Precision Dosing in Children

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Key Issues:

* There are fewer choices of medicines to treat specific conditions in paediatrics than in adult medicine; therefore selection of the optimum dose is of particular importance
* Most paediatric doses are not personalised as the dose suggested (usually in mg/kg) is the same for a large age range of children.
* There are well established medications used extensively in paediatrics (e.g. treatment of acute asthma) where, due to a lack of data, the optimal dose of a medicine to produce maximal efficacy (or avoid adverse effects) is not known
* Optimal doses of a medication for a specific condition may be expected to change across childhood due to normal developmental alterations in physiology
* There has been little consideration of paediatric obesity with regard to dosing of medicines, even in conditions where obesity is a common factor (e.g. Growth Hormone use in Turner’s syndrome)
* Pharmacogenomic data may be able to assist with dose personalisation (e.g. Warfarin)
* Repurposing of medicines to a new indication needs to be done with full consideration of dose, which takes into account not only the new indication but also the specific age groups being treated.

# Abstract

Unlike adult medicine, there are fewer choices of medicines per condition in children, and for existing medications, supporting data on pharmacokinetics, pharmacodynamics, or pharmacogenomics is often incomplete. Many paediatric doses are calculated using body weight to produce a dose for the individual child, but this is not true personalisation as the dose suggested (usually in mg/kg) is the same for a large age range of children. The challenge for implementation of precision medicine in paediatrics is therefore to develop an appropriate evidence base (particularly for unlicensed and off label medications), then add onto it the relevant genotype, environmental and lifestyle data to guide both medication selection (where choices exist) and the dose required. This review will consider where consideration of dose is crucial in paediatrics, including the developmental changes across childhood, paediatric obesity, and old and new medicines where data on dosing are scarce and/or inadequately extrapolated from adults.

# Introduction

Precision medicine considers an individual’s genotype, environmental exposure, and lifestyle choices, to enable best therapy to be selected [1]. In an adult population, this leads to a focus on medication selection, as there are often multiple potential medications for treating a particular problem, for which data on the pharmacokinetic (PK), pharmacodynamic (PD), and pharmacogenomic (PGx) parameters may be available. Despite this, the dose of many medications is often identical for every patient who receives it – a “one-dose-fits-all” approach.

Within paediatrics, there are fewer choices of medicines per condition, and the supporting data on PK, PD or PGx is often incomplete. Many paediatric doses are calculated using body weight to produce a dose for the individual child, but this is not true personalisation as the dose suggested (usually in mg/kg) is the same for a large age range of children. The dosing for children does also consider clinical factors including age, renal function (including normal developmental variation), hepatic function, variation in body composition, and the underlying disease being treated, and compared to adult medicine, there is a greater emphasis placed on formulation tolerability and palatability.

However, due to the lack of data upon which paediatric does are based, there are many situations where the optimal dose of a medicine to produce maximal efficacy (or avoid adverse effects) is not known, and many of the factors determining inter-individual variability remain to be determined. The situation in paediatrics is compounded by the lack of PK and PD data for some medicines in children, which leads to a high rate of off-label and unlicensed medication use. This can lead to inadequate efficacy or adverse drug reactions (ADRs). Indeed, ADRs have been associated with the use of off-label and unlicensed medications in children [2-4]. A contributory factor here is likely to be imprecise dosing which can only be overcome by further research in children including specific PK and PD studies. It is clear that there are medicines where there is large inter-individual variation in both the serum concentrations achieved for a given dose (in mg/kg) (e.g. phenytoin [5]) and in the subsequent clearance (e.g. carbamazepine[6]). This has not been fully appreciated in the past, with drug development studies failing due to incorrect doses being used [7].

Finally, it is becoming clear that while many children do not require medications, amongst those hospitalised there is a high prevalence of polypharmacy, especially for those with rare conditions [8]. Drug-drug interactions have been identified that can alter the dose of a medicines required to be effective or prevent an adverse reaction [9]. Of course, drug-drug interactions can be avoided by preventing the co-prescription of drugs that adversely interact with each other. However, this is not always possible, in which case, alteration of dosing becomes a key factor in preventing any adverse consequences.

The challenge for implementation of precision medicine in paediatrics is therefore to develop an appropriate evidence base (particularly for unlicensed and off label medications), then build upon existing clinically individualised practice and improve upon it by adding in the relevant genotype, environmental and lifestyle data to guide both medication selection (where choices exist) and the dose required.

