

Dose estimation for children

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Introduction

There is a wide perception that the paediatric population has been badly served by pharmaceutical companies, drug regulators and governmental funding bodies, in that too little resource has been committed to developing effective and safe medicines for children, and in particular defining the right dose(s) for appropriate paediatric populations (see for example reference [1]). Paediatricians, clinical pharmacologists and clinical pharmacists have for many years struggled to make the best use of information available to them, as evidenced by local paediatric formularies, and, more recently, the formulary published by the Medicines Committee of the Royal College of Paediatric and Child Health and the Neonatal and Paediatric Pharmacists Group [2].

This review explores three areas of this problem:

- 1 Is this perception true?
- 2 Does it matter? What is the evidence of harm?
- 3 If it does matter, what can be done about it?

Is it true?

With some notable exceptions, the vast majority of drugs have been developed for use in adult populations. The reasons for this have been well explored already [1, 3–7] and include ethical objections to conducting clinical trials in children, the resource (expense and time) that is required to discover and develop new drugs where the use in paediatric populations represents a poor return on investment, and the uncertainty of types of clinical trials in children that will satisfy both regulatory authorities and prescribers as to the efficacy, safety and quality of new potential medicines.

It is worth considering this latter point in some detail. Defining the optimal dose, the dose range for a given patient population, and the dose adjustments required as a result of physiological, pathological or iatrogenic interventions (such as drug interactions) remains one of the most challenging tasks in drug development and clinical care. It is not uncommon that the dose or dose range for a given drug established at the time of marketing

authorization is significantly modified with experience in clinical practice. Adjustments are most frequently downwards (e.g. treatment of essential hypertension) [8]. Often these dose changes for adult populations take many years to establish. Further, it is only with the passage of time and clinical experience that differences in dose–response in populations emerge; for example, the greater response in young white hypertensives to β -blockers, compared with older and black patients.

The realization of defining ‘the right drug for the right patient (at the right dose)’, according to genotypic and phenotypic profile for the vast majority of drugs lies well into the future. Our ignorance of the inherent heterogeneity of an apparently homogeneous group of adult patients has served us rather well for many commonly used drugs, especially for those drugs with wide therapeutic ratios and whose pharmacokinetic variables are well understood. One major stumbling block for dose estimation in children is the very definition of the word ‘children’. Most guidelines now use the age bands recommended in *Licensing Medicines for Children 1996*, a joint report of the British Paediatric Association and the Association of the British Pharmaceutical Industry [9]; namely newborn (birth to 1 month), 1 month to 2 years, 2–12 years and 12–18 years. The drug monograph on *Medicines for Children*, prepared by the Medicines Committee of the Royal College of Paediatric and Child Health and the Neonatal and Paediatric Pharmacists Group [2], expresses dosing using these age bands. The monograph also highlights another problem: what units should be used. In *Medicines for Children* specific doses are generally stated on a per weight or by an age/weight basis. Occasionally, doses are stated on a specific ‘dose/surface area basis’ [2, 10]. It is presumed that these dosages are based on the information in the Summary of Product Characteristics (SPC) provided by the pharmaceutical companies, and supplemented by information from ‘off-label’ use in clinical trials and in clinical practice.

Does it matter?

Several implications from this lack of evidence of dose–response data in children can be envisaged. First, a majority of new medicines are not licensed for use in children or are being used ‘off label’, i.e. for an indication not specified in the product licence. Off-label drug use

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ranges from 25% of prescriptions in a study conducted in hospital wards, to 90% on a neonatal intensive care unit [3, 5, 6].

Second, the lack of a paediatric indication in the SPC, or where the Marketing Authorization Holder has chosen not to market the product for children, frequently results in the absence of a suitable paediatric formulation. This, in turn, may result in the need for an extemporaneous preparation of a medicinal product in a registered pharmacy, hospital or health centre. The lack of a paediatric indication also leads to single unit systems such as capsule and tablets being split. Extemporaneous formulations and splitting of single dosage units can lead to a reduction in drug effect and toxicity. In addition, suitable strengths of medications, which are essential to minimize the risk of medication errors for children, are often not manufactured. Tenfold errors are more likely to occur in newborn infants and young children, where one injection vial contains more than 10 times the dose required [7].

