A prospective study of adverse drug reactions as a cause of admission to a paediatric hospital

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- 1 A total of 512 consecutive paediatric hospital admissions of children 2 years old or less were evaluated to assess the extent and pattern of admission caused by suspected adverse drug reactions (ADRs). The proportion of suspected ADRs related to hospital admissions was 4.3%.
- 2 The organ-systems most commonly implicated were the central nervous system (40.5%), digestive system (16.7%), and skin and appendages (14.3%). Together, they accounted for 71.5% of admissions attributed to ADRs. The most common clinical manifestations inducing admission were convulsions (4 cases), dizziness (4), vomiting (3), and tremor, fever, itching and apnoea (2 cases each).
- 3 The four classes of drugs most frequently suspected in admissions due to ADRs were respiratory drugs (35%), anti-infective agents (25%), drugs active on the central nervous system (15%) and drugs used in dermatology (10%). The most common drugs related to ADRs were a combination of chlorpheniramine, diphenhydramine, phenylephrine, guaiphenesin and salicylic acid (4 cases), followed by fenoterol, adrenaline, paracetamol, DTP vaccine and antipolio vaccine (2 cases each).
- 4 There were no significant differences between children older and younger than 1 year (odds ratio 0.89; 95% CI 0.37–2.17) or between the sexes as regards hospital admittance due to suspected ADRs (odds ratio 1.94; 95% CI 0.72–5.42).
- 5 The results of this kind of study may be influenced by patterns of drug utilization. Nevertheless, the lack of specific studies of drug effects in young children makes it desirable to carry out pharmacoepidemiological studies in this age group.

Keywords adverse drug reactions hospital admission paediatric patients

Introduction

It is well known that adverse drug reactions (ADRs) are a frequent cause of hospital admission, but their frequency is influenced by many factors including the type of hospital studied and the characteristics of patients included.

The first study published on this subject was that of Hurwitz in 1968 [1]. Since then, several other studies of adults patients have been published [2–6]. To our knowledge, few studies of ADRs as a cause of hospital

admission in children have appeared in the literature. In this context, Mitchell *et al.* in 1979 and 1988 reported data on children in the age range of under 30 days to over 15 years, from the Boston Collaborative Drug Surveillance Program [7, 8].

We present the results of a prospective study involving the surveillance of 512 paediatric hospital admissions affecting 490 children. We estimated the proportion of hospitalizations resulting from suspected ADRs related to out-patient drug use out of the total hospitalizations in children aged 1–24 months. We also studied the

characteristics of these patients and compared them with patients admitted for causes unrelated to drugs.

Methods

The study was carried out in the Hospital Infantil Universitario La Fe in Valencia (Spain). This hospital has 291 beds and covers a population of 700 000, of which 15 000 are children 2 years old or less.

The admissions evaluated corresponded to use of 47 beds during two different periods, summer (105 days) and winter (99 days). Patients 1 to 24 months old with a hospitalization period of at least 24 h were included in the study. Oncological patients and cases of HIV infection were excluded.

During the study periods, the hospital records of all admitted patients were screened by one of the authors (M.G.L., a paediatrician). Data were recorded using a structured questionnaire including sociodemographic and anthropometric information, personal and family medical history, cause of admission and main clinical data. Questions regarding previous drug use covered the preceding month and were answered by the parents, relatives, home nurses or others, as necessary. To maximize the rate of recall, interviewees were asked if children had taken any medication, including vitamins, for various common symptoms of childhood. Information on the pharmaceutical form and dosage was also recorded. All patients were followed-up until hospital discharge, in order to ascertain the final diagnosis.

The clinical charts of patients were evaluated in joint meetings to select those cases for which a suspected ADR had contributed to admission. The evaluation followed a two-dimensional scheme: (i) the temporal relationship between drug intake and a subsequent adverse event, (ii) the role of the latter as a cause of hospital admission. Details on those patients in whom drug therapy was thought to have contributed in any way to their admission were documented using the spontaneous reporting system of the Regional Drug Surveillance Center maintained by the Spanish Drug Surveillance Scheme of the Ministerio de Sanidad y Consumo.

