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Paediatric pharmacokinetics: key considerations

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A number of anatomical and physiological factors determine the pharmacokinetic profile of a drug. Differences in physiology in paediatric populations compared with adults can influence the concentration of drug within the plasma or tissue. Healthcare professionals need to be aware of anatomical and physiological changes that affect pharmacokinetic profiles of drugs to understand consequences of dose adjustments in infants and children. Pharmacokinetic clinical trials in children are complicated owing to the limitations on blood sample volumes and perception of pain in children resulting from blood sampling. There are alternative sampling techniques that can minimize the invasive nature of such trials. Population based models can also limit the sampling required from each individual by increasing the overall sample size to generate robust pharmacokinetic data. This review details key considerations in the design and development of paediatric pharmacokinetic clinical trials.

Introduction

Although paediatric patients are now recognized as a special population for drug therapy, many physiological changes take place during childhood which may have an impact on the pharmacokinetics and dynamics of a compound. For that reason childhood can be divided into various classes of age where each group should be considered as a special population. Any classification of the paediatric population into age categories is to some extent arbitrary. For the purposes of this review International Conference on Harmonization (ICH) E11 classifications are used [1] where the paediatric population is divided into:

- Preterm newborn
- Newborn (0–28 days)
- Infant (>28 days–12 months)
- Toddler (>12 months–23 months)
- Preschool child (2–5 years)
- School age child (6–11 years)
- Adolescents (12–18 years)

Although many anatomical and physiological differences between paediatric and adult populations will be highlighted within this review, this topic has been the subject of some excellent reviews and the reader is directed to these papers for a full discussion [2–4].

Factors that influence tissue drug concentrations over time include absorption, distribution, metabolism and excretion (ADME). These ADME processes differ in paediatric populations compared with adults and have consequences on the pharmacokinetic profile of a drug. An understanding of these ADME differences and likely outcome is important to ensure effective therapy in paediatric populations.

Pharmacokinetic studies measure the concentration of drug found within body fluids, usually blood or plasma, over time. Such studies are particularly useful where there is a clear link between the pharmacokinetic profile and the pharmacodynamics of a drug. The aim of a pharmacokinetic study is typically to match the exposure in paediatric patients to that found in adults. In paediatric

populations, particularly in the very young, pharmacokinetic analysis is usually simpler than pharmacodynamic studies owing to the complexity of the latter. For example, measurement of subjective symptoms such as pain requires different assessment instruments for patients of different ages [1].

There are many examples of drugs in which the pharmacokinetic profiles differ between children and adults, highlighting the importance of understanding paediatric physiology and the potential effects on drug concentration. The incidence of intra-operative awareness under anaesthesia is reported to be much higher in paediatric patients compared with adults. This is probably a consequence of poor understanding of the pharmacokinetic and pharmacodynamic characteristics of commonly used drugs within paediatric populations [5].

This review is limited to a discussion of key differences in physiology and anatomy of children compared with adults and how these factors affect the pharmacokinetic profile of drugs. A second element considers obtaining pharmacokinetic data from paediatric populations and how best this is currently managed and used.

Physiological processes involved in pharmacokinetics

Absorption

A lack of high quality pharmacokinetic data from clinical studies undertaken in paediatric populations limits exhaustive knowledge regarding absorption mechanisms within this population.

Liberation of drug from a formulation can differ in children since gut transit time and intestinal fluid composition (including pH) can significantly affect drug dissolution. Intestinal transit time has been reported to be shorter in young children which may reduce the amount of drug absorbed, particularly for poorly soluble drugs or sustained release products (e.g. theophylline) [6, 7].

It is generally agreed that gastric pH is neutral at birth although there is debate over the time taken for the pH to reduce following birth with reports of 24–48 h to reach pH 3 [8] with a further rise to neutral after 72 h, or 10 days at neutral followed by a decrease to acidic values comparable with adults at 2 years [9]. The impact of these differences in gastric pH can be significant, with greater peak concentrations of penicillin, an acid labile drug, observed in newborns where gastric pH is higher compared with infants and children [10]. Weakly basic drugs, such as itraconazole (pKa = 3.7) are also affected by gastric pH, with higher serum concentrations being obtained at lower gastric pH levels. Therefore there may be lower than expected values in newborns [11].