Third, what is the evidence that inaccurate dosing recommendations result in either inadequate response or increase in adverse events? This is a difficult question to tease out.

What is the evidence?

Recent studies have suggested that there is an increased risk of adverse drug reactions associated with off-label prescribing, particularly in children less than 2 years old [11–13]. In a study by Horen *et al.* [14], the risk of adverse reactions related to off-label drug usage in paediatric outpatients was reported. The authors found that in a sample of 1419 children under the age of 16 years of age, 42% of patients were exposed to at least one off-label prescription which was associated with a relative risk of an adverse reaction of 3.44 [96% confidence interval (CI), 1.26, 9.38]. This rose to 4.42 (CI 1.60, 12.25) when the adverse reaction was associated with an indication different from that on the SPC. Interestingly, the relative risk of adverse drug reactions for off-label use associated with a higher or lower dose was 1.12 (CI 0.19, 6.53) and 1.71 (CI 0.2, 13.80), respectively.

In a recent study [15] which investigated the extent of dose-related off-label paediatric prescribing of antibacterial agents in 5–11-year-olds, under-dosing was associated with a significant increase in the number of antibiotic courses during the study year. Whilst the relevance of this is unclear, the widespread use of lower doses than those recommended could potentially facilitate the development of antibiotic resistance.

However, there are limitations to these studies; in particular, an adverse event report itself does not establish a causal link between the event and the medication.

Further, it is not possible to establish from these data a causal link between off-label usage or dosage problems and adverse drug reactions. There are many confounding factors in these studies, such as the possibility that children prescribed 'off-label' medicines are more ill or are on more medicines than those not receiving unlicensed drugs.

Other examples to support a link between incorrect dose and adverse event in children may be cited. The grey baby syndrome, which was initially described in the 1950s, resulted in many deaths, due to chloramphenicol toxicity. Neonates developed cyanosis and respiratory failure, due to impaired metabolism and increased bioavailability of chloramphenicol [16].

A more recent example of overdosing leading to fatalities is the propofol infusion syndrome [17]. Since 1992, several fatal cases have been described following long-term sedation with high doses of propofol in children on intensive care units. Characteristic features of this syndrome are myocardial failure, metabolic acidosis, lipaemic serum and multiorgan failure. Recent pharmacokinetic and pharmacodynamic studies [17] indicate that children have a lower pharmacodynamic sensitivity to propofol, and that subjects with the syndrome were overdosed to achieve the desired level of sedation. In Europe, propofol is no longer recommended for paediatric sedation.

Long-term steroid usage is associated with many adverse effects, particularly in children. There has been recent concern over adrenal crisis associated with inhaled fluticasone [18]. A survey published in 2002 revealed that numbers of cases of adrenal crises due to inhaled corticosteroids were higher than expected. Ninety-four percent of cases were caused by fluticasone at doses supported by British Guidelines on Asthma Management, but which were higher than the licensed dosage. The Committee for Safety of Medicines has therefore recommended that the licensed dosage of 400 µg day⁻¹ should not be exceeded, unless the patient is supervised by a physician experienced in the management of problematic asthma.

Lack of data in children can lead to the creation of arbitrary therapeutic ranges. Initial dosage recommendations by the Food and Drug Administration (FDA) for theophylline [19] for the treatment of neonatal apnoea in 1983 were suboptimal. Neonates treated within the recommended therapeutic range showed a poor response rate, due to under-dosing, and were predisposed to apnoea and increased morbidity.

Early efficacy studies of phenobarbitone for neonatal seizures [20] restricted serum concentrations from 10 to 30 mg dl⁻¹ based on experience in older age groups. This lack of data led to the exposure of children to multiple drug therapy in an attempt to control unresponsive seizures. Subsequent efficacy studies expanded the thera-

peutic range to 40 mg dl⁻¹ and enabled monotherapy in most patients.

