Adverse drug reactions leading children to the Emergency Department

Reações adversas a medicamentos levando crianças a atendimento na emergência hospitalar

Abstract

The aim of the study was to determine the incidence of adverse drug reactions (ADR) that led children to hospital emergency care in a university hospital in São Paulo, SP. Medical charts (MC) of patients seen at the pediatric emergency department were selected according to International Classification of Diseases (ICD) codes consistent with ADR. Of 23,286 cases studied, 2,409 records were selected. An ADR was observed in 83 (0.36%) MC. Most ADR occurred in children aged 1-5 years with a slight predominance in males (51.8%). The drugs most commonly involved were antibiotics for systemic use (53.0%), vaccines (9.6%) and analgesics (7.2%). Most ADR were dermatological (54.2%) or gastrointestinal (22.9%) manifestations. Two ADR were considered severe (2.4%) while 61.4% were mild and 36.1% were moderate. The incidence was lower than in the literature, probably because it is a retrospective study that used the ICD for selecting the data assessed. The characteristics of ADR are similar to those found in other countries. Interventions are needed to improve the diagnosis and the use of antibiotics, as they were the drugs most involved in the ADR observed. Research in hospital emergency is important to acknowledge ADR that occur outside the hospital setting and may help to identify the most severe ones. Despite limitations, the method requires few resources and materials, and is a good alternative to initial diagnosis. The present study should be followed by studies with higher sensitivity to detect these reactions in order to propose prevention measures.

Keywords: Pharmacoepidemiology. Adverse drug reaction. Emergency care. Product surveillance. Drug utilization.

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Resumo

Determinou-se incidência de reações adversas a medicamentos (RAM) que levaram crianças a atendimento de emergência em um hospital universitário de São Paulo, SP. Foram analisadas, retrospectivamente, 23.286 fichas de atendimento (FA) em emergência pediátrica, a partir de código CID que indicasse possível RAM. Observaram-se 83 (0,36%) RAMs. A maioria ocorreu na faixa etária entre 1 a 5 anos com leve predominância no sexo masculino (51,8%). Os medicamentos mais implicados foram antibacterianos para uso sistêmico (53,0%), vacinas (9,6%) e analgésicos (7,2%). A maior parte das RAMs foram manifestações dérmicas (54,2%) ou gastrointestinais (22,9%). Duas RAMs foram consideradas graves (2,4%) e levaram a internação; enquanto 61,4% foram leves e 36,1% foram moderadas. A incidência foi inferior à literatura, provavelmente por ser estudo retrospectivo, utilizando-se o CID para seleção das FA. Observou-se que, no Brasil, as RAMs levam crianças a atendimento de emergência, com características semelhantes às de outros países. Intervenções são necessárias para melhorar o diagnóstico e a utilização de antimicrobianos, uma vez que foram os medicamentos mais implicados nas RAMs observadas. A pesquisa no setor de emergência hospitalar é importante para se conhecer as RAMs que ocorrem fora do contexto hospitalar, podendo contribuir para identificar aquelas de maior gravidade. A metodologia utilizada, apesar das limitações, requer poucos recursos humanos e materiais, sendo uma boa alternativa para um diagnóstico inicial, que deve ser sucedido por estudos mais elaborados e de maior sensibilidade para detectar essas reações e propor medidas dirigidas à sua prevenção.

Palavras-chave: Farmacoepidemiologia. Reação adversa a medicamento. Atendimento de emergência. Estudos de avaliação pós-comercialização. Uso de medicamentos.

Introduction

Adverse drug reactions (ADRs) are defined as "a noxious and unintended response to the use of a drug, which occurs at doses normally used in humans for prophylaxis, diagnosis or treatment of diseases or to modify a physiological function". [1] They are a particular type of adverse drug events (ADE) [2], occurring despite the proper use of these inputs.

A review of the literature suggests that the incidence of ADRs in hospitalized patients may range from 1.2% to 24.1%. The authors also found a rate of fatal adverse reactions of 0.23% to 0.41% and singled ADRs out as being between 4th and 6th leading cause of death in the United States[3]. It is estimated that such incidents occur among 2 and 5% of children[4].

In general, research on drug-related problems is conducted during hospitalization or seeks to determine the frequency of reactions that are serious enough to require hospitalization. However, the latter do not express the frequency of visits to emergency services because many of these do not result in hospitalization[5].

