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ORIGINAL ARTICLE / *ARTIGO ORIGINAL*

Trends of drug-related poisoning cases attended to at a poison control center

Tendências de eventos toxicológicos relacionados a medicamentos atendidos por um Centro de Informações Toxicológicas

Thays Lopes Mathias[I], Camilo Molino Guidoni[II], Edmarlon Girotto[II]

ABSTRACT: ***Introduction*:** Drug-related poisonings have a high impact on morbidity and mortality, representing the first cause of intoxication in Brazil. ***Objective*:** To describe the trends of cases of drug-related poisonings attended to by a poison control center. ***Method*:** A quantitative approach (cross-sectional trend study) with data analysis of cases of drug-related poisonings attended to at the Poison Control Center of University Hospital of the State University of Londrina. Data were collected from service notification records for the period 1985 to 2014. For statistical analysis, a simple linear regression model was used. ***Results*:** Of the 36,707 cases attended to by the service, 22.5% (n = 8,608) were drug-related poisonings. There was an increase in the proportion of cases for both sexes ($R^2 = 0.195$, $p = 0.014$) and males ($R^2 = 0.403$, $p < 0.001$). There was a trend towards a higher proportion of cases involving the analgesic, anti-inflammatory and immunosuppressive drug classes ($R^2 = 0.521$, $p = 0.018$), antidepressants ($R^2 = 0.923$, $p < 0.001$) and antipsychotics ($R^2 = 0.869$; $p < 0.001$). Antibiotics showed a trend toward a lower proportion of cases ($R^2 = 0.773$, $p = 0.001$). ***Conclusions*:** There was a trend for a higher proportion of cases of drug-related poisonings in males. Also, there was an increased trend towards cases involving analgesics/anti-inflammatories/immunosuppressants, antidepressants and antipsychotics.

Keywords: Poisoning. Drugs. Trends.

[I]Pharmacy Course, State University of Londrina – Londrina (PR), Brazil.
[II]Department of Pharmaceutical Sciences, State University of Londrina – Londrina (PR), Brazil.
Corresponding author: Edmarlon Girotto. Departamento de Ciências Farmacêuticas. Universidade Estadual de Londrina. Avenida Robert Koch, 60, CEP: 86038-440, Vila Operária, Londrina, PR, Brasil. E-mail: eddieuel@yahoo.com.br
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RESUMO: ***Introdução*:** Os eventos toxicológicos relacionados a medicamentos têm alto impacto na morbimortalidade, representando a primeira causa de intoxicação no Brasil. ***Objetivo*:** Descrever as tendências de casos de eventos toxicológicos relacionados a medicamentos atendidos por um Centro de Informações Toxicológicas. ***Método*:** Estudo com abordagem quantitativa (transversal e de tendência), com análise dos dados referentes aos casos de eventos toxicológicos relacionados a medicamentos atendidos pelo Centro de Informações Toxicológicas do Hospital Universitário da Universidade Estadual de Londrina. Os dados foram coletados das fichas de atendimento, referentes ao período de 1985 a 2014. Para a análise estatística, utilizou-se um modelo de regressão linear simples. ***Resultados*:** Dos 36.707 casos atendidos pelo serviço, 22,5% (n = 8.608) foram eventos toxicológicos relacionados a medicamentos. Houve um aumento da proporção de casos em ambos os sexos ($R^2 = 0,195$; $p = 0,014$) e no sexo masculino ($R^2 = 0,403$; $p < 0,001$). Detectou-se tendência de elevação da proporção de casos envolvendo a classe de analgésicos, anti-inflamatórios e imunossupressores ($R^2 = 0,521$; $p = 0,018$), antidepressivos ($R^2 = 0,923$; $p < 001$) e antipsicóticos ($R^2 = 0,869$; $p < 0,001$). Os antimicrobianos apresentaram tendência de redução da proporção de casos ($R^2 = 0,773$; $p = 0,001$). ***Conclusões*:** Observou-se tendência de aumento da proporção de casos de eventos toxicológicos relacionados a medicamentos no sexo masculino. Também houve aumento nas tendências envolvendo analgésicos/anti-inflamatórios/imunossupressores, antidepressivos e antipsicóticos.

Palavras-chave: Intoxicações. Medicamentos. Tendências.

