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EDITORIAL

Solving the problem of dose optimization of children's medicines

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The optimal dose of a medication is that which provides the most acceptable balance of benefit and risk for an individual patient. Achieving this can be complicated, and an optimal dose for an individual will be affected by numerous patient, disease, and health-care resource factors. For children, the complexity is greater still, as many older medicines were developed when regulations did not require specific pediatric assessments. Even for newer drugs, where regulations in the U.S. and EU now mean that there are early-phase studies in children upon which to base the doses, there are still gaps in the evidence base such as repurposing of the drugs beyond their licensed indication(s). There are also important patient differences to consider, such as growth, alterations in body composition, ontogeny of drug metabolizing enzymes, and obesity, which affect the optimal dose of a medicine in children. These problems can be even more pronounced in neonates and preterm infants, and specifics of dosing relating to neonates have recently been reviewed [1].

Worldwide, children still experience considerable morbidity and mortality, with over seven million deaths in childhood per year [2]. While optimizing dosage is important for the treatments of the major causes of childhood mortality (lower respiratory tract infections and diarrheal illnesses), as well as conditions such as TB, HIV, and malaria, they form part of broader package. As the WHO initiative around HIV therapy shows [3], focus is also needed many other aspects of health care, such as simplifying treatment regimens to allow widespread utilization.

In developed nations, childhood mortality is considerably lower. Of the medicines used, analgesia, antibiotics, and anti-asthmatic medications dominate inpatient prescribing for children [4]. In addition, there are between 6 and 8000 rare diseases [5].

The combination of these multiple rare diseases and historic exclusion from the drug development process explains why many of the medications prescribed for children are given 'off-label' – outside their licensed indication [6]. Pediatricians are encouraged to use evidence, not label indication, as the gold standard when selecting treatments [7]. On the other hand, higher rates of adverse drug reactions (ADRs) have been noted with off-label and unlicensed medicines in children [8], which would suggest that there is a good case for looking at dose optimization in the older medicines.

Intravenous salbutamol for acute severe asthma is a good example of how the dose of older medicines may be well established, but may not be optimal. Both the 2014 British Thoracic Society guidelines [9] and the British National Formulary for Children [10] recommend an initial loading dose of 15 µg/kg. At the Royal Melbourne children's hospital in Australia, the loading dose is 0.3–0.6 mg/kg over an hour [11], while in Starship Children's hospital New Zealand, the dose is 10 mg/kg over 2 min [12]. These doses appear to be derived from a single Australian randomized controlled trial conducted in 1997 [13]. This trial involved 29 children, only 14 of whom received the active drug. This regimen means that children aged 2 and above who weigh 20 kg or over will receive the same bolus dose as an adult [14]. Pharmacokinetic simulations predict that this dosing regimen puts children at significant risk of experiencing systemic salbutamol concentrations in the toxic range, and thus increases the risk of adverse effects [14].

Newer drugs used in children are not exempt from issues around dosing as well. Since the U.S. Best Pharmaceuticals for Children Act [15], and European Union Pediatric Drug Regulation [16], pharmaceutical companies hoping to bring new medicines to market have been incentivized to develop the pediatric uses of medicines. This has led to an increase in the proportion of clinical trials involving children [17]. However, there are still issues around dosing; incorrect dose selection contributes to failure of 23% of drug development trials in children [18], while re-purposing of medicines to additional indications in children remains commonplace.

Rituximab, a monoclonal antibody which causes lysis of B-lymphocytes, has received a license for use in adults for the treatment of non-Hodgkin's lymphoma, chronic lymphocytic leukemia, rheumatoid arthritis, and granulomatosis with polyangiitis and microscopic polyangiitis. The originator product (Mabthera) is not licensed to treat children in the U.S. or U.K. [19,20], yet is being used for an increasing number of indications. In a large secondary and tertiary pediatric center in the U.K., we have identified that rituximab is being used for 17 different indications [21]. Children with different conditions receive varied doses and dosing intervals, such that

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annualized doses administered range from 750 to 2250 mg/m^2 [21]. The origin of these dose variations is unclear.

Despite these difficulties, there is progress being made. Aminoglycoside antibiotics, such as gentamicin and tobramycin, have well-established efficacy and toxicity. Improved understanding of the physiological changes in neonates has helped improve the dosing of gentamicin in the treatment of neonatal sepsis. Due to the low glomerular filtration rate (GFR) in neonates, clearance of gentamicin is reduced. To account for this, extended-interval dosing has been developed (between 24 and 48 h) [10]. While GFR is low, neonates also have a high percentage of body water compared to all other age groups. They therefore demonstrate a relatively larger volume of distribution for aminoglycosides. Neonates therefore require relatively larger doses of gentamicin to achieve the high peak concentrations required for their concentration-dependent antibacterial effect, whilst extended interval dosing allows for adequate clearance, reducing the risk of renal toxicity [22].