A prospective study carried out in a hospital on the Canary Islands showed that 1.73% of the visits to the emergency room were related to an ADR[6]. A similar study conducted in India, but with diverse results, observed, over a six-month period, a rate of 4.2% of the care provided at hospital emergency rooms were related to ADEs, 90% of which derived from ADRs[7].

A meta-analysis of ADR studies in pediatric patients showed an average incidence of 1.46% (0.7 to 2.7%) of outpatient ADRs[8], while a more recent systematic review found that the incidence of ADRs in pediatric ambulatory patients ranged from 0.75% to 11.1%[9]. In French emergency services there was a 0.93% incidence of ADRs among children which lead to the provision of care[10].

In Brazil, there were 26,540 reported cases of poisoning by drugs (26.4% of all poisonings) in 2009. Of these, 11,242 (42.4%) occurred among children aged fewer than 14

years[11]. Part of the incidents, 2,792 (10.5%), was reported as having occurred due to therapeutic use[12]. However, despite this magnitude, studies on emergency room visits or hospital admissions of children on account of problems related with drugs are scarce in the country.

The most serious incidents, particularly the acute ones, tend to be cared for in hospitals. Therefore, researching this issue in emergency rooms is justified, since this is the interface between primary care and hospital care. The emergency room can be a good observatory, as that is where the most relevant reactions can be identified and analyzed.

The purpose of this study was to determine the incidence of ADRs that led children to hospital emergency care.

Material and Methods

A descriptive, retrospective and cross-sectional study was conducted on the medical charts of the Pediatric Emergency Room at a university hospital in São Paulo that provides care to an average of 250 children aged up to 15 years every day.

The charts were surveyed for ADRs, i.e., harm or injury, mild or severe, caused by a drug therapy or by the lack of such therapy when one was needed[2]. The events were rated in two ways: 1) if the emergency treatment chart had some report of drug misuse or of any deviation from its therapeutic use, e.g., attempted suicide, such events were called medication errors; 2) when the report excluded product use deviations, there was a temporal relationship between use and effect, and when there was a pharmacological plausibility for the occurrence of a clinical manifestation, the events were rated as adverse drug reactions.

For this study, we only analyzed charts with suspected ADRs.

The expected frequency of adverse events in pediatric emergency services that appears in the literature, i.e. between 0.86% and 10.6%[13] was considered.

An emergency room data collection period that would allow meeting a level of confidence of 95% was used. A random choice was made to begin collecting data regarding services provided in May 2006.

In order to calculate the total period of analysis, both the incidence of the variable from month to month and the expected error in the established confidence interval were examined. The observation period was determined by comparing the differences between two population proportions. The hypothesis test[14] validated the sufficiency of the observation for 3 consecutive months. Therefore, the medical charts for the months of May, June and July 2006 were studied.

The information collected from the charts included demographics, drug use, reported signs and symptoms and diagnoses. The latter, classified according to the International Classification of Diseases - ICD 10[15], was copied as it appeared in the medical charts. The description of each code was analyzed independently by two researchers, and the code was classified as compatible or not with a possible ADE even if it was not clear that this was the reason why the person had sought care. In the event of disagreement, consensus was sought.

All ICD grouped in Chapter XII (Skin and subcutaneous tissue diseases - L00-L99) were selected as compatible, as were others that described cutaneous manifestations. ICDs grouped in Chapter XIX (Injury, poisoning and other consequences of external causes - S00-T98) and in Chapter XX (External causes of morbidity and mortality - V01-Y98) were also searched for. The charts whose ICDs mentioned infectious or parasitic diseases or traumas were excluded. The remaining ones were examined one by one. From among the discarded ICDs, a random sample of 10% among those related to specific symptoms such as nausea and vomiting (R11) or cough (R05) were included for examination.

The ADRs were considered severe according to the criteria set forth by the World Health Organization[16]. When they required changes in therapy or specific treatment, they were considered moderate. Those not

requiring specific treatment or antidotes, and those that did not require the drug to be suspended were considered as mild.

The drugs were classified using the Anatomical Therapeutic Chemical Classification Index (ATC)[17].

The project was approved by the Ethics Committee on Human Research at the University Hospital - USP. There was no conflict of interests.

Results

The ICD codes for a universe of 23,286 visits occurred during the study period were examined, of which 2,463 met the inclusion criteria. A total of 54 charts were not found, resulting in a loss of 2.2%. Thus, 2,409 charts were selected. A total of 136 suspected cases were singled out in the analyses. Adverse drug events were noticed in 96 of them (0.4% of all visits), 11 were dismissed as ADEs and 28 could not be classified due to a lack of information. Of the 96 ADEs, 13 (0.06%) were medication errors (suicide attempts, accidental ingestion, lack of adherence to treatment, among others) and 83 (0.36%) were considered as ADRs and analyzed for this study.

