Discontinuities and disruptions in drug dosage guidelines for the paediatric population

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Structured summary

Aims: This study investigates paediatric drug dosage guidelines with the aim of investigating their agreement with body surface area (BSA) scaling principles.

Methods: 454 drug dosage guidelines listed in the AMH-CDC 2015 were examined. Data extracted included the administration, frequency and dose per age bracket from 0-18 years. Drug treatments were categorized as follows: 1) The same dose recommendation in milligrams per kilogram (mg/kg) for all age/weights; 2) Change in the mg/kg dosing according to age/weight; 3) Change in dose in mg according to age/weight; 4) Change from mg/kg dosing to a dose in mg according to age/weight; 5) The same recommendation for all age/weight groups in mg or 6) BSA dosing. Example drugs were selected to illustrate dose progression across ages.

Results: Most drug treatments (63%) have the same mg/kg dose for all age/weight groups, 14% are dosed in mg/kg across all ages with dose changes according to age/weight, 13% were dosed in mg across all ages with dose changes, 10% switched from mg/kg to a set dose in mg, 4.2% have the same dose in mg for all age and weight groups and 2.2% are dosed according to BSA.

Conclusions:

Paediatric dosage guidelines are based on weight-based formulas, available dosing formulations, and prior patterns of use. Substantial variation from doses predicted by BSA scaling are common, as are large shifts in recommended doses at age thresholds. Further research is required to determine if better outcomes could be achieved by adopting biologically based scaling of paediatric doses.

What's Known on This Subject

- Minimal pharmacokinetic understanding in children has led to arbitrary dosing across the paediatric age range
- Arbitrary dosing may consequent in unwanted side effects due to overdose, or lack of effect due to underdosing.

What This Study Adds

- Recommended paediatric doses appear to be based on simple formulas (such as mg/kg), available dosing formulations, and prior patterns of use.
- Two or more-fold variation from doses predicted by allometric scaling are common, as are arbitrary large shifts in recommended doses at age thresholds.

Introduction

In an ideal world, pharmacokinetic and pharmacodynamic profiles for every paediatric drug would be established and the results would inform dosage guidelines. Unfortunately, for most paediatric drugs these profiles have not been established leaving a remarkable lack of empirical data to guide dose selection for people under 18 and great variability in quantity and quality of information supporting dose recommendations. Many dosage guidelines rely on the extrapolation of data from adults and animals in conjunction with application of various scaling principles. Often this makes the assumption that children are equivalent to 'small adults' physiologically, physicochemically and biochemically, disregarding the impact of ontogeny on the pharmacokinetics, safety and efficacy of the drugs(1). Clinicians are aware however, that development of paediatric drug dosing requires a thorough and rigorous consideration of the effect of developmental changes in medication response, and the large differences in physiological characteristics between children and adults, most notably variation in body composition, differential liver and kidney functioning and drug-metabolizing capacity (2, 3). It is noteworthy that there are also considerable differences within these parameters across the paediatric age spectrum. For example, some metabolizing enzymes are only a fraction of adult levels during infancy leading to decreased drug clearance and dosing requirements in this age group (4-6).

Allometric scaling approaches dosage such that dose for children is a partial adult dose, dependent on variable factors of age, height and weight (2). Recommended doses are provided, with paediatricians left to determine a more appropriate dose on a patient case-by-case. Determining doses based on body surface area (BSA; mg/m^2), is one such favoured allometric scaling approach. BSA can be used as a surrogate for drug metabolism - based on the premise that BSA is proportional to heat loss from the body (7). Furthermore, many other physiological parameters are associated with BSA, such as tissue volume, blood flow and organ size (8). Dosing based on BSA is not without its limitations. It assumes that adults and children are geometrically similar. While this may be true for children, term and preterm neonates do not have similar morphology to adults, for example, their heads are relatively bigger and body trunks relatively larger. The implication of this is that scaled clearance in infants may be underestimated leading to the underestimation of maintenance dose (9).

