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Drug toxicity and surveillance in children

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The use of medicines in children is an area of increasing interest [1]. Many medicines are being used outside the terms of their product licence [2] thereby increasing the risk of drug toxicity. Clinicians need to ensure not only that toxicity is kept to a minimum but also that children are not denied the use of appropriate medicines. This can only be achieved by the scientific study of drug toxicity in children and is ideally carried out by prospective studies of drug surveillance. This involves specifically monitoring for drug toxicity, either in relation to particular drugs [3,4] or selected patient groups [5,6]. Drug use in children may be accompanied by problems not seen in adults, or cause adverse drug reactions that are more frequent than in adults. An example of this is metoclopramide which causes dystonia in teenagers and Parkinsonism in the elderly [7].

Antibiotic toxicity in neonates

Infections have always been a major problem in neonates with significant mortality and morbidity. The introduction of antibiotic therapy resulted in major clinical advances [8]. However, antibiotic therapy also produced particular clinical problems. Silverman *et al.* reported considerably higher mortality in neonates receiving a combination of penicillin and sulphisoxazole than those receiving oxytetracycline [9]. There was a significantly higher incidence of kernicterus, both clinically (opisthotonos, spasticity, seizures, oculogyric movements) and pathologically (yellow staining of the brain) in the children who died following penicillin and the sulphonamide. Subsequently, others have shown that sulphonamides are highly protein bound and displace bilirubin from albumin [10]. As the preterm infant is usually jaundiced, the sulphonamide displaced bilirubin from albumin and this is thought to increase the incidence of kernicterus.

Newborn infants receiving chloramphenicol developed abdominal distension, vomiting, cyanosis, cardiovascular collapse, irregular respiration and subsequent death [11]. This was termed the grey baby syndrome. Shortly after this syndrome was noted, pharmacokinetic studies showed that newborn infants had impaired metabolism of chloramphenicol and that a reduction of the dosage from 100 mg kg^{-1} daily to 50 mg kg^{-1} daily prevented the development of this syndrome [12].

Toxicity in young children

Although these initial studies described clinical problems in newborn infants, and the preterm infant in particular, problems with other drugs have highlighted the enhanced toxicity of some medicines in children. Hepatotoxicity in association with the anticonvulsant sodium valproate was initially reported in 1979 [13]. Subsequently more than 100 patients died, the majority of whom were children. A retrospective review [14] of 37 patients who died in the USA, showed that those patients at greatest risk fell into one of three categories: (i) age under 3 years; (ii) receiving other anticonvulsants as well as valproate; (iii) developmental delay. Subsequent changes in prescribing habits resulted in a dramatic reduction in the number of deaths due to sodium valproate [15]. The mechanism of valproate hepatotoxicity is not fully understood but is thought to relate to abnormal metabolism [16]. Other anticonvulsants result in enzyme induction and, therefore, enhance certain metabolic pathways resulting in the formation of toxic intermediate metabolites. These pathways may be more prominent in children under the age of 3 years and it is important to realise that drug metabolism in children differs from that of adults.

The other drug causing hepatotoxicity specifically in children was aspirin. The use of salicylates in children with a mild viral infection resulted in a greater risk of developing Reye's syndrome—a life threatening illness associated with drowsiness, coma, hypoglycaemia, seizures and liver failure. Epidemiological work confirmed the association between salicylate ingestion and the development of Reye's syndrome [17], although the possible association had been postulated 15 years previously [18]. Starko *et al.* [17] studied children

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admitted to hospital with Reye's syndrome and their ill classmates as control subjects, during an outbreak of influenza A. The seven children with Reye's syndrome all took salicylates in comparison with eight of the 16 control subjects. The patients took larger doses of salicylates than the control group and the level of salicylate consumption correlated with the severity of the Reye's syndrome. The subsequent warning that salicylate should not be used for children in general, led to a dramatic reduction in the incidence of Reye's syndrome. The mechanism of the toxicity remains unknown and salicylates, in the absence of viral infection, do not predispose to the development of Reye's syndrome or hepatotoxicity.

Drug metabolism and toxicity

The toxicity of sulphonamides and chloramphenicol in the neonate, and sodium valproate and salicylates in young children have emphasised the need to study the relationship between drug metabolism and age in more detail. The major pathways for drug metabolism include oxidation by hepatic cytochrome P450 enzymes and also conjugation to glucuronides and sulphates [19].

The activity of many of the P450 enzymes is reduced in the neonatal period [20]. The rate by which enzyme activity subsequently increases varies considerably. This is illustrated by the drug caffeine which has markedly diminished clearance in preterm neonates and adult clearance values by the age of 6 months [21]. The metabolism of caffeine is complex and whereas 8-hydroxylation activity reaches adult levels by the age of 1 month, N3 and N7 demethylation do not reach adult levels until the age of 4 months [22]. Midazolam undergoes oxidation predominantly by CYP3A4. The clearance of midazolam is impaired in infants and children under the age of 3 years, in comparison with children aged 3 years and older [23]. The variation in maturation of different enzymes makes it difficult to predict dosage requirements accurately at different ages. This results in an increased susceptibility to toxicity.

