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ORIGINAL ARTICLE

Adverse Drug Reactions and quality deviations monitored by spontaneous reports

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KEYWORDS

Pharmacovigilance;
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Abstract *Objectives:* The aim of this study was to determine the frequency and profile of spontaneous reports of Adverse Drug Reactions (ADRs) and quality deviations in a Brazilian teaching hospital and propose a consistent classification to study quality deviations.

Methods: This is a descriptive and retrospective study involving the analysis of spontaneous reports of ADRs and quality deviations in 2010. ADRs were classified according to the reaction mechanism, severity, and causality. The drugs were classified according to their therapeutic classes and symptoms according to the affected organ. The quality deviations were classified according to the type of deviation and type of medicine available in the Brazilian market.

Results: A total of 68 forms were examined; ADRs accounted for 39.7% of the notifications, while quality deviations accounted for 60.3%. ADRs occurred more frequently in men (51.9%) and adults (63.0%). The skin (28.0%) was the most affected organ, while anti-infectives (40.7%)

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were the therapeutic class that caused the most ADRs. The most common ADRs were type B (74.0%), moderates (37.0%), and probables (55.6%). In relation to quality deviations, the most frequent notifications were breaks, splits and leaks (20.9%) and related to generic drugs (43.9%).

Conclusion: The classification system to study quality deviations was clear and consistent. This study demonstrated that practices and public policies related to more effective pharmacovigilance need to be implemented so that the number of spontaneous reports increases.

1. Introduction

Pharmacovigilance is defined as the science and activities related to detection, evaluation, understanding and prevention of adverse effects or any other drug related problem (WHO, 2002). Postmarketing surveillance on the effects of drugs in clinical practice is essential and spontaneous reporting of Adverse Drug Reactions (ADRs) is important because it increases drug safety knowledge (Wyswski and Swartz, 2005). The World Health Organization (WHO) defines ADR as any response to medication that is harmful and unintended that occurs at doses normally used in humans for prophylactic, diagnostic or therapeutic purposes (WHO, 2002). Therapeutic failures such as drug abuse, accidental or intentional poisoning and adverse events that occur as a result of non-adherence to pharmacotherapy or medication errors are not considered an ADR (Lazarou et al., 1998).

The detection and evaluation of ADRs in hospitals are required because of the possibility of identification of severe reactions, reactions of new drugs, increased frequency of known reactions, unknown effects, identification of the risk factors and possible dissemination of information among clinicians and health professionals (Cereza et al., 2010). Many studies have been conducted to characterize the ADR profile found in hospitals, evaluating medicaments, therapeutic classes and demographic data of affected patients, medications concomitantly used for a certain person, type of ADR, affected organs, severity and causality relation (Jose and Rao, 2006; Sriram et al., 2011; Lobo et al., 2013).

In several countries, pharmacovigilance is based on the spontaneous reporting aimed at ADR detection after commercialization (Cereza et al., 2010). However, a major limitation of this model is that only a small part of all ADRs are reported (Hazell and Shakir, 2006). A previous reports showed that several factors were associated with under-reporting such as ignorance (only severe ADRs need to be reported), diffidence (fear of appearing ridiculous for reporting merely a suspected ADR), lethargy (e.g., lack of interest or time), indifference (one case from an individual practitioner does not contribute to medical knowledge), insecurity (causality between a drug and an adverse event is hard to determine) and complacency (only safe drugs are allowed on the market) (Lopez-Gonzalez et al., 2009).

Another issue of pharmacovigilance is quality deviation. This notification occurs when the required quality parameters are not followed for commercialization or the registration process of a pharmaceutical product and can result in health problems. Quality deviations are simple to evaluate, because as the absence of a label, the presence of foreign bodies or color changes of a drug are issues that are obvious to observe (Capucho, 2008). Few studies have reported on quality deviations and strict classifications for quality deviations do not exist; however, monitoring the quality of products used in patient care is extremely important because it may pose a risk to patient safety. This study is the first to propose a consistent quality deviation classification.

