Commentary

Theme: Challenges and Opportunities in Pediatric Drug Development

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Practical Considerations for Dose Selection in Pediatric Patients to Ensure Target Exposure Requirements

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Abstract. Pediatric dosing recommendations are often not based on allometry, despite recognition that metabolic processes in mammals scale to the $\frac{3}{4}$ power. This report reviews the allometric size model for clearance and its implications for defining doses for children while considering practical limitations. Fondaparinux exposures in children were predicted using allometric and mg/kg dosing. Additional simulations further refined the dose based on the predicted C_{max}, target exposure range, complexity of the dosing regimen, and previous exposure/response data. The percent reduction of the adult dose of an oral lozenge fixed-dose formulation which would predict similar exposures in children and adults was recommended based on simulations. Allometric dosing predicted a consistent fondaparinux exposure across the weight range. Size-optimized mg/kg dosing, which partially approximates the allometric relationship, allows for consistent fondaparinux exposures (i.e., 0.12 mg/kg $\leq$ 35 kg or 0.1 mg/kg $>$ 35 kg). Simulations of the oral lozenge formulation demonstrated rapidly changing clearance in children less than 6 years prohibiting practical dosing recommendations for satisfying all conventional exposure metrics (C_{max} and AUC) in this age group. In children between 13 and 18 or 6 and 13 years, a 8.6% and 54% reduction in dose would maintain target exposures but dose reductions of 12.5% or 62.5% were ultimately recommended as deemed manufacturable. Dose selection in children should consider the known and/or predicted covariate relationships which affect exposure. Presented examples applied the allometric model in dose selection with the goal of PK bridging and considered practical limitations in dose selection.

KEY WORDS: allometry; dose selection; pediatrics; population pharmacokinetics.

INTRODUCTION

Pediatric clinical trials are becoming more prevalent and are now typically mandatory within clinical development plans. While it is understood that the aim of dose selection in children is to elicit the target pharmacodynamic (PD) effect, far more pediatric studies focus on pharmacokinetics (PK) rather than PD or PK/PD (1). This is likely due to the numerous challenges that arise during pediatric clinical trials which may not be apparent during clinical trials in adults such as recruitment difficulties, lower limits on blood collection volumes, the lack of surrogate markers which predict clinical outcome and the difficulty of dose selection in a rapidly changing population.

Although a PD target linked to clinical outcomes is most appropriate for pediatric dose selection, as mentioned above,

in the absence of information on the exposure/response relationship, a PK bridging approach is often taken. In this approach, the dose in pediatric patients targets exposures similar to those achieved in adults that are known to be safe and efficacious, making the assumption that exposure/response relationships (both efficacy and safety) are similar between adults and pediatric patients (2). The relationship between ontogeny and PK is complex and dependent on a compound's unique ADME (absorption, distribution, metabolism, and excretion) properties, requiring careful consideration when developing an initial pediatric dosing strategy. The ontogeny of drug metabolism has been well-reviewed elsewhere (3). Once the maturation processes are complete, dosing in pediatric patients is primarily determined based on body size, i.e., body weight considerations.

It is well-established that metabolic processes in mammals, such as clearance, scale to the $\frac{3}{4}$ power (4). Most pharmacometricians understand this and develop appropriately scaled clearance models when developing population PK models. However, once these models are developed, simulations are often then performed using mg/kg dosing. Although this method of describing doses has the appearance of accounting for size, in fact, it has some undesirable properties which are often not well-appreciated, despite

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previous work in this area (5,6). The purpose of this report is to review the allometric size model for clearance and its implications for defining doses for children while also considering practical limitations in dose selection which may be encountered. In this paper, we focus on dosing implications of the allometric size model for clearance which are compared to mg/kg dosing. Additional comparisons (e.g., dosing scaled based on body surface area) can be found in Holford (5).