This review will consider specific examples where consideration of dose is crucial to the successful implementation of precision medicine in children. We will initially consider the dosing implications of the normal physiological variation across childhood, and consider paediatric obesity, where this variation is particularly marked. We will then look at a precision medicine success story in paediatrics, where successful implementation of personalised dosing has been achieved (Thiopurine Methyl-transferase [TPMT] and 6-mercaptopurine [6MP]) improving the treatments efficacy and adverse effect profile. Following this, we will then review an area where optimal paediatric dosing is not well established, and hence although multiple therapeutic options do exist and there is potential for precision medicine to improve treatment, more work is needed. Finally we will look at new biologic agents, where new therapeutic indications for these agents are emerging, but the data on how to use them is incomplete. The focus throughout will be on why children need better individualisation of doses, rather than how to calculate a dose for children (which has been reviewed recently [10]).

# Variation within the paediatric population

## Developmental changes across the population

There are several established methods of dose adjustment for children, including age, allometric scaling, body weight and body surface area, although all have limitations [11, 12], and none account for the wide inter-individual variation seen in practice for a specific dose (Table 1).

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| --- | --- | --- |
| Method of dose adjustment | Advantages | Disadvantage |
| Age | Very easy to use in clinical practice | Inaccurate. Requires wide therapeutic index to be safe. |
| Body weight (BW) | Easy to apply in clinical practice | Nonlinear relationship between weight and dose. Also, for pre-clinical work: smaller species are generally more tolerant of drug treatment than larger species [13]. |
| Body Surface Area (BSA) | More accurate than BW, particularly during infancy and childhood [14] | Over-predicts clearance in neonates [14]. Harder to use in routine clinical practice. |
| Allometric Scaling | Superior to BW and BSA for scaling some PK parameters such as plasma clearance, volume of distribution and elimination half-life [15] | Complex calculation, difficult to apply to clinical practice. |

Table 1: Advantages and Disadvantages of various methods of dose adjustment for children

Part of the reason for the difficulty in adapting dose is that although the kidneys and liver are fully formed in a term infant, there are well established variations in renal and hepatic function across childhood that affect how children handle drugs [16].

With regard to renal function, a healthy adult has a glomerular filtration rate (GFR) of approximately 100–120 ml/min/1.73 m2. A healthy term neonate however only has a GFR of 30 ml/min/1.73 m2, despite having a full complement of glomeruli, as the surface area of the glomerular basement membrane at this age is reduced [17]. A preterm infant (<34 weeks gestation) will also have fewer glomeruli, reducing GFR further [18]. There are also age related changes in proximal tubular function, collecting duct, and water homeostasis, particularly in the late pre-term and early neonatal period, that can have significant effects on how a young baby will handle medications (reviewed here [17]).

In the liver, the expression and function of cytochrome P450 (CYP) enzymes responsible for phase 1 oxidation of drugs is not constant across childhood. In adult patients, CYP3A4 is the most abundant CYP3A isoform, and is responsible for metabolising over 50% of drugs. However, there is low expression (and hence function) of CYP3A4 at birth, and the function only increases to reach adult levels by approximately 1.3 years of age [19]. Prior to delivery, the most abundant CYP3A isoform is CYP3A7, which despite having >90% identical amino acid bases with CYP3A4, has very different preferences for endogenous substrates [20], and for most drugs, the activity of CYP3A7 is lower than CYP3A4 [21]. Conversely, CYP1A2 has increased metabolic clearance compared to adults in those aged 0-3 years [19], while CYP2D6 has approximately 20% of adult function at birth, increasing to adult levels at approximately 1 year of age [22].

There are also well recognised changes in the proportions of body fat, water and lean tissue across childhood. Total body water (TBW) as a percentage of body weight is greatest at birth [23]. This rapidly decreases, from approximately 78% of total body weight for a healthy term baby at the time of delivery, to around 60% at 10 years of age, and is also accompanied by alterations in the intra-cellular (ICW) and extracellular water (ECW) composition. ECW decreases from 44.5% of body weight at birth, down to 22% at 10 years, while ICW stays relatively constant, with values of 33.9% at birth and 42.3% at 10 years [23]. In clinical practice this means that although babies will have a much smaller circulating volume than an older child or adult (350ml v 5.5l), the volume of blood per kg is actually larger in the youngest patients, at approximately 100ml/kg (compared with ~70ml/kg in healthy adults [24]).

