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Drug Toxicity and Adverse Drug Reactions in Children – A Brief Historical Review

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Abstract

Drug toxicity in association with adverse drug reactions is common in hospitalised children. The toxicity of medicines in children is different to that seen in adults. There are also differences between different age groups of paediatric patients with neonates being generally at greater risk for experiencing a drug-associated adverse event. The major examples of drug toxicity that have occurred in paediatric patients are reviewed ranging from percutaneous toxicity over 100 years ago to formulation errors and toxicity associated with normal, developmental alterations in drug metabolism . The need to learn from previous cases of drug toxicity to prevent future cases is paramount.

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Introduction

Adverse drug reactions (ADRs) are common clinical problems in both paediatric and adult medicine. Over 9% of hospitalised children have adverse reactions to therapy and up to 4% of all hospital admissions are the consequence of ADRs[1-9]. Among the well recognised patterns of ADRs is drug toxicity, of particular importance because of the relatively higher risk for morbidity and mortality as compared to many other patterns of ADRs (Table 1). The toxicity of many medicines in children is different to that seen in adults. Indeed, there are some groups of paediatric patients, such as babies in the Neonatal Intensive Care Unit, in whom drug toxicity appears to be quite common (11–30%)[7-9].

It can be difficult to evaluate drug toxicity in children. Studies of drug-induced toxicity are generally comprised of retrospective reviews and isolated case reports. It is difficult to be certain about the association between drug exposure and possible toxicity in the majority of cases. Thus it is critical to maintain a high index of suspicion for the occurrence of drug toxicity in infants and children. The identification of new patterns of ADRs is dependent upon health professionals being alert and being consistently mindful of the possibility of drug toxicity. This brief historical review highlights some of the major cases of ADRs manifested by drug induced toxicity that have occurred in paediatric patients and draws some conclusions from them in relation to what lessons can be learned.

Percutaneous drug toxicity

One of the earliest recognised drug toxicities was the recognition of methaemoglobinaemia due to the effects of aniline dye, which had been used

Table 1. Classification of adverse drug reactions			
Predictable	**Example**	**Unpredictable**	**Example**
Side Effects	Hand tremor during beta-agonist therapy	Intolerance	Intractable vomiting during erythromycin therapy
Secondary Effects	Pseudomembranous colitis to lincomycin	Allergic or Pseudoallergic	Urticaria during penicillin therapy
Interactions	Bleeding during concurrent use of warfarin and cimetidine	Idiosyncratic	Stevens-Johnson Syndrome to anticonvulsants
Toxicity	Renal failure with high serum concentrations of gentamicin		

Modified from Patterson R, DeSwarte RD, Greenberger PA et al. Drug allergy and protocols for management of drug allergies. New Engl Rev Allergy Proc 1986; 7: 325–42

to stamp the name of the institution on diapers[10]. As reported in the British Medical Journal over a century ago, seventeen newborn infants developed cyanosis after absorbing the dye percutaneously. Subsequently, there have been other cases of infants developing cyanosis due to percutaneous absorption of aniline dye[11].

This particular ADR illustrates the possibility of enhanced drug toxicity through percutaneous absorption in infants. In general, absorption of compounds is enhanced by issues such as the prolonged contact of a wet diaper with the perineum. Newborn infants have a higher surface area to weight ratio than both children and adults. Therefore medicines that are administered topically result in greater relative exposure in newborn infants. As well, a relative increase in the water content of the dermis and a thinner stratum corneum in young infants facilitates transcutaneous diffusion of small molecules. There have been several other examples of percutaneous toxicity occurring both in newborn infants and in children. Antiseptic agents such as hexachlorophene[12], iodine[13] and isopropyl alcohol[14] have all been associated with neurotoxicity, hypothyroidism and metabolic acidosis, respectively.