Using gestational rather than chronological age may allow optimal dosing that accounts for neonate ontogenesis, although this methodology is not widely adopted and dosage guidelines rarely include preterm newborns. Furthermore, BSA dosing is also prone to errors, because of the complexity of mathematical calculations. Other allometric scaling approaches include the ⅔ power surface area model, using a fixed exponent of 0.67 (1, 10) and the ¾ power surface area model, using a fixed exponent of 0.75. (11).

Weight based dosing assumes there is a linear relationship between weight and dose (7), though drug clearance is better correlated with lean body weight or fat free weight than total body weight (12) and there is currently no bedside method of estimating lean body weight in order to better estimate dose. This is particularly of significance in obese children. However, drug dosage guidelines still are often delivered in terms of mg/kg or as a set dose and how well this reflects a desirable BSA scaling method is not immediately evident. Commonly a switch between the dosing regimens (set dose to mg/kg or vice versa) will occur at a particular age cut off somewhere between infancy and childhood, or childhood and adolescence. While these age cut-offs are designed to account for developmental changes in drug metabolism, in the real world the dosing regimen changes seem rather arbitrary and titration between one developmental stage and another is not apparent. Considering paediatric dose recommendations –whether as a set dose or mg/kg - in their equivalent weight and height (mg/m^2) dosage, offers the opportunity to assess the consistency across age groups.

Furthermore, when used in children a significant proportion of medications are used on an off-label basis (13, 14). A 10-week study of a neonatal intensive care unit reported 47% of prescriptions to be off-label (15). Further, a retrospective study of paediatric inpatients in an Australian teaching hospital reported 31.8% of prescriptions to be off-label (13) and a one year study including Australian emergency department, inpatient and outpatient clinics at a paediatric teaching hospital reporting off-label use of medications to be at around 25.7% (16). The significant proportion of off-label medication use highlights the need for consistent, evidence-based research to guide dosing regimens in paediatric patients.

In the absence of the pharmacodynamic and pharmacokinetic studies required to inform optimal dosing in children, clinicians rely on national formularies to assist prescribing practices. In Australia,

the formulary used for children is the Australian Medicine's Handbook Children's Dosing Companion (AMH-CDC) (17). The resource, like all national formularies, is guided by the best available evidence and undergoes a rigorous editorial and expert review process to formulate its recommendations. Given that the evidence base for dosing simply does not exist for most drugs in children, allometric scaling principles are considered the "next best" and therefore should be present in dosing guidelines. Using the AMH-CDC, this study investigates dosage guidelines for the paediatric population.

This study aimed to identify various dosage inconsistencies and discontinuities across the age range thereby highlighting the need for research and development of allometric models for paediatric dosing. Notwithstanding the priority for complete pharmacokinetic data and established dosing guidelines.

Methods

Data extraction

Information on all 674 dosage guidelines listed in the AMH-CDC 2015 were extracted and collated in Microsoft Excel (2016). Dosing data extracted from the guide for each drug indication included the administration, frequency and dose per age bracket from birth to 18 years (mg/kg). The average weights and heights for each age group as specified in the AMH-CDC were used. We excluded medications that are not dosed in a way that makes sense to apply dose scaling principles. This includes drugs with the following administration routes: eye, topical, nasal, inhalant, ear, hair, intra-tracheal, intra-articular. For the same reason we have excluded drugs with no specific regimen. In order to examine dosing guidelines for medications that can be used during most of the paediatric lifespan we have also excluded medications contraindicated in children under 6 and medications only used in neonates (see Figure 1 for inclusion flow chart).

From the excel workbook, the included drug treatments were examined in terms of the progression of dosing guidelines from birth until age 18. Based on our observations the following dosing groups were determined as the best way to categorize the drug dosing patterns across all included medicines:

1. The same dose recommendation for all age or weight groups in milligram/kilogram (mg/kg);
2. Change in the mg/kg dosing according to age or weight;
3. Change in the set dose in milligrams (mg) according to age or weight;
4. Change from mg/kg dosing regimen to a set dose in mg according to age or weight;
5. The same dose recommendation for all age or weight groups in mg; or
6. Drugs dosed according to BSA (mg/m^2).

