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USE OF MEDICINES IN CHILDREN

-  Many medicines used in children, have not undergone extensive evaluation in children
-  The developmental stage of a child influences their response to a medicine
-  The age of the child may determine the formulation required
-  Recent EU initiatives aim to improve the safety, efficacy and availability of medicines for children

INTRODUCTION

Medicines require a licence (marketing authorisation) before they can be put on the market.^{1,2} This means that they have undergone appropriate clinical evaluation to confirm an acceptable benefit/risk balance for their proposed use. In practice, the vast majority of medicines prescribed in adults are used according to the licence. However **many medicines, currently used to treat the paediatric population, may not have been investigated in children in the same way as in adults.** Children represent >25% of the population and receive an average of three prescription medications before 5 years of age.³ The recent European Union (EU) initiative entitled “Better medicines for children” has put in place a legal process for ensuring that medicines for use in children are of high quality, ethically researched and appropriately authorised.⁴

This bulletin describes how the developmental stages of children can affect medicines, the issues associated with prescribing for children and how the new EU legislation will increase the availability of appropriate medicines and improve the health of children. The next bulletin will address some of the frequently asked questions received by the NMIC, relating to the use of medicines in children.

AGE CLASSIFICATION OF PAEDIATRIC POPULATIONS

Children are not just “small adults”, and it is important to appreciate that **more physiological changes occur in the first 2 years of life and during puberty than in any other period of life.**⁵ This results in different children populations, ranging from premature babies, born as early as 24 weeks gestation, to 17-year old adolescents, all of which have specific prescribing requirements.⁶ There are various classifications for the different paediatric populations, one of which is described in Table 1. This is the classification used by the European Medicines Agency (EMA), where 12 to 17 years defines the adolescent population.

Table 1: Age ranges and definitions of paediatric populations⁷

Pre-term newborn	<37 weeks gestation
Term newborn	0 – 27 days
Infants and toddlers	28 days - 23 months
Children	2 - 11 years
Adolescents	12 - 16 to 18 years (dependent on region e.g. EU, USA)

Pre-term infants - this group is not a homogenous population and varies from a 25-week gestation, 500-gram newborn to a 37-week gestation newborn weighing 3,000 grams. Important factors to consider in this population include: gestational age, post-natal age, immaturity of all organ systems and of the hepatic and renal clearance systems, penetration of medicinal products into the central nervous system (CNS), unique neonatal diseases and the rapid and variable maturation of physiological and pharmacological processes, leading to the need to alter the dosing regimen frequently with chronic exposure.⁷

Term newborn infants - are more mature than preterm newborn infants, however drug absorption, metabolism and excretion are affected by many of the factors which apply to preterm infants. Many examples of increased susceptibility to toxic effects of medicinal products result from immature clearance systems in these patients (e.g. chloramphenicol associated with “grey baby syndrome”, ototoxicity with gentamicin).⁷

Infants and toddlers - undergo a period of rapid CNS maturation, immune system development and total body growth. Oral absorption becomes more reliable, and the hepatic and renal clearance continues to mature rapidly so that by the age of 1-2 years the clearance of many medicines equals or exceeds that of adults. There is however considerable inter-individual variability in maturity.⁷

Children - Most pathways of drug clearance are mature in this group, with clearance often exceeding adult values e.g. carbamazepine. CNS-active medicines may adversely affect children's developmental milestones. The onset of puberty is highly variable and occurs earlier in girls, in some as early as 9 years of age. Puberty can affect the activity of enzymes that metabolise medicines, and dose requirements of some medicines may decrease (e.g. theophylline).⁷

Adolescents - This group experiences a period of rapid growth, continued neurocognitive development and sexual maturation. Medicines and diseases that delay or accelerate the onset of puberty can have a profound effect on the pubertal growth spurt e.g. sex hormones, chemotherapy. Many diseases are also influenced by the hormonal changes around puberty e.g. diabetes, migraine. Adolescents are also assuming responsibility for their own health and noncompliance can be a problem. The use of recreational drugs, alcohol and tobacco should also be considered in this population.⁷

THE INFLUENCE OF DEVELOPMENTAL STAGES ON MEDICINES

Safe and effective drug treatment for children requires an understanding of the wide variability and constant changes in pharmacokinetic handling and pharmacodynamic response to medicines, which occur from birth to adulthood.^{6,8,9} The maturation stage of a child can also influence drug interactions. Rational prescribing in children requires the ability to individualise a child's treatment based upon the known developmental differences that impact on drug disposition and action.⁸ Table 2 summarises the developmental changes affecting drug disposition and the pharmacokinetic and clinical implications.