Formulation

The introduction of sulphonamides for the treatment of infection in 1935 was a major advance in medical care and indeed has been credited with being the start of the Therapeutic Revolution. However, sulphonamides are relatively insoluble in water and consequently there was a problem in preparing a paediatric formulation. In 1937 the use of diethylene glycol as a solvent to prepare elixir of sulphanilamide – done without appreciation that the vehicle was a potent toxin – was responsible for the deaths of at least 76 American children and adults[15]. Unfortunately, this historical tragedy has been repeated numerous times during the past decade. Diethylene glycol has subsequently been used as a solvent for paracetamol resulting in the death of 47 children in Nigeria[16] in 1992, 51 children in Bangladesh[17] in 1995 and 85 children in Haiti[18] in 1998. This reminds us that it is important to remember that medicines contain not only the desired active compound but also numerous other chemicals which are added to make the drug more palatable, more soluble, more stable or for a variety of other reasons (e.g., to add colouring, to enhance drug suspension). Thus, it is important to consider every component of a drug formulation as a substance with the potential of producing an ADR in the paediatric patient.

Benzyl alcohol is used for its antibacterial properties in ampoules of sodium chloride and water that are intended for intravenous administration. Metabolic acidosis, hepatic and renal failure and cardiovascular collapse (i.e., gasping syndrome) have been described among 10 premature newborn infants who were receiving multiple injections of sodium chloride for flushing catheters and bacteriostatic water in association with medicines that have been reconstituted[19]. Both solutions contained 0.9% benzyl alcohol, which was postulated as the causative agent in neonates and young infants with a reduced capacity to metabolise and excrete this toxic "inactive ingredient" in the doses that were unwittingly administered.

In 1984 an intravenous formulation of vitamin E was withdrawn from the market following the death of 38 neonates. It was postulated that the emulsifiers used to make the vitamin E water

Table 2. Major formulation errors in paediatric patients

Year	Drug	Error	Deaths	Age group	Country
1937	Sulphanilamide elixir	Diethylene glycol used as solvent	76	Children and adults	USA
1972	Talc baby powder	Contained 6.3% hexachlorophene	36	Infants and young children	France
1982	Sodium chloride Water	Benzyl alcohol concentrations high	10	Neonates	USA
1984	Vitamin E	Emulsifiers toxic?	38	Neonates	USA
1992	Paracetamol	Diethylene glycol used as solvent	47	Children	Nigeria
1995	Paracetamol	Diethylene glycol used as solvent	51	Children	Bangladesh
1996	Magnesium sulphate	Concentration doubled	?	Neonates	UK
1998	Paracetamol	Diethylene glycol used as solvent	85	Children	Haiti

miscible for intravenous use may have been responsible for the deaths[20].

Inappropriate formulation of a baby powder containing talc in France resulted in the death of 36 infants and young children[21]. The baby powder contained 6.3% hexachlorophene, which is a known neurotoxin. The affected children developed an encephalopathy; in total 204 children became ill and 36 died. A similar incident occurred in the USA in the 1970s when a significant number of newborn infants developed neurotoxicity consequent to bathing them with a hexachlorophene-containing product in an attempt to reduce the transmission of antibiotic resistant strains of *Staph. Aureus*[22]. The major formulation errors are highlighted in Table 2.

Sulphonamides and protein binding

Newborn infants who received a combination of penicillin and sulphisoxazole were found to have a significantly higher mortality that those who received oxytetracycline[23]. In particular, the newborn infants who received the sulphonamide had a higher incidence of kernicterus. These infants developed seizures and on post mortem examination, had yellow staining of the brain. Although this higher mortality was described in 1956, it was almost a decade later that studies showed that sulphonamides have a higher binding affinity than bilirubin for albumin. This results in a marked increase in the free fraction of bilirubin in the plasma[24]. The conjugation of bilirubin is minimal due to reduced activity of the glucuronosyltransferase in the neonate (Table 3).

Impaired metabolism in the neonate

A few years after the reported mortality of sulphonamides in sick neonates, the grey baby syndrome was reported in association with the use of the antibiotic chloramphenicol[25]. The affected infants developed abdominal distension, vomiting, cyanosis, cardiovascular collapse, irregular respiration and subsequent death shortly after therapy with chloramphenicol was started. Pharmacokinetic studies in the neonate showed accumulation of chloramphenicol in plasma, which subsequently impaired cellular oxidative metabolism leading to cardiovascular instability and collapse. Despite a recognition of the association between impaired glucuronosyl-transferase activity and bilirubin toxicity in the neonate and that the major route for chloramphenicol metabolism involved conjugation with glucuronic acid, this knowledge was not translated into an age-specific dose requirement for chloramphenicol in infants. Subsequently, it was demonstrated that a reduction in the total daily dosage from 100 mg per kg to 50 mg per kg would prevent the development of the grey baby syndrome[26]. This illustrates the importance of understanding the impact of developmental changes in drug disposition and metabolism, notably in the first year of life and among pre-term infants, and using this information to design age-appropriate drug dosing regimens. It should be noted that had

