

# Medication rather than intoxication: acute occurrences by antihistamine in children

## Medicar e não intoxicar: ocorrências agudas por anti-histamínico em crianças

Gabriela Góes Costa<sup>1</sup>, Wilson Lopes Miranda<sup>1</sup>, Maria Apolônia da Costa Gadelha<sup>2</sup>, Pedro Pereira de Oliveira Parda<sup>2</sup>

<sup>1</sup> Universidade Federal do Pará, Faculdade de Medicina, Instituto de Ciências da Saúde, Belém, Pará, Brasil

<sup>2</sup> Hospital Universitário João de Barros Barreto, Centro de Informações Toxicológicas, Belém, Pará, Brasil

### ABSTRACT

**OBJECTIVE:** To analyze cyproheptadine poisoning cases from 2007 to 2015 in children between 1 to 12 years old, registered in the Toxicological Information Center database in Belém, Pará State, Brazil. **MATERIALS AND METHODS:** Descriptive and retrospective study of poisoning cases in children from the Belém Toxicological Information Center. All poisonings caused by vitamin-associated cyproheptadine formulas from 2007 to 2015 were considered. The following variables were analyzed: gender, age, month, years, zone, time elapsed from exposure, signs, symptoms, and evolution of the cases. Epi Info™ v6.6 was used for data analysis. **RESULTS:** Of the 1,719 cases of drug poisoning, 60 (3.5%) were caused by cyproheptadine in the study age group. The most affected groups were the male gender (75.0%) and the age group of 1 to 4 years old (80.0%). The cases occurred mainly in the urban area (96.7%), with the time between the accident and the attendance of 1 to 5 h (38.3%). The most frequent symptoms were agitation, drowsiness, and mental confusion. **CONCLUSION:** The circumstances of the cases were mainly due to accidental ingestion of more than the recommended amount, which mostly evolved to cure. These data serve to alert healthcare professionals about the use of appetite stimulants such as cyproheptadine.

**Keywords:** Poisoning; Child; Cyproheptadine; Drug Misuse.

### RESUMO

**OBJETIVO:** Analisar as intoxicações por ciproheptadina, no período de 2007 a 2015, em crianças de 1 a 12 anos de idade, registradas no banco de dados do Centro de Informações Toxicológicas de Belém, estado do Pará, Brasil. **MATERIAIS E MÉTODOS:** Estudo descritivo e retrospectivo dos casos de intoxicação em crianças, oriundos do Centro de Informações Toxicológicas de Belém. Foram consideradas todas as intoxicações com formulações contendo a ciproheptadina associada a vitaminas, registradas de 2007 a 2015, ponderando as variáveis: sexo, idade, mês, anos, zona, tempo decorrido da exposição, sinais, sintomas e evolução dos casos. Foram utilizados os softwares Epi Info™ v6.6 e Microsoft Excel Starter 2010 para a análise dos dados. **RESULTADOS:** Dos 1.719 casos de intoxicações por medicamentos, 60 (3,5%) foram causados pela ciproheptadina na faixa etária do estudo. O sexo masculino foi o mais acometido (75,0%), na faixa etária de 1 a 4 anos (80,0%). Os casos aconteceram majoritariamente na zona urbana (96,7%), com o tempo entre o acidente e o atendimento de 1 a 5 h (38,3%). Os sintomas mais frequentes foram agitação, sonolência e confusão mental. **CONCLUSÃO:** As circunstâncias dos casos foram principalmente por ingestão acidental de quantidade acima da recomendada, que evoluíram, em sua maioria, para a cura. Estes dados servem para alertar os profissionais de saúde sobre o uso de estimulantes de apetite, tal como a ciproheptadina.

**Palavras-chave:** Intoxicação; Criança; Ciproheptadina; Uso Indevido de Medicamentos.

### Correspondence / Correspondência:

Gabriela Góes Costa

Hospital Universitário João de Barros Barreto, Centro de Informações Toxicológicas

Rua dos Mundurucus, 4487. Bairro: Guamá. Zip Code: 66073-000 – Belém, Pará, Brasil – Phone #: +55 (91) 3249-6370

E-mail: gabrielagoesmed@gmail.com

## INTRODUCTION

Drug intoxication is a significant cause of children's morbidity, representing a severe health problem in the world<sup>1,2,3</sup>. According to the World Health Organization, in 2016, children under 5 years old were the most affected<sup>4</sup>. Studies show that 2% of deaths in childhood occur due to drug intoxication in developed countries, and, in emerging countries, this cause is responsible for 5% of infant mortality<sup>5</sup>.

