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. 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, the association between aspirin and Reye’s syndrome, liver toxicity caused by sodium valproate, metabolic acidosis caused by propofol, 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. 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
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 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 1  Groups of drugs associated with fatalities

<table>
<thead>
<tr>
<th>Class of suspected drug</th>
<th>Number of times suspected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticonvulsants</td>
<td>78</td>
</tr>
<tr>
<td>Cytotoxics</td>
<td>42</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>31</td>
</tr>
<tr>
<td>Anaesthetics (intravenous)</td>
<td>20</td>
</tr>
<tr>
<td>Anaesthetics (inhaled)</td>
<td>17</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>14</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>13</td>
</tr>
<tr>
<td>Lung surfactants</td>
<td>13</td>
</tr>
<tr>
<td>β2 agonists</td>
<td>12</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>12</td>
</tr>
<tr>
<td>Immunosuppressants</td>
<td>8</td>
</tr>
<tr>
<td>Muscle relaxants</td>
<td>10</td>
</tr>
<tr>
<td>Other bronchodilators</td>
<td>10</td>
</tr>
<tr>
<td>Immunosuppressants</td>
<td>8</td>
</tr>
<tr>
<td>Antihistamines</td>
<td>7</td>
</tr>
<tr>
<td>Nasal decongestants/cough medicines</td>
<td>6</td>
</tr>
<tr>
<td>Growth hormone</td>
<td>6</td>
</tr>
<tr>
<td>Intravenous nutrition</td>
<td>6</td>
</tr>
<tr>
<td>Antivirals</td>
<td>6</td>
</tr>
<tr>
<td>Insulin</td>
<td>5</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>74</td>
</tr>
<tr>
<td>Total</td>
<td>390</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Years</th>
<th>No. with fatal outcome</th>
<th>Total number of yellow cards for children</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1964-65</td>
<td>4</td>
<td>45</td>
<td>8.9</td>
</tr>
<tr>
<td>1966-70</td>
<td>20</td>
<td>350</td>
<td>5.7</td>
</tr>
<tr>
<td>1971-75</td>
<td>25</td>
<td>859</td>
<td>2.9</td>
</tr>
<tr>
<td>1976-80</td>
<td>39</td>
<td>3742</td>
<td>1.0</td>
</tr>
<tr>
<td>1981-85</td>
<td>47</td>
<td>4620</td>
<td>1.0</td>
</tr>
<tr>
<td>1986-90</td>
<td>45</td>
<td>5942</td>
<td>0.76</td>
</tr>
<tr>
<td>1991-95</td>
<td>83</td>
<td>9580</td>
<td>0.87</td>
</tr>
<tr>
<td>1996-2000</td>
<td>68</td>
<td>18617</td>
<td>0.37</td>
</tr>
<tr>
<td>Total</td>
<td>331</td>
<td>43755</td>
<td>0.76</td>
</tr>
</tbody>
</table>

Table 3  Suspected ADRs associated with a fatal outcome

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

Table 4  Fatalities and individual drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>No. deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valproate</td>
<td>31</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>13</td>
</tr>
<tr>
<td>Propofol</td>
<td>13</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>11</td>
</tr>
<tr>
<td>Halothane</td>
<td>12</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>9</td>
</tr>
<tr>
<td>Vigabatrin</td>
<td>8</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>7</td>
</tr>
<tr>
<td>Berastin</td>
<td>7</td>
</tr>
<tr>
<td>Vincristine</td>
<td>7</td>
</tr>
<tr>
<td>Total</td>
<td>118</td>
</tr>
</tbody>
</table>
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.

Daunomycin 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 intrathetically in two cases, and in each of these paralysis 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. 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 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. 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. No previous studies have looked at fatalities in association with ADRs in children.

### Table 6 Fatalities associated with corticosteroids

<table>
<thead>
<tr>
<th>Fatality</th>
<th>No.</th>
<th>Drugs associated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenal insufficiency</td>
<td>4 (1 case inhaled fluticasone)</td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>3 (1 case inhaled budesonide)</td>
<td></td>
</tr>
<tr>
<td>Asthma</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Chickenpox</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>1 (halothane anaesthesia)</td>
<td></td>
</tr>
</tbody>
</table>