The aim of this study was to determine the frequency and profile of spontaneous reports for ADRs and quality deviations, report the types of drugs involved and characterize the most common clinical manifestations associated with ADRs and its severity in a Brazilian teaching hospital so as to alert health professionals, regulatory authorities and patients who use medicaments on the importance of reporting ADRs and quality deviations.

2. Methods

This was a descriptive and retrospective study which was conducted in a teaching hospital (403 beds) in São Paulo, Brazil. The study occurred from January 2010 to December 2010 and it involved the analysis of ADRs and quality deviations of spontaneous reports. This study was evaluated and approved by the Ethics Committee of the Institution.

Health professionals from different specialties could report alleged ADRs and quality deviations with an application form which was sent to the pharmacovigilance section of the hospital. The pharmacist analyzed the ADR and quality deviation notifications to supplement the data. In the case of an ADR, the notification was reviewed, interviews with the professionals involved in the case were made and the patients were observed, to obtain more details and update monitoring, until the case was resolved or the patient was discharged.

2.1. Adverse Drug Reactions (ADRs)

Each application form for the patients (in- and outpatients) was analyzed, such that ADRs that occurred during hospitalization and ADRs that led to hospitalization were examined. Patients of both genders and all ages were included in this study while excluded notifications that involved patients that were accidentally or intentionally poisoned, had ADRs that were associated with blood products from transfusions, drug overdose and intoxication.

The notifications included in this study were analyzed according to the patient's gender, age, comorbidities, possible risk factors, allergies, ADR description and start date as well as the involved and suspected medicaments (generic name, administration, dose and posology). Ages were separated into three groups: pediatric (0–18 years old), adults (19–59 years

old), as well as geriatric populations (over 60 years old) (Lobo et al., 2013).

The Anatomical Therapeutic Chemical Classification (ATC) (WHO, 2013b) was used to classify medicaments in therapeutic classes while the World Health Organization-Adverse Reaction Terminology (WHO-ART) (WHO, 1997) was used to classify the organs affected by the ADR. Each reaction was characterized according to the reaction mechanism, which used the type A and type B classification system proposed by Rawling and Thompson, 1998; causality, which used the doubtful, possible, probable, and definite classification system according to Naranjo Algorithm (Naranjo et al., 1981); and severity, which used mild, moderate, severe, and lethal classifications according to Coêlho et al. (1999). The management strategies for the ADRs were categorized as drug withdrawal, dose reduction, additional treatment or a stable regimen without additional treatment (Lobo et al., 2013).

2.2. Quality Deviations

Since the International Nonproprietary Names (INN) (WHO, 2013a) aid in identifying the active pharmaceutical ingredients, the notifications of the quality deviations were examined by collecting the medicament's trade name that was causing the deviations, its dosage forms, the supplier's name, the notifying unit and the description of complaints. This information was classified according to the types of medicaments available in the Brazilian market and the type of deviation (Table 1).

The types of medicaments were classified as brand-name drugs, generic drugs, similar drugs and compounded drugs. A brand-name drug is a prescription medication that has been approved by the Food and Drug Administration (FDA) based on comprehensive toxicological data and human clinical trials that demonstrate that the drug is safe and effective and chemical evaluations prove that the product can be made consistently to a high quality standard (Gudeman et al., 2013). After the patent protection period of the brand-name drug expires, generic drugs may be approved by the FDA. Generic drugs have been tested and confirmed to be bioequivalent to the brand-name product (Gudeman et al., 2013); thus, generic drugs are copies of brand-name drugs and are the same as those brand-name drugs in dosage form, safety, strength, route of administration, quality, performance characteristics, and intended use (FDA, 2013). A similar drug is one that has the same active ingredients, concentration, dosage form, route of administration, dosage and therapeutic indication, which is equivalent to the drug registered in the federal agency responsible for monitoring health. It can differ in characteristics related to size and shape of the product, shelf life, packaging, and labeling, excipients and vehicle must always be identified

Table 1 Type of quality deviations.

