

ORIGINAL ARTICLE

Surveillance for fatal suspected adverse drug reactions in the UK

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Aim: To determine the nature and number of suspected adverse drug reactions (ADRs) associated with fatal outcomes in children reported through the yellow card scheme.

Methods: All reports of suspected ADRs with a fatal outcome in children received by the UK Committee on Safety of Medicines through its Yellow Card Scheme from 1964 until December 2000 were reviewed. Reports associated with vaccines and overdose were excluded. The medicine, date of the report, diagnosis, ADR, and the age of the child were analysed. No formal causality assessment was performed.

Results: There were 331 deaths with 390 suspected medicines reported for children aged 16 years or less. Medicines most frequently mentioned were anticonvulsants (65 deaths), cytotoxics (34 deaths), anaesthetic agents (30 deaths), and antibiotics (29 deaths). The individual drug most frequently mentioned was sodium valproate (31 deaths). The nature of the reported ADRs were diverse, with hepatic failure the most frequent. In the past decade, there has been an increase in both the total number of suspected ADRs reported in children and the number of reports with a fatal outcome.

Conclusions: A wide range of suspected ADRs are associated with fatalities in children. Anticonvulsants were associated with the greatest number of reports of fatalities and hepatotoxicity in particular.

The toxicity of medicines in children is clearly different from that in adults.¹ This is caused by a combination of factors, including differences in pharmacokinetics and pharmacodynamics, organ development, growth, and the development of puberty through childhood. There are numerous medicines where children have been shown to be more sensitive to particular toxic effects, for example, the grey baby syndrome caused by impaired metabolism of chloramphenicol,² the association between aspirin and Reye's syndrome,³ liver toxicity caused by sodium valproate,⁴ metabolic acidosis caused by propofol,⁵ and serious skin reactions with lamotrigine.

The recognition of the effects of chloramphenicol on the newborn infant and thalidomide on the developing fetus led to the setting up of the Yellow Card Scheme (YCS) and subsequently the Medicines Act of 1968 which ensured medicines were tested scientifically before licensing.⁶ The YCS is a voluntary scheme whereby doctors, dentists, coroners, and pharmacists can report suspected adverse drug reactions (ADRs). The YCS also receives reports via pharmaceutical companies under statutory obligation. It is important to note that reports received are of *suspected* ADRs and in many cases, ascribing causality is difficult or impossible. However, individuals are encouraged to report even if they are uncertain about the causal association.

In order to try to determine the nature of drug related mortality in children, we have retrospectively reviewed all suspected ADRs with a fatal outcome reported via the YCS to the Medicines Control Agency (MCA), to try to draw lessons regarding the safety of medicines used in children.

METHODS

The Adverse Drug Reactions On-line Information Tracking (ADROIT) database is the MCA's national database for ADRs. It contains details of reports of suspected ADRs that have been reported to the MCA since 1964 via the YCS.

The ADROIT database was searched for reports received by the MCA for children aged 16 years or less where the outcome of the suspected reaction to a drug was fatal. The database was searched from 1964 until December 2000. Reports associated with vaccines or overdose were excluded from the analysis. For each report the data retrieved included, where available: date of report and reaction; report number; sex, age, and weight of patient; suspected drug name and dose; duration of therapy; indication for suspected drug; suspected reaction; outcome of the reaction; certified cause of death; other drugs taken by the patient; and other medical history.

Each report was then assigned a report number in chronological order based on the lists prepared by the MCA. The group of drugs to which the suspected drug belonged was added to each report. The reports were then grouped according to the type of drug reported as associated with the suspected reaction. Groups that were suspected of causing a number of deaths were looked at more closely to identify any trends within the reports.

Where the suspected ADR listed as causing death was the same as the disease being treated, we listed death as being either a result of the underlying disease or as a sudden unexplained death. The possible causal association between drug exposure and the suspected ADR was not formally assessed in this study. However, the authors have reviewed the case details and have recorded the ADR they considered most likely to be associated with death. The age distribution of the patients for whom reports had been received was determined. The distribution of the number of reports received over time was also investigated.

