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Multicentric study on the incidence and preventability of medication-related incidents in patients visiting pediatric emergency departments

Estudio multicéntrico de la incidencia y evitabilidad de los incidentes por medicamentos en pacientes que acuden a los servicios de urgencias pediátricas

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Abstract

Objective: To determine the incidence, severity, and preventability of medication-related incidents in patients visiting pediatric emergency departments, and to identify the highest-risk age groups and the drugs most frequently involved.

Method: This is a multicenter prospective observational study carried out between March and June 2017 in patients between 0 and 16 years of age who visited the pediatric emergency department of eight Spanish public hospitals. We recorded and assessed three different types of incidents: adverse drug events, medication errors, and accidental self-poisoning. Incidents were characterized according to severity, preventability, age groups affected, and drugs involved.

Results: During the study period, a total of 99,797 visits were recorded to the pediatric emergency departments following 334 drug-related incidents in as many patients, of whom 52.4% were male, with a mean age of 47.1 ± 44.4 months. The incidence of patients with drug-related incidents

Resumen

Objetivo: Determinar la incidencia, gravedad y evitabilidad de los incidentes por medicamentos detectados en los pacientes que acuden a los servicios de urgencias pediátricas, e identificar los grupos de edad de mayor riesgo y los medicamentos implicados.

Método: Estudio multicéntrico observacional prospectivo, realizado entre marzo y junio de 2017, en pacientes entre 0 y 16 años que acudieron a los servicios de urgencias pediátricas de ocho hospitales públicos españoles. Se recogieron tres tipos de incidentes: eventos adversos por medicamentos, errores de medicación e intoxicaciones accidentales. Los incidentes se caracterizaron atendiendo a su gravedad, evitabilidad, grupos de edad afectados y medicamentos implicados.

Resultados: Durante el periodo de estudio se registraron 99.797 visitas a los servicios de urgencias pediátricas y se recogieron 334 incidentes por medicamentos en 334 pacientes, de los cuales el 52,4% fueron varones, con una media de edad de 47,1 ± 44,4 meses. La incidencia de pacientes

KEYWORDS
Children; Drug-related side effects and adverse reactions/epidemiology; Medication errors/statistic and numerical data; Emergency services.

PALABRAS CLAVE
Niños; Efectos adversos asociados a medicamentos y reacciones adversas/epidemiología; Errores de medicación/estadística; Servicios de Urgencias.

was 0.3%. Of the total incidents, 264 (79%) were considered preventable and 158 (47.3%) had caused harm to patients. Incidents detected included 144 (43.1%) adverse drug events, 218 (65.2%) medication errors (74 of them leading to harm; these are also included as preventable drug-related adverse events), and 46 (13.7%) cases of accidental self-poisoning. Preschoolers (1-5 years of age) represented 60.8% of incidents and were the age group with the highest percentage of preventable incidents (64%). A total of 351 drugs were involved in the 334 incidents detected, most of which fell into one of three therapeutic groups: anti-infectives for systemic use (171; 48.7%), nervous system (66; 18.8%) and respiratory system (41; 11.7%).

Conclusions: The incidence of drug-related incidents in pediatric patients presenting to emergency departments was lower than that reported for adult patients, although almost half of the incidents identified were associated with harm. Preschool patients (1-5 years of age) were identified as the age group at the highest risk. The recorded incidents were caused by a small number of drugs. A high percentage of incidents were preventable, which confirms the urgent need to implement medication incident prevention strategies for this population.

con incidentes fue del 0,3%. Del total de incidentes, 264 (79%) fueron considerados prevenibles y 158 (47,3%) produjeron daño a los pacientes. Los incidentes detectados fueron 144 (43,1%) eventos adversos por medicamentos, 218 (65,2%) errores de medicación (74 de ellos errores con daño, que se incluyen asimismo como eventos adversos prevenibles) y 46 (13,7%) intoxicaciones accidentales. Los preescolares (edad: 1-5 años) presentaron el 60,8% de los incidentes, siendo también el grupo de edad con un mayor porcentaje de incidentes prevenibles (64%). Un total de 351 medicamentos estuvieron implicados en los incidentes y pertenecieron mayoritariamente a tres grupos terapéuticos: antiinfecciosos de uso sistémico (171; 48,7%), sistema nervioso (66; 18,8%) y sistema respiratorio (41; 11,7%).