Glucuronidation is a major process of drug elimination in adults, but is significantly reduced in neonates. Paracetamol and morphine are both drugs where glucuronidation is the major metabolic pathway. In the case of paracetamol there is compensatory sulphation so the half-life is similar in children of all ages [24]. This is in contrast to morphine where sulphation is a minor pathway in all ages including neonates [25]. The glucuronidation of morphine is reduced in the neonatal period but because there is no enhanced sulphation the half-life in neonates is considerably longer [26].

Hepatotoxicity is common following an overdose of paracetamol in adults and adolescents. In children, however, severe hepatotoxicity is uncommon and only seven deaths in children have been reported world wide [27]. Following an overdose in adults, the normal metabolic pathways (glucuronidation and sulphation) are saturated. Paracetamol then undergoes oxidation with the production of hepatotoxic oxidative metabolites. Children, however, have an enhanced capacity for sulphation and therefore less paracetamol undergoes oxidation and less hepatotoxic oxidative metabolites are formed. The liver has the capacity for detoxifying these oxidative metabolites utilising glutathione. Children are thought to have greater hepatic stores of glutathione which also helps to minimise hepatotoxicity [28].

Renal excretion and toxicity

The other major elimination pathway involves renal excretion. This is impaired in fullterm neonates in the first few days of life [29]. It is also impaired in preterm infants in the first few weeks of life and, therefore, drugs that are excreted renally, such as aminoglycosides, are administered less frequently during the neonatal period. In infants and children outside the neonatal period, renal function is normal and does not predispose children to enhanced toxicity.

Formulation

It is important to realise that medications given to children contain not only the desired drug but also other compounds which are added to make the drug more soluble, palatable etc. The most tragic example of an adverse reaction to ingredients is the use of diethylene glycol as a solvent for sulphanilamide which resulted in the death of at least 76 Americans in 1937 [30]. Subsequently, diethylene glycol has been used as a solvent for paracetamol resulting in the death of 47 children in Nigeria [31] and 51 in Bangladesh [32].

It is a credit to colleagues in these two countries that further deaths were avoided by the awareness of clinical suspicion of ADRs due to a constituent rather than the primary component of the medicine administered.

Drug surveillance in children and neonates

Although some cases of drug toxicity such as chloramphenicol were recognised rapidly and dosage modified, the toxicity of other drugs such as aspirin and sodium valproate were not recognised for many years. In order to anticipate drug related toxicity in children, drug surveillance schemes were carried out in paediatric in-patients. These initial studies were carried out in North American hospitals [33,34] and subsequently similar studies were carried out in British hospitals [35,36].

Adverse drug reactions (ADRs) occurred in between 5.6 and 16.8% paediatric inpatients in these studies [33–37]. It is difficult, however, to extrapolate this data which is based on studies in highly specialised children's hospitals to smaller paediatric units or the community. The incidence of ADRs is heavily biased by the inclusion of certain types of patients who are more likely to

experience an ADR. Patients receiving cytotoxic medications, or anticonvulsants, have a significantly higher incidence of ADRs than children receiving bronchodilator therapy or antibiotics [6,36–38].

There have only been a few studies of adverse drug reactions in Neonatal Intensive Care Units [37,39–41]. These studies have suggested a very high incidence of ADRs with figures ranging from 10.6 up to 30%. Many of these adverse drug reactions were thought to be severe and this is, obviously, an area that requires further studies.

The benefit of surveillance schemes is that they can identify which types of drugs are more likely to cause ADRs in children. Subsequent studies can help to minimise ADRs due to these drugs. Prospective surveillance is important in that it enables one to draw more appropriate conclusions than either retrospective studies or isolated case reports. This is illustrated by opiate induced respiratory depression which is a severe ADR which can be life threatening [42]. Prospective surveillance shows that the incidence of opiate induced respiratory depression is very low and should not be used as a justification to deprive children of appropriate analgesia [4].

Which health professionals?

Most studies of paediatric drug surveillance have involved either nurses or pharmacists in the reporting of ADRs. The yellow card scheme operated by the Committee on the Safety of Medicines within the UK, relies primarily on doctors reporting ADRs. We have established an inhouse ADR reporting scheme which enables any health professional to report a suspected ADR. We have found that the presence of a Drug Surveillance Scheme within our hospital has increased awareness of possible ADRs [43]. Despite this increased awareness, we have still found that most ADRs are reported by nurses and pharmacists with only a few reported by doctors [5]. We feel it is appropriate to include other health professionals, notably pharmacists and nurses in the National Drug Surveillance Scheme operated by the Committee on Safety of Medicines.

The future

A weakness of many of the existing studies is that they have not commented on the preventability of ADRs. This is important as our aim should be to minimise subsequent ADRs. Also, most studies have involved paediatric inpatients. There have been few studies in outpatients [38,44,45] and only two involving children in the community [46,47]. There have been few dose response studies in children and doses are often extrapolated from adult data. More studies are required alongside surveillance schemes to improve our understanding of the differences between children and adults.

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