INTRODUCTION

Human poisoning involves a wide variety of pathophysiological processes related to the interaction between a chemical or biological agent and the body. Poisoning is a serious global public health problem[1], victimizing approximately 500,000 people per year according to the World Health Organization (WHO) [2,3].

Drugs are important therapeutic tools used for the prevention of health problems and recovery and maintenance of health; however, their irrational and indiscriminate use causes many negative consequences, such as not controlling or resolving the health problem, poisoning and even death. Drugs rank first in poisoning records and are the second cause of mortality related to human poisoning[4,5]. Besides, the potential years of life lost due to drug intoxication indicate large social and economic losses for the public[6].

A study based on poisoning cases at the National Network of Poison Control Centers in Brazil points to suicide attempt (41%) and individual accidents (35.3%) as the main circumstances of drug poisoning. Regarding the therapeutic classes, benzodiazepines are the drugs that most resulted in intoxication, followed by anticonvulsants, antidepressants and analgesics[3].

However, studies conducted in Brazil on drug poisoning are commonly performed on children and adolescents[7,8] or elderly[9]. Only the study by Margonato et al.[10], carried out on poisoning cases occurring in 2004, evaluated drug intoxications in the general population. Nevertheless, studies have not shown trends in the outcome of drug poisoning cases over years.

With regard to drug poisoning, the most important services are those provided by a poison control center (PCC) for critical instances of guidance for cases of poisoning and envenomation[11]. Thus, it is essential to systematize the cases reported by these services, especially drug-related ones, which are little explored in scientific studies. Knowledge of drug poisoning profiles may lead to control strategies and implementation of appropriate assistance for the inappropriate and indiscriminate use of these therapeutic resources. Therefore, the aim of this work was to investigate the cases of drug-related poisoning (DRP) seen at a PCC.

METHOD

This was a cross-sectional trend study, conducted with data from the PCC of the University Hospital of the State University of Londrina (CIT/HU/UEL), in the city of Londrina, Brazil. CIT/HU/UEL provides guidance in the event of accidents with poisonous animals and intentional or accidental intoxications, as well as any contact with an exogenous substance, even if it does not generate clinical manifestations. For this study, the term "drug-related poisoning (DRP)" was used, not "drug intoxication",[12] since not only cases of intoxication were analyzed, but all drug-related toxic events, including exposures and adverse reactions.

All the cases of DRP treated by the CIT/HU/UEL in the period from 1985 to 2014 were analyzed. These cases were attended to in person (emergency room of University Hospital) or long distance (telephone service), giving clinical support to the health care professional caring for the patient.

The data were collected from the service's notification forms and outcome of cases of intoxications and poisonings. The study variables used to describe the cases were the following: age (in years); age group (4 years or less, 5 to 9 years, 10 to 14 years, 15 to 19 years, 20 to 39 years, 40 to 59 years, 60 years and older); sex (male or female); exposure (acute, chronic); circumstance (suicide attempt, accidental, administration error, therapeutic use, self-medication, medical prescription, other), occurrence (intoxication, exposure only, adverse reaction, other), exposure route (oral only, parenteral only, other), toxicological analysis (yes, no), hospitalization (yes, no), time of hospitalization (in days), outcome (discharge, death, other) and drug classes, which were defined on the basis of the criteria used by the service itself (CIT/HU/UEL). The service notification forms allowed the inclusion of only three agents, so for intoxications involving four or more agents (only drugs or drugs in combination with other substances), it was not possible to identify some of these agents. In these situations, the notifying professional was directed to record the substances that could be more serious.

Trends were calculated according to the proportion of cases of DRP according to sex (male and female), in relation to total cases (dependent variable) and per year of analysis (1985 to 2014) (independent variable). The trends in drug classes were calculated on the basis of the proportion of cases per class in relation to total cases of DRP (dependent variable),

for three years of analysis (1985-1987 to 2012-2014) (independent variable). Trend analyses throughout the three-year periods were carried out only with the five classes of drugs that showed the highest frequency. The choice of the period from 1985 to 2014 was due to the option for three-year periods in the trend analyses of drug classes, starting in the year of operation of the CIT/HU/UEL (1985), forming ten triennia.