Bile secretion in the first 2–3 weeks of life is known to be poor with luminal concentrations lower than in adult intestines (2–4 mM *vs.* 3–5 mM respectively) [12, 13]. It is known that drug solubility increases with bile salt concentration and therefore a difference in concentration may have an impact on absorption in younger patients. This is a particular risk for poorly soluble drugs (e.g. hydrocortisone) [14].

Intestinal permeability is reported to be high at birth with progressive reduction during the first week of life [15]. This may be related to the reduced surface area : volume ratio within the intestine owing to the villi being broader and providing a smaller overall surface area. This phenomenon is well documented in rats [16].

Intestinal permeability in preterm babies is typically assessed using sugar absorption tests. The differential excretion of lactulose and mannitol is measured in urine following enteral administration of a test solution. In a healthy intestine mannitol is readily absorbed via the transcellular pathway but larger disaccharides (e.g. lactulose) are only absorbed through the paracellular pathway. Therefore the ratio of lactulose : mannitol in the urine is a measure of intestinal integrity. Intestinal permeability, assessed using sugar absorption, was reported to be higher in preterm babies than in healthy newborns [17]. A decrease in the first week of life following birth was also reported [18].

Kalach *et al*. reported a decrease in the lactulose : mannitol ratio from 0.5 months–14 years of age [19]. This was due to an increase in mannitol permeability with age suggesting that the transcellular pathway becomes more permeable with age.

Active transport processes are usually responsible for the absorption of nutrients and ions in the intestine. These active transporters are typically expressed in line with the needs of the growing child. The absorption of lead, a compound absorbed by these transporters, was greater in infants (40–50%) compared with school children (10–15%) [20].

The few bioavailability studies that have examined the absorption of drugs (e.g. phenobarbital, sulfonamides and digoxin) and nutrient macromolecules (e.g. arabinose and xylose) suggest that the processes of both passive and active transport are fully mature in infants by approximately 4 months of age.

The enteral absorption of drugs has been studied in children. D(+)xylose, which is absorbed by an active mechanism in the upper small intestine, showed no difference in the amount absorbed with age [21]. However, the rate constant, K_a, for enteral absorption of D(+) xylose was non-linear with age where K_a was less for newborns and infants compared with preschool children [21]. Prolonged gastric emptying time and reduced intestinal motility may be somewhat responsible for the similarity observed in total mass absorbed despite the slower absorption rate of D(+)xylose in younger patients. A further study was conducted to measure the effects of intestinal motility on absorption of D(+)xylose using metoclopramide to reduce gastric emptying time. The results showed an increase in K_a

in both newborns and infants yet the ratio of K_a : age remained constant [21]. These results suggest that the reduced K_a observed was not solely due to longer transit times or reduced motility but other factors are also involved. In conclusion, generally, the rate at which most drugs are absorbed is slower in newborns and infants; although the cause of this slower absorption is unknown [22].

The efflux transporter P-glycoprotein (P-gp) is responsible for cellular drug efflux, transporting substances from the intracellular to the extracellular compartments within the membranes of the gastrointestinal tract. P-gp can markedly affect the bioavailability of certain drugs, particularly those with low solubility. The ontogeny of expression of P-gp in the gastrointestinal tract in paediatric populations is unclear. Johnson & Thomson reported that the expression of P-gp appears to increase rapidly during the first 3–6 months of life, reaching adult levels by approximately 2 years of life [23], whereas Fakhoury *et al*. reported that P-gp expression in the intestine was not influenced by age with mature expression in neonates and infants [24].

Metabolism in the gut lumen and wall can decrease the absorption of a wide variety of drugs including ciclosporin, nifedipine, midazolam and verapamil [25–28]. The major enzyme family involved in gut wall metabolism of drugs is cytochrome P450 (CYPs). The CYP3A subfamily is predominant, accounting for approximately 70% of the cytochromes in the adult small intestine and is involved in the metabolism of more than 70% of currently administered drugs [29]. CYP3A substrates (specifically CYP3A4 and CYP3A5) are present in abundance in the small intestine in adults, yet data regarding their expression in paediatric populations is limited. Fakhoury *et al*. demonstrated that CYP3A was expressed in duodenal biopsies from Caucasian children aged 6 months and older and in half those from 1–6 months of ages [24]. However, CYP3A levels declined with age from 1–17 years [24]. In contrast, a study by Johnson *et al*. reported that an increase in CYP3A expression was observed with age that was mirrored by a corresponding change in CYP3A4 enzyme activity [30].

