Analysis of hospitalizations of children under one year of age due to drug intoxication and adverse events in Brazil

Análise das internações hospitalares de crianças menores de um ano relacionadas a intoxicações e efeitos adversos de medicamentos no Brasil

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Abstract

The widespread use of drugs without medical prescription, nearly always ignoring the adverse effects they can cause, is the main cause for human intoxications registered in Brazil. Children are the greatest victims of the practice of self-medication due to the lack of appropriate studies on safe use of medicines in this age group, errors linked to the inappropriate delivery of medicines, besides the fact that the natural curiosity due to their age leads to accidental ingestion. The purpose of this study is to identify the main therapeutic classes responsible for drug intoxications or adverse events related to the hospitalization of children under one year old, registered by the Hospital Information System of the Unified Health System in the years 2003-2005. A total of 1.063 hospitalizations were analyzed, 151 of them involving children aged less than one month and 912 children aged 1-11 months. Sedative-hypnotics were responsible for 15.2% of hospitalizations related to drug intoxication and adverse effects in children under one month of age and for 21.2% of such events in children aged 1-11 months. Antibiotics responded for 12.6% and 18.9% of hospitalizations for the same age groups, respectively. Analgesics/antipyretics had a smaller participation, with 7.3% of hospitalizations in the group under 1 month and 6.7% in the group aged 1- 11 months. A great number of cases has been observed on zero day old children, leading us to consider possible intoxications through placenta or nursing. Therefore the study shows the importance of a good pre-natal care, as well as the extra attention required when drugs are prescribed to both mother and child.

Keywords: poisonings, medicaments, hospitalization, infancy

Resumo

O amplo uso de medicamentos sem orientação médica, quase sempre acompanhado do desconhecimento dos malefícios que pode causar é apontado como uma das causas destes constituírem o principal agente tóxico responsável pelas intoxicações humanas registradas no país. As crianças são as maiores vítimas, pois sofrem com as conseqüências da prática da automedicação, erros de administração, prescrição médica inadequada, com a falta de pesquisas adequadas para a liberação do consumo destes medicamentos em sua faixa etária e com a curiosidade natural da idade. Diante destes dados, objetivou-se identificar as principais classes terapêuticas presentes nas internações de crianças menores de um ano relacionadas a intoxications and adverse effects of medications, registradas pelo Sistema de Informações Hospitalares do SUS nos anos de 2003 a 2005. Foram analisadas 1.063 internações, sendo 151 de menores de um mês e 912 entre um e onze meses. Os antiepilépticos, sedativos-hipnóticos e antiparkinsonianos foram responsáveis por 15,2% das internações relacionadas a intoxications and adverse effects of medications em menores de um mês e 21,1% em crianças de um a onze meses. Os antibióticos sistêmicos responderam para essas mesmas faixas etárias por 12,6% e 18,5% das internações, respectivamente. Os analgésicos, antitérmicos e anti-reumáticos não opiáceos tiveram participação menor, com 7,3% das internações para menores de um mês e 6,6% para crianças de um a onze meses. Um grande número de casos foi observado para crianças de zero dias, levando a considerar possíveis intoxicações por via transplacentária e por aleitamento materno. Dessa forma, o estudo aponta para a importância de um bom acompanhamento pré-natal, bem como para uma criteriosa prescrição de medicamentos para a mãe e a criança.

Palavras-chave: intoxicações, medicamentos, internações, infância

Introduction

Modern society attributes high value to the consumption of medications in its daily life. Many people actually believe they are buying "health" off drugstore counters.

The market constantly offers therapeutic novelties, and some drugs that are already on the market get new use indications. These facts contribute to a significant increase in non-rational medication use[1].

The population is under pressure from several sectors to consume an increasing amount of the medications that are on the market, such as from the pharmaceutical industry, advertising agencies, and communication companies[2]. In 2002, according to data published by the National Health Surveillance Agency (ANVISA), there were 15,831 medications being marketed in Brazil, and the total volume of medication units marketed in the retail market topped at 1,277,336,635[3]. Such an excessive consumption increased the number of intoxications and adverse effects; after all, it is a known fact that all medications pose potential risk[4].

Arrais et al.[5], while investigating the self-medication profile in Brazil, collected data that support the hypothesis of the current society's naïve and excessive belief in the power of medications. This contributes to the increasing demand for pharmaceutical products to treat any type of ailment, no matter how ordinary or self-limited. Many are used without medical indications, leading to countless cases of intoxication. Children are part of this reality. According to a study carried out by Silva et al.[6], there is a high level of medication consumption in nearly all age groups. This study also reveals that, in the absence of medical guidance, the mother is the main adviser for medication consumption.

Data of the National Toxicopharmacological Information System – SINITOX[7] for the 2003-2005 period indicate children aged less than five years are the main victims of medication intoxication (31.8%). Children aged less than a year do not stand out in

the intoxication rates (3.4%); however, their morbidity coefficient is high, 23.2 per 100,000 inhabitants, only lagging behind the coefficient of children aged one to four years: 46.6. According to Schvartsman[8], when one considers the pediatric age group, acute intoxications stand out. Among children aged less than a year, medications account for 60% of the intoxications, twofold the general population's rate.

Considering the importance of medicamentous intoxications among children aged less than a year and on account of the fact that this age group is poorly explored in the literature, it is possible to identify the groups of medications involved the most in hospitalizations related to intoxications and adverse effects among this age group, associating it to the age of children subdivided in days and months and with the possible causes to justify them.