In Brazil, data from the National System of Toxic-Pharmacological Information revealed that most cases of intoxication occur in the age group of 1 to 4 years old, with the most common toxic agents being drugs<sup>6</sup>.

Varied factors influence the susceptibility of children to poisoning. Some risk factors were defined as being essential for exposure to toxic agents, such as little parental supervision during risk actions, medicinal substances stored in easily accessible places, characteristics related to child development, parental negligence, and little incentive for preventive measures. On the other hand, factors inherent to the product characteristics can influence the occurrence of intoxication, such as packaging with attractive colors and formats, easy to open, and pleasant flavor<sup>1,2,3</sup>.

Several studies have shown cyproheptadine intoxication cases in childhood and adolescence, probably due to its wide use in these age groups<sup>7,8,9,10,11</sup>. This drug is a first-generation antihistamine, usually associated with vitamin supplements, and is extensively used as an appetite stimulant. This substance is a competitive histamine antagonist, which also has an antiserotonergic action, with weak anticholinergic activity, and its properties make it a mild central nervous system depressant. Antihistamines, in general, when overdosed, cause serious effects on the body, such as tachycardia, muscle spasms, hallucinations, seizures, and cardiac arrest<sup>8,12</sup>.

As adverse effects of cyproheptadine, especially when administered to younger children, drowsiness, abdominal pain, excitement, visual changes, changes in cognitive functions, and mental confusion have been reported<sup>13</sup>. The scientific literature has already registered deaths in overdose with suicidal intentions<sup>12,14</sup>.

It is noteworthy that, as it is a non-specific blocker of serotonin receptors, cyproheptadine ends up being indicated in the treatment of serotonergic syndromes, even with little evidence of its therapeutic effects<sup>15,16</sup>. However, the doses administered in these crises occur in the hospital environment, being duly monitored, contrary to the reality found in the intoxication of this substance when present in appetite stimulants<sup>16</sup>.

Therefore, this study aimed to analyze cases of cyproheptadine intoxication in children aged 1 to 12 years registered in the Belém Toxicological Information Center database, Pará State, Brazil, from 2007 to 2015.

## MATERIALS AND METHODS

This is a descriptive and retrospective study referring to cases of cyproheptadine poisoning from 2007 to 2015 in children aged 1 to 12 years old registered in the database of the Belém Toxicological Information Center, placed at João de Barros Barreto University Hospital. Data collection was realized during September and October 2016. For the research, intoxications with drugs that had cyproheptadine associated with vitamins in their formulation were considered. Due to cyproheptadine being described in the collected medical records as the primary substance inducing the clinical condition, and due to the actions directed towards this substance, the associated formulations in the vitamins were not described.

Sex, age, month, years, zone, time variables elapsed since exposure, signs, symptoms, circumstances of intoxication and case evolution were considered. Data were obtained from the Epi Info™ v6.6 software database and analyzed in absolute numbers and percentages.

This study was approved by the Research Ethics Committee of João de Barros Barreto University Hospital (CAAE: 73537217.5.0000.0017) on September 6, 2017.

## RESULTS

During the study period, 11,693 cases were registered. Among all the poisoning causes registered at the service, 1,719 (14.7%) were due to medication, followed by industrial chemicals (6.7%), household cleaning products (5.8%), agricultural pesticides (4.3%), domestic use (1.5%), and others (67%). According to drug intoxications, 60 (3.5%) occurred due to cyproheptadine in children aged 1 to 12 years.

Cases were prevalent in males (45; 75.0%), aged 1 to 4 years old (48; 80.0%), occurring in the urban area (58; 96.7%), with a time interval between the accident and care from 1 to 5 h (23; 38.3%) of these occurrences (Table 1).

The occurrences were divided into three circumstances regarding the dose of medication administered: in 60.0% (36) of the cases, there was ingestion above the amount recommended by the medication leaflet; in 16.7% (10), there was ingestion of a therapeutic dose; and, in 23.3% (14), the dose was not stipulated, thus being disregarded as intoxication. As for the patients' evolution, 58.3% (35) evolved to cure, 40.0% (24) had no confirmed cure, and only 1.6% (one) resulted in death (Table 1). This death rate was linked to the case particularities, such as the high doses ingested by the child and the delay in helping.

During the study period, four cases were registered per year. In 2010, there was no registration; however, in 2011 (eight cases), 2012 (12 cases), 2013 (14 cases), 2014 (seven cases), and 2015 (seven cases), considerable numbers of intoxications by cyproheptadine were found, compared to previous years.

