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Pharmacovigilance of compounded drugs - Part 1: profile of Brazilian notifications

Farmacovigilância de medicamentos manipulados - Parte 1: perfil das notificações no Brasil

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ABSTRACT

Introduction: Compounded drugs are extemporaneous pharmaceutical preparations, mostly used to enable the pharmacotherapy of special populations through personalized formulations. In this way, they are not subjected to clinical tests prior to their use, and pharmacovigilance actions are fundamental to guarantee their safety. **Objective:** to describe the profile of compounded drugs registered in the notifications of technical complaints reported to the National Health Surveillance Notification System (NOTIVISA). **Method:** Descriptive exploratory study, retrospective to the period 2006-2016, of the notifications of compounded drugs reported to Notivisa. **Results:** 303 notifications of technical complaints regarding 26 officinal, 268 magistral and 09 unclassified medicines were analyzed. 107 different assets were identified. Those with action on the Digestive System and Metabolism were the most frequent (42.00%), followed by those with action on the Blood and Hematopoietic Organs (10.00%), Dermatological (10.00%) and Cardiovascular System (9.70%). The main quality deviations reported were related to liquid dosage forms, with the presence of foreign bodies, particles or precipitates being the most frequent (22.40%), followed by changes in packaging and labeling (18.60%). **Conclusions:** It was possible to describe the main compounded drugs notified to Notivisa, their characteristics and active substances conveyed in the formulations, which can contribute to the actions of Health Surveillance in the masterful scope, which is still incipient in Brazil.

KEYWORDS: Pharmacovigilance; Health Surveillance; Compounded Drugs; Pharmacy compounding; Notivisa

RESUMO

Introdução: Medicamentos manipulados são preparações farmacêuticas extemporâneas, em sua maioria utilizadas para viabilizar a farmacoterapia de populações especiais por meio de formulações personalizadas. Desta forma, não são submetidos a testes clínicos anteriores a sua utilização, sendo as ações de farmacovigilância fundamentais para a garantia de sua segurança. **Objetivo:** Descrever o perfil dos medicamentos manipulados registrados nas notificações de queixas técnicas reportadas ao Sistema Nacional de Notificação em Vigilância Sanitária (Notivisa). **Método:** Estudo exploratório descritivo, retrospectivo ao período de 2006-2016 das notificações de medicamentos manipulados reportadas ao Notivisa. **Resultados:** Foram analisadas 303 notificações de queixas técnicas referentes a 26 medicamentos oficinais, 268 magistrais e nove não classificadas. Foram identificados 107 diferentes ativos. Os de ação no aparelho digestivo e metabolismo foram os mais frequentes (42,00%), seguidos daqueles com ação no sangue e órgãos hematopoiéticos (10,00%), dermatológicos (10,00%) e aparelho cardiovascular (9,70%). Os principais desvios de qualidade notificados foram relacionados às formas farmacêuticas líquidas, sendo a presença de corpo estranho, partículas ou precipitados, a mais frequente (22,40%), seguida de alterações na embalagem e rotulagem (18,60%). **Conclusões:** Foi possível descrever os principais medicamentos manipulados notificados ao Notivisa, suas

características e substâncias ativas veiculadas nas formulações, o que pode contribuir para as ações de vigilância sanitária no âmbito magistral, tão incipiente ainda no Brasil.

PALAVRAS-CHAVE: Farmacovigilância; Vigilância Sanitária; Medicamento Manipulado; Farmácia com Manipulação; Notivisa

INTRODUCTION

The compounded drugs can be classified as magisterial formulas, when they are prepared according to a medical prescription that specifies the patient for whom the drug is intended; or officinal preparations, when the drug is prepared according to compendial indications, from a pharmacopoeia or form[1]. In this way, compounded drugs are fundamental pharmaceutical preparations to enable the pharmacotherapy of special populations, and neglected by the pharmaceutical industry, such as pediatrics and neonatology, as these formulations currently address the lack of adequate formulations for these age groups[2,3,4]. These formulations are also necessary to meet the demand of a patient who needs a personalized drug, not available, or in situations of extemporaneous formulations, due to the difficulty of stabilizing the drug in a pharmaceutical form for prolonged periods[5].