Methodology

The study's design is retrospective, and it covers hospitalizations registered in Brazil by SUS' Hospital Information System (SIH-SUS) from 2003 to 2005. The source of the data are the SUS Hospitalization Authorization Movement CD-ROMs[9,10,11].

"Cases" of hospitalization of children aged less than one year presenting, in the main and/or secondary diagnosis, codes related to intoxication by medications or to adverse effects of medications, according to the 10th Revision of the International Classification of Diseases (ICD-10)[12], were considered, as detailed in Chart 1.

Codes X42, X62, and Y12 were suppressed in order to avoid the selection of codes from the ICD-10 that would not allow for the distinction between complications associated to the use of medications and those caused by the use of licit and illicit drugs. This approach was also adopted by Rozenfeld[13], when performing a wider-ranging study on the complications caused by medications in hospitals in the State of Rio de Janeiro.

To undertake the descriptive data analysis, the cases were divided into two groups. The first included children aged less than a month, with ages represented in days, while the second, children aged one to 11 months, with ages represented in months.

The analysis considered four situations caused by possible main and secondary diagnoses presented by the case studies, as detailed in Chart 2. Situation 1 suggests the child was hospitalized for a reason other than the one we are considering in this study, but which, when treated, ended up turning into a case, i.e., there are signs that the intoxication or adverse effect of medications occurred in the hospital. Situation 2 suggests the child was being medicated outside the hospital to treat the cause of the secondary diagnosis, and such treatment ended up causing an adverse effect due to the therapeutic use of the medication, i.e., an adverse reaction or even an intoxication, which might have occurred due to circumstances such as administration errors, inappropriate indications, use without medical guidance, rather by layman indication. The circumstances involved are not made very clear by the data, since the ICD-10 codes that bring this information are in chapter 20, which, in turn, is used to fill-in the secondary diagnosis, and not the main one, as it is the case in this situation. Situation 3 also suggests the child was not in the hospital when a case of intoxication or adverse effect caused by medication happened. Since there is no description of the pathology associated to the use of the medication, it is more likely the event occurred accidentally. However, this situation may point to more information about the circumstances of the incident, if the secondary diagnosis is duly filled-in with the codes of chapter 20 listed in Chart 1. Situation 4 also suggests the child was not in the hospital when it became a case. This is the situation that offers the least information, as it does not present data on the secondary diagnosis and, thus, on the circumstance of the event. All of these situations must be interpreted carefully for children aged zero day, as well as for those aged one or two days who were already in the hospital due to their birth,

Chart 1 - Codes of the 10th Revision of the International Statistical Classification of Diseases and Health-related Problems (ICD-10), regarding Intoxication by Medications and Adverse Effects of Medications

Chapter 5: Mental and behavioural disorders	
F10-F19	**Mental and behavioural disorders due to psychoactive substance use**
F11.0	Use of opioids. Acute intoxication
F13.0	Use of sedatives or hypnotics. Acute intoxication
F15.0	Use of other stimulants, including caffeine. Acute intoxication
F19.0	Use of multiple drugs and due to the use of psychoactive substances. Acute intoxication
F50-F59	**Behavioral Syndromes Associated to Physiological Dysfunctions and Physical Factors**
F55	Abuse of substances that do not produce dependence. Acute intoxication
Chapter 19: Injury, poisoning and certain other consequences of external causes	
T36-T50	**Poisoning by drugs, medicaments and biological substances**
T36	Poisoning by systemic antibiotics
T37	Poisoning by other systemic anti-infectives and antiparasitics
T38	Poisoning by hormones and their synthetic substitutes and antagonists, not elsewhere classified
T39	Poisoning by nonopioid analgesics, antipyretics and antirheumatics
T40.2	Poisoning by other opioids (Codeine, Morphine)
T40.3	Poisoning by methadone
T40.4	Poisoning by other synthetic narcotics (Pethidine (meperidine))
T41	Poisoning by anaesthetics and therapeutic gases
T42	Poisoning by antiepileptic, sedative-hypnotic and antiparkinsonism drugs
T43	Poisoning by psychotropic drugs, not elsewhere classified
T44	Poisoning by drugs primarily affecting the autonomic nervous system
T45	Poisoning by primarily systemic and haematological agents, not elsewhere classified
T46	Poisoning by agents primarily affecting the cardiovascular system
T47	Poisoning by agents primarily affecting the gastrointestinal system
T48	Poisoning by agents primarily acting on smooth and skeletal muscles and the respiratory system
T49	Poisoning by topical agents primarily affecting skin and mucous membrane and by ophthalmological, otorhinolaryngological and dental drugs
T50	Poisoning by diuretics and other and unspecified drugs, medicaments and biological substances
T80-T88	**Complications of surgical and medical care, not elsewhere classified**
T80.5	Anaphylactic shock due to serum
T80.6	Other serum reactions
T88.6	Anaphylactic shock due to adverse effect of correct drug or medicament properly administered
T88.7	Unspecified adverse effect of drug or medicament
Chapter 20: External causes of morbidity and mortality	
X40-X44	**Accidental poisoning by and exposure to**
X40	Nonopioid analgesics, antipyretics and antirheumatics
X41	Antiepileptic, sedative-hypnotic, antiparkinsonism and psychotropic drugs, not elsewhere classified
X43	Other drugs acting on the autonomic nervous system
X44	Other and unspecified drugs, medicaments and biological substances