Table 2: Summary of developmental-dependent changes in drug handling^{6,8,10-12}

Physiological system	Age-related trends	Pharmacokinetic implications	Clinical implications
Gastrointestinal tract	<p>Neonates and young infants: reduced/ irregular peristalsis with ↑ gastric emptying time. Neonates: ↑ intragastric pH (>4) relative to infants.</p> <p>Infants: enhanced lower GI motility</p>	<p>Potential ↓ rate of drug absorption</p> <p>Potential ↑ or ↓ absorption of certain medicines</p> <p>Potential ↓ retention of suppository formulations</p>	<p>Potential delay in onset of drug action following oral admin</p> <p>↑ absorption of acid labile medicines e.g. penicillin & ↓ absorption of weak acids e.g. phenobarbitone</p> <p>Potential ↓ absorption from rectally administered medicines, [however some medicines e.g. diazepam are successfully absorbed rectally]</p>
Skin & mucosal surfaces	<p>Neonates and young infants: greater cutaneous perfusion, enhanced hydration and larger ratio of total body surface area to body mass</p>	<p>Potential ↑ percutaneous drug absorption. ↑ relative exposure of topically applied medicines compared to adults</p>	<p>↑ bioavailability and potential toxicity from systemic absorption of topical medicines. Need to ↓ amount of medicines applied topically e.g. corticosteroids</p>
Body compartments	<p>Neonates and infants: ↓ fat, ↓ muscle mass, ↑ extracellular and total body water spaces</p>	<p>↑ apparent vol. of distribution for medicines distributed to body water spaces, and ↓ apparent vol. of distribution for medicines that bind to muscle and or fat</p>	<p>Medicines with high vol. of distribution can accumulate in the body and cause toxicity</p> <p>In general, the vol. of distribution of medicines tends to be ↑ in infants, which ↓ to adult levels during childhood e.g. gentamicin, theophylline</p>
Plasma protein binding	<p>Neonates: ↓ concentrations of albumin and α1-acid glycoprotein with ↓ binding affinity for albumin bound weak acids</p>	<p>↑ unbound concentrations of highly protein-bound medicines and potential ↑ level of free drug in the body</p>	<p>Potential for toxicity in neonates e.g. phenytoin</p> <p>[differences in plasma protein binding are not clinically significant beyond this period]</p>
Drug metabolising enzyme (DME) activity	<p>Neonates and young infants: immature and discordant patterns of DME development</p> <p>Children 1-6 years: apparent ↑ activity for selected DMEs over adult normal values</p>	<p>Neonates and young infants: ↓ plasma drug clearance early in life with ↑ in apparent half-life ($t_{1/2}$)</p> <p>Children 1-6 years: ↑ plasma drug clearance (i.e. reduced elimination $t_{1/2}$) for specific pharmacological substrates of DMEs</p>	<p>Neonates and young infants: ↑ drug dosing intervals and/or ↓ maintenance doses e.g. phenytoin, theophylline, morphine</p> <p>Children 1-6 years: for selected medicines may need to ↑ dose and/or ↓ interval in comparison to usual adult dose e.g. carbamazepine, phenytoin, ethosuximide</p>
Renal drug excretion	<p>Neonates and young infants: ↓ glomerular filtration rates (first 6 months) and active tubular secretion (first 12 months) with adult values attained by 24 months</p>	<p>Neonates and young infants: accumulation of renally excreted medicines and/or active metabolites with ↓ plasma clearance and ↑ elimination $t_{1/2}$, greatest during first 3 months of life</p>	<p>Neonates and young infants: ↑ drug dosing intervals and/or ↓ maintenance doses during the first 3 months of life e.g. ibuprofen, penicillins</p>

In summary, the developmental stage of the child and how the drug is handled needs to be taken into account when considering the drug and/or dose of a medicine for a child, especially in the younger age groups. Doses of medicines for children cannot be extrapolated from adult doses, therefore the dose of each medicine needs to be individualised to the particular age group of the child. A reliable paediatric reference should be consulted for dosing information e.g. the British National Formulary for Children (BNFC) - see other useful sources below.