### Table 5 Fatalities associated with anticonvulsants

<table>
<thead>
<tr>
<th>ADR</th>
<th>n</th>
<th>Drugs associated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatic failure</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Epilepsy</td>
<td>5</td>
<td>Gabapentin, lorazepam, trimethadione, polypharmacy 2</td>
</tr>
<tr>
<td>Bone marrow suppression</td>
<td>5</td>
<td>Carbamazepine 2, ethosuximide, polypharmacy 2</td>
</tr>
<tr>
<td>Hepatic and renal failure</td>
<td>4</td>
<td>Carbamazepine, valproate, topiramate, polypharmacy 2</td>
</tr>
<tr>
<td>Unexplained</td>
<td>8</td>
<td>Vigabatrin 3, topiramate 2, carbamazepine, lamotrigine, lamotrigine, valproate</td>
</tr>
<tr>
<td>Stevens-Johnson syndrome</td>
<td>2</td>
<td>Phenytoin 2</td>
</tr>
<tr>
<td>Respiratory arrest</td>
<td>1</td>
<td>Diazepam 1</td>
</tr>
<tr>
<td>Sepsis</td>
<td>1</td>
<td>Lamotrigine</td>
</tr>
<tr>
<td>Disseminated intravascular coagulation</td>
<td>2</td>
<td>Lamotrigine, valproate</td>
</tr>
<tr>
<td>Cerebral tumour</td>
<td>1</td>
<td>Polypharmacy (carbamazepine, topiramate)</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>1</td>
<td>Valproate</td>
</tr>
<tr>
<td>Gastrointestinal haemorrhage</td>
<td>1</td>
<td>Carbamazepine</td>
</tr>
<tr>
<td>Pulmonary oedema</td>
<td>1</td>
<td>Valproate</td>
</tr>
<tr>
<td>Abdominal malignancy</td>
<td>1</td>
<td>Valproate</td>
</tr>
<tr>
<td>Epidermal necrolysis</td>
<td>1</td>
<td>Valproate</td>
</tr>
<tr>
<td>Withdrawal seizure</td>
<td>1</td>
<td>Vigabatrin</td>
</tr>
</tbody>
</table>

Total 65
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, 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 1987.7 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 studies 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 1992.1 The propofol infusion syndrome was described in detail in 1998.13 Despite warnings from the Committee on Safety of Medicines1 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 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

### Table 7 Fatalities associated with NSAIDs

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

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8. 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. 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. Guidelines for reducing the risk of sodium valproate hepatotoxicity were first described in 1987. 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 studies are required to evaluate the risk to children of both the new anticonvulsants and older anticonvulsants such as sodium valproate.

9. The association between propofol and metabolic acidosis was first described in the UK in 1992. The propofol infusion syndrome was described in detail in 1998. Despite warnings from the Committee on Safety of Medicines 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.

10. 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. The four deaths included in this report aged 12–14 years following the development of Reye's syndrome in association with aspirin, in combination with two cases recently described, support the recent recommendation that salicylates should be avoided in children under the age of 16 years with a febrile illness.

11. 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. 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.

12. 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. Pulmonary haemorrhage is a recognised ADR associated with surfactant therapy. The relative risk of pulmonary haemorrhage, however, is small in comparison with the documented benefits of surfactant therapy.

13. 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.
Prospective studies are the only way to determine the risk benefits of medicines and the true incidence of ADRs. 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.

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, 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 children 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.

ACKNOWLEDGEMENTS
Sarah Davis, Victoria Newbold, Katharine Cheng, and Peter Arlett from the Medicines Control Agency helped to provide the data and useful comments on the manuscript. IC initiated and designed the study, supervised the collection of data, analysed the data, and was involved in writing the paper. AC collected and analysed the data and was involved in writing the paper. IC is the guarantor for the paper. AC was jointly funded by Trent NHS and the Medicines Control Agency. IC has a grant from Astra Zeneca.

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REFERENCES


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 of difficulties in their source of 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.

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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

REFERENCE

IMAGES IN PAEDIATRICS

Infant oxygen chair (Oxychair)

Inspired by Dr P Davies’ presentation at this year’s Royal College Spring Meeting, 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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Intravenous atropine treatment in infantile hypertrophic pyloric stenosis

Hypertrophic pyloric stenosis (HPS) is a disorder of early infancy with typical clinical features and well-established radiological appearances of the pyloric canal. Many studies in surgical and medical treatment have been reported over the past fifty years. Pyloromyotomy has tended to become the favoured method of treatment as with expert paediatric, surgical, anaesthetic, and nursing services and specialised accommodation for infants, the outcome is good with low mortality, short stay in hospital and few complications. However, a variety of studies of medical treatment with anticholinergic drugs and successful outcomes in some large series of cases have also been reported from Sweden, United States of America and the United Kingdom.