Abbreviations: ADR, adverse drug reaction; ADROIT, Adverse Drug Reactions On-line Information Tracking; MCA, Medicines Control Agency; NSAID, non-steroidal anti-inflammatory drug; YCS, Yellow Card Scheme

Table 1 Groups of drugs associated with fatalities

Class of suspected drug	Number of times suspected
Anticonvulsants	78
Cytotoxics	42
Antibiotics	31
Anaesthetics (intravenous)	20
Anaesthetics (inhaled)	17
Corticosteroids	14
Cardiovascular	13
Lung surfactants	13
β_2 agonists	12
NSAIDs	12
Immunosuppressants	8
Muscle relaxants	10
Other bronchodilators	10
Immunosuppressants	8
Antihistamines	7
Nasal decongestants/cough medicines	6
Growth hormone	6
Intravenous nutrition	6
Antivirals	6
Insulin	5
Miscellaneous	74
Total	390

RESULTS

There were 390 deaths with 389 suspected drugs. The median age of children for whom reports were received was 5 years, with the greatest number of reports for infants in the first year of life.

A wide range of drugs were reported as being associated with children's deaths; table 1 outlines the classes of drugs. The number of reported deaths has increased, with at least 10 deaths each year in the past decade (table 2). There has, however, been an increase in the total number of yellow cards received for children, with little change in the proportion of yellow cards associated with fatalities over the past 25 years (0.37–1.00%) Table 3 shows the wide variety of suspected ADRs. Table 4 shows the 10 drugs most frequently associated with fatalities.

Anticonvulsants

Sixty five reports involved at least one anticonvulsant. More than one anticonvulsant was suspected in 10 cases, and the total number of anticonvulsants suspected was 78. Table 5 gives details of the anticonvulsants associated with fatalities. Valproate was associated with 31 cases. In five of the seven

Table 2 Number of suspected ADRs with a fatal outcome in children reported to the CSM/MCA (excluding vaccines and overdoses)

Years	Number with fatal outcome	Total number of yellow cards for children	%
1964–65	4	45	8.9
1966–70	20	350	5.7
1971–75	25	859	2.9
1976–80	39	3742	1.0
1981–85	47	4620	1.0
1986–90	45	5942	0.76
1991–95	83	9580	0.87
1996–2000	68	18617	0.37
Total	331	43755	0.76

Table 3 Suspected ADRs associated with a fatal outcome

ADR	No.
Hepatic failure	50
Bone marrow suppression	21
Sudden unexplained death	18
Respiratory failure	16
Asthma disease	15
Pulmonary haemorrhage	13
Cardiac arrest	13
Cardiac failure	11
Sudden infant death syndrome	10
Shock/collapse	9
Arrhythmia	9
Anaphylaxis	9
Gastrointestinal perforation	9
Stevens-Johnson syndrome/epidermal necrolysis	7
Hepatorenal syndrome	6
Epilepsy disease	7
CVA	6
Cardiomyopathy	8
Pneumonia	7
Cerebral oedema	5
Adrenal insufficiency	5
Reye's syndrome	5
Renal failure	6
Pulmonary embolus	4
Metabolic acidosis	2
Fat embolus	4
Disseminated intravascular coagulation	4
Neoplasm	6
Cardiorespiratory failure	7
Malignant hyperthermia	5
Sepsis	4
Encephalopathy	3
Pulmonary oedema	3
Pulmonary hypertension	2
Paralysis	2
Hypoglycaemia	2
Suicide	2
Miscellaneous	16
Total	331

cases where the underlying disease of epilepsy contributed to the death of that child, the suspected drug included at least one anticonvulsant. Newer anticonvulsants—vigabatrin, lamotrigine, topiramate, and gabapentin—were associated with 20 of the 65 deaths (31%).

Cytotoxics

A cytotoxic drug was associated with a fatal outcome in 34 children. More than one cytotoxic was reported in five cases, and the total number of cytotoxics suspected was 42.

Table 4 Fatalities and individual drugs

Drug	No. deaths
Valproate	31
Doxorubicin	13
Propofol	13
Carbamazepine	11
Halothane	12
Dactinomycin	9
Vigabatrin	8
Lamotrigine	7
Beractant	7
Vincristine	7
Total	118

The first report of a death from a cytotoxic was in 1972. Doxorubicin was suspected in 13 cases and was reported to cause either cardiomyopathy or cardiac failure in 11 cases. The majority of these reports were in the 1970s and 1980s.

Dactinomycin was suspected in nine reports, and in eight of these was reported as causing a hepatic reaction such as failure, necrosis, or veno-occlusive liver disease. A cytotoxic vinca alkaloid was administered intrathecally in two cases, and in each of these paralytic was reported.

Antibiotics

Twenty nine reports involved at least one antibiotic, with 31 antibiotics in total. There were 17 different antibiotics associated with a fatal outcome; the five which were reported the most number of times were co-trimoxazole (n = 6), amoxicillin (n = 3), erythromycin (n = 3), chloramphenicol (n = 3) and ceftazidime (n = 3). The remaining 11 antibiotics were suspected two times or less. The most common ADRs were agranulocytosis (n = 4), aplastic anaemia (n = 4), and renal failure. Reports for antibiotics have been received since 1965, with the most recent in 2000.