To ensure that these dosing categories were not only a reflection of Australian guidelines the British National Formulary (BNF) for Children (18) was also checked. For each included drug in the CDC we searched the drug recommendations in the BNF when indicated for the same or equivalent indication, administration route and formulation. The BNF doses for these drugs were then examined and categorised according to the same dosing groups determined for the CDC.

In the current analysis we have used BSA as an example allometric scaling principle. BSA makes similar adjustments to the dose as other scaling principles such as exponent 0.75 and 0.67. This similarity is demonstrated in Figure 2. To illustrate differences in BSA across the paediatric lifespan, we arbitrarily selected example drugs from the CDC from dose group categories 1 - 4. Category 5 was not graphed as these drugs did not change dose recommendation according to age or weight and category 6 was not graphed as it includes medications already dosed according to BSA. For each selected drug the minimum and maximum dosage in mg, mg/kg and the equivalent, milligrams per body surface area (mg/m^2) for each age group was calculated using the average weights and heights per age bracket provided in the AMH-CDC. Body surface area was calculated using the Mosteller formula as follows:

$$\text{BSA} = \frac{\sqrt{(\text{weight (kg)} \times \text{height (cm)}}}{3600}$$

The minimum and maximum mg/kg doses were then converted to GraphPad Prism Version 6 for Windows (GraphPad Software, La Jolla California USA), where graphs were plotted, providing a function to observe the trends progressing through age, birth to 17, average weight, 3.3kg to 62kg and average height, 50cm to 160cm. Discontinuities were defined as a disruption in mg/m^2 dosage across

age groups as a result of change in dose from mg/kg to a set dose or vice versa. As well as cross-referencing to the BNF the selected drugs were also compared to the American Hospital Formulary Service (AHFS)(19) to assess the international similarities and differences in dosing recommendations.

Nomenclature of Ligands

Key ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY(20).

Results

There were 465 included drug treatments. Close to two-thirds of the drug treatments (n = 289, 63%) had the same dose mg/kg dose for all age and weight groups (dose category 1), 14% (n = 65) of drug treatments were dosed in mg/kg across all ages but the dose changed one or more times according to changes in weight or age (dose category 2), 13% (n = 61) of drug treatments were dosed in mg across all ages but the set dose changed one or more times according to changes in weight or age (dose category 3), 10% (n = 48) of drug treatments switched from dosing according to mg/kg to a set dose in mg according to changes in weight or age (dose category 4), 4.2% (n=19) had the same dose in mg for all age and weight groups and the remaining 2.2% (n = 10) were dosed according to BSA. All included CDC drug treatments and their dose group categories are shown in Supplementary Material 1. Of the 454 included drug treatments from the CDC, 325 were also present in the BNF with equivalent administration routes, formulations and indications. Over a third of those (n = 126, 38.8%) fit into dose category 1, 14.1% (n=46) in dose category 2, 12.6% (n = 41) in dose category 3, 27.4% (n = 89) in dose category 4, 3.7% (n = 12) in dose category 5 and the remaining 3.4% in dose category 6. Table 1 details the example drug treatments chosen from categories 1 - 4. For each example drug treatment, figures 2 – 9 show the respective varying dosage recommendations across the age range with the equivalent mg/m^2 dosage.

Figure 3, dexamethasone, is an example from CDC dosing category 1. As can be seen in the figure, it is dosed at a constant range of 0.15mg/kg-0.3mg/kg, which is equivalent to almost a 10-fold increase in total mg across the age range and a doubling of the mg/m2. The maximum dose of dexamethasone recommended in the BNF is slightly lower than that of the AMH-CDC (0.45mg/kg vs.

0.60mg/kg, respectively). Figure 4, digoxin, is an example from dosing category 2. The figure shows a stepwise decrease in the mg/kg dosing through the age groups which is equivalent to mg/m^2 fluctuations between 0.22 and 0.12. Dosing of digoxin is fairly similar between AMH-CDC, BNF and AMH, except that the BNF recommends a fixed dose of 62.5 - 250 µg between 10 – 17 years. Figure 5, desmopressin, is an example from dosing category 3. The stepwise increase in recommended mg/age can be seen in the figure, with a range introduced at age 12. Maximum dose recommendation for desmopressin in the BNF is higher for all age categories, whereas the AHFS recommends a fixed dose however individualized dosing according to needs is advocated.

