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Severe drug interactions in acetaminophen poisoning in Brazil: A cross-sectional study based on the Notifiable Diseases Information System

Letícia Mariano LAGEMANN¹ , Julia Hiromi OKUYAMA¹ , Marcus Tolentino SILVA¹ 

¹Programa de Pós-graduação em Ciências Farmacêuticas, Universidade de Sorocaba, Sorocaba, Brasil;

Corresponding author: Silva MT, marcusts@gmail.com

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Abstract

Objective: To describe poisoning by acetaminophen combined with other drugs and to analyze factors associated with severe drug interactions. **Methods:** Cases of poisoning involving acetaminophen available in the 2017 Notifiable Diseases Information System were analyzed. Records containing association with pesticides, food, alcohol, and drugs of abuse were excluded. The medications related to poisoning were identified, coded and grouped according to the Anatomical Therapeutic Chemical classification system. Intensity of the interaction was analyzed to determine its severity according to Micromedex®. To investigate the factors associated with severe drug interactions, we estimated the prevalence ratios (PRs) by means of Poisson regression, which considered the following variables: region, age group, gender, ethnicity, month of occurrence, day of the week, association with analgesics, association with anti-inflammatories, and suicide attempts. **Results:** In 2017, 763 notifications of poisoning by acetaminophen combined with other drugs were identified. There were 5.6 cases of attempted suicide for each unintentional case. The multivariate analysis indicated that severe drug interactions were more frequent in those aged over 37 years old (PR=2.73; 95% CI 1.35-5.54), and users of analgesics (PR=2.56; 95% CI 1.52-4.30) and of anti-inflammatory drugs (PR=4.04; 95% CI 2.41-6.78). **Conclusion:** Serious drug interactions in cases of acetaminophen poisoning have been associated with analgesics, anti-inflammatory drugs, adults, and suicide attempts.

Keywords: poisoning; acetaminophen; pharmacovigilance. Drug interactions; database; suicide attempted.

Interações medicamentosas graves em intoxicações por acetaminophen no Brasil: estudo transversal baseado no Sistema Nacional de Agravos de Notificação

Resumo

Objetivo: Descrever as intoxicações de acetaminophen associadas a outros medicamentos e analisar os fatores associados às interações medicamentosas graves. **Métodos:** Foram analisados os casos de intoxicação envolvendo acetaminophen disponíveis no Sistema de Informação de Agravos de Notificação de 2017. Foram excluídos os registros contendo associação com agrotóxicos, alimentos, álcool e drogas de abusos. Os medicamentos relacionados às intoxicações foram identificados, codificados e agrupados de acordo com a classificação Anatomical Therapeutic Chemical. A intensidade da interação foi analisada para determinar a gravidade de acordo com o Micromedex®. Para investigar os fatores associados às interações medicamentosas graves, estimamos as razões de prevalência (RP) por regressão de Poisson, a qual considerou as seguintes variáveis: região, faixa-etária, sexo, etnia, mês de ocorrência, dia da semana, associação com analgésicos, associação com antiinflamatórios e tentativas de suicídio. **Resultados:** Em 2017, foram identificadas 763 notificações de intoxicações por acetaminophen com outros medicamentos. Ocorreram 5,6 casos de tentativa suicídio por um caso não intencional. A análise multivariada indicou que as interações medicamentosas graves foram mais frequentes na idade maior que 37 anos (RP = 2,73; IC 95% 1,35-5,54), usuários de analgésicos (RP= 2,56; IC 95% 1,52-4,3) e usuários de antiinflamatórios (RP = 4,04; IC 95% 2,41-6,78). **Conclusão:** Interações medicamentosas graves em casos de intoxicação por acetaminophen têm sido associadas a analgésicos, antiinflamatórios, adultos e tentativas de suicídio.

Palavras-chave: intoxicação; acetaminophen; farmacovigilância; interações medicamentosas; banco de dados, tentativa de suicídio.



Introduction

In the 1960s, acetaminophen became a renowned non-opioid analgesic¹ most consumed in Brazil and in the entire world. At the recommended doses, the medication is safe and has few adverse events when compared to acetylsalicylic acid in individuals of all ages, from children to older adults.² The possibility of purchasing acetaminophen without a medical prescription, usually known as over-the-counter, is reflected in its greater consumption and, consequently, in the increased number of cases of acetaminophen poisoning. At high doses, it results in important adverse effects, such as liver failure.³ According to these studies, the adverse effects are differentiated between age groups, intentionality and use of isolated or compounded substances.