The most registered signs and symptoms were agitation (30; 50.0%), drowsiness (23; 38.3%), and mental confusion (16; 26.7%) (Table 2). The age group from 1 to 4 years old was the most affected and the one that presented the most diverse symptoms

of neurological, motor, digestive, and other types, including coma. The range from 5 to 8 years old presented neurological and motor symptoms. The age group from 9 to 12 years old presented exclusively neurological symptoms.

**Table 1** – Frequency of epidemiological parameters of cyproheptadine intoxication cases in children aged 1 to 12 years, recorded in the database from Belém Toxicological Information Center, Pará State, Brazil, from 2007 to 2015

Parameters	N = 60	%
Sex		
Male	45	75.0
Female	15	25.0
Age range (years)		
1–4	48	80.0
5–8	9	15.0
9–12	3	5.0
Zone		
Rural	2	3.3
Urban	58	96.7
Time to help (hours)		
< 1	9	15.0
1–5	23	38.3
6–10	10	16.7
11–15	7	11.7
> 15	4	6.6
Ignored	7	11.7
Circumstance		
Intake above the recommended amounts	36	60.0
Intake of therapeutic amount	10	16.7
Intake of an undetermined amount	14	23.3
Evolution		
Cure	35	58.3
Unconfirmed cure	24	40.0
Death	1	1.7

**Table 2** – Frequency of cyproheptadine intoxication signs and symptoms in children cases aged 1 to 12 years registered in the database of Belém Toxicological Information Center, Pará State, Brazil, from 2007 to 2015

Classification	Signs and symptoms*	N	%
Neurological	Agitation	30	50.0
	Somnolence	23	38.3
	Mental confusion	16	26.7
	Hallucinations	13	21.7
	Aggressiveness	4	6.6
	Convulsion	4	6.6
	Mydriasis	3	5.0
	Agitation	2	3.3
Motor	Tremors/Spasms	5	8.3
	Dyslalia	3	5.0
Digestive	Emesis	2	3.3
	Abdominal distension	3	5.0
Other	Erythema	9	15.0
	Fever	7	11.7
	Tachycardia	2	3.3
	Cry	2	3.3
	Other symptoms†	13	21.7

\* Each patient had more than one sign or symptom; † Arm numbness, nausea, epigastric pain, prostration, blurred vision, headache, euphoria, dizziness, cough, dry mouth, clouding, yellow skin, insomnia, pruritus.

## DISCUSSION

Medications represent one of the intoxication main causes in Brazilian children and around the world, even in developed countries<sup>6,17</sup>. In 2014, the 55 toxicological assistance centers in the United States released more than 93,000 records of poisoning that occurred only in children under 6 years old, largely justified by the same causes. This occurs due to the natural curiosity of age, colorful and easy-to-open packaging, pleasant flavors, inappropriate use, and negligence by those responsible<sup>1,6</sup>.

According to the National System of Toxic-Pharmacological Information, 5-year-old children accounted for 39.4% of drug poisoning cases in Brazil in 2014<sup>6</sup>. Alcântara et al.<sup>7</sup> found 77.0% in Ceará State, which corroborates the findings of this study.

Appetite stimulants with cyproheptadine in their formulation have a pleasant taste, which may be one of the intoxication causes. There are rare cases in which lack of appetite in children should be pharmacologically treated, and, in other countries, these stimulants are indicated for anorexia treatment, cachexia, and severe malnutrition<sup>18</sup>. However, the frequent concern of parents with their children's eating habits makes the common use of these drugs, even without a medical prescription. Lulebo et al.<sup>19</sup> stated that self-medication and recommendations from friends were the most common reasons for using cyproheptadine, with only 7.4% of users reporting using it on medical advice.

In this study, cyproheptadine was responsible for a significant portion of poisonings. Alcântara et al.<sup>7</sup> showed that this medication was responsible for 8.5% of intoxications registered at Toxicological Assistance Center in Ceará State.

The age group from 1 to 4 years old was predominant in this study, reflecting the beginning of motor development and the curious nature of the ability to handle medications and take them to the mouth<sup>7,20</sup>.

In general, the recorded poisonings occurred in the urban area, probably due to the ease of communication by telephone, since the Toxicological Information Center, which guides health professionals, receives notifications through this route. Similar data were found by Santos et al.<sup>21</sup>.

Most of the study victims were rescued within 1 to 5 h. Oliveira and Suchara<sup>17</sup> found a higher case prevalence in which this information was ignored; however, in those informed, children from 0 to 4 years old were seen within 1 h. In Portugal, Macedo et al.<sup>22</sup> showed an average of 3.6 h.

