Solving the problem of dose optimisation of children’s medicines

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 healthcare resource factors. For children, the complexity is greater still, as many older medicines were developed when regulations did not require specific paediatric assessments. Even for newer drugs, where regulations in the US 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 re-purposing of the drugs beyond their licenced indication(s). There are also important patient differences to consider, such as growth, alterations in body composition, ontogeny of drug metabolising 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 has recently been reviewed [1].

Worldwide, children still experience considerable morbidity and mortality, with over seven million deaths in childhood per year [2]. While optimising dosage is important for the treatments of the major causes of childhood mortality (lower respiratory tract infections and diarrhoeal 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 healthcare, such as simplifying treatment regimens to allow widespread utilisation.

In developed nations, childhood mortality is considerably lower. Of the medicines used, analgesia, anti-biotics, and anti-asthmatic medications dominate inpatient prescribing for children [4]. In addition, there are between 6-8000 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 licenced indication [6]. Paediatricians 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 optimisation in the older medicines.

Intravenous (IV) 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 micrograms/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 10mg/kg over 2 minutes [12]. These doses appear to be derived from a single Australian randomised 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 20kg 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 US Best Pharmaceuticals for Children Act [15], and European Union Paediatric Drug Regulation [16], pharmaceutical companies hoping to bring new medicines to market have been incentivised to develop the paediatric 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 licence for use in adults for the treatment of non-Hodgkin’s lymphoma, chronic lymphocytic leukaemia, rheumatoid arthritis, and granulomatosis with polyangiitis and microscopic polyangiitis. The originator product (Mabthera) is not licensed to treat children in the US or UK [19, 20], yet is being used for an increasing number of indications. In a large secondary and tertiary paediatric centre in the UK 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 annualised doses administered range from 750mg/m2 to 2250mg/m2 [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 GFR in neonates, clearance of gentamicin is reduced. To account for this, extended-interval dosing has been developed (between 24 and 48hours) [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 24hours) 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 paediatric 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 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 (IBW), 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 optimisation studies comparing actual weight with either 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 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 randomised 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 paediatric 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. Modelling and simulation approaches may then be used to navigate the paediatric study decision tree proposed by the EMA [31] in order to optimise the design of paediatric studies and minimise 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]. Paediatric 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 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 minimise 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 towards optimising 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 optimise 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 utilised. 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 paediatric cohorts would allow attention to be focussed on the drugs causing greatest harm to children, leading to optimisation of dosage, in order to maximise efficacy and minimise harm.

References

1. Ku, L.C. and P.B. Smith, *Dosing in neonates: Special considerations in physiology and trial design.* Pediatric research, 2015. **77**(0): p. 2-9.

2. Kyu, H.H., C. Pinho, J.A. Wagner, J.C. Brown, et al., *Global and National Burden of Diseases and Injuries Among Children and Adolescents Between 1990 and 2013: Findings From the Global Burden of Disease 2013 Study.* JAMA Pediatr, 2016. **170**(3): p. 267-87.

3. Gilks, C.F., S. Crowley, R. Ekpini, S. Gove, et al., *The WHO public-health approach to antiretroviral treatment against HIV in resource-limited settings.* The Lancet, 2006. **368**(9534): p. 505-510.

4. Conroy, S., I. Choonara, P. Impicciatore, A. Mohn, et al., *Survey of unlicensed and off label drug use in paediatric wards in European countries.* BMJ, 2000. **320**(7227): p. 79-82.

5. Alliance, G. *What is a rare disease?* 2017 [cited 2017 15th November]; Available from: <http://www.raredisease.org.uk/what-is-a-rare-disease/>.

6. Choonara, I. and S. Conroy, *Unlicensed and Off-Label Drug Use in Children.* Drug Safety, 2002. **25**(1): p. 1-5.

7. Neville, K.A., D.A. Frattarelli, J.L. Galinkin, T.P. Green, et al., *Off-label use of drugs in children.* Pediatrics, 2014. **133**(3): p. 563-567.\*

\*Summarises the impact of US regulation on paediatric drug labels, and how clinicians should use evidence not label indication to select medicines for children.

8. Bellis, J.R., J.J. Kirkham, A.J. Nunn and M. Pirmohamed, *Adverse drug reactions and off-label and unlicensed medicines in children: A prospective cohort study of unplanned admissions to a paediatric hospital.* British Journal of Clinical Pharmacology, 2014. **77**(3): p. 545-553.

9. British Thoracic, S., *British guideline on the management of asthma.* Thorax, 2014. **69**: p. 1-192.

10. Committee, P.F., *British National Formulary for children 2014-2015.* 2014.

11. Melbourne, R.C.s.H. *Clinical Practice Guidelines*. 2018; Available from: <http://ww2.rch.org.au/clinicalguide/forms/drugDoses.cfm>.

12. Hospital, S.C.s. *Life Threatening asthma Guideline*. 2018 [cited 2018 8th January]; Available from: <http://www.adhb.govt.nz/starshipclinicalguidelines/_Documents/Asthma,%20Life-Threatening.pdf>.

13. Browne, G.J., A.S. Penna, X. Phung and M. Soo, *Randomised trial of intravenous salbutamol in early management of acute severe asthma in children.* Lancet, 1997. **349**(9048): p. 301-305.

14. Starkey, E.S., H. Mulla, H.M. Sammons and H.C. Pandya, *Intravenous salbutamol for childhood asthma: Evidence-based medicine?* Archives of Disease in Childhood, 2014. **99**(9): p. 873-877.

15. *Off-Label Use of Drugs in Children.* Pediatrics, 2014. **133**(3): p. 563-567.