Since 1996 this group of workers from Osaka, Japan, has revived an interest in medical treatment with reports of a new regime using methyl atropine nitrate intravenously. To achieve satisfactory short term outcomes considerable variation in drug dosage and modified feeding regimes were necessary which involved much medical supervision and careful monitoring for toxic effects of the drug, which were minimal. The treatment was successful in the relatively small number of infants in the trial (19) with two infants being referred for pyloromyotomy, no mortality and no serious complications. An interesting part of this paper is the long term clinical follow up of the successfully treated infants over two years and ultrasonography of the pyloric canal which demonstrated the changes in muscle thickness and length of the canal. The disadvantages of the treatment mentioned by the authors are length of stay in hospital and the necessity to continue atropine medication orally after discharge home.

Comparing the use of this anticholinergic drug intravenously with oral treatment using methyl scopolamine nitrate and similar restricted feeding regime, oral methyl scopolamine nitrate suppressed vomiting more quickly and reliably, was also available for subcutaneous injection if vomiting recurred as size of feeds was increased, and no toxic effects were seen in any dosage used. It would be interesting if these workers would be prepared to try the use of methyl scopolamine nitrate intravenously as pharmalogically this compound was reported to have a spasmyloctic effect on gut two to three times greater than methyl atropine nitrate1 with lesser central nervous effects.

This paper serves to emphasise once more that these infants should always be treated in paediatric centres where there is a high level of experienced paediatric care and nurses trained for neonatal special care.

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Author’s reply

We appreciate the interest shown by Dr Beryl Corner with regard to our article.1 Unfortunately, intravenous atropine therapy is not widely accepted in European countries or the United States; it is however now becoming popular in Japan.

We are truly honoured to receive the comments of Dr Corner, who is a pioneering neonatologist and reported medical treatment with methyl scopolamine nitrate for infantile hypertrophic pyloric stenosis (HIPS) in 1955.2 She pointed out that methyl scopolamine might be better than atropine sulphate in terms of effectiveness and side effects. One of the reasons why atropine was used in our study is that methyl scopolamine is not available in our country. Scopolamine butyromide is an available quaternary ammonium derivative of scopolamine and lacks toxic side effects. However, this agent tastes bitter and is difficult to give orally to infants. Therefore, this agent is only given intravenously in infants with HIPS.

We do not know if it is worthwhile to attempt combination therapy with intravenous scopolamine butyromide and oral atropine rather than the intravenous and oral atropine therapy. Secondly, we already knew that an intravenous atropine injection of 0.01 mg/kg was effective enough to abolish transiently the phasic and tonic pyloric contractions characteristics of HIPS.3 We used an intravenous atropine injection of 0.01 mg/kg in our study to confirm that those pyloric contractions were the cause of disturbed transpyloric flow in this condition by seeing that their inhibition with the dose of atropine ameliorated symptoms.

We agree with Dr Corner’s last comment, but believe that intravenous atropine therapy is possible not only in high level paediatric centres, but also in general hospitals where infusion therapy with intravenous atropine injections can be done safely in small infants. Clinical trials are now ongoing to establish more efficient treatment strategy for HIPS with medical and surgical therapy in our country.

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References


Hypothermia in a child secondary to ibuprofen

A 7 year old girl was admitted with right lower lobe pneumonia. On admission her temperature was 39.7°C. After five hours she received ibuprofen (6 mg/kg). Subsequent to this single dose her temperature decreased to 33.5°C (core temperature 34.9°C) over four hours.

On examination her pulse was 90/min, blood pressure 90/50 mm Hg, SaO2 96% in air, and respiratory rate 20/min. Respiratory examination was consistent with signs of right lower lobe consolidation. The rest of the examination, including the central nervous system, was unremarkable.

Results of investigations included: Hb 125 g/l; white blood cell count 10.7 × 10^9/l platelet count 81 × 10^9/l; C reactive protein 180 mg/l; blood glucose 4.6 mmol/l. Electrolytes and all other biochemical investigations were normal. Thyroid and cortisol assays were normal. Results of all tests to determine possible bacterial or viral aetiology were all negative (blood and urine culture, viral serology, and tests for mycoplasma). Magnetic resonance imaging (MRI) of the brain was normal.

The hypothermia was so marked that we had to use a hot air spacer blanket to raise her temperature. Despite all the efforts she remained persistently hypothermic for four days (see fig 1).
A single dose of hydrocortisone and an albumin infusion were given initially. She was subsequently treated with warmed intravenous fluids for three days and antibiotics for 10 days. She recovered completely and continued to enjoy good health.