Distribution

The distribution of drugs affects efficacy and duration of action. Ginsberg *et al*. compared the pharmacokinetic parameters of 45 drugs in children and adults and concluded that there was a tendency towards larger volumes of distribution of these compounds in children of all age groups [31].

The distribution of drugs is dependent upon body composition. Lipophilic drugs have a relatively larger volume of distribution in infants compared with older children owing to their higher comparative levels of fat (22.4% at 12 months *vs.* 13% at 15 years [32]). For example, diazepam, a lipophilic drug has a ratio of adult volume of distribution to that of a newborn of 0.7 [33].

Table 1

Comparative protein binding in paediatric populations compared with reference adult values [36])

Parameter	Neonate	Infant	Child
Total protein	Decreased	Decreased	Equivalent
Plasma albumin	Decreased	Equivalent	Equivalent
Plasma globulin	Decreased	Decreased	Equivalent
α_1-acid glycoprotein	Decreased	No data available	Equivalent
Free fatty acids	Increased	Equivalent	Equivalent
Unconjugated bilirubin	Increased	Equivalent	Equivalent

Hydrophilic drugs also have larger volumes of distribution in preschool children as extracellular water decreases during development, from 70% total body weight in newborns to 61.2% in 1-year-old infants [32]. As a consequence of higher volumes of distribution of water soluble drugs in infants, for example gentamicin [34], higher doses per kilogram bodyweight must be given to infants compared with adults to achieve comparable plasma and tissue concentrations [35].

Protein binding also affects the volume of distribution of drugs. The physiological variables that influence protein binding within paediatric populations are presented in Table 1. In newborns, total plasma protein concentrations are 86% of adult values.

Examples of drugs where lower protein binding has been documented in newborn babies include phenytoin, salicylates, ampicillin, nafcillin, sulfisoxazole and sulfamethoxyphrazine [37–40]. Consequently, greater free fractions of these drugs are circulating and thus are able to penetrate various tissue compartments, yielding higher distribution volumes.

In general terms, one can assume that the influence of protein binding on free plasma drug concentrations is limited to drugs which have a high degree of protein binding (>95%). As protein levels reach adult values in infancy this effect is likely to be most pronounced in newborn babies and infants.

Metabolism

Recently the microsomal protein content within the liver has been reported to increase with age from an estimated of 26 mg g^{-1} in newborns rising to a maximum of 40 mg g^{-1} in a 30-year-old adult [41]. Generally drugs that are highly metabolized are administered at a lower mg kg^{-1} dose in newborns compared with preschool children due to these differences in enzyme levels. However, the hepatic clearance of drugs can be higher in infants and preschool children as liver blood flow is increased compared with adults, owing to the larger ratio of liver to total body mass in the former population [42]. This can increase the first pass effect where a drug is cleared on first passage through the

liver although the level of enzyme activity will influence this parameter. The observed age-dependent clearances for theophylline, caffeine, carbamazepine, and valproic acid seem to reflect liver size to body weight differences rather than differences in intrinsic clearance per gram of liver weight [43]. This has consequences in terms of dosage adjustment where scaling based on mg kg^{-1} is not appropriate.

Recently the microsomal protein content within the liver has been reported to increase with age from an estimated of 26 mg g^{-1} in neonates rising to a maximum of 40 mg g^{-1} in a 30-year-old adult [41]. However, the ontogeny of specific metabolic pathways needs to be understood to enable extrapolation of adult data into paediatric populations. The example of the grey baby syndrome resulting from dosing chloramphenicol to neonates at doses extrapolated from adult data is often used to highlight the importance of understanding ontogeny of metabolic pathways [44]. Differences in enzyme expression and activity can result in altered metabolism of drugs (e.g. midazolam and zidovudine [45, 46]) or production of metabolites in paediatric populations that are not observed in adults (e.g. caffeine production in newborns receiving theophylline, differences in metabolite production in children with valproic acid, paracetamol, chloramphenicol, cimetidine and salicylamide [47]). There are several extensive reviews on metabolism within paediatric populations including ontogeny of drug metabolizing enzymes [48, 49] and age related changes in the metabolism of drugs [8, 48, 50–53].