The concentration of albumin in newborn infants is also 15% lower than that seen in adults [25], and the change across childhood is not a simple linear increase; for example, children aged 6-13 years have serum albumin levels 11% greater than that seen in the adult population [25]. The absolute values of other serum proteins (including alpha, beta and gamma globulins) also vary with age across infancy and childhood [25]. Further dose adjustments may then need to be undertaken depending on the hydo- or lipo-philicity of the molecule and the location of the target, the nature of the underlying condition, and the adverse effect profile expected at the age the dose is going to be used.

The establishment of the correct dose of a drug for children of different ages is therefore a fairly complex process, and although the ability of population based pharmacokinetic (PBPK) software has greatly improved in recent years [6], there is still a need for early phase studies in children of the age the drug is intended to be used in. This is true for both new drugs, and in some instances for older drugs where these data are missing, or new indications are established.

## Thiopurine S-Methyltransferase & 6-Mercaptopurine

There is an established example within paediatrics where personalisation of dose based on the principles of precision medicine is already well established: the treatment of childhood acute lymphoblastic leukaemia (ALL).

Thiopurines (6-mercaptopurine [6MP] and thioguanine) are purine analogues that act via conversion into “fraudulent” nucleotides in cells. For paediatric ALL, 6-MP is used as an oral maintenance therapy in many international protocols. The dose is crucial to the successful use of this medication. Too low a dose can result in treatment failure, but too high a dose results in potentially fatal bone marrow suppression. Thiopurine S-methyltransferase (TMPT) is the enzyme that catalyses the inactivation of 6MP and thioguanine in haematopoietic tissues, and protects the patient from the bone marrow suppression. It is now recognised that the TMPT gene has several polymorphisms, leading to a trimodal distribution, with 90% of the population being homozygous wild type with adequate functional enzyme levels, while a significant minority are heterozygotes (10%) with intermediate metabolism capacity, and 1 in 300 are homozygous for the variant alleles with low activity of the enzyme [26, 27]. The latter in particular are susceptible to the adverse effects; in one series, low and intermediate metabolisers combined accounted for 70% of cases of bone marrow toxicity (despite only accounting for approximately 10% numerically) and the poor metabolisers received only 7% of the scheduled weeks of 6MP therapy [28]. Different dosing regimens have therefore been developed for poor, intermediate and rapid metabolisers, and children presenting in the UK with newly diagnosed ALL and treated as part of both the MRC’s UKALL 2003 and 2011 studies are routinely phenotyped and genotyped for TMPT alleles. Those found to be poor metabolisers have a 90% reduction in their 6MP dose [29]. This intervention has been shown to effective in reducing 6MP adverse effects [27], while the test has been shown to be cost effective in clinical practice [30].

## Paediatric Obesity

It is well recognised that in many populations across the world, the proportion of children who are overweight and obese is increasing, but there is wide geographical variation. For example, recent estimates have shown obesity is present in 16.9% of US children and 11.7% in Canada, but only in 2% in the Netherlands and 0.5% in Denmark [31-34].

Obesity has obvious direct effects on the dosing strategies required, for example increasing the lipid proportion of total body weight and providing a reservoir for lipophilic medications. It may also lead to inadvertent overdosing of medications that are protein bound within the intravascular compartment as this does not increase in proportion with the increase in weight. In adult populations, studies into the effects of dosing in obese patients have been published for more than 30 years [35, 36], and show differential effects of obesity on different drugs. Within paediatrics, there has been less focus on this area, but there has been increased interest over the last 5 years [37, 38]. However, it remains the case that many of the clinical studies researching the effects of obesity are limited by poor design and insufficient sample size [37]. Moreover, clinical studies conducted during paediatric drug development rarely include (or are required to include) obese subjects.

Validated algorithms exist to manipulate a child’s actual weight to either an ideal or lean body weight, but these are not currently widely used within paediatrics [39]. From a precision medicine perspective, there are specific conditions where obesity may or may not contribute to the overall illness, and the current treatment modalities do not account for this. For example, recombinant human growth hormone (rhGH) treatment is indicated for a number of conditions in childhood.

