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TOXICOLOGICAL EVENTS ASSOCIATED WITH PARACETAMOL MANAGED BY A TOXICOLOGY INFORMATION AND ASSISTANCE CENTER

EVENTOS TOXICOLÓGICOS ASSOCIADOS A PARACETAMOL ATENDIDOS POR UM CENTRO DE INFORMAÇÃO E ASSISTÊNCIA TOXICOLÓGICA

Eduarda Carolina do Nascimento[I], Camilo Molino Guidoni[II], Edmarlon Girotto[III*]

ABSTRACT. This study aimed to analyze the toxicological events associated with paracetamol managed by a Toxicological Information and Assistance Center. It was a cross-sectional, retrospective study based on cases of toxicological events associated with the drug paracetamol attended by the Toxicological Information and Assistance Center of Londrina (CIATox/Londrina). The data was extracted from the Brazilian Poison Data System (DATATOX) from 2017 to 2021. The data was analyzed using the Statistical Package for the Social Sciences (SPSS), version 19.0. This study was approved by the Research Ethics Committee of the State University of Londrina. Between 2017 and 2021, CIATox/Londrina received 685 cases of toxicological events associated with paracetamol, of which the vast majority (75.0%) were women who had attempted suicide (83.2%) as their main circumstance. Most cases (37.7%) occurred in the afternoon on Saturdays and Sundays, the days of the week with the highest number of cases (15.7% and 16.2%, respectively). Paracetamol was combined with other substances in 156 (22.8%) cases. Almost 80.0% of the cases had clinical manifestations, with 36.4% requiring hospitalization (minimum of one and maximum of 37 days). Most cases were categorized as mild (57.7%), and four (0.6%) deaths were identified among all the cases. The antidote N-acetylcysteine was administered to 37.1% (N=255) patients. In general, toxicological events associated with paracetamol occurred predominantly in women in the afternoon and on Saturdays and Sundays, and involved suicide attempts. It is, therefore, essential to develop campaigns that encourage the correct use of medication and other public health campaigns, especially for those individuals who are more susceptible to suicide attempts.

KEYWORDS: Poisoning. Pharmaceutical preparations. Acetaminophen. Descriptive epidemiology.

RESUMO. A pesquisa tem como objetivo analisar os eventos toxicológicos associados a paracetamol atendidos por um Centro de Informações e Assistência Toxicológica. Este foi um estudo transversal, retrospectivo, baseado nos casos de eventos toxicológicos associados ao medicamento paracetamol atendidos pelo Centro de Informação e Assistência Toxicológica de Londrina (CIATox/Londrina). Os dados foram extraídos do Sistema Brasileiro de Dados de Intoxicações (DATATOX), referentes aos anos de 2017 a 2021. A análise dos dados foi realizada com uso do programa Statistical Package for the Social Sciences (SPSS), versão 19.0. Este estudo foi aprovado pelo Comitê de Ética em Pesquisa da Universidade Estadual de Londrina. Entre 2017 e 2021, o CIATox/Londrina atendeu 685 casos de eventos toxicológicos associados a paracetamol, dos quais a grande maioria (75,0%) era de mulheres e teve a tentativa de suicídio (83,2%) como principal circunstância. A maior parte dos casos (37,7%) ocorreu no período vespertino e o sábado e domingo foram os dias da semana com o maior número de casos (15,7% e 16,2%, respectivamente). Em 156 (22,8%) casos houve associação do paracetamol com outras substâncias. Quase 80,0% dos casos apresentaram manifestações clínicas, com 36,4% precisando de internação (mínimo de um e máximo de 37 dias). A maioria dos casos foi classificado como leve (57,7%) e identificados quatro (0,6%) óbitos entre todos os atendimentos. O antídoto N-acetilcisteína foi administrado em 37,1% (N=255) pacientes. De forma geral, os eventos toxicológicos associados ao paracetamol ocorreram predominantemente com mulheres, no período vespertino e aos sábados e domingo, além de envolverem tentativas de suicídio. Assim, é importante o desenvolvimento de campanhas que estimulem o uso correto de medicamentos e de outras campanhas de saúde pública, principalmente para aqueles indivíduos mais susceptíveis às tentativas de suicídio.