***Chart** 1 – Continuation*

Chapter 20: External causes of morbidity and mortality	
X60-X64	**Intentional self-poisoning by and exposure to**
X60	Nonopioid analgesics, antipyretics and antirheumatics
X61	Antiepileptic, sedative-hypnotic, antiparkinsonism and psychotropic drugs, not elsewhere classified
X63	Other drugs acting on the autonomic nervous system
X64	Other and unspecified drugs, medicaments and biological substances
X85	**Assault by drugs, medicaments and biological substances**
Y10-Y14	**Poisoning by and exposure, undetermined intent, to**
Y10	Nonopioid analgesics, antipyretics and antirheumatics
Y11	Antiepileptic, sedative-hypnotic, antiparkinsonism and psychotropic drugs, not elsewhere classified
Y13	Other drugs acting on the autonomic nervous system
Y14	Other and unspecified drugs, medicaments and biological substances
Y40-Y59	**Drugs, medicaments and biological substances causing adverse effects in therapeutic use**
Y40	Systemic antibiotics
Y41	Other systemic anti-infectives and antiparasitics
Y42	Hormones and their synthetic substitutes and antagonists, not elsewhere classified
Y43	Primarily systemic agents
Y44	Agents primarily affecting blood constituents
Y45	Analgesics, antipyretics and anti-inflammatory drugs
Y46	Antiepileptics and antiparkinsonism drugs
Y47	Sedatives, hypnotics and antianxiety drugs
Y48	Anaesthetics and therapeutic gases
Y49	Psychotropic drugs, not elsewhere classified
Y50	Central nervous system stimulants, not elsewhere classified
Y51	Drugs primarily affecting the autonomic nervous system
Y52	Agents primarily affecting the cardiovascular system
Y53	Agents primarily affecting the gastrointestinal system
Y54	Agents primarily affecting water-balance and mineral and uric acid metabolism
Y55	Agents primarily acting on smooth and skeletal muscles and the respiratory system
Y56	Topical agents primarily affecting skin and mucous membrane and ophthalmological, otorhinolaryngological and dental drugs
Y57	Other and unspecified drugs and medicaments

when the medication-related intoxication or adverse effect occurred.

The event's circumstance is considered in two ICD-10 chapter 19 codes regarding adverse effects (T88.6 and T88.7) and in ICD-20 chapter 20 codes regarding the other circumstances, as well as adverse effects (X40-X44, X60-X64, X85, Y10-Y14, and Y40-Y57), as defined in Chart 1. So, only the hospitalizations that used these codes to define the main or secondary diagnosis could have their circumstance described by one of the following categories: accidental, aggression, self-intoxication, adverse effect, and undetermined. The "ignored" category was selected for the others.

According to the specified circumstance or based on a few codes presented for the main and/or secondary diagnosis, when the circumstance is ignored, the cases were classified as intoxications or adverse effects, as described in Chart 3.

Chart 2 - Combinations of main and secondary diagnoses presented by the cases

Situation	Main Diagnosis	Secondary Diagnosis
1	Not related to the Event of Interest	Related to the Event of Interest
2	Related to the Event of Interest	Not Related to the Event of Interest
3	Related to the Event of Interest	Related to the Event of Interest
4	Related to the Event of Interest	Blank

Event of Interest = Intoxication or Adverse Effect to Medications

Chart 3 – *Classification of cases*

Classification	Circumstance	Main and/or Secondary Diagnostic Code
Intoxication	Accidental	-
	Aggression	-
	Self-Intoxication	-
	Undetermined	-
	Ignored	F13.0, F11.0, F13.0, F15.0, F19.0, F55, T36 a T50, T80.6
Adverse Effect	Adverse Effect	-
	Ignored	T80.5

The procedures that were performed were classified in two groups. The first one regarded specifically intoxication by medications, while the second one regarded the other procedures adopted to treat the cases. The relationship between these two groups of procedures and the four above-mentioned situations was also taken into account during data analysis.

The therapeutic classes can be better detailed for hospitalizations in which the main or secondary diagnosis has been filled-in with the four digits foreseen by chapter 19 codes and for the Y40 to Y57 groupings of chapter 20 of the ICD-10, as described in Chart 1. However, due to the wide-spread use of digits 8 and 9, related to the "other" and "non-specified" categories, the results found for certain substances cannot be representative and, thus, will not be explored.

A table (Tables 1 & 2) was prepared for each of the age groups relating the 4 situations described above to the age, gender, circumstance, case classification, procedure carried out, and therapeutic class variables. Lethality was calculated for each variable category, in addition to the 4 situations. Ages were grouped as follows: 0 day, 1 to 7 days, 8 to 14 days, 15 to 21 days, and 22 to 29 days for the group of children aged less than 1 month, and 1 month, 2 to 3 months, 4 to 5 months, 6 to 7 months, 8 to 9 months, and 10 to 11 months, for the group of children aged 1 to 11 months.

To analyze the main therapeutic classes involved in the cases classified as intoxication or adverse effect, a table (Table 3) was prepared to show the number of cases and the therapeutic class percentages for each of the case classifications, considering the group of children aged less than 1 month and the group of those aged 1 to 11 months separately.