However, despite their indispensability, compounded drugs bring with them a risk associated with the formulation, which is the uncertainty about bioavailability and stability[6]. The production of any drug necessarily implies a degree of risk. Thus, there are several risks inherent to the handling of this type of drug, starting at the stage of acquisition and receipt of raw material and packaging material, going through the handling process, such as weighing, mixing, cross-contamination, among others, which can generate quality deviation problems in these drugs. In addition, problems can occur with incorrect evaluation of prescriptions, which directly affects the handling process and patient safety[6].

Drug quality deviation is the departure from the established quality parameters for a product or process and must be continuously monitored[7]. They can be related to organoleptic alterations (change in color, odor, flavor, turbidity), physicochemical alterations (precipitation, difficulty in dissolution, homogenization, photosensitivity, and thermolability), or even general alterations, such as: foreign particles, lack of label information, registration problems, label or content change, cracks and bubbles in the packaging material[8].

Therefore, the continuous surveillance of these problems can generate information about a pattern of occurrences, contributing to the knowledge and planning of health actions and increasing the safety of patients and drug users. In this context, pharmacovigilance is health action that addresses a set of activities related to the detection, assessment, understanding, and prevention of adverse events (AE) or any other drug-related problems[7]. In the case of compounded drugs, pharmacies are responsible for monitoring their products, having to carry out pharmacovigilance as a routine procedure. It is worth mentioning the surveillance related to new preparations, especially those that convey associations of undescribed drugs and have to inform the health authorities of the occurrence of AE, with emphasis on adverse reactions and/or unforeseen drug interactions[1]. In addition, the pharmacist, in the exercise of their activities, must notify the health professionals and the competent health bodies of the AEs about intoxications, whether voluntary or not, and the pharmacological dependence observed and recorded in the practice of pharmacovigilance[9].

The National Health Surveillance Notification System (Notivisa) is an online platform in Brazil that systematizes, investigates and manages AE reports and technical complaints (TC) provided by health services, liberal professionals, and institutions holding product registration. This platform receives information on materials in health surveillance in the following categories: techno-surveillance, pharmacovigilance, hemovigilance, and bio-surveillance. The QT of product quality deviations have an important impact on the Unified Health System (SUS), as they can lead to an increase in morbidity, mortality, treatment and patient care time[10]

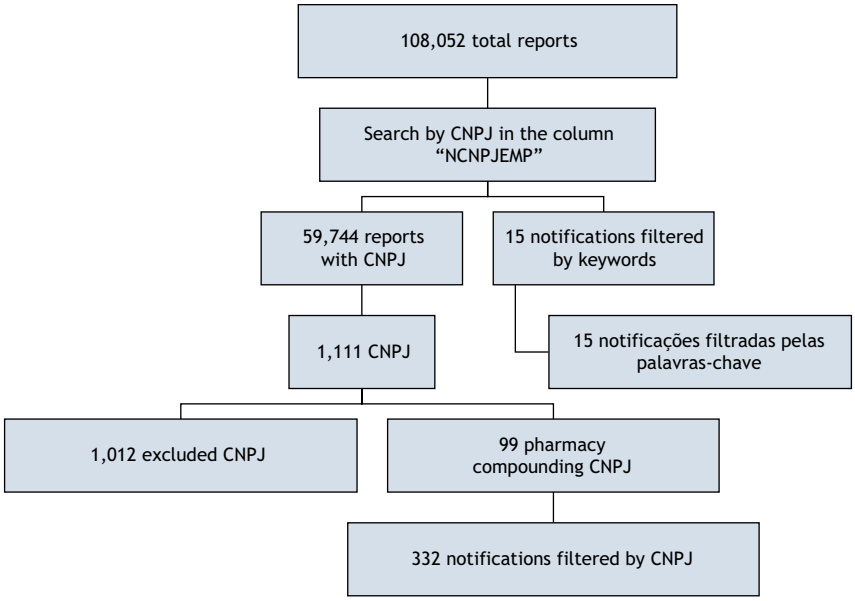
The present study aimed to identify and characterize the manipulated drugs present in the records related to TC reported to pharmacovigilance, in Notivisa, from 2006 to 2016.

METHOD

A descriptive exploratory study was carried out, with a quantitative approach, in which the TC notifications of manipulated drugs registered in the Notivisa database were collected, with a time lapse from January 2006 to June 2016.

