Drug Saf (2014) 37:91–98
DOI 10.1007/s40264-013-0133-8

LEADING ARTICLE

Pharmacovigilance for Children's Sake

Kristina Star · I. Ralph Edwards

Published online: 21 January 2014

Abstract Child age-specific information on efficacy and risk of medicines can be limited for healthcare professionals and patients. It is therefore very important to make the best use of a risk planned approach to the pharmacological treatment of children. This means pharmacovigilance in the broadest sense of gaining the best data from the use of medicines in clinical practice. We consider issues that complicate safe medication use in paediatric care, as well as current progress and provide suggestions for building knowledge within paediatric pharmacovigilance to be used to minimise patient harm. The continuous development in children constitutes a challenge to prescribing and administering age-suitable doses for individual children. Children are not only different from adults but differ vastly within their own age group. Physical growth during childhood is apparent to the eye, but less obvious is the ongoing maturation of organ function important for drug disposition and action. Systematic issues such as medication errors, off-label use and the lack of age-suitable formulations are considerable obstacles for safe medication use in paediatrics. The recognition of emerging adverse drug reactions could be more challenging in developing children. Initiatives to improve the situation have been made by the WHO and regulators in the USA and EU. Age-specific changes in physiology, pharmacology and psychology, as well as systematic issues specific for children need to be considered in the work of assessing spontaneous reports in children. Pharmacovigilance needs to broaden its aims considerably beyond merely capturing new associations between drugs and events, and encompass careful collection on patient characteristics and circumstances around the reported adverse drug reaction to provide essential information that will give clues on how to prevent harm to children.

K. Star (✉) · I. R. Edwards
Uppsala Monitoring Centre, WHO Collaborating Centre for International Drug Monitoring, Box 1051, S-751 40 Uppsala, Sweden
e-mail: kristina.star@who-umc.org

K. Star
Department of Public Health and Caring Sciences, Uppsala University, Uppsala, Sweden

1 Introduction

Physicians require information on the efficacy and risk of a medicinal product when prescribing medicines. Patients, and/or in our context parents or caregivers, need a balanced and understandable description of the benefits, precautions and adverse drug reactions (ADRs) in order to consent to take/administer a medicine. Pharmacists need product details to adequately dispense the medicine and provide user instructions to the patient/parent. Nurses require evidence-based medication guidance to enable safe preparation and administration of medicines.

The knowledge base for health professionals and patients starts with pharmacological and toxicological information, which is supplemented before marketing by clinical trial information on selected adults and sometimes identifiable risk populations, particularly the elderly. The body of information on adults grows as the medicinal product is marketed and used in large populations of adults. However, the situation is different for children. Most people have a strong protective attitude towards children [1], particularly their own, and these desires are reflected in the United Nations' Convention on the Rights of the Child [2]. There is some natural unwillingness to include children in clinical trials because of our reluctance to cause any

discomfort to them, but also there is a need to consider 'children', not as a group, but in a much more differentiated way when considering the benefits and risks of medication so that all age groups that may be exposed are covered. This not only applies to the very important developmental differences that occur with age from birth onwards to adulthood, but also the needs for consent both for clinical trials and treatment in children as they develop awareness, a matter that can lead to controversy [3, 4]. One way around the difficulties of conducting trials (and particularly when safety is a primary matter) is to consider computer modelling of age-relevant physiological, pharmacological and toxicological data [5]. Whatever approach is considered, it seems likely that there will be less clinical data available for assessing benefit and risk in all paediatric age groups than in adults. It is therefore very important to make the best use of a risk planned approach to the treatment of children using medicines. This means pharmacovigilance in the broadest sense of gaining the best data from the use of medicines in clinical practice. Pharmacovigilance is "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem" [6]. The scope of pharmacovigilance has widened during recent years and now encompasses collection and analysis of problems related to lack of effect, product quality defects, drug dependence, drug abuse and medication errors.

Below, we consider issues that complicate safe medication use in paediatric care, as well as current progress and provide suggestions for building knowledge within paediatric pharmacovigilance to be used to minimise patient harm.

2 Intrinsic to the Drug

Children—foremost the youngest—are often excluded from premarketing clinical trials unless the medicine is specifically developed for this population, limiting access to age-specific information on dose recommendations, efficacy and risks [7, 8]. Necessary therapy cannot be withheld from children, and medicines are therefore used despite a lack of documented regulatory support. In a recent review of paediatric studies, off-label use ranged between 18 and 65 % of prescriptions in hospital and between 11 and 31 % in primary care [9]. The higher proportion of off-label use is found in neonatal hospital care. Off-label/unlicensed use in paediatrics probably increases the risk of ADRs [10–13]. Given the widespread routine off-label use of some medicines in children, there is still uncertainty around their safe and effective use in routine clinical practice.