Figures 5 – 8 are examples from dosing category 4. Oseltamivir (Figure 6) fluctuates within 100 – 138mg/m^2 range from birth to 15, before steadily dropping to 87.8 mg/m^2 at age 17. Cefuroxime (Figure 7) shows an abrupt increase in mg/m2 at age 2 before dropping steadily back to the starting dose at age 12, where ranges are then introduced. Dosing recommendations for both osetamivir and cefuroxime are similar between the AMH-CDC, BNF and AHFS. Voriconazole (Figure 8) linearly increases from 400mg/m2 at age 2 to ~550mg/m2 at age 11, before decreasing slightly before a range is introduced. Vigabatrin (Figure 9) shows wide ranges from birth equivalent to ~ 2000mg/m2 differences between the minimum and maximum dose at some points. Dosing recommendations for voriconazole and vigabatrin provided in the AMH-CDC are similar to those of BNF. The AHFS recommends a fixed dose for all age groups for voriconazole and does not provide a recommendation for vigabatrin doses for those under 10 years.

Discussion

This study aimed to investigate paediatric dosing recommendations in terms of their adherence to the BSA scaling principle and the associated inconsistencies or sudden dose transitions across age groups. The illustrated drug treatments chosen from the AMH-CDC had dose recommendations that were overall similar to recommendations provided by the BNF for children and the AHFS. The drugs showed various dosages patterns, some associated with dose disruptions or discontinuities across the paediatric age range. Those that allow for quite consistent dosing across the age range are those with

large dose ranges, though in some cases having such broad therapeutic recommendations can be unhelpful in terms of prescribing individualized treatment.

With a lack of the appropriate pharmacodynamic and pharmacokinetic studies to guide more accurate dosing, we considered current dosage guidelines that allows similar physiological concentrations across between birth to age 18 (as reflected in the equivalent mg/m^2 graph) as the next best. It is noteworthy, that only around 2% of drugs in the CDC and 3.4% of the equivalent drugs in the BNF were dosed according to BSA. Although, drugs commonly dosed according to BSA such as chemotherapy agents, are not commonly listed in the CDC as they are protocol specific. From the illustrated drug treatments, the BSA equivalent doses for oseltamivir, dexamethasone and vigabatrin best demonstrate opportunity for fairly consistent dosing across children of different age groups. Dexamethasone is dosed at a constant mg/kg which corresponds to a BSA dosage which increases greater than two-fold between birth to age 18, the acceptable range of dosing would allow fairly consistent mg/m^2 dosing throughout the age range (Figure 3). Likewise, vigabatrin shows a drug with wide ranges from birth which allow consistent mg/m^2 dosing, however its minimum and maximum doses display inconsistent patterns (Figure 9). Known pharmacokinetic data of vigabatrin (Sabril, Sanofi Aventis) in the paediatric population reports a comparison of neonates (age 15-26 days), infants (age 5-22 months) and children (age 4.6-14.2 years), showing decreased clearance with age groups, however similar renal clearance of children to adults (21). In an early clinical trial, sixty-six children aged between 2 and 15 treated with vigabatrin found optimal efficacy between 40 -80 mg/kg/day with doses over 100mg/kg/day resulting in no significant adverse events (22), supporting the wide therapeutic window reflected in vigabatrin dosing guidelines. Pharmacokinetic modeling has indicated that in children 1 – 12 years, a dose of 2mg/kg results in a cumulative dose similar to that which is safe and effective in adults (23). A randomized control trial using this dosage was well-tolerated and showed efficacy for influenza (23), though this not the recommended dosage in the AMH-CDC (Figure 6).

Digoxin is an example drug treatment with a very narrow therapeutic range. As can be seen in Figure 4 there is much less variability in the BSA dose than the mg/kg dose, highlighting the strength of this approach. Yet fixed dosing according to a fixed mg/kg remains the dominant recommendation. For other treatments, ranges are available but not until age 12 for example, desmopressin (Figure 5) and

cefuroxime (Figure 7), which display very similar BSA equivalent dosage patterns despite different recommended treatment regimes. Both treatments show inconsistent and disrupted dosage, even when ranges are introduced in early adolescence.

