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Amoxicillin overdose in the pediatric emergency department: A descriptive study

Sobredosificación por amoxicilina en urgencias pediátricas: Estudio descriptivo

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Abstract

Objective: To describe the characteristics of pediatric patients treated in the emergency department due to amoxicillin overdosing.

Method: A retrospective single-center observational study was conducted on patients aged 0 to 16 years treated in a pediatric emergency department due to amoxicillin overdosing between 2011 and 2021. Epidemiological and anthropometric data was collected as well as information on the circumstances of overdosing, clinical manifestations, emergency department management, and discharge destination.

Results: The study comprised 15 patients, 66.6% of them male, with a median age of 3.8 years (interquartile range: 1.9). The most frequent cause of overdosing was accidental ingestion (8/15; 53.3%). Amoxicillin was mainly ingested in liquid form, except for one case with autolytic attempt, where it was ingested in the form of tablets. Eighty percent of subjects (12/15) received a single dose of the drug. The median time to presentation to emergency department was 2.1 hours from ingestion (interquartile range: 2.7) and the median dose of amoxicillin was 219 mg/kg/dose (interquartile range: 148). All patients were asymptomatic, with a normal physical examination. Blood tests were performed in 7 patients (46.6%) and urinary sediment analysis in 2 (13.3%), all of them without alterations. Activated charcoal was administered to 5 (33.3%), patients with a median time to administration of one hour (interquartile range: 1.2). All patients were discharged to their homes. Eleven cases (73.3%) required withdrawal of amoxicillin.

KEYWORDS
Amoxicillin; Drug overdose; Hematuria; Crystallization; Pediatrics; Drug-related side effects and adverse reactions.

Resumen

Objetivo: Describir las características de los pacientes pediátricos atendidos en urgencias por sobreingesta de amoxicilina.

Método: Estudio unicéntrico observacional, retrospectivo, en pacientes de 0-16 años atendidos en urgencias pediátricas por sobreingesta de amoxicilina entre 2011 y 2021. Se analizaron datos epidemiológicos, antropométricos, circunstancias de la sobreingesta, síntomas, manejo y destino.

Resultados: Se incluyeron 15 pacientes, 66,6% varones, mediana de edad de 3,8 años (rango intercuartílico 1,9). La causa más frecuente de sobreingesta fue la ingesta accidental por el paciente (8/15; 53,3%). Fue administrada en forma de suspensión en todos los casos, excepto en un paciente con intención autolítica (comprimidos). El 80% (12/15) recibieron una única dosis. La mediana de tiempo de llegada a urgencias desde la sobreingesta fue de 2,1 horas (rango intercuartílico 2,7) y la mediana de dosis de 219 mg/kg/dosis (rango intercuartílico 148). Todos estaban asintomáticos con exploración normal. Se realizó analítica sanguínea en 7 (46,6%) y sedimento urinario en 2 (13,3%), sin alteraciones. Cinco (33,3%) recibieron carbón activado, con una mediana de tiempo hasta la administración de 1 hora (rango intercuartílico 1,2). Todos fueron dados de alta, suspendiendo el tratamiento 11 (73,3%).

PALABRAS CLAVE
Amoxicilina; Sobredosis de droga; Hematuria; Cristalización; Pediatría; Efectos colaterales y reacciones adversas relacionados con medicamentos.

Conclusions: Amoxicillin overdosing in this study did not appear to result in adverse effects, despite the fact that the recommended doses were significantly exceeded.

Conclusiones: En este estudio, la sobredosificación de amoxicilina no se relacionó con efectos adversos, a pesar de exceder las dosis recomendadas.

Introduction

Amoxicillin is a penicillin-derived beta-lactam antibiotic regarded as first-line treatment for the main pediatric infections thanks to its broad spectrum of activity and its high bioavailability[1].

However, amoxicillin tends to be overused at community level. This has been corroborated by the European Centre for Disease Prevention and Control in a report on the consumption of systemic antibacterial agents at community level in Europe during 2020[2], which also found that Spain was the sixth largest European antibiotic consumer in Europe. In addition, beta lactams are the most widely prescribed systemic antibiotics in Spain and their use in the community exceeds that of all other antibiotics taken together[3].