Reports from Toxicology Information Centers indicate that medications are one of the major causative agents of human poisoning,⁴ with acetaminophen taking the leading role in several countries.⁵ The intentional cases are related to use above the dosage approved by the regulatory bodies, usually in a single dose and associated with other medications. Unintentional poisoning occurs in children and adults and corresponds to incorrect use or to inadequate dosage for a prolonged period of time. Reports are driven by lack of knowledge about the medication and by inadequate prescription.⁶

The studies on the effects of the drug interaction between acetaminophen and other medications lack quality, since randomized clinical trials conducted with this purpose are scarce.⁵ The possible interactions are due to changes in the pharmacokinetics of acetaminophen, such as changes in its absorption due to delayed gastric emptying or to competition for liver metabolism through the cytochrome P-450 pathway.⁷

In Brazil, increased consumption⁸ and knowledge of estimations about poisoning cases in the population are indispensable to devise political guidelines.⁹ Severe interactions, resulting from the possible interference with gastric emptying, or from changes in pharmacokinetic parameters in the presence of other medications, are hardly reported or shown in robust studies.⁵ In addition to the typical adverse reactions related to the hepatic risks of acetaminophen, there is the need for further information about the harms of its use in combination with other medications and of its long-term use.⁷ Public health initiatives to prevent intentional poisoning due to easily accessible chemical substances are suggested by several studies, in order to reduce suicide attempts with acetaminophen.¹⁰

This study aimed at describing poisoning by acetaminophen combined with other medications and to analyze factors associated with severe drug interactions with acetaminophen.

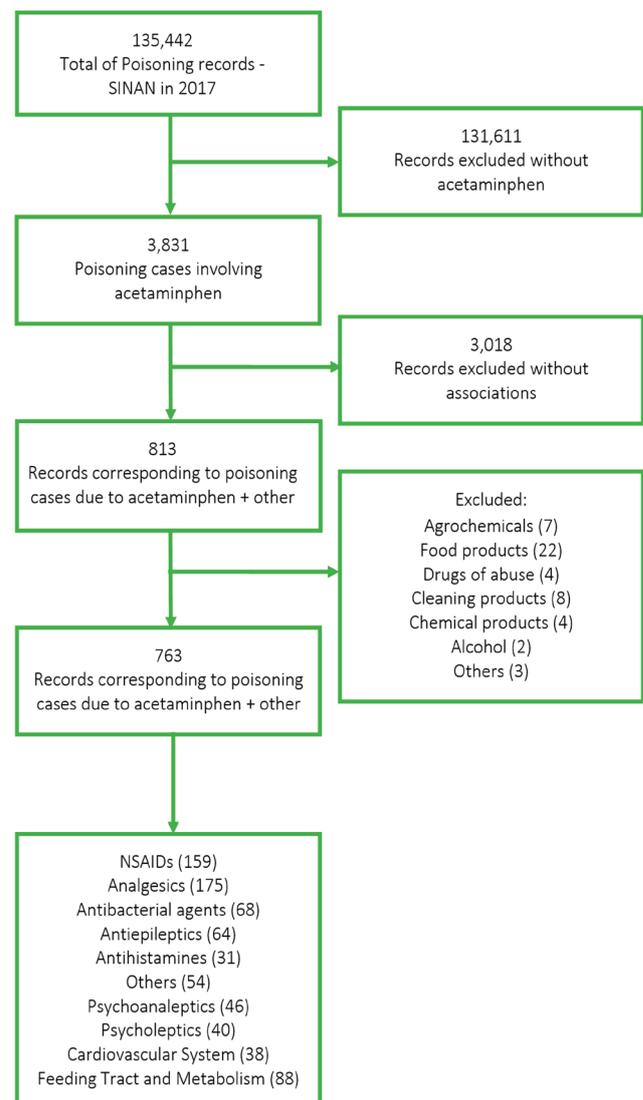
Methods

This is a cross-sectional study of the data coming from the Notifiable Diseases Information System (*Sistema de Informações de Agravos de Notificação*, SINAN). The SINAN was implemented in Brazil in the 1990s and is supplied with information about the investigation of cases of diseases included in the national list of compulsory reporting diseases, and its update is mandatory since 1998 at the municipal, state and federal levels.¹¹ In addition to collecting information, this system aims at disseminating data generated from the Epidemiological Surveillance System and

to support the monitoring of compulsory reporting diseases.¹² The poisoning cases were included in this list in 2010, with the intention of mapping such occurrences in Brazil.¹³