To obtain the data, initially, data from all 108,052 notifications from the Notivisa database collected for the respective period were recorded in a database created in the Excel® program for managing the information. In order to extract data related to manipulated medicines, a survey was carried out of all the registered National Registries of Legal Entities (CNPJ). Then, the registration situations available on the Special Department of Federal Revenue of Brazil website[11] were consulted, looking for economic activity code number 47.71-7-02, which refers to the "Retail trade of pharmaceutical products, with manipulation of formulas". Of the 1,111 CNPJ registered, 99 were found with the description of pharmacy with manipulation, totaling 332 notifications. In addition, a search was carried out, in the notifications without CNPJ, in the company's trade name column for the following words: manipulation(s), manipulated, masterful, and officinal, in which 15 more notifications were found. By the sum of the research carried out, 347 notifications were found that will be the object of study of this work, as described in Figure 1.

The notifications raised were characterized and evaluated according to: the active substances; the pharmaceutical forms,



Source: Elaborated by the authors from data at Notivisa, 2021.
CNPJ: National Registry of Legal Entities.

Figure 1. Extraction flow of notifications related to compounded drugs from Notivisa.

the detailed description of the notification, the technical name of the notified product, the notifying institution, and the CNPJ of the notified company. To analyze the data, the following variables were created: reason for the occurrence and physical form of the drug. The drugs were classified as: masterful or officinal, as to the nature of the active in vegetable, biological, or synthetic. The drugs were also ordered according to the Anatomical Therapeutic Chemical Code (ATC) classification, considering the first level in anatomical/pharmacological groups.

To obtain the physical form of the drug variable, the description of the packages, the pharmaceutical forms, and the routes of administration were regrouped and classified as: liquid, solid, semi-solid and gas, and not informed.

According to Ansel e Allen[5], According to Ansel and Allen[5], preparations with solid physical form correspond to powders, granules, tablets, dragees, capsules, suppositories, and eggs; preparations in liquid physical form correspond to syrups, elixirs, suspensions, emulsions, injectables, tinctures, and extracts; semi-solids are gels, lotions, ointments, liniments, cerates, pastes, creams, and ointments; and the gaseous ones are aerosols (sprays).

Data analysis

The absolute and relative frequencies of notifications for the variables presented were analyzed. In order to obtain more detailed information, data were cross-referenced between the variables "reason for notification" and "physical form of pharmaceutical preparation of notified products".

The results found were organized in tables and graphs for better presentation and analysis of the results.

Ethical aspects

The study was based on the analysis of secondary data from the Notivisa database, not directly involving human subjects. The evaluation was restricted to the aggregated analysis of the variables, keeping anonymous the subjects related to the notifications, the identification of the notifier, company or user of the medication, situation in which consideration by the Research Ethics Committee (CEP) is waived, observing the recommendations of the National Health Council (CNS) in its Resolution No. 510, of April 7, 2016.

Study limitations

The main limitation of this research concerns incomplete information in the Notivisa database, which impacts the quality of the analysis of the data collected.

RESULTS

There were 347 notifications related to manipulated drugs reported to Notivisa, among which 303 records related to TC. The amplitude varied from 0 to 82 notifications in the period, with an annual average of 31.54 notifications and a standard deviation of 23.34. Among the 303 reports, 22 did not describe the active substance, 13 were related to parenteral nutrition, and 268 reports were related to 107 different actives. Among the actives, seven are of a plant nature, four of a biological nature, and 96 of a chemical-synthetic nature. As for the type of preparation, 26 notifications were related to officinal medicines and 268 of magistral medicines, not being possible to classify the remaining nine products. The 15 most frequent active substances in the reported pharmaceutical preparations were:

calcium gluconate (20), parenteral nutrition (13), silver nitrate (10), papain (10), chloral hydrate (10), tincture of benzoin (10), neomycin (nine), cholecalciferol (eight), potassium chloride (eight), omeprazole (seven), calcium carbonate (six), caffeine citrate (six), dexamethasone (six), chlorhexidine gluconate (five), sodium bicarbonate (five), captopril (five), and furosemide (five). As for drugs with a low therapeutic index, the occurrence of Minoxidil (one) was observed in this study. Considering the drugs under special control of the sanitary surveillance, the occurrence of ten actives was observed: chloral hydrate (10), codeine (three), citalopram (two), locarserine (two), risperidone (two), sertraline (one), amfepramone (one), cloxazolam (one), sibutramine (one), and venlafaxine (one), which belong to the anorectic, amphetamine, sedative, and antidepressant therapeutic classes. There was only one association of drugs in the same pharmaceutical form, which refers to the capsule pharmaceutical form containing the active piroxicam, prednisone and sulfadiazine in the same formulation, as described in Table 1.