To test the independence between the different age groups considered in the study and the situation variables, the case's circumstance and classification, a chi-square test was applied with a level of significance of 5%[14].

To test if there is any difference among the situations based on ages and on the time the patient remained hospitalized, the Kruskal-Wallis non-parametric test was applied, since the suppositions of variance normalcy and homogeneity were

Table 1 - Cases and deaths of hospitalization related to drug intoxication and adverse effects in children less than one month old distributed by age, gender, procedure, cause, classification and therapeutic classes. Brazil, 2003 to 2005.

Variable	Situation*				Total	Lethality (%)
	1	2	3	4		
Age (days)						
0	12	18	14	4	48	-
1 to 7	36	5	6	1	48	-
8 to 14	14 (1 death)	1	4	5	24 (1 death)	4.17
15 to 21	3	5	6	3	17	-
22 to 29	3 (1 death)	3	6	2	14 (1 death)	7.14
Gender						
Masculin	38 (2 deaths)	10	12	7	67 (2 deaths)	2.99
Feminin	30	22	24	8	84	-
Procedure						
Intoxication by Medications	1	29	31	15	76	-
Other	67 (2 deaths)	3	5	-	75 (2 deaths)	2.67
Circumstance						
Accidental	8 (1 deaths)	-	21	-	29 (1 death)	3.45
Aggression	1 (1 death)	-	-	-	1 (1 death)	100.00
Self-Intoxication	3	-	3	-	6	-
Adverse Effect	51	-	5	-	56	-
Undetermined	4	-	7	-	11	-
Ignored	1	32	-	15	48	-
Classification						
Intoxication	17 (2 deaths)	32	31	15	95 (2 deaths)	2.11
Adverse Effect	51	-	5	-	56	-
Therapeutic Classes						
Enzymes, not elsewhere classified (Y43.6)	44	-	-	-	44	-
Other drugs and non-specified substances (T50.9, T88.7, X44, X64, Y14, Y57.8, Y57.9)	11 (1 death)	8	14	-	33 (1 death)	3.03
Antiepileptic, sedative-hypnotic and antiparkinsonism drugs (F13.0, T42, X41, Y11,Y46, Y47)	1	2	5	15	23	-
Systemic antibiotics (T36, Y40)	-	11	8	-	19	-
Nonopioid analgesics, antipyretics and antirheumatics (T39, X40, X60, Y10, Y45)	4	3	4	-	11	-
Topical agents (T49, Y56)	1	3	-	-	4	-
Psychotropic drugs (T43, Y49)	2	1	-	-	3	-
Other systemic anti-infectives and antiparasitics (T37, Y41)	1	1	-	-	2	-
Agents primarily acting on the respiratory system (T48.3 a T48.7, Y55.3 a Y55.9)	1	-	1	-	2	-
Drugs primarily affecting the autonomic nervous system (T44, X43, Y51)	-	-	2	-	2	-
Anaesthetics and therapeutic gases (T41, Y48)	-	1	1	-	2	-
Agents primarily affecting the gastrointestinal system (T47, Y53)	-	1	-	-	1	-
Hormones and their synthetic substitutes and antagonists (T38, Y42)	-	-	1	-	1	-
Others	3 (1 death)	1	-	-	4 (1 death)	25.00
Total	68 (2 deaths)	32	36	15	151 (2 deaths)	1.32
Lethality (%)	2.94	-	-	-	1.32	

Source: SIH-SUS

*Classification of Situation selon Chart 2

Table 2 - Cases and deaths of hospitalization related to drug intoxication and adverse effects in children from one to eleven months old distributed by age, gender, procedure, cause, case classification and therapeutic classes Brazil, 2003 to 2005.

