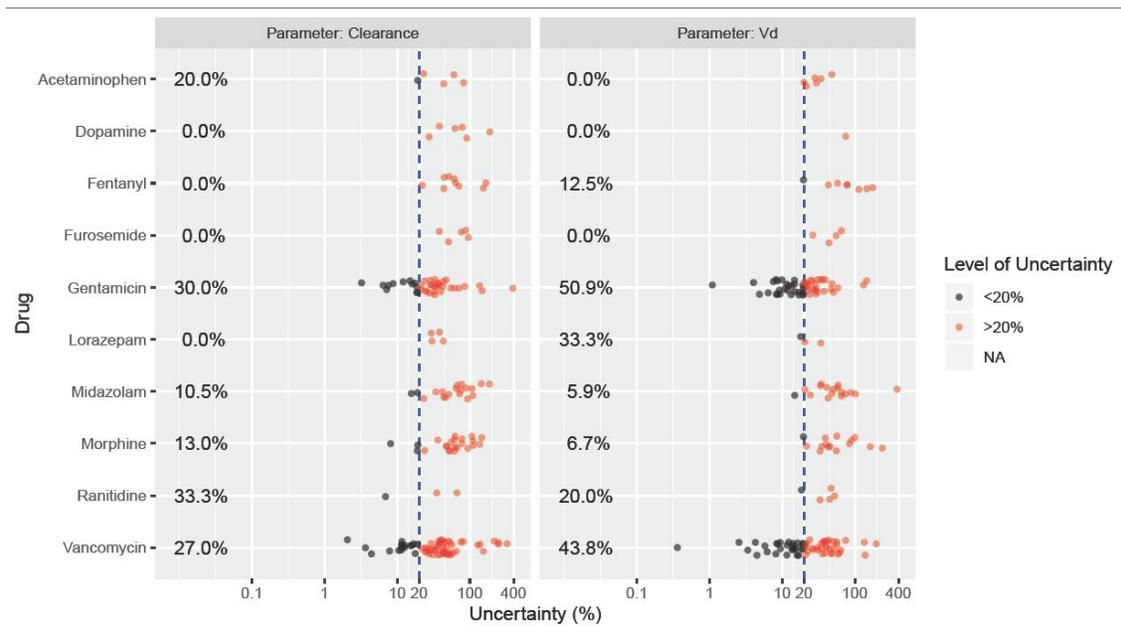

Figure 3: Uncertainty of pharmacokinetic parameter estimates by drug and parameter. Uncertainty of clearance and volume of distribution estimates from 138 peer-reviewed studies. The dark dots represent studies where the uncertainty was <20% by parameter and by drug. The red dots represent those studies where the uncertainty of the population estimate was >20%. The percentage beside each drug is the proportion of studies that fell within the predefined acceptable uncertainty range of <20%.

The precision of PK parameter estimates by drug and age

The largest heterogeneity was found within the pharmacokinetic parameter estimates for dopamine clearance. The smallest heterogeneity was found within estimates for clearance of lorazepam (Figure 4). A large degree of heterogeneity was still found within studies with single age groups by drug (Supplementary Material Figure 1, Table 1).
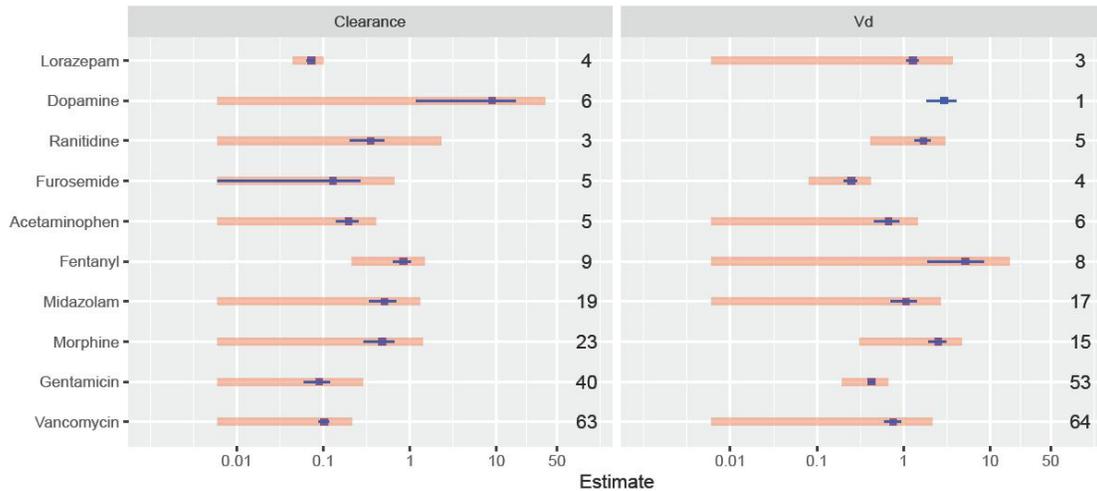

Figure 4: Pooled pharmacokinetic parameter estimates by drug. Pooled estimates of each pharmacokinetic parameter by drug are demonstrated. The blue bars represent the estimated mean and confidence interval for the mean of parameter by drug. The pink overlying bars represent prediction intervals demonstrating the heterogeneity found within each estimate. The number beside each parameter estimate by drug represents the number of pharmacokinetic parameter estimates that were included in each prediction interval.