Type of deviation	Description
Package anatomical problems	Deviations related to the shape of the product and package. Since it is an integral part of the product, it also includes the technical problems found during product handling, difficulty in opening (which may cause injury to the manipulator) and type of primary package incompatible with the characteristic of the medicament (as colorless glass ampoules for medicaments subject to photolysis)
Breaks/splits/leaks	Breaks, splits, holes and microholes in vials, ampoules, and sealed flask ampoules. It can cause leaks bringing on environmental and individual contamination with the substance
Lack of identification – information	Lack of identification, such as label and/or fundamental information that determine the best use of the product, such as concentration, dosage, name and administration of the medicine
Poor quality of information	Information presented on the package, labels and instructions that generate some kind of confusion or difficulty in reading. This includes package or commercial names similar to another product, difficulty in reading information due to poor print quality or small letters and the presence of more than one lot number and/or validity
Lack of the product – lower volume	Lack of the product in a sealed primary package and/or the absence of primary package in a sealed secondary package and/or volume below that declared in the label
Foreign body – dirtiness	The presence of a foreign body in the product (undissolved particulate material contaminants such as dust, fabric fibers, glass fragments, leachate material in covers/plastic and any other material that may pass into the product during manufacturing or develop during storage) and dirtiness in the primary package
Organoleptic changes	Color changes, odor, taste, limpidity (related to turbidity, and does not include particulate material), viscosity and original consistency of the product
Physicochemical changes of solids products	Quality deviations that compromise the physical and chemical characteristics such as hardness, friability, thickness and coating of tablets, capsules oscillation and fissures and difficulties in rebuilding powder into solution/injectable suspension
Physicochemical modifications of liquid and semisolid products	Crystallization, precipitation, incomplete redistribution of the dispersed phase in the dispersion environment (sedimentation, flocculation and aggregation of suspended particles) and emulsion coalescence

by its trade mark (ANVISA, 2013). A compounded drug is necessary when an FDA-approved drug is not available or appropriate for the patient, or must be altered in some manner, such as strength or route of delivery (Gudeman et al., 2013). It is produced by pharmacy compounding, defined by the FDA as the combining, mixing, or altering of the ingredients to create a customized medication for an individual patient in response to a licensed practitioner's prescription (Galson, 2003).

To evaluate the amount of quality deviations distributed according to the type of the medicament, an assessment was made to estimate the number of generic, similar, brand-name and compounded drugs purchased by the hospital. Since medicaments are purchased by price analysis, the suppliers and distributors may vary from one purchase to another; thus assessing the hospital's stockroom is only one way to evaluate the amount of quality deviations distributed according to the type of the medicament.

3. Results

The pharmacovigilance section of the hospital received 68 notifications in 2010, 27 were ADRs (39.7%) and 41 were quality deviations (60.3%).

Three of 27 ADRs could have been avoided; one with a dose adjustment according to renal clearance; one by changing the posology and velocity of the infusion and one by previously checking for drug interactions. The most frequent routes of administration were intravenous (17; 63.0%), oral (9; 33.3%) and intramuscular (1; 3.7%).

Three cases of ADRs led to hospitalization (11.1%) while 12 (44.4%) patients were already in the hospital and the remaining 12 (44.4%) were outpatients that did not require hospitalization. The ADRs occurred more frequently in males (14; 51.9%) than in females (13; 48.1%). and more often in adults (17; 63.0%) as compared to the geriatric (8; 29.6%) and pediatric patients (2; 7.4%).

The therapeutic classes and affected organs are presented in Tables 2 and 3, respectively. Anti-infective drugs (systemic) were involved in 11 notifications (40.7%), followed by antineoplastic and immunomodulating agents (10; 37.0%). Infliximab was the medicament that caused the most ADRs. The most frequent symptom associated with ADRs was skin reactions which were present in 16 forms (28.0%) and, in most cases, involved a rash and urticaria.