Drug metabolism in the gut lumen and gut wall An alteration in bacterial colonization of the intestine with age has implications in terms of drug metabolism within the gut. There are known differences in bacterial composition based on age and diet [54]. Metabolism in the gut lumen and wall can decrease the bioavailability and the pharmacological effects of a wide variety of drugs including ciclosporin, nifedipine, midazolam and verapamil [25–28].

The excretion of digoxin by inactivation within the gut lumen has been shown to increase with age from 1–3% in infants, 7% in school children, 10% in adolescents compared with 40% in adults [55]. Yet Linday and co-workers demonstrated that digoxin-inactivating bacteria (*Eubacterium lentum*) were present as early as the second week of life, indicating that metabolic activity rather than bacterial presence is critical for understanding the ultimate effects of digoxin within the gut lumen. The consequences of the differences in digoxin inactivation within the gut are factored into therapy with loading doses decreasing with age on a μg kg^{-1} basis from 45 μg kg^{-1} in infants to 35 μg kg^{-1} in pre-school children and 25 μg kg^{-1} in school children [56].

Andrieux and co-workers compared the activity of bacterial enzymes (β-galactoside, α-galactoside, β-glucoside, β-glucuronidase, neuraminidase, N-acetylgalactosaminidase, α-fucosidase, nitrate reductase and azoreductase) of the faecal microflora from children (3–15 years), adults and elderly adults. There were no significant differences in the enzyme activities between the three populations, although the data from children was more variable [57]. This finding agrees with other sources reporting that intestinal colonization reaches adult-like composition by 1–4 years of age [58–60].

Enzymes are responsible for gut wall metabolism. Therefore variations in enzyme expression and activity with age can affect pre-systemic metabolism of a range of drugs. The CYP3A subfamily is a predominant gut wall enzyme, which is involved in the metabolism of more than 70% of currently administered drugs [29]. CYP3A4 and CYP3A5 are present in abundance in the small intestine of adults, yet there are limited data regarding their expression in paediatric populations. Expression of CYP3A has been measured in Caucasian children. Data showed expression in all children aged 6 months–18 years, with only 50% of those under 6 months expressing CYP3A in the duodenum [24].

Elimination

Elimination of drugs and their metabolites occurs predominantly via the kidneys.

The glomerular filtration rate (GFR) is 2 to 4 ml min^{-1} 1.73 m^{-2} in term neonates, and it doubles by 1 week of age, reaching adult values by the end of the first year of life. This has been demonstrated by the similarity in time course of drug metabolism of three drugs (morphine, paracetamol and dexmedetomine), cleared by glucuronide conjugation in the kidney and GFR maturation [61].

The renal excretion of unchanged drug is generally lower in newborns owing to the immaturity of renal function. However a similar or greater rate of renal excretion has been observed in infants and preschool children compared with adult values for some drugs, including levetiracetam [62], cimetidine [63] and cetirizine [64]. This is likely to be related to the observation that the kidney relative to age is several-fold greater in preschool children compared with adults [43]. The ontogeny of renal tubular transport mechanisms can also influence the elimination of drugs. Digoxin serves as an excellent example for ontogeny of renal elimination. Digoxin is extensively secreted via P-gp within the tubular cell. Preschool children require three-fold higher doses of digoxin kg^{-1} body weight than adults, which may be linked to P-gp ontogeny [65].

Creatinine clearance is often used to estimate GFR in children [66] where a reduction in drug dose is advised if creatinine clearance is less than the normal GFR.

Urinary pH value can influence the reabsorption of weak acids or bases which, in turn, will influence the elimination. Infant urinary pH is lower than adult values which may increase the reabsorption of weakly acidic drugs [67].

Table 2

Summary of pharmacokinetic differences in paediatric populations compared with adults