Discussion

This systematic review was conducted to identify peer-reviewed publications of primary data describing paediatric pharmacokinetic parameters in 10 of the most commonly administered drugs in critically ill children. The main findings relate to the wide range of precision parameter estimates factors that may contribute to the observed precision, the importance of precise pharmacokinetic data and utility of parameter estimate ranges, and the feasibility and extrapolation of pharmacokinetic parameter estimates.

First, we found limited literature to guide allometric dosing - the predominant method used for most drug dosing recommendations - in the ten commonly used drugs we studied. For both volumes of distribution and clearance parameters, there was significant uncertainty within studies and considerable heterogeneity between studies. Prediction intervals for the parameters for the next study of the same drugs in the same age – in purportedly similar patients - were wide. Variations from paediatric dosing recommendations have been reported as 'routine' by frontline staff in a large paediatric hospital [151], they may reflect the limited utility, availability and scientific grounding of current paediatric dosing recommendations [152,153]. The majority of patients studied 9908 (89%) and studies 82 (59%) included were of vancomycin and gentamycin. Therapeutic levels are frequently measured for these two drugs

reflecting the limited expectations of pharmacokinetic precision in practice. Studies incorporating patient level data in these, and other drugs, highlight the need for ongoing research.

Second, we found the heterogeneity between studies of the same drug in the same age group was similar to the heterogeneity between age groups. One interpretation of this finding is that physiologic changes associated with age [154,155], are less important than the other physiologic changes occurring in the patients studied receiving drugs used in critically ill children. Another interpretation is that relative contributions of inter-individual differences to drug metabolism and excretion [156-158], may be greater than those of either age or underlying disease processes. Precedents of approaches that combine data across age groups include the use of adult pharmacokinetic data in physiologically based pharmacokinetic models to calculate estimates for paediatric parameters. These calculated parameters had precision of +/-50% values [159], similar to the precision we found in primary studies. Other methods integrating other biologically relevant variables into multivariable pharmacokinetic models have demonstrated higher degrees of precision in model development and validation. These suggest that there is more precise prediction of levels for drugs such as midazolam [160], caffeine [161] and meropenem [162], than is currently extrapolated from pharmacokinetic data, and complement estimates derived from our meta-analyses.

Third, 141 parameters estimates were derived from single age groups that have an endorsed biologic basis [163], and quarter of studies had a sample size of ten or less. The addressable origins of variability include the specificity of definitions of populations - age and other conditions, the sample sizes supporting calculation of precise estimates. Robust knowledge of pharmacokinetic parameter estimates may be especially useful in instances where volume of distribution, and clearance would be altered clinically. Though these parameters are difficult to directly correlate to one another, understanding variations in each and the potential for impact on another parameter could be important. For example, if dosing for specific drugs were to be driven by clearance rather than volume of distribution, variance in the parameter estimates for volume of distribution becomes less impactful. These include instances with the use of technology such as renal replacement or extracorporeal membrane oxygenation where paediatric drug dosing guidelines and data may be scarce and pharmacokinetic parameters such as volume of distribution and clearance could be impacted both in general and in relation to each other [164,165].

Limitations

There are several potential limitations to this work. First, data on study quality factors was not analysed or reported in relation to the pharmacokinetic parameters studied. Second, we chose only 10 commonly used drugs in critically ill children. This sample is unlikely to be representative of drugs administered to children in other settings, however we believe it likely to accurately reflect the extent of peer-reviewed pharmacokinetic data for children in other medicines. Third, despite the development of a comprehensive strategy, by an academic librarian, this systematic review may have missed relevant pharmacokinetic studies. We included only English language articles, and chose a manual study selection approach [166], but excluded grey literature – including unpublished studies conducted by pharmaceutical companies, these may include relevant data that has not been subjected to the scrutiny of peer-review [167]. Finally, our analytic approach was conservative. By assuming parameters were normally distributed, we probably under-estimated the confidence intervals for each pharmacokinetic parameter, and thus our results may under-state the current true uncertainty of paediatric pharmacokinetic data.

Conclusions

In this systematic review of 10 commonly used drugs in critically ill children we found that heterogeneity in the estimates of pharmacokinetic parameters, with similar precision within and between age groups. Meta-analysis provides pooled estimates that could be used to provide a rational basis for therapy, however the prediction interval highlights opportunities for ongoing pharmacokinetic research, to improve our understanding of drug handling in the paediatric patient, about the potential value of dose titration and customized therapy.

Acknowledgments

Author Contributions

Melany Gaetani contributed though acquisition, analysis, and interpretation of data as well as drafting of the manuscript and statistical analysis. She had full access to all of the data in the study and shares responsibility for the integrity of the data and the accuracy of the data analysis. George Tomlinson made substantial contributions to the intellectual content through conception, design and statistical analysis.

Baseer Yasseen and Elizabeth Uleryk contributed though acquisition of data. Christopher Parshuram contributed in the conceptualization of the study question, study design, and had full access to all of the data in the study and shares responsibility for the integrity of the data, the accuracy of the data analysis, revision of the manuscript for important intellectual content.

Conflicts of Interest

The authors declare no conflicts of interest.

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