Table 4 shows the results regarding the reaction mechanism, severity, causality and management of ADRs. Analysis of the reaction mechanism of the ADRs identified 20 type B (74.0%) for example severe cases of anaphylaxis and the Stevens–Johnson syndrome, while 7 type A (26.0%) as the case of coagulation disorders, ecchymosis and petechiae after warfarin administration. In regard to severity, 10 reactions (37.0%) were classified as moderate and these cases included hallucinations to haloperidol and pancreatitis to atazanavir. Nine reactions were classified as mild (33.3%) and one (3.7%) reaction was lethal, which resulted in the patient's death after agranulocytosis by clozapine. According to the relation analysis of causality, which uses the Naranjo Algorithm, 15 reactions (55.6%) were considered probable and only one reaction (3.7%) was defined because of edema where paclitaxel was infused. For management analysis, a patient could have one or more treatments. Drugs were added to relieve the symptoms for 55.6% of the patients while treatment with the offending drug was interrupted in 51.3% of the patients and another drug was substituted with the offending drug in 29.6% of cases. Treatment remained the same in 11.1% of the patients and management information for one patient (3.7%) was unavailable.

Twelve quality deviations (29.2%) were not identified to the notifying unit, 8 were from the central pharmacy (19.5%) and 7 were from the chemotherapy pharmacy (17.1%). The dosage forms involved in quality deviations were an injectable solution (17; 41.4%), powder for solution/injectable suspension and oral solution (7; 17.1% and 7; 17.1%, respectively), tablet (6; 14.7%), enema (2; 4.9%), syrup and oral suspension (1; 2.4% and 1; 2.4%, respectively).

Table 5 shows the notification frequency of the types of quality deviations. Breaks, splits and leaks were the deviations that appeared the most as well as the lack of product and lower volume; thus, each of these deviations had the same number of notifications (9; 20.9%). There were 8 notifications of broken products (18.6%) and of these 8, 2 were related to biological risk (ifosfamide and 5-fluorouracil) and 4 were of high financial value (ifosfamide, 5-fluorouracil, human serum albumin and zoledronic acid).

The lack of identification – information are deviations that require attention because the can induce errors in medication administration to the patient. Five (11.7%) quality deviations were related to this production defect, and 4 (9.3%) corresponded to unidentified products (i.e., missing labels) and 1 (2.3%) notification was about 180 bottles of neomycin (an antibiotic compounded drug) that lacked information regarding the dispensing of medication. Deviations related to the poor quality of information (7.0%) may also harm the patient as was the case of 2 similar ampoules, amiodarone (antiarrhythmic) and acetylcysteine (mucolytic agent) which had the information written very clearly in yellow with the product name and concentration. The anatomical packing problems appeared in 5 notifications (11.7%).

A few product cases contained foreign bodies and dirtiness (4; 7.0%) and this potential problem may indicate biological contamination. The complaints related to this deviation corresponded to medicaments that contained foreign bodies such that 5 bottles of L-carnitine syrup (a compounded drug) contained a dark fiber which after microbial analysis was confirmed as *Penicillium* sp. Additional complaints were related to an enema glycerin solution that contained dark fiber inside the bottle. After analysis, a microhole was found in the primary packaging that allowed air entry and consequently microbial contamination.

The notification frequency of quality deviations regarding the type of drugs available in the Brazilian market were 18 notifications (43.9%) involved in generic drugs, 11 (26.8%) involved in similar drugs, 7 (17.1%) involved in compounded drugs and 5 (12.2%) involved in brand-name drugs. After sampling the 187 medicaments in the hospital stockroom, it was estimated that 48.7% are similar drugs, 36.4% are generic drugs, 11.7% are brand-name drugs and 3.2% are compounded drugs.