This overuse results in a higher risk not only of selecting resistant bacteria but also of developing an intoxication as a result of dosing errors or other accidents. Consultations due to potential intoxications for any cause handled at pediatric emergency care units account for around 0.3% of total consultations, and the drugs most commonly responsible for pharmacological intoxication are paracetamol and antihistamines, which account for around one-third of all all drug intoxications[4]. References to antibiotic intoxication in children are scarce in the literature, particularly those related to amoxicillin overdosing.

In Spain, intoxications have been an important concern of the Spanish Society of Pediatric Emergencies. In 2008, the Society created a National Toxicologic Observatory, supported by 55 hospitals from all over the country[5]. In spite of this, no standardized protocols or guidelines exist on amoxicillin intoxication or overdosing.

The purpose of this study was to describe the clinical and analytical manifestations observed in pediatric patients who presented to our emergency department following amoxicillin overdosing.

Methods

This was a retrospective single-center observational study performed in a third-level hospital with a mean of 50,000 patients admitted annually to its pediatric emergency unit. Subjects were all under 16 years of age and had been admitted to the pediatric emergency unit between January 2011 and December 2021 due to amoxicillin overdosing. The study was approved by the hospital's Research Ethics Committee on 24 February 2022 (HULP: PI-5153).

Table 1 provides the Spanish Pediatrics Association's[6] definitions regarding the recommended dose and maximum recommended dose (MRD) of amoxicillin. Patients where the ingested dose was below the MRD considering their age and weight were excluded.

The collection of data was carried out by means of a retrospective analysis of clinical records. Data recorded included epidemiologic data (age and sex); antropometric data (weight); data related to the circumstances leading to the intoxication (dose, cause of overdosing, reason why amoxicillin was administered); data on associated symptoms; data on the care provided at the emergency room (complementary tests, treatment); time elapsed between ingestion and administration of treatment; and discharge destination.

The data was analyzed using the SPSS for Windows v. 21.0 statistical software. Quantitative variables were expressed as central tendency measures and dispersion [median and interquartile range (IQR)]; qualitative variables were expressed as absolute frequencies and percentages. Mann-Whitney's U test was used to compare quantitative variables not showing normal distribution.

Results

A total of around 2,000 emergencies secondary to intoxications (0.35% of all pediatric emergencies) were handled during the study period. Forty-six percent of them were secondary to drug therapy and 17 patients (0.9%) had experienced amoxicillin overdosing. Two patients were excluded on account of having ingested a dose lower than the MRD (both of them had accidentally ingested 50 mg/kg). Median patient age was 3.8 years (IQR: 1.9) and 80% (12/15) of them were between 1 and 5 years of age. Table 2 presents the patients' characteristics, the most frequent causes of overdosing and the reason why subjects were treated with amoxicillin. Eighty percent (12/15) of patients received one single dose of the drug. No concomitant ingestions of other medicines were recorded.

The mean time elapsed between overdosing and presentation to the emergency room was 2.1 hours (IQR: 2.7). The median amoxicillin dose administered was 219 mg/kg/dose (IQR: 148).

All patients were asymptomatic, with normal physical findings. The National Toxicology Institute was asked for guidance in 11 cases (73.3%). Blood tests were performed in 7 patients (46.6%). The median amoxicillin dose in that group (263.1 mg/kg; IQR: 126.4) was higher than that administered to patients where no blood tests were ordered (177.1 mg/kg; IQR:143.7), although the difference was not statistically significant ($p = 0.28$). No patient presented with hepatotoxicity, signs of renal failure or electrolytic alterations. Urine lab tests were requested only in two patients (13.3%), with no hematuria being detected.

Activated charcoal was administered to five patients (33.3%). The median time elapsed between amoxicillin ingestion and administration of activated charcoal was one hour (IQR: 1.2) and never exceeded 3 hours. All patients were discharged, including the patient who had made an autolytic attempt, who was evaluated by the psychiatry department during their stay. An indication was made to discontinue amoxicillin in 11 cases (73.3%).