The procedures involved in the reporting system and the assessment of the data have been described previously [9–11]. Briefly, in order to validate the cases,

for every adverse effect reported efforts are made to collect the maximum amount of information about patient characteristics (sex, age, medical history, underlying diseases, etc.), drug treatment (suspected drug, dosage, route of administration, indication, date of beginning and stopping therapy, concomitant drugs, etc.) and characteristics of the adverse event (date of onset, clinical details, etc.). Once the case was validated, to obtain an imputability score we used the algorithm utilized in the Spanish Drug Surveillance Scheme [10], based on successive evaluation of five criteria where each has several degrees, and which provides grades of the causal association between drug and adverse event.

The clinical manifestations experienced by the patients were classified according to the Adverse Reaction Terminology of the WHO [12]. A reactions profile was made by calculating the number of reports of each system-organ class of reaction as a percentage of all the reports. The reactions profile was graphically represented as a histogram. Severity was classified into four categories according to the Spanish Drug Surveillance Scheme: fatal, severe (directly life-threatening), moderate and mild. The suspected drugs were classified according to the Anatomical-Therapeutic-Chemical classification (ATC) of the Norwegian Medicinal Depot [13].

To examine potential risk factors for ADR as a cause of admission, the same methodology as outlined above was used for patients admitted without drug-related problems.

All data from questionnaires and medical records were coded for subsequent analysis. Statistical study of the data was made using the Student's *t*-test with a significance level of $P < 0.05$. Comparison of proportions was made using Chi-squared tests with the results expressed as odds ratios (OR) and 95% confidence intervals.

Results

During the two study periods 512 admissions affecting 490 patients were included. Table 1 shows the distribution of patients admitted in the two study periods; the admissions were higher in winter, but there were similar numbers of males and females in both periods. There were no statistical differences between the two periods in terms of age, weight, height and length of stay in hospital (Table 1). The highest proportions of

Table 1 Patient characteristics, number of admissions and length of hospital stay (mean $\pm$ s.d.), in the two study periods

	Sex	Number of admissions (children)	Age (months)	Weight (kg)	Height (cm)	Length of stay (days)
1st period (21–06/03–10–92)	Male	93 (90)	9.7 $\pm$ 6.6	8.0 $\pm$ 3.0	70.4 $\pm$ 11.5	6.9 $\pm$ 6.3
	Female	89 (89)	9.7 $\pm$ 7.1	7.2 $\pm$ 2.5	68.5 $\pm$ 10.5	7.2 $\pm$ 5.1
2nd period (10–01/27–04–93)	Male	156 (142)	8.2 $\pm$ 5.9	7.5 $\pm$ 2.5	66.1 $\pm$ 11.2	6.9 $\pm$ 5.7
	Female	174 (169)	8.4 $\pm$ 6.6	7.0 $\pm$ 2.6	66.9 $\pm$ 10.5	8.3 $\pm$ 7.9
Total	Male	249 (232)	8.7 $\pm$ 6.2	7.7 $\pm$ 2.7	68.6 $\pm$ 10.5	6.9 $\pm$ 5.9
	Female	263 (258)	8.8 $\pm$ 6.8	7.1 $\pm$ 2.6	67.0 $\pm$ 11.0	7.9 $\pm$ 7.0

patients studied were from the emergency room ($n=415$, 81%) and from the paediatric intensive care ($n=71$, 13.7%). The rest were from several medical paediatric units ($n=26$, 5.3%). Of the total of 512 admissions, including three patients who had three separate admissions and 16 who had two separate admissions, 21 (4.3%) were thought to be due to an ADR. There was a female predominance among patients admitted for suspected ADR (seven males, 14 females). The characteristics of patients with ADRs (age, weight, height and length of stay in hospital) were no different to those admitted for other reasons (data not shown).

Figure 1 summarizes the suspected ADRs which caused admission according to the organ-system affected. It should be noted that a single report can contain several clinical manifestations. The total number of adverse reaction terms coded was 42, with a mean of two per case. The results show that the most commonly affected organ-systems were the central nervous system (40.5%), digestive system (16.7%) and skin and appendages (14.3%). Together, they accounted for 71.5% of admissions attributed to ADRs. The most common clinical manifestations inducing admission were convulsions (4 cases), dizziness (4), vomiting (3) and tremor, fever, itching or apnoea (2 cases each).