If the medicine has been primarily manufactured to be used in adults, child age-suitable formulations might be lacking [14–16]. Growing children have various needs at different developmental stages, which constitute a challenge. Tablets often cannot be administered to an infant whole and the use of rectal dosage forms suitable for young children can be perceived to be unacceptable by an older child. The taste of a liquid formulation can be refused by a child and must be concealed. Excipients, such as solvents, flavouring, colouring and preservatives, need to be added to formulations, especially liquids commonly used in children. However, some excipients have been shown to be harmful to children and particularly the very young [17]. The solvent diethylene glycol used in paediatric preparations has caused outbreaks of child fatalities from acute renal failure a number of times in history, first in the USA in 1937 [18] and later in several developing countries, with the latest in Nigeria in 2008 [19]. Initiatives have been taken to construct a database, the Safety and Toxicity of Excipients for Pediatrics (STEP), to store evidence-based information on excipients [20]. Age-suitable formulations are important to assure safe administration and uptake of a medicine. It is therefore surprising that publications on clinical trials in highly cited journals often fail to account for details on what formulation was used, which hinders the results from being reproduced [21, 22].

Advances on developing solid dosage forms that are more acceptable for children have been made, which includes tablets that melt in the mouth, oro-dispersible and chewable tablets, granules, powders and sprinkles that usually will be mixed with food or drinks [23]. In the absence of age-suitable formulations, tablets are crushed and mixed in with liquids or foods, unless extemporaneously prepared by pharmacists for individual patients, despite an absence of continuing evidence for efficacy, tolerability and stability.

3 Intrinsic to the Child

The continuously developing child puts high demands on healthcare personnel to adjust doses and dose intervals and select suitable formulations for the individual child to achieve optimal benefit and minimal risk. Children are not only different from adults but differ vastly within their own age group. A premature infant can weigh 0.5 kg and a teenager more than 100 kg. Physical growth during childhood is apparent to the eye but less obvious is the ongoing maturation of organ function important for drug absorption, distribution, metabolism and excretion.

Young infants have fewer drug-binding proteins and reduced affinity of proteins, which will affect the volume of distribution of medicines as will changes in the muscle-to-fat ratio [24, 25]. The hepatic metabolizing enzyme activity is low in premature infants and neonates resulting

in a prolonged half-life of some medicines [24, 25]. Chloramphenicol, for example, can cause grey baby syndrome with cardiovascular collapse in newborn infants unless given lower doses of this medicine [26]. At birth, the activity of the hepatic metabolizing enzymes begins to increase over time to exceed adult activity in toddlers and older children [24, 25]. The increase in plasma clearance can result in a reduced therapeutic effect of medicines metabolised in the liver unless dose and dose intervals are adjusted.

Renal function is not fully mature until the first year of life, which needs to be considered when using medicines eliminated via the kidneys [24, 25]. The skin of an infant is thin and well-hydrated and allows greater cutaneous perfusion and absorption of drugs than in adults [24]. In addition, infants and young children have a different total body surface area to body mass ratio than adults. This can result in small skin areas exposed to medicines causing toxic effects, for example with topical corticosteroids and hexachlorophene [27]. One example of this was the severe virilisation that occurred in toddlers that came into accidental contact with anabolic steroid cream and spray bought off the internet and used by parents for body building [28]. Older children and adolescents undergo total body fat reduction, rapid growth and start producing sex hormones. The hepatic metabolizing enzyme activity varies considerably during puberty [29]. During this developmental stage, many medicines that are used for chronic diseases, such as depression and epilepsy, are cleared differently via hepatic metabolizing enzymes: doses used for chronic illnesses before puberty might become too high or too low when the patient enters puberty, resulting in toxicity or lack of effect [29]. In one study on antiretroviral therapy among adolescents and children, adherence and age predicted whether undetectable HIV RNA could be achieved [30]. Undetectable viral load was less likely to be reached for adolescents (13–18 years) than for younger children (<13 years). The odds of achieving undetectable levels of HIV RNA decreased by 10 % for every increasing year of age despite controlling for self-reported adherence. It is possible that treatment failure during puberty can be caused by either non-adherence and/or changes in drug disposition [29].

4 Medication Errors

4.1 Hospital Environment

Medication errors with potential for harm in paediatric hospital care are three times more common than in adult hospital care [31]. Medication error-related terms are also commonly reported for young children in globally collected pharmacovigilance data [32, 33]. In a UK prospective study, 13 % of the medication orders included prescribing errors and 19 % of the medication administrations were erroneous [34]. Dosing errors are the most common type of error and can lead to serious consequences [35]. There are many opportunities for mistakes when calculating individualised doses in the prescribing, transcribing, preparing and administering medicine delivery process in paediatric care.