Table 1. Frequency of active substances present in pharmaceutical preparations registered in notifications of technical complaints reported to the Health Surveillance Notification System (Notivisa), Brazil, in the period 2006-2016.

ACTIVE	N	ACTIVE	N	ACTIVE	N	ACTIVE	N
Calcium gluconate	20	Adenosine	2	Amfepramone	1	Potassium iodide	1
Parenteral nutrition	13	Bicarbonated water	2	Aquasept	1	Iodine	1
Silver nitratre	10	Alprostadil	2	Turkey balm	1	Povidone iodine	1
Chloral hydrate	10	Citalopram	2	Acetic acid	1	Lidocaine	1
Papain	10	Sildenafil	2	Calcium	1	Losartan	1
Tincture of benzoin	10	Calcium chloride	2	*Caralluma fimbriata*	1	Minoxidil	1
Neomycin	9	Sodium chloride	2	Carbachol	1	Mitomycin	1
Cholecalciferol	8	Ferric chloride	2	Activated charcoal	1	Garlic oil	1
Potassium chloride	8	*Cold cream*	2	Cephalothin sodium	1	Coconut oil	1
Omeprazole	7	Lanette cream	2	Slimming tea	1	Zinc oxide	1
Calcium carbonate	6	Phenylephrine	2	Cisplatin	1	Polyethylene glycol	1
Caffeine citrate	6	Fluconazole	2	Potassium citrate	1	Pyrimethamine	1
Dexamethasone	6	Potassium phosphate	2	Potassium citrate	1	Piroxicam/Prednisone/ Sulfadiazine	1
Chlorhexidine gluconate	5	Heparin	2	Cisplatin	1	Prostaglandin	1
Sodium bicarbonate	5	Sodium hyposulfite	2	Sodium citrate	1	Resveratrol	1
Captopril	5	L-carnitine	2	Papaverine hydrochloride	1	Nicotine salicylate	1
Furosemide	4	Lorcaserin	2	Cloxazolan	1	Sibutramine	1
Vitamin B1	4	Lugol	2	Foot antiperspirant deodorant	1	Mansell solution	1
Glucose	4	Mannitol	2	Isosorbide dinitrate	1	Sulfadiazine	1
Cardioplegic solution	1	Ranitidine	2	Herbs	1	Chondroitin sulfate	1
Tacrolimus	4	Risperidone	2	Scopolamine	1	Magnesium sulfate	1
Lactulose	4	Artificial saliva	2	Spironolactone	1	Baby powder	1
Methylene blue	4	Electrolyte solution	2	Finistro forte plus	1	Tiratricol	1
Ferric perchloride	3	Mg Sulfate Monohydrate	2	Fluorescein	1	Triamcinolone	1
Sholl solution	3	Zinc sulfate	2	Calcium phosphatase	1	Venlafaxine and Sertraline	1
Tricalcium phosphate	3	Ferrous sulphate	2	Guaco and honey	1	Verapamil	1
Sterile vaseline	3	Tadalafil	2	Immunostimulant	1	Vitamin B6	1
Codeine	3	Vitamin D	2	Hemogin	1	Vitamin and minerals	1
Sodium l-thyroxine	3	Trichloroacetic acid	1	Hydroxyzine	1	Vitamin k	1
Absolute alcohol	2	Acetic acid	1	Growth hormone	1	Mansell solution	1
Hyaluronidase	2	Azelaic acid	1	*Hypericum perfloratum*	1		
TOTAL							**303**

Source: Elaborated by the authors, 2021.

The assets were classified according to the first level of the ATC classification, according to the organ or system on which they act, considering their chemical, pharmacological, and therapeutic properties. In this classification, the total number of drugs included was 170, since, for 128 products, it was not possible to classify the active substance (Figure 2).

Drugs acting on the digestive system and metabolism were the most frequent (42.00%) and include vitamins, glucose, and electrolytes. Then, blood and hematopoietic organs (10.00%), dermatological (10.00%), and cardiovascular system (9.70%).