The 40 drugs suspected, alone or in combination, of causing admission are shown in Figure 2. The mean number of pharmaceutical formulations was 1.9 per patient, corresponding to eight groups of the ATC classification. The drugs most commonly associated with suspected ADRs were respiratory drugs ($n=14$; 35%), anti-infective agents ($n=10$; 25%), drugs active on the central nervous system ($n=6$; 15%), and drugs used in dermatology ($n=4$; 10%). Together, they accounted for 85% of drugs related to suspected ADRs which caused admission. The most common ADR-related pharmaceutical formulations were a combination of chlorpheniramine, diphenhydramine, phenylephrine, guaiphenesin and salicylic acid in fixed proportions (observed in four cases), followed by fenoterol, adrenaline, paracetamol, Diphtheria-Tetanus-Pertussis vaccine and antipolio vaccine (in two cases each).

The mean number of pharmaceutical formulations

Figure 1 Profiles of the proportion of the total number of suspected adverse drug reactions as a cause of admission for each of the major organ-systems. Note that a single admission can have several clinical manifestations and several suspected drugs.

Figure 2 Profiles of the proportion of the total number of suspected adverse drug reactions as a cause of admission for each therapeutic group. Note that a single admission can have several clinical manifestations and several suspected drugs. R = Respiratory system; J = Anti-infective; N = Central Nervous System, including analgesics; D = Dermatological; A = Digestive system, including vitamins; C = Cardiovascular; H = Hormones.

consumed during the month before admission for suspected ADR was 5.8 ± 3.1 per patient, which is not statistically different to the number consumed by patients admitted for other reasons (4.6 ± 2.6).

Suspected ADRs reported as a cause of hospitalization were of mild severity in 4.8% (1 case), moderate in 57.1% (12 cases) and severe in 38.1% (8 cases). During the study no deaths were directly attributable to ADR. It is not possible to compare the two study periods due to the small numbers of cases in each. Table 2 shows details of the eight suspected ADR classified as severe. Six of these are recognized reactions to the implicated drugs; however, the remaining two ADRs involve only anecdotal reports in the literature. Except in these last two cases, in which the effects of the suspected ADR proved permanent, all patients recovered without long-term sequelae.

Regarding imputability, according to Spanish causality terms [10], the ADRs were considered to be definite in 1 case (4.8%), probable in 15 (71.4%), possible in 2 (9.5%) and conditional in 3 (14.3%).

Table 3 shows the age and sex distribution of patients admitted with suspected ADRs. There were no significant differences between children older and younger than 1 year (OR = 0.89; 95% CI 0.37–2.17) or between sexes as regards hospital admittance due to ADRs (OR = 1.94; 95% CI 0.72–5.42).

Discussion

During the 204 days of the study, 21 of 512 paediatric out-patients were hospitalized for an adverse reaction due to medication taken out of hospital. In agreement with Mitchell *et al.* [8], there was a female predominance among patients admitted for ADR, although this was not significant. Einarson [14] suggested in a review that studies in adult patients show a female predominance, although some of the studies cited reported a higher proportion of males [14]. Our results contrast

Table 2 Details of adverse drug reactions classified as severe

Age (months)	Sex	Indication	Suspected drugs		ADR effects	Imputability
			(*)	In combination (fixed proportions)		
11	Female	Cough	Codeine		Coma	Probable
8	Male	Upper airways infection	Acetylsalicylic acid; chlorpheniramine, phenylephrine, diphenhydramine, guaiphenesin and salicylic acid (*).		Haematemesis Melaenas	Probable
11	Male	Bronchiolitis	Theophylline; adrenaline; fenoterol		Tachycardia	Probable
3	Male	Bronchospasm	Hydrocortisone		Apnoea	Probable
2	Female	Bronchospasm	Adrenaline i.v.		Abscess in injection zone with ulceration and secondary sepsis	Probable
16	Female	Convulsions; upper airways infection	Chlorpheniramine, phenylephrine, diphenhydramine, guaiphenesin and salicylic acid (*); and rectal diazepam		Apnoea	Possible
8	Male	Immunization	Diphtheria-Tetanus-Pertussis and antipolio vaccines		Convulsions (West syndrome)	Possible
16	Female	Immunization	Diphtheria-Tetanus-Pertussis vaccine		Convulsions with encephalopathy (Kinsbourne syndrome)	Possible

Table 3 Summary of records from the age and sex distribution of patients admitted with suspected adverse drug reactions (ADR)

	Female	Male	Total	<1 year	>1 year	Total
ADR	14	7	21	14	7	21
No ADR	249	242	491	340	151	491
Total	263	249	512	354	158	512

with those obtained through spontaneous reporting of ADRs, which reflect a male predominance [9, 15].