Variable	Situation*				Total	Lethality (%)
	1	2	3	4		
Age (months)						
1	15	28 (1 death)	26	13 (1 death)	82 (2 deaths)	2.44
2 to 3	30	52	69	30	181	-
4 to 5	36 (2 death)	56	48	36 (1 death)	176 (3 deaths)	1.70
6 to 7	34 (2 deaths)	51	51	30	166 (2 deaths)	1.20
8 to 9	22 (1 death)	47	34	31	134 (1 death)	0.75
10 to 11	50 (1 death)	52 (1 death)	45	26	173 (2 deaths)	1.16
Gender						
Masculin	97 (4 deaths)	148 (1 death)	138	82 (2 deaths)	465 (7 deaths)	1.51
Feminin	90 (2 deaths)	138 (1 death)	135	84	447 (3 deaths)	0.67
Procedure						
Intoxication by Medication	19	263 (2 deaths)	253	159 (2 deaths)	694 (4 deaths)	0.58
Other	168 (6 deaths)	23	20	7	218 (6 deaths)	2.75
Circumstance						
Accidental	72 (3 deaths)	1	135	-	208 (3 deaths)	1.44
Aggression	2	-	2	-	4	-
Self-Intoxication	15	-	21	-	36	-
Adverse Effect	53 (3 deaths)	10	60	1	124 (3 deaths)	2.42
Undetermined	39	-	52	1	92	-
Ignored	6	275 (2 deaths)	3	164 (2 deaths)	448 (4 deaths)	0.89
Case Classification						
Intoxication	134 (3 deaths)	274 (2 deaths)	213	165 (2 deaths)	786 (7 deaths)	0.89
Adverse Effect	53 (3 deaths)	12	60	1	126 (3 deaths)	2.38
Therapeutical classes						
Other drugs and non-specified substances (T50.9, T88.7, X44, X64, Y14, Y57.8, Y57.9)	101 (4 deaths)	90	103	-	294 (4 deaths)	1.36
Antiepileptic, sedative-hypnotic and antiparkinsonian drugs (F13.0, T42, X41, Y11,Y46, Y47)	7	8	15	161 (2 deaths)	191 (2 deaths)	1.05
Systemic antibiotics (T36, Y40)	-	121 (1 death)	48	-	169 (1 death)	0.59
Nonopioid analgesics, antipyretics and antirheumatics (T39, X40, X60, Y10, Y45)	38	9	11	2	60	-
Other systemic anti-infectives and antiparasitics (T37, Y41)	1	17	8	-	26	-
Agents primarily acting on the respiratory system (T48.3 a T48.7, Y55.3 a Y55.9)	-	2	18	-	20	-
Agents primarily affecting the gastrointestinal system (T47, Y53)	1	7	11	-	19	-
Topical agents (T49, Y56)	4	7	7	-	18	-
Agents primarily affecting the cardiovascular system (T46, Y52)	-	3	10	-	13	-
Psychotropic drugs (T43, Y49)	2 (1 death)	2	8	-	12 (1 death)	8.33
Hormones and their synthetic substitutes and antagonists (T38, Y42)	8	1	3	-	12	-
Drugs that affect, mainly, the autonomic nervous system (T44, X43, Y51)	-	2	10	-	12	-
Antiallergic and antiemetic drugs (T45.0, Y43.0)	2	1	8	-	11	-
Substances primarily systemic (Y43.1 a Y43.9)	7	-	-	-	7	-
Anesthetics and therapeutic gases (T41, Y48)	4 (1 death)	1	2	-	7 (1 death)	14.29
Narcotics (T40.2, T40.4, X42)	-	4	1	-	5	-
Others	12	11 (1 death)	10	3	36 (1 death)	2.78
Total	187 (6 deaths)	286 (2 deaths)	273	166 (2 deaths)	912 (10 deaths)	1.10
Lethality (%)	3.21	0.70	-	1.20	1.10	

Source: SIH-SUS

*Classification of Situation selon Chart 2

Table 3 - Cases and percentages of hospitalization distributed by therapeutic classes, classification and age group. Brazil, 2003 to 2005.

Therapeutic classes	< 1month				1 to 11 months			
	Intoxication		Adverse Effect		Intoxication		Adverse Effect	
	Nº	%	Nº	%	Nº	%	Nº	%
Enzymes, not elsewhere classified (Y43.6)	-	-	44	78.6	-	-	-	-
Other drugs and non-specified substances (T50.9, T88.7, X44, X64, Y14, Y57.8, Y57.9)	32	33.7	1	1.8	241	30.7	53	42.1
Antiepileptic, sedative-hypnotic and antiparkinsonism drugs (F13.0, T42, X41, Y11,Y46, Y47)	21	22.1	2	3.6	189	24.0	3	2.4
Systemic antibiotics (T36, Y40)	17	17.9	2	3.6	162	20.6	7	5.6
Nonopioid analgesics, antipyretics and antirheumatics (T39, X40, X60, Y10, Y45)	10	10.5	1	1.8	53	6.7	7	5.6
Other systemic anti-infectives and antiparasitics (T37, Y41)	1	1.1	1	1.8	23	2.9	3	2.4
Agents primarily acting on the respiratory system (T48.3 a T48.7, Y55.3 a Y55.9)	1	1.1	1	1.8	14	1.8	6	4.8
Agents primarily affecting the gastrointestinal system (T47, Y53)	1	1.1	-	-	16	2.0	3	2.4
Topical agents (T49, Y56)	3	3.2	1	1.8	13	1.7	5	4.0
Agents primarily affecting the cardiovascular system (T46, Y52)	-	-	-	-	11	1.4	2	1.6
Psychotropic drugs (T43, Y49)	1	1.1	2	3.6	8	1.0	4	3.2
Hormones and their synthetic substitutes and antagonists (T38, Y42)	1	1.1	-	-	3	0.4	9	7.1
Drugs primarily affecting the autonomic nervous system (T44, X43, Y51)	2	2.1	-	-	11	1.4	1	0.8
Antiallergic and antiemetic drugs (T45.0, Y43.0)	-	-	-	-	6	0.8	5	4.0
Substances primarily systemic (Y43.1 a Y43.9)	-	-	-	-	-	-	7	5.6
Anaesthetics and therapeutic gases (T41, Y48)	2	2.1	-	-	3	0.4	4	3.2
Narcotics (T40.2, T40.4, X42)	-	-	-	-	4	0.5	1	0.8
Others	3	3.2	1	1.8	29	3.7	6	4.8
Total	95	100.0	56	100.0	786	100.0	126	100.0

Source: SIH-SUS

not complied with, and these are required in order to apply a more powerful, better known parametric test, the Variance Analysis (ANOVA)[14].

To test for differences between cases classified as "intoxication" or "adverse effect," based on the ages and on the amount of time the patient remained hospitalized, the Wilcoxon-Mann-Whitney non-parametric test was applied, since the suppositions of normalcy and homogeneity were not complied with, as required to apply the t parametric test[14].