Sleeping position and sudden infant death syndrome is extremely rare in children aged 5 years or over. Results of investigations excluded infective and endocrine causes. A normal MRA brain scan showed there was no lesion of the hypothalamus or corpus callosum.

Ibuprofen is commonly prescribed for a raised temperature and is well tolerated in children. Side effects are not common, even in overdose, and we postulate that ibuprofen was responsible for hypothermia in this case. We are not aware of any published evidence documenting hypothermia after a single therapeutic dose of ibuprofen, but it has been recorded in a few cases of accidental and deliberate overdose. Although patients may sometimes receive ibuprofen in toxic quantities, hypothermia is not a consistent feature. 1 Hypothermia in overdose is attributed to central nervous system depression. 4

References

Vagal overactivity: a risk factor of sudden infant death syndrome?

Since early 1990, the incidence of sudden infant death syndrome (SIDS) has dropped sharply because of public health campaigns decrying the dangers of the prone sleep position. The other known risk factors for SIDS have not changed much, although public health campaigns against the prone sleep position have sharply decreased the incidence of sudden infant death syndrome (SIDS) since early 1990. Since early 1990, the incidence of sudden infant death syndrome (SIDS) has dropped sharply because of public health campaigns decrying the dangers of the prone sleep position. The other known risk factors for SIDS have not changed much, although public health campaigns against the prone sleep position have sharply decreased the incidence of sudden infant death syndrome (SIDS) since early 1990.

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References
Glucose metabolism in sleep disordered breathing

An association between sleep disordered breathing (SDB) and impaired glucose tolerance has been reported in adults. Although SDB has been reported in diabetic children, no data are available on glucose metabolism in children with SDB. We used glycated haemoglobin (HbA1c) for the preliminary assessment of glucose metabolism in paediatric SDB patients.

HbA1c was measured in 12 children aged 26–116 months (mean 63) with suspected SDB owing to adenotonsillar hypertrophy. Informed consent was obtained from the guardians of each patient, and consent was obtained from the child if older than 5 years of age. Overnight polysomnographic studies were performed once for each patient by the standard method described elsewhere. The desaturation time (percentage of total sleep time with oxygen saturation <90%), minimum oxygen saturation level, and apnoea-hypopnoea index (AHI) were calculated. Complete blood count, blood gases, and blood chemistry (glucose, total protein, albumin, urea nitrogen, creatinine, uric acid, sodium, chloride, potassium, calcium, phosphate, lactate dehydrogenase, glutamic oxaloacetic transaminase, glutamic pyruvic transaminase, γ-glutamyl transpeptidase, alkaline phosphatase, total bilirubin, total cholesterol, and triglyceride) were also determined. The patients had no respiratory failure, heart failure, or coma. None of their weights exceeded 120% of their ideal weight for their heights. Desaturation time clearly divided the patients into two groups: six patients whose desaturation time was 0 or 0.1 (mild SDB group); and six whose desaturation time exceeded 4.0 (severe SDB group). The average HbA1c value for the severe SDB group (3.0, SE 0.07) was significantly higher than that for the mild SDB group (4.6, SE 0.10) (p = 0.01), although the actual HbA1c values were all within normal range. No other items showed significant differences between the two groups.

The severity of respiratory disturbances during sleep in diabetic children has been known to correlate with the duration of diabetes and with the HbA1c value. Recently, SDB parameters were found to be associated with worsening insulin resistance independent of obesity in adults. The current study shows that serum HbA1c is increased in association with the degree of desaturation in non-obese paediatric SDB patients; HbA1c levels should, however, be monitored after treatment. SDB and glucose metabolism are hypothesized to be closely associated in children as well as adults.

Short versus standard duration antibiotic treatment for UTIs: a comparison of two meta-analyses

Having recently published a meta-analysis on the same clinical question, it was with great interest that we read Michael et al’s systematic review of short versus standard duration antibiotic therapy for urinary tract infections (UTIs) in children. Given the publication (in close succession) of two meta-analyses on the same question with (on the surface) strikingly different results, we thought a comment was in order.