Table 3. Major adverse drug reactions in paediatric patients				
Year	**Drug/Compound**	**Age group**	**ADR**	**Mechanism**
1886	Aniline dye	Neonates	Methaemoglobinaemia	Percutaneous absorption
1956	Sulphisoxazole	Neonates	Kernicterus	Protein displacing effect on bilirubin
1959	Chloramphenicol	Neonates	Grey baby syndrome	Impaired metabolism
1979	Sodium valproate	Young children (< 3 years)	Hepatic failure	Abnormal metabolism?
1980	Salicylate	Children	Reye's syndrome	Unknown
1990	Propofol	Children	Metabolic acidosis	Unknown Dose related?
1996	Lamotrigine	Children	Skin reactions	Unknown Associated with comedication with sodium valproate

appropriate clinical trials been conducted so as to characterise the impact of age on chloramphenicol disposition, the tragedy associated with the "grey baby syndrome" could well have been averted.

Hepatotoxicity and sodium valproate

Hepatotoxicity is one of the most feared adverse effects of anticonvulsants both in children and adults. However, there are differences between the rates of hepatic complications to the anticonvulsants between adults and children. Hepatotoxicity in association with sodium valproate given as monotherapy is much more frequent in children. A majority of the 100 patients who have died were children; the difference in relative risk between children on polytherapy and adults on monotherapy is 1:500 versus 1:5000. A retrospective American study showed that children under the age of 3 years were a high risk group along with patients on polypharmacy and those with developmental delay[27].

The mechanism of sodium valproate hepatotoxicity is thought to be related to abnormal drug metabolism, either reductions in fatty acid beta-oxidation (the major detoxification pathway for valproic acid)[28] and/or age-associated increases in the activity of specific cytochromes P450 responsible for the generation of putative hepatoxic metabolic intermediates. This may occur in specific vulnerable sub-sets of patients on a pharmacologic (e.g., those with induced cytochrome P450 activity consequent to concomitant treatment with carbamazepine, phenytoin, or phenobarbital) or pharmacogenetic basis.

In contrast, there are some adverse hepatic events that are more common among adults than children, notably infants and toddlers. As an illustration, young infants tolerate paracetamol overdose much better than do adults. This difference appears to be related to an enhanced activity of sulfotransferase isoforms (relative to adults)[29] and possibly due to reduced activity of bioactivating cytochromes P450 capable of producing the N-acetyl-benzoquinonimine intermediate during the first few months of life.

Reye's syndrome and salicylates

Reye's syndrome was originally described in 1963[30]. Children usually had a preceding viral infection and subsequent drowsiness, which led to coma, hypoglycaemia, seizures and liver failure. The association between Reye's syndrome and salicylates had been raised as a possibility in 1965 by an observant physician who noted that 15 of the 31 cases reported had received aspirin prior to admission[31]. In 1980 the association between Reye's syndrome and the use of salicylates during a preceding viral infection was confirmed[32]. During an outbreak of influenza A, seven children were admitted to hospital with Reye's syndrome. These seven children were compared with 16 controls from the same class who did not have signs/symptoms compatible with the diagnosis of Reye's syndrome. All of the children with Reye's syndrome took salicylates whereas only 8 of the 16 controls took salicylates. The patients took a larger dose of salicylates as compared to those in the control group and the level of salicylate consumption was associated with the severity of the Reye's syndrome.

The restriction of the use of salicylates for general antipyresis and analgesia in children aged 12 and under has led to a dramatic reduction in the incidence of Reye's syndrome in this particular patient population[33]. Several cases have recently been reported of salicylates associated with the production of Reye's syndrome in children between the ages of 12 and 16[34,35] thus demonstrating the propensity for this drug-associated adverse event to occur well into adolescence. The mechanism of the toxicity is unknown with respect to the apparent interaction between salicylate pharmacodynamics and the multifactorial physiologic abnormalities associated with viral infection.