There have been some safety concerns about the use of rhGH, particularly with regard to long term cardiovascular and oncology effects in children and adults who receive it, and a meeting of the the European Society of Paediatric Endocrinology, the Growth Hormone Research Society and the Pediatric Endocrine Society was recently convened appraise this aspect of rhGH use [40]. To reduce the risk in paediatric patients, monitoring of IGF-1 levels was recommended, aiming to keep them in the normal range [40], as safety of maintaining IGF-1 levels outside the normal range has “not been rigorously evaluated” [40]. Conversely, the same position statement also noted that when growth on rhGH treatment was not sufficient in certain subgroups (including Turner’s syndrome [TS]), the GH dose could be increased within the recommended range and higher than normal IGF-1 levels tolerated in order to achieve improved growth response [40], although these doses were very high (91 micrograms/kg daily) and the safety data here is considered insufficient [41]. No recommendations for obesity were included.

Although not a necessary feature of TS, obesity is well recognised in children with this condition, and unlike “healthy” obese children who grow very well but lose some adult height due to an earlier puberty, obesity does not drive growth in girls with TS. The volume of distribution of exogenous delivered rhGH has been calculated at approximately 78L [42], which is consistent with the drug being distributed in the total body water compartment (with the intravascular proportion predominantly bound to growth hormone binding protein [43]). In the obese, the increase in total body water is only a small percentage of the increase in weight [44]. So for obese children with TS, using current dosing strategies calculated using body weight exposes them to higher doses of GH than a short stature child of a similar age and height who is not obese.

Currently, there is no consensus on the correct dose of rhGH to start with in clinical practice [41]. Current practice in paediatric endocrinology is to start with a dose at the lower end of the range, and titrate. This titration may be done using the patients height, their IGF-1 level, or prediction model based dosing (using a combination of biochemical and auxological data) [41]. The only randomised controlled trial of the prediction model against standard weight based dosing did not identify any significant differences in the height achieved or dose administered [45], although this only included idiopathic short stature and GH deficiency patients, and the mean BMI SDS scores in the population recruited were negative (underweight). There is thus much more work that needs to be done for rhGH dosing to ensure that the benefit-risk ratio is optimised for each patient.

# Existing medicines where paediatric dose is not clear

## Paediatric Asthma

Asthma is a common condition, affecting millions of children worldwide. During an acute asthma attack, the most seriously ill children require intravenous (IV) therapy [46]. Unlike many areas of paediatrics, there are several therapeutic options available, including aminophylline, salbutamol, and magnesium.

### Salbutamol

A recent prospective nationwide survey of children presenting to hospital in the UK and Ireland showed that the most common intravenous salbutamol loading dose used was 250 mg over 5–15 min (33.3% of all patients received this dose) [47]. This dose differs from that recommended in the 2014 British Thoracic Society Guidelines (15 micrograms/kg over 10 minutes, no maximum dose [46]) and the British National Formulary for Children (BNFc) (15mcg/kg, maximum dose 250mcg - the current recommended adult dose) [48].

The 15 micrograms/kg iv loading dose of salbutamol appears to have been derived from a single Australian randomised controlled trial study conducted by Browne et al involving 29 children, only 14 of which received active drug [49]. This dose was derived by “linear pharmacokinetic modelling with parameters obtained from salbutamol studies in adults”. However, the cited study from which this was derived (Goldstein et al [50]) used 1.5mg of iv salbutamol in 16 subjects, given over 30 minutes. The adult subjects had an average weight of 72kg, meaning that they received an average dose of 21mcg/kg over 30 minutes, or 7mcg/kg over 10 minutes, a much larger dose. In addition, the adults in the study were salbutamol naïve, unlike the children who arrive at A&E and who receive inhaled, and nebulised salbutamol. A full review of the differences between adult and paediatric iv salbutamol doses has recently been published, and has shown that using the dosing regimens recommended by the BNFc, a child weighing 20 kg and over 2 years of age will receive the same intravenous bolus dose as that recommended for a 70 kg adult [51]. This is potentially problematic, as salbutamol toxicity is dose-related, and symptoms include heightened patient anxiety; lactic acidosis and tachycardia (all of which are also symptoms of worsening asthma) [51]. There is therefore a pressing need to determine the optimal dose of iv salbutamol in children with acute severe asthma.