Among the actives of action in the digestive system and metabolism, the most frequent was injectable calcium gluconate. In addition to this, there are two actives that are for calcium replacement: cholecalciferol and calcium carbonate.

The reasons that describe the characteristics of QT are presented in Table 2, with the products being grouped into five categories of physical form (liquid, solid, semi-solid, gaseous, and not informed) after analyzing each notification individually.

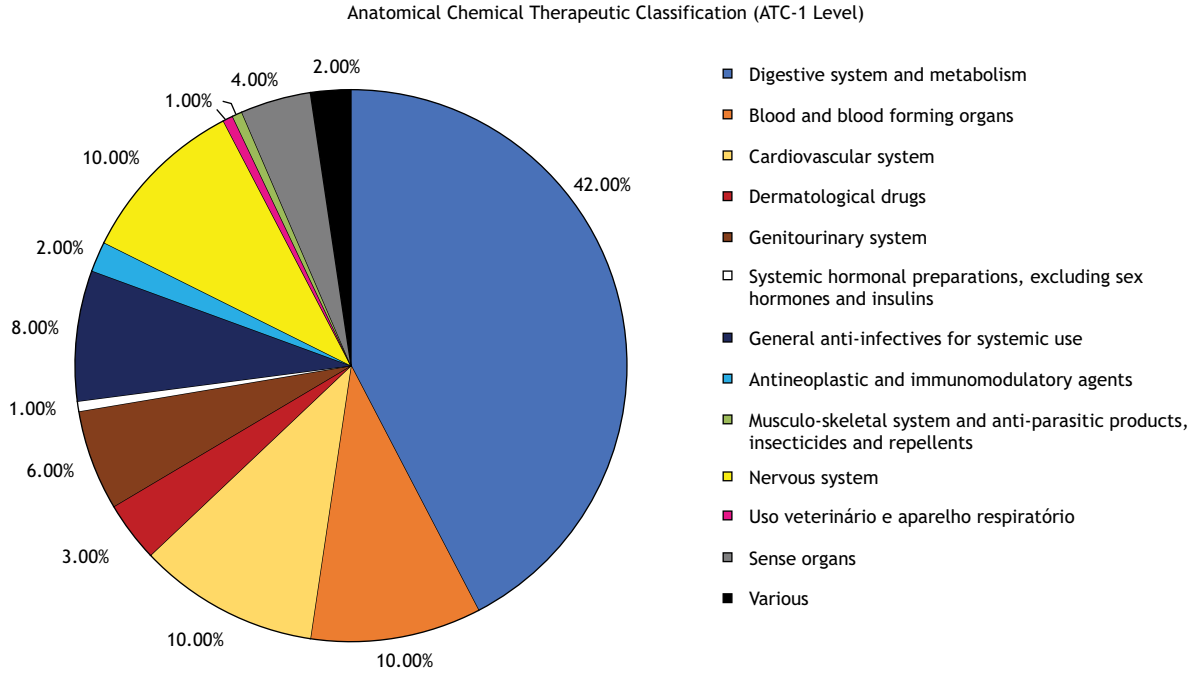
This analysis included 285 products, 18 of which were excluded because there was no information on physical form. Thus, it was not possible to classify the physical forms in all notifications. The absence or the wrong description of these items was observed and, in several cases, only the description of the type of drug container or primary packaging was observed, when the TC was related to the label, packaging, leakage, among others.

The results indicated that 69.40% of the drugs present in the notifications were of a liquid physical nature, 17.80% were solid, and 6.60% were semi-solid. Among drugs in liquid pharmaceutical form, the presence of foreign bodies, particles or precipitates were the main reported deviations (22.40%), with changes in packaging and labeling being the second most frequent reason (18.60%). Among the solid physical forms, the change in the label and packaging was predominant (24.00%), among the semi-solids were changes in color, stain, and odor (6.60%), while for the formulations in the gaseous form, there was only one occurrence, and for the rest (6.00%) it was not possible to perform the classification.

DISCUSSION

The production of medicines has its roots in the manipulation of pharmaceutical preparations since the beginning, being fundamental the sanitary regulation that guides the conducts related to its quality. Recently, these pharmaceutical standards have also contemplated aspects related to the safety and efficacy of compounded drugs[1].

