Paediatric and Perinatal Drug Therapy **Volume 7, Issue 2, 2006**

Contents

Paediatric and Perinatal Drug Therapy, 2006; 7 (2)

Paediatric pharmacovigilance

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Paediatric pharmacovigilance studies were first carried out in inpatients in large teaching hospitals 30 years ago. These studies involved looking for adverse drug reactions (ADRs) prospectively. More recently, investigators have reported ADRs using data obtained by the regulatory authorities. These recent studies have been useful in identifying more severe ADRs. Future pharmacovigilance studies in children should involve collaboration between paediatric health professionals and the regulatory agencies in order to reduce ADRs.

Paed Perinat Drug Ther 2006; 7: 50–53

Keywords: adverse drug reactions – surveillance – children

Introduction

Adverse drug reactions (ADRs) are a significant problem in paediatric patients of all ages[1,2]. Children, infants and neonates experience similar ADRs to adults. They also experience additional ADRs associated with the growth and development of a child. The mechanisms associated with drug toxicity in children have been reviewed[2].

Pharmacovigilance has been defined as the process of evaluating and improving the safety of marketed medicines[3]. Many medicines used in children, however, are not specifically marketed for use in this age group[4-6], i.e. they are used off-label or are unlicensed. An appropriate definition for paediatric pharmacovigilance would therefore be the process of evaluating and improving the safety of medicines used in paediatric patients of all ages.

The first pharmacovigilance studies, specifically involving children, were carried out in paediatric inpatients in the 70s and 80s in large teaching hospitals in the USA and Europe[7-11]. These studies have all involved a pharmacist prospectively looking for ADRs by attending ward rounds and reviewing prescription charts. Suspected ADRs have been evaluated by the paediatric pharmacist often in conjunction with a paediatric doctor or a paediatric clinical pharmacologist.

A systematic review of prospective studies in paediatric inpatients has shown that the overall incidence of ADRs was 9.5% (95% confidence intervals, 6.81, 12.26)[1]. This systematic review also evaluated five studies and showed that approximately 2% of admissions to a children's hospital are due to ADRs. The incidence of ADRs in children attending hospitals as outpatients[12-14] is considerably lower than inpatients with a mean incidence of 1.5% (confidence intervals 0.70, 3.03). There have also been studies looking at the incidence of ADRs in the paediatric population covered by primary care[15].

More recent studies have confirmed the previous findings in relation to the epidemiology of ADRs in paediatric patients[16-25]. These studies have also looked at the influence of licensing in relation to the frequency of ADRs[16,17,21,26]. A prospective study of over 1000 inpatients in a large children's

Table 1 Aims of paediatric pharmacovigilance

- Establish the epidemiology of ADRs in paediatric patients
- Detect new ADRs
- Increase awareness of ADRs
- Reduce ADRs
- Establish the safety of a medicine in a clinical trial

hospital detected a total of 116 ADRs[17]. The children received over 4000 drug prescriptions. ADRs were associated with 3.9% of the licensed drug prescriptions and 6% of the unlicensed or off label drug prescriptions. The percentage of unlicensed and off label drug use was significantly associated with the risk of an ADR. A prospective study in over 1000 paediatric outpatients detected 20 ADRs[21]. The risk of an ADR was greater in those patients who received at least one off label drug prescription. These two studies have confirmed the greater risk associated with off label and unlicensed drug prescribing.

Future direction

Studies over the last 30 years have established the epidemiology of ADRs in paediatric patients. The purpose of pharmacovigilance, however, is not simply to maintain an epidemiological database. Some of the aims in relation to pharmacovigilance are given in Table 1. These specific objectives are described in greater detail below. Although the epidemiology of ADRs in paediatric patients as a whole is now established, further work is required in selected patient groups such as neonates where there have been relatively few studies.

Reducing ADRs

The long-term aim should always be to reduce drug toxicity in children. This involves a variety of methods. Spontaneous reporting is more likely to detect signals, i.e. new ADRs which have previously been unsuspected[27]. Targeted pharmacovigilance is more likely to result in guidelines that will reduce drug toxicity. Several groups have shown that this is possible in relation to the use of individual drugs[28,29] and specific groups of drugs[30]. Depending upon the clinical indication for the drug and the toxicity, it may be appropriate to carry out a clinical trial to establish the risk/benefit ratio of different medicines[31]. On some occasions a clinical trial is not required and this is illustrated by avoiding the use of salicylates as an over the counter medicine for use in children. Such action has virtually eliminated Reye's syndrome.

Regulatory authorities

Regulatory authorities throughout the world have established spontaneous reporting systems in order to facilitate the detection of new ADRs. These spontaneous reporting systems have been aimed specifically at adult patients where the majority of ADRs occur in the community. The system has, however, picked up signals in relation to ADRs that have occurred in paediatric patients which have led to changes in licensing and also guidance about the use of medicines in specific situations in paediatric patients. An example is the visual field defects associated with the anticonvulsant vigabatrin[32]. More recently the regulatory agencies have taken a proactive approach to increase awareness and reporting of ADRs in paediatric patients. The establishment of a paediatric regional monitoring centre within the UK was shown to be highly successful during a three year time period[33]. Unfortunately paediatric patients are rarely considered a priority by regulatory agencies and therefore funding for initiatives such as these are limited.