### Aminophylline

The most commonly used loading dose of iv aminophylline is 5 mg/kg over 20–30 min (used in 96.2% of paediatric patients in the UK and Ireland) [47] (also the dose shown in the BNFc). Aminophylline has a narrow therapeutic range and high inter-individual variation in clearance; therapeutic drug monitoring is therefore recommended with the aim of getting concentrations within the range of 10-20mg/L. However, in common with salbutamol, the data upon which the IV loading dose has been determined is sparse. Pharmacokinetic work form the 1970’s in children aged 1-4 (n=10) showed that a loading dose of 5.6mg/kg would be sufficient to achieve a concentration of 10mg/l [52]. As shown above, a loading dose of 5mg/kg is routinely used, but based on these data, we would expect 1/3 of children to be below the current recommended therapeutic range [53]. Subsequently, a PK study used a higher loading dose (6mg/kg) and achieved serum theophylline levels between 10-20mg/l in all children (n=11) [54]; however, this was not replicated in clinical practice when this higher dose was used as the majority of children were still sub-therapeutic and required additional boluses [55]. Assuming that the recommended therapeutic range reflects the optimal serum concentration to treat acute severe asthma in children, current IV loading dosing regimens are likely to be under dosing children.

### Choice of IV therapy

Currently there is no clear evidence that that either IV Salbutamol or IV aminophylline are preferable to the other in paediatric acute severe asthma [46]. The British Thoracic society have summarised the evidence in their UK national guideline, and this is shown in table 1, along with the full range of doses used in a UK nationwide survey of children presenting to hospital [47].

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| --- | --- | --- |
| Intravenous therapy choices for life threatening asthma in children (age >2y) | British Thoracic Society Guideline Recommendations 2014 [46] | Doses used in UK wide prospective study of childhood acute severe asthma [47] |
| IV Salbutamol | Consider early addition of a single bolus dose of intravenous salbutamol (15 micrograms/kg over 10 minutes) in a severe asthma attack where the patient has not responded to initial inhaled therapy. | Bolus/load: 2–15 mg/kg over 5–40 min  Infusion: 0.3–5 mg/kg/min |
| IV Aminophylline | Consider aminophylline for children with severe or life-threatening asthma unresponsive to maximal doses of bronchodilators and steroids. | Bolus load: 10 mg/kg–200 mg (total) over 30 min  Infusion: 0.5–1.0 mg/kg/h |
| IV Magnesium Sulphate | Intravenous magnesium sulphate is a safe treatment for acute asthma although its place in management is not yet established | Bolus: 5–54 mg/kg over 20–30 min  Infusion: N/A |

**Table 2 British Thoracic Society Guidelines on IV treatment for acute severe asthma in childhood and the range of doses used in a prospective UK survey [46, 47]**

Ideally, a well-designed randomised controlled trial (RCT) could be undertaken to determine the optimal first line treatment in children presenting with acute severe asthma. However, as noted above, there insufficient evidence upon which to base the optimal dose of either IV aminophylline or IV salbutamol. Children in the UK continue to receive a wide variety of doses [47] (table 2). Despite the dose uncertainty, there have been two RCT. The first RCT recruited 44 children age 1-16 years and comparing iv salbutamol and iv aminophylline [56], and used either a short intravenous bolus of salbutamol (15 micrograms/kg over 20 minutes), or in the other arm, an aminophylline infusion (5 mg/kg over 20 minutes) [56]. There was limited evidence of shorter hospital stay following IV aminophylline in this trial. The second RCT recruited 40 children and compared three arms, iv aminophylline, iv terbutaline and a combination [57]. The doses used here for aminophylline were age banded: age 3–8 yrs 0.96 mg/kg/hr theophylline, 9–12 yrs 0.80 mg/kg/hr theophylline, 12–15 yrs 0.64 mg/kg/hr theophylline (local policy at unit undertaking RCT, aiming for serum concentration of 12-20 mg/L), and all ages received 20 µg/kg terbutaline [57].

Key for the delivery of optimal management of paediatric acute severe asthma is establishing the best doses of the medicines already in clinical use, as only then can definitive RCTs be undertaken. For salbutamol particularly, additional PK studies are required. Much of the work to date has been undertaken in salbutamol naïve adults, not children who have been exposed to nebulisers and inhalers containing salbutamol prior to starting IV treatment. Knowing the salbutamol concentration likely to be present in the child’s system prior to commencing IV therapy may affect the dose chosen. Subsequently there will also be a place for physiologically based pharmacokinetic (PB-PK) studies for both IV salbutamol and aminophylline, as acute severe asthma in children is a medical emergency and while possible, it is technically challenging to accurately carry out accurate PK studies. PB-PK modelling of large populations may be an efficient way of narrowing the choice of doses down, prior to comparative studies of each drug at different doses, and then finally the definitive RCT comparing both drugs.