The challenges of administering medicines to children were described by paediatric hospital nurses in a recent qualitative study [36]. The individualised doses needed for each child required extra time and concentration. The doses needed adjustment according to a wide range of body sizes. Meticulous preparation of the drug was required during calculation and dose measurement, as well as when diluting very small amounts of medicines. Extra time and sensitivity was required during the act of administration in order for the child to accept taking the medicine. Information given to the patient before administration needed to be fine-tuned according to age and maturity. Despite successful preparation and administration, the medication process might end with the child spitting out or vomiting the medicine. The nurses also highlighted that many of the aids in hospital healthcare, such as computerised physician order entry systems, are developed and streamlined towards adult care, creating unnecessary obstacles in paediatric care. The nurses' accounts illustrated the complexity of medication use in paediatric hospital care. They were left to solve the inadequacies of the medication development process for the paediatric patients.

The prevention of medication errors and potential harm to patients in hospital settings require multidisciplinary and multifaceted efforts, which include technical solutions [37]. A good example of sustainable improvement over time is presented in a recent Australian paediatric hospital study [38]. An evidence-based model for safe prescribing and improved multidisciplinary communication and education was introduced at the hospital. Both voluntary reporting and chart reviews were used to measure its impact. In the first year, they succeeded in decreasing medication errors and harm by >50 %, a level which was retained after 4 years.

4.2 Out-Patient Environment

Medication errors have often been related to the clinical environment in hospitals where there are obvious time pressures that can adversely affect the dose calculations and necessary communication and care that is needed in administering medicines [36]. Less well managed are the difficulties that occur in out-patient situations where the stress of medicating young children is borne by the parents

and family and where it is known that errors occur frequently [39]. There are initiatives to reduce systematic errors by improvements in medication packaging, easier to use dosing measures and educational campaigns [40].

Over-the-counter medicines for children come with the risk of being overused or accidentally overdosed by a parent or child. In the USA, cough and cold medicines for children <2 years old were withdrawn from the market because these medicines were related to a high number of emergency visits following unsupervised ingestions and these medicines did not demonstrate a favourable benefit–risk profile [41]. Parents and prescribers should be conservative and always ask if pharmacotherapy is indicated, since all medicines come with a risk. Restrictive prescribing of antibiotics, for example, can prevent children from serious ADRs and antibiotic resistance [25].

5 Diagnosing Adverse Reactions

Approximately one in ten children in hospital experience ADRs [42]. ADRs can be age-specific, as for sulphonamide-induced kernicterus in premature infants [43]. Serum bilirubin is increased at these young ages, and when exposed to sulphonamide the bilirubin gets displaced from its protein-binding site to accumulate to toxic levels in the brain, causing kernicterus [44]. Young children can also be more vulnerable to certain ADRs, as seen for valproic acid-induced hepatotoxicity, of which children aged 0–2 years with antiepileptic polytherapy and developmental delay are at greatest risk [45, 46]. Various mechanisms for valproic acid-induced hepatotoxicity have been suggested but gaps in the knowledge remain [47]. Spontaneous reports of ADRs in children reveal a characteristic pattern both compared with adults and within their own age group [33]. Age-specific developmental behaviour might result in an increased risk of drug toxicity. For an exploratory toddler, the mere presence of medicines can result in unintentional overdose [39], and medicines easily accessed by teenagers can end up being intentionally overdosed or abused [48].

The recognition of emerging ADRs is perhaps more challenging in childhood and requires consideration. Young children have limited ways to communicate discomfort. The child is therefore dependent on observant caregivers to acknowledge any unexpected changes of skin or behaviour, inconsolable crying, drowsiness or sleeplessness [49]. In primary care where the caregiver is most likely the parent, clear information on how to monitor the child following medicine use is needed in order for ADRs to be acknowledged, treated and reported. The challenge of detecting ADRs in the community might be part of the explanation of why the incidence and reporting of ADRs in the community is low [42, 50].

The knowledge of ADRs in relation to age-specific diseases or behaviour might be limited, which can hinder the ADR from being recognised [51]. A clinician might not associate suicidal tendency in a teenager as being drug induced or excessive sleepiness in a teenager as being vaccine related. If these occurrences are reported as a suspected ADR, the receiver assessing the report might judge the event to be caused by the age characteristics of a teenager. Adolescents with chronic diseases such as asthma and diabetes mellitus can sometimes have very serious denial and clever avoidance behaviour that can lead to poor control situations for which the medication may be blamed. Conversely, awkward and irrational behaviour, and even suicide, that may be due to the effects of some drugs is sometimes missed because of an assumed ‘difficult teenager’ [52].

The limited verbal capacity of a child results in uncertainty as to whether the medicine had effect or not, for example whether it relieved pain. Lack of effect might therefore go unnoticed. On the other hand, symptoms originating from lack of effect can be mistaken for ADRs, or at least make the causal relationship between the drug and event uncertain.