The project was approved by the Committee for Ethics in Research on Human Beings of the Fundação Oswaldo Cruz's (Fiocruz) Evandro Chagas Clinical Research Institute (IPEC), under opinion No. 028/2008.

Results

In total, 1,063 hospitalizations of children aged less than a year related to intoxications and adverse effects of medications, occurring between 2003 and 2005, were analyzed.

Table 1 shows the distributions of age, in days, gender, the procedure carried out, the circumstance, case classification, and

therapeutic class according to the situation of the 151 cases and 2 deaths during the hospitalizations of children aged less than a month related to intoxications and adverse effects of medications, as well as the lethality for all of the categories of these variables. The major concentration of these cases among children of zero day (31.8%), as well as in situation 1 (45.0%) is remarkable. However, it is noteworthy that in this situation, 64.7% of the cases involve a single therapeutic class, enzymes (Y43.6). In the analysis of the procedure that was carried out, it can be noticed that situation 1 differs from the other ones, as it concentrates its data per medication. Among the 103 cases with non-ignored circumstances, adverse effects accounted for most cases (56 – 54.4%), followed by the accidental ones (29 – 28.2%). However, the circumstance of the event could only be analyzed for situations 1 and 3. In 31.8% of the hospitalizations, the circumstance is ignored. Adverse effects accounted for most (51 – 76.1%) of the 67 cases of situation 1 with non-ignored circumstances, while for the 36 cases of situation 3 with non-ignored circumstances the accidental category appeared in more than half of the cases (21 – 58.3%). Concerning the 151 hospitalizations of children aged less than 1 month, 95 were classified as cases of intoxication (62.9%) and 56 as adverse effects (37.1%). The two deaths that were registered occurred in situation 1, involving boys aged eight and 27 days. The lethality observed by the study for this age group was 1.32%. However, lethality for situation 1 is higher, 2.94%, a fact that can be an indicator of case severity, something that may be relative on account of the small number of deaths registered. Although enzymes are present in a larger number of cases (44 – 29.1%), their participation is not limited to situation 1 and to the cases classified as adverse effects. The therapeutic class represented by other drugs, medications and biological substances and non-specified factors is listed in 33 cases (21.9%), appearing in situations 1, 2, and 3 with participations of 16.2%, 25.0% and 38.9%, respectively. The anti-epileptic, sedative-hypnotic and antiparkinsonian drugs were present in 23 cases (15.2%), and although appearing in all situations, they concentrate in situation 4 (15 cases – 65.2%). The antibiotics listed in 19 cases (12.6%) were only registered for situations 2 and 3. Analgesics, antipyretics and non-opiate anti-rheumatics, listed in 11 cases (7.3%), are present in situations 1, 2, and 3.

Table 2 shows the distributions of age, in months, gender, procedure performed, circumstance, case classification, and therapeutic class per situation in the 912 cases and 10 deaths during hospitalization of children aged one to 11 months, as related to intoxications and adverse effects of medications. It is noteworthy that beginning with the 2 to 3 month age group, the number of cases decreases, until reaching the 10 to 11 month age group, when it goes up. Situations 2 and 3 stand out, adding up to 559 cases (61.3%), but with a lethality of only 0.36%. Of the 10 deaths, six occur in situation 1, two in situation 2 and two in situation 4, 7 of which of males and 3 females. The lethality observed for this age group was 1.10%, below that of the group of children aged less than 1 month (1.32%). However, lethality for this group with regard to situation 1 is above that observed for the group of children aged less than 1 month, 3.21% compared to 2.94%. The difference between the lethality per gender and per case classification, in which the male and adverse effect ones are twice as frequent as the female and intoxication ones, respectively, is noteworthy. In 49.1% of the hospitalizations, circumstances are ignored, a figure that is higher than that seen for children aged less than 1 month (31.8%). Of the 464 cases of non-ignored circumstances, most were accidental events (44.8%), followed by adverse effects (24.4%). The accidental circumstance is more present in situation 3, in which of 270 cases with non-ignored circumstances, 135 were accidental (50.0%). For situation 1, the percentage of accidental and adverse effect circumstances were closer, 39.8% and 29.3%, respectively. Of the 912 hospitalizations of children aged 1 to 11 months,

786 were classified as cases of intoxication (86.2%), while 126 as adverse effects (13.8%). The therapeutic class represented by other drugs, medications, and biological substances, in addition to the non-specified ones, is listed in 294 cases (32.2%), appearing in situations 1, 2 and 3, with participations of 54.0%, 31.5% and 37.7%, respectively. The anti-epileptic, sedative-hypnotic and antiparkinsonian class was present in 191 cases (21.1%), systemic antibiotics in 169 hospitalizations (18.5%), and analgesics, antipyretics and non-opiate anti-rheumatic, with a smaller participation, appear in 60 cases (6.6%).

Table 3 shows the distribution of the cases and the percentages of the main therapeutic classes for the cases classified as intoxication and as adverse effects, for the two groups of children, aged less than 1 month, and from 1 to 11 months. It can be seen that cases classified as adverse effects do not have the same distribution for the therapeutic classes as those listed as intoxication. For the group of children aged 1 to 11 months, the low participation of anti-epileptic, sedative-hypnotic and antiparkinsonian substances observed for adverse effect cases stands out, 2.4%, as does the small participation of the systemic antibiotics, 5.6%, compared to the involvement of the same therapeutic classes for cases of intoxication, 24.0% and 20.6%, respectively. Also based on this group of children and on the cases classified as adverse effects, it can be seen that the class of hormones, their synthetic substitutes and their antagonists was the one that had the second biggest percentage participation (7.1%), only lagging behind other and non-specified drugs (42.1%).