Discussion

This study was intended to analyze the clinical and analytical manifestations of amoxicillin overdosing in pediatric patients. Although the doses ingested significantly exceeded those recommended in the guidelines, no adverse effects were identified in any patient.

Sex distribution and age ranges were in line with the literature, which reflects the predominance of males between 2 and 9 years of age[7-9].

Syrups and suspensions are the drug forms of choice in children given their multiple advantages (greater bioavailability, decreased stomach irritation, ease of ingestion and dosing). However, they are not without disadvantages. The most common amoxicillin drug form in Spain is dry pow-

Table 1. Definition of recommended amoxicillin dose and maximum recommended amoxicillin dose adopted by the Medicines Committee of the Spanish Pediatrics Association

Weight	Recommended dose	Maximum recommended dose
< 40 kg	• Infections caused by group A β-hemolytic Streptococcus pyogenes: 50 mg/kg/day in 2-3 doses (25 mg/kg/dose every 12 hours or 16.6 mg/kg/dose every 8 hours) • Potentially pneumococcal respiratory infections: 80-90 mg/kg/day in three doses (26.6-30 mg/kg/doses)	• 150 mg/kg/day (< 2 months: 40 mg/kg/day)
> 40 kg	500 mg 3 times a day or 1 g 2 or 3 times a day	• 6 g a day

Table 2. Patients treated in the pediatric emergency room due to amoxicillin overdosing between 2011 and 2021

Case nr	Age (years)	Sex	ID (mg/kg/dose)	Drug form	Administered due to	RD (mg/kg/dose)	ED	Reason for overdose	Blood test	Urine test	Indication at discharge
1	1	Male	570.0	Suspension (250 mg/5 mL)	AOM	26.6	21.4	Dosing error	Yes	Yes	Discontinue amoxicillin
2	3.6	Male	263.0	Suspension (250 mg/5 mL)	AOM	26.6	9.9	Accidental	Yes	No	Discontinue amoxicillin (switch to another antibiotic)
3	3.8	Male	326.0	Suspension (250 mg/5 mL)	Respiratory infection	26.6	12.3	Dosing error	Yes	No	Discontinue amoxicillin
4	2.7	Male	170.0	Suspension (250 mg/5 mL)	AOM	26.6	6.4	Accidental	No	No	Adjustment of amoxicillin dose
5	5	Female	200.0	Suspension (250 mg/5 mL)	APT	26.6	7.5	Dosing error	Yes	No	Discontinue amoxicillin
6	4	Male	147.0	Suspension (250 mg/5 mL)	Respiratory infection	26.6	5.5	Dosing error	Yes	No	Discontinue amoxicillin
7	5	Female	238.0	Suspension (250 mg/5 mL)	APT	16.6	14.3	Accidental	Yes	Yes	Discontinue amoxicillin (switch to another antibiotic)
8	4	Female	295.0	Suspension (250 mg/5 mL)	APT	16.6	17.8	Accidental	No	No	Discontinue amoxicillin
9	2.9	Male	Exact amount unknown (powder spoonfuls)	Unreconstituted dry powder	Scarlet fever	16.6	–	Dosing error	No	No	Resume amoxicillin within 48 hours
10	2.6	Male	185.5	Suspension (250 mg/5 mL)	APT	16.6	11.2	Accidental	No	No	Discontinue amoxicillin
11	3	Male	151.5	Unreconstituted dry powder	AOM	26.6	5.7	Dosing error	Yes	No	Discontinue amoxicillin
12	4.7	Male	117.0	Suspension (250 mg/5 mL)	Salmonellosis	26.6	4.4	Accidental	Yes	No	Discontinue amoxicillin
13	3	Female	350.0	Suspension (250 mg/5 mL)	*	–	–	Accidental	No	No	–
14	4	Male	125.0	Suspension (250 mg/5 mL)	Decision to initiate antibiotic treatment by father	–	–	Accidental	No	No	Discontinue amoxicillin
15	13.7	Female	130.0	Tablets	Autolytic attempt	–	–	Autolytic attempt	No	No	Psychiatric evaluation

AOM: acute otitis media; APT: acute pharyngotonsillitis; ED: excess dose (number of times the recommended dose was exceeded); ID: ingested dose; RD: recommended dose (administered every 8 hours).