Conclusiones: La incidencia de incidentes por medicamentos en los pacientes pediátricos que acudieron a servicios de urgencias fue inferior a la referida en pacientes adultos, si bien prácticamente la mitad de los incidentes detectados causaron daños a los pacientes. Los niños preescolares (1-5 años) fueron identificados como el grupo de edad con mayor riesgo. Los incidentes registrados estuvieron causados por un número reducido de medicamentos. Un elevado porcentaje de los incidentes fueron prevenibles, lo que confirma la imperiosa necesidad de implementar medidas de prevención de incidentes en esta población.

Introduction

Pediatric patients are one of the population groups at greatest risk of suffering medication-related incidents, as there are multiple factors that can lead to the occurrence of such incidents in these patients[1]. Medication errors in children are more common than in adults and the risks that these errors may result in adverse events is up to three times higher[2]. Also, their clinical and social impact is more significant than in adults because children are usually less able to physiologically tolerate a medication error[3]. For that reason, the third Global Patient Safety Challenge of the World Health Organization ("Medication without Harm") considers it a priority to take steps to reduce medication errors in this population segment[4].

Several studies have been conducted on the incidence and characteristics of adverse drug events in the pediatric population, as well as on their clinical impact. However, the incidence and/or prevalence data reported in the literature vary significantly depending on the clinical setting considered, the methodology employed, and the type of incident analyzed. Moreover, only a small proportion specify the methodology used to characterize the incidents[5].

In the specific case of emergency setting, most studies in the literature have focused on adult patients. This means that the incidence and the specific nature of the adverse events that motivate visits to pediatric emergency departments (EDs) are currently poorly understood. A systematic review carried out in 2013, which included 11 studies on pediatric patients conducted between 1996 and 2010, estimated an incidence of adverse events leading to visits to EDs or hospital admissions between 0.5% and 3.3% and 0.16% and 4.3%, respectively. Of these, from 20.3% to up to 66.7% were considered preventable[6].

No study has to date been published in Spain that estimates the magnitude and analyzes the characteristics of medication-related incidents suffered by patients visiting pediatric EDs in our country. For this reason, taking into account the importance of improving the clinical safety of such a vulnerable patient population as children, it was considered important to carry out a study aimed at detecting and evaluating the medication-related incidents suffered by pediatric patients visiting Spanish pediatric EDs with a view to determining their incidence and severity, and identifying the most affected age groups as well as the medications involved.

Methods

A 4-month multicenter prospective observational study was undertaken from March 1 2017 to June 30 of 2017 at the pediatric ED of eight Spanish public hospitals, seven of which were general hospitals with over 500 beds that included obstetrics, and the eighth was a children`s-only hospital. The number of emergencies registered at these hospitals in 2017 ranged between 28,826 and 60,174.

The study included incidents experienced by patients under the age of 16 presenting to the ED of any of the hospitals included, regardless of whether the incident was the reason why they visited the ED, or not. Incidents were classified into three groups:

a) Adverse drug events (ADEs), defined as any serious or mild harm associated to the clinical use (or lack thereof) of a drug[7], or any kind of harm resulting from the clinical use of a drug[8]. According to the methodology used in studies of this kind[9]. ADEs were classified into two groups according to their preventabilidy: preventable adverse events (caused by medication errors) and non-preventable adverse events (occurring in spite of an appropriate use of a drug).
b) Medication errors (MEs), defined as any preventable incident that may cause harm to a patient or lead to an inappropriate use of medications when these are under the control of healthcare professionlas, patients or consumers[10].
c) Accidental self-poisoning, defined for the purposes of the study as preventable incidents arising from a fortuitous self-administration of an incorrect medication (or an incorrect dose) by the patient as a result of lack of supervision by their parents, family members or caregivers.

Deliberate self-poisoning incidents were excluded from the analysis.

