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Pharmacovigilance: profile and notifications of the adverse drug reaction in a teaching hospital

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Abstract

Objective: To identify the profile of adverse drug reactions (ADRs) in a tertiary public teaching hospital after the inclusion of active search, through screeners, in the pharmacovigilance service, as well from inform managers about the epidemiological data of ADRs. **Method:** Observational, descriptive, and exploratory study conducted in a tertiary teaching hospital in western Paraná, between July and December 2018. The search was performed by consulting the Microsoft Office Excel® program database of the Pharmacovigilance Service and the Quality and Patient Safety Sector (SQSP). It identified the profile of adverse drug reactions and notifications to the pharmacovigilance service regarding the system of spontaneous notification and tracers by active search, as well as made a brief survey of costs related to the topic. **Results:** In the period studied 536 notifications were reported, 74 of these were considered adverse reactions. The hospital team that reported most frequently was the nursing staff. The screeners related to antiallergic and antidotes to anticoagulants were the most sensitive with a positive predictive value of 9 and 3%, respectively. The Emergency Room (ER) was the ward with the highest number of notifications (215), mainly due to the use of the screeners. The drugs with the highest prevalence were morphine (17%) and dipyrone (10%). The exclusive cost of the reactions was R$ 1,097.56. **Conclusion:** The conclusion is that this study allowed the characterization of the main ADR tracers after the inclusion of active search and that in-hospital actions are needed to avoid underreporting in order to ensure efficacy and therapeutic safety.

Key-words: Notification systems for adverse drug reactions; Patient safety; Pharmacovigilance; Clinical pharmacy; Tracers.

Farmacovigilância: perfil e notificações das reações adversas a medicamentos em hospital de ensino

Resumo

Objetivo: Identificar o perfil das reações adversas a medicamentos (RAM) em um hospital público universitário e terciário após a inclusão da busca ativa, por meio de rastreadores, no serviço de farmacovigilância, bem como informar aos gestores sobre os dados epidemiológicos das RAM. **Método:** Estudo observacional, descritivo e exploratório realizado em um hospital escola terciário do oeste do Paraná, entre julho e dezembro de 2018. A busca foi realizada através da consulta do banco de dados do programa Microsoft Office Excel® do Serviço de Farmacovigilância e do Setor de Qualidade e Segurança do Paciente (SQSP). Identificou o perfil das reações adversas a medicamentos e notificações ao serviço de farmacovigilância quanto ao sistema de notificação espontânea e rastreadores por busca ativa, bem como fez um breve levantamento de custos relacionados ao tema. **Resultados**: No período estudado foram relatadas 536 notificações, 74 destas foram consideradas reações adversas. A equipe do hospital que notificou com maior frequência foi a dos profissionais da enfermagem. Os rastreadores relacionados aos antialérgicos e antídotos de anticoagulantes foram os mais sensíveis com valor preditivo positivo de 9 e 3%, respectivamente. O Pronto Socorro (PS) foi a ala com maior número de notificações (215), principalmente pelo uso dos rastreadores. Os medicamentos com a maior prevalência foram a morfina (17%) e a dipirona (10%). O custo exclusivo das reações foi R$ 1.097,56. **Conclusão:** Conclui-se que o estudo permitiu caracterizar os principais rastreadores de RAM após inclusão da busca ativa e que são necessárias ações intra-hospitalares para combater a subnotificação de modo a garantir eficácia e segurança terapêutica.

Palavra-chave: Sistemas de notificações de reações adversas a medicamentos; Segurança do paciente; Farmacovigilância; Farmácia clínica; Rastreadores.

Introduction

Patient safety has been a recurrent subject of discussion[1–9], especially after institution of the National Patient Safety Program (*Programa Nacional de Segurança do Paciente*, PNSP) by Ordinance No. 529/2013[10], which encompasses pharmacovigilance and the practice of reporting adverse events as measures that certify safety of the health system users, competencies and knowledge desired in the training of future professionals in the area[5,9,11]. It is to be noted that quality of the service, as well as patient safety, is responsibility of all professionals with whom patients come into contact[12].

Adverse Drug Event (ADE) is a broad term corresponding to any harmful medical/therapeutic instance that may occur during drug treatment, even not causally related[13,14]. In turn, Adverse Drug Reactions (ADRs) only refer to unintentional and/or harmful responses that can occur in prophylactic, diagnostic or therapeutic doses[5,14].

The frequency of events is not equally distributed across countries, or even within the same country. A systematic review that evaluated the occurrence of ADEs in hospitals from 13 countries observed a frequency of 1.6% to 41.4%[15]. A Spanish study, with 245,320 cases analyzed, identified that 6.8% of the patients suffered at least one adverse event, with a mean cost between € 5,260 and € 11,905 in expenses[16]. Another one, conducted in 58 hospitals from 5 Latin American countries reported 10.5% prevalence, where 28% caused permanent harms, 6% resulted in deaths and 60% were considered avoidable[17].

