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Optimising medicines for children: considerations for clinical pharmacists

Chloe E Benn

Correspondence to
Chloe Elizabeth Benn, Principal Pharmacist for Women's and Children's Services, Royal Free London NHS Foundation Trust, Pond St, London, NW3 2QG, UK; Chloe.benn@nhs.net

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INTRODUCTION

The scope of the pharmacist working within paediatrics is broad, involving optimising medicine use for patients from newborn to young adult, where there are large changes in physiology, psychology, vulnerabilities, abilities and needs impacting both physical handling of medicines and medicines adherence. This provides a hugely rewarding and fascinating career.

While the provision of safe and effective medicines for children should be imperative, it has lagged behind that available to adults since licensing was introduced in the 1960s. In recent years, regulatory and strategic initiatives have led to some significant and positive movements towards this goal, but there is further progress to be made. Challenges, complexity and risk are common and necessitate highly skilled pharmacists to be included in the team delivering healthcare to children.

PHYSICAL DEVELOPMENT

The developmental changes throughout childhood and their impact on drug handling provide the most obvious contrast between children and adults. From premature neonates of 24 weeks' gestation under 500 g to teenagers of adult size; developmental changes in body composition and function alter pharmacokinetic parameters and influence the dosing and provision of medicines. Medicines do not always have the efficacy and adverse effects in children that we would expect from experience in adults. The requirement for appropriate growth and the immature immune system of children are other areas affecting medical treatment that are unique to paediatrics. Paediatric pharmacists use their knowledge and understanding of these factors to optimise regimes for individual patients.

PHARMACOKINETICS

The maxim 'children are not small adults' is often quoted to highlight that medicines cannot be assumed to work in the same way at proportional doses to body size; however, Anderson and Holford argue that by 2 years of age 'children are small adults' due to maturation of drug-handling systems (although with an allometric scaling factor applied).[1] It is in infants and neonates that age-related differences in pharmacokinetics are most significant. In these age groups, gastrointestinal absorption is affected by pH and motility, distribution is altered by body composition and clearance systems are immature. Hence, it is this group where the greatest care must be taken, and where dosing proportionally on weight without appropriate pharmacokinetic evaluation is most likely to lead to incorrect dosing. HIV treatment is an example of where this has occurred, and pharmacokinetic studies have produced more effective doses (see table 1 for pharmacokinetic details and administration considerations).[2]

PHARMACODYNAMICS

The relationship between drug levels and effect in children does not always follow what would be expected from experience in adults and is often poorly studied. Density or sensitivity of receptors in children may differ, leading to unexpected responses to drugs such as ciclosporin in infants where low levels produce higher immunosuppression than expected, and warfarin (enhanced anticoagulation) and adverse effects such as hepatotoxicity with valproate[3] or suicide risk with SSRIs and other antidepressants.[4]

GROWTH

Paediatric clinicians must consider the normal growth of children in their therapeutic plan; both the impact of the disease and treatment must be balanced; for example, in inflammatory bowel diseases, uncontrolled inflammation and malabsorption can limit growth, and while corticosteroid use may induce remission they may also reduce growth[5]. Therefore, the use of 'steroid sparing' agents such as azathioprine or infliximab would be considered. In asthma—clinicians, children and parents may be concerned about the adverse effects of inhaled corticosteroids but can be reassured that corticosteroid inhaler use will only limit final height by a maximum of 1 cm.[6] Drugs including heparin, methotrexate and anticonvulsants can impact bone mineral density.[7] Tetracyclines can result in the formation of tetracycline–calcium complexes that irreversibly deposit in developing bones and teeth causing permanent tooth discolouration. Tetracyclines should therefore be avoided in children under 12 years.[8]

IMMUNITY AND INFECTION

Due to the immaturity of their immune system, children are more susceptible to certain infections; this risk is highest in the first 3 months of life. Contrary to good practice in other age groups, it is necessary to treat newborns for sepsis based on risk factors and in the absence of signs and symptoms as group B *Streptococcus* or *Escherichia coli* can rapidly lead to overwhelming sepsis that has a poor prognosis in up to 50%.[9] In older children presenting with signs of infection, their immunisation status should be taken into account when considering the potential causative organism and therefore antibiotic choice.