Anaesthetics

There were 18 deaths reported in association with the use of intravenous anaesthetics alone, 10 with the use of inhaled anaesthetics alone, and two where both intravenous and inhaled anaesthetics were suspected. There were 13 deaths in association with the use of propofol; 12 of these were in relation to its use as a sedative agent. Ten cases involved the use of propofol as a sedative between 1988 and 1993. Hyperlipidaemia, hepatomegaly, metabolic acidosis, and multi-organ failure have been described in five of these cases.^{5,7} The remaining three cases occurred between 1995 and 1999. Only one of these involved the use of propofol as an anaesthetic agent; the reported reaction was bronchospasm and chest wall rigidity. One case occurred in 1999 following the use of propofol as a sedative and the development of metabolic acidosis.

Corticosteroids

Corticosteroids were associated with fatalities in 13 cases (see table 6). The first of these deaths was reported in 1965. No details were available regarding the length of time over which

Table 6 Fatalities associated with corticosteroids

Fatality	No.
Adrenal insufficiency	4 (1 case inhaled fluticasone)
Pneumonia	3 (1 case inhaled budesonide)
Asthma	3
Chickenpox	2
Arrhythmia	1 (halothane anaesthesia)

the corticosteroids had been taken. In three cases, the underlying disease (asthma) appears to be the cause of the death. In two cases inhaled corticosteroids were involved (budesonide and fluticasone). In one case the child also received halothane anaesthesia.

Lung surfactants

There were 13 reports of a fatality in association with a lung surfactant between 1992 and 1995. Respiratory tract haemorrhage was reported for all but one of the babies, and in that remaining baby, cerebral haemorrhage was reported. There were six reports for Exosurf, a protein free synthetic surfactant, and seven for Survanta, which is a bovine lung extract.

Non-steroidal anti-inflammatory drugs (NSAIDs)

There were 12 fatalities in association with the use of an NSAID (table 7). All reports for NSAIDs have occurred since 1990. There were four cases of Reye's syndrome where aspirin was the suspected drug. These children were 12–14 years old and it was not known whether the aspirin had been prescribed by a doctor or was self administered. One young child received ibuprofen and developed cerebral oedema, which may have been caused by Reye's syndrome. Gastrointestinal perforation occurred in four patients and ibuprofen was suspected in two of these cases.

DISCUSSION

There is increasing interest in the safety of medicines used in children.⁸ There have been numerous studies of ADR surveillance of children in hospital, and a systematic review found that approximately 9% of children experience ADRs while in hospital.⁹ No previous studies have looked at fatalities in association with ADRs in children.

Table 5 Fatalities associated with anticonvulsants

ADR	n	Drugs associated
Hepatic failure	30	Valproate 21, vigabatrin 2, lamotrigine, phenobarbitone, primadone, polypharmacy 4 (carbamazepine 4, valproate 2, lamotrigine, vigabatrin)
Epilepsy	5	Gabapentin, lorazepam, trimethadione, polypharmacy 2 (topiramate 2, diazepam, lamotrigine, phenytoin, vigabatrin)
Bone marrow suppression	5	Carbamazepine 2, ethosuximide, polypharmacy (carbamazepine, valproate, topiramate, pheneturide, phenobarbitone, primadone)
Hepatic and renal failure	4	Carbamazepine, valproate, topiramate, polypharmacy (lamotrigine, paraldehyde)
Unexplained	8	Vigabatrin 3, topiramate 2, carbamazepine, lamotrigine, valproate
Stevens-Johnson syndrome	2	Phenytoin 2
Respiratory arrest	1	Diazepam 1
Sepsis	1	Lamotrigine
Disseminated intravascular coagulation	2	Lamotrigine, valproate
Cerebral tumour	1	Polypharmacy (carbamazepine, topiramate)
Pancreatitis	1	Valproate
Gastrointestinal haemorrhage	1	Carbamazepine
Pulmonary oedema	1	Valproate
Abdominal malignancy	1	Valproate
Epidermal necrolysis	1	Valproate
Withdrawal seizure	1	Vigabatrin
Total	65	

Table 7 Fatalities associated with NSAIDs

ADR	n	Drug	Ages (y)
Reye's syndrome	4	Aspirin	12–14
Gastrointestinal perforation	1	Mefenamic acid	15
	1	Diclofenac	15
	1	Ibuprofen	2
	1	Ibuprofen	Neonate
Cerebral oedema	1	Ibuprofen	1
Haemorrhage (gastrointestinal and cerebral)	1	Indomethacin	Neonate
	1	Aspirin	13
Neutropenia	1	Naproxen	13