First, we applaud the authors on their methodologically sound review. The literature search was explicitly described and exhaustive. In fact, the authors identified a few studies that we had missed. “The study outcomes for meta-analysis (frequency of positive urine cultures at 0–7 days after treatment and at 10 days to 15 months after treatment, and development of resistant organisms and reinfection UTIs) were relevant and clearly defined.” The authors provided appropriate and important meta-analysis measures including summary relative risks (RRs) and a quasi-NNT calculation with varying risk of treatment failure in the standard treatment group and confidence intervals corresponding to “best” and “worst” case scenarios.

For their primary outcome, frequency of positive urine cultures 0–7 days after treatment, the authors found no significant difference between short course (3 days) and standard (7–14 days) treatment (RR 1.06; 95% CI 0.64 to 1.76). This is in contrast to our finding of a 94% increased pooled risk of treatment failure with short course treatment (0–3 days) compared to standard treatment (7–14 days) (RR 1.94, 95% CI 1.19 to 3.15; NNT=15, 95% CI 100 to 7). Why the discrepancy? We postulate a few possible explanations and conclude that the two meta-analyses, on closer inspection, actually have very similar results.

Our omission of certain studies identified by Michael and colleagues may have biased our results. However, of the three studies that we missed and that they included in their analysis of treatment failure at 0–7 days after completion of treatment, two favoured standard duration treatment, which would have supported our pooled RR result. Another possible explanation for the divergence was the use of different definitions of treatment failure. For our definition of treatment failure we pooled persistent infection and treatment failure to eradicate the organism (0–7 days after initiation of treatment) and relapse (recurrence of symptoms and reinfection within 2 weeks of cessation of treatment after initial bacteriological cure), whereas Michael et al used frequency of positive cultures 0–7 days after cessation of treatment as their primary outcome measure of treatment failure. If reinfections later than 7 days after cessation of treatment occurred more often in recipients of short course treatments, then Michael et al’s definition of treatment failure could have failed to capture the therapeutic advantage of standard duration treatment.

However, the most likely explanation for the divergent results was the different ways in which the study question was framed and the resulting differences in studies included in the meta-analyses. We compared 3 days of treatment to 7–14 days of treatment, whereas Michael et al compared 2–4 days of treatment to 7–14 days of treatment and excluded 13 studies comparing single-dose or single-day treatment to standard duration treatment.

The reasons for this exclusion are unclear, although we presume that they felt single-dose or single-day treatment was not a fair comparison with 7–14 day treatment. However, a number of randomised controlled trials (RCTs) made this comparison, suggesting that clinicians are, in fact, interested in the potential efficacy (and significantly increased case of short course treatment) of single-dose or single-day treatment. Inclusion of these studies in our analysis strongly influenced the pooled risk of treatment failure. Using short-course with single-dose treatment was included in the meta-analyses. When we excluded these studies in a sub-group analysis of 3-day versus long course (7–14 day) treatment, the risk of treatment failure fell to 1.36 (95% CI 0.68 to 2.72) (NNT=50; 95% CI 33 - 13).

Thus, our meta-analysis demonstrates clearly that single dose or single day antibiotic treatment is not as effective as long-course treatment for UTIs in children. The two meta-analyses together suggest that: (1) “longer” short-course therapies may be as effective as 7–14 days of antibiotics and
(2) there is probably a duration of treatment threshold for “short-course” antibiotic treatment, above which longer duration of treatment confers no therapeutic advantage.

Michael and colleagues suggest that as little as 2 days of treatment may be sufficient. However, only one of the trials in their meta-analysis studied 2-day treatment and that one favoured long-course treatment with a RR of UTI 0–7 days after completing short course treatment of 2.17 (95% CI 0.48 to 9.76). The duration of treatment threshold may be 3 days, but the point estimate of relative risk of treatment failure with 3 day treatment in our meta-analysis suggests otherwise. If the duration of short-course treatment for which there is no difference in efficacy compared with standard treatment is actually greater than 3 days, then the added convenience and cost-savings of “short-course” treatment become marginal. In the absence of appropriately powered RCTs (or meta-analyses) examining outcomes (treatment failure, re-infection, emergence of resistant organisms and cost) with “longer” short course treatment regimens (3, 4, and 5 days), we think that clinicians should continue to treat UTIs in children with at least 7 days of antibiotic therapy.

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References

Table 1 Results of three systematic reviews of randomised controlled trials comparing short duration with standard duration of antibiotic treatment for lower tract urinary tract infection.