PRACTICAL ISSUES ASSOCIATED WITH PRESCRIBING IN CHILDREN

The prescribing of medicines in children offers specific challenges, which are different to those encountered with adult patients.^{5,13,14} In addition to the child's medical history, physical assessment and diagnosis, a number of other factors should be considered. As outlined above the developmental changes which occur in the different paediatric populations, profoundly affect the response to medicines.^{6,8,9} For example, a medicine, which is commenced in a neonate would need its dose adjusted several times over a few months while adults can continue for years without changing the dose of a drug. Evidence suggests that **children have a potential threefold greater risk of suffering an adverse drug event than adult patients.**¹⁵

Range of diseases in childhood - The range of diseases affecting children differs from those affecting adults.⁵ Between 15-20% of a general practitioner's work is with children,^{16,17} of which respiratory system disorders are the commonest, followed by skin conditions, infectious diseases, gastrointestinal disorders and problems with the eyes and ears.¹⁷ Only 10% of children's disorders are judged to be serious, and of these less than half will be prescribed a medicine.¹⁷ Table 3 outlines the 10 most prescribed medicine groups in decreasing frequency for the different paediatric age-ranges compared to the adult population.

Table 3: 10 most prescribed medicine groups in children (by age-range) and adults in 2007 (from the GMS database)

0-4 years	5-11 years	12-15 years	Adults
Antibacterials	Antibacterials	Antibacterials	Antibacterials
Respiratory	Respiratory	NSAIDs	NSAIDs
Topical corticosteroids	Topical corticosteroids	Respiratory	Analgesics
Systemic corticosteroids	NSAIDs	Analgesics	Anti-ulcer
Ophthalmic	Systemic corticosteroids	Topical corticosteroids	Anxiolytics & antipsychotics
NSAIDs	Systemic antihistamines	Systemic antihistamines	Anti-thrombotic agents
Topical antifungals	Cough & cold	Cough & cold	Lipid lowering products
Emollients	Gastrointestinal	Gastrointestinal	ACE inhibitors
Analgesics	Ophthalmics	Systemic corticosteroids	Anti-depressants
Gastrointestinal	Topical antibiotics	Ophthalmics	Respiratory

Formulation issues - The age of the child will influence the type of formulation that can be used. The oral route is the principal route of drug administration to paediatric patients; liquid formulations are required for children < 5-7 years and some older children may not accept tablets.¹⁸ Some liquid formulations have unpleasant tastes, which can be disguised by giving a favourite food or drink immediately afterwards, but the potential for food-drug interactions should always be considered.¹⁸ Unless specifically permitted, a medicine should not be mixed with large quantities of food, as the full dose may not be taken and the child may develop an aversion to food if there is an unpleasant taste from the medicine.¹⁹ Medicine should not be mixed in a baby's bottle.¹⁹ It is also important to be aware that most **liquid formulations contain excipients** (including: alcohol, aspartame, gluten, sulphites, tartrazine, arachis (peanut) oil, sesame oil), **which may cause reactions in specific groups of children.** Domestic teaspoons should not be used for administration, as they vary in size and are not reliable; plastic oral syringes should be used when possible. Crushing tablets or opening capsules alters the formulation of a medicine, which is an unlicensed administration. Information should be sought before crushing tablets, as in some cases to do so may affect the efficacy of the medicine. **Some medicines, such as those with a slow release formulation or enteric coating, should never be crushed.** Inhalers are commonly used for asthma; teaching the correct technique, use of an appropriate spacer device and regular review are essential for success.¹⁸

Off-label or unlicensed use - Many medicines administered to children are used outside the terms of the product licence. Such off-label use includes changing the licensed dose or route of administration, use for a different indication or age group, or in an unlicensed manner (modified formulation, extemporaneous preparations).^{6,20} **In the EU it is estimated that 50% of the medicines used in children have only been studied in adults, and not necessarily for the same indication.**²¹ The off-label or unlicensed use of a medicine does not reflect inappropriate prescribing, but may occur because there is a lack of a suitable licensed medicine for children.^{6,20} However this practice may expose children to unwanted side-effects or under-dosing without the expected efficacy.²¹ Off-label or unlicensed prescribing presents additional dilemmas for prescribers who have to balance clinical experience with a lack of suitable data for paediatric indications and formulations.^{8,13,20} The extent of prescribing off-label/unlicensed medicines varies from 11-90%, with more off-label prescribing occurring in certain conditions and in the hospital setting.²⁰ An observational study on the prescribing of respiratory medicines in primary care in the Netherlands showed that the 1-year cumulative risk of children receiving at least one prescription for a respiratory drug, which was unlicensed/off-label was 45%.²²

Useful information sources - The Summary of Product Characteristics (SmPC) should be consulted initially for information on particular medicines, although many medicines are unlicensed for use in children. In a UK survey of general practitioners

published in 2005, the British National Formulary was reported as the most consulted source of information for paediatric prescribing followed by personal experience.²⁰ The BNFC which is also available electronically on www.bnfc.org and is now in its fifth edition, is a very useful resource for healthcare professionals involved in prescribing for children. This has been prepared under the guidance of the UK Paediatric Formulary Committee.¹⁹ The NMIC has a number of other paediatric sources and is happy to deal with any specific enquiries that prescribers may have (e-mail: nmic@stjames.ie).