The data were entered in a database created in Epi Info version 3.5.4 for Windows®, and statistical analysis was performed using the Statistical Package for Social Sciences (SPSS), version 19.0 for Windows®. The simple and relative frequencies of the qualitative variables and the measures of central tendency of the quantitative ones (mean and standard deviation) were then determined. Trend analysis was performed using simple linear regression models. Statistical modeling considered the proportion of cases in the study outcomes as a dependent variable and the chronological time under analysis as an independent variable. The estimated model could be written as: $Y = \beta 0 + \beta 1 (X - 1985$ [ou 1985–1987]). In these models, Y corresponds to the proportion of cases, $\beta 0$ the mean annual rate, $\beta 1$ the coefficient of linear effect (velocity) and X the year or triennium[13]. The trend was considered significant when the model resulted in $p < 0.05$. As a measure of the accuracy of the models, the coefficient of determination (R^2) was used. This research was approved by the Ethics Committee on Research Involving Human Beings of the State University of Londrina (CEP-UEL) (CAAE No. 45986415.1.0000.5231).

RESULTS

During 1985 to 2014, CIT/HU/UEL registered 36,707 cases involving intoxications or poisonings. Of these cases, medications accounted for 8,608 (23.5%). Of the cases of DRPs (n = 8,608), there was a combination with other chemical agents in 7.4% (Table 1). Of the cases only with medications (n = 7,972), 1,994 (25%) involved 2 or more drugs.

Females accounted for the majority of DRPs (n = 5,138; 65.1%). The mean age was 19.1 ± 16.3 years, ranging from newborn to 90 years. The most frequent age groups were those of 4 years or less (30.6%) and 20 to 39 years (32.0%). Acute exposure was the most frequent (99.4%). Suicide attempt (53.1%) and accidental occurrence (35.1%) represented the main circumstances of DRPs (Table 2).

In addition, 31.4% (n = 2,702) of patients with DRPs required hospitalization, with 0.6% (n = 50) resulting in death. Regarding the number of days of hospitalization, a mean of 2.7 ± 4.6 days, with a maximum of 103 days, was obtained. The majority of cases were by telephone (n = 6,313, 73.3%) and in the urban area (n = 8,234, 95.7%). Toxicological analyses were conducted in 1.2% (n = 107) of patients with DRPs.

Regarding the medications, anticonvulsants, sedatives or hypnotics (29.5%), analgesics, anti-inflammatories or immunosuppressants (13.0%) and antidepressants (12.8%) were the main classes involved with a total number of 11,162 (Table 3).

In the analysis of the proportion of cases of DRPs according to sex, there was a trend for an increase in the proportion of total cases in both sexes ($R^2 = 0.195$, $p = 0.014$) and in males ($R^2 = 0.403$, $p < 0.001$) (Figure 1). In proportional numbers, the increase for the period 1985-2014 was 2.3% for both sexes and 64.0% for males. We should also point out the proportional decline in cases (total, male and female) in 1997.

Among the five main classes involved in the DRPs according to the predetermined triennia, there was a trend for an increase in the proportion of cases with analgesics, anti-inflammatories and immunosuppressants ($R^2 = 0.521$; $p = 0.018$), antidepressants ($R^2 = 0{,}923$; $p < 0.001$) and antipsychotics ($R^2 = 0.869$; $p < 0.001$). The antibiotics showed a trend towards a reduced proportion of cases ($R^2 = 0.773$; $p = 0.001$) (Table 4).

DISCUSSION

The proportion of cases involving drugs (23.5%) is similar to the results of other studies conducted in Brazil[4,14-16] and the data published by the National System of Toxic-Pharmacological Information (Sinitox) (28.5%)[5]. It is also worth noting the combination of medications with other agents, especially drugs of abuse, which tends to make intoxication more serious. In addition, it may be suggested that the use of drugs of abuse increases the risk of DRPs, especially in the circumstances of attempted suicide[17].

In relation to the age group most affected by the MES, we highlight the 20-39 years, probably related to intentional circumstances (such as attempted suicide)[18] and to children aged 4 years or less, who are more subject to administration errors or to accidental causes[19,20]. Other studies in Brazil have identified children and young adults as the main age groups involved in DRPs[19,21]. Information from Sinitox also reinforces the notion that these age groups are exposed the most to this type of intoxication[4,22].