Regarding the number of product units showing deviation, besides the 180 bottles of neomycin that lacked information regarding the dispensing of the medication, the 2 notifications (4.6%) of physicochemical changes in solids corresponded to a

total of 4500 tamoxifen tablets (similar drug) which had a change in its hardness property such that the tablets became fragmented when it was removed from the blister. Thus, in absolute numbers, 198 compounded, 26 generic, and 4 brand-name drugs presented quality deviations, but quantifications were made by notification; thus, from the 4515 units of similar products that presented quality deviations, 4500 units corresponded to only 2 quality deviation notifications.

4. Discussion

A major limitation of the spontaneous ADR reporting system is that ADRs are under reported (Gonzalez-Gonzalez et al., 2013). In 2010, the pharmacovigilance sector received 27 notifications of ADRs which is not much if the number of hospital beds and its complexity level are taken into consideration; thus, the under-reporting phenomenon caused by this spontaneous reporting method, prevents the health system from expanding knowledge regarding the safety and quality of medicaments, which makes it difficult to improve and prevent ADRs. One-hundred and sixteen reporting forms that involved 269 medications and 204 reactions were recorded from a study that was conducted in a hospital in Fortaleza (Brazil). That study occurred from January to December 2007 in a teaching hospital, with 425 beds. Only 1 form (0.9%) was spontaneously reported, and the other forms were obtained by active surveillance (115; 99.1%); thus, this study reinforced that higher professionals need to be involved in spontaneous reporting and showed the importance of the active surveillance (Romeu et al., 2011).

In the present study, the ADRs occurred more frequently in men and in the adult patients. These data are consistent with the previous Indian study that showed the same characteristics in gender (61% for men) but differed in age since ADRs occurred more frequently in patients over the age of 60 years (56%) (Sriram et al., 2011). In the hospital in Fortaleza, Brazil, ADRs were mostly prevalent in men (81.9%) and in 15–29 year olds (42.4%); the medicament that was most frequently associated with ADR was dipyrone (32.8%), and the skin was the most affected organ (59.3%) (Romeu et al., 2011). In the present study, dermatological reactions also comprised the ADR profile, which was often observed as a rash, urticaria, and a severe case of the Stevens–Johnson syndrome.

The group of medicaments most often involved with ADR, in this study, was the anti-infectives (systemic) which are the most prescribed medicament in hospitals. A prior study demonstrated an association between antibiotic use and risk of adverse reactions, which caused dermatological, hepatical, cardiovascular and central nervous system reactions (Aagaard and Hansen, 2009). In addition to adverse reactions, irrational use of antibiotics leads to the resistance of microorganisms and an increase incidence of multi-resistant bacterial infections in hospitals (Sharma et al., 2005).

Infliximab, an immunomodulating agent, was the main medicament that was involved with ADR and was associated with reactions of urticaria, dyspnea, redness and facial swelling at the time of infusion. Infliximab consists of an anti-TNF monoclonal antibody that is used to treat Crohn's disease and rheumatoid arthritis. Since it is composed of a murine protein, adverse effects related to hypersensitivity occur frequently

Table 2 Therapeutic classes and drugs associated with Adverse Drug Reactions (ADRs).

Therapeutic Classes (ATC)	Code (ATC)	Drug	Total number (%)
Anti-infectives for systemic use (J)			11 (40.7)
	J01XA01	Vancomycin	2 (7.4)
	J02AA01	Amphotericin	2 (7.4)
	J01CA04	Amoxicillin	1 (3.7)
	J01GB03	Gentamicin	1 (3.7)
	J01MA02	Ciprofloxacin	1 (3.7)
	J01XX08	Linezolid	1 (3.7)
	J04AC01	Isoniazid	1 (3.7)
	J04AK01	Pyrazinamide	1 (3.7)
	J05AE08	Atazanavir	1 (3.7)
Antineoplastic and immunomodulating agents (L)			10 (37.0)
	L04AB02	Infliximab	3 (11.1)
	L01XA01	Cisplatin	2 (7.4)
	L01CB01	Etoposide	1 (3.7)
	L01CD01	Paclitaxel	1 (3.7)
	L01CD02	Docetaxel	1 (3.7)
	L01DC01	Bleomycin	1 (3.7)
	L01XA02	Carboplatin	1 (3.7)
Nervous system (N)			4 (14.9)
	N03AF01	Carbamazepine	1 (3.7)
	N05AD01	Haloperidol	1 (3.7)
	N05AH02	Clozapine	1 (3.7)
	N06DA03	Rivastigmine	1 (3.7)
Alimentary tract and metabolism (A)			1 (3.7)
	A11CC04	Calcitriol	1 (3.7)
Blood and blood forming organs (B)			1 (3.7)
	B01AA03	Warfarin	1 (3.7)