The issues outlined above, including the immature clearance systems in certain age-groups, the paucity of trial data for children, the lack of suitable formulations and the potential need to calculate doses of medicines for children based on body weight, increases the risk of **medication errors**. Such errors occur in up to 25% of drug charts in paediatric hospital wards.²³ Factors which can reduce the risk of medication errors include: avoiding the use of trailing zeros when prescribing (e.g. 5.0mg may be misread as 50mg), using a leading zero (e.g. 0.5mg rather than .5mg) and double checking of a dose calculation by a colleague. Parents and/or carers should also understand the correct method of administration of the medicine to the child, which will increase compliance and reduce the risk of error.

RECENT REGULATORY INITIATIVES IN THE DEVELOPMENT OF MEDICINES FOR CHILDREN

The lack of development of authorised medicines in children has occurred for a number of reasons including: little incentive for pharmaceutical companies to develop medicines in children (studies are expensive to carry out and separate trials are required in multiple age groups), difficulties in developing formulations for children and the perceived reluctance of parents to allow their children to be research subjects.²⁰ In recent years, there have been policy changes both in the United States and the EU to encourage the development of medicines in children in the different paediatric populations. The Paediatric Regulation entered into force in the EU in January 2007.²⁴ The objective of the regulation is to improve the health of children in Europe by: 1) facilitating the development and availability of medicines for children aged 0 to 17 years, 2) ensuring that medicines for use in children are of high quality, ethically researched, and authorised appropriately and 3) improving the availability of information on the use of medicines in children, all without subjecting children to unnecessary trials or delaying the authorisation of medicines for use in adults.²⁴ Table 4 outlines the principal features of the legislation. In addition to these measures, the regulation aims to improve communication and transparency of paediatric information by including in the prescribing information data from all completed paediatric studies (including negative studies). Further details of the paediatric regulation and the EU initiatives on medicines for children are available on <http://www.emea.europa.eu/htms/human/paediatrics/introduction.htm>

Table 4: Principal features of the Paediatric Regulation²⁴

Paediatric Investigation Plan (PIP)

- A PIP must be submitted by pharmaceutical companies [and agreed by the Expert Paediatric Committee (PDCO)] for all new medicines in the early stages of development
- A PIP includes a paediatric development plan for the various paediatric populations (with age-appropriate formulations)
- Once agreed by the PDCO, the PIP is binding on companies
- Pharmaceutical companies, if they comply with the PIP are eligible for rewards including a 6-month extension of their patent
- A **waiver** or **deferral** (agreed with the PDCO) can be granted if the proposed indication does not occur in children or until there is sufficient data to demonstrate the efficacy of the medicine in adults

The Expert Paediatric Committee (PDCO)

- The PDCO includes paediatric experts from all member states and representatives from patient/family and healthcare professionals' organisations
- The main responsibility of the PDCO is to decide on the content of the PIP by taking into consideration the needs of children
- It will also establish an inventory of paediatric needs in major therapeutic areas in 2010

Authorised medicines still under patent

- Companies must submit a PIP when applying for any change to their marketing authorisation including: new indication, new pharmaceutical form or new route of administration

Off-patent medicines

- These may be developed specifically for paediatric use and the company will benefit by receiving a new marketing authorisation, with marketing exclusivity of 10 years for that indication and formulation(s)

SUMMARY

Prescribing in children can be a more complicated procedure than it is in adults for a number of reasons. Children are affected by different diseases compared to adults, and are prescribed different groups of medicines. Children at different developmental stages can have different pharmacokinetic and pharmacodynamic considerations relating to medicines. For authorised medicines, prescribers should review the SmPC for age specific information on the appropriate dose of a medicine for children. Many medicines used in children however, are not authorised and age specific information on dosages should be sourced from a reliable paediatric reference e.g. BNFC.

There have been recent EU initiatives to improve the safety and efficacy of medicines for children, which include facilitating the development and availability of medicines in all age groups. It is anticipated that this new initiative will result in the availability of appropriate medicines for all age groups of children in the future.

List of references available on request. Date of preparation: November 2009

Every effort has been made to ensure that this information is correct and is prepared from the best available resources at our disposal at the time of issue.

Prescribers are recommended to refer to the individual Summary of Product Characteristics (SmPC) for specific information on a drug

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