16. Hawcutt, D.B. and R.L. Smyth, *The New European Regulation on Pediatric Medicines*. 2008, Springer.

17. Turner, M.A., M. Catapano, S. Hirschfeld and C. Giaquinto, *Paediatric drug development: The impact of evolving regulations.* Advanced Drug Delivery Reviews, 2014. **73**: p. 2-13.

18. Momper, J.D., Y. Mulugeta and G.J. Burckart, *Failed Pediatric Drug Development Trials.* Clinical Pharmacology and Therapeutics, 2015. **98**(3): p. 245-251.

19. Compendium, e.M. *Rituximab (Mabthera) Summary of Product Characteristics*. 2017 [cited 2017 15th November]; Available from: <https://www.medicines.org.uk/emc/medicine/2570>.

20. Administration, F.a.D. *RITUXAN (rituximab) label*. 2017 [cited 2018 8th January]; Available from: <https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/103705s5367s5388lbl.pdf>.

21. Price, V., H. Lythgoe, L. Oni and D. Hawcutt, *G261 Prescribing practices of rituximab in children: a 5-year retrospective review*. 2016, BMJ Publishing Group Ltd.

22. Mohamed, A.F., E.I. Nielsen, O. Cars and L.E. Friberg, *Pharmacokinetic-pharmacodynamic model for gentamicin and its adaptive resistance with predictions of dosing schedules in newborn infants.* Antimicrobial Agents and Chemotherapy, 2012. **56**(1): p. 179-188.\*

\*Used PKPD modelling to show how extended dosing intervals can be as efficacious as shorter intervals.

23. Touw, D.J., A.A.T.M.M. Vinks, J.W. Mouton and A.M. Horrevorts, *Pharmacokinetic optimisation of antibacterial treatment in patients with cystic fibrosis. Current practice and suggestions for future directions.* Clinical Pharmacokinetics, 1998. **35**(6): p. 437-459.

24. Smyth, A.R. and J. Bhatt, *Once-daily versus multiple-daily dosing with intravenous aminoglycosides for cystic fibrosis.* The Cochrane database of systematic reviews, 2014. **2**.

25. Hanley, M.J., D.R. Abernethy and D.J. Greenblatt, *Effect of obesity on the pharmacokinetics of drugs in humans.* Clinical pharmacokinetics, 2010. **49**(2): p. 71-87.

26. Hawcutt, D.B., J. Bellis, V. Price, A. Povall, et al., *Growth hormone prescribing and initial BMI SDS: Increased biochemical adverse effects and costs in obese children without additional gain in height.* PloS one, 2017. **12**(7): p. e0181567.

27. Xiong, Y., T. Fukuda, C.A.J. Knibbe and A.A. Vinks, *Drug Dosing in Obese Children: Challenges and Evidence-Based Strategies.* Pediatr Clin North Am, 2017. **64**(6): p. 1417-1438.\*\*

\*\*comprehensive overview of drug dosing and obestiy

28. Hawcutt, D.B., L. Cooney, L. Oni and M. Pirmohamed, *Precision dosing in children.* Expert Review of Precision Medicine and Drug Development, 2016. **1**(1): p. 69-78.

29. CRAWFORD, J.D., M.E. Terry and G.M. Rourke, *Simplification of drug dosage calculation by application of the surface area principle.* Pediatrics, 1950. **5**(5): p. 783-790.

30. Johnson, T.N., *The problems in scaling adult drug doses to children.* Archives of disease in childhood, 2008. **93**(3): p. 207-211.\*

\*A nice summary of the pros and cons of different methods of scaling doses

31. Manolis, E. and G. Pons, *Proposals for model-based paediatric medicinal development within the current European Union regulatory framework.* British Journal of Clinical Pharmacology, 2009. **68**(4): p. 493-501.

32. Van Wart, S.A., A. Forrest, T. Khariton, C.M. Rubino, et al., *Population pharmacokinetics of ceftaroline in patients with acute bacterial skin and skin structure infections or community-acquired bacterial pneumonia.* The Journal of Clinical Pharmacology, 2013. **53**(11): p. 1155-1167.

33. Riccobene, T.A., T. Khariton, W. Knebel, S. Das, et al., *Population PK Modeling and Target Attainment Simulations to Support Dosing of Ceftaroline Fosamil in Pediatric Patients With Acute Bacterial Skin and Skin Structure Infections and Community-Acquired Bacterial Pneumonia.* Journal of Clinical Pharmacology, 2017. **57**(3): p. 345-355.

34. De Cock, R.F., A. Smits, K. Allegaert, J. de Hoon, et al., *Population pharmacokinetic modelling of total and unbound cefazolin plasma concentrations as a guide for dosing in preterm and term neonates.* Journal of Antimicrobial Chemotherapy, 2014. **69**(5): p. 1330-1338.

35. Hawcutt, D.B., P. Mainie, A. Riordan, R.L. Smyth, et al., *Reported paediatric adverse drug reactions in the UK 2000–2009.* British Journal of Clinical Pharmacology, 2012. **73**(3): p. 437-446.

36. Hawcutt, D.B., N.-J. Russell, H. Maqsood, K. Kouranloo, et al., *Spontaneous adverse drug reaction reports for neonates and infants in the UK 2001–2010: content and utility analysis.* British Journal of Clinical Pharmacology, 2016. **82**(6): p. 1601-1612.

37. Trust, T.C.F. *UK CF registry*. 2017 [cited 2018 5th January]; Available from: <https://www.cysticfibrosis.org.uk/the-work-we-do/uk-cf-registry>.

Funding Details

SJM is a NIHR Academic Clinical Lecturer.

DH is part funded by the NIHR.

Financial and competing interests disclosure

The authors report no conflicts of interest.