<table>
<thead>
<tr>
<th>Systematic review</th>
<th>Comparison of duration of therapy</th>
<th>Number of data sets</th>
<th>Risk for persistent bacteriuria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tran et al. 2001†</td>
<td>1–4 days v &gt;5 days</td>
<td>13</td>
<td>RD: 4.26 (95% CI: 0.95, 9.48)</td>
</tr>
<tr>
<td>Keren &amp; Chan, 2002‡</td>
<td>3 days v &gt;7–14 days</td>
<td>5</td>
<td>RR: 1.36 (95% CI: 0.68, 2.72)</td>
</tr>
<tr>
<td>Michael et al. 2002 à</td>
<td>2–4 days v &gt;7–14 days</td>
<td>8</td>
<td>RR: 1.06 (95% CI: 0.64, 1.76)</td>
</tr>
</tbody>
</table>

*RD, risk difference; †, CI, confidence intervals; ‡, RR, relative risk

Authors’ reply
In response to Keren and Chan’s thoughtful letter regarding our recent systematic review, we need to emphasise that the study question we addressed was different from that addressed by Keren and Chan in their own systematic review of randomised controlled trials comparing short with standard duration treatment in the treatment of children with urinary tract infection (UTI). The aim of our study was to determine the relative efficacy of short (2–4 days) and standard duration (7–14 days) treatment with the hypothesis that short duration may be as effective as standard duration treatment and provide potential advantages such as improved compliance. Therefore, we did not include trials in which single dose treatment was compared with standard duration treatment. In addition we chose to limit the review to trials in which the same antibiotic was used to treat each group, to avoid confounding.

The response to single dose treatment appears different from short course, suggesting that it is inappropriate to pool studies comparing single dose and standard treatment with those comparing short course and standard treatment. Three systematic reviews1–3 have now demonstrated that there is no significant difference in the number of children with persistent bacteriuria after short duration or standard duration treatment (see table 1). In contrast, Keren and Chan found that significantly more children had persistent bacteriuria following single dose compared with standard duration treatment (7 data sets, RR: 2.17; 95% CI: 1.88 to 10.89). Because there is no significant difference between short duration and standard duration treatment in the number of children with persistent UTI after treatment, it is not possible to calculate a number needed to treat to prevent one episode of persistent bacteriuria.

From our systematic review, we are not able to determine whether there is an “optimum duration of treatment threshold” as postulated by Keren and Chan.4 Only one study included in the meta-analysis, examining the effects of short duration and standard duration treatment in clearing bacteriuria, compared 2 days of treatment with 10 days’ treatment. In that letter above, Keren and Chan argue that this study favours short duration treatment. However, there was no significant difference between treatments in the number of children with persistent bacteriuria at the end of treatment (RR: 2.17; 95% CI 0.48 to 9.76) although the wide confidence intervals do not exclude the possibility that short duration treatment could be more or less effective than standard duration treatment.

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References

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Management of childhood osteoporosis

I read with interest this recent review article that summarises current knowledge about this subject. I have a number of comments that are pertinent to the discussion. As the authors allude to, there is currently a lack of good evidence on which we can base preventive management. Although calcium and vitamin D supplements are routinely used by some paediatric rheumatologists, there appears to be only one short term study suggesting this may be beneficial for bone density.1 The lack of evidence in relation to growth hormone therapy are methodologically flawed because neither have accounted for the change in apparent bone density, which will occur in any child who grows better for any reason when assessed by modalities such as dual energy x ray absorptiometry.2

As illustrated by another article in the August 2002 edition of Archives,3 there is a lack of evidence on which to base much paediatric management and it is imperative that further research, especially randomised controlled trials, is undertaken in the area of prophylaxis against osteoporosis in children with chronic disease on steroids. Paediatric endocrinologists will be familiar with the flurry of small uncontrolled studies undertaken in numerous groups of children with short stature when recombinant growth hormone became available. Many reports of short term improvements in growth velocity have not been supported by long term outcomes in height. There is a risk that a similar phenomenon will occur with the use of bisphosphonates in children with chronic disease and low bone density without properly designed studies and satisfactory outcome measures.

The use of glucocorticoids in children with chronic disease occurs across many paediatric subspecialties and I would argue strongly that the management and prevention of osteoporosis requires specialist expertise just as the management of growth retardation currently does. It is important that in each tertiary centre such a specialist service is provided by one department that has expertise in the interpretation of bone density scans in children and the management of children with osteoporosis. Such individuals may not only be paediatric endocrinologists but may be a paediatric rheumatologist, a general paediatrician with a special interest in bone disease or a metabolic bone disease subspecialist. It is only in this way that we can learn more about the management of this condition and avoid children being treated inappropriately.