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Table 1 Pharmacokinetic considerations

Absorption of medicines	Administration of medicines
Oral absorption in neonates can be altered by:Immature transporter expression and increased intestinal permeability. Slower gastric emptying at birth limits access of medicines to absorption sites. Reduced gastric acid secretion increases bioavailability of acid-labile drugs (eg, ampicillin) and decreases that of weakly acidic drugs (eg, phenobarbital), which are less able to exist in non-ionised form.[3] Intestinal transit and transport processes mature by 4 months.[3]	Medicines not formulated for children only available in solid dose forms that young children cannot swallow, in strengths that do not provide dose flexibility. Liquid medicines may contain excipients unsuitable for children, for example, alcohol, propylene glycol or tartrazine. Specific challenges in drug administration and absorption in children with surgical short bowel or jejunal feeding tubes.
Rectal absorption may be unreliable and affected by formulation, site of placement in rectal cavity and duration of retention (infants have increased rectal pulsatile contractions). Bioavailability can be increased in infants due to reduced 'first pass' hepatic metabolism.[3]	Rectal route useful for child not tolerating oral medication or intravenous access not available. Rectal drug therapy not well accepted by UK patients and used infrequently in hospital practice.
Absorption from intramuscular injections in young children can be reduced due to low muscle mass and poor perfusion.[3] However, intramuscular vitamin K at birth provides a depot to prevent deficiency bleeding (haemorrhagic disease of the newborn).[21]	Intramuscular injections usually avoided in children due to pain and distress but may have a place for single doses.[8]
Intravenous administration is used to avoid absorption problems and ensure rapid achievement of therapeutic levels, for example, for antibiotics in sepsis.	Difficulty maintaining intravenous access in small veins limits acceptability longer-term and central access may be needed. Specific technical requirements for intravenous administration, for example, need to account for displacement values when reconstituting and taking a portion of a vial; infusion fluids, volumes, rates must take into account age/weight/renal function.
Intraosseous route (infusion directly into bone marrow) is relatively easily accessible in children (due to ease of access to the anterior tibial marrow and vascularity of marrow)	Intraosseous used in emergencies when central vascular access cannot be achieved in timely fashion. Majority of emergency resuscitation drugs can be infused via intraosseous route.[22]
In neonates and young infants, *transdermal* absorption may be enhanced due to greater surface area to weight ratio and immature epidermal barrier. Has lead to unintentional toxicities, for example, with iodine or corticosteroids.	Transdermal absorption can be exploited in formulations such as patches (eg, hyoscine, methylphenidate); iontophoretic devices and needleless systems (eg, growth hormone).[23]
Inhaled medicines target lungs for local effect, but systemic exposure may occur, for example, inhaled corticosteroids can suppress cortisol and affect growth.[24] *Intranasal* route avoids hepatic first-pass metabolism; however, hydrophilic drugs have poor absorption. Diamorphine, midazolam, fentanyl, sumatriptan and desmopressin are used intranasally in children.	Inhalation route can be convenient and effective for a targeted effect. Intranasal administration of drugs has advantages including ease of administration, speed of action, good tolerance; however, it is limited by acceptable volume of administration.

Distribution
Body water composition as % body mass in neonates significantly higher than adults (80% vs 60%). Body fat varies through childhood.[3] Higher doses of water-soluble drugs (eg, gentamicin) per kg body weight required to reach target concentrations.
Albumin/total protein concentrations lower in neonates but approach adult levels by age of 1. Persistence of foetal albumin for ≤3 months, which has a lower affinity for binding some drugs. Protein binding in neonates reduced by circulating bilirubin and free fatty acids competing for binding sites; increased free drug concentrations leading to pharmacological and adverse effects at lower total drug concentrations. Phenytoin target plasma level range is ~1/3rd lower in infants <3 months.[8] In neonates ceftriaxone displaces protein binding of bilirubin; increased free circulating bilirubin may cross blood–brain barrier and cause brain damage (kernicterus).[25]

Metabolism and elimination
Drug metabolism and elimination pathways are immature at birth; drugs commonly have plasma half-lives ≥ 2–3 times longer in neonates vs adults. So while higher volumes of distribution require higher loading doses, lower clearance reduces dosing frequency; for example, penicillins, barbiturates.
Hepatic drug metabolism via CYP450 enzymes is immature at birth; Phase I metabolism (oxidation, reduction, hydrolysis) low in neonates, matures during the first 6 months, exceeds adult rates in childhood and slows during adolescence to adult rates. Phase II metabolism (hydroxylation and conjugation) increases over the first 3 months and matures by 3 years. Delayed hepatic glucuronidation is responsible for 'grey baby syndrome' when high-dose intravenous chloramphenicol used in neonates.[3] Hepatic metabolism high for some drugs in children <10 years; voriconazole clearance threefold higher in children than adults due to a higher contribution of specific oxidative pathways. Other drugs predominantly metabolised by same pathway (CYP2C9/19), for example, phenytoin, omeprazole and sirolimus show higher clearance in children 2–10 years than in adults.[26]
Renal elimination reduced in the first 2 years. In premature neonates is dependent on gestational age due to nephrogenesis and changes in renal blood flow. GFR is 2 to 4 mL/min/1.73 m^2 at birth in term infants but may be as low as 0.6 to 0.8 mL/min/1.73 m^2 in preterm neonates. GFR increases rapidly during the first 2 weeks rising steadily to adult values at 8 to 12 months.[3]