When a young infant or child receives a medicine, it might be the first time ever for the individual child. There is limited patient history to learn from, which requires extra care and vigilance. This is particularly true for newborns. One recently published case illustrates this well. A premature infant (week 30 gestational age) was administered rasburicase to reduce uric acid levels and developed haemolytic anaemia and hyperbilirubinaemia with a fatal outcome [53]. Post-mortem investigations revealed that the infant had an inherited enzyme deficiency that could have triggered the onset of the ADRs.

ADRs, such as allergic reactions, that do occur in childhood need careful documentation. Children will need to carry this knowledge with them for the rest of their life. It might, therefore, be even more crucial to investigate possible reasons for an ADR in the individual patient to avoid or minimise risk in the future. The plausibility of a drug-induced skin reaction must carefully be investigated and diagnostically confirmed, documented and explained to the patient, or in our case the parents.

Another feature, characteristic for childhood in connection to ADRs, is that negative consequences for young children taking medicines might not be revealed until later in life [54]. For example, certain cancer treatments in childhood increase the risk for skeletal- and cardiac-related ADRs in adulthood [55]. It is also more challenging to relate an event detected later in life to drug therapy used in childhood (unless there is a clear and well-known mechanism of a drug) because of exposure to a multitude of other possible causes during a lifetime.

6 The Link with Pharmacovigilance

The sometimes sparse information on risks, precautions and warnings of medicines specific for children, together with the multiple factors that can hinder an optimal dose from reaching a child (see Fig. 1), creates a scenario where patient, medicine and medication safety is utmost important. The pharmacovigilance community collects unique information on medicine-related problems and has the opportunity to compile knowledge to be used to prevent children from harm. Here we discuss the current progress and what can be done within pharmacovigilance to improve the situation for medicines safety in children.

6.1 Regulation

Encouraging initiatives have been taken to improve the situation of medicines safety in the child population during recent years. A useful WHO publication available called "Promoting Safety of Medicines in Children" was developed collaboratively by several pharmacovigilance experts worldwide [56]. The WHO has taken initiatives to promote research, improve paediatric formulations, set up a regulatory network and produce a model list of essential medicines for children [57]. The European Medicines Agency has written a guideline to conduct pharmacovigilance of medicines used by children, which states the need for inclusion of specific paediatric issues in the risk management plan [58]. Regulatory bodies in the USA and Europe have worked to increase the number of clinical trials in the paediatric population by rewarding the pharmaceutical industry with a prolonged patent when conducting trials in the paediatric population [59]. In the most current US regulation, 436 studies on paediatric patients were completed between September 2007 and April 2013 [60]. We hope that the increased knowledge gained on efficacy and safety from the increased number of clinical trials in the paediatric population will reach the public arena and will be well-presented. It has been highlighted that the reporting of ADRs in published randomised controlled trials (RCT) is of low quality [61]. In only 31 % of the 107 paediatric RCTs in this review were adverse events tabulated and ADRs were not mentioned in 22 % of the publications [61]. Also, where children are included alongside adults, the child-specific data are most often not presented separately in the study results of publically available RCTs [62]. Efforts must be made to give more attention to the importance of safety in children by both authors and journal editors. Later phase pre-marketing RCTs are most often focused on efficacy and are restricted in duration, number of patients and type of patients. Rare and serious ADRs and problems specific for certain risk groups will be less likely to be detected in RCTs, and this is where the monitoring of medication use by clinicians, pharmacovigilance centres and regulators plays an important part [63].

6.2 Collect Informative Reports

Spontaneous reports for children are important. For rare reactions, published literature cases might be the only source of ADR information for clinicians. The addition of high-quality de-identified spontaneous reports that are summarised in a comprehensive way for health professionals might fill some of the void of information [52]. However, information specific to and important for certain patient groups might be more difficult to retrieve, since the collected data on spontaneous reports is standardised and generic. The data collected are focused on details related to the medicine and reaction and less on the actual patient characteristics, such as medical history or circumstances around the event, the latter being important for the assessment of medication errors. The reports are designed to capture enough data to perform causality assessment between a suspected drug and reaction.