The greatest discontinuities we observed were a result of a switch in dosing guidelines between a set dose or a dose based on weight, which commonly occurred between age 12 - 14. The Center for Drug Evaluation and Research generally categorizes paediatric age groups into: neonates (birth to one month); infants (1 month to two years); children (two – 12 years) and adolescents (12 – 16). Though in their working guidance for industry document, the Food and Drug Administration recognizes these specific age groups do not necessarily need to be used in studies but alternative age groupings based on physiology should be scientifically supported (FDA (24)). In the case of weight based dosing, there is less variability during infancy and childhood until about the age of 13 when the variation of age with weight is highest (25) – which reflects the dosing switches seen across drugs in this study.

Commonly what is seen is dose recommendations based on available drug formulations. For example, cefuroxime, one of the example drug treatments with the most inconsistent and disrupted BSA equivalent dosing, is one in which the recommendations align with exact multiples of the tablet formulation (250mg). On the other side of the coin, how well clinicians are able to meet the recommended oral dosing guidelines are based on the available formulations of the drug. For example, treating a typical ~9kg 1-year-old child for central diabetes insipidus with desmopressin (Figure 5) according to oral dose recommendations requires 10 µg of the medication twice or three times daily yet the medication is only available in tablet formulations of 200 µg. Further, the guidelines commonly provided dosages in simple weight based formulas, which are less complicated and as such less prone to error that those prescribed according to BSA. Although current technology enables electronic calculation and decreases the risk of error.

The implications of the inconsistent and discontinuous drug recommendations identified in our investigation are more important for some drugs than others. With continuing medications such as pamidronate, digoxin and vigabatrin requiring a much greater dosing consistency across age groups compared to medications with a shorter course length, such as those for infections. That said it is

important to consider that a 13-year old adolescent with a serious fungal infection would be recommended a voriconazole dose of 480 mg/m^2 and a child one year older could receive a dose as low as 265 mg/m^2. It is unknown how, on the population level, that these discontinuous recommendations are treated clinically. An analysis of prescribing data would be very useful in that sense, in order to utilize real world data to further guide dose recommendations.

Dose finding studies in children are difficult (7). Therefore, many drugs used in children do not have paediatric labelling information (26). Formularies can be improved by utilizing model-based methods to determine optimal paediatric dosage of existing drugs. For example, paediatric models have been successfully developed for various drugs including, midazolam, lorazepam, tramadol, acetaminophen, and voriconazole (27). In several countries, new drug development for children requires paediatric investigation plans (28, 29) and model based methods for dose optimization are required (30). Interest in model-based methods for personalized medicine is increasing, particularly for genotype-directed therapy (31). Furthermore, physiology-based pharmacokinetic models have been used to evaluate drugs for potential drug–drug interactions (32). Thus, the effect of various dosing regimens on interacting drugs can be established and drugs can be individually optimized for polytherapy (33).

Conclusion

Paediatric dosage guidelines appear to be based on simple formulas (such as mg/kg), available dosing formulations, and prior patterns of use. Two or more-fold variation from doses that would be predicted by allometric scaling are common, as are arbitrary large shifts in recommended doses at age thresholds. While doses may be safely approximated for drugs with large therapeutic margins, accurate dose estimation for drugs with narrow therapeutic margin is imperative in order to minimise the risk of drug toxicity. Drugs used to treat childhood leukaemia are routinely dosed using BSA (34, 35), which has contributed to achieving impressive improvement in outcomes in recent years (35).

In absence of pharmacokinetic and pharmacodynamic studies, further research is required to determine if better outcomes could be achieved paediatric conditions by adopting biologically based scaling of paediatric doses.

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Conflicts of Interest

Nicholas Buckley is a member of the Editorial Advisory subcommittee for the Australian Medicines Handbook, Children's Dosing Companion. No other authors have any conflicts of interest relevant to this article to disclose.