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Newborn screening for Duchenne muscular dystrophy

Elliman, Dezauteux, and Bedford, in their recent leading article on newborn and childhood screening, include reference to newborn screening for Duchenne muscular dystrophy (DMD). They argue that the main value of such a screening programme is to warn parents that future sons may be affected, and support this statement with reference to Jarvinen et al.4 This paper does not report a newborn screening study but the results of a retrospective study of 23 females in Finland carrier tested for DMD during childhood. However, a newborn screening programme for DMD has been running in Wales since 1990 (1990–8 as a research funded). During the research period interim evidence was published.5 More recently the full results of our prospective study have been published.6 Our evaluation has demonstrated that a newborn screening programme for DMD can be acceptable to both parents and health professionals, providing that a rigorous service delivery protocol is in place and the programme is supported by an effective infrastructure, in particular by paediatric and genetic services.

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References


Sanctions were imposed on the people of Iraq in 1990. Iraqi people are still suffering, especially children. Infant mortality (IM) has increased more than five times. Previously it had decreased from 139 in 1960 to 20 in 1989, which was comparable to developed countries. In 1992 it went up to 111. In 1999, a decade later, IM was still high at 104. The Gulf War and trade sanctions caused a threefold increase in mortality among Iraqi children under 5 years of age. It has been estimated that more than 46,000 children died between January and August 1991.1

The study of the UN Food and Agricultural Organisation, published in a letter to the BMJ in 1995, concluded that deaths of more than 50,000 children could be attributed to UN sanctions. It also stated that the death rate among children under 5 years in Baghdad had increased fivefold since the war ended in 1991.2 Data for 1994–99 showed that mortality rate of under 5 years was 131 per 1000 live births, compared with 56 for 1984–9, before sanctions. The reasons for excess deaths are clear—economic collapse with plummeting wages, soaring food prices, poor sanitation, lack of safe water, and inadequate provision of health care.3

The rate of low birth weight (<<2500 grams) which was in the region of 9% in the period 1980–88, increased to 21% in 1994.4 The 1995 Baghdad nutrition survey of children under five years of age showed that the percentage of children below ~2SD in urban Baghdad was 28% for stunting, 29% for underweight, and 12% for wasting.5 All three were malnutrition (=2SD) was noted among children, 10% for stunting, 7% for underweight, and 3% for wasting. The survey by FAO in the year 2000 indicated the prevalence of wasting and undernutrition of children under 5 years old at acceptably high level of 10% or only a marginal difference from the 1995 survey.6

In school children aged 6–8 years the prevalence of wasting ranged from 1% in the upper class to 6.7% in rural areas. Similar differences were found for stunting and underweight.7 In a 1994 survey 1.6% of children under 5 years were reported to have night blindness, indicating vitamin A deficiency. A survey of school children in the north in 1994 showed a 30–50% prevalence of goitre, and evidence of iodine deficiency disease elsewhere throughout the country. Richer children were reported from hospitals at a rate of 3–5 cases per week.8

Diphtheria and malaria were due to dehydration were well under control prior to the Gulf War; there was a threefold increase from May 1990 to May 1991.9 Other water born infections increased from 1990 to 1999, for example typhoid by 60% and cholera almost fivefold.10 A measles epidemic occurred in 1998.11 There were alarming rises in cases of malaria and leishmaniasis. Other infections like tetanus, poliomyelitis, diphtheria, and pertussis all showed an increase after the Gulf War.12

The National Immunization Programme which had begun in 1985 came to a complete halt between January and April 1991.13 The percentage of fully immunised one year old children fell from 94 for tuberculosis, 83 for diptheria, tetanus, and pertussis, 83 for polio, and 82 for measles to 79, 63, 64, and 68 respectively.14

A child psychology study (1991) revealed a level of psychological stress and pathological behaviour which was the highest the authors had seen in 10 years of conflict research. It revealed a highly disturbed population of children. Fear and anxiety were associated with memories of crisis. Seventy five per cent felt sad and unhappy, and four out of five expressed fear of losing their family by death or separation. There was a threefold increase in leukaemia in the southern provinces, sites of the Gulf War battlefield. A WHO investigation in 1995 suggested a possible link to products—now derived from depleted uranium used in piercing artillery shells. There were staggering serious problems with lighting, cleaning, water supply, and sewage. The population had been burdened by a rapid rise in serious infections, nutritional deficiencies among children and pregnant women, and other treatable conditions for which neither drugs nor operations were available.15