This study of fatalities associated with suspected ADRs in children has utilised the YCS which, while it has a proven track record in detecting signals of drug safety,¹⁰ cannot reliably be used to assess causality. Details that may explain the deaths, such as the nature of the underlying disease or co-administered drugs, may be lacking from the report. Thus the YCS acts largely as an early warning system generating hypotheses of previously unrecognised adverse reactions, as well as identifying increases in the frequencies or severity of previously recognised reactions. It is important to realise that the scheme invites reports of *suspected* ADRs. Limitations of the YCS include under reporting of reactions, lack of a denominator (that is, exposure to medicines), reporting rates being affected by factors such as time that the drug has been on the market, any media attention, and the variable quality of the data received.

The broad range of suspected ADRs associated with fatalities described in this paper shows that paediatric patients of all ages are prone to ADRs that are traditionally thought of as being restricted to adults. A wide range of medicines may be responsible for the ADRs. We believe that the 331 deaths reported as associated with suspected ADRs is likely to be an underestimate, as it is well recognised that ADRs are significantly under reported. Our study has not looked at evaluating the benefit of medicines, but for all the medicines studied the overall benefit to children is likely to be far greater than the risk. The evaluation of drug toxicity in paediatric patients is essential in order to improve the clinical use of medicines in a section of the population, where scientific information is limited.¹¹

The group of drugs most likely to be associated with a suspected ADR associated with death was anticonvulsants. Even if we exclude the seven cases where the fatality was thought to be associated with a seizure that failed to respond to treatment, there were still a significant number of deaths associated with anticonvulsants. The association between sodium valproate and hepatotoxicity is well recognised.⁴ However, the possibility of an underlying metabolic disease being responsible for some of the deaths needs to be considered, as this has been previously reported.¹² Guidelines for reducing the risk of sodium valproate hepatotoxicity were first described in 1987.⁴ These guidelines suggested either completely avoiding the use of sodium valproate or only using it with caution in children aged 2 and under, those with developmental delay, and those taking other anticonvulsants. It is not known how many of the children had developmental delay, but we note that since 1987 there have been four children aged 2 years or under who died following a suspected ADR of hepatotoxicity. Almost one third of the fatalities reported in children with epilepsy were associated with the newer anticonvulsants. Prospective stud-

ies are required to evaluate the risk to children of both the new anticonvulsants and older anticonvulsants such as sodium valproate.

The association between propofol and metabolic acidosis was first described in the UK in 1992.⁵ The propofol infusion syndrome was described in detail in 1998.¹³ Despite warnings from the Committee on Safety of Medicines⁷ and the manufacturer, doctors involved in the care of critically ill children are still continuing to use propofol as a sedative. As recently as 1999 our study found two reported fatalities. We are concerned that doctors may not have taken the advice given.

There is increasing recognition that pain is inadequately treated in children. NSAIDs are useful in the management of pain. Increasing use of NSAIDs may, however, be associated with an increased risk of toxicity. Gastrointestinal perforation in association with NSAIDs is well recognised in adults, but often not considered in children. There were, however, four deaths in children aged 9 days to 15 years following gastrointestinal perforation. The association between salicylates and Reye's syndrome is well established. In the UK, aspirin is now contraindicated in children under the age of 12 years. A review of Reye's syndrome in the USA shows a significant number of cases involving children between the ages of 12 and 15 years.¹⁴ The four deaths included in this report in children aged 12–14 years following the development of Reye's syndrome in association with aspirin, in combination with two cases recently described,¹⁵ support the recent recommendation that salicylates should be avoided in children under the age of 16 years with a febrile illness.¹⁶

Inhaled corticosteroids have played a significant role in the management of asthma, and it is important to recognise that the vast majority of children do not experience ADRs. A recently published report described symptomatic adrenal insufficiency in association with the use of inhaled corticosteroids.¹⁷ The two fatalities reported in our study in association with the use of inhaled corticosteroids involved recognised complications of systemic corticosteroids—that is, adrenal insufficiency and sepsis.

Surfactant replacement therapy for the treatment of hyaline membrane disease in the neonatal period has been a major advance in the care of newborn infants and has saved many lives.¹⁸ Pulmonary haemorrhage is a recognised ADR associated with surfactant therapy.¹⁹ The relative risk of pulmonary haemorrhage, however, is small in comparison with the documented benefits of surfactant therapy.