Table 3 Frequency of Adverse Drug Reactions (ADRs) in affected organ.

Affected organ	Description	Total number (%) $n = 57$
Skin		16 (28.0)
	Rash	5 (8.8)
	Urticaria	4 (7.0)
	Hyperpigmentation	2 (3.4)
	Itch	2 (3.4)
	Stevens–Johnson syndrome	1 (1.7)
	Maculopapular rash	1 (1.7)
	Alopecia	1 (1.7)
General		13 (22.8)
	Malaise	3 (5.3)
	Fever	2 (3.4)
	Anaphylaxis	1 (1.7)
	Infusion site swelling	1 (1.7)
	Sweating	1 (1.7)
	Fatigue	1 (1.7)
	Prostration	1 (1.7)
	Generalized edema	1 (1.7)
	Intrathoracic pressure	1 (1.7)
	Facial edema	1 (1.7)
Gastrointestinal		7 (12.3)
	Nausea	4 (7.0)
	Vomiting	1 (1.7)
	Pancreatitis	1 (1.7)
	Epigastric pain	1 (1.7)
Central and peripheral nervous system		5 (8.8)
	Dizziness	2 (3.4)
	Trembling	2 (3.4)
	Restlessness	1 (1.7)
Extra-cardiac vascular system disturbance		3 (5.3)
	Facial redness	3 (5.3)
Blood dyscrasias		3 (5.3)
	Agranulocytosis	1 (1.7)
	Thrombocytopenia	1 (1.7)
	Leukocytosis	1 (1.7)
Psychiatric disorder		1 (1.7)
	Hallucination	1 (1.7)
Other		9 (15.8)
	Dyspnea	5 (8.8)
	Acute renal failure	1 (1.7)
	Hypotension	1 (1.7)
	Ecchymosis	1 (1.7)
	Petechiae	1 (1.7)

during infusion, because of the formation of infliximab antibodies (Kolho et al., 2007). In this study, the adverse reactions occurred on the eighth and tenth application, one of them in a female patient, aged 14.

The profile of ADRs in this study can be characterized as type B, moderate severity and probable causality. This indicates that the reactions are often unpredictable, not dose-related, that changes the patient's normal activity and causes or prolongs hospitalization. Also, reactions whose signs and symptoms are well described in the literature, are evident, easily diagnosed, but difficult to prove since there are an immense number of diseases and medications and the suspected medicament was not re-administered to the patient. In a Brazilian study, most reactions were mild (72.0%) and probable (47.5%) (Coêlho et al., 1999) while in the Indian study, 42% of the reactions were possible, 30% were defined and 23% were probable (Jose and Rao, 2006).

The quality deviations revealed technical problems during production, possible biological contamination, inadequate storage and transportation of the product (temperature, luminosity and humidity). The medicaments with quality deviations may cause adverse events in cases of contamination or lead to ineffective therapy in patients if the active ingredient is degraded. The quality deviations were reported more frequently than ADRs in this study and the same results were also observed by Bezerra et al. (2009), in a hospital in the Mid-West Region of Brazil.

Breaks and leaks accidentally expose professionals and patients to biological risks. Quality deviations in expensive medicaments that are essential for a procedure or therapy may impair the performance of vital activities that are required for patient survival. Thus, for quality deviation classifications in "severe" and "not severe", it should be developed as well as the Naranjo algorithm for ADR, that took into account the possibility of harm to patients and health professionals, according to their financial importance and its relevance to the patient.