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Table 1. Example drug treatments chosen for investigation

Dosage category	Drug	Indication	Administration	Formulation
1. Same dose recommendation for all age/weight groups	Dexamethasone	Croup	Oral/IV/IM	Inj, 4mg/ML; tab (scored), 500mcg, 4mg
2. Change in mg/kg dosing according to age or weight	Digoxin	Atrial tachyarrhythmia	Oral	Tab, 62.5mcg; tab (scored), 250 mcg
3. Change in the set dose in mg according to age or weight	Desmopressin	Central diabetes insipidus	Oral	Tab (scored), 200mcg
4. Change from a mg/kg dosing regimen to a set dose in mg according to age or weight	Oseltamivir	Influenza	Oral	Cap, 30mg, 45mg, 75mg
	Cefuroxime	Bacterial infections	Oral	Tab, 250mg
	Voriconazole	Fungal infections	Oral	Tab, 50mg, 200mg
	Vigabatrin	Adjunct refractory partial seizures	Oral	Tab (scored), 500mg

Figure 1. Flow diagram of included drug regimens and the relative dosing groups based on categorization as follows: Dosing category 1: same dose recommendation in milligrams per kilogram (mg/kg) for all age/weight groups; Dosing category 2: change in the mg/kg dosing according to age or weight; Dosing category 3: change in the set dose in milligrams (mg) according to age or weight; Dosing category 4: Change from a mg/kg dosing regimen to a set dose in mg according to age or weight; Dosing category 5: The same dose recommendation for all age or weight groups in mg; Dosing category 6: Drugs dosed according to BSA

Figure 2. Line graph representing dosing using allometric principles versus dosing according to mg/kg (black dotted line). Doses represented as the percentage of adult dose. Allometric principles shown on the graph include body surface area (grey dash), 0.67 exponent model (solid black line) and 0.75 exponent model (black dashed line).

Figure 3. Recommended daily dosages for **dexamethasone** (Left: mg, Middle: mg/kg, Right: mg/m^2). Figure based on oral/intravenous/intramuscular treatment of croup. Shaded areas indicate the range for minimum and maximum dose. Equivalent doses calculated from the recommended dose based on average weight or body surface area per age group.

Figure 4. Recommended daily dosages for **digoxin** (Left:mg, Centre: mg/kg, Right: mg/m^2). Figure is based on oral maintenance treatment of atrial arrhythmia. Shaded areas indicate the range for minimum and maximum dose. Equivalent doses calculated from the recommended dose based on average weight or body surface area per age group.

Figure 5. Recommended daily dosages for **desmopressin** (Left:mg, Centre: mg/kg, Right: mg/m^2). Figure based on oral treatment of central diabetes insipidus, dosed 3 times daily. Shaded areas indicate the range for minimum and maximum dose. Equivalent doses calculated from the recommended dose based on average weight or body surface area per age group.

Figure 6. Recommended daily dosages for **oseltamivir** (Left:mg, Centre: mg/kg, Right: mg/m^2). Figure based on oral oseltamivir treatment dosage of influenza. Shaded areas indicate the range for minimum and maximum dose. Equivalent doses calculated from the recommended dose based on average weight or body surface area per age group.

Figure 7. Recommended daily dosages for **cefuroxime** (Left:mg, Centre: mg/kg, Right: mg/m^2). Figure is based on oral treatment of bacterial infections. Shaded areas indicate the range for minimum and maximum dose. Equivalent doses calculated from the recommended dose based on average weight or body surface area per age group.

Figure 8. Recommended daily dosages for **voriconazole** (Left:mg, Centre: mg/kg, Right: mg/m^2). Figure based on oral maintenance dosage for treatment of serious fungal infections. Shaded areas indicate the range for minimum and maximum dose. Equivalent doses calculated from the recommended dose based on average weight or body surface area per age group.

Figure 9. Recommended daily dosages for **vigabatrin** (Left:mg, Centre: mg/kg, Right: mg/m^2). Figure based on oral vigabatrin for maintenance treatment of adjunct refractory partial seizures. Shaded areas indicate the range for minimum and maximum dose. Equivalent doses calculated from the recommended dose based on average weight or body surface area per age group.