Table 1. Characterization of drug-related poisonings. Poison Control Center of University Hospital of State University of Londrina, 1985–2014 (N = 8,608).

Agents	N	%
Medications	7,972	92.6
Medications and drugs of abuse	360	4.2
Medications and household cleaning products	63	0.7
Medications and rodenticides	56	0.7
Medications and farm pesticides	41	0.5
Medications and household pesticides	38	0.4
Other combinations	78	0.9
Total	8,608	100.0

Table 2. Characterization of cases of drug-related poisoning attended to by Poison Control Center of University Hospital of the State University of Londrina, 1985–2014 (N = 8,608).

Variables related to poisoinings	N	%
Age group (years)*		
4 or less	2,633	30.6
5 to 9	472	5.5
10 to 14	500	5.8
15 to 19	1,212	14.1
20 to 39	2,756	32.0
40 to 59	866	10.1
60 or more	166	1.9
Exposure		
Acute	8,556	99.4
Chronic	52	0.6
Circumstance		
Suicide attempt	4,568	53.1
Accidental	2,906	33.8
Administration	339	3.9
Therapeutic use	213	2.5
Self-medication	179	2.1
Prescription	106	1.2
Others**	297	3.4
Occurrence		
Intoxication	6,463	75.1
Exposure only	1,955	22.7
Adverse reaction	140	1.6
Others**	50	0.6
Exposure route		
Oral only	8,280	96.2
Parenteral only	107	1.2
Others**	221	2.6

*Three records with no information on age; **situations with frequency less than 1.0%.

According to Datasus, suicide attempt (35.6%), accidental cause (40.1%) and therapeutic use (8.7%) have been the main causes of exogenous intoxication by medications since 2007[22]. These circumstances were highlighted in a study of DRP cases attended to by a PCC in the state of Rio Grande do Sul[23]. Among these three circumstances, suicide attempt tends to be the most serious, since the individual has intentionality in taking a large amount of the drug[24], which requires a more careful handling of the cases.

There has been a trend towards an increase in the proportion of cases of DRPs over the years, as seen specifically for males. The reason for the increase in this trend may be related to the easy acquisition of these products and their great availability in households, as well as the

Table 3. Distribution of therapeutic classes of medications involved in cases of drug-related poisoning. Poison Control Center of University Hospital of State University of Londrina, 1985–2014 (N = 11,162).

Class of medications	N	%
Anticonvulsants/sedatives/hypnotics	2,915	29.5
Analgesics/anti-inflammatories/immunosuppressants	1,282	13.0
Antidepressants	1,267	12.8
Antibiotics	751	7.6
Antipsychotics	695	7.0
Cardiotonics/antihypertensives	528	5.3
Respiratory tract	516	5.2
Antihistamines	515	5.2
Homeopathics	387	3.9
Hormones	336	3.4
Gastrointestinal tract	305	3.1
Vitamins/minerals/iron	218	2.2
Topical dermatological drugs	207	2.1
Anorexigenic/stimulant agents of the central nervous system	183	1.9
Topical agents for eyes, ears, throat and nose	134	1.4
Anticholinergics	126	1.3
Diuretics	117	1.2
Others*	283	2.9
Unknown/Not classified	397	4.0
Total	11,162	100.0

*Other: referring to drug classes with frequency less than 1.0%.