The characterization of the children who experienced ADRs, by gender and age, appears in Table 1. The drugs involved in the adverse reactions are shown in Table 2. In 77.1% of the cases, there was only one drug involved. In two situations, the drug could not be determined, since the child used two different medications and the ADR was compatible with both.

In terms of severity, of the 83 ADRs, 51 (61.4%) were mild, 30 (36.1%) required some type of intervention such as suspension (8), drug replacement (6), the prescription of an antidote drug or a specific medication for the symptomatology (13) or, also, combined interventions such as the suspension or replacement of the medication and prescription of an antidote (3) and were considered moderate. Two (2.4%) led to hospitalization and were considered severe. One was attributed to amoxicillin, while the other to metoclopramide. Fifteen adverse reactions to amoxicillin were considered as mild and 11 as moderate. Most of them (70%) had dermal manifestations such as a rash or hives, while the remaining were gastrointestinal reactions, mainly diarrhea. Two reactions attributed to amoxicillin-clavulanate were dermal and moderate.

All vaccine reactions were considered mild fever peaks with the exception of a seizure after a DPT vaccine, which was considered moderate in accordance with the criteria used in this study.

Considering all ADRs observed, most

Table 1 – Distribution, by age and sex, of children with adverse drug reactions seen in a pediatric emergency department, May - July 2006.
Tabela 1 *– Distribuição do sexo e faixa etária de crianças atendidas num Setor de Emergência Pediátrica Hospitalar, entre maio e julho de 2006, com reação adversa a medicamento.*

Age	Gender		
	Female N (%)	Male N (%)	Total N (%)
Aged less than 1 month	3 (75.0)	1 (25.0)	4 (100.0)
1 month to 11 months	12 (54.5)	10 (45.5)	22 (100.0)
1 to 5 years	13 (38.2)	21 (61.8)	34 (100.0)
6 to 10 years	5 (35.7)	9 (64.3)	14 (100.0)
11 to 15 years	7 (77.8)	2 (22.2)	9 (100.0)
Total	**40 (48.2)**	**43 (51.8)**	**83 (100.0)**

Table 2 – Drugs associated with adverse drug reactions that led to care in a pediatric emergency department according to the Anatomical Therapeutic Chemical classification - May - July 2006.

Tabela 2 *– Medicamentos implicados em reações adversas a medicamentos que levaram a atendimento no Setor de Emergência Pediátrica Hospitalar, no período de maio a julho de 2006, segundo a classificação ATC - Anatomical Therapeutic Chemical.*

Therapeutic Group	ATC	N (%)
Antibacterials for systemic use (J01)		**43(51.8)**
Amoxicillin	J01CA04	27 (32.5)
Cephalexin	J01DB01	5 (6.0)
(sulfamethoxazole + trimethoprim)	J01EE01	3 (3.6)
amoxicillin + clavulanate	J01CR02	2 (2.4)
Ceftriaxone	J01DD04	2 (2.4)
Others (cefaclor, cefuroxime, erythromycin, unspecified)		4 (4.8)
Vaccines (J07)		**8 (9.6)**
DPT Vaccine	J07	4 (4.8)
Other vaccines (BCG, Hepatitis B, Tetravalent, unspecified)		4 (4.8)
Analgesics (N02)		**6 (7.2)**
Dipyrone	N02BB02	3 (3.6)
Paracetamol	N02BE01	2 (2.4)
Aspirin	N02BA01	1 (1.2)
Antiinflammatory and antirheumatic products (M01)		**3 (3.6)**
Nimesulide	M01AX17	2 (2.4)
Diclofenac potassium	M01AB05	1 (1.2)
Drugs for functional gastrointestinal disorders (A03)		**4 (4.8)**
Bromopride	A03FA04	2 (2.4)
Metoclopramide	A03FA01	2 (2.4)
Corticosteroids for systemic use (H02)		**3 (3.6)**
Dexamethasone	H02AB02	1 (1.2)
Prednisolone	H02AB06	2 (2.4)
Drugs for obstructive airway diseases (R03)		1 (1.2)
Ophthalmologicals (S01)		1 (1.2)
Antihistamines for systemic use (R06)		1 (1.2)
Vitamins (A11)		1 (1.2)
Antibiotics and chemotherapeutics for dermatological use (D06)		1 (1.2)
Antianemic preparations (B03)		1 (1.2)
Antihistamine (D04)		1 (1.2)
Nasal preparations (R01)		1 (1.2)
Antiemetics and antinauseants (A04)		1 (1.2)
Cough and cold preparations (R05)		1 (1.2)
All other therapeutic products (V03)		1 (1.2)
Drug combinations		**2 (2.4)**
Amikacin + crystalline penicillin	J01GB06 + J01CE01	1 (1.2)
Ibuprofen + prednisolone	M01AE0 + H02AB06	1 (1.2)
Non-rated		3 (3.6)
Total		**83 (100.0)**

