
Adverse Drug Reactions in Children

Abstract: Medicines for children are frequently provided off label or off licence. Because of the changing physiology during childhood, it is likely that children have more than average adverse drug reactions but the MHRA yellow card system is notoriously unreliable in this group. The project aims to develop an effective active surveillance system for adverse drug reactions in children. This proof of concept study will examine a system in Scotland to evaluate how best to carry out surveillance across the UK. Involvement: The project is run from the Research Division of the Royal College of Paediatrics and Child Health (RCPCH) and the guidance of a subcommittee of the Medicines Committee, which includes paediatricians with an interest in medicines and also involves the Neonatal and Paediatric Pharmacists of the UK.

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Coverage Scotland

Duration January 2006– February 2007 (14 months)

Background Most drugs currently on the market have not undergone clinical trials involving children. The effect is that many medicines in use on children are used "off label" and "off licence". Little is also known about adverse drug reactions (ADRs) and their relation to age in children. Given that there is good reason to believe that drugs/medicines are dealt with differently by children at different ages (premature, newborns, school children, adolescents) as their physiology and biochemistry changes with age, their use can give rise to anxiety in parents and paediatricians.

The Committee for Safety of Medicine (CSM) of the Medicines and Healthcare Products Regulatory Agency (MHRA) recognises the need to be more pharmacovigilant. This committee is responsible for monitoring adverse drug reactions through the yellow card spontaneous reporting system. Yellow cards are completed by physicians when an ADR is suspected and sent to the CSM who with advice from the subcommittee on Efficacy and Adverse Reactions process the information and if necessary recommend the removal of the medicine from the market. The system assures the safety of licensed medicines by removing medicines associated with unacceptable levels of ADRs not detected during clinical studies. As many of the medicines used in paediatrics are not licensed, passive surveillance of ADRs via the MHRA yellow card system is notoriously incomplete for children. ADRs are in general under-reported in children and even with a regional drive returns were probably incomplete.

Previous studies have concluded that 9.5% of paediatric admissions have ADRs and 12% of these may be serious. Just over 2% of admissions are a result of ADRs and 40% of these are life threatening. A recent British Paediatric Surveillance Unit (BPSU)/MHRA study identified 18 deaths in one year.

ADRs are thought to be quite common but it is often difficult to be sure whether a reaction is an ADR or part of the disease process, therefore a high index of suspicion and active reporting is warranted. ADRs are known to increase with the number of drugs given - is this just proportional, or is it because of drug interactions?

Major ADRs seen in children in the past have been: Aniline dyes - methaemoglobinaemia; Sulphonamides - kernicterus; Chloramphenicol - the grey baby syndrome; Valproate - hepatic failure; Salicylate – Reye’s syndrome; Propofol - metabolic acidosis.

The development of a national active surveillance system for ADRs in children could address some of these concerns. Given that there is a long tradition of epidemiological surveillance by paediatricians via the BPSU (90% of paediatricians surveyed each month reporting on a panel of rare diseases) there is no reason to believe they would not respond positively to such a paediatric led ADR system.

Case Definition For the following Ibuprofen , Ceftriaxone, Fluticasone , Sodium valproate or sedative (please state); any drug reactions severe enough to precipitate admission to hospital – **OR** – that occur because of an outpatient medicine prescription – **OR** – that occur in hospital should be reported.

Research Questions

1. Can an active ADR reporting system be established with Paediatricians?
2. What level of reporting of ADRs can a card based surveillance system achieve?
3. Can an electronic – email based – surveillance system deliver returns as good or better than a card based system?
4. How does baseline reporting using this system compare with that of the MHRA system?

Methodology A monthly yellow postal card will be sent out from the RCPCH research division. The card will contain a list of drug groups for which ADRs are sought. Clinicians will be asked to return the card each month whether or not they have anything to report. This is important, as it will measure compliance to the system. If they have seen a case of one of the five drug groups listed they should tick the appropriate box entering in the sex and age of the case report. This is also important, as it will help in identifying duplicate reports. Only drug reactions severe enough to precipitate admission to hospital OR - that occur in hospital will be surveyed. We do recognise that this will miss more minor ADRs in general practice.

After 6 months of card reporting the paediatric respondents will split into two groups. Half will continue to receive the card mailing while the other half will receive email reporting. Those not responding to the email/card will receive a reminder letter after eight weeks of the card being sent.

Once a case has been reported a letter of thanks will be sent and the clinician will be asked to confirm the detail sent. They would also be asked to identify the type of ADR presented e.g. rash, fever, vomiting etc.

Returns using this system will be compared with the returns made to the MRHA on their national yellow card system. At the end of one year the paediatricians will be surveyed for their opinions about the 2 reporting systems. A Research nurse will be recruited for 3 months from the start of the study to advertise the project in the Scottish hospitals. In this way we hope to increase compliance

Reporting Instructions Please report any cases seen within the last month that meet the case definition. Please note that this surveillance does not replace the statutory surveillance carried out by the MHRA.

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Ethical approval This study has been approved by the East London & The City HA LREC 1.

References

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