Frequency of adverse drug reactions in children: A prospective study

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Aims To assess the frequency of adverse drug reactions (ADRs) in children in France.

Methods In a prospective study over a period of 1 week, we evaluated the incidence of ADRs (1) as a cause of admission to a regional children's hospital; (2) occurring during hospitalization in a regional children's hospital; and (3) as a cause of consultation with private paediatricians.

Results Four out of 260 children were admitted to the regional children's hospital for ADRs (1.53% [0.42, 3.89]) and six developed ADRs during hospitalization (2.64% [0.97, 5.66]), 4/428 attended the Accident and Emergency Department for ADRs (0.93% [0.25, 2.37]) and 8/1192 consulted a private paediatrician for ADRs (0.67% [0.29, 1.31]).

Conclusions Our results are in agreement with the incidence of ADRs in children found in others countries.

Keywords: adverse drug reactions, children, incidence, prospective study

Introduction

It is usually stated that the frequency of adverse drug reactions (ADRs) is higher in adults than in children but no study has specifically focused on the frequency of paediatric ADRs in France. Some findings have been published on the frequency of ADRs in children in other countries [1–9], but to our knowledge no study has concomitantly estimated the frequency of ADRs in children obtained from different sources in the same district.

This study was therefore undertaken to assess the frequency of ADRs in children as a cause of admission to a regional children's hospital and occurring during hospitalization, as well as being a cause of consultation with private paediatricians.

Methods

The first part of the prospective study was carried out in the Regional Paediatric Hospital, University of Tours

(France). This hospital has 175 beds, covers a population of 3 000 000 and includes nine wards and one Accident and Emergency Department. We analysed admissions to the Accident and Emergency Department separately, because this department has a specific activity. Intensive monitoring of all admissions to the nine wards was performed over a period of 1 week between 4th May and 16th June 1998. Patients with a planned hospitalization of less than 24 h were excluded.

On each day of the study period, a specific form was completed for all children admitted by the nurse in charge. Data were recorded using the structured questionnaire designed for this purpose including: ward, date, name, sex, age, reason(s) for admission, treatment, if the admission was for an ADR and previous history of adverse drug reaction(s). The day after admission, the hospital records of all children admitted were screened by one of the authors (PB) in order to confirm reasons for admission. All children were followed up until discharge in order to ascertain the final diagnosis. In order to validate cases, for each suspected ADR, a file was opened by one of us (PB) containing all the information necessary for analysis of the ADR.

To estimate the frequency of ADRs occurring during hospitalization, all the children admitted during the week of the study were followed up until discharge. Adverse clinical events that occurred during hospitalization were

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recorded by visiting the wards daily, examining medical and nursing records and attending ward rounds. When necessary, information was obtained from nurses and physicians, and for each suspected ADR a file was opened by one of us (PB) containing all the information necessary for analysis of the ADR.

To estimate the frequency of ADRs seen by private paediatricians, all the 35 private paediatricians in the district were asked to participate in the study. During a given week in June 1998, they were asked systematically to record the reason(s) for consultation for all children seen. They noted all the consultations for each day on a specific form including age, treatment, reason(s) for consultation, if the consultation was for an ADR and previous history of adverse drug reactions for each child. A specific file was opened by the paediatrician for each suspected ADR including all the information necessary for analysis of the ADR.

All ADRs were analysed by the Regional Drug Monitoring Centre of Tours using the French evaluation of causality [10]. Only ADRs with a suspected relationship with the prescription were retained.

Results (Table 1)

During the week of the study, 260 children were admitted to the nine paediatric wards: 12 to the neonatology unit, 99 to the two general medical wards, 6 to the nephrology unit, 56 to visceral surgery, 41 to orthopaedic surgery, 5 to oncology, 6 to the intensive care unit and 35 to neurosurgery. One hundred and nineteen children (45.8%) were taking at least one drug before admission (median number of drugs: 2 [range 1–11]). Their mean age ($\pm$ s.d.) was 76.1 ± 61.5 months and 157 were boys (60.4%). Four children were admitted for ADRs (1 convulsion with an antiepileptic drug, 1 myoclonia with an analgesic, 1 melaena with acetyl salicylic acid and 1 neonatal withdrawal syndrome with methadone), i.e. a frequency of 1.53% of the paediatric admissions (4/260) (95% CI 0.42, 3.89). During hospitalization (median stay 3 days [range 1–70]), 227 children (88%) received at least one drug (median number of

drugs: 3 [range 1–14]). Six of them developed ADRs (4 vomiting with antineoplastic or opioid, 1 diarrhoea and 1 rash with an antibiotic), i.e. 2.64% of children hospitalized taking a drug (6/227) (95% CI 0.97, 5.66). None of the ADRs prolonged hospitalization. The incidence was also evaluated according to length of hospitalization (6 ADRs for 1281 days) i.e. 0.47 per 100 hospitalized children days (bootstrap 95% CI 0.14, 0.92). [The 1281 days are actually associated with 227 subjects. The 95% CI is therefore estimated by means of a re-sampling scheme (bootstrap) where subjects are re-sampled].