The results of this study indicate that in the ten-year period (2006 to 2016) only 303 notifications of chemotherapy for compounded drugs were registered, which represents, in percentage terms, 0.32% of the total notifications of all drugs reported to Notivisa. With due regard for the differences between manipulated and industrialized drugs, this result could be considered coherent, since industrialized drugs are marketed in much larger



Source: Elaborated by the authors, 2021.

Figure 2. Percentage distribution of active pharmaceutical ingredients according to the first level of the therapeutic chemical anatomical classification, Brazil, in the period 2006-2016 (n = 170).

Table 2. Characteristics of technical complaints according to the physical forms of compounded pharmaceutical preparations reported to the Health Surveillance Notification System (Notivisa), Brazil, in the period 2006-2016.

Reason for notification	Physical form of the pharmaceutical formulation					
	Liquid	Solid	Semi-solid	Gaseous	NI	Total
Changes in color, stains, and smell	15	3	6	0	0	24
Changes to the label, packaging	39	13	3	0	2	57
Appearance different from described or usual	12	5	2	0	0	19
Irregular COA	0	1	0	0	4	5
Foreign body/Particles/Precipitate	47	5	5	0	0	57
Irregular packaging	22	3	2	0	0	27
Handling error or GMP failure	7	2	0	0	0	9
Raw material suspected of being unregistered	4	2	0	0	6	12
Irregular batch production	3	3	0	1	4	11
Irregular marketing	1	1	0	0	1	3
Less than labeled amount or absence of drug	23	4	0	0	0	27
Suspected other irregular practices	5	5	0	0	1	11
Counterfeit product suspected	1	1	0	0	0	2
Leak	31	6	2	0	0	39
Total	**210**	**54**	**20**	**1**	**18**	**303**

Source: Elaborated by the authors, 2021.
COA: Company Operation Authorization; GMP: Good Manufacturing Practices; NI: not informed.

pharmaceutical presentations. Furthermore, notification of quality deviation and AE is mandatory for holders of registration of industrialized drugs in Brazil for much longer than for compounding pharmacies.

In the absence of specific studies on the notification of manipulated drugs, the results obtained were compared with those that evaluated TC reported to Notivisa, especially industrialized drugs and health products. Lima et al.[11] analyzed 50,824 notifications referring to medicines in the period from 2012 to 2015, of which 399 (0.79%) corresponded to notifications of products based on plant species, 389 related to TC, a result that corroborates the result found in the present study. However, in the study carried out by Lima et al.[12], in a large hospital, it was found that, in the period of two years, there were 199 medication notifications, 70% of which related to TC. In the study carried out in the technosurveillance sector by Oliveira et al.[10], there were 5,353 notifications from 2007 to 2016 related to TC related to vascular catheter received by Notivisa.

This result clearly indicates the inferiority of the number of reports of manipulated medicines when compared to the records of other products, even in different environments, suggesting the occurrence of underreporting. According to the Pan American Health Organization[7] underreporting is a common phenomenon in all countries and it is difficult to correct it since its extent is unknown and very variable. In Brazil, recent studies[13,14] identified deficiencies in knowledge, attitudes, and practices in pharmacovigilance among health professionals[13]. These studies mainly included pharmacists (76%), verifying that most professionals interviewed were classified as underreporters. The main reason for underreporting was also identified as the lack of access to the patient's vital data for the notification of cases and the difficulty with information technology[14].

The systematic literature review study carried out by Varallo et al.[15] described as the main causes of underreporting by health professionals: ignorance, insecurity, and indifference. According to these authors, underreporting occurs due to: complacency in the belief that only safe drugs are released for commercialization, fear of being involved in litigation, guilt for feeling responsible for the harm observed in the patient, ignorance in how to describe a report, the belief that only serious and unexpected cases should be reported, the insecurity in reporting cases of suspected adverse drug reaction (ADR) due to the belief that notification should only occur "in the certainty" that the damage was caused by the use of a specific medication, lack of time, and also lack of training in pharmacovigilance.

Through the ATC classification, one can verify, by the characteristics of the notifications, the presence of different active substances/drugs with action on the Digestive System and Metabolism (DSM). This result can be explained by the high frequency of injectable calcium gluconate, which must be related to parenteral nutrition (TPN) preparations, since TPN is an extemporaneous formulation obtained through masterful preparation.