What has been done?

Much has been done to increase awareness of the public and health professionals. Paediatricians, clinical pharmacologists and regulators are working together at national and European level. In the UK, the Committee on Safety of Medicines has established a Paediatric Working Group, which has, as one of its remits, to increase the 'on-label' use of medicines in children according to best available data, and to consider alternative options for dose-ranging in children. The Medicines Healthcare products Regulatory Agency (MHRA) has developed a paediatric strategy, which considers use of medicinal products in children at every step of the regulatory process, i.e. at new drug application, variation, renewal and reclassification of medicines. Marketing Authorization Holders are encouraged to consider paediatric indications and safety at each step. MHRA is looking at ways of enhancing pharmacovigilance specifically in children through a limited Yellow Card Scheme, and a Pilot Paediatric Regional Monitoring Centre has been set up in the Trent region (UK) to monitor safety of drugs in paediatric patients [21].

The need for more clinical pharmacologists trained in paediatrics is recognized and a Registrar Training Scheme for paediatric pharmacology is now being proposed. In addition, there has been a British Forum for the Use of Medicines in Childhood, which has promoted a network of centres for drug research, as in the USA [4, 7, 22].

Within the European Medicines Evaluation Agency (EMA), a Paediatric Expert Group, under the leadership of the Chairman of Committee on Proprietary Medicinal Products (CPMP), himself a paediatrician, has been established. How to tackle 'off-label' medicines and dose-ranging is one of its remits. The European Commission, following consultation, is developing a strategy similar to that in the USA [23], which may include incentives such as patent or licence exclusivity to Marketing Authorization Holders (MAHs) who conduct paediatric clinical studies as part of the clinical development plan.

What can be done? Approaches to drug dosing regimens in paediatrics

The most conservative and comprehensive drug development programme would follow the classical phase I, IIA, IIB and III approach [24]. In the perfect world it may be argued that a novel drug that has potential utility in a wide paediatric age-span should be tested in all age bands by this route. There is no doubt that strenuous efforts must be made to increase the number of drugs that have been evaluated in paediatric populations in

well-conducted trials. For some drugs it will be inappropriate to study certain age-bands, but even where extensive paediatric usage is anticipated, the sheer scale, cost and risk could make such a comprehensive programme impracticable.

What alternative strategies for dose ranging are available?

Population kinetic (and dynamic) approach Classical clinical pharmacokinetic analysis requires frequent blood samples from each individual in a study, so that a complete plasma concentration profile over time can be obtained. This is frequently impracticable and unethical in small children, and so a population-PK approach can be applied, in which only a very few (perhaps two or three) data points per subject are collected. All the data from the different individuals are 'fitted' simultaneously, and post hoc individual kinetic variables can be calculated. Various software packages are available, using, most often, a Bayesian algorithm. Co-variables such as weight, sex, age and concomitant drugs can be investigated in the same model.

The effect of selected kinetic parameters (e.g. parent drug or principle active metabolite concentration) on the selected dynamic effect can be studied, using, for example, logistic regression. The FDA *Guidance for Industry: Population Pharmacokinetics in 1999* [25] sets out the mechanics and philosophy for dose development.

A recent example of this approach to dose estimation in children is the pharmacokinetics and pharmacodynamics of oral midazolam by Johnson *et al.* [26]. This showed the contribution made by the active 1-hydroxy metabolite of midazolam (1-OH MDZ) to sedation in 45 children, median age 5 years, and gives guidance on the dosing regimen for young and smaller children. 1-OH MDZ has approximately 50% the activity of midazolam. It can compensate at least in part for the decreased effect of midazolam due to increased metabolism of parent drug in children. However, in this study the authors concluded that a 50% increase in the current suggested dosage might be required in order to achieve adequate sedation in all subjects. In the UK, no licensed oral preparation is available for usage. These data are nevertheless extremely relevant for clinical practice.

