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# Surveillance for adverse drug reactions in children: a paediatric regional monitoring centre

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**The safety of medicines in children is a major issue. In order to increase the detection of adverse drug reactions (ADRs) in children a Paediatric Regional Monitoring Centre (PRMC) was established in the Trent region of the UK for a period of three years. The PRMC operated as an extension of the UK's national spontaneous reporting (Yellow Card) scheme. A comparative region with a similar proportion of children was identified. Four hundred and fifty six reports were received by the PRMC and 155 reports in the comparative region during the three years. There were 10 fatalities reported to the PRMC as opposed to four in the comparative region. The establishment of a PRMC resulted in increased awareness and reporting of suspected ADRs in children.**

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## Introduction

Almost 10% of children in hospital experience an adverse drug reaction (ADR)[1]. A recent systematic review of prospective studies of ADRs in hospitalised children only involved paediatric teaching hospitals (tertiary centres)[2-10]. Few studies have looked at children in district general hospitals (secondary centres)[11-13].

Many ADRs that are recognised in hospital are not reported to the regulatory authorities[4-5]. In order to increase awareness and stimulate reporting of ADRs, a pilot Paediatric Regional Monitoring Centre (PRMC) was established in the Trent region of the UK. The scheme ran as an extension of the UK's national spontaneous ADR reporting scheme – the Yellow Card Scheme. This scheme includes documenting all suspected ADRs without a causality assessment. We have previously described the findings after the first 12 months of the scheme[14] and now report the findings after a three year period.

## Methods

The PRMC was established in 1998 in the Academic Division of Child Health, University of Nottingham at the Derbyshire Children's Hospital. The scheme was funded for a period of three years by the Medicines Control Agency (MCA) and Trent NHS. A paediatric clinical research pharmacist and a part-time data entry clerk were employed.

Twenty hospitals were identified in the Trent region with paediatric patients (16 years and under, including neonates). Paediatricians, paediatric pharmacists, paediatric anaesthetists and paediatric surgeons who practised in each of the hospitals were identified using membership registers or by contacting the relevant hospital department directly. Each person identified was included in a mailing list.

A monthly reminder and update letter with a spare yellow ADR reporting card were sent to each person

on the mailing list. The reminder letter was intended to stimulate reporting for certain drugs and reactions. It was requested that reports of any suspected ADRs be submitted for certain black triangle drugs, serious reactions to any drugs and patients with Stevens-Johnson syndrome where a drug was suspected as the cause. There was also a list of specific reactions to certain drugs with the aim of increasing the number of reports for these and thereby enabling any predisposing factors leading to ADRs to be identified. These included skin reactions to lamotrigine and topical local anaesthetics, arrhythmias to cisapride, visual field defects with vigabatrin, systemic ADRs to inhaled or nasal corticosteroids and any ADRs to leukotriene antagonists.

This information was sent either by post or electronically. Electronic and telephone reporting of ADRs were encouraged. The scheme was promoted by presentations to the staff at the hospitals involved in the scheme as well as regional presentations. The reporters sent the completed yellow card to the PRMC and the information was forwarded to the MCA. If any information was missing from the card it was requested from the reporter along with any other useful information. All suspected ADRs were included in the analysis.

East Anglia and Oxford was chosen as a comparative region with a similar population of children (approximately one million) and with no CSM regional monitoring centre. ADR reports were deemed medically significant if they were fatal, potentially life threatening or disabling[14].

## Results

In the three years of the scheme, 456 yellow cards were received by the PRMC. Eighty six yellow cards were received reporting skin reactions to local anaesthetics, which were specifically asked for in the letter. In the second year of the scheme meningococcal C vaccine was introduced throughout the country and this led to a significant rise in the reporting of suspected ADRs. A total of 127 yellow cards were received with a suspected reaction to meningococcal vaccine. Excluding reports due to local anaesthetics and meningococcal C vaccine, there were 242 yellow cards received during the three year period. Eighty four of the 242 yellow cards involved a drug that was either unlicensed or used in an off-label manner (35%).

There were 165 medically significant suspected ADRs reported of which 45 involved unlicensed or off-label medicines (27%). There were 10 fatalities associated with a suspected ADR (Table 1), four of which involved a drug used in an off-label manner (for age) and two involved an unlicensed drug.

Five hundred and seven suspected medicines were reported on the 456 yellow cards. The types of medicines associated with suspected ADRs are shown in Table 2. Excluding vaccines and local anaesthetics, anticonvulsants and antibiotics were the medicines most likely to be associated with a suspected ADR. Eighty five of the 244 medicines (excluding vaccines and local anaesthetics) were either unlicensed or used in an off-label manner (35%). This was not significantly greater than would be expected based on the number of unlicensed and off-label medicines likely to be used in a similar population of paediatric inpatients[15] (Chi-squared test 1.86, $P > 0.1$).