The following variables were analized for each incident: 1) variables related to the patients' demographic characteristics: sex, date of birth, age group (5 groups were defined: neonates —from birth to 28 days—, infants —from 1 to 12 months—, preschoolers —from 1 to 5 years—, schoolers —between 6 and 12 years— and adolescents —from 13 to 16 years), allergies and reason for consultation; 2) variables related to patients' pharmacological treatment on presentation to the ED: brand name, active pharmaceutical substances, dose and dosage form, route of administration, duration of treatment and indication. Therapeutic groups and subgroups were assigned according to the Anatomical Therapeutic Chemical (ATC) Classification System. The percentage of events that resulted in admissions to observation and to inpatient care was recorded.

All of these variables were included in a checklist that was distributed among the staff of the different pediatric EDs, who were in change of detecting incidents (voluntary reporting system). They were also provided with a decision-making algorithm to help them identify patients eligible for the study, and a series of instructions on how to obtain the most relevant information about an event during the interview with the patients' parents or caregivers. The emergencies medical staff were required to gather a minumum amount of data to make the subsequent analysis possible. They also had to differentiate between preventable and non-preventable incidents and report whether the latter had caused the patient any harm.

The principal investigator of each hospital visited the ED five days a week (from Monday to Friday) to collect the checklists containing the basic information on patients suspected of having suffered an incident. They were also in charge of collecting all the additional information required to properly characterize the incidents. To do that, they reviewed the ED's admission reports, the current and previous months' laboratory reports, and the

medical prescriptions issued on discharge from hospital and from primary care. Data on patients presenting to the ED at weekends or on public holidays were gathered on the following working day.

The pediatrician in charge in every hospital together with the hospital's pharmacist classified incidents according to type, severity, and preventability. Severity was determined using the classification of the National Coordinating Council for Medication Error Reporting and Prevention[11]. Preventability was evaluated by means of an adapted version of Schumock & Thornton's preventability assessment scale, published by Otero *et al.*[12]. In cases where an ADE was suspected, the potential cause-effect relationship with the suspected medication(s) was evaluated using the Karch-Lasagna modified algorithm[13]. Each investigator introduced the information collected into a web-based medication-related incident registration platform specifically developed for the study on the Spanish Institute for Safe Medication Practices (ISMP-Spain)'s platform. To ensure patient confidentiality, data were deidentified assigning each patient a sequential numerical code preceded by the hospital's initials. The principal investigator reviewed and validated the data introduced by other investigators to ensure homogeneity of the sample.

Before commencing work on the study, approval was obtained from the ethical committees of the different hospitals as well as from the corresponding agencies of the autonomous regions involved.

A descriptive statistical analysis was carried out of the characteristics of the subjects with respect to the explanatory variables considered in the study. The analyses included frequency distributions for qualitative variables and a calculation of means and 95% confidence intervals for quantitative variables. The statistical analysis was carried out using the SPSS® 2.0 software package. Statistical significance was assumed if p = 0.05.