Paediatricians have been isolated by the intellectual embargo. There is an international medical community. Physicians who wish to attend international conferences face travel restrictions, like denial of visas to European countries or the USA. In 1990, the delivery of European and American paediatric journals were abruptly stopped. This intellectual embargo served to undermine the care of patients, and denies Iraqi doctors the right to share scientific advancement and its benefits.16

We just read the short report of Galanakis et al.1 We have been involving in periodic fever management for many years. At present, PFAPA is an unclear clinical entity, classified among non-hereditary fevers. It is an unclear nosological entity. Pharyngitis, cervical lymphadenopathies and oral aphthae are exclusive findings in PFAPA. Among periodic fevers, cervical lymphadenopathy and episodic fever can occur in patients with HyperlgD and periodic syndrome (HIDS). Oral aphthae (as minor sign), cervical adenopathies, and isolated fever can be in children affected by FMF. Pharyngitis, oral aphthae, cervical adenopathies, and recurrent fever also characterise Crohn’s disease (CD). Lastly, oral aphthae and recurrent febrile attacks characterise the onset of Behçet’s disease (BD) in children. The efficacy of steroids does not confirm the diagnosis of PFAPA; BD and CD are responsive to steroids, too. The lack of familiar involvement is not a criteria to exclude an inherited disorder, as FMF and HIDS are recessive and BD and CD are multi-factorial diseases. Furthermore, the initial clinical picture of these disorders can be asymptomatic and incomplete and change during the clinical course.

So, considering the provenance of Galanakis’ series (Greece), we not be surprised if some cases had BD or FMF, that will be recognised in the future. Nowadays, with increased diagnostic sensitivity and multi-ethnic societies, periodic fevers are being recognised outside their traditional area of incidence. Close follow up is essential in future years, in these patients. A possible genetic screening for gene causing FMF, HIDS, or immunological assay for HLA B51 could also be useful.

References

Differential diagnosis of periodic fevers

Casano et al describe a case of refractory pulmonary hypertension with severe Botella pertussis infection.2 Their description of the literature is incomplete. We report four cases of fatal pulmonary hypertension (PHT) in a series of 13 critically ill infants with B pertussis.3 The cases that developed PHT all presented with severe hyperleukocytosis (WCC>100 × 109/L) which was unresponsive to all currently available modalities including extra-corporeal membrane oxygenation. Hyperleukocytosis was an independent predictor of death when corrected for presentation age and presenting syndrome.2,4 Barlow and colleagues suggested that extreme leukocytosis predisposes to the formation of lymphocyte aggregates in the pulmonary vasculature and increased pulmonary vascular resistance via obstruction rather than

References
3. Renna LM, Nucera G, Diaco M, Ranna M, Gasbarrini G. Centre of Periodic Fevers, Catholic University of Rome, Italy. Correspondence to Dr L Renna, mrmannajm.unicatt.it
hypoxic vasoconstriction. Therefore Dr Casano’s recommendation for the early use of pulmonary vasodilators is unlikely to be sufficient in this context. We are assessing the impact of strategies aimed at reducing lymphocyte numbers and adhesion in addition to standard treatments for pulmonary hypertension.

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References

Authors’ reply
As Peters comments in his letter, we know that hyperleukocytosis has been postulated as a factor for pulmonary hypertension in Pertussis infection, but necessary brevity did not make it possible to report. Nevertheless, our patient never reached these values of leukocytosis; it’s possible, as in many other diseases, that several pathogenic mechanisms contribute to pulmonary hypertension, making a concomitant treatment approach necessary.

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CORRECTIONS
In the paper by Clarkson and Choonara in the December issue of ADC (Arch Dis Child 2002;87:462–7) the following corrections have been noted:

Results; first sentence: there were 331 deaths with 390 suspected drugs (not 390 and 389 respectively as stated in the paper).
Results; section “Corticosteroids”: the third sentence starting “No details were avail-
able...” should be deleted.
Results; section “Non-steroidal anti-inflammatory drugs (NSAIDs)”: the second sentence “All reports for NSAIDs have oc-
curred since 1990” should be deleted.
Discussion; fifth paragraph: the penulti-
mate sentence should be “as recently as 1999 our study found a single fatality” (not 2 reported fatalities).

Figure 1 Scimitar syndrome. Chest x ray showing a curvilinear density which extends from the right hilum towards the right hemi-diaphragm which represents the anomalous pulmonary vein.

The following figure should have appeared with the letter by Desai and Babu in the October issue of ADC (Arch Dis Child 2002;87:357).