THEORY

Drug exposure (approximated by the area under the concentration-time curve for the dosing interval, AUC) may be described as the ratio of dose to systemic clearance with oral doses scaled to bioavailability (F), (Eq. 1)

$$AUC_{TV} = \frac{F_{TV} \text{Dose} \cdot (\text{mg})}{CL_{TV}} \quad (1)$$

CL scales with body weight to the $\frac{3}{4}$ power as in Eq. 2,

$$CL_i = CL_{TV} \left(\frac{WT_i}{WT_{centered}} \right)^{\frac{3}{4}} \quad (2)$$

Where CL_i is the clearance for the i th individual, CL_{TV} is the typical value (TV) of clearance representing the clearance at the median body weight (centered) of the population, WT_i is the weight of the i th individual, and $WT_{centered}$ is the centered population weight, e.g., 70 kg. Since AUC is a ratio of the bioavailable dose divided by clearance, it necessarily follows that for it to remain constant across varying body weights, dose and clearance must change in the same way, as in Eq. 3.

$$AUC_i = \frac{F_i \times \text{Dose}(\text{mg})}{CL_{TV}} \times \frac{\left(\frac{WT_i}{WT_{centered}} \right)^{\frac{3}{4}}}{\left(\frac{WT_i}{WT_{centered}} \right)^{\frac{3}{4}}} \quad (3)$$

By contrast, note that when dose is scaled on a mg/kg basis Eq. (4),

$$AUC_i = \frac{F_i \times \text{Dose} \left(\frac{\text{mg}}{\text{kg}} \right)}{CL_{TV}} \times \frac{WT_i}{\left(\frac{WT_i}{WT_{centered}} \right)^{\frac{3}{4}}} \quad (4)$$

it is obvious that AUC cannot remain constant across the weight range in this situation; the numerator and denominator are changing by different functions of body weight.

This is demonstrated in Fig. 1, where allometric (scaled to the $\frac{3}{4}$ power) and linear (scaled as 0.1 mg/kg) body weight transformations of dose are used to generate AUC response for a theoretical pediatric drug over a body weight continuum. Clearance is assumed to scale with body size to the $\frac{3}{4}$ power. Adjusting the dose by a simple mg/kg factor in this situation results in lower exposures in children who weigh the least. By contrast,

Fig. 1. Comparison of AUC across the weight range when dose is scaled by mg/kg, by an allometric expression to the $\frac{3}{4}$ power, or with a size-optimized dosing strategy

scaling the dose in the same manner as clearance is scaled results in consistent exposure across the entire weight range. The third line in the graph, labeled “size-optimized” represents a compromise between the two methods, where suitable bins for body weight (in this hypothetical example 5–20 kg, 25–40 kg, 45–60 kg, and >65 kg) are determined that will approximate dosing by allometry with mg/kg dosing. This allows mg/kg dosing to be used, which is generally easier for clinicians to do at the bedside, but maintains a reasonably constant drug exposure across the weight range to be treated. This concept will be further illustrated in example 1 below.

MOTIVATING EXAMPLES

Example 1: Fondaparinux Dose Selection for Pediatric Patients

Fondaparinux is an antithrombotic agent whose activity is the result of inhibition of factor Xa via potentiation of antithrombin III neutralization of factor Xa (7). Fondaparinux is primarily eliminated as unchanged drug in the urine (8), and drug interactions with drugs metabolized by CYP450 are not expected as *in vitro* data demonstrate fondaparinux does not inhibit these enzymes (9). One of the indications in the US in adults is treatment of acute deep vein thrombosis (DVT) and pulmonary embolism (PE) in conjunction with warfarin (7). A previously published population PK model for fondaparinux, which was developed using data from pediatric patients with deep vein thrombosis and normal renal function and healthy adult volunteers (10), demonstrated that clearance scaled based on body weight using a power model and an exponent of $\frac{3}{4}$ (centered on 70 kg). The structural model was a two-compartment model with first-order absorption and elimination. Body weight was the only

significant covariate on clearance identified in this population. Body weight was also significant on central volume of distribution, and again, a power model (centered on 70 kg) was used with the typical allometric exponent on volume terms (one) to describe the relationship. This model was used to calculate an individual's clearance (L/h) based on body weight, where body weight ranged from 5 kg to 70 kg in 5 kg increments. Once clearance was calculated, the predicted exposure (AUC at steady state) was calculated based on the dose. The dose was calculated in two ways

1. Simple adjustment based on body weight (0.1 mg/kg)
2. Allometric scaling of dose

$$\text{Dose}_i = \text{Dose}_{70\text{kg}} \left(\frac{\text{WT}_i}{70\text{kg}} \right)^{3/4} \quad (5)$$

Once the allometric doses were determined, the resulting predicted exposures were compared to achieved exposures in adult patients from a previous dose ranging study (11). It was assumed that the median exposure (AUC) in pediatric patients should remain within the interquartile range achieved in adults receiving the ultimately approved dose in adults weighing between 50–100 kg for the treatment of deep vein thrombosis or pulmonary embolism of 7.5 mg QD. Note that AUC was selected in this exercise as the primary PK parameter to assess for PK bridging but other PK parameters (i.e., trough (C_{min}) and peak (C_{max})) may be just as relevant if not more relevant depending on PK/PD relationships. The PK/PD of fondaparinux in children is unknown at this time. Simulations were performed ($N=5,000$ patients/dose group) in NONMEM 7.2.0 to examine possible dosing algorithms and examine how other pharmacokinetic parameters (i.e., C_{max} and C_{min}) compared to the selected target. AUC, C_{max}, and C_{min} were derived, summarized, and plotted using R (version 2.15.0). Doses are represented as the sodium salt while concentrations and PK parameters are represented as the free acid.