were dermal manifestations (54.2%) such as rashes and/or hives or gastrointestinal (22.9%), such as vomiting, diarrhea or nausea.

Discussion

The incidence of adverse reactions seen in 0.36% of the provisions of care was lower than that portrayed in the literature, possibly due to factors such as methodology, population and data collection. Other studies performed with similar objectives use different concepts to define the events they are investigating. Sometimes the definition includes, for example, intentional overdoses[20] or use other than that specified for the product[21]. A review of the literature found that the variety of terms used to define drug events leads to disparities in results and publications and, in daily practice, can be confusing to the professionals, who often do not know how to classify an event they witness or will report. This prevents the knowledge of the true impact caused by these events and is an obstacle to a true understanding of the issue[20].

Using the ICD code to select the charts to be analyzed contributed to the low incidence rate observed. One can assume that the results are underestimated, since there may be other events in the universe of charts that were analyzed whose codes prevented them from being identified. It was also not possible to analyze all forms with suspected ADRs given the difficulty of locating some of them or on account of the lack of information in these documents, which may have underestimated the results. Problems related to lack of information in emergency room medical records had already been singled out as an issue in a similar study conducted in a Canadian hospital[21]. Moreover, in retrospective studies, the lack of contact with the patient to supplement the recorded data and information often precludes quality assessments. In general, retrospective studies show lower incidence rates than prospective ones[13].

Most adverse events were seen in children aged 1-5 years. This is not surprising, given that among the care provided by these services during the study period, 42.3% were for children in this age group.

There was a slight predominance of ADRs among males. This was noticed in Spain[22], in a Canadian hospital[21] and in a study that used data from the VigiBase, the database belonging to the WHO's Uppsala Monitoring Center, located in Uppsala, Sweden[23]. In adults, however, adverse reactions have been predominantly observed among women[24,25,26].

In general, the studies show adult women as the most susceptible to ADRs and suggest that the risk is associated with the number of drugs used, with the therapeutic class, the type of adverse reactions, age and to the physiological condition of women, such as lower body mass, reduced hepatic clearance, and differences in metabolism, among other factors[27]. Some authors also cite differences in metabolism between the genders and regarding drug classes. For example, boys have a higher prevalence of hypersensitivity to NSAIDs than girls. They mention, however, that this diversity requires further study[28]. Other studies report that it is unclear whether, in general, boys have more severe health problems and require the use of drugs favoring an ADR. Alternatively, they suggest that the young male population may be physiologically more sensitive to these events[23]. These inequalities may help explain why in this and in other ADRs studies, these events occurred predominantly among males.

Unlike other authors[8,9], polypharmacy was not a factor associated with adverse reactions in this case, since most of the events that were observed reported the use of a single drug.

The therapeutic drug classes associated with adverse reactions in children are, with variations in order, the same as those found in this study. This was noticed for outpatient ADRs[9, 29], i.e., occurring outside the hospital, and those leading to visits to the emergency room[18, 21, 30, 31], as in this case. It was also noticed in spontaneous reports

made to national pharmacovigilance systems, such as those in Spain[22] and Sweeden[32]. In the assessment of the National Injury Mortality Surveillance System regarding events leading to care in the emergency room in U.S. hospitals, it was found that in 91.5% of cases, the events were associated with an antimicrobial agent and 2.8% of cases with vaccines[33]. In all cases, antibiotics were among the drugs that resulted in the most ADRs. This is not surprising, since studies show that these drugs are the most commonly prescribed for children.

An editorial says that the risks associated with the use of antibiotics continue on the rise and, depending on the antibiotic, 5 to 25% of patients have diarrhea associated with their use, about 2% will develop a dermatological reaction, and about 1 in 5000 users will have an anaphylactic reaction[34].

