Amoxicillin overdose in the pediatric emergency department: A descriptive study

Sobredosificación por amoxicilina en urgencias pediátricas: Estudio descriptivo

Paula García-Sánchez1, Carolina del Pino-Bellido2, Cristina de Miguel-Cáceres3, Francisco Javier Guijarro-Eguinoa4, Miguel Ángel Molina-Gutiérrez2

1Pediatric Emergency Department, Hospital Universitario La Paz, Madrid. Spain. 2Department of Pediatrics, Hospital Universitario La Paz, Madrid. Spain. 3Clinical Pharmacology Department, Hospital Universitario La Paz, Madrid. Spain.

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; Crystallization; 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.

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.

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, 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.

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 consults, and the drugs most commonly responsible for pharmacological intoxication are paracetamol and antihistamines, which account for around one-third of all drug intoxications. 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. 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 (HUUP-PI-5153).

Table 1 provides the Spanish Pediatrics Association’s definitions regarding the recommended dose and maximum recommended dose (MRD) of amoxicillin. Patients where the ingested dose was below the MRD considered 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), anthropometric 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.

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 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.

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 powder.

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

<table>
<thead>
<tr>
<th>Weight</th>
<th>Recommended dose</th>
<th>Maximum recommended dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 40 kg</td>
<td>• 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)</td>
<td>• 150 mg/kg/day (&lt; 2 months: 40 mg/kg/day)</td>
</tr>
<tr>
<td></td>
<td>• Potentially pneumococcal respiratory infections: 80-90 mg/kg/day in three doses (26.6-30 mg/kg/doses)</td>
<td></td>
</tr>
<tr>
<td>&gt; 40 kg</td>
<td>500 mg 3 times a day or 1 g 2 or 3 times a day</td>
<td>• 6 g a day</td>
</tr>
</tbody>
</table>
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. 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, 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 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.

Some authors have described renal adverse events both with appropriate doses 5 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; however, its incidence is low. In a retrospective study on the ingestions reported to the National Poison Data System, 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 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.

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

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

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).
Amoxicillin overdose in the pediatric emergency department: A descriptive study

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.

Funding
No funding.

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.

Bibliography

3. Plan Nacional Resistencia Antibióticos (PRAN). Mapas de consumo en salud humana [Internet] [accessed 03/22/2022]. Available at: https://www.resistenciaantibioticos.es/es/profesionales/vigilancia/mapas-de-consumo/consumo-antibioticos/humana
6. Amoxicilina. Asociación Española de Pediatría [Internet]. 2015 [date updated 04/21/2021]; [accessed 03/22/2022]. Available at: https://www.aeped.es/comite-medicamentos/pediamicrom/amoxicilina