All cases of acetaminophen poisoning recorded in 2017 were selected, except for reports that included association with pesticides, foods, alcohol and drugs of abuse. The year 2017 was chosen at the time due to the availability of a free-access File Transfer Protocol (FTP) file. When combined with acetaminophen, the medications related to poisoning were identified, classified and grouped according to the Anatomical Therapeutic Chemical (ATC) classification system. Hospitalization severity was analyzed with Micromedex®, Figure 1.

Figure 1. Flowchart corresponding to the poisoning cases due to acetaminophen associated with other medications



The cases were characterized in terms of age group, previously defined for including a greater number of events, n > 10, (0-17; 18-36; 37+ years old), gender (female; male), race (white; non-white), pharmacological group (non-steroidal anti-inflammatory drugs [NSAIDs]; analgesics; antibacterials; antiepileptics; antihistamines; psychoanaleptics; psycholeptics; cardiovascular system; food tract and metabolism; other), trimester of the year

(1st; 2nd; 3rd; and 4th), day of the week (Monday to Friday; weekend), type of interaction (mild; moderate; severe), and suicide attempt (yes; no). To characterize the geographical region, it was decided to combine the North and Northeast regions, as well as the South and Midwest regions, due to the low number of notifications (n < 10) (North/Northeast; Southeast; South/Midwest).

The potential differences between the groups (with or without severe drug interaction) were investigated using the chi-square test. To investigate the factors associated with severe drug interactions, Poisson regression was calculated to estimate prevalence ratios (PRs) with 95% confidence intervals (95% CI). Wald's test was performed to identify the statistically significant differences. The statistically significant variables (p<0.05) were subjected to adjusted analysis and assessed using a graph with the probabilities of severe drug interactions. All calculations were made in STATA 14.2 (Stata Corporation, College Station, United States).

Results

A total of 763 records of poisoning cases due to acetaminophen or other medications were included in the analysis. Table 1 presents the characteristics of the poisoning cases involving acetaminophen with some type of medication. Predominance of a young and female population is noticed in the South and Midwest regions of the country. Frequency was higher in the last trimester (2.9 cases/day) and on weekdays (from Monday to Friday, 2.3 cases/day). There were 5.6 suicide attempts for every accidental poisoning case.

Table 1. Characteristics of the sample under study (Brazil, 2017)

Characteristics	Total N=763	Severe drug interactions	p-value
Region n (%)			
North/Northeast	68 (8.9)	4 (5.9)	0.553
Southeast	311 (40.8)	23 (7.4)	
South/Midwest	384 (50.3)	35 (9.1)	
Age group (years old) n (%)			
0-17	257 (33.7)	16 (6.2)	0.021
18-36	406 (53.2)	31 (7.6)	
>37	100 (13.1)	15 (15.0)	
Female gender ² n (%)	542 (71.3)	49 (8.3)	0.757
Ethnicity ³ n (%)			
White	433 (56.7)	40 (9.2)	0.344
Black/Brown/Indigenous	239 (31.3)	17 (7.1)	
Trimester n (%)			
First	160 (21.0)	16 (10.0)	0.727
Second	167 (21.9)	11 (6.6)	
Third	192 (25.2)	15 (7.8)	
Fourth	244 (32.0)	20 (8.2)	
Week period n (%)			
Monday-Friday	596 (78.1)	51 (8.6)	0.410
Weekend	167 (21.9)	11 (6.6)	
Did not use any analgesic ² n (%)	529 (69.3)	34 (6.4)	0.010
NSAIDs ^{1,2} not used n (%)	559 (73.3)	29 (5.2)	<0.001
Suicide attempt ² n (%)	647 (84.8)	53 (8.2)	0.743

¹NSAIDs: Non-Steroidal Anti-Inflammatory Drugs. ²Dichotomous variable for which only one category was presented. ³There are unknown data.