	Developmental change	PK consequence	Drugs affected	Examples
Absorption	↓Intestinal transit	↓C_{max} and ↓AUC	Poorly solubles Sustained release formulations	Theophylline
	↓Gastric pH	↑C_{max} for weak acids ↓C_{max} for weak bases	Weak acids Weak bases	Penicillin Itraconazole
	↓Intestinal bile concentration	↓C_{max} and ↓AUC	Poorly solubles	Hydrocortisone
Distribution	Body composition	↔V_d (neonates have relatively reduced fat whereas infants have relatively increased fat compared with adults; extracellular water is relatively higher in neonates compared with preschool children)	Lipophilic drugs ↓V_d in neonates and ↑V_d in infants compared with adults Hydrophilic drugs ↑V_d in infants compared with neonates	Diazepam Aminoglycosides (e.g. gentamycin)
	↓plasma protein	↑free fraction of drug in plasma ↑V_d	Highly protein bound drugs	Phenytoin, salicylates, ampicillin, nafcillin, sulfisoxazole and sulfamethoxyphrazine
Metabolism	Larger relative size of liver	↑hepatic clearance of drugs	Those extensively metabolized	Theophylline, caffeine, carbamazepine and valproic acid
	Ontogeny of liver enzymes	↔hepatic metabolism of drugs	Drugs metabolism by specific pathways eg UDP glucuronosyl transferase	Chloramphenicol
	Bacterial colonization of the intestine	↑C_{max} and ↑AUC	Those metabolized within the gut	Digoxin
Elimination	Larger relative size of kidney	↑renal clearance in infants and preschool children	Those excreted unchanged in urine	Levetiracetam, cimetidine and certirizine
	Ontogeny of tubular transporters	↔renal clearance of drugs	Those susceptible to tubular transport	Digoxin

A summary of pharmacokinetic differences in paediatric populations is provided in Table 2.

Design and delivery of pharmacokinetic studies in children

Paediatric pharmacokinetic clinical studies are generally undertaken to support formulation development and determine plasma profile concentrations to support dosing recommendations. Recent regulations have increased the number of clinical trials conducted in children in the last 10 years although there is still a substantial discrepancy between paediatric burden of disease and the amount of clinical trial research within this population [68].

Pharmacodynamics in paediatric populations

Whilst pharmacokinetics involves absorption, distribution, metabolism and elimination of drugs and can be measured via blood/plasma sampling; pharmacodynamics comprises the physiological and biological response to the drug and is not always directly related to pharmacokinetics. The relationship between pharmacokinetics and pharmacodynamics in children is vital for rational dosing and cannot be ignored. Pharmacokinetic analysis uses biological samples to quantify drug concentration over time. Pharmacodynamic analysis requires endpoint measures that have been validated in children. For further details on pharmacodynamics and pharmacokinetic–pharmacodynamic relationships within paediatric populations the reader is directed to the following excellent reviews on this topic [69–73].

Paediatric dose selection

Dose adjustment is undertaken to provide similar internal exposure and similar pharmacodynamic effects. However, these parameters are dependent upon specific drug properties and the ontogeny of relevant physiology of the patient.

There are several references indicating that children 'are not small adults', yet most methods of paediatric dose adjustments are based on simple algorithms, rather than pharmacokinetic data, that extrapolate an adult dose based on body weight, height or a combination of both expressed as body surface area. However, analysis of scaling models to predict maintenance doses for children demonstrated that body weight was the better method in terms of precision and bias for children from 1 month to 1 year, whereas, body surface area was better in older children [74], with the overall conclusion that there is not a single dosing algorithm appropriate for all age ranges. It was only in the March 2006 51st British National Formulary that the statement, 'children's doses may be calculated from adult doses by using age, body weight or body surface area or by a combination of these factors' was replaced by 'consult BNFc or seek advice from medicines

information centre'. There are still instances where dosage information for children is unavailable and scaling from adult doses is the only available method to enable medication supply. In such cases the therapeutic index of the drug, its toxicity profile, the age of the child and the route by which the drug is cleared need to be carefully considered. In regulatory terms the FDA's paediatric decision tree highlights the importance of establishing whether disease progression is similar in paediatric and adult populations and if there is a similar response to the drug in terms of extrapolation of pharmacokinetics from an adult into a paediatric population [75].

A review conducted by Rodriguez and co-workers reported that dosing changes were made for more than 20% of 108 drugs in response to the results from a required paediatric pharmacokinetic study. This highlights the limitations of extrapolation of adult dosages into paediatric populations [76].

Paediatric clinical study design

Clinical study designs that reduce the burden on paediatric participants are preferred where possible with several innovative approaches referenced in relevant regulatory guidelines [1, 77]. These novel methods include sequential design, adaptive design, Bayesian approach, randomized withdrawal design, randomized placebo phase design and three-stage clinical trial, which go some way to overcome the limitations of small sample numbers and of the ethical acceptability of the trial [78]. Consideration of appropriate methods for a paediatric pharmacokinetic clinical study should involve the formulation, dose, route of administration, sampling interval and population.