PSYCHOLOGICAL DEVELOPMENT: IMPACT ON COMMUNICATION AND COMPLIANCE

Identifying a drug and dose regime appropriate for the physical development of the child is only the first step in providing optimal treatment; the child and/or their family need to understand and undertake to comply with the treatment plan. Children and young people have specific developmental differences in their abilities, behaviours and communication. Healthcare professionals must take into account the young person's understanding and capacity to make independent decisions and the roles of their parents in the therapeutic partnership.

Children, young people and their parents can have different health beliefs, treatment goals and needs for information. It is important the child is involved in healthcare discussions so that their perspective can be taken into account. Children and young people need to feel respected, heard and understood—this will impact their future behaviour. Even where it is the parent's responsibility to consent for treatment, children should be encouraged to understand and give their assent. The rights of

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the child, the responsibilities of the parent and the duty of care of the professional must all be balanced. It is important that professionals working with children learn good communication techniques.

Parents may struggle to get young children to comply with medication that is unpleasant, whether that is due to poor palatability or discomfort (eg, eye drops). Young children are often unable to swallow solid dose forms, so liquid medicines are needed. Often these are products licensed for adults or extemporaneously prepared—the flavour and texture of these products is often poorly accepted by children and can lead to refusal. In acute care, certain liquid antibiotics are particularly bitter and unacceptable to children—for example, flucloxacilin and clindamycin, while cefalosporins are more pleasant.[10] Arranging for a child to receive medicines during school hours can be a barrier, and in older children and adolescents it can be changing priorities, social pressures and lifestyle changes that can lead to intentional and non-intentional poor adherence.

Techniques for improving adherence in children and young people with chronic disease are not well proven; a review published in 2010 found mixed educational and behavioural interventions were more often successful than education alone.[11] Innovative technology can be used to minimise unintentional non-adherence—in asthma, dose monitoring devices can alert the patient/parent if doses are about to be missed.[12] Pharmacists can support adherence through simple strategies such as providing formulation options to the young person, choosing regimes that avoid the need for dosing during school and tailoring information to the individual needs.

LEGAL AND REGULATORY ISSUES

Since the introduction of the medicines licensing process in the 1960s, availability of appropriately formulated medicines with information on their safe and effective use in children has been limited by the ethical and technical difficulties and small commercial benefit of conducting the studies required to obtain a paediatric licence. This has led to the frequent use of medicines outside of their product license (off-label) or with no licence (unlicensed) in children. It has been reported that in the late 1990s and early 2000s between 36 and 90% of European hospitalised children received an off-label or unlicensed medicine.[13] Off-label medicines may be used in younger age groups than the license, in different indications, or formulations may be used in ways that differ from intended; for example, crushing tablets or using injectable medicines orally. Licensed medicines used off-label in children may contain unsuitable excipients for the age group such as benzyl alcohol, which can be fatal in neonates.[3] Unlicensed medicines may be imported or extemporaneously prepared. These options present significant potential risks to children's health as the safety, efficacy and quality are not assured.

In order to reduce this inequality and improve the health of children, new regulations have been put into place in the European Union (EU) and the USA. The EU Regulation on Paediatric Medicines came into force in 2007 with a system of requirements and incentives to increase the availability of and information about medicines and increase high-quality research into medicines for use in the paediatric population. Products can be awarded extensions of market exclusivity and the new paediatric use marketing authorisation (PUMA) with 10-year market protection for off-patent products has been created. In the first 5 years following the regulations, 131 new drugs or paediatric licences were granted and nearly 400 label changes were made.[14] Studies done as a result of US federal legislation (the Best Pharmaceuticals for Children Act of 2001 and the Pediatric Research Equity Act of 2003) have provided additional paediatric information on dosing or safety within the label of 500 drugs.[15] The buccal midazolam formulation (Buccolam) is the first product to be launched having been granted a PUMA and meets specific clinical and safe usage requirements for carers to administer to children with epilepsy.[16]