PB-PK modelling has been successfully used to estimate doses of many medicines in children [6], but in these instances, the modelling did not have to consider either previous exposure (such as for acute asthma and iv salbutamol), or the effects of polypharmacy (common in many children with chronic diseases, and so successful demonstration in this area would be a significant advance for the technology.

## Warfarin and other anti-coagulants

This is an area where adult medicine is progressing towards a personalised approach using the principles of precision medicine [58]. Multiple large scale studies in adult populations have shown that CYP2C9 and VKORC1 genetic polymorphisms impact on warfarin dose requirements [59]. There have been nine paediatric studies of warfarin pharmacogenomics, although these are significantly smaller (as warfarin is used much less in this population), with very different indications to adult practice (primarily following surgery for congenital heart disease), and with varied outcome measures used. Despite these limitations, seven of the nine found associations with VKORC1 and two with CYP2C9 polymorphisms (Table 3) with regards to efficacy, and one found VKORC1 polymorphisms associated with adverse effects [60]. A systematic review and meta-analysis of the pharmacogenomic association between VKORC1 and paediatric warfarin dose has recently been published [61]. This concluded, as many of the individual studies did, that the VKORC1 -1639G>A polymorphism, as well as clinical factors such as age and indication for treatment, affected the dose used to achieve a therapeutic INR. However, this work did not manage to use individual patient data from the individual studies, necessary to overcome the heterogeneity of the data. This may be achievable through international collaborations such as the consortium on paediatric warfarin Pharmacogenetics, currently in development along similar lines to the adult group. However, the implementation of a paediatric warfarin dosing algorithm still appears distant.

The direct oral anticoagulants (DOACs) are not currently licensed in children, but there is interest in their application in this population as they have once daily dosing, a wider therapeutic range, and less onerous monitoring procedures than warfarin [62]. Currently, the EU clinical trials database has two studies listed for Rivaroxaban (one complete PK study, one ongoing PK/PD study) and two for Dabigatran (both ongoing) [63]. All these studies relate to treatment of venous thromboembolism, but there is no published data available, so it is likely to be some time before the place of DOACs in the treatment of childhood venous thromboembolism becomes clear.

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| Study | Year | Sample size | Anticoagulant | Ethnicity | SNPs analysed | Positive Genetic outcomes |
| Nowak-Gottl [64] | 2010 | 59 | Warfarin 34 (55.9%) Phenprocoumon (26 (44.1%) | White 100% | VKORC1: (-1639G>A)  CYP2C9 (\*2 & \*3) | VKORC1 and stable dose |
| Kato [65] | 2011 | 48 | Warfarin 48 (100%) | Japanese 100% | VKORC1 (1173C>T)  CYP2C9 (\*3) | VKORC1 and stable dose  VKORC1 and INR achieved for given dose |
| Biss [66] | 2012 | 120 | Warfarin 120 (100%) | White 91 (75.8%) | VKORC1: (-1639G>A)  CYP2C9 (\*2 & \*3)  CYP4F2 (V433M) | VKORC1, CYP2C9\*2 & \*3 and stable dose |
| Moreau [67] | 2012 | 118 | Warfarin 83 (70.3%)  Fluindione 35 (29.7%) | White >90% | VKORC1:  CYP2C9 (\*2 & \*3)  CYP4F2 | VKORC1 and stable dose |
| Nguyen [68] | 2013 | 37 | Warfarin 37 (100%) | White 73% | VKORC1 1173C>T and CYP2C9 (\*2 & \*3) | VKORC1 and stable dose |
| Hirai [69] | 2013 | 37 | Warfarin 37 (100%) | Japanese 100% | VKORC1: (-1639G>A)  CYP2C9 (\*2 & \*3)  CYP4F2 (rs2108622) | CYP4F2 and stable dose |
| Hawcutt[60] | 2014 | 100 | Warfarin 100 (100%) | White 97% | VKORC1: (-1639G>A)  CYP2C9 (\*2 & \*3) | VKORC1 and CYP2C9\*2 and stable dose  VKORC1 and time in treatment INR range  VKORC1 and risk of haemorrhage |
| Vear [70] | 2014 | 100 | Warfarin (100%) | White 85%  African American 8% | VKORC1: (-1639G>A)  CYP2C9 (\*2 & \*3)  CYP4F2 (rs2108622) | VKORC1 and CYP2C9\*2 or \*3 and stable dose. VKORC1 effect varied with age |
| El Din [71] | 2014 | 41 | Warfarin (100%) | Egyptian (100%) | VKORC1 (-1639G>A & 1173C>T)  CYP2C9 (\*2 & \*3) | None |