Example 2: Oral Lozenge Formulation Dose Selection for Pediatric Patients

An oral lozenge formulation, which was initially developed for adults, was to be submitted for approval based on achieving similar exposure profiles between adults and children. The drug product was targeted for an analgesia indication as it is in adults. Other pediatric formulations with this and other compounds in this class have confirmed similar mechanism of action and disease progression suggesting the exposure matching with the adult target should ensure a comparable therapeutic window in children. Similar to the first example, AUC was the main metric used for dose evaluation in children with the goal of maximizing the overlap in AUC between adults and children. While no formal quantitative requirements were specified a priori, the mean AUC in children was expected to remain within the interquartile range for AUC in adults. Also similar to above, ultimate dosing recommendations considered other

PK parameters in addition to the AUC (e.g., C_{max} and T_{max}).

Pooled single-dose adult phase I data which contained 60 subjects and 2,571 observations was used to develop a population PK model in adults [unpublished work]. This model was a two-compartment body-model with first-order absorption and first-order elimination. Standard visual predictive checks and comparison to external data and published models confirmed the adequacy of the initial adult model for pediatric extrapolation. The adult model was then refined by applying standard allometric relationships to all clearance and volume parameters to explain the expected PK differences considering size alone [unpublished work]. Additional models incorporating maturational and ontogenic effects were evaluated for children less than 2 years of age given that the compound is both hepatically and renally cleared and is a CYP 3A4 substrate. These models were not employed in the final extrapolation as the formulation was deemed inappropriate for this age strata. The modified model was used to simulate various dosing regimens (presented as a % of the fixed dose in adults) and compare the predicted PK parameters in children (i.e., AUC, C_{max}, and T_{max} (time to C_{max})) to those in adults. Simulations were conducted in an iterative (trial and error) manner with considerations to overlap and formulation strengths scalable based on feedback from the formulations group. Simulations ($n=500/\text{scenario}$) were performed in NONMEM version 6 using 16 pediatric patients/age strata. Weights were obtained for each age strata via randomized resampling procedure from the National Health and Nutrition Examination Survey (NHANES) database. Run management and subsequent graphical analysis were conducted using Census version 1.2b/XPOSE and Prism version 5.04.

RESULTS

Example 1: Fondaparinux Dose Selection for Pediatric Patients

Simple exposure calculations based on either allometric scaling of dose or based on a 0.1 mg/kg dose are presented in Table I. These data show that exposures in patients which weigh the least are lower than adults and greater mg/kg doses are needed for lower weight patients if exposure is to remain constant across the weight range.

Simulated AUC and C_{max} values at steady state based on a 0.1 mg/kg dose or based on sized optimized mg/kg dosing, which were predicted to maintain a more constant exposure (AUC), are presented in Fig. 2. It can be seen that the median predicted AUC from mg/kg dosing is below the target exposure range for the youngest patients, similar to what was demonstrated in Table I. A 0.12 mg/kg dose in patients weighing less than or equal to 35 kg and 0.1 mg/kg in patients weighing more than 35 kg approximately maintains the target exposure for AUC. Additionally, while the median maximum concentration just missed the target concentration range at a dose of 0.1 mg/kg, increasing the dose to 0.12 mg/kg in the patients weighing ≤ 35 kg did not result in exceptionally high maximum concentrations and the preselected C_{max} target was now maintained across the projected weight range.

