Identification of suspected fatal adverse drug reactions by paediatricians: a UK surveillance study

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ABSTRACT

This British Paediatric Surveillance Unit study on adverse drug reactions (ADRs) in children was initiated because of concern that there might be under-reporting of serious ADRs in children using the Yellow Card scheme. We aimed to quantify the frequency of fatal ADRs in children below the age of 16 years in the United Kingdom (UK) and Ireland.

The surveillance period ran for 13 months from June 2002 to June 2003 inclusive and approximately 2000 cards were sent out monthly by the BPSU to consultant paediatricians in the UK and Eire. In total, seven reports meeting the study criteria were received.

Causality assessment was undertaken by an independent expert panel using formal, published criteria. In two of the deaths, the panel did not reach consensus and causality assessments varied from possible to certain. Five of the seven deaths were unanimously thought to be unlikely to be causally related to the index drug.

Overall this study does not provide evidence of a major public health concern relating to fatal ADRs in children. However the limitations of the study mean that some fatal ADRs may have been unrecognised or unreported.
"What is already known on this topic?"

- Extensive off-label prescribing of medicines in children increases the need for detection of suspected adverse drug reactions
- When relying on spontaneous reporting systems, there is well-established under-reporting of adverse drug reactions in adults
- We are not aware of any studies that have documented the extent of fatalities following adverse drug reactions in children

“What this study adds?”

- We used an active surveillance scheme to quantify the frequency of fatal adverse drug reactions in children below the age of 16 years in the United Kingdom and Ireland.
- The frequency of fatal adverse drug reactions in children appears to be low (two detected by this surveillance over a 13 month period)
- This study does not provide evidence of a major public health concern relating to fatal adverse drug reactions in children
BACKGROUND

Many drugs are prescribed for children outside their licence (‘off-label’) [1],[2],[3] including drugs not licensed for a certain age-group, for a particular route, or for a specific disease. The UK spontaneous reporting system, the Yellow Card scheme, is a key source of pharmacovigilance data, receiving reports from doctors, dentists, coroners, pharmacists and nurses. However, spontaneous reporting under-reports ADRs [4]. Under-reporting may be compounded by fears of litigation following unlicensed prescribing, and ADRs may be increased with unlicensed drugs [5].

We are not aware of any studies of the extent of fatalities following ADRs in UK children. A meta-analysis of 39 studies in US hospitals estimated 2,216,000 patients, predominantly adults, experienced a serious ADR during 1994 and 106,000 died [6]. Risk of fatality increased with number of drug exposures and increasing age and length of hospital stay, all suggesting lower risk in children. Of more than 500,000 adverse event reports to the FDA (including from the public) from 1997 to 2000, 7111 were in children under two years including 243 deaths annually associated with drug therapy. Of these, on average, 204 were under one year including 100 in neonates [7]. 24% of all adverse events were associated with maternal drug therapy in pregnancy or lactation and when excluded, only 17 drugs or biological products were suspected in 54% of all serious and fatal adverse events. These included two prophylactics against respiratory syncytial virus, six antibiotics, and two analgesics. The limitation of this study was that no causality assessment was undertaken.

The British Paediatric Surveillance Unit (BPSU) operates an active surveillance mechanism (the ‘orange card’ scheme), mailing monthly all consultant paediatricians in the UK and Ireland who are members of the Royal College of Paediatrics and Child Health. 92% of cards sent out were returned during the period of surveillance [8]. This paper reports a one-year BPSU study of fatal ADRs in children.

METHODS

Surveillance was from June 2002 to June 2003. Approximately 2000 orange cards are sent out monthly.

Case definition = suspected fatal adverse drug reaction in a child under 16 years in the previous month.

The Medicines and Healthcare products Regulatory Agency (MHRA) obtained anonymised case details through a questionnaire sent to the reporter. There was no contact with the family or any other health professional. Causality assessments were undertaken independently by an expert panel, including specialists in paediatric pathology, paediatric pharmacy, neonatology, paediatrics and pharmacovigilance.

ADR was defined as ‘an appreciably harmful or unpleasant reaction resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product.’. Causality was classified as certain, probable/likely, possible, unlikely conditional/unclassified or
unassessable/unclassifiable[9] based on temporal relationship; concurrent disease or other drugs; and the results of dechallenge/rechallenge (if available).

**Ethical approval was granted by the Multicentre Research Ethics Committee for London.**

**RESULTS**

From 1 June 2002 to 30 June 2003, 16 suspected fatal ADRs in children < 16 years were notified. Of these 16, two cases were each reported by three different reporters and one case was reported twice by the same reporter. In two cases, the reporter subsequently denied the report and one was outside the time frame. One questionnaire was not returned, despite repeated requests. Therefore, seven reports met the study criteria.

**Case 1**
An ex-preterm infant started persistent crying three hours after thyroxine 7.5 micrograms for congenital hypothyroidism (dose 5 micrograms/kg, consistent with Medicines for Children[10]). Progressive bradycardia developed five hours after thyroxine followed by cardiac arrest. Post-mortem showed bronchopneumonia.

*Panel discussion*
There was a reasonable timeframe for absorption but not for pharmacological action of thyroxine. Thyroxine causes tachycardia but bradycardia may have been the terminal event. Pneumonia was not consistent with a thyroxine ADR. All panel members independently assessed causality as unlikely.