The symptoms identified in this study corroborate those described by Hargrove and Molina<sup>12</sup>, which justify all the effects induced in the body by the exacerbation of cyproheptadine's non-selective antagonistic potential. The substantial capability of crossing the blood-brain barrier and functioning as a non-selective antagonist of histamine receptors explains

the occurrence of neuropsychological symptoms, such as drowsiness, and the development of anticholinergic, antidopaminergic, and antiserotonergic adverse effects. These events in the central nervous system are arguably the primary life-threatening factors in cases of intoxication<sup>12,23</sup>.

The circumstances found in this study do not specify which cases fall under self-medication. However, it is believed to be a considerable number since this medication is usually purchased without a prescription, which can endanger the health of those who use it, as adverse effects can be quite serious. In the victim's evolution of cyproheptadine intoxication, there was one death in a 3-year-old child who, according to reports, had been taking a dose 15 times higher than the recommended for about a month. This fatality is rarely reported and, when described, is associated with the simultaneous consumption of other medications, and in adults, an association with alcohol or suicidal intentions is reported<sup>12,14</sup>.

Currently, antihistamines, including cyproheptadine, can be purchased over the counter in pharmacies without the need for a medical prescription. According to the National Health Surveillance Agency<sup>24</sup>, over-the-counter drugs must meet specific criteria, such as presenting a low potential risk to the patient, having known adverse reactions, and low toxicity. The fragility of this regulation is due to the drugs' pharmacological diversity in the class in question, which can be used for different pathologies<sup>25</sup>.

Self-medication is a worldwide phenomenon, and Brazil has a specific context. Difficulties in accessing healthcare, media and cultural issues strengthen the habit of using drugs without a medical prescription<sup>25</sup>. A study realized in São Paulo state showed that 62% of the interviewed guardians self-medicate their children under 15 years old<sup>26</sup>.

Drug advertising has a strong influence on self-medication and, consequently, on intoxication. In Brazil, the Law no. 9,782/99 controls the advertising of products subject to health surveillance, restricting any substance that may pose life risks. However, promoting products that promise to stimulate children's appetite and create a new need to encourage their consumption is historical. Furthermore, there is a weakness in the regulation of advertisements that still encourage self-medication<sup>27,28</sup>.

Thus, the need for health education in primary care is evident to prevent poisoning. It is up to the professionals in contact with those responsible for guiding self-medication and intoxication. In addition, it would be essential to create informative and alert government campaigns for the lay population, as well as a reassessment of over-the-counter drugs.

Individuals with a clinical picture of cyproheptadine intoxication should be referred for emergency hospital treatment with a view to adequate clinical management<sup>10</sup>. Initially, the use of activated charcoal is recommended in recent ingestions. For larger

ingestions (above 1 g), consider performing gastric lavage with protection of the airways<sup>13,29</sup>. Intravenous fluid replacement should be administered when signs of dehydration are present, alongside monitoring levels of consciousness, blood pressure, and heart rate<sup>30</sup>.

Most patients recover gradually with the elimination of the ingested medication<sup>30</sup>; however, in severe or potentially fatal cases, intravenous administration of physostigmine salicylate is considered<sup>13,14,31</sup>. These data may alert health professionals about the use of appetite stimulants that contain cyproheptadine in their formula. In addition, professionals have available the Toxicology Information Center in their region for more information.

This study had some limitations as it does not represent the prevalence of a specific region, given that calls from one state can be routed to other centers in Brazil depending on the line availability. Additionally, it was conducted retrospectively; hence, it is possible that not all medical data were reviewed or documented in the patients' records.

## CONCLUSION

The cases of cyproheptadine intoxication in children reported at the Belém Toxicological Information Center were mainly characterized by drug intake above the recommended amount, most of which progressed to cure.

These poisonings should be considered a public health issue due to the involvement of various factors and agents, ranging from the caregivers' behaviors in the home environment to the child's development characteristics and conditions of exposure in that environment. Thus, the need for health education among the general population is highlighted, as they are sometimes influenced by pharmaceutical industry advertising, information available on the Internet, and an increasingly prevalent habit of self-medication. It is crucial to emphasize the urgency of improved oversight by regulatory bodies in monitoring advertisements and regulating access to medication.

Therefore, the documentation of several variables and the identification of common factors can be of great importance for therapeutic planning and implementing measures to prevent such accidents.

## CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest regarding the research.

## AUTHORS' CONTRIBUTION

All authors were involved in the research conception and design, writing of the manuscript, critical review of the present study, and approval of the final version for submission. Gabriela Góes Costa and Wilson Lopes Miranda were also responsible for obtaining, analyzing, and interpreting the data.



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