The regulatory authorities are unique in that they have a significant amount of data in relation to suspected ADRs in paediatric patients. Only recently have the regulatory authorities evaluated this data specifically in relation to drug toxicity in paediatric patients. Studies in Spain, Sweden, the USA and the UK have all collated data which has been useful in highlighting groups of drugs which are more likely to be associated with drug toxicity in paediatric patients[34-37]. These studies are shown in Table 2 as well as details of the paediatric regional monitoring centre established in conjunction with the regulatory authorities in the UK[33].

It is important to note that fatalities following a suspected ADR are not usually detected in prospective pharmacovigilance studies as the incidence of fatal ADRs is fortunately low. Information regarding fatalities is useful in that it identifies which drugs are more likely to be

Table 2 Regulatory agencies and paediatric pharmacovigilance studies

Country	Age group (years)	Period of study	No of suspected ADRs	Fatalities	Comments	Reference
Spain	0–14	1982–1991	1419	4	ADRs most frequent in 1–4 year olds	34
Sweden	0–15	1987–2001	2297	8	ADRs most frequent in 0–4 year olds	35
UK	0–16	1964–2000	331	331	Specifically looked at fatalities	36
UK	0–16	1998–2001	456	10	Increased reporting	33
USA	0–2	1997–2000	7111	769	4 drugs assoc with 38% fatalities	37

associated with fatalities, either individually or as a group. The American study identified four drugs that were responsible for 38% of fatalities in infants under the age of two years: palivizumab, nitric oxide, indomethacin and cisapride[37]. The British study identified anticonvulsants as the group of medicines most likely to be associated with fatalities[36]. Unfortunately, the regulatory agencies have been reluctant to utilise their data in this manner. Previous prospective studies involving ADR surveillance within a children's hospital have not detected fatalities[1,7-11,16-19,22]. Retrospective studies have, however, reported fatalities[24]. The only prospective study to identify fatalities was that involving the establishment of a paediatric regional monitoring centre in the UK. This identified ten fatalities over a three year time period within a single region in the UK. The regulatory agencies should work in conjunction with paediatric health professionals and academia to ensure that all safety information is made available. A more proactive approach has been advocated by the regulatory agencies in Europe (the EMEA) in a consultation document and this is to be welcomed[38].

The studies carried out in conjunction with the regulatory authorities have identified those individual medicines and those groups of medicines most likely to be associated with significant drug toxicity. It would therefore be appropriate to try and carry out targeted pharmacovigilance in relation to individual drugs such as palivizumab or groups of drugs such as anticonvulsants. This may significantly reduce drug toxicity in paediatric patients.

Clinical trials

Clinical trials are the gold standard in providing an evidence base for paediatric health professionals to use medicines safely and effectively. It is important to ensure that clinical trials are carried out safely and appropriately. This may involve the creation of a data monitoring committee (DMC)/ independent safety monitoring board (ISMB). The working of such committees has been described in detail[39].

The use of propofol as a sedative in critically ill children should act as a cautionary tale. Propofol had been licensed as an anaesthetic agent and studies had shown it to be exceptionally safe. It was subsequently used as a sedative in critically ill children and by 1998, 15 deaths had been reported following its use[40,41]. Subsequently a clinical trial in the USA was performed evaluating propofol as a sedative in critically ill children. The results of the trial have not been published but have been included in a review of the effects of legislation in the USA in relation to improving drug therapy[42]. This review highlighted the fact that there were 21 deaths in the propofol group in comparison to only 4 deaths within the group of children receiving standard sedation[42]. The dose of propofol used in the study (5.5 mg/kg/h) was greater than that previously reported as being a risk factor for the development of propofol infusion syndrome in children (4 mg/kg/h). Crucially, the American propofol study had no independent DMC/ISMB which is surprising in view of the previously reported toxicity associated with this drug. Clearly, in all studies designed to assess the safety and efficacy of a drug (or device) in children, investigators should ensure that an independent DMC/ISMB is appropriately constituted and engaged during the course of the study.

Conclusions

Over the last 30 years paediatric pharmacovigilance has developed considerably. It is important that over the next 30 years we do not simply repeat the studies that have previously been performed. We need to work with the regulatory authorities to ensure that information that they have regarding the safety of medicines (both from spontaneous reporting systems and from clinical trials performed prior to licensing) are made available to the public. We need to use this information alongside prospective studies of pharmacovigilance targeted at those medicines/ clinical situations where drug toxicity is likely to be greatest. The aim should be to reduce ADRs in paediatric patients.

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Paper PPDT-0150_1, *Accepted for publication*: 2 February 2006
Published Online: 26 April 2006
doi:10.1185/146300905X75352