Results

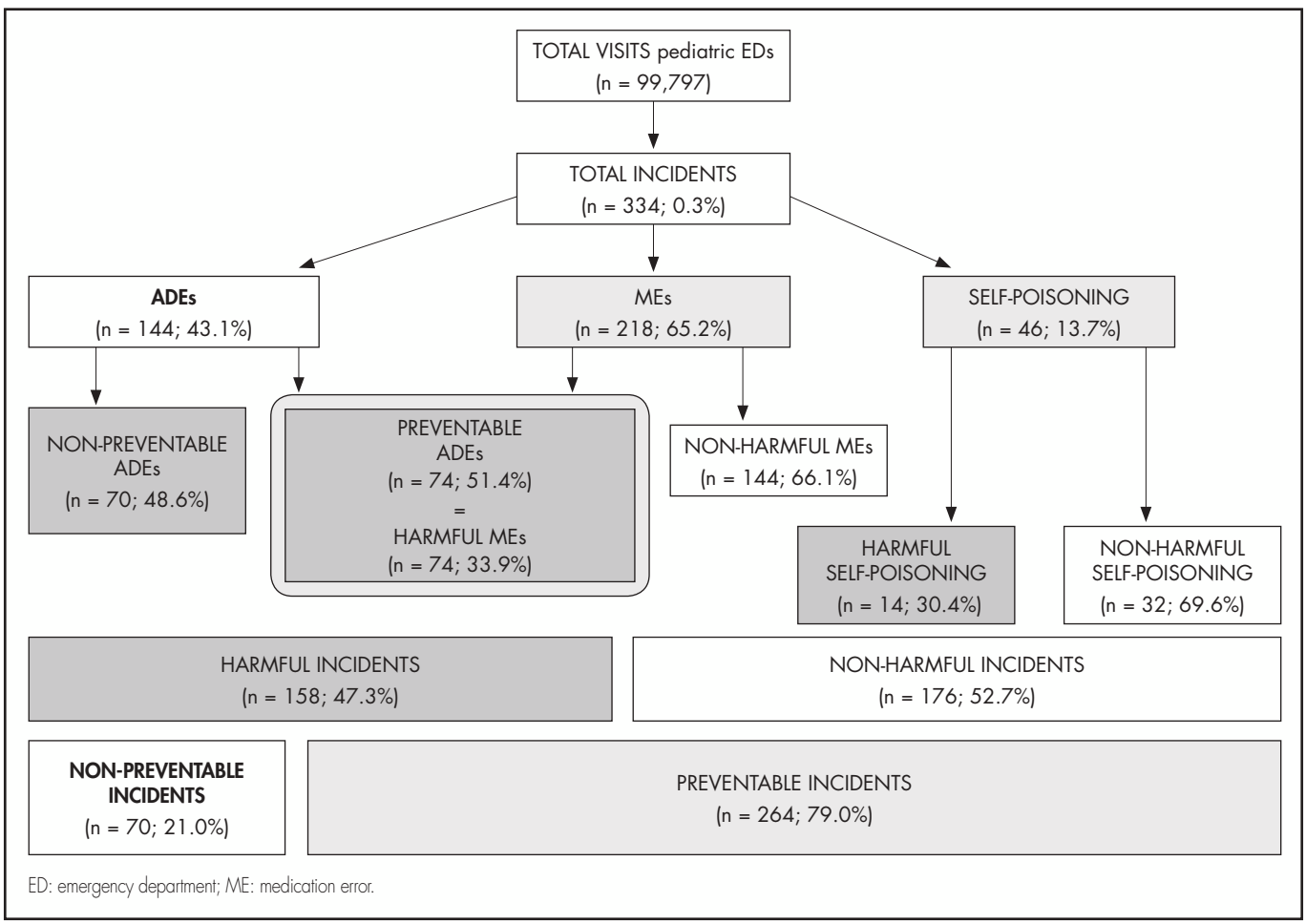
A total of 99,797 visits to the different pediatric EDs were recorded during the study period. Medication-related incidents were identified in 334 patients, of whom 52.4% were male, with a mean age of 47.1 ± 44.4 months. Incidence per patient was 0.3%. No patient experienced more than one incident.

Seventy-nine percent of the incidents recorded were considered preventable (Figure 1). These incidents comprised MEs (218; 82.6%) with harm (preventable ADEs) and without harm, as well as accidental self-poisoning (46; 17.4%). Of all the incidents detected, 158 (47.3%) were harmful to patients. These included 144 ADEs and 14 cases of accidental self-poisoning. A total of 55.7% of these harmful incidents were considered preventable.

As far as severity was concerned, 122 (36.5%) incidents were ascribed to group C (the incident reached the patient but did not cause patient harm); 54 (16.2%) to group D (no harm was caused but the patient was admitted for observation), of which 48.2% (26/54) required observation for 24-48 hours in the ED to ensure that no damage was present; 146 (43.7%) were classified as group E (the incident resulted in temporary harm); and 12 (3.6%) were considered to fall under group F (patients required hospital admission).

Table 1 shows the characteristics of patients who experienced medication-related incidents, as well as the types of incidents experienced per age group, and their preventability. Preschoolers (1-5 years) were identified as the group at the highest risk of suffering medication-related incidents. This group of patients accounted for 60.8% of all patients who experienced incidents, 65.6% of those requiring observation or hospital admission, and

Figure 1. *Classification of incidents according to type, preventability and potential harm to patients.*



ED: emergency department; ME: medication error.