Prescribing a medicine outside of a product license increases the professional responsibility and liability, and must be justifiable based on options, evidence and be in accordance with professional opinion. The UK General Medical Council produced prescribing guidance in 2013 that sets out when prescribing off-label or unlicensed medicines is likely to be appropriate and the steps that the prescriber should take when doing so including providing information and consent from patients.[17] Access to information on the safe and effective use of medicines outside the product licence is therefore essential to support this practice; in the UK, a national paediatric formulary—the BNF for Children—has been published annually since 2005.[8]

ROLE OF PAEDIATRIC PHARMACIST

The scope of practice of the pharmacist in paediatrics is wide; including 'patient facing' clinical services, new prescribing roles, risk management, education, research and public health.

Clinical pharmacists in the UK, both generalist or specialist, commonly provide a service through attending the clinical areas on a daily basis, often contributing to multidisciplinary ward rounds. The pharmacist's role involves taking drug histories and performing medicines reconciliation for all new patients, reviewing the current prescriptions for accuracy and appropriateness, providing assessment of adherence, information and advice to patients about their medicines, monitoring of medicine efficacy and toxicity through review of observations, test results and patient symptoms, and ensuring safe transfer of medicines information at discharge. The pharmacist provides proactive advice to the other professionals involved in the care, for instance, nurses on appropriate medicines administration and doctors on dosing adjustments, monitoring or appropriate choice of medicines based on guidelines. UK hospital pharmacy standards support this standard of care.[18] There is as much or greater need for these services on neonatal and children's wards as adult wards. The complexity of dosing across the age group for children, the requirement for calculations of most doses on an individual patient basis and the use of unlicensed and off-label preparations make the clinical and accuracy checking of prescriptions a primary and fundamental role of the paediatric pharmacist; the most common intervention is to correct dosing errors, which can be potentially fatal.[19]

Medicines reconciliation includes a need to review the formulation of a medicine usually taken to minimise risks in altering the form or strength. Where a child takes liquid medicines, their parents or carers usually know the dose volume but not necessarily the dose in mg. If therefore, following a transfer of care, a different strength of medicine is supplied but the volume administered remains the same, the dose may be up to tenfold higher or lower than intended. This risk is highest for unlicensed medicines and those that come in a wide range of strengths; for example, unlicensed spironolactone suspension is commonly available from 5 to 50 mg/5 mL. Where a change in strength is intended or unavoidable, carers must be carefully advised of the change in dose volume. Different forms can also contain different drug salts requiring a dose conversion if forms are changed; for example, sodium fusidate and fusidic acid.

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The requirement for close monitoring of patients and their response to medicines is also greater in the context of poorly studied medicines. Pharmacists combine their understanding of pharmacokinetics, applied to the clinical context of the patient to advise on appropriate monitoring while minimising unnecessary and traumatic venepunctures.

Pharmacists also need to supply appropriate formulations, appreciating the advantages and disadvantages of the options, including off-label and unlicensed medicines and taking into account the suitability (or not) of the excipients (see table 2, case study).

Specialist pharmacists will be involved in the formulation and manufacture of medicines, parenteral nutrition (PN) and cytotoxics. The provision of individualised PN is a specialist skill for paediatric and neonatal pharmacists who must liaise with the multidisciplinary team (MDT) to assess the nutritional, fluid and electrolyte requirements, the available fluid allowance taking into account other drug infusions and then apply their understanding of PN compounding and chemical stability to advise on a suitable PN regime.

Since unlicensed and off-label medicines are not supplied with appropriate patient information leaflets, the pharmacist can ensure that children and their families are provided with appropriate verbal and written information to support their understanding and use of the medicines. The UK 'Medicines for children' initiative has led to the availability of over 180 quality assured leaflets specifically tailored to parents' needs.[20] Pharmacists are encouraged to volunteer to write further leaflets.

As well as responding to immediate clinical issues, paediatric pharmacists have an important role in reducing risk proactively through the development of medicines use guidelines, local, regional and national formularies, electronic prescribing systems and training other healthcare staff, particularly prescribers and nurses.

In my personal view, it is the variety within the patient group, the breadth of clinical conditions encountered, the challenges of providing safe and effective medicines where information and products are difficult to obtain and the recognition within the

Table 2 Case study

Mathew, an 8 year old with cerebral palsy, attends his appointment with Dr P, his neurologist. Sarah, Matthew's mum, reports that she is concerned that he is struggling to clear his excessive saliva and upper airway secretions, and feels this is contributing to his choking fits and chest infections. Dr P decides that a trial of glycopyrronium bromide would be beneficial, and he calls Jenny, the paediatric pharmacist, for advice on how to prescribe this.