It is estimated that 142,505 emergency room visits took place between 2004 and 2006 in the United States due to adverse events to antibiotics. These drugs, targeted for systemic use, were involved in 19.3% of all visits related to adverse events and 25.9% occurred among children aged fewer than 14 years[35]. The editorial claims that these findings are only the tip of the iceberg, since many patients have mild reactions that do not take them to the emergency room or they simply stop taking the antibiotic[34].

Some authors consider that because the more immediate risks related to the use of antimicrobials are considered mild and infrequent, campaigns to reduce inappropriate use do not include messages about these issues, but are focused on antimicrobial resistance[35]. A change of focus to this other perspective could improve the use of these products.

Among the antibiotics, the use of amoxicillin was the most cited, and the most frequently observed reactions were gastrointestinal and dermal, predominantly the latter. The same was observed in the Netherlands[29] and in Spain[22]. However, in the latter case, the amoxicillin-clavulanate ADRs were more frequent than those related to amoxicillin, unlike what happened here. In Italy, an analysis was made of a database of spontaneous reports of adverse reactions to compare the safety profile of these two antibiotics. The percentage of dermal reactions was higher for amoxicillin than for amoxicillin-clavulanate, whereas gastrointestinal, liver and blood reactions were more prevalent for the latter, which also had the highest proportion of severe adverse reactions. The authors recommend that, given the severity of the reactions that amoxicillin-clavulanate may cause, the risk-benefit of its use should be thoroughly evaluated before it is prescribed, favoring the indication of amoxicillin as the first choice of antibiotics for uncomplicated infectious diseases[36].

From 1987 to 2001, 40% of the adverse reactions in Sweden, in the pediatric population, were related to vaccines. Among the 10 drugs most commonly involved with ADRs was a vaccine or a combination vaccine including dual DT (diphtheria-tetanus), a vaccine for *Haemophilus influenza* B and DPT (diphtheria-tetanus-pertussis). The most severe reactions were fever and febrile seizures[32]. In the Spanish Pharmacovigilance System, vaccine reactions were preceded by reactions to antimicrobial agents for systemic use and drugs for the respiratory tract, a fact that has been attributed to differences in drug use patterns between those two countries. Seventy percent of febrile reactions were related to vaccines[22].

The combined vaccine against diphtheria, pertussis and tetanus (DPT) is the one that is most frequently associated with adverse events among those of routine use. In fact, among the 8 vaccine reactions identified in this study, four were associated with this vaccine. An assessment of adverse events following DPT vaccinations reported in the state of São Paulo in the period ranging from 1984 to 2001, among children aged fewer than 7 years, identified 10,059 of such events. The most common were fever below 39.5°C, local reactions, hypotonic-hyporesponsive episodes and seizures[37]. In this study, all children had fevers, one had irritability and there was one seizure.

Identifying these events is important in order to maintain trust and adherence to immunization programs.

Most ADRs were considered as mild, with no need for intervention. The proportion of severe reactions was lower than in similar studies[19,21], probably because in those studies, the definition of the studied event was more comprehensive than that used in this one.

The most frequently observed symptoms were similar to those seen in other studies of ADRs in children[18, 19, 23] likely because the therapeutic classes involved were also similar.

This study shows that ADRs lead children to emergency care in Brazil. The frequency in the service studied was lower than that seen in the literature. However, the characteristics of the individuals affected, the symptoms observed and drugs involved were similar to those noticed in other countries. Since antimicrobial drugs appear to be the ones that cause the most ADRs in children, educational interventions are needed to improve the diagnosis and control of infections and to mitigate the consequences of the unnecessary use of this therapeutic class.

The research into emergency hospital care is important in order to get to know events related to drugs that occur outside the hospital setting and can help identify the more serious ones.

It is difficult to compare with other studies, particularly in Brazil, on account of the paucity of studies investigating ADRs in children leading to emergency care here. As already mentioned, the diversity in the definitions and methodology of the studies that have been published also renders it difficult to make comparisons. Retrospective studies allow for little accuracy in determining the observed events. However, despite the limitations, the methodology requires few human and material resources in order to be implemented. It was also shown to be a good choice for an initial diagnosis of the service, and may be succeeded by more elaborate studies. Prospective studies, for example, may include interviews with prescribers and patients, obtaining additional information that will improve the knowledge about ADRs that lead children to emergency care and their characteristics so it will be possible to propose measures to prevent them.

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