PALAVRAS-CHAVE: Intoxicações. Medicamentos. Paracetamol. Epidemiologia descritiva.

[I] Pharmacist, Resident in Clinical Analyses, State University of Londrina
CEP: 86039-440, Londrina. Paraná, Brazil
Orcid: https://orcid.org/0009-0009-8386-3189.

[II] Pharmacist, PhD in Pharmaceutical Sciences, State University of Londrina, Department of Pharmaceutical Sciences
CEP: 86039-440, Londrina. Paraná, Brazil
Orcid: https://orcid.org/0000-0001-5844-143X.

[*III] Pharmacist, PhD in Community Health, State University of Londrina, Department of Pharmaceutical Sciences
CEP: 86039-440, Londrina. Paraná, Brazil
Email: edmarlon78@gmail.com
Orcid: https://orcid.org/0000-0001-9345-3348.

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INTRODUCTION

Poisoning is a pathological process caused by substances that come into contact with the body, causing a physiological imbalance and, consequently, biochemical changes (BATISTUZZO; CAMARGO; OGA, 2008). In 2022, there were 180,022 cases of toxicological events. Of these, 58.2% were related to medicines, 11.7% were drugs of abuse, 4.4% were food or drink, and 4.3% were household products (BRASIL, 2024). Most events involved suicide attempts (52.7%), followed by accidental suicide (12.9%) and abuse (12.1%) (BRASIL, 2024). Among the cases involving medicines (N=104,734), 72.9% were suicide attempts, and 6.8 were accidental. In addition, 74.2% affected women (BRASIL, 2024). This high prevalence of toxicological events associated with medicines is due to their availability in homes, often stored incorrectly (FERNANDES et al., 2020), making them a viable alternative for victims attempting suicide and easily accessible for accidental cases. In addition, the potential years of life lost as a result of drug poisoning indicate significant social and economic losses for society (MAIA et al., 2019).

The main classes of drugs involved in poisoning in Brazil are benzodiazepines, anticonvulsants, antidepressants, and analgesics (RAMALHO et al., 2023). Mathias, Guidoni, and Girotto (2019) developed a cross-sectional and tendency study with data from a Toxicological Information Center (CIT). Anticonvulsants ranked first in the distribution of therapeutic classes of drugs involved in cases of drug-related toxicological events, representing 29.5%, followed by analgesics (painkillers), anti-inflammatories, and immunosuppressants (13.0%) and antidepressants (12.8%).

Analgesics also have the potential for toxicity, contrary to what many people think about this group. According to Gummin (2019), paracetamol (Acetaminophen) is the second leading cause of suspected poisoning in adults in Portugal. In the USA, paracetamol poisoning causes tens of thousands of hospital admissions every year, many of which result in liver transplants and fatalities (GUMMIN, 2019). Paracetamol is one of the most popular over-the-counter medicines in the world. As a non-opioid analgesic and antipyretic agent, paracetamol is one of the most consumed drugs in Brazil (ARRAIS et al., 2016; DAL PIZZOL et al., 2016). It can be easily purchased with or without a prescription, representing a common cause of accidental or intentional exposure (OKUYAMA; GALVÃO; SILVA, 2022).

A study that evaluated cases of toxicological events associated with paracetamol from 2017 and 2020 in Brazil found that this agent accounted for 3.3% of all poisoning cases in the country, with the state of Paraná having the highest number of cases per million inhabitants (OKUYAMA; GALVÃO; SILVA, 2022). Given this context, this study aims to analyze the toxicological events associated with paracetamol managed by a Toxicological Information and Assistance Center in Paraná.