In the same three years in the comparative region of East Anglia and Oxford there were 155 yellow cards received. Over half of these (86) were yellow cards in response to a suspected reaction to meningococcal C vaccine. A comparison between

**Table 1** Fatalities in suspected adverse drug reactions reported to the PRMC

| Age | Suspected drug | Licensing status | Suspected ADR | Underlying diagnosis |
|---|---|---|---|---|
| 2 days | Atracurium | OL | Cardio respiratory arrest | Preterm RDS |
| 2 days | Atracurium | OL | Cardio respiratory arrest | Preterm RDS |
| 7 days | Atracurium | OL | Cardio respiratory arrest | Preterm RDS |
| 2 months | Men C vaccine<br>DTP, Hib vaccines | L | Seizures | Epilepsy |
| 3 months | Men C vaccine | L | SIDS | Healthy infant Immunisation |
| 3 months | Palivizumab | L | Cardio respiratory arrest | Ex preterm, chronic lung disease, subglottic stenosis.<br>Prevention of RSV infection |
| 10 months | Adenosine | OL | Asystole | Supraventricular tachycardia and ALL |
| 4 years | Pegaspargase | UL | Pulmonary haemorrhage | ALL |
| 14 years | Pegaspargase | UL | Pulmonary haemorrhage | ALL |
| 10 years | Sodium valproate | L | Hepatic failure | Epilepsy |

ALL = Acute lymphoblastic leukaemia
SIDS = Sudden Infant Death Syndrome
L = Licensed
OL = Off label
UL = Unlicensed

**Table 2** Drugs involved in suspected ADRs reported to the PRMC

| | |
|---|---|
| Vaccines | 176 |
| Topical local anaesthetics | 87 |
| Anticonvulsants | 56 |
| Antibiotics | 46 |
| Cytotoxics and immunosuppressants | 28 |
| Antiemetics | 11 |
| Non-steroidal anti-inflammatory drugs (NSAIDs) | 10 |
| Bronchodilators | 9 |
| Corticosteroids | 8 |
| Antivirals | 8 |
| Atracurium | 7 |
| Methylphenidate | 6 |
| Pancreatic enzymes | 5 |
| Opiates | 4 |
| Miscellaneous | 46 |
| **Total** | **507** |

the reports received in the two regions is shown in Table 3. Excluding reactions to local anaesthetics and meningococcal C vaccine, there were over three times as many reports to the Trent PRMC.

## Discussion

The presence of a PRMC resulted in a significant increase in the number of reports of suspected ADRs in comparison with East Anglia and Oxford. The study shows that a proactive scheme focusing on a particular age group, in this case paediatric patients can be successful.

It is important to recognise the significant differences between surveillance in children as opposed to adults. The majority of reported ADRs in adults are in the community and this includes serious ADRs. In children, however, although the majority of yellow cards relate to children in the community, medically significant ADRs are associated with children either in hospital or presenting to hospital. It is important to recognise that the numbers of ADRs occurring in children is significantly less than that occurring in adults[1,16].

As well as generating an increase in the number of suspected ADRs, the PRMC has shown that a greater awareness of drug surveillance can be achieved. In the last two years of the scheme there were 10 fatalities where the clinician suspected an ADR. In contrast, only 68 fatal suspected ADRs were reported during the five years from 1996 to 2000 in children throughout the UK[17]. The population of children in Trent is less than 10% of the total UK paediatric population. Our findings suggest that the number of nationally reported suspected fatal ADRs in children is a considerable under-estimate. It also suggests that a PRMC can be extremely useful in detecting possible signals, e.g. suspected atracurium toxicity in neonates[18].

**Table 3** Comparison between the two regions over a three year period

| | Trent PRMC | East Anglia & Oxford |
|---|---|---|
| Total number of yellow cards | 456 | 155 |
| Meningococcal C vaccine reports (A) | 127 | 86 |
| Local anaesthetic reports (B) | 87 | 2 |
| Total excluding A & B | 242 | 67 |
| Fatalities | 10 | 4 |
| Medically significant ADRs | 165 | 82 |

There is considerable interest in the risk associated with the use of either unlicensed or off-label medicines. Off-label involves the use of a licensed medicine outside the terms of its product licence[19]. This may involve a different dose, indication, route or use in an age group different to that which it is licensed for. Unlicensed medicines are usually preparations of licensed medicines in a different form to that specified in the product licence (extemporaneous preparation). It also includes the use of medicines which do not have a product licence within that country[19]. Studies of the prevalence of unlicensed or off-label prescribing have shown considerable variation depending upon the patient population and the country[15,20]. A British study of GP prescribing found that 11% of drug prescriptions for infants and children are either unlicensed or off-label[21]. British studies of paediatric inpatients have suggested a range of 25-30% of unlicensed and off-label drug prescriptions[15,22]. Newborn infants, however, are exposed to considerably higher levels of unlicensed and off-label drug prescriptions with one study suggesting that 65% of such drug prescriptions are unlicensed or off-label[20].

This study was not designed to evaluate the risk associated with the use of unlicensed or off-label medicines. Therefore, the lack of a significant association between the reported ADRs and the use of unlicensed or off-label medicines should not be used as confirmation that there is no greater risk associated with the use of such medicines. Six of the 10 suspected medicines associated with a fatality involved either off-label use or unlicensed medicines. This is consistent with previous studies which have suggested that there is a greater risk of a severe ADR occurring in association with the off-label or unlicensed use of medicines[5].

There is currently considerable interest in pharmacovigilance in relation to medicines for children. In North America a specific reporting programme for paediatric ADRs has been established[23]. Our experience would support pro-active methods of surveillance that focus specifically on children. The costs involved in employing two individuals are small in relation to the significant cost of ADRs[23]. Such surveillance should hopefully minimise ADRs in children.

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