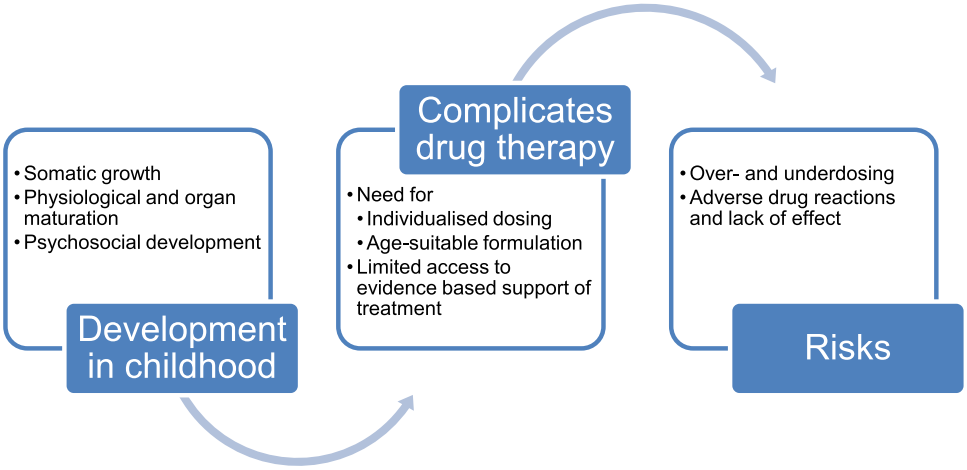

Fig. 1 Factors that influence medicines and medication safety during childhood

Considering paediatric pharmacovigilance, it is crucial that age is specified on incoming reports. Reports with an unspecified age will be missed in database screenings using age criteria, paediatric signal detection and in case series investigations of clinical issues specific for the age group. The generic nature of spontaneous reports can result in insufficient information around a specific issue, meaning important age-specific factors that could trigger or bias the event might be missed. Other information important in the assessment of paediatric reports, which might seem peripheral considering overall reporting, includes weight. Information on weight is critical in order to determine if prematurity is indicated in a newborn. Height, in addition to weight, is also important to establish if the dose recorded on the report is out of bound. Free-text fields on reports give the reporter a chance to include important information for the case that is not captured via the standardised fields. However, these free-text fields are often not shared between countries because of patient confidentiality. In these situations, the monitoring and evaluation of reactions in children on an international level will be impaired. Careful follow-up and collaboration with the clinician regarding individual cases to capture targeted information is important. The reports collected should encompass drug-related outcomes in children resulting from non-regulated use, such as off-label, unlicensed and pharmacy prepared drugs.

6.3 Build Networks with Paediatric Experts

Paediatric expertise might not be available at all national pharmacovigilance centres but we can build and maintain networks with local paediatric healthcare personnel, and support or be involved in hospital-based pharmacovigilance initiatives [56, 64]. One example of a paediatric nationwide network is in Norway, where physicians, nurses and pharmacists collaborate in working for better use and safety of medicines in children [65]. A home page has been set up to ease information flow and collaboration for members of the network, who have access to various knowledge sources, such as the British National Formulary for Children and information about ADR reporting. Local and national efforts are necessary and can provide insight into specific medication risks caused by ethnicity and genetics; nutrition, diseases and co-morbidities; culture and climate; the public health system; and production, regulations and use/availability of medicines [56].

Education and training in pharmacology for physicians, nurses and pharmacists need to incorporate the specifics of drug treatment in children and outline the importance of safety monitoring and reporting in this population. One of the core objectives of a recently initiated network, the Global Research in Paediatrics (funded by the EU), is to increase the "expert capacity for the development, scientific study and regulatory assessment of paediatric medicines", which aims to benefit clinicians to use medicines safely in children [66].

Paediatric and pharmacovigilance experts can collaborate to provide education on how to capture, diagnose and report ADRs in children [50, 67]. In a Canadian clinically based network of children's hospitals, substantial effort is made to minimise the risk of ADRs by using pharmacogenetic testing in conjunction with collecting high-quality ADR reports [68]. Biomarkers for anthracycline-induced cardiotoxicity and cisplatin-induced hearing loss have been detected in this network. Another important finding is the discovery of biomarkers in mothers taking codeine whilst breastfeeding, resulting in life-threatening CNS depression in infants caused by opioid toxicity [69]. Part of the success of the Canadian initiative is the close collaboration with paediatric clinicians, who receive feedback on their contributions and are given input on how the compiled results can be applied to their clinical setting [68].

The pharmacovigilance centre can sometimes access pharmacological or other information concerning a reported case that could be of value to the reporting clinician [70]. Informative case summaries of spontaneous reports in the child population nationally and/or globally could be shared in this network. ADR reports can be sparse on a national level; therefore, international collaboration is essential and the reason for the establishment of the WHO Programme for International Drug Monitoring. Within the programme, we can work on ways to provide information on individual report summaries without revealing the identity of a patient and still provide meaningful information on especially rare ADRs to clinicians.

6.4 Consider Age-Specific Features in Case Assessment

Age-specific features, such as physiological and psychological maturity or the underlying disease or behaviour, need to be considered when assessing individual incoming reports or case series on patient harm in children. We also need to consider that previously documented ADRs might be less known in the child population and need further dissemination. To down-prioritise the assessment of reports on old substances, without considering which patient group the report concerns, might involve losing signals in specific risk groups. In reports, particularly for children, we also need to consider whether the formulation or any excipient could have influenced the development of the reported patient harm.