Table 1. Characteristics of patients who experienced medication-related incidents, types of incidents experienced per age groups, and their preventability

	Total patients with incidents N = 334 (%)	Patients with incidents who required hospital admission or observation N = 61 (%)	Preventability		Types of incidents		
			PREVENTABLE n = 264 (% of total preventable incidents)	NON- PREVENTABLE n = 70 (% of total non-preventable incidents)	ADE n = 144 (% of total ADEs)	ME n = 218 (% of total MEs)	Accidental self-poisoning n = 46 (% of all instances of poisoning)
Age							
Mean ± SD (months)	47.1 ± 44.4	57.5 ± 48.8	44.0 ± 40.3	58.2 ± 57.1	42.1 ± 38.4	45.6 ± 42.5	36,0 ± 24,5
Median (months) (IQR)	24 (51)	42 (75)	24 (39)	24 (92)	24 (42)	24 (53)	24 (20)
Distribution into age groups							
Neonates (0-28 days)	5 (1.5)	-	3 (1.1)	2 (2,9)	2 (1.4)	3 (1.4)	-
Infants (1-12 months)	56 (16.8)	7 (11.5)	43 (16.3)	13 (18.6)	26 (18.0)	42 (19.3)	1 (2.2)
Preschoolers (1-5 years)	203 (60.8)	40 (65.6)	169 (64.0)	34 (48.6)	69 (47.9)	126 (57.8)	43 (93.5)
Schoolers (6-12 years)	58 (17.4)	11 (18.0)	44 (16.7)	14 (20.0)	37 (25.7)	42 (19.3)	2 (4.3)
Adolescents (13-16 years)	12 (3.6)	3 (4.9)	5 (1.9)	7 (10.0)	10 (6.9)	5 (2.3)	-

ADE: adverse drug event; IQR: inter-quartile range; ME: medication error; SD: standard deviation.

93.5% of those suffering accidental self-poisoning. Preschoolers were also the age group with the highest rate of preventable incidents (169; 64%). Preventable incidents accounted for at least 60% of all incidents across all groups, except that of adolescents.

A total of 351 medications were involved in the 334 incidents analyzed, with 79.2% being associated with preventable incidents (Table 2). Ninety-six different drugs were involved in the different incidents. Nearly 80% of the drugs associated with the incidents belonged to three therapeutic groups: systemic anti-infectives, neurological drugs, and respiratory agents.

Anti-infectives were the group most frequently involved in the incidents recorded (48.7%), 71.3% of which would have been preventable. Amoxi-

Table 2. Drugs involved in the incidents analyzed

Drugs involved*	Nr of drugs (% of total drugs)	PREVENTABLE (% of total in each group)	NON PREVENTABLE (% of total in each group)
Systemic anti-infectives	***171 (48.7)***	***122 (71.3)***	***49 (28.7)***
Systemic anti-bacterials	**157 (44.7)**	121 (77.1)	36 (22.9)
– Amoxicillin	93 (26.5)	68 (73.1)	25 (26.9)
– Amoxicillin/clavulanic acid	36 (10.2)	28 (77.8)	8 (22.2)
– Others	28 (8.0)	25 (89.3)	3 (10.7)
Vaccines	**13 (3.7)**	-	13 (100.0)
Others	**1 (0.3)**	1 (100.0)	-
Nervous system	***66 (18.8)***	***55 (83.3)***	***11 (16.7)***
Analgesics	**37 (10.5)**	37 (100.0)	-
– Paracetamol	32 (9.1)	32 (100.0)	-
– Others	5 (1.4)	5 (100.0)	-
Psycholeptics	**14 (4.0)**	10 (71.4)	4 (28.6)
Psychoanaleptics	**7 (2.0)**	3 (42.8)	4 (57.2)
Antiepileptics	**7 (2.0)**	4 (57.2)	3 (42.8)
Others	**1 (0.3)**	1 (100.0)	-
Respiratory system	***41 (11.7)***	***40 (97.6)***	***1 (2.4)***
Bronchodilators and inhaled corticosteroids	**17 (4.8)**	16 (94.1)	1 (5.9)
Systemic antihistamines	**10 (2.8)**	10 (100.0)	-
Cold and cough medicines	**10 (2.8)**	10 (100.0)	-
Nasal preparations	**4 (1.1)**	4 (100.0)	-
Musculoskeletal system	***23 (6.5)***	***22 (95.6)***	***1 (4.4)***
Anti-inflammatory and anti-rheumatic drugs	**23 (6.5)**	22 (95.6)	1 (4.4)
– Ibuprofen	22 (6.3)	21 (95.5)	1 (4.5)
– Others	1 (0.3)	1 (100.0)	-
Systemic hormonal preparations	***14 (4.0)***	***13 (92.8)***	***1 (7.1)***
Systemic corticosteroids	**12 (3.4)**	12 (100.0)	-
Others	**2 (0.6)**	1 (50.0)	1 (50.0)
GI tract and metabolism	***14 (4.0)***	***14 (100.0)***	***-***
Antispasmodics and prokinetics	**8 (2.3)**	8 (100.0)	-
Antiacids	**4 (1.1)**	4 (100.0)	-
Antidiarrheals	**2 (0.6)**	2 (100.0)	-
Other therapeutic groups	***22 (6.3)***	***12 (54.5)***	***10 (45.5)***
TOTAL	**351**	**278**	**73**