Silver nitrate eye drops were the second most frequent medication. This medication is for ophthalmic use in newborns and should be used immediately after birth to clean the eyes[16]. The main quality deviation among the manipulated eye drops was product leakage or change in the color of the solution. These problems can be caused due to lack or non-compliance with good compounding practices, such as: contamination of the preparation, problems in the compounding process, lack of water quality parameters for eye drops, problems in the sterilization process, and lack of quality of the drop bottle[17].

Papain and tincture of benzoin are preparations used for wound debridement, healing, and asepsis[18]. Papain was reported as a gel dosage form, and different reasons for the quality deviation were described, such as: change in dosage form viscosity to a more liquid consistency, lack of therapeutic efficacy, formulation leakage, and color change. This drug must be stored in a refrigerator (5°C ± 2°C) and, therefore, if the ideal storage condition is not followed, the stability of the gel is compromised, as well as the effectiveness of the drug[19]. In the case of tincture of benzoin, the highest frequency of TC was due to leakage or defect in the packaging, which may favor product contamination.

Regarding the active caffeine citrate and those with cardiovascular action, such as captopril and furosemide, this could be explained by the high demand for compounding these drugs in liquid dosage forms for oral administration, their use in pediatrics and neonatology, since there are no industrialized preparations suitable for this population in Brazil[3,4].

Also, the notification of medicines containing drugs for: sedation – chloral hydrate (3.28%); antimicrobials – neomycin; anti-inflammatories – dexamethasone; and gastric and esophageal discomfort such as omeprazole. These data show a wide variety of actives that were mainly manipulated in masterful preparations. In view of this, it is emphasized that the pharmacy can transform pharmaceutical specialty, exceptionally when the raw material is unavailable on the market and the lack of specialty in the dose and concentration and/or pharmaceutical form compatible with the clinical conditions of the patient, in order to adapt it to the prescription[1] Thus, the compounded drugs should be an alternative for the individualization of dosage regimens, and not replacement of drugs already available[18]. However, Pontes and Zamith[20] found a low frequency of medicines handled in individual doses in community compounding pharmacies. In the study carried out by these authors, it was found that only 34% of the manipulated drugs had doses different from those standardized in the pharmaceutical specialties available in the Brazilian market, which mischaracterized them as masterful, personalized medicines, indicating the need for a careful risk assessment that justifies the handling of really masterful medicines.

The present study indicated the notification of ten active substances with action on the central nervous system (CNS), which are part of the list of controlled drugs[20] because they cause chemical or psychic dependence and/or produce severe nervous disorders. Among these are: amfepramone, citalopram, cloxazolam, codeine, chloral hydrate, locarserine, risperidone, sertraline, sibutramine, and venlafaxine, which belong to the anorectic, amphetamine, antidepressant, and sedative therapeutic classes.

This result corroborates Pontes and Zamith[21], who carried out a study on compounding pharmacies with special authorization, located in the city of Nova Friburgo (RJ), in which it was found that out of a total of 12,253 formulas, less than 1.0% of compounded drugs were considered officinal (pharmacopoeic), with the highest frequency of magisterial preparations in capsule pharmaceutical form (83%), which included 15 drugs from therapeutic classes of great clinical importance, such as: antidepressants, anorectics, and antipsychotics. This profile of the compounded drugs evaluated may represent, in terms of public health, a potential health risk regarding safety and efficacy, since adverse reactions caused by anorectic psychotropic drugs include: convulsions (epileptic), changes in the electroencephalogram, psychoses, anxiety, euphoria, depression, dysphonia, irritability, tension, insomnia, tremor, mydriasis, headache, hypertension or hypotension, angina, circulatory collapse, among others[22].

It was also verified the record of quality deviation by 0.5% Minoxidil solution, which is a drug that integrates the list of low therapeutic index actives. It is worth mentioning other known cases that demonstrated the risk related to active substances with a low therapeutic index, as in the case of eight patients who died due to an error in the colchicine dosage, compounded for the treatment of gout[23,24].

Regarding the reasons for the TC notifications, in the present study, it was found in general, regardless of the physical form of the drug, that there was a greater predominance of changes in the label and packaging of the drugs, presence of foreign body, particle or precipitate in drugs, amount of drug lower than that labeled, and changes in the color and odor of drugs. The study by Caon et al.[25] corroborates our results, as it also reported that the most recurrent reason recorded in the TC of drugs in a large hospital was related to packaging problems (54.1%), followed by color change/crystallization/foreign body inside the packaging (21.1%); as well as verified in the study by Lima et al.[12], who raised leakage problems (17%), different color than usual (10.8%), and absence of product in the bottle.