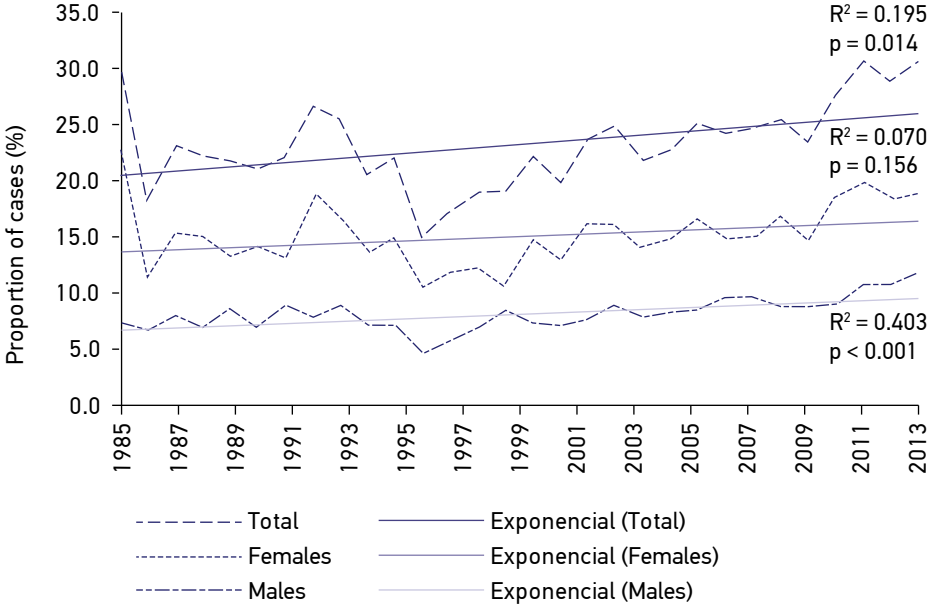
wide variety of drugs in the retail pharmacy[7]. In addition, the precariousness of some public services, combined with the ease of obtaining medicines in pharmacy, which still have a commercial character to the detriment of care, increases the availability of these products to society[25].

In addition, many health care professionals and patients ignore the dangers of drug combinations, increasing the risk of administration errors or adverse reactions. Also, it should be mentioned that drug advertising has been a frequent stimulus for inappropriate drug use, above all by highlighting benefits and omitting or minimizing risks and possible adverse effects, giving the impression that they are innocuous products, thereby influencing consumption as with any other commodity[25,26].

Although women represent the main group affected by DRPs, as demonstrated in this study and in others conducted in Brazil[4,14-16,18,23], the trend towards an increase in the proportion of male cases may be related to the higher consumption of these products by men in the last decade[16,27,28] compared to previous decades[29,30].

It should also be noted that there was a general reduction in the proportion of DRPs registered in 1997. This decrease was due to the systematic reporting of exogenous intoxications, which in 1997 became the obligatory notification of injuries, being included in the Brazilian Information System for Notifiable Diseases (SINAN).

As regards the most common classes of drugs in the DRPs during the period of analysis (1985-2014), those that act on the central nervous system, the analgesic/anti-inflammatory/



*Proportion of cases of drug-related poisonings in relation to total cases.

Figure 1. Trends of cases of drug-related poisonings (%) according to sex. Poison Control Center Universitary Hospital of State University of Londrina, 1985 to 2014*.

immunosuppressive drugs and antibiotics were the most prominent. These data corroborate the National Survey on Access, Use and Promotion of the Rational Use of Medicines (PNAUM), which identified that drugs acting on the nervous system (with analgesics representing 40.8% of them) and on the musculoskeletal system (including inflammatory and antirheumatic drugs) are respectively used by 18.6 and 8.7% of the population surveyed[31]. The high consumption of analgesics, anti-inflammatories and antirheumatics, shown by PNAUM[31], indicates that the public is exposed to a greater risk of DRPs by these therapeutic groups.

The fact that many DRPs involve those that act on the central nervous system may be related to the increasing use of these substances[32], mainly due to the increase in the number of patients diagnosed with psychosomatic illnesses, such as depression, anxiety, panic syndrome and others [33,34].

Analgesics, which have also been highlighted in cases of intoxication, are the most popular and safe medications when administered under recommended therapeutic conditions[35],

Table 4. Tendências dos casos de eventos toxicológicos relacionados a Medications (%) segundo classe terapêutica. Centro de Informações Toxicológicas do Hospital Universitário da Universidade Estadual de Londrina, 1985 a 2014.