Health professionals need to be aware of the risk of ADRs in children. Initiatives such as the establishment of a Paediatric Regional Monitoring Centre in Trent have shown that increased awareness of the risk of ADRs can be achieved.²⁰

Prospective studies are the only way to determine the risk benefits of medicines and the true incidence of ADRs.^{21, 22} A prospective study of 122 instances where diazepam was used for children with acute seizures in a children's emergency department identified 11 cases of respiratory depression.²² Studies are required to assess the risk–benefit of medicines, and the pharmaceutical industry, drug regulatory authorities, and the Department of Health need to work with paediatricians and paediatric clinical pharmacists to ensure that such data are collected. The American Paediatric Pharmacology Research Unit Network has shown that such studies can be carried out,²³ and we believe there is a clear need for a similar network in the UK. Prospective studies of the risk–benefit of new anticonvulsants in children with epilepsy, and NSAIDs for pain and pyrexia, are needed to ensure that children receive optimal therapy.

Doctors need to be more aware of guidelines which recommend avoiding medicines in certain high risk groups. The use of propofol in the critically ill child and sodium valproate in young children under the age of 3 years, with developmental delay or polypharmacy, are examples where we hope further deaths might be avoided. An evidence based approach to drug therapy in children²⁴ is needed to minimise drug toxicity, which at worst could lead to death. Following guidelines and a greater awareness of the toxicity of certain medicines in specific age groups or situations is likely to minimise fatalities in children.

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COMMENTARY

When we decided to publish Clarkson and Choonara's paper we realised that the media might misinterpret their findings, whether unwittingly or mischievously. Consequently children and their families might reasonably be alarmed or unreasonably misled. They might even stop taking their prescribed medicine if it was one mentioned as associated with an adverse reaction. We had seen, and deplored, damage done to the public health by poorly informed publicity over alleged risks of MMR vaccine after the *Lancet* published a contentious paper.¹

We worked closely with the authors to make sure the language used was unambiguous and the conclusions borne out by the data. Nevertheless we and they realise that some doctors find it difficult enough to distinguish between a statistical association and cause-and-effect—so surely news journalists are even less likely to spot the difference.

Clarkson and Choonara provide numerous caveats. They are careful to point out that they did not “formally assess” causality, predominantly because the source of their data—the Yellow Card Scheme of the UK Committee on Safety of Medicines—was not designed for this purpose. They point out that the adverse drug reactions they identify are suspected rather than proven. They state that for all of the drugs listed, benefits are likely to be far greater than risks.

We hope that responsible journalists who decide to report on the study bear these comments in mind before deciding on the message they wish to convey. For example, we hope they will not read too much into two infants dying suddenly, who happened to be taking an antibiotic at the time and whose doctors thought this worth reporting; the odds are they were also consuming proprietary brands of baby food and their parents may have owned a mobile phone. We hope no parent of a child with epilepsy will be provoked by inaccurate news reports into stopping treatment.

But we also hope that paediatricians will learn from the prime message of this paper, namely that they should make themselves aware of guidelines which recommend avoiding certain medications in high risk groups. The authors single out propofol in the critically ill and valproate in those under 3 with developmental delay or being treated with more than one anticonvulsant. We echo their call for more risk-benefit analyses of medicines used by children, particularly newer anticonvulsants.

Above all we hope that UK based colleagues will respond with their usual diligence to the current British Paediatric Surveillance Unit enquiry into suspected adverse drug reactions in children, funded by The Medicines Control Agency, UK. The Yellow Card scheme is too blunt an instrument to tell us anything useful about causation or about balancing risks and benefits.

Harvey Marcovitch

Editor, ADC

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IMAGES IN PAEDIATRICS.....

Infant oxygen chair (Oxychair)



Inspired by Dr P Davies' presentation at this year's Royal College Spring Meeting,¹ I offer the following plan for the provision of oxygen for infants (up to 13 kg). The design is essentially a low cost update on the Derbyshire children's chair useful in the management of infants with cardiorespiratory disorders who may with advantage be nursed in the sitting position. Required is a Kangol infant car safety seat which is no longer in production, but can easily be found from a variety of sources (cost £10–20); this design has a better carrying handle for the purpose of supporting a Mothercare weathershield costing £8. The oxygen supply is best provided by making a number of perforations in the terminal 10 cm of the tubing rather than relying on the single end opening. Oxygen concentrations from 30% to 50% are achievable with oxygen flow rates between 2 and 15 l/min. As this device is not a piece of medical equipment use would be at user's risk, but we have successfully nursed infants with bronchiolitis and similar disorders in our unit with this chair. Many infants will have had previous experience of this device (without oxygen)!

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