Our proportion of 4.3% of admissions related to ADRs is higher than that reported by Mitchell *et al.* [8] and Whyte & Greenan [16], though these authors used larger populations and included children up to and over the age of 12 years. These differences may be related to variations in both the characteristics of the populations studied and to the patterns of drug utilization. Wessling *et al.* [17] suggest that drug consumption in children is greatest in younger age groups. Similar studies in adults have shown that the proportion of ADRs causing admission is higher than in our study [2, 4–6].

We found no differences in the number of drugs used in the month preceding admission among patients admitted for suspected ADRs and patients admitted for other reasons. This finding does not support the observations of other authors in studies of adults, where a higher average number of drugs taken by patients in the ADR group are reported [4, 6]. However, it is difficult to make comparisons because these studies do

not report on the period covered by the questionnaires regarding drug use prior to admittance. In this sense, the observation period in our study regarding the use of drugs was relatively long, and this could induce recall bias.

The morbidity of ADRs causing hospitalization in our study is similar to that described by McKenzie *et al.* [18], although in the present study there were no fatal reactions. This difference may be explained by the fact that we have not included the oncological and HIV-infected patients who often receive drugs with low therapeutic indices. On other hand, McKenzie *et al.* [18] included children over 10 years of age, and the usual age of onset of many severe diseases (e.g. acute leukaemia, acute glomerulonephritis, seizures) is in the 6- to 15-years age range. We would emphasize the increased proportion of severe reactions (38.1%), and among these were two cases of neurological syndromes related to vaccines. Although vaccines commonly produce mild reactions [19], there are data in the literature suggesting that serious complications can occur with DTP vaccines, as happened in two patients in our study [20, 21]. Studies analysing serious acute neurological illnesses such as the West and Kinsbourne syndromes report contradictory results [22–24]; however, these studies support the hypothesis that there could be a purely temporal and non-causal relation between vaccination and neurological syndromes because the vaccination calendar coincides with the age period in which both pathologies are most frequent. Further studies should be designed to clarify this relationship, though they may be limited by the low frequency of these syndromes. The fact that the central nervous system is

the most commonly affected body system supports the hypothesis of increased neurological sensitivity among younger children [25].

With respect to the therapeutic class implicated, it is difficult to make comparisons with the study by McKenzie *et al.* [18], because these authors included antineoplastic drugs (representing 37.8% of the drugs) and these drugs were excluded from our study. In the present study the high proportion of reactions to respiratory drugs leading to hospitalization is mainly due to bronchodilators. This finding is in agreement with the results reported by Kramer *et al.* [26]. Moreover, the drug most frequently related to ADRs was a combination of antihistamines, sympathomimetics and salicylic acid much used as a decongestant in general paediatric out-patients but of unproven efficacy [27]. This kind of pharmaceutical formulation has been frequently related to ADRs in Sweden, where they are now little used [17]. The second most important group of drugs related to ADRs was broad-spectrum antibiotics. Following the recommendations of Lee *et al.* [28], it is not advisable to compare the patterns of drug utilization seen in the present study with those described elsewhere, for they did not define the season in which the studies were made, and the pattern of drug use may have differed considerably as a result.

We did not find a higher proportion of admittance due to ADRs among children under 1 year of age compared with those aged 1–2 years, although the small sample-size makes it difficult to conclude this with certainty. In this respect, there seem to be no other studies with which to compare our results [15].

Safe drug use in children presents some problems related with patient age, adult-dependent dosing, and limitations on the inclusion of children on clinical trials. In agreement with Meyboom [25], the post-marketing surveillance of the drugs used in children is becoming necessary in order to further knowledge and improve the safety of medicines in this population group. In this sense, our study suggests that variations in prescribing practices may alter the frequency with which reactions occur, at least in relation to suspected ADR caused hospital admissions. Since drug utilization may vary considerably between regions [29], a factor which may also affect the external generalizability of a survey, it is important to carry out regional studies to establish the frequency and nature of the ADRs, and to evaluate prescribing practices to identify groups of drugs which are not used optimally.

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