Table I. Comparison of Achieved Exposures Based on Simple mg/kg Dosing vs Allometric Doses

Weight (kg)	CL ^a (L/h)	Simple mg/kg scaling			Allometric scaling		
		Dose (mg/kg)	Dose (mg)	AUC ^{b,c} (mg*hr/L)	Dose (mg)	Dose (mg/kg)	AUC ^{b,c} (mg*hr/L)
5	0.047	0.1	0.5	9.4	1.0	0.21	19.4
10	0.078	0.1	1	11.1	1.7	0.17	19.4
15	0.106	0.1	1.5	12.3	2.4	0.16	19.4
20	0.132	0.1	2	13.3	2.9	0.15	19.4
25	0.156	0.1	2.5	14.0	3.5	0.14	19.4
30	0.179	0.1	3	14.7	4.0	0.13	19.4
35	0.200	0.1	3.5	15.2	4.5	0.13	19.4
40	0.221	0.1	4	15.8	4.9	0.12	19.4
45	0.242	0.1	4.5	16.2	5.4	0.12	19.4
50	0.262	0.1	5	16.7	5.8	0.12	19.4
55	0.281	0.1	5.5	17.1	6.3	0.11	19.4
60	0.300	0.1	6	17.4	6.7	0.11	19.4
65	0.319	0.1	6.5	17.8	7.1	0.11	19.4
70	0.337	0.1	7	18.1	7.5	0.11	19.4

^a Population clearance 0.337 L/h obtained from Young *et al.*(10). Individual Clearance=CL_{TV}×(Weight/70)^{3/4}

^b Target range of exposure 15.2–21.9 mg*hr/L

^c Note that dose represents fondaparinux sodium and concentrations are measured as the free acid (fondaparinux). As such, AUC is calculated as AUC=Dose(mg)/Salt Factor/Clearance. Salt Factor=1.146

Finally, if trough values (Cmin) are the primary PK parameter most correlated to PK/PD outcomes, a 0.1 mg/kg dose would meet the target, allowing for a slightly less complex dosing regimen.

Fig. 2. Simulated exposures and maximum concentrations of fondaparinux in pediatric patients receiving fondaparinux sodium. *Top* patients dosed at 0.1 mg/kg fondaparinux sodium. *Bottom* patients weighing less than or equal to 35 kg dosed at 0.12 mg/kg and patients weighing greater than 35 kg dosed at 0.1 mg/kg. Approximate target exposure range defined as the interquartile range (black lines) achieved in adult patients receiving 7.5 mg QD (box plot all adult values), the approved dosing regimen for the treatment of deep vein thrombosis or pulmonary embolism used in conjunction with warfarin. *Connected points* median, *thick dashed lines* upper 75th and lower 25th, *thin dashed lines* upper 95th and lower 5th

Fig. 3. Plasma concentrations of drug candidate in healthy adults administered conventional marketed dose with population model typical value profile in adults and simulated across various age strata assuming the same fixed dose and typical allometric relationships of clearance and volume

Example 2: Oral Lozenge Formulation Dose Selection for Pediatric Patients

Figure 3 displays the expected population predicted concentration-time profile in various pediatric age strata if the same (adult) fixed dose is given across the age continuum. From Fig. 3, the need to develop age-appropriate formulations is demonstrated, adding a layer of complexity compared to the first example as only fixed doses would be available. Practical considerations had to be made concerning the number of pediatric formulations which should be developed in addition to the appropriate nominal dose. Ultimately, it was decided that fixed-dose formulations were not reasonable for children <6 years of age due to the strong relationship between body size and clearance over this age range. Results of the iterative simulation process suggested maximal overlap (pediatric and adult AUC) for a reduction of 8.6 and 54% of the adult dose for the 13 to 18 and 6 to 13 year age strata, respectively. Final recommendations included a dose reduction of 12.5% for children age 13 to 18 years and a 62.5% dose reduction for children between 6 and 13 years based on formulation strengths deemed manufacturable (Fig. 4). These dose strengths are predicted to yield substantial overlap with the adult interquartile range for AUC and acceptable difference in C_{max} and T_{max}.

DISCUSSION

Table I demonstrates that by scaling the dose based on recognized allometric relationships, a constant exposure may be maintained across the weight range. The downside to this approach is that the dosing scheme may be perceived as complex by caregivers. A simple solution to this problem is to dose in what appears to be step functions based on body

weight. This step function is a simple way to approximate the allometric relationship using the traditional and more common mg/kg dosing paradigm (Fig. 1), which we term size-optimized dosing. One key to dosing in a step function manner is to pick an acceptable target exposure range rather than targeting an exact exposure match. In this example, the target range was selected as the interquartile range of exposures (AUCs) calculated from adult patients in a dose ranging study who received the ultimately approved dose, 7.5 mg QD (11). From Table I, it is clear that a dose transition is needed so that pediatric patients weighing less than 35 kg receive a higher mg/kg dose to achieve the target.