Table 3: Pharmacogenomic associations shown in paediatric warfarin studies (adapted from Yip et al [72])

# Optimising new medicines

The introduction of legislation in the US (Best Pharmaceuticals for Children act 2002 [73] and the Pediatric Research Equity Act 2003 [74]) and EU (Regulation on Medicines for Paediatric Use [75]) has increased early phase work done in children of all ages. If a drug is developed for a particular purpose, it is now very unlikely that we would have the dearth of data such as outlined for asthma. However, even in the studies required by these laws related to the expected use of a new drug, use of the incorrect dose (leading to lack of efficacy) was been a contributory factor in 23% of failed drug development trials in children [7]. In addition, re-purposing of medications within paediatric practice is not uncommon, either to the same indication but a different age group, or for a completely new indication. In these cases, additional PK work should ideally be done, but rarely is. Rituximab is a particularly good example in this regard.

Rituximab is a biologic agent, first approved by the European Medicines Agency for the treatment of adult lymphoma in 1988 [76]. It is a chimeric monoclonal antibody, acting against CD20 (located on B cells), reducing both naïve and memory B cells. Since then, its uses have multiplied such that it is prescribed for many other conditions (over 60 different clinical indications in one large Australian study [77]), often in an off-label manner [78]. The most common indication for using rituximab in adults include malignancy (acute lymphoblastic leukaemia (ALL), B-cell lymphoma), and autoimmune diseases (systemic lupus erythematosus (SLE), immune mediated thrombocytopenia (ITP), vasculitis), and neuro-inflammatory conditions [79].

Although it currently has no licensed paediatric indications within the UK [80], it is used to treat many different conditions in childhood. There are no recent publications that show the full breadth of rituximab use, but review of a single combined secondary and tertiary paediatric centre in the UK has shown that rituximab is used for juvenile idiopathic arthritis, childhood cancer (including post-transplant lymphoproliferative disease, pre-bone marrow transplantation, and severe graft versus host disease), neuro-inflammatory, haematological conditions, SLE, vasculitidies, nephrotic syndrome and Graves’ disease (personal communication L Oni – data available on request). The use of rituximab in juvenile-onset SLE and children with neuro-inflammatory diseases has also been shown to be increasing over time [81, 82]. The dose used, and frequency of infusions, varies depending on the condition being treated. In the 17 different unlicensed indications we have identified, the doses administered ranged from 375-750mg/m2. The annualised total dose administered can therefore range from 375-1500mg/m2 (data available on request).

The main immediate adverse effects of rituximab are infusion-related [83]. However, questions remain about longer term safety, as there are some rare but very severe ADRs (such as progressive multifocal leukoencephalopathy). When compared to adults, where the currently longest published follow up period is 9.5 years in rheumatoid arthritis [84], in children, the potential period of use, and life-span after use, is much greater (especially in the chronic diseases such as juvenile idiopathic arthritis), with potential implications for long-term safety. It would therefore be prudent to use the lowest effective dose possible to minimise the chance of such long term adverse effects. However it is currently not clear what the correct dose for any indication is, whether the same dose would be effective, or if the doses of the new biosimilar agent coming onto the markets need to be the same as for the originator product.

# Expert Review

There is considerable potential for dose manipulation to be used in the personalisation of medicines for children. This will vary depending on the medicine, and will largely fall into the groups shown in table 4.

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| Group | Examples |
| Older medicines where PK data is obscure/incomplete | Salbutamol  Aminophylline  Phenytoin  Neonatal antimicrobials |
| Old medicines where robust PK data is available and new medicines used as per intended original use | Warfarin  Antimicrobials in older children |
| New medicines “re-purposed” to new diseases | Rituximab  Infliximab |
| Improved stratification of disease | Asthma subtypes (through development of biomarkers of subtypes of the disease)  Paediatric oncology |
| Implementation of pharmacogenomic data | 6-MP (paediatric oncology and gastroenterology)  Asthma (maintenance therapy) |

Table 4: Exemplars of different dosing scenarios in children. This is a small selection of examples and is not meant to be a comprehensive list.