Spontaneous reports can highlight risks related to suboptimal use of a medicine in the child population [71], which must be investigated even when the problem

concerns use outside the product license. There might be an incentive to develop better medication packaging, dosage instructions, easier to use dosing measures and educational campaigns to improve safer use of medicines in children.

7 Conclusions

Patient harm can be caused by the direct mechanism of a drug, specific patient vulnerabilities or by suboptimal use of a medicine. The challenges reviewed here highlight that medicines and medication safety in paediatrics is governed by age-specific features. Development of drugs and systems for their use in medication need to be produced with full consideration of the needs of the different paediatric age groups. The presentation of dosage forms and packaging may be of help in preventing problems: both innovation and regulation in this area should continue. This puts demand on regulators and industry to cover age/weight/organ maturity adjusted dose recommendations in the product information.

Pharmacovigilance needs to broaden its aims considerably beyond merely capturing new associations between drugs and events, and encompass careful collection on patient characteristics and circumstances around the reported ADR to provide essential information that will help prevent harm to children.

Acknowledgments No sources of funding were used to assist in the preparation of this article. Kristina Star and I. Ralph Edwards have no conflicts of interest that are directly relevant to the content of this article. The opinions and conclusions in this study are not necessarily those of the various national pharmacovigilance centres or of the WHO.

References

1. Berry DC. Interpreting information about medication side effects: differences in risk perception and intention to comply when medicines are prescribed for adults or young children. Psychol Health Med. 2004;9:227–34.
2. United Nations. General Assembly. Convention on the rights of the child. http://www.ohchr.org/en/professionalinterest/pages/crc.aspx. Accessed 11 Sep 2013.
3. Devereux JA, Jones DP, Dickenson DL. Can children withhold consent to treatment? BMJ. 1993;306:1459–61.
4. Hunter D, Pierscionek BK. Children, Gillick competency and consent for involvement in research. J Med Ethics. 2007;33:659–62.
5. Johnson TN, Rostami-Hodjegan A. Resurgence in the use of physiologically based pharmacokinetic models in pediatric clinical pharmacology: parallel shift in incorporating the knowledge of biological elements and increased applicability to drug development and clinical practice. Paediatr Anaesth. 2011;21:291–301.
6. World Health Organization. The importance of pharmacovigilance. Safety monitoring of medicinal products. Geneva: WHO; 2002. http://apps.who.int/medicinedocs/pdf/s4893e/s4893e.pdf. Accessed 28 Mar 2013.
7. Permala J, Hassali MA, Awaisu A, Shafie AA. Dosing information in a standard drug reference: are pediatrics still therapeutically neglected? Pediatr Int. 2010;52:290–5.
8. Tan E, Cranswick NE, Rayner CR, Chapman CB. Dosing information for paediatric patients: are they really "therapeutic orphans"? Med J Aust. 2003;179:195–8.
9. Kimland E, Odlind V. Off-label drug use in pediatric patients. Clin Pharmacol Ther. 2012;91:796–801.
10. Horen B, Montastruc JL, Lapeyre-Mestre M. Adverse drug reactions and off-label drug use in paediatric outpatients. Br J Clin Pharmacol. 2002;54:665–70.
11. Santos DB, Clavenna A, Bonati M, Coelho HL. Off-label and unlicensed drug utilization in hospitalized children in Fortaleza, Brazil. Eur J Clin Pharmacol. 2008;64:1111–8.
12. Turner S, Nunn AJ, Fielding K, Choonara I. Adverse drug reactions to unlicensed and off-label drugs on paediatric wards: a prospective study. Acta Paediatr. 1999;88:965–8.
13. Bellis JR, Kirkham JJ, Nunn AJ, Pirmohamed M. Adverse drug reactions and off-label and unlicensed medicines in children: a prospective cohort study of unplanned admissions to a paediatric hospital. Br J Clin Pharmacol. Epub 2013 Aug 7.
14. Nahata MC. Lack of pediatric drug formulations. Pediatrics. 1999;104:607–9.
15. Schirm E, Tobi H, de Vries TW, Choonara I, De Jong-van den Berg LT. Lack of appropriate formulations of medicines for children in the community. Acta Paediatr. 2003;92:1486–9.
16. Nahata MC, Allen LV Jr. Extemporaneous drug formulations. Clin Ther. 2008;30:2112–9.
17. Pawar S, Kumar A. Issues in the formulation of drugs for oral use in children: role of excipients. Paediatr Drugs. 2002;4:371–9.
18. Geiling E, Cannon PR. Pathologic effects of elixir of sulfanilamide (diethylene glycol) poisoning. JAMA. 1938;111:919–26.
19. Bonati M. Once again, children are the main victims of fake drugs. Arch Dis Child. 2009;94:468.
20. Walsh J, Mills S. Formulating better medicines for children: 4th European paediatric formulation initiative conference. Future Sci. 2013;4:21–5.
21. Standing JF, Khaki ZF, Wong IC. Poor formulation information in published pediatric drug trials. Pediatrics. 2005;116:e559–62.
22. Pandit S, Shah U, Kirby DJ, Nunn T, Tuleu C. Inappropriate oral formulations and information in paediatric trials. Arch Dis Child. 2010;95:754–6.
23. Nunn T, Williams J. Formulation of medicines for children. Br J Clin Pharmacol. 2005;59:674–6.
24. Kearns GL, Abdel-Rahman SM, Alander SW, Blowey DL, Leeder JS, Kauffman RE. Developmental pharmacology-drug disposition, action, and therapy in infants and children. N Engl J Med. 2003;349:1157–67.
25. Kearns GL, Wilson JT, Neville KA, Springer MA. Drug therapy in pediatric patients. In: van Boxtel CJ, Santoso B, Edwards IR, editors. Drug benefits and risks international textbook of clinical pharmacology. 2nd ed. Amsterdam: IOS Press; 2008. p. 181–201.
26. Sutherland JM. Fatal cardiovascular collapse of infants receiving large amounts of chloramphenicol. AMA J Dis Child. 1959;97:761–7.
27. West DP, Worobec S, Solomon LM. Pharmacology and toxicology of infant skin. J Invest Dermatol. 1981;76:147–50.
28. Kunz GJ, Klein KO, Clemons RD, Gottschalk ME, Jones KL. Virilization of young children after topical androgen use by their parents. Pediatrics. 2004;114:282–4.
29. Kennedy M. Hormonal regulation of hepatic drug-metabolizing enzyme activity during adolescence. Clin Pharmacol Ther. 2008;84:662–73.