METHODS

This cross-sectional, observational, and descriptive study uses secondary data from the Toxicological Information and Assistance Center (CIATox), located in Londrina-PR, at the University Hospital of the State University of Londrina (HU-UEL). Since 2017, each patient assisted by CIATox/HU-UEL has had their data stored in the Brazilian Poisoning Data System (DATATOX), which records and monitors poisoning cases.

CIATox provides technical advice and guidance in cases of poisoning, exposure to toxic agents, and accidents involving venomous animals. Its staff members serve health professionals, the general population, students, and professionals from other areas of activity in virtually all of Paraná's 399 cities, as well as other states. Their activities include providing information in person or by telephone in cases of exposure to or poisoning by chemical substances or toxins of plant or animal origin.

This study analyzed all toxicological events associated with paracetamol treated by CIAox/HU-UEL and recorded in DATATOX between 2017 and 2021. The researchers extracted the data by accessing the DATATOX System's Business Intelligence (BI-DATATOX), which allows data to be mined and explored using pre-established criteria.

The variables used to characterize the cases of toxicological events associated with paracetamol were:

• Sociodemographic::
-Sex (male; female)
-Age group (0 to 12 years old; 13 to 18 years old; 19 to 29 years old; 30 to 49 years old; 50 years old and above)
-Skin color (white/yellow, brown/black)
-Education (illiterate; incomplete primary education; complete primary education; incomplete secondary education; complete secondary education; incomplete higher education; complete higher education; other)

• Exposure-related:
-Exposure zone (urban/peri-urban; rural; other)
-Year of exposure (2017; 2018; 2019; 2020; 2021)
-Month of exposure (January to December)
-Day of the week of the exposure (Monday to Sunday)
-Exposure period (00h-05h59; 06h00-11h59; 12h00-17h59; 18h00-23h59)
-Circumstances of exposure (suicide attempt, self-medication, medication error, and accident)
-Number of agents involved in toxicological events (including paracetamol)
-Agents involved (apart from paracetamol)
-Dosage of paracetamol use in exposure (in milligrams)
-Time from exposure to CIATox assistance (in minutes)

• Clinics:
-Hospitalization (yes; no)
-Clinical manifestations (yes; no)
-Signs and symptoms
-Treatment
-Final severity (null; mild; moderate; severe; fatal)

After obtaining the data from the DATATOX system, it was exported to a Microsoft Excel® spreadsheet and then analyzed using the Statistical Package for the Social Sciences® (SPSS), version 19.0. A descriptive data analysis was carried out, using absolute and relative frequency distribution for the qualitative variables and measures of central tendency for the quantitative ones. Finally, the proportion of cases of toxicological events associated with paracetamol was calculated in relation to the total number of cases of medication and the total number of cases of toxicological events. The latter excludes cases of venomous and non-venomous animal accidents.

This study is part of a larger project entitled "Analysis of the activities developed and cases attended by a toxicological information center" and approved by the Research Ethics Committee of the State University of Londrina (UEL) (Report 2.855.554/2018; CAAE No. 45986415.1.0000.5231).

RESULTS

Between 2017 and 2021, CIATox-Londrina handled 14,468 cases of toxicological events, of which 8,209 (56.7%) involved drugs. Of the toxicological events associated with drugs, 685 (8.3%) occurred with the use of paracetamol, with 2021 recording the highest number of occurrences (27.0%). Figure 1 shows that the number of toxicological events associated with paracetamol rose significantly between 2017 and 2019 and between 2020 and 2021. In addition, the proportion of paracetamol cases in relation to total drug cases and total toxicological events