In children with cystic fibrosis (CF), higher doses of intravenous aminoglycosides are required to treat respiratory exacerbations. There are a number of reasons for this dose adjustment. There are resistant organisms (in particular *Pseudomonas aeruginosa*) that require higher peak concentrations for adequate antimicrobial effect. These higher circulating concentrations are also required to ensure adequate penetration of the antibiotic to the site of infection in the lung [23]. Furthermore, patients with CF have a larger volume of distribution and greater clearance of aminoglycosides [23] than other children of a similar age. Whilst higher doses are required for adequate antimicrobial effect, extended-interval dosing (usually every 24 h) has been demonstrated to reduce nephrotoxicity [24].

However, as some problems are solved, new ones can appear. In many countries, the proportion of obese children is increasing. Pharmacokinetic data for obese patients do not exist for many drugs [25], especially in children. Current pediatric dosing often uses age bands, which do not take account of weight at all, or vary the dose according to actual body weight (e.g. mg/kg). This takes account of the weight, but has limitations. One of these is with drugs that have a small volume of distribution, and are primarily retained in the intravascular compartment. Growth hormone is a drug with these characteristics. When treatment outcomes (height, and change in insulin-like growth factor 1 (IGF-1), a marker of metabolic syndrome, and insulin resistance) following mg/kg actual dosing of recombinant human growth hormone have been compared with the patient's body mass index at start of treatment [26], patterns emerge. The thinnest children had the least growth, while the obese children (already at risk of insulin resistance) did not grow more than overweight children, but had markedly greater increases in IGF-1 [26]. Evidence-based dosing in children must include an understanding of how obesity affects both the pharmacokinetics and pharmacodynamics of a medicine [27]. Future studies will need to identify the most important measure to use for dosing to improve outcomes for both thin and obese children.

If actual body weight is not providing the best dose, then other options include age bands, ideal body weight (IBW), lean body weight (LBW), body surface area (BSA), or allometric scaling. Age bands are easy to use in clinical practice, but can be very inaccurate, and requires the drug in question to have a wide therapeutic index to be safe [28]. IBW and LBW may have advantages for drugs that are predominantly intravascular, but there are few dose optimization studies comparing actual weight with either ideal or lean body weight in children. BSA may have advantages over actual body weight, but can over-predict clearance in neonates, while the more complex calculation makes it harder to use in routine clinical practice [29]. Allometric scaling is superior to actual body weight and BSA for scaling some pharmacokinetic (PK) parameters such as plasma clearance, volume of distribution and elimination half-life, but is a very complex calculation that is not routinely used in clinical practice [28,30].

There is no single solution to achieve optimal dosing for medicines in children, but awareness that there may be a problem is a good start. With many of the diseases treated being rare, there is limited opportunity for large-scale randomized controlled trials to establish optimal dosing. Instead, smaller studies could be undertaken in children, to examine the link between pharmacokinetic parameters and clinically important pharmacodynamic outcomes (both efficacy and harm). However, pharmacokinetic studies can be difficult to undertake in children due to the burden of frequent blood tests. They can also be expensive, as the studies come with significant regulatory burdens, especially if the drug is used in children off-label.

Extrapolation of information and conclusions from adult data to children, if done robustly, can reduce the amount of additional information required from pediatric studies. Extrapolation can be done if the disease is similar in adults and children, the expected mechanism of action of the drug is the same in children, and if the pharmacokinetic–pharmacodynamic relationship is the same. Modeling and simulation approaches may then be used to navigate the pediatric study decision tree proposed by the European Medicines Agency (EMA) [31] in order to optimize the design of pediatric studies and minimize the additional data required. Population PK models, created using existing adult data, can be used to identify the factors influencing variability, which will inform the data required in children. For instance, a population PK model of ceftaroline in adults identified creatinine clearance as the primary determinant of exposure [32]. Pediatric PK studies were designed to provide adequate data across age groups, and were mainly focused on PK and safety data. The data from these was used to update the population PK model, and the new model used to run simulations to predict important pharmacodynamic outcomes (percentage of time above minimum inhibitory concentration) [33]. This model directly led to dosing recommendations in children which were different from those used in the trials, and have been accepted by both EMA and US FDA. Similar work has been undertaken in neonates using cefazolin [34]. Physiologically based PK models can also been used to predict the impact of maturation on factors affecting PK. The advantages of this approach are clear in terms of informing the most appropriate study designs in children, and in particular to minimize the numbers of children required, and the burden of the studies in terms of time and frequency of sampling.

For existing medicines, perhaps the simplest first step toward optimizing the dose would be improving the

identification, and quantification, of harm from medicines given to children. There is evidence that the under-reporting noted for ADRs in national spontaneous reporting schemes is as true for children and neonates [35,36] as for adults. As we have seen, knowledge of the potential for nephrotoxicity with aminoglycosides, and an understanding of their pharmacokinetics, has resulted in steps to optimize the dosage. Secondly, it is important to collect data on efficacy of medicines in children. Unlike ADRs where post-marketing surveillance is generally conducted through national reporting schemes, schemes collecting efficacy data are not widely utilized. The best examples are in disease-specific registries, such as the UK CF Registry [37] which collects efficacy data related to CF-specific therapies. High-quality pharmacodynamic data from large pediatric cohorts would allow attention to be focussed on the drugs causing greatest harm to children, leading to optimization of dosage, in order to maximize efficacy and minimize harm.

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