Metabolic acidosis and propofol

Propofol is an ultra-short acting, parenteral anaesthetic agent that has gained wide acceptance for the induction and maintenance of anaesthesia in both adults and children. It's short elimination half-life and rapid distribution kinetics allows patients to recover rapidly upon discontinuation of infusion with much fewer adverse effects than have been observed with other parenteral anaesthetic agents (eg, barbiturates, ketamine). Propofol has also been used as a sedative to facilitate prolonged mechanical ventilation in critically ill children. To date, there have been reports of 10 children dying following the use of propofol as a sedative[36,37]. These children have developed severe metabolic acidosis and lipaemia. Many of the children were originally admitted to hospital with upper airway obstruction and thus, were not expected to suffer multi-organ failure. The mechanism(s) associated with the production of metabolic acidosis by propofol in children without concomitant hypoxemia is not known. It is, however, noted that the dose of propofol used in the children who died was considerably higher than has been recommended by other groups [37] thus implying an enhanced risk associated with the extent of drug exposure (i.e. dose).

Skin reactions and anticonvulsants

Skin reactions as an adverse effect associated with certain anticonvulsants are well recognised. At least 5% of children will develop a skin rash in association with initial therapy of both carbamazepine and phenytoin[38]. The true incidence of this particular adverse effect in children as compared to adults is unclear. Although the majority of skin reactions are mild, there is a small but real risk of Stevens-Johnson syndrome or toxic epidermal necrolysis, which probably again represents an ADR that manifests in individuals who, consequent to developmental, pharmacogenetic and/or pharmacologic (e.g., concomitant therapy) factors, are uniquely susceptible[39].

Another example of an apparent age-associated difference in the incidence of a severe ADR occurs with lamotrigine. Severe skin reactions associated with this drug are seen in approximately 1 in 1000 adult patients as compared to children where the incidence is estimated to be between 1 in 330 or 1 in 100[40]. It is more frequent when sodium valproate is used in combination with lamotrigine and at higher doses[41].

Respiratory depression in association with drugs

Side effects such as respiratory depression occur in both adults and children, in association with opiates and sedative agents. There have, however, been few studies documenting the extent of respiratory depression in neonates and children [42-46]. The risk of respiratory depression following opiates is low both in neonates and children (Table 4). In contrast, the risk of respiratory depression following the use of diazepam in children with acute seizures is considerably greater than reported for adults[46]. While not implicitly discussed in these comparisons, clinicians must remain mindful of the developmental,

Table 4. Incidence of drug-related respiratory depression

Drug	Number receiving drug	Number of cases of respiratory depression	Patients	Reference	Year
Opiates	>600	1	Paediatrics	40	1987
Opiates	131	11	Neonates	41	1987
Morphine	99	6	Neonates	42	1994
Opiates	9,000 (est)	15	Paediatrics	43	1996
Diazepam	130	11	Paediatrics	44	1999

pharmacogenetic (e.g., in the case of CYP2D6 substrates such as codeine and tramadol) and disease-associated differences in drug disposition that frequently occur in sick children and can alter the dose vs. plasma concentration vs. effect profile for any drug that acts on the central nervous system and has the capacity to centrally alter the control of respiration.

Conclusion

Although drug therapy has been one of the major advances in the medical care of children over the past 100 years, it has not occurred without problems. One of the major problems has been the risk of ADRs, which is compounded in many instances as a function of the increasing complexity of pharmacotherapy. We have highlighted some of the major ADRs that have occurred in children over the last 120 years. Although these adverse effects have often advanced the drug regulatory process and our understanding of paediatric pharmacology, it has been at a cost, which in most instances has been unacceptable to the affected children and their families.

This places the onus for both discovery and prevention of ADRs in children on paediatricians and other child health care workers. We need to be vigilant and aware of the possibility of ADRs in infants and children, including ADR patterns that are not the same as ones we may have encountered in the past[47]. There are many case reports of possible ADRs[48] which frequently, in the absence of complete information, will alter and/or determine standards of paediatric medical care. What is not known is which of these ADRs are disease and/or drug-related events and most importantly, which ones are likely to result in significant morbidity and/or mortality. The identification and characterisation of new patterns of ADRs is critical for patient safety and to guide mechanistic research to study the pathogenesis of these events. This represents a major challenge for investigators in paediatric clinical pharmacology and drug safety.

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