Allometric scaling Allometric scaling is commonly used by drug developers to extrapolate animal data to humans. Examples of this include scaling by body weight (W), surface area [W (2/3)] or by the allometric 3/4 power model [W (3/4)]. Both the allometric 3/4 power model and the surface area model have been shown to be superior to body weight for scaling physiological parameters. The allometric 3/4 power model has also proved to be superior for scaling pharmacokinetic parameters

such as plasma clearance, volume of distribution and elimination half-time. The use of these models for scaling drug doses in children has recently been reviewed by Meakin and Andersen [27]. Because of the complex nature of pharmacokinetic and pharmacodynamic parameters, the authors note that allometrics could not be used to extrapolate doses from adults to children. However, allometrics could be used to narrow the dosage range selected for clinical studies, and it could be used to improve the computer modelling of population PK parameters.

The 'in-silico model' This method uses a computer model to predict the variability in the pharmacokinetics of drugs in children, and hence try to establish practical dosing regimens and predict drug interactions. The basic concept for the model is that the pharmacokinetic and dynamic components of drug response change from birth onwards, as a consequence of organ maturation, changes in body composition and enzymology, especially in the cytochrome P450 superfamily. A suitable computer program can be built based on knowledge of the *in vitro* enzyme activities against drugs of interest, together with a range of physiological variables such as liver size, liver blood flow, renal function and protein binding, and of population parameters (age, weight, height).

Initial studies in children could then be performed on drugs where the pharmacokinetics are known (e.g. midazolam) and predicted and compared with actual data. After further development of the model, predictions can be made for drugs used in children where pharmacokinetics have not been studied [28–30]. Data thus generated can be used to confirm current dosage regimens, or inform further clinical studies. The SIMCYP program [28–30] is a development of one used to simulate population PK/PD drug responses *in vivo* and *in vitro*. An important feature of the program is that it includes population variability so that extremes within a population are presented, as well as mean effects.

So far, SIMCYP has been successfully applied to the prediction of paediatric clearance of midazolam, caffeine and carbamazepine.

Discussion

The arguments and examples in this paper, along with other publications, indicate that there is a lack of robust, evidence-based data in paediatric populations to establish both efficacy and safety, and more specifically, optimal dosing procedures in children.

The full extent of the adverse consequences from under- or over-dosing in children is unknown, and will be difficult to quantify, but there are some early warning signals in the literature. There are some well-substantiated examples of drug dosing inaccuracies, leading to adverse

events and even fatalities in children. In addition, poor quality data on dose definition leads to off-label prescribing, the use of unsuitable formulations, and the use of extemporaneous liquid formulations, and the splitting of tablets and capsules.

Whilst the controlled clinical trial will remain the mainstay of paediatric drug development, the pressing need to generate data in children to provide a rational basis for dosage determination without expanding into unrealistic programmes means that other methods such as allometric scaling and 'in-silico' model programmes could prove useful tools in order to develop protocols for the evaluation of population-based studies. They could help focus dose selection in controlled trials, and through the population approach their use could avoid the need for large-scale trials in many cases.

It is encouraging that Governments through their regulatory agencies, pharmaceutical companies and academics are working together at national and European level to address prescribing needs of children.

Conclusions

There is considerable evidence that drug dosing inaccuracies leads to adverse events and even fatalities in children. In addition, it leads to off-label prescribing, unsuitable formulations, the preparation of extemporaneous liquid formulations, lack of suitable formulations and the splitting of tablets and capsules. This can lead to decreased drug effect and increased toxicity.

There is a pressing need to generate data in children in order to provide a rational basis for dosage determination, and to establish safety and efficacy in children.

Methods such as allometric scaling and 'in-silico' models could prove useful tools to develop protocols for the evaluation of population-based studies, which would avoid the need for large scale drug trials in many cases.

Much is being done nationally and in Europe to address the prescribing needs of children. In particular, new European legislation is expected early next year, which will encourage pharmaceutical companies to undertake clinical research in children.

Pharmaceutical companies, government, researchers and healthcare providers need to work together in order to develop knowledge of drug disposition and effects in children.

We have the moral responsibility to provide the best possible drug treatments for children.

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