30. Khan M, Song X, Williams K, Bright K, Sill A, Rakhmanina N. Evaluating adherence to medication in children and adolescents with HIV. Arch Dis Child. 2009;94:970–3.
31. Kaushal R, Bates DW, Landrigan C, McKenna KJ, Clapp MD, Federico F, et al. Medication errors and adverse drug events in pediatric inpatients. JAMA. 2001;285:2114–20.
32. Star K. Safety of medication in paediatrics. Diss. Uppsala University, Sweden: Acta Universitatis Upsaliensis; 2013.
33. Star K, Noren GN, Nordin K, Edwards IR. Suspected adverse drug reactions reported for children worldwide: an exploratory study using VigiBase. Drug Saf. 2011;34:415–28.
34. Ghaleb MA, Barber N, Franklin BD, Wong IC. The incidence and nature of prescribing and medication administration errors in paediatric inpatients. Arch Dis Child. 2010;95:113–8.
35. Wong IC, Ghaleb MA, Franklin BD, Barber N. Incidence and nature of dosing errors in paediatric medications: a systematic review. Drug Saf. 2004;27:661–70.
36. Star K, Nordin K, Poder U, Edwards IR. Challenges of safe medication practice in paediatric care—a nursing perspective. Acta Paediatr. 2013;102:532–8.
37. Conroy S, Sweis D, Planner C, Yeung V, Collier J, Haines L, et al. Interventions to reduce dosing errors in children: a systematic review of the literature. Drug Saf. 2007;30:1111–25.
38. Gazarian M, Graudins LV. Long-term reduction in adverse drug events: an evidence-based improvement model. Pediatrics. 2012;129:e1334–42.
39. Schillie SF, Shehab N, Thomas KE, Budnitz DS. Medication overdoses leading to emergency department visits among children. Am J Prev Med. 2009;37:181–7.
40. Centers for Disease Control and Prevention. The PROTECT Initiative: advancing children's medication safety. http://www.cdc.gov/medicationsafety/protect/protect_initiative.html. Accessed 12 Sep 2013.
41. Hampton LM, Nguyen DB, Edwards JR, Budnitz DS. Cough and cold medication adverse events after market withdrawal and labeling revision. Pediatrics. 2013;132:1047–54.
42. Clavenna A, Bonati M. Adverse drug reactions in childhood: a review of prospective studies and safety alerts. Arch Dis Child. 2009;94:724–8.
43. Silverman WA, Andersen DH, Blanc WA, Crozier DN. A difference in mortality rate and incidence of kernicterus among premature infants allotted to two prophylactic antibacterial regimens. Pediatrics. 1956;18:614–25.
44. Rang H, Dale M, Ritter J, Moore P. Pharmacology. 5th ed. London: Churchill Livingstone; 2003.
45. Dreifuss FE, Langer DH, Moline KA, Maxwell JE. Valproic acid hepatic fatalities. II. US experience since 1984. Neurology. 1989;39:201–7.
46. Dreifuss FE, Santilli N, Langer DH, Sweeney KP, Moline KA, Menander KB. Valproic acid hepatic fatalities: a retrospective review. Neurology. 1987;37:379–85.
47. Chang TK, Abbott FS. Oxidative stress as a mechanism of valproic acid-associated hepatotoxicity. Drug Metab Rev. 2006;38:627–39.
48. Micallef J, Star K, Palmaro A, Lapeyre-Mestre M. Detection and magnitude of methylphenidate abuse and misuse using VigiBase and correlation with level of use in Europe [poster; abstract]. Pharmacoepidemiol Drug Saf. 2012;21:450.
49. Babl FE, Lewena S, Brown L. Vaccination-related adverse events. Pediatr Emerg Care. 2006;22:514–9 (quiz 20-2).
50. Arencibia ZB, Sotomayor DN, Mollinedo NC, Choonara I, Manzano EF, Leyva AL. Adverse drug reactions in children in Camaguey Province, Cuba. Arch Dis Child. 2010;95:474–7.
51. Edwards IR. The management of adverse drug reactions: from diagnosis to signal. Therapie. 2001;56:727–33.