*The 334 incidents involved 96 different drugs and 351 medicines in total.

cillin was the single drug associated with the largest number of incidents (26.5%).

Neurological drugs were second in terms of frequency (18.8%), 60% of incidents caused by these medicines resulting from accidental self-poisoning. In this group, analgesics were the most frequently involving drugs, with paracetamol as the one responsible for most incidents (86.5%; 32/37), provoking 26% of all self-poisoning incidents. Lastly, respiratory agents accounted for 11.7% of cases, an overwhelming majority of which could have been prevented (97.6%). The remaining therapeutic groups were associated to a lower proportion of incidents. It should be noted that of all anti-inflammatory agents, ibuprofen was involved in 22 cases, and among antispasmodics and prokinetics, there were 3 cases of accidental self-poisoning associated with the ingestion of a homeopathic drug containing belladonna.

Discussion

This study was intended to fill a gap in the Spanish literature with respect to the incidence and preventability of medication-related incidents in children presenting to the ED. Our results showed that 0.3% of children presenting to the different pediatric EDs analyzed experienced medication-related incidents, which is less than the figures reported for both adult patients[14,15] and for most pediatric patients in studies carried out in the same setting, which range from 0.2% to as much as 8%[16-22]. However, it must be noted that nearly half of the incidents reported in this study were harmful to patients (47.3%) and that the percentage of patients with incidents resulting in admission to observation in the ED or to inpatient care was 18.3%. Although it is difficult to make comparisons with other studies, mainly because of differences in the methodology employed to detect incidents and in the types of incidents included, the morbidity rates observed in this analysis were higher than those reported in the published retrospective studies[16,19,21]. Nevertheless, our results are similar to those published by Zed *et al.*[20] in a prospective study like this one.

Of all medication-induced incidents included in this study, 79% were considered preventable, which is more than reported by other studies carried out in the same healthcare setting. This could be attributable to the fact that those studies only focused on ADEs while ours also included non-harmful MEs and cases of accidental self-poisoning, which are —by definition— preventable. Indeed, retrospective studies on ADEs such as those by Sikdar *et al.*[19] and Lombardi *et al.*[22] reported preventability values around 20%, while prospective analyses by Cohen *et al.*[16] and Zed *et al.*[20] found 45% and 65% of preventable ADEs, respectively. The latter are in line with our findings, probably because the prospective nature of those authors' study allowed them, like it allowed us, to analyze the incidents' preventability. It is also important to mention that the percentage of harmful incidents considered preventable in our study was 55.7%. This preventability rate unquestionably warrants the WHO's third Global Patient Safety Challenge ("Medication without Harm"), which considers the pediatric population to be a priority action area and sets the goal of reducing the incidence of preventable ADEs by 50% over the next 5 years[4].