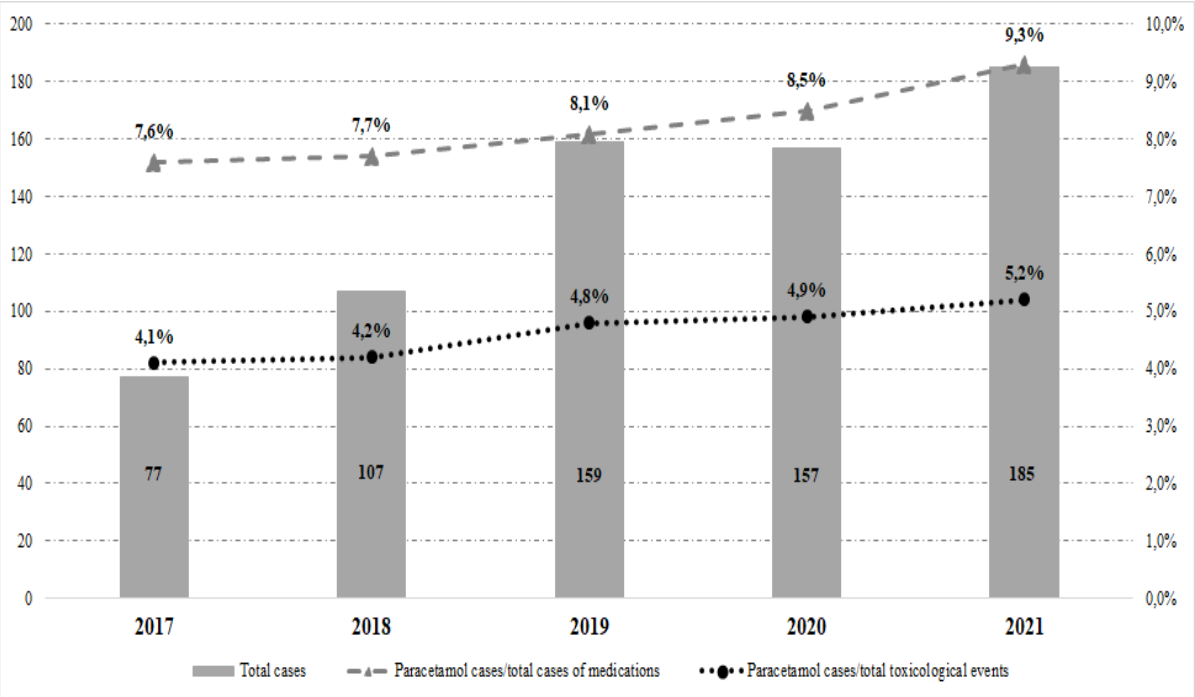

Figure 1: Distribution of total toxicological events involving drugs and paracetamol attended by CIATox--Londrina, 2017-2021. (N=685)

The majority of toxicological events were women (75.0%) (Table 1), 14 of whom were pregnant women. The 19-29 age group was the most prevalent, accounting for 36.9% of the cases (Table 1); the average age was 22.3 (±12.4) years. In addition, most of the cases were white (78.4%) and had incomplete (24.3%) or complete (31.3%) secondary education (Table 1).

The events occurred mainly in urban/peri-urban areas (94.6%). Of the cases, attempted suicide (83.2%) was the main circumstance, followed by accidental suicide (6.5%) and self-medication (4.9%). Of the patients treated, 79.0% had clinical manifestations. In addition, 21.1% had null final severity (asymptomatic), 3.1% severe, and 0.6% fatal (4 cases) (Table 1).

The months with the highest rates were November, March, and December (10.7%, 10.1%, and 9.9%, respectively). Regarding the days of the week, events occurred mainly on weekends, Saturdays (15.8%), and Sundays (16.2%). The period of day when the most toxicological events were recorded was from 12 pm to 5:59 pm (35.5%) and from 6 pm to 11:59 pm (31.8%).

In total, 1,805 signs or symptoms presented by patients with clinical manifestations were identified (N=541). Among the signs and symptoms identified, vomiting (41.9%), drowsiness (40.0%) and nausea (28.9%) stood out. The most frequent signs and symptoms are shown in Table 2.