Considering the group of children aged less than 1 month, no significant differences were seen between the ages and the time the patient remained hospitalized while comparing the situations, circumstances and case classifications.

Regarding the group of children aged 1 to 11 months, when applying the Kruskal-Wallis test, significant differences were seen in the time the patient remained hospitalized when comparing the four situations (p-valor = 0.0038), and it was situation 1 that had the biggest average (4.4 days). So far as case classification is concerned, the average time the patient remained hospitalized for those classified as adverse effects was 3.6 days, while 2.9 days for those rated as intoxication. However, the Wilcoxon-Mann-Whitney test concluded this time is not any longer than that involved in the cases classified as adverse effects (p-valor = 0.0761).

During the analysis of children aged less than a month, it was noticed that all 44 hospitalizations related to code "Y43.6 – Adverse effect of enzymes, not classified elsewhere" (29.1%) occurred in the State of São Paulo, at a same hospital, identified by the CGC, information contained in SUS' Hospital Information System database (SIH-SUS). These cases were seen in all of the years of the study, in an increasing trend: six cases in 2003, 13 in 2004 and 25 in 2005. Code Y43.6 appeared as a secondary diagnosis, while the primary diagnosis for 86.4% of the cases involved codes "P58 – Neonatal jaundice due to excessive haemolyses" and "P59 – Neonatal jaundice due to other causes and non-specified causes." In the analysis of the procedures carried out during these 44 hospitalizations, neonatal jaundice appears again, in 77.3% of the cases. The age group varied from 2 to 23 days, 43 of whom aged 2 to 13 days. The gender distribution was 25 boys and 19 girls. The time the patient remained hospitalized ranged from 1 to 24 days, with 95.4% of the cases lasting less than seven days. No death was registered in this case.

Another piece of information the study identified was the correlation between intoxication caused by medications and falls. In total, 101 cases were identified involving this association, 12 among children aged less than a month, and 89 among those aged one to 11 months. It is important to emphasize that in these cases, the fall was associated to the secondary diagnosis, while the intoxication or the adverse effect to the

primary one (situation 2), leading to the hypothesis that the first event was the fall, which, when treated, ended up intoxicating the child and caused the need for hospitalization. The use of systemic antibiotics, including the non-specified, macrolides, penicillin, antifungal antibiotics, among others, was associated to 42.6% of these 101 cases. For the group of children aged less than a month, this percentage is 33.3%, while for those aged 11 months it is 43.8%. The age group affected most by this type of relation was that of children aged zero day, representing 50% of the 12 hospitalizations registered for the group of children aged less than 1 month and those aged 10 to 11 months, who represented 40.4% of the 89 hospitalizations in the group aged 1 to 11 months. Gender distribution was 3 boys and 9 girls aged less than 1 month, and 47 boys and 42 girls aged 1 to 11 months. No death was registered here either.

Discussion

It must be emphasized that the cases of intoxication and adverse effects of medications covered in this study derive from hospitalizations and, thus, are presumably more severe. As such, comparisons to data derived from other sources must be made with great care.

The 48 hospitalizations registered of children aged zero day bring up questions ranging from the quality of the record made at such an age to the causes of an intoxication or adverse effect of medication at such a tender age. A few medications can reach the fetus through the placenta, or the newborn through breastfeeding. In this context, it is important to value the quality of the prenatal exam which is offered in the country, warning the pregnant women of the importance of not using any unprescribed medication, as this can put their fetuses at risk. This warning must also be made during the breastfeeding period. Regarding data quality, there is a significant loss of information when registering the age of children aged less than 1 day as zero day, instead of specifying the number of hours, as the system calls for. Such information would be very useful to explain the cause of the intoxication. With regard to the causes, vertical intoxication could explain the appearance of a few therapeutic classes such as anti-epileptic, sedative-hypnotic and antiparkinsonian drugs (9 cases – 18.8%) and psychotropics (2 cases – 4.2%) in this age group.

The fact that all 44 enzyme-related hospitalizations occurred at a same hospital in São Paulo was notified to the state's health surveillance. It is necessary to investigate if there were problems related to the application or even to the lot of enzymes. Errors made while filling-in the Hospitalization Authorization (HA) cannot be discarded and also demand investigation. Additionally, this finding causes these events to be considered "atypical" compared to the national context, and can generate biases in the analyses. An example of this can be noticed in the fact that the lethality of situation 1 obtained for the group of children aged less than 1 month (2.94%) was lower than lethality observed for the group of children aged 1 to 11 months (3.21%). However, if we do not consider the 44 enzyme-related cases, the lethality for the group of children aged less than 1 month goes up to 8.33%. Additionally, the chi-square test was not used to determine the independence between the age and situation, circumstance and case classification variables, since it showed distinct results when these 44 hospitalizations were or were not considered.

Of the 10 deaths registered among children aged 1 to 11 months, 3 occurred at a same hospital in the state of São Paulo, two in situation 1 and one in situation 2. This result also merits investigation by the state's health surveillance.