The age group that exhibited the highest number of incidents was that of preschoolers, with 60.8%, of total, a percentage comparable to the results of an epidemiological study that also included accidental self-poisoning. In that study 60% of a total of 8,585 pediatric visits to the ED because of medication-related incidents corresponded to children below 5 years of age[23]. Preschoolers were also the children with the highest percentage of ADEs (47.9%). This finding is in line with different studies in the literature according to which children aged 4 or younger are those who most frequently present to the ED following an ADEs[16-18,21]. More specifically, Cohen *et al.*[16] reported that the incidence of ADEs is four times higher in children under age 5, and up to 10 times higher if the ADEs considered include incidents caused by overdoses resulting from inappropriate storage of the medicines or errors by parents or caregivers.

The incidents recorded in our study were caused by a small number of medicines, with systemic anti-infectives, particularly β-lactam antibiotics, accounting for the majority of cases (48.7%). If only preventable ADEs are considered, anti-infectives were involved in an even higher percentage of incidents (63.5%), which is in line with the situation in other countries[21,22]. For that reason, this drug class must be subjected to specific preventive measures, centered on their availability and accessibility, based on electronic prescription systems like those advocated in the latest pediatric clinical guidelines, and on a close collaboration between primary and specialized healthcare providers.

Neurological drugs were mostly associated with preventable incidents (83.3%), particularly analgesics, which accounted for 10.5% of all incidents. These values are comparable to those reported in the literature[20-22]. Respiratory drugs were overwhelmingly involved in preventable incidents (97.6%), although this group of medicines accounted for only 6.7% of all harmful MEs, a percentage similar to that reported by other authors[18,21]. Cold and cough preparations deserve a special mention given their frequent use in pediatrics to treat respiratory infections. Families should be educated about the scarcity of clinical evidence for these treatments and warned about the potential risk that they could interact with other medicines or even with some kinds of food[24].

The incidence of accidental self-poisoning (0.05%) was lower than previously reported in Spain (0.3%)[25]. A total of 4.3% of these incidents were harmful to the patients resulting in hospital admissions; most of them occurred in preschoolers, with paracetamol being the most commonly involved drug (26%). Over a decade ago, Mintegui *et al.* reported that ED admissions in Spain were most commonly motivated by accidental ingestions in children younger than 5-6 years and that paracetamol was responsible for nearly 20% of accidental poisoning events in those patients[26]. A more recent publication by the same authors claims that the most frequent cases of self-poisoning are related to psychoactive drugs, prompting a reflection on children's access to adult medicines[27]. Our results indicate that self-poisoning remains a serious problem with regard to the safe use of medicines by children under 5 years of age. Despite the improvements introduced by the pharmaceutical industry in the packaging of medicines, educational campaigns are required to ensure that medications are safely stored in people's homes away from children. Steps in this direction have already been taken at an international level[28], an example of which is the *Up and Away and Out of Sight* educational program put together by the Centers for Disease Control and Prevention and other organizations in the United States. This program is a clear example of a proactive initiative to educate parents and other caregivers about the importance of improving medication safety at home[29].

The main limitation of the present study is that many incidents were missed as a result of the high workload of EDs, the high turnover of medical staff, and the unavailability of an onsite pharmacist 24/7. It should also be mentioned that, as with the majority of these kinds of studies, the use of a well-defined methodology reduces, yet does not eliminate, the subjectivity inherent in the analysis of incidents, particularly when it comes to evaluating their preventability.

In summary, this study shows that the incidence of medication-related incidents in the pediatric population presenting to an ED is lower than that for adult patients. However, a significant part of such incidents are harmful to patients and the overwhelming majority of them can be prevented. These data reaffirm the urgent need to implement specific strategies in our country aimed at preventing medication-induced incidents in pediatric patients, following the recommendations of the WHO.

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Conflict of interests

No conflict of interests.

Contribution to the scientific literature

The study provides a valuable insight into the incidence, severity, and preventability of medication-related incidents in patients presenting to the pediatric emergency departments of Spanish hospitals. It also demonstrates that the frequency of incidents is also age-related. Moreover, certain therapeutic groups have been found to be associated with a greater risk of incidents. In short, the study, which presents revealing data about a topic that has seldom been discussed in the Spanish literature, will allow planning the areas in which medication safety initiatives should be prioritized.

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