TABLE 1: Sociodemographic, exposure, and clinical characterization of toxicological events associated with paracetamol, CIATox-Londrina, 2017-2021. (N=685)*

Characteristics of toxicological events associated with paracetamol	N	%
Sex		
Female	514	75.0
Male	171	25.0
Age group (N=684)		
0 to 12 years old	117	13.6
13 to 18 years old	159	26.7
19 to 29 years old	253	36.9

30 to 49 years old	133	19.4
50 years old and above	22	3.2
Skin color (N=681)		
Yellow	5	0.8
White	534	78.4
Brown	110	16.1
Black	32	4.7
Education (N=680)		
Illiterate	1	0.1
Incomplete primary education	98	14.4
Complete primary education	39	5.7
Incomplete secondary education	165	24.3
Complete secondary education	213	31.3
Incomplete Higher education	64	9.4
Complete Higher education	33	4.9
Other	67	9.9
Exposure Zone (N=685)		
Urban/peri-urban	648	94.6
Rural	34	5.0
Other	3	0.4
Circumstance of exposure (N=685)		
Suicide attempt	570	83.2
Accident	45	6.5
Self-medication	33	4.9
Medication error	22	3.2
Other	15	2.2
Clinical Manifestations (N=685)		
Yes	541	79.0
No	144	21.0
Final Severity (N=678)		
Null	143	21.1
Mild	395	58.2
Moderate	115	17.0
Severe	21	3.1
Fatal	4	0.6

*There are variables with N lower than the total number of cases evaluated (N=685) due to the absence of information in DATATOX.

Of all the patients, 37.2% were treated with NAC (N-acetylcysteine), while other treatment methods were adopted for the rest, especially observing signs and symptoms (91.7%), symptomatic and supportive treatment (85.6%) and intravenous hydration (53.1%). Hospitalization was necessary in 30.2% of cases, with a minimum stay of one day and a maximum of 37 days. The main treatments given to patients are shown in Table 3.

TABLE 2: Main signs and symptoms of poisoning involving paracetamol (15 most frequent signs or symptoms), CIATox-Londrina, 2017-2021.*

Signs or symptoms	N	%
Vomiting	227	41.9
Drowsiness	217	40.0
Nausea	156	28.9
Tachycardia	106	19.5
Epigastralgia	84	15.5
Agitation	76	14.0
Hypotension	74	13.7
Abdominal pain	61	11.2
Altered Level of Consciousness	57	10.5
Headache	52	9.6
Hypertension	52	9.6
Dizziness / Vertigo	50	9.2
Lethargy / Drowsiness	44	8.1
Mental confusion	41	7.5
Tremor	22	4.0

*Cases with a frequency equal to or greater than 4.0% were presented.

Of the toxicological events, 22.6% involved paracetamol exclusively. On average, the number of agents involved was 4.0 (±3.0), with a maximum of 26 agents in a single toxicological event. Among the agents that were associated with toxicological events associated with paracetamol, dipyrone (21.9%), diclofenac (17.0%), carisoprodol (15.0%), ibuprofen (14.3%), and caffeine (12.5%) stood out (Table 4).

TABLE 3: Main treatments for patients involved in paracetamol-related toxicological events, CIATox-Londrina, 2017-2021.*

Main treatments provided	N	%
NAC (N-acetylcysteíne)		
Yes	255	37.2
No	430	62.8
Other treatments (apart from NAC)		
Observe signs and symptoms	628	91.7
Symptomatic and Supportive	587	85.6
Intravenous hydration (fluids and/or electrolytes, IV)	364	53.1
Hospitalization	207	30.2
Gastric lavage < 1 hour after ingestion	156	22.7
Parenteral analgesia	10	1.4
Sedation	15	2.1

Antibiotic therapy	13	1.9
Endotracheal intubation	13	1.9
Diazepam	13	1.9
Oxygen	11	1.6
Flumazenil	10	1.4
Hydrocortisone	9	1.3

*Cases with a frequency equal to or greater than 1.0% were presented.