For old medicines where there is not sufficient PK data to determine the optimal dose for either efficacy or adverse effects, then clearly there will be a considerable amount of work to do. For the asthma example cited above, research groups within paediatrics are currently working on salbutamol and aminophylline, with the ultimate goal of having an RCT of these two in acute severe asthma, although this is likely to be some years away. Despite the altruism of children [85], and the ethical arguments in favour of including children in research [86], it is not always easy to recruit children to PK studies where multiple blood samples are taken in order to improve dosing. However, the improvements PB-PK modelling of paediatric populations mean that it is now possible to model the effects of older medicines, and check the accuracy using routine therapeutic drug monitoring (TDM) data [5]. As confidence in this technology grows, we would anticipate more PB-PK studies looking for areas where doses could be optimised to either increase efficacy, or decrease ADRs. Over time, this group of older medicines will eventually either become a) adequately understood to allow precision dosing, or b) obsolete as newer agents whose dose we are more confident of become available.

Fastest implementation of precision dosing in children will be in those medicines where robust PK is available. Warfarin is probably the best example of an “old” medicine in this regard, as there are now good PK studies and increasingly established pharmacogenomic associations that affect the dose required. Developing international collaboration is key here, as individual countries will not have sufficient children having surgery for congenital heart disease to be able to power a single definitive study; to harmonise the outcomes access to individual patient data is likely to be required. Antimicrobial therapy in neonates is in a similar position, with “old” medicines being used at a wide variety of doses (up-to 32 different dose regimens for a single drug reported [87]). Here international collaborations are starting to generate the data needed to develop effective and safe doses [88]

Within international paediatric oncology studies there are usually pharmacogenomic sub-studies to ensure that dose variation (or, where alternatives exist, drug substitution) is considered, primarily for the avoidance of adverse effects (such as recent Hodgkin’s lymphoma studies comparing procarbazine and dacarbazine to reduce the incidence of long term infertility [EuroNet-PHL-C1]).

Careful consideration of dosing will need to be given to medicines re-purposed to new diseases within paediatrics. This will be more than just application of the established physiological changes or body surface area, and fat/fluid/lean tissue across childhood, as different diseases may have effects on PK (cystic fibrosis in particular can affect the PK of drugs in those with the condition compared to healthy volunteers [89]), and the differential expression of cytochrome P450 enzymes (and their polymorphisms) will also have an effect. As we have noted in the body of the article, Rituximab is an excellent example of a new drug being re-purposed to multiple disease areas, with current doses being selected with little evidence to support them. Estimating the active drug from a biologic medicine is not straightforward, and standard PK methodologies will not be sufficient.

A further improvement which will facilitate the implementation of personalised dosing in children is more accurate stratification of disease. If we consider asthma, all children and adults are currently classified as having the same disease, with the same treatment algorithms. However, between adults (including smokers and exposure to occupational pollution) and children there are considerable differences, and within paediatrics there will also be sub-types of asthma, but we are not currently able to reliably distinguish between them. Improvements in disease stratification will permit dosing strategies for each sub-type to be investigated, and bring personalisation of dose nearer to clinical practice, although this may mean new studies in disease areas which were considered to be understood.

Finally there are the pharmacogenomic interventions, which with the exception of TPMT mentioned above, are rarely used in paediatric clinical practice. We are aware of many studies collecting DNA for a variety of efficacy and ADR related studies, and increasingly, international collaborations bring the critical mass of patient samples to ensure accurate analyses. However, replication of pharmacogenomic associations in independent cohorts is required to ensure that these findings are able to be delivered into clinical practice. This is particularly clear in respect of paediatric asthma, where multiple studies have shown various associations, but none of them are currently used in clinical practice [90]. Hopefully this will improve as there are now international collaboration in paediatric asthma. Over 20 groups are now working together in the Pharmacogenomics of Childhood Asthma (PiCA) consortium, allowing additional analyses by combining existing cohorts [91], and hopefully improving on the previously contradictory study results in this area.

In conclusion, a lot of work needs to be done to improve dosing in children. Although progress have been frustratingly slow, we remain optimistic, as a number of developments that will assist this process are now being increasingly utilised. These include more paediatric specific PK studies, developments in PB-PK modelling, international collaboration to ensure adequate sample sizes are recruited in studies, routine collection of genomic data in many paediatric research projects, and improved regulatory requirements requiring pharmaceutical companies to undertake paediatric testing of new drugs in appropriate conditions. These factors will help to deliver the evidence needed for personalisation of doses, and thereby improve the efficacy and ADR profiles of medicines given to children.

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