*According to data obtained from clinical records it seems that ingestion was accidental, and that the child had not been taking amoxicillin previously. But this data had not been properly collected.

der suspension (250 mg/5 mL). This preparation requires a reconstitution process that must be performed with great care. In a study that analyzed reconstitution and preparation errors associated with liquid oral medicines administered to children by their caregivers, Berthe-Aucejo *et al.*[10] found up to 46% of amoxicillin formulations to be incorrectly prepared. Two children in our series received their amoxicillin dose directly as a powder, without reconstituting. This shows the need and the importance of conveying appropriate information after issuing the prescriptions.

The foreseeable initial symptoms following amoxicillin overdosing are typically of a gastrointestinal nature (nausea, vomiting and diarrhea). These symptoms can also arise when the drug is taken at therapeutic doses[11]. Cases of interstitial nephritis, crystalluria and seizures following overdosing (the latter following high intravenous or intraventricular doses[11]) have also been reported.

Some authors have described renal adverse events both with appropriate doses[9] and with excessive doses above 500 mg/kg[7,8]. As with other antibiotics, cases have been described of amoxicillin-induced urinary crystal formation[12]. Crystals have been characterized as looking like "needles" or "sheaves of wheat"[12]. They may be asymptomatic or result in abdominal or lumbar pain or hematuria, potentially progressing to renal insufficiency. The renal consequences of amoxicillin ingestion may be due to the drug's crystallization on the kidney's tubules, to direct cell toxicity or to vasoconstriction resulting from a hypersensitivity mechanism[8]. The appearance of renal insufficiency has been described in both children and adults, following accidental ingestion of large amounts of amoxicillin in the former and after administration of high intravenous doses of the drug in the latter[13]; however, its incidence is low. In a retrospective study on the ingestions reported to the National Poison Data System[14], only five (0.03%) of a total of 14,717 children under 6 years of age exposed to amoxicillin experienced renal disorders, all of them resolving within 3 days exclusively with serum therapy. Moreover, an ingestion above 250 mg/kg was confirmed in only two cases. Nonetheless, according

to a French pharmacovigilance program, reports of cases of nephropathy associated to amoxicillin-induced crystal formation seem to be on the rise[15].

No reference to these adverse events exists in Spanish or international guidelines, probably due to amoxicillin's remarkable safety profile. At the same time, there is wide variability in the management of these complications in the emergency care setting. The rare appearance of the symptoms mentioned, which typically arise following ingestion of highly variable doses of the drug, suggests a difficult-to-anticipate, idiosyncratic mechanism. The variability in the way complementary tests were conducted in our patients is attributable to several factors. Firstly, the amoxicillin dose administered could have prompted a request for blood tests (the dose ingested by this group was higher). Although the National Toxicology Institute was contacted 11 times, the attitude was not uniform. Lastly, the emergency department in our hospital does not have a specific protocol for these situations. There was, however, uniformity in the treatment with activated charcoal, which was invariably administered within three hours from ingestion.

The main limitations of this study have to do with its retrospective and single-center nature, together with the reduced size of the sample. In addition, patients were not followed up after being discharged from the emergency room. Given that none of the patients reported back to the emergency department it was assumed that they did not develop any further symptoms. However, the appearance of complications in the long term cannot be ruled out.

In a nutshell, amoxicillin overdosing was not associated in our study with the appearance of adverse events. The lack of action protocols for the management of these patients meant that their management was somewhat variable. Caregivers must be painstakingly trained following the prescription of amoxicillin.

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Presentation at congresses

Poster presentation at the 26th Meeting of the Spanish Society of Pediatric Emergencies (SEUP), Pamplona, June 2022.

Conflict of interest

No conflict of interests.

Contribution to the scientific literature

There is a growing concern about the overuse of amoxicillin in pediatric as it involves a high intoxication risk.

This study is focused on amoxicillin overdosing, an area that has not received much attention in the literature.

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