The lack of an age-appropriate formulation has previously limited paediatric clinical studies. However, there are currently several initiatives to assist in the development of age-appropriate products for use in paediatric populations. Ideally paediatric formulations should be bioequivalent to the formulation used in adults, yet this is not always achievable. Therefore caution is required when switching products.

The drug assay used in paediatric studies needs to be sensitive as the volume of body fluid samples collected in paediatric patients is often much smaller compared with adult volumes (~1–10 ml at a time) required by most drug assays. The size of blood samples is restricted in newborns by regulatory guidelines that state; 'trial-related blood loss should not exceed 3% of the total blood volume during a period of 4 weeks and should not exceed 1% at any single time' [79]. In a newborn the total volume of blood is estimated at 80–90 ml kg^{-1} body weight. Therefore 1% corresponds to 3 ml per sample with an overall maximum volume of 9 ml over a period of 4 weeks. Alternatives to blood sampling have been used in some paediatric clinical studies and include saliva sampling [80], and urine sampling [81] which is often preferred by patients and their parents. Dried blood spots from finger or heel pricks are more common in newborns and have also been used in older children to avoid venipuncture [82]. Combining drug analysis with routine clinical blood sampling can be useful in paediatric studies although it is essential that the timings of sampling relative to the dose administration are recorded accurately. These scavenged samples have been used successfully in studies in pre-term infants [83, 84].

Population based pharmacokinetic modelling

Population based pharmacokinetic modelling to support clinical trials can reduce the number of samples required from each individual within a population by increasing the overall population size. This technique was first introduced into paediatric clinical pharmacology in the mid-1980s [85], and has remained popular owing to the ability to analyze studies with sparse and unbalanced pharmacokinetic data, typical of paediatric trials with ethical and logistical constraints. Regulatory guidance now recommends this approach for paediatric pharmacokinetic studies [86, 87]. Population based pharmacokinetic modelling allows a reduction to 2–3 samples per individual compared with in excess of 12 that is often required in traditional pharmacokinetic studies [82].

Physiologically based pharmacokinetic modelling

Physiologically based pharmacokinetic (PBPK) models have been developed that incorporate paediatric developmental physiology to predict drug exposure in children based on existing clinical data from adults. These models provide increased understanding of ADME processes for a drug and are useful to extrapolate between age groups within paediatric populations [88, 89]. The physiological nature of model parameters means that age-related differences in biological components can be incorporated to simulate paediatric pharmcokinetics across all age categories. These models are proven to be superior to allometric scaling of many pharmacokinetic parameters including clearance [90, 91]. The limitations of PBPK models are well documented. However, their development is reliant on accurate physiological input data from the relevant populations and this information is very limited in newborns and infants [92]. This lack of accurate data limits extrapolation of findings across paediatric age brackets, as reported by Cella *et al*. [93]. A further limitation of PBPK modelling lies in the appropriate validation (particularly statistical) of such models [89, 91]. There are several excellent reviews on PBPK models in paediatric populations and the reader is directed to these for further information [92, 94, 95].

Additional advantages include the incorporation of compound-related and physiological information which can aid in predicting formulation performance or bioequivalence of products as well as dose or route of administration effects [94, 96]. PBPK tools are then useful in the design of paediatric clinical studies, particularly with

reference to sampling times and the number of subjects required. Such models are gaining favour with regulatory agencies. The FDA vision is that design of paediatric studies will be performed entirely by simulation in the future [97, 98].

Conclusions

Determining appropriate dosing regimes in paediatric populations is complex owing to the physiological and anatomical changes that occur during childhood. Pharmacokinetic data provide information to improve the fundamental understanding about these changes in order to extrapolate data better from adults into paediatric populations and also to extrapolate within paediatric populations. A recent review of registered clinical trials in children reported that pharmacokinetic data would be collected from only 24% of all eligible trials, with the majority conducted in children in North America aged over 2 years [99]. However, the greatest differences from adult pharmacokinetic profiles are reported to exist in children below 2 years of age/ Therefore there is a mismatch in current trials and knowledge gaps. There is also a need to link pharmacokinetic and pharmacodynamics better within a paediatric population. There is a need to overcome ethical constraints and include the most vulnerable population in paediatric clinical trials.

Competing Interests

Both authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: HKB had support from National Institute for Health Research Medicines for Children Research Network for the submitted work, no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years and no other relationships or activities that could appear to have influenced the submitted work.

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