Of the 763 records analyzed, there were severe drug interactions in the acetaminophen poisoning cases in 8.1% (95% CI: 6.4-10.3). Table 2 presents the analysis of the characteristics studied in the population at risk of severe drug interactions. These interactions increased according to the age of the population under study and to the consumption of analgesics and of NSAIDs. It was identified that the severe drug interactions were 2.56 and 4.04 times more prevalent when the association involved analgesics and in the presence of NSAIDs, respectively.

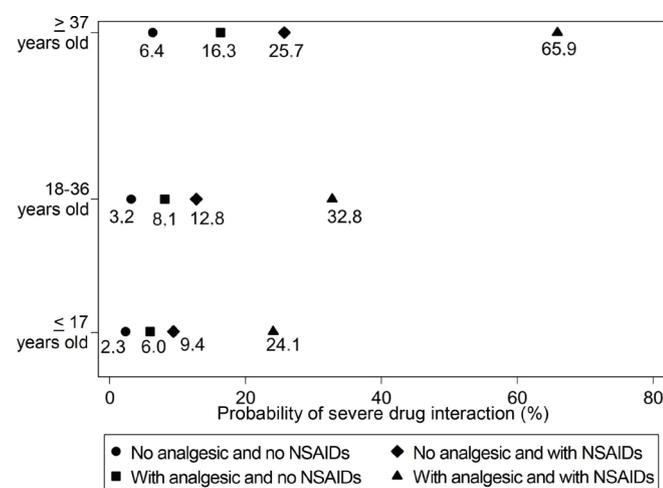
Table 2. Investigation of the factors associated with the severe drug interactions in acetaminophen poisoning cases in Brazil during 2017.

Characteristics	Unadjusted PR (95% CI)	p-value	Adjusted PR (95% CI)	p-value
Region		0.414		
North/Northeast	1.00			
Southeast	1.65 (0.58-4.7)			
South/Midwest	1.87 (0.67-5.23)			
Age group (years old)		0.007		<0.001
0-17	1.00		1.00	
18-36	1.18 (0.67-2.05)		1.36 (0.74-2.48)	
37+	2.62 (1.41-4.88)		2.73 (1.35-5.54)	
Gender		0.479		
Female	1.00			
Male	0.81 (0.46-1.44)			
Ethnicity		0.319		
White	1.00			
Black/Brown/Indigenous	0.77 (0.46-1.29)			
Trimester		0.790		
First	1.00			
Second	0.70 (0.34-1.43)			
Third	0.91 (0.48-1.72)			
Fourth	0.90 (0.49-1.65)			
Week period		0.779		
Monday-Friday	1.00			
Weekend	0.92 (0.53-1.6)			
Analgesics		0.017		<0.001
Not used	1.00		1.00	
Used	1.86 (1.13-3.07)		2.56 (1.52-4.3)	
NSAIDs¹		<0.001		<0.001
Not used	1.00		1.00	
Used	3.11 (1.89-5.13)		4.04 (2.41-6.78)	
Suicide attempt		0.985		
No	1.00			
Yes	1.01 (0.53-1.91)			

¹NSAIDs: Non-Steroidal Anti-Inflammatory Drugs.

Figure 2 presents the probability of severe drug interactions in the acetaminophen poisoning cases by age extracts. A greater risk trend is observed in those aged over 37 years old and with an analgesic or NSAID association. It is also emphasized that the combination of these factors (age > 37 years old + analgesics + NSAIDs) increased the probability of a severe drug interaction in notifications of acetaminophen poisoning.

Figure 2. Frequency of severe drug interactions among users of analgesics and non-steroidal anti-inflammatory drugs according to age group



Discussion

Our main findings indicate that, for every one hundred acetaminophen poisoning cases recorded at the SINAN in 2017, eight involved severe drug interactions. Such instances increase according to the consumption of analgesics and of NSAIDs, as well as to increases in age and suicide attempts.

Our data are based on poisoning records, of a national scope, obtained from the SINAN. Notifications are mandatorily available to health professionals, which provides a greater number of notifications when compared to those obtained by the Poisoning Control Centers. Conversely, open and non-standardized fields allow for errors; furthermore, their proper interpretation requires data recording, on a case-by-case basis, to identify the active ingredients and categorize according to pharmacological groups. Lack of standardization in open fields can induce misreporting and information bias, situations that reduce the quality of the records and favor underreporting, a fact that has already been reported in other research studies.^{9,14-16} With regard to the number of medications associated with acetaminophen, these limitations in the quality of information hinder a more accurate assessment of poisoning cases by different toxic agents in the country and hamper the development of preventive and corrective control actions by the regulatory agencies.