During the same period 428 children attended the Accident and Emergency Department. Their mean age ($\pm$ s.d.) was 90.5 ± 57.7 months and 237 were boys (55.4%). Seventy-three (17%) were taking at least one drug (median number of drugs: 2 [range 1–5]). Four of the 428 children attended for ADRs (2 diarrhoea with an antibiotic and magnesium sulphate, and 2 rash with MMR vaccine and antibiotic), i.e. 0.93% of paediatric admissions to the Accident and Emergency Department (95% CI 0.25, 2.37).

Sixteen private paediatricians agreed to participate in the second part of the study and reported seeing 1192 children during the week of the study. Their mean age ($\pm$ s.d.) was 45.4 ± 46 months. Eight children consulted for ADRs, i.e. 0.67% of paediatric consultations (95% CI 0.29, 1.31) (4 rash with an antibiotic, 2 fever with vaccines, 1 diarrhoea with an antibiotic and 1 vomiting with an antibiotic). None of them required hospitalization.

Discussion

Between 2%–4.3% [2, 4] of paediatric hospitalizations are for ADRs. These findings are in agreement with our study and with a study conducted in French public hospitals on the frequency of hospital admissions related to ADRs [11]. This study found a frequency of 3.45% (95% CI 2.78, 4.22) for adults and a frequency of 1.91% (95% CI 0.91, 3.5) before 16 years of age, increasing with age ($P=0.005$). If we compare our results to the frequency of hospital admissions related to ADRs

Table 1 Incidence of ADRs in children obtained from different sources in the same district.

	Number	Incidence (%)	95% Confidence Interval
Children admitted to hospital for ADR	4/260	1.53	[0.4, 3.89]
Children developing ADR during hospitalization	6/227	2.64	[0.97, 5.66]
Children attending the AED* for ADRs	4/428	0.93	[0.25, 2.37]
Children consulting a private paediatrician for ADRs	8/1192	0.67	[0.29, 1.31]

*Accident and Emergency Department.

in adults we cannot conclude that the frequency of hospital admissions related to ADRs is higher in adults than in children (Exact Fisher test $P=0.19$), probably because of a lack of power. However, one can assert that unlike adults, children are more often treated with fewer drugs (usually with few adverse effect such as antibiotics), for only one condition and do not have impaired renal or hepatic function. This could explain why ADRs in ambulatory paediatric patients are rare, mild and transient [12]. Given that the nature of disease and treatment in children is different from that in adults, it is not surprising to find that ADRs are responsible for a smaller proportion of hospital admissions of children than adults for whom a frequency of 1.8%–6.8% of hospitalizations for ADRs has been reported [13].

The frequency of ADRs in hospitalized patients found in this survey is lower than that reported by others such as Martinez (16.6%) [9] and Gonzalez-Martin (13.7%) [7]. Only Dharnidharka [8] reported a frequency of 1.73%. Our lower frequency could perhaps be explained by the fact that oncology and intensive care units, in which the drugs used may be more likely to cause ADRs [2, 14, 15], were small wards and had few admissions. Moreover, 12% of the hospitalized children did not require any medication, which may, at least in part, be due to the large number of admissions to surgical wards. Recently published studies concerning off-label usage of drugs in children have shown that most drugs prescribed in paediatric wards are off-label [16] and Turner [17] reported that ADRs in paediatric inpatients are more frequently associated with unlicensed or off-label drug prescriptions than with licensed drug prescriptions. Finally, Gonzalez-Martin [7] reported that the frequency of ADRs in hospitalized children was lower than the frequency in adults hospitalized at the same hospital using the same surveillance method.

Our results for ambulatory paediatric patients are in agreement with recent studies on the prevalence of ADR, suggesting that they are uncommon in primary care. In a study extending over 1 year in a general paediatric group practice, Kramer [1] found only 24 definite ADRs and 176 probable ADRs in 4244 separate courses of drug therapy (4.7%). The most common ADRs were antibiotic-associated gastrointestinal complaints and rashes. Cirko-Begovic [3] monitored 2359 children over 3 months: 97.3% received drug therapy and 71 ADRs were reported (3.1%). None was severe. Menniti-Ippolito [5] recently recorded an incidence of ADR of 15.1 per 1000 children seen by private paediatricians. Because the drugs most frequently associated with ADRs (antibiotics, analgesics-antipyretics, ...) are less commonly used in spring, the low incidence of ADRs in our study in ambulatory paediatric patients may be explained by the season in which the study was performed. In our

study, all ADRs seen by private paediatricians were mild and none required hospital admission, although this study did not have sufficient size to identify rare and serious ADRs.

Certain limitations must be considered in interpreting our findings. First, a single week may be viewed as short period, and if the study had been performed over a longer period this would have led to greater accuracy of the estimates (with lower confidence interval widths), but this was not possible for practical reasons. Second, it is not possible to exclude under-notification by private paediatricians, but the paediatricians involved in this study are in a network and regularly take part to our pharmaco-epidemiological studies.

Finally, the frequency of ADRs in children in France as assessed by this prospective epidemiological study conducted over a period of 1 week is in agreement with the frequency found in other countries.

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