Having confirmed that Matthew does not have any contraindications or drug interactions to prevent the use of glycopyrronium, Jenny notes that it is not licensed for the management of upper airway secretions but that the BNF for Children provides dosing recommendations for this indication. Jenny confirms that the oral route would be appropriate, and Sarah tells Jenny that Matthew receives his feeds and medicines via a PEG tube due to his swallowing problems.

As Matthew weighs 23 kg and the BNF_C recommends a dose of 40–100 μg/kg (max 2 mg) 3–4 times daily,[8] Jenny calculates the dose range for Matthew would be 920–2000 μg. They agree to start at the lower end of the range to minimise side effects and allow the dose to be adjusted according to Matthew's response.

Jenny considers the options to supply glycopyrronium; The only licensed formulation available in the UK is ampoules for injection; however, the BNF-C notes that 1 and 2 mg tablets are available by import, and also the injection may be given orally or the tablets crushed and suspended in water.[8]

Options:

Form dose cost	*Advantages*	*Disadvantages*
Ampoules: 920 μg from 200 μg/mL (supply 2×600 μg (3 mL ampoules)) = 4.6 mL	▶ UK licensed formulation ▶ In stock in hospital dispensary ▶ Liquid ▶ Measurable dose ▶ Flexibility to adjust dose	▶ Off-label use ▶ Not routinely stocked outside of hospitals (may be difficult to obtain from community pharmacy), ▶ Glass ampoule—risk of injury on opening, risk of glass fragment administration unless filtered (requires filter straws to be supplied) ▶ Complexity of technique may preclude school staff administering ▶ Difficult to do when not at home
Imported tablets:dose rounded up to 1 mg=1 mg tablet dispersed in 10 mL water.	▶ EU licensed formulation ▶ Simple preparation ▶ Measurable and accurate dose ▶ Simple to transport and prepare away from home ▶ Can be kept in stock on dispensary shelf (1 year + expiry)	▶ Unlicensed use ▶ Not liquid—requires manipulation ▶ May be difficult to obtain from community pharmacy ▶ Less flexibility to adjust dose—only 1 and 2 mg strengths available ▶ Labelling not in English ▶ Long lead time if not in stock at importer
Extemporaneously prepared liquid: (using injection solution)	▶ Liquid ▶ Measurable dose ▶ Flexibility to adjust dose ▶ Possible to make same day within pharmacy	▶ Unlicensed ▶ Quality assurance low ▶ Stability data lacking—only 7-day expiry, requires fridge storage (poor convenience) ▶ May be difficult to obtain from community pharmacy
'Special' liquid from licensed manufacturer	▶ Liquid ▶ Measurable dose ▶ Flexibility to adjust dose ▶ Better quality assurance than extemporaneously prepared product	▶ Unlicensed ▶ Unknown availability (time to source manufacturer) ▶ Only 28-day expiry, requires fridge storage ▶ Delay in obtaining from manufacturer ▶ May be difficult to obtain from community pharmacy ▶ Possible variability in formulation between different manufacturers

Jenny discusses the options with Dr P and Sarah. They agree that while a 'special' may be the ideal option, the imported tablets are an option if Dr P agrees to start at 1 mg dose. They have the benefit of a reasonably simple manipulation, and are kept in stock for Matthew to try today. They agreed they could consider prescribing a liquid in the future if Matthew required a fine dose adjustment.

Dr P prescribes glycopyrronium bromide tablets 1 mg three times a day for 1 month.

Jenny advises Sarah to disperse the 1 mg tablet in 10 mL water and to administer the entire quantity of liquid and any solid particles. Sarah should monitor Matthews bowel and bladder opening, as he may be come constipated or develop urinary retention. Jenny gives Sarah a letter for her general practitioner (GP) and community pharmacy explaining what product to prescribe and how to obtain it.

The following month Jenny sees Sarah and checks how they have been getting on. Sarah reports that Matthew seems to have tolerated the medicine quite well and it has made some improvement so they have agreed with Dr P to increase the dose to 1 mg four times a day for the next month. The GP has agreed to prescribe and the community pharmacy are ordering this in for them in accordance with the information provided by Jenny.

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MDT of pharmacists expertise in the safe use of medicines that make this career so interesting and rewarding.

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