TABLE 4: Agents combined with paracetamol in toxicological events attended by CIATox-Londrina, 2017-2021. (N=1.359)*

Medicines	N	%
Dipyrone	150	21.9
Diclofenac	116	17.0
Carisoprodol	103	15.0
Ibuprofen	98	14.3
Caffeine	86	12.5
Phenylephrine	67	9.7
Caffeine	59	8.6
Ethyl alcohol (alcoholic drink)	38	5.5
Amoxicillin	37	5.4
Chlorpheniramine	36	5.2
Orphenadrine citrate	34	5.0
Fluoxetine	31	4.5
Nimesulide	31	4.5
Omeprazole	31	4.5
Clonazepam	24	3.5
Prednisone	23	3.3
Chlorpheniramine	22	3.2
Sertraline	22	3.2
Scopolamine butylbromide	21	3.0
Loratadine	21	3.0
Others	309	45.1
Total	**1.359**	**100.0**

*Cases with a frequency equal to or greater than 3.0% were named.

Of the 685 events, it was possible to confirm or estimate the dose of paracetamol ingested in 613, which ranged from 300 milligrams to 111.25 grams, with a median of 5 grams. A total of 32.5% of the patients seen ingested 7.5 grams or more of paracetamol.

DISCUSSION

In all the years recorded, 2021 was responsible for the highest number of poisonings, and the age group comprising young people from 19 to 29 was the most affected by toxicological events associated with paracetamol. In addition, the vast majority were female, had completed secondary education (high school), and the main circumstance was attempted suicide. These variables reveal a major social problem that silently wastes patients' lives and, consequently, reduces the quality of public health provided to the population.

The highest increase in the proportion of paracetamol cases occurred between 2017 and 2021, among other poisoning cases. This increase may be related to greater access to and use of paracetamol in recent years. However, prior to the period of this study, the trend in the use of analgesics in the French adult population (2006 to 2015) increased, with paracetamol increasing the most steadily (52.6%) (DAVELYU et al., 2020). In Finland, in a survey of elderly people with musculoskeletal pain, paracetamol showed the greatest increase in use, from 2% in 1999 to 11% in 2019 (LEHTI et al., 2021).

The high percentage of female cases could be explained by the fact that women when motivated to take their own lives, have characteristic ways of doing so. Men have higher suicide rates because they use more violent methods, such as lethal objects. Women, on the other hand, mostly use less radical methods, such as medication (PARENTE et al., 2007). It should be noted that a national study carried out between 2017 and 2020 also identified women as the most frequent victims of toxicological events involving paracetamol (OKUYAMA; GALVÃO; SILVA, 2022).

As for education level, according to Borba et al. (2020), education has repercussions on the means of promotion to work and the individual's financial condition in a competitive society. Hence, schooling is a relevant predictor of getting a job. Thus, it is suggested that low socioeconomic conditions are associated with an increase in attempted suicide and suicide, especially when considering the possible exacerbation of psychological suffering caused by social disadvantages (BORBA et al., 2020). In addition, according to the Continuous National Household Sample Survey (PNAD), a large part of the Brazilian population has a complete secondary education level or less, which is similar to the results of this study and may indicate that toxicological events do not affect groups with specific levels of education (IBGE, 2020).

Several studies have highlighted the relationship between drug poisoning and suicide, a fact that already occurs in most developed countries, where these substances occupy first place in cases of intentional poisoning (GUNNELL; EDDLESTON, 2003; CABALLERO-VALLES et al., 2008; VÄRNIK et al., 2009). Drug poisoning is very likely and, in a way, very easy to happen and to be practiced because most of the drugs used are over-the--counter, found in the most diverse places, and have a low cost. These characteristics explain the ease with which drugs such as paracetamol are used to attempt suicide (OLIVEIRA; SUCHARA, 2014).

There was a high frequency of toxicological events between 6 pm and 11 pm, which may be related to suicide attempts, which generally occur at night. As the flow of people in communal areas of homes tends to be lower at night, there is a predisposition to these events when suicide attempts are more likely to occur (OLIVEIRA et al., 2020). Also, at night, there is a higher consumption of alcoholic drinks and/or illicit drugs, which are consolidated as risk factors for suicide attempts (MENDES; LOPES, 2007; ZUPANC et al., 2013). The high frequency in the period between 12 pm and 5:59 pm may be more related to unintentional events, which are more common in children (ROCHA et al., 2019), and is related to the period of greatest activity or the fact that they are at home, which is more common in the afternoon.