**Case 2**
A teenager with repaired congenital heart disease developed liver failure 22 days after starting enalapril 5mg for heart failure. The patient died six days later. Post-mortem liver biopsy showed severe acute damage without evidence of chronic liver disease. The reported differential diagnosis included acute viral hepatitis and toxic/drug related injury.

*Panel discussion*
Enalapril is not licensed for use in children and hepatic failure is a recognised ADR [11]. The liver biopsy demonstrated eosinophils suggesting drug-related damage. An onset time of 1–8 weeks has previously been reported for acute hepatitis associated with captopril [12]. Two members assessed causality as possible, two as probable and one as certain.

**Case 3**
An ex-preterm infant developed fatal exacerbation of chronic lung disease three days after immunisation with Prevenar (streptococcal pneumoniae conjugate) vaccine, Meningococcal C vaccine and a study vaccine DT5aP-Hib-IPV (combined diphtheria, tetanus, acellular pertussis, haemophilus-b and inactivated polio).

*Panel discussion*
Apnoea has been reported in preterm infants in the three days following DTP and Hib immunisation, [13] [14]. However, the slow deterioration was more likely due to
pulmonary hypertension. An immunological response would be expected either sooner or later. Prevenar is licensed for use in children > 2 months old. All panel members independently assessed causality as unlikely.

Case 4
A teenager had nasal packing under general anaesthesia [isoflurane, suxamethonium, fentanyl and propofol (all licensed for children)]. One hour postoperatively, following self-extubation, the patient had a cardiorespiratory arrest. Post-mortem liver histology showed acute central zonal necrosis and appearances thought due to isoflurane reaction.

Panel discussion
The panel considered the arrest due to upper airway obstruction, not isofluorane. Liver histology showed ischaemic necrosis rather than drug reaction. The patient had not previously undergone anaesthesia. Isoflurane can produce hepatic injury very rarely. All panel members independently assessed causality as unlikely.

Case 5
A primary school child with developmental delay and seizures presented with vomiting and drowsiness four months after starting sodium valproate 280mg twice a day. The child died of acute pancreatitis and liver failure.

Panel discussion
Pancreatitis and hepatic failure are recognised ADRs of sodium valproate [15]. The timing and pharmacological pattern were considered to be plausible and a fatty acid oxidation disorder had been eliminated. One member assessed causality as possible, two as probable and two as certain.

Case 6
A newborn baby arrested 10 hours after zidovudine 4mg/kg (recommended dose 2mg/kg every 6 hours [16]). Her HIV positive mother took zidovudine, lamivudine and nevirapine in pregnancy and then changed to abacavir, lamivudine, zidovudine and co-trimoxazole. The baby died one week later. Muscle biopsy ante-mortem showed normal respiratory chain enzyme activity.

Panel discussion
The clinical picture was not consistent with anaphylaxis. All panel members independently assessed causality as unlikely.

Case 7
A young infant arrested one day after immunisation with diphtheria/tetanus/pertussis, (DTP), Haemophilus b, Meningococcal C and oral Polio vaccines. Six hours previously the infant had developed difficulty in feeding and had been irritable. Post-mortem showed haemophagocytosis in the spleen and bone marrow (responsible for the low haemoglobin 4.5 g/dl). The anaemia had induced cardiac failure.

Panel discussion
The timing and pharmacological pattern in association with the vaccine was not thought to be plausible. All panel members independently assessed causality as unlikely.
DISCUSSION

Seven valid suspected fatal ADR reports were received over 13 months. Five were thought unrelated to the index drug. In two, the independent panel did not reach consensus. Two of these seven cases were also reported to the Yellow Card scheme. During the same period there were an additional 16 reports of ADRs with a fatal outcome in children under 16 years reported through the Yellow Card scheme. These reports were of varying quality and it is not possible to compare these with those received through the BPSU. Over the same 13 month period, in England and Wales, there were 5,458 deaths in children aged under 18 (4,633 excluding accidents, cancer and self-poisoning). The number of death certificates citing adverse drug reactions as a contributing factor was 14 [17]. Again, the anonymous nature of the dataset means that we cannot compare these.

As the response rate to the BPSU scheme is high, approximately 92%, this study may suggests that the true frequency of fatal ADRs in children appears to be low. However, even well-recognised, severe ADR’s are under-reported. e.g. only 4% of known cases of toxic epidermal necrolysis (almost exclusively due to drug exposure) [18]. Furthermore, our study had limitations. Firstly, it is possible that ADRs with a fatal outcome were under-recognised because they tend to occur in sick children receiving multiple drugs. Moreover there may have been a reluctance to report, even in an anonymised way, deaths thought to be due to off-label or unlicensed prescribing, although such prescribing is legal in the UK. Surveillance was restricted to paediatricians. Other schemes extend reporting to other professionals, the lay public and the pharmaceutical industry. This is a possible reason for the significantly higher suspected numbers from the United States [7] where a number of different routes were available for reporting. Although significant children’s prescribing occurs in primary care, most child deaths would come to the attention of hospitals.

Overall this study does not provide evidence of a major public health concern relating to fatal ADRs in children.

ACKNOWLEDGEMENTS

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COMPETING INTERESTS

Dr Cheng and Mr Masters were employed by the Medicines and Healthcare products Regulatory Agency, and Professor Stephenson was a member of the UK Committee on Safety of Medicines when the study was conducted.
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