For the group of children aged less than 1 month, the therapeutic class represented by other drugs, medications, and biological substances, in addition to the non-specified ones added up to 21.9% of the cases. Meanwhile, for the group of children aged 1 to 11 months, this class accounted for 32.2%, a

percentage that would be even bigger if we only considered the cases rated as adverse effects, 42.1%. Since this therapeutic class represents the fact that the medication involved in the case is unknown, it can be inferred that the bigger its participation, the worse the quality of the information. In this way, while on one hand it is not hard to admit, as the data suggest, that with the increase in the age the participation of this therapeutic class goes up, on the other hand it is more intuitive to believe that a case rated as an adverse reaction would, theoretically, bring more information about the medication than one involving intoxication. However, the data show exactly the opposite, a fact that requires more investigation.

Considering the group of children aged 1 to 11 months, the chi-square test indicated the non-independence between the 1 to 9 month and the 10 to 11 month age groups with regard to the 4 situations pointed to previously (p-valor = 0.0209). For children aged 10 to 11 months, the frequency observed for situation 1 is above expected, while the opposite occurs for situation 3. This behavior disagrees with the hypothesis that the 10 to 11 month range accidental intoxication cases go up, since this is when the child gains mobility and is capable of crawling (Behrman et al.[15]) and, as such, could reach poorly stored medications. These incidents would be connected to situations 3 and 4 and not situation 1. Also going against this hypothesis, no relationship was seen between the 1 to 9 month and the 10 to 11 month age groups and the classification of the case as intoxication or adverse effect (p-value = 0.6075). However, this behavior can be justified by the limited movement of these children, who cannot reach the medications yet or, even if they do reach them, the intoxications can result in less severe cases that do not require hospitalization. Another issue to be discussed is that the accidental circumstance, according to the ICD-10, considers, in addition to the accidents, other non-intentional causes such as errors of administration, inappropriate medical prescriptions, undue use and abstinence, rendering it difficult to analyze the impact of the 10- to 11-month age group.

Self-medication, as layman medication administered by parents without medical guidance, is an intentional circumstance and should not be considered accidental. For this reason, it is believed that the self-intoxication circumstance presented by ICD-10 should include intentional circumstances such as abuse, attempted suicide, attempted abortion, and self-medication and layman medication. This fact would explain the 24 cases of self-intoxication that occurred in situation 3, outside of the hospital environment. The 18 cases of self-intoxication registered in situation 1 imply reflections on the inference previously drawn from the fact that was made previously regarding the fact that all cases rated in situation 1 occurred in the hospital, and on a careful analysis of the quality of the registration of these 18 cases.

The care taken with the filling-in of the secondary diagnosis for situations 1, 3 and 4, measured by the number of non-ignored circumstances, revealed to be bigger for the group of children aged less than 1 month. A hypothesis yet to be tested with new studies is the loss of the quality of this information the older the child is.

It is important for all medications used for the pediatric age group to have their doses calculated properly based on the child's weight. According to Kaushal et al.[16], the classes of medications that are often associated to dosage or even administration errors are anti-infectious, painkillers and sedatives. Pediatric patients are the ones who suffer the most with these errors.

There are ethical standards that prevent research using human subjects, particularly children. According to Meiners et al.[17], many medications available in the market are used in an empirical, often questionable manner due to the lack of full research appropriate for pediatric patients. The proper dosages, the harmful medicamentous interactions, and the side-effects are unknown. Practice will provide these answers, but intoxications may occur in this search.

In an assessment of the prescriptions given to 51 children aged one month to 13 years, ICU patients at the Porto Alegre General Hospital, carried out between July and August 2002, it was noticed that 10.5% of the medications that were used were non-approved, while 49.5% of them non-standardized. All patients considered in this study had at least one non-standardized medication prescribed to them[18].

About 80% of the medications prescribed for children in the United States are not approved by the FDA (Food and Drug Administration) for use in this age group[19].

A study carried out in a hospital for children in the Netherlands also showed countless non-licensed medications being prescribed to treat this age group, and many licensed medications are used in a way other than that they were regulated for use for[20].

According to Pizzol et al.[21], in Brazil it is easy to have access to medications, both due to the large number of pharmacies and drugstores available, and because of the ethically and legally questionable commercial practices carried out by several establishments. The population must be warned about the harm caused by uncontrolled medication consumption.

Conclusion

In the period between 2003 and 2005, 1,063 children aged more than a year were hospitalized in public or private hospitals holding agreements with the public system in the country as a direct or indirect consequence of intoxication or adverse effects of medications.

There were more cases of intoxication than adverse medication effects, both for the group of children aged less than a month and for that of children aged 1 to 11 months.

When working with children aged less than 1 year, accidental intoxications caused by the children themselves, so common in the 1- to 4-year age group, practically do not appear in this study.

The main causes that justified hospitalizations of children aged less than 1 year, related to intoxication by medications, were: administration errors, inappropriate medical prescriptions, medication administration made by those responsible for the child and without medical guidance, abstinence, and, above all, the maternal use of medications, with or without medical guidance, which ends up intoxicating the child, whether through the placenta or via breastfeeding.

Consequently, the study imposes differentiated strategies to face these incidents, including reflections on the rational use of medications among children aged less than 1 year, generating guidance for parents and health professionals, more prenatal attention and more attention in the first months of the child's life with regard to medications dispensed to the mother and to her child.

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