It is important to point out that although a simple method to guide dose selection based on a target exposure (i.e., AUC) and clearance is proposed, the other pharmacokinetic characteristics (i.e., C_{max} and C_{min}) should also be evaluated based on the PK target and additional clinical information should be considered. In the first example, a dose of 0.12 mg/kg in patients weighing ≤35 kg, results in a median AUC below the 25th percentile of the AUC in adults, i.e., AUCs are predicted to be below the target in children who weigh the least. However, greater doses (e.g., 0.13 mg/kg) result in median C_{max} values which exceed the upper 75th percentile in adults, i.e., C_{max} values are predicted to exceed the target in some children. As two hemorrhagic adverse events were observed in the previous study (i.e., a minor, clinically significant gastrointestinal bleed and an intracranial hemorrhage, which may have preceded study medication) (10), it was thought more acceptable to fall below the AUC target than exceed the C_{max} target due to possible safety concerns. Depending on PK/PD relationships, trough values may be just as relevant or more relevant to consider and in this case, a 0.1 mg/kg dose (a simpler dosing paradigm) would

Fig. 4. Simulated exposure metrics (AUC, C_{max} , and T_{max}) across pediatric age strata following dose reductions of 12.5% (A, B, and C) and 62.5% (D, E, and F). Shaded area adult metrics

maintain consistent trough values within the interquartile range in adults across the age range (Fig. 2). Again, in this example, PK bridging was primarily based on AUC values with considerations of known safety information for dosing recommendations. Ultimate dosing recommendations for future studies with fondaparinux may rely on additional information or have the primary focus of dose ranging rather than PK bridging.

The second example illustrates that a potential lack of agreement between PK metrics can occur even more

dramatically than the first example, especially when fixed-dose formulations are proposed across age strata. Depending on the consensus on therapeutic exposure metrics (e.g., AUC versus peak-mediated correlation with activity and/or clinical outcomes), it may be very reasonable to propose comparable exposure requirements (with adults) for one metric and not the other. In both examples, simulation was used to examine how the exposure metrics in children compared to adults. This is important as clearance is not the only PK parameter influenced by maturational process. Additionally, performing

simulations followed by graphical analysis can further guide where dose transitions should occur.

Another important consideration when comparing these two examples is the feasibility and practicality of the simulation-based dosing strategies. In the first example, fondaparinux is dosed as a subcutaneous injection and therefore allows for a considerable degree of flexibility in practical dosing algorithms. For example, in the previous study (10), it was determined that the minimum dose adjustment which could be accurately and safely administered was 0.25 mg. However, even with this flexibility and the fact that two dose transitions predicted targets to be maintained for all metrics, it was thought a single dose transition at 35 kg could be a simpler and, subsequently, more practical dose. On the other hand, in the second example, only a fixed dose was available at the time the simulations were done. As a result, simulations and recommendations were proposed with reference to the currently available dose with an understanding that additional pediatric formulation(s) may need to be developed. Also, considering that initially only fixed doses would be developed, it was proposed that this formulation would not be suitable for children less than 6 years of age. Likewise, important considerations with fixed-dose formulations are the appropriateness of preselected age strata versus more data driven age bins and the target versus manufacturable dose constraints. Again, simulation is an excellent medium from which such comparisons can be made.

In summary, dosing on a mg/kg basis is routinely performed when designing pediatric studies. While this dosing paradigm partially adjusts for weight differences, it is important to remember that scaling dose on a mg/kg basis will not result in constant exposure across a wide weight range as clearance scales with an exponent of $\frac{3}{4}$ not 1. When designing bridging studies with the objective of targeting exposures known to be safe and effective in adults, an expedient method to identify an appropriate dosing regimen may be to scale dose in a similar manner as clearance and then decide upon appropriate dose transitions based on a target exposure range to arrive at a feasible dosing recommendation. Dosing recommendations should be further evaluated through simulation techniques, and practical considerations should be made to arrive at final recommendations. A practical dosing strategy, to achieve PK bridging, may in fact contain a mg/kg dosing recommendation but also may need to include a step-based approach to account for the slight disparity between the mg/kg approach compared to the allometric approach. Again, however, pediatric dose selection would optimally be based on PK/PD relationships in children or aim

to define these PK/PD relationships (i.e., through dose ranging in children with careful consideration of the risk/benefit relationship). For example, if the goal was to achieve a larger exposure range, a dose based on a mg/kg basis (e.g., 0.1 mg/kg of fondaparinux) would certainly serve that purpose.

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