Quality deviations may be inconvenient to the hospital in the medication process; however, the suppliers must replace the defective medications or improve the product's quality. Thus, most of notified suppliers replaced the defective products and the industries issued quality control and quality assurance reports that claimed the products were not qualified; however, and in regard to the microhole in the primary packaging of the enema glycerin, the company offered to change the supplier of the bag.

Bismuth subsalicylate, a compounded product, had a validity of 180 days but after observing the instability in suspension,

Table 4 Reaction mechanism, severity, causality and management of Adverse Drug Reactions (ADRs).

	Frequency	
	n	%
Reaction mechanism		
Type A	7	26.0
Type B	20	74.0
Severity		
Lethal	1	3.7
Severe	7	26.0
Moderate	10	37.0
Mild	9	33.3
Causality		
Definite	1	3.7
Probable	15	55.6
Possible	11	40.7
Management		
Added another drug to relieve the symptoms	15	55.6
Stopped the medication	14	51.9
Substituted another drug	8	29.6
No change	3	11.1
Reduced the dose	1	3.7
No informations	1	3.7

Table 5 Frequency of notifications regarding the types of quality deviations.

Type of quality deviations	Description of quality deviations	Total number (%) (n = 43*)
Breaks/splits/leaks		9 (20.9)
	Breaks	8 (18.6)
	Split	1 (2.3)
Lack of product/lower volume		9 (20.9)
	Lower volume than declared on the label	4 (9.3)
	Secondary package without primary package	3 (7.0)
	Primary package without the product	2 (4.7)
Lack of identification – information		5 (11.6)
	Ampoules and flask without identification/label	4 (9.3)
	Lack of administration information	1 (2.3)
Package anatomical problems		5 (11.6)
	Problem during handling	3 (7.0)
	Ampoule very hard	1 (2.3)
	Deviation of blister quality	1 (2.3)
Poor quality of information		3 (7.0)
	Similar ampoules	2 (4.7)
	Reading difficult	1 (2.3)
Foreign body – dirtiness		4 (9.3)
	Dark filament	4 (9.3)
Organoleptic changes		3 (7.0)
	Color change	2 (4.7)
	Turbidity	1 (2.3)
Physicochemical changes (liquid/semi-solid)		3 (7.0)
	Crystallization	2 (4.7)
	Formation of solid matter	1 (2.3)
Physicochemical changes (solid)		2 (4.7)
	Hardness change	2 (4.7)

* Total of 43 quality deviations, because two medicaments presented more than one type of quality deviations.

its validity was changed to 90 days to ensure medicament's stability. In the case of the alteplase, a packing anatomical problem was evident during product handling and the hospital staff learned how to properly handle it from a nurse in another sector.

The hospital where this study was conducted acquires medicament through a price analysis; thus, most medicaments are similar and generic drugs. The acquisition of similar medicaments is higher than the generic drug but the number of generic notifications was higher than the similar notifications; thus, this may suggest that a higher quality control and inspection should be performed, even if these generic drugs have fulfilled the quality requirements. There is a lack of information in the literature regarding quality deviations; thus, further discussion of quality deviations is impossible.

5. Conclusions

The classification system to study quality deviations was clear and consistent. This study demonstrated that practices and public policies related to more effective pharmacovigilance need to be implemented so that the number of spontaneous reports increases. In conclusion, it is necessary to increase the number of spontaneous reports and improve the quality of notifications, promote active surveillance in hospitals, and conduct training of healthcare professionals. Further, education related to pharmacovigilance activities and its importance in hospitals (which notify and how to notify) as well as improving the production, quality control, transport, storage, and distribution of pharmaceutical products, primarily in generics and similar drugs, and will ensure safer drug use in Brazilian hospitals.

Disclosure

There is no conflict of interest in this study.

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