Triennium	Total cases of medications	Anticonvulsants, sedatives or hypnotics		Analgesics, anti-inflammatories and immunossuppressants		Antidepressants		Antibiotics		Antipsychotics	
		Cases	%	Cases	%	Cases	%	Cases	%	Cases	%
1985–1987	366	154	42.1	48	13.1	8	2.2	44	12.0	8	2.2
1988–1990	417	158	37.9	59	14.1	16	3.8	69	16.5	13	3.1
1991–1993	570	216	37.9	78	13.7	21	3.7	87	15.3	38	6.7
1994–1996	748	254	34.0	96	12.8	41	5.5	88	11.8	47	6.3
1997–1999	747	229	30.7	91	12.2	51	6.8	71	9.5	58	7.8
2000–2002	870	247	28.4	125	14.4	120	13.8	81	9.3	54	6.2
2003–2005	1,089	350	32.1	148	13.6	204	18.7	72	6.6	86	7.9
2006–2008	1,129	349	30.9	161	14.3	237	21.0	70	6.2	94	8.3
2009–2011	1,222	427	34.9	218	17.8	247	20.2	73	6.0	128	10.5
2012–2014	1,450	531	36.6	258	17.8	322	22.2	96	6.6	169	11.7
Total	8,608	2,915	33.9	1,282	14.9	1,267	14.7	751	8.7	695	8.1
Coefficient of determination (R^2); p value		0.267; 0.141		0.521; 0.018		0.923; < 0.001		0.773; 0.001		0.869; < 0.001	
Trend		Stable		Increasing		Increasing		Decreasing		Increasing	
Variation of 1985–1987 and 2012–2014 (%)		-19.5		+13.7		+568.2		-27.5		+268.2	

but they have been an important cause of drug intoxication among children and adults, since they are sold without the need for a prescription[35], which makes access easy.

The trends towards an increased proportion of cases involving antidepressants and antipsychotics found in this study refer to the process of medicalization of society. Medicalization exposes the public to too much to medical sciences[36] to the detriment of social, cultural and behavioral issues, which increases the prescription of psychotropic drugs for the treatment of psychosomatic disorders[36].

A report by the National Health Surveillance Agency (ANVISA) in Brazil showed that amitriptyline (antidepressant) was the fourth most used psychoactive drug in the country in 2010[37]. A study carried out in the city of Pelotas (RS) found that, among psychoactive drugs, the use of antidepressants increased from 8.4% in 1994 to 31.6% in 2003[38]. This increasing trend is also observed in other studies[39,40], and is associated with the increased diagnosis of depressive illnesses and the expansion of treatment options for treatment[38].

Studies have reported increasing trends in cases and hospitalizations for psychoses in recent years[41], which tends to increase the use of antipsychotics, associated with the greater extent of the therapeutic arsenal for the treatment of this group of diseases. This situation exposes individuals to an increased risk of DRPs with antipyschotics, as demonstrated in the present study.

On the other hand, there was a decreasing trend in DRPs with antibiotics, which refers to the rational prescription of this therapeutic group, but also to new regulations that govern the prescription and acquisition of these products. In 2011, ANVISA issued a resolution regarding a mandatory doctor's prescription to obtain antibiotics, and the need for pharmacies to retain the prescription[42]. Previous studies demonstrated that the acquisition of these products occurred without the need for a prescription[43,44], which could result in the irrational use of antibiotics.

Some methodological aspects should be pointed out in relation to this study. Because it was a study using secondary data (PCC notification forms), the information may have been erroneously recorded and/or illegible, in addition to being "ignored" or " lacking information". In this regard, it is noteworthy that only three records had no entry for the item "age". Also important was the limitation in the number of medications to be registered on the CIT/HU/UEL forms (maximum of three), which affects the completeness and consistency of the information. In addition, non-notification of injuries, especially mild ones, may lead to underreporting of cases. Nevertheless, despite the limitations presented, the study gathered consistent and unpublished data on the trends of DRPs, which can contribute to new explorations of secondary data on these diseases.

The results obtained raise a concern about the access and use of psychoactive drugs, indicating the need for measures to promote the rational prescription of these products and more control in their acquisition. In addition, they reveal the need for a more rigorous follow-up of the patient to achieve therapeutic goals, reducing the risk of suicidal thoughts. In addition, easy access to analgesics and anti-inflammatories can be an important contributor to the increasing trend towards intoxications with these drugs, and therefore, policies that foster their rational use can contribute to a decrease in DRPs in this group.

CONCLUSIONS

DRP cases showed a predominance of women, individuals aged 20 to 39 years and children 4 years or less, and suicide attempts and accidental causes as the main circumstances for their occurrence. The proportion of DRPs showed an increasing trend, especially in males. The main medications involved were those that work on the central nervous system, with antidepressants and antipsychotics showing the greatest proportional increase between 1985 and 2014.

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