Toxicological events associated with paracetamol occurred more frequently on weekends. It has been suggested that excessive alcohol consumption on weekends may induce suicidal behavior in a population affected by high psychosocial stress (KALEDIENE; PETRAUSKIENE, 2004). In addition, on weekends, there is a false understanding that there is a new start to life, which can encourage individuals to attempt suicide, especially those with psychiatric disorders (JOHNSON et al., 2005).

This predisposition to use paracetamol or other over-the-counter medicines, especially dipyrone (present

here in 21.9% of cases of poisoning associated with paracetamol), can also be explained by toxicological events caused accidentally or by self-medication. They are easy to obtain and administer, making them a major contributor to toxicological events, regardless of the circumstances involved in events with these drugs (ARRAIS et al., 2016; GAMA; SECOLI, 2020). Diclofenac and ibuprofen are also drugs that are systematically used through self-medication (ARRAIS et al., 2016; GAMA; SECOLI, 2020) and, consequently, are easily accessible. On the other hand, carisoprodol, caffeine, and phenylephrine are not active ingredients that are often found in association with many analgesics, such as paracetamol.

The treatment of cases of drug poisoning is carried out with supportive treatment actions, prevention of absorption of toxic compounds, strengthening their elimination, and specific treatments, including the use of antidotes. These procedures can contribute to a good and desirable outcome in cases of poisoning (OLIVEIRA; SUCHARA, 2014). In this sense, one of the crucial measures in reducing mortality from paracetamol poisoning is its antidote, N-acetylcysteine (NAC), identified in this study in 37.2% of cases. NAC has been used for more than four decades in paracetamol poisoning and acts as a precursor to our body's "detoxifying" molecule, Glutathione, helping to restore its reserves. NAC can also replenish cellular energy levels, serving as a precursor for the Krebs cycle (MOREIRA, 2016).

Some limitations of this study should be highlighted. The fact that this study used secondary data sources affects the quality of the information, as well as the lack of information on some of the variables analyzed. In addition, there were many losses due to a lack of information on the dose of paracetamol used, and, in this case, it is difficult to understand the clinical aspects, as the ingested doses play a decisive role in this process. Another factor that should be highlighted is the possible underreporting of toxicological events associated with many medicines, either for intentional reasons or because they are considered to be harmless to health. Despite the limitations, the study is strengthened because it is one of the few studies to examine the epidemiological profile of toxicological events associated with paracetamol in Brazil.

This makes it clear that it would be essential to increase campaigns to encourage the correct use of medication and other public health campaigns, especially for those individuals most susceptible to suicide attempts. Public actions and the monitoring of these patients by properly qualified health professionals could also help to reduce these suicide attempt rates, significantly reducing the number of intentional poisonings.

Health professionals must establish strategic actions to promote, prevent, educate, and reduce harm to society, stimulate research, lines of care, and continuing education to recognize people who need comprehensive and humanized care (KOHLRAUSCH, 2012). In addition, it is essential to highlight the importance of effectively implementing the National Guidelines for Suicide Prevention (BRASIL, 2006) in all of the country's federal units.

CONCLUSION

There was an increase in the proportion of cases of toxicological events associated with paracetamol in relation to the total number of cases during the study period, the majority of which were among women and involved suicide attempts. Cases occurred more frequently on weekends and in the afternoon and evening. The most common signs and symptoms were vomiting, drowsiness, and nausea, and the main drugs associated with paracetamol in toxicological events were analgesics, muscle relaxants, and anti-inflammatories. Around a third of the toxicological events had an ingested dose of paracetamol equal to or greater than the toxic dose for the use of the antidote N-acetylcysteine.

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