52. Star K, Iessa N, Almandil NB, Wilton L, Curran S, Edwards IR, et al. Rhabdomyolysis reported for children and adolescents treated with antipsychotic medicines: a case series analysis. J Child Adolesc Psychopharmacol. 2012;22:440–51.
53. Zaramella P, De Salvia A, Zaninotto M, Baraldi M, Capovilla G, De Leo D, et al. Lethal effect of a single dose of rasburicase in a preterm newborn infant. Pediatrics. 2013;131:e309–12.
54. Carmichael M. Drug safety: double jeopardy. Nature. 2013;498:S14–5.
55. Diller L. Clinical practice. Adult primary care after childhood acute lymphoblastic leukemia. N Engl J Med. 2011;365:1417–24.
56. Couper MR, Kaplan SE. Promoting safety of medicines in children. Geneva: World Health Organisation; 2007.
57. World Health Organization. Essential medicines for children. http://www.who.int/childmedicines/en/. Accessed 10 Sep 2013.
58. European Medicines Agency. Guideline on conduct of pharmacogivilance for medicines used by the paediatric population. London: European Medicines Agency; 2007. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003764.pdf. Accessed 10 Sep 2013.
59. Hoppu K, Anabwani G, Garcia-Bournissen F, Gazarian M, Kearns GL, Nakamura H, et al. The status of paediatric medicines initiatives around the world—what has happened and what has not? Eur J Clin Pharmacol. 2012;68:1–10.
60. FDA U.S. Food and Drug Administration. Breakdown of FDAAA completed pediatric studies. 2013. http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm190622.htm. Accessed 11 Sep 2013.
61. de Vries TW, van Roon EN. Low quality of reporting adverse drug reactions in paediatric randomised controlled trials. Arch Dis Child. 2010;95:1023–6.
62. Anderson M, Choonara I. A systematic review of safety monitoring and drug toxicity in published randomised controlled trials of antiepileptic drugs in children over a 10-year period. Arch Dis Child. 2010;95:731–8.
63. Choonara I. Educational paper: aspects of clinical pharmacology in children–pharmacovigilance and safety. Eur J Pediatr. 2013;172:577–80.
64. Menniti-Ippolito G, Raschetti R, Da Cas R, Giaquinto C, Cantarutti L. Active monitoring of adverse drug reactions in children. Italian Paediatric Pharmacosurveillance Multicenter Group. Lancet. 2000;355:1613–4.
65. Nasjonalt kompetansenettverk for legemidler til barn. http://www.legemidlertilbarn.no/Sider/default.aspx. Accessed 11 Sep 2013.
66. Global Research in Paediatrics—Network of Excellence. http://www.grip-network.org/index.php/cms/en/home. Accessed 17 Dec 2013.
67. Barzaga Arencibia Z, Lopez Leyva A, Mejias Pena Y, Gonzalez Reyes AR, Fernandez Manzano E, Choonara I. Pharmacovigilance in children in Camaguey Province, Cuba. Eur J Clin Pharmacol. 2012;68:1079–84.
68. Carleton B, Poole R, Smith M, Leeder J, Ghannadan R, Ross C, et al. Adverse drug reaction active surveillance: developing a national network in Canada's children's hospitals. Pharmacoepidemiol Drug Saf. 2009;18:713–21.
69. Madadi P, Ross CJ, Hayden MR, Carleton BC, Gaedigk A, Leeder JS, et al. Pharmacogenetics of neonatal opioid toxicity following maternal use of codeine during breastfeeding: a case–control study. Clin Pharmacol Ther. 2009;85:31–5.
70. van Puijenbroek E, Conemans J, van Grootheest K. Spontaneous reports and pharmacogenetics: the role of the pharmacovigilance centre. Drug Saf. 2009;32:357–8.
71. Uppsala Monitoring Centre. Rotavirus vaccine and incorrect administration route—a patient safety signal. WHO Signal. 2010 Dec;13–14.