Considering the physical nature of the pharmaceutical forms, liquid preparations for oral use were predominant, with more than two thirds of the notifications. This result is probably due to the scarcity of liquid drugs for use in children, since these preparations are the most suitable for pediatrics, due to the ease of dose adjustment and organoleptic characteristics, as well as the ease of swallowing and administration. Therefore, physicians often prescribe adaptations of solid dosage forms in liquid formulations and use masterful preparations to deal with these limitations[24]. As for the characteristics of the reason for notification, for liquid dosage forms, it can be seen that most are related to the aspect of the formulation, in which the reason is the change by foreign body, particles, and precipitates.

According to Costa et al.[26], the adaptation of a solid dosage form in a liquid formulation can offer risks, such as dose inaccuracy, contamination during compounding, loss of stability, incompatibilities, and interactions and, therefore, a higher frequency of complaints reported to Notivisa

Another risk of the liquid dosage form is the occurrence of drug leakage. Such a deviation requires attention, as it may compromise the treatment, as the leak may lead to the lack of the drug inside the bottle, which may generate an excess cost for the patient, in case they need to acquire a new drug to finish the treatment.

In addition, the leakage of liquid form compounded drugs can also make it difficult to read the label and the information contained therein, as it can erase the information or stain it, resulting in difficult visualization, impairing, or making the treatment unfeasible[24]. According to the Resolution of the Collegiate Board of Directors (RDC) No. 67, of October 8, 2007[1], all dosage and storage information must be described on the label[7], however, problems in the labeling and packaging of liquid dosage forms were recorded in 39 notifications and contributed to 17.30% of the notifications. As for solid drugs, four of the 61 notifications occurred due to lack of medication. When compared to liquid and semi-solid dosage forms, which need precision equipment to measure volume, in solid forms are easier to identify the lack of medication. The lack of a tablet or capsule also carries a risk, as the patient will not be able to complete the treatment.

Quality deviation was also verified in the packaging and/or labeling of solid drugs, showing the importance of sanitary inspection to improve the quality control of the compounded products. In 21 notifications, it was not possible to verify the physical form of the drug, since it is not a category of the Notivisa form, therefore, the notifiers do not include this field in the body of the description of the reason for the TC, resulting in the omission of this information. In this way, the notifier needs to describe the pharmaceutical form according to their own judgment, which makes the study of the variable subjective, since, due to lack of knowledge, the notifier may indicate or classify incorrectly, making it difficult for pharmacovigilance to understand which dosage forms have a higher frequency of quality deviations and AE.

In the study carried out by Mota et al.[27] it was found that Notivisa was considered complex and with low potential for acceptability, since 95 variables were identified for a complete completion of the form for health professionals, when the maximum reference value should be 60 variables. That is, filling in some form variables makes the notification process even more time-consuming and complex. According to the authors, Notivisa's performance in terms of pharmacovigilance was considered satisfactory for the validity attribute, but deficient in terms of simplicity, acceptability, representativeness, completeness, consistency, and timeliness of reporting, contributing to underreporting.

CONCLUSIONS

The present study allowed us to know the main compounded drugs notified to Notivisa, their characteristics and active substances conveyed in the formulations, which can contribute to the actions of sanitary surveillance in the masterful scope, so incipient still in Brazil. However, although the compounding pharmacy has had a great impact on the pharmaceutical scenario in recent years, a reduced number of notifications has been demonstrated, which can make it difficult for pharmacovigilance activities to be effective, delaying the promotion of safety and the management of health risk related to these products.

Thus, permanent monitoring of the quality of this type of medication is necessary, especially for magistral formulations, given their impact on public health, emphasizing that masterful pharmacovigilance should be a common responsibility among users, notifying professionals, and within the regulatory framework, so that it can in fact be disseminated as a health practice.

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Author's Contributions

Passos MMB, Pimenta TL – Conception, planning (study design), acquisition, analysis, data interpretation, and writing of the work. Monteiro MSSB - Acquisition, analysis, data interpretation, and writing of the work. Oliveira DR, Freitas ZMF – Writing of the work. All authors approved the final version of the work.

Conflict of Interests

The authors inform that there is no potential conflict of interest with peers and institutions, politicians, or financial in this study.