We identified an important relationship between severe interactions and presence of analgesics and NSAIDs. Severe interactions with acetaminophen were 2.56 and 4.04 times more frequent among users of analgesics and users of NSAIDs, respectively. As it is an over-the-counter medication, acetaminophen is very used as an analgesic in cases of mild and moderate pain and also as an antipyretic – mainly in children and sometimes in pregnant women. Therefore, continuous and exaggerated use of acetaminophen has become common because it is an easily accessible medication with a significant number of commercial presentations and limited information on its toxicity – which can be increased when acetaminophen is combined with other medications.^{17,18}

Intentional or accidental poisoning with analgesics is considered as major public health concern. Although over-the-counter analgesics, with acetaminophen standing out, are safely used by millions of people every year, high doses result in adverse effects such as death.¹⁹

We also identified a relationship between the severe interactions and an increase in age and suicide attempts. The results obtained in this study reveal that 8.1% of the cases analyzed were classified as severe drug interactions with acetaminophen, and that the age group from 18 to 36 years old was the most affected. Diverse international evidence indicates that there is predominance of the youngest population in acetaminophen poisoning cases due to intentional causes.^{20,21} Suicide attempt in the youngest population can be a response of a more impulsive action facilitated by the use of more accessible medications.²² The use of acetaminophen in the management of chronic pain can explain its concomitant use with several presentations of analgesics, especially in the aged population, leading to an increased risk of poisoning and interactions.²³

Intentional poisoning cases, that is, those driven by suicide ideation, impose an additional challenge. In such scenarios, assessing the notification and the causes that motivated the action is a complex and difficult task, because there are difficulties or impediments in obtaining this information and interpreting the motivating facts. Conversely, the SINAN is considered an easy to complete tool, has a nationwide coverage, contributes to democratize information, and has favorable acceptance. These elements favor its adherence by the health professionals, which proves to be efficient in the monitoring of adverse events.^{24,25}

With regard to generalization of the results, it is possible to initiate a discussion on the implementation of regulatory measures to prevent free access by customers to these medications, such as removing them from shelves near the cashier, reducing the number of pills inside the package or blister, including warnings about hepatic damage on the label and about the maximum dose on the medication packages, which tend to reduce the number of poisoning cases and associated injuries.^{3,26-28}

In the USA, half of the cases of acute liver failure are associated with the use of acetaminophen.²² According to a study conducted in 2005, 63% of the cases of unintentional overdose result in liver failure. Given these numbers, in 2011, the Food and Drug Administration recommended limiting the acetaminophen dose to 325 mg per tablet or capsule in combinations with opiates, with a maximum of 650 mg per administration.²⁹ In Brazil, medications represent the second leading agent causing human poisoning, and analgesics are the second therapeutic group among the agents. According to the research results regarding the type of causative agents, educational actions for specific population groups are suggested. Control of acetaminophen combined with opiates is intensified by every new control system that electronically monitors the handling of medications used under medical prescription, in order to hinder their loss and misuse.

Conclusion

This is the first analysis of information routinely obtained in health services at the national level, which gave priority to poisoning with a commonly used medication. Despite the intrinsic limitations of this type of information, this study reveals the use

potential of the SINAN in monitoring adverse events. Of every one hundred acetaminophen poisoning reports associated with other medications, eight present severe drug interactions. It was observed that the number of these events tend to increase when they are related to combination with analgesics and NSAIDs, increased age, and suicide attempts. Measures to warn about hepatic adverse events, as well as limiting dosage, amount and access to acetaminophen, are important strategies to reduce the incidence of poisoning.

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Collaborators

LML: Writing of the article, data analysis and interpretation. JHHO: Design, data analysis and interpretation. MTS: Conception, relevant critical review of the intellectual content, data analysis and interpretation. Article review and conduction of the research. All the authors made the reviews and agree with all the information contained in the paper.

Conflict of interests statement

The authors declare that there are no conflicts of interests in relation to this article.

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