A study carried out in 3 hospitals from Rio de Janeiro[18] indicated 7.6% prevalence of adverse events, of which 66.7% were considered avoidable, that is, those that incur infringements of norms and standards, active failure or latent conditions that cause harms to the patients[19]. In another Brazilian study on the topic, conducted in 2000, the incidence reached 25.9% in a tertiary-level hospital, where 80.8% of these instances took place while the patients were hospitalized in the institution[20].

The World Health Organization (WHO) proposes that pharmacovigilance should aim at identifying, evaluating, understanding and preventing any drug-related adverse event, whether ADRs, quality deviations, ineffectiveness or therapeutic interactions, intoxications, medication errors or use for an indication not approved in the record[21–23].

The positive effect of a well-structured and active pharmacovigilance service within the hospital service, a place where complex pharmacotherapies are generally used, is undeniable, as ADEs can cause an increase in hospitalization time and in clinical complications, in addition to contributing to death, generating a social and financial impact that should not be disregarded[3,4,7,13,15,18,24,25].

The health system usually depends on Spontaneous Notifications (SNs) to learn about adverse reactions. In Brazil, we moved from Notivisa, which received notifications of incidents, Adverse Events (AEs) and Technical Complaints (TCs) to an exclusive electronic system for reporting adverse events related to the use of medications and vaccines, VigiMed, offered by the WHO itself as part of its International Medication Monitoring Program and which can be confidentially updated by health professionals and citizens[14,24,26,27].

In the hospital environment, SNs are of utmost importance to identify potential ADEs and ADRs. According to Fernanda Maciel Rebelo, former head of the General Management for Monitoring Products Subjected to Sanitary Surveillance (*Gerencia Geral de Monitoramento de Produtos Sujeitos à Vigilância Sanitária*, GGMON) of the National Health Surveillance Agency (*Agência Nacional de Vigilância Sanitária*, ANVISA), they contribute to assessing the risk/benefit ratio of a medication, its rational use and consequent improvement of the therapeutic practice[26]. The SN system works especially well with the engagement of the entire health team, with emphasis on the crucial role of the Nursing team, as they spend a greater amount of time caring for patients[7].

A program implemented in Brazil in 2001 that sought to improve the SN practice was the Sentinel Hospital Project (*Projeto Hospital Sentinela*, PHS) and has 208 notifying hospitals across the country, including all federal states, which are classified as large-sized and of high complexity, primarily public and charities, involved with teaching and training professionals in the area. The main goal is to generate good quality information about the products used, establish their risk-benefit ratio and improve surveillance of these materials, in addition to promoting better health services, mainly in the three major areas encompassed by the project (Pharmacovigilance, Technovigilance and Hemovigilance)[28].

However, SNs face some obstacles that can generate underreporting. We can mention the following: lack of knowledge of what ADRs are, how to identify them and their clinical and financial impact; fear of punishment and criticism; difficulties of how and what to effectively report, and in the adopted system itself, which may represent, especially in the absence of information, more documentation to be filled-in and bureaucracy[5,7]. It was shown that the fact that health professionals know about the pharmacovigilance service and about ADRs is related to better notification practices[5].

Even acting on the factors that generate underreporting in order to combat them, other reliable ways to generate these data are required[29]. In this premise, the use of trigger tools or trackers has spread, which can be considered data or information related to the patients that serve as a warning and which, in this case, can assist in the detection of potential ADRs and, in combination with SNs, create a more efficient system[4,11,30,32].

Triggers allow the pharmacovigilance service itself to conduct an active, intelligent and guided search through the computerized database and medical records, acting independently from SNs. There are groups of triggers already established in the literature, an example is the 19 Trigger tools recommended by the Institute for Healthcare Improvement (IHI) comprising medications, tests and decisions such as “abrupt medication discontinuations” and “transfer to a more complex care level”[32].

Thus, an efficient system for detecting possible harms caused by medications, such as ADRs, is required[30]. The current study sought to identify the profile of adverse drug reactions in a public university and tertiary-level hospital after the inclusion of Active Search (AS), through triggers, in the pharmacovigilance service, as well as their efficiency through the Positive Predictive Value (PPV); in addition to verifying the profile of spontaneous notifications by the hospital’s wards and professionals.

Methods

This is an observational, descriptive and exploratory study, carried out by consulting the database (Excel®) of the Pharmacovigilance Service and the Quality and Patient Safety Sector (SQSP) of the University Hospital of Western Paraná (*Hospital Universitário do Oeste do Paraná*, HUOP) between July and December 2018, when the AS service was effectively established, combined with the existing SN system. Currently, filling-in of the database is part of the everyday pharmacovigilance routine, allowing traceability of the events, future consultation and data analysis.

SNs can be made by the hospital users by filling-in a standardized form for the "Notification of an Incident/Adverse Event". In this form, data are filled in in order to identify the notifying sector and the event, such as date, patient, place and whether or not there was harm to the patient. In addition to these traceability data, fields are also filled in that allow investigating the case to assist in determining the ADR or not, such as name of the product, manufacturer, validity and batch, description of the event and actions at the time of occurrence. Subsequently, this form is used by the quality sector with a description of the investigation of the situation, as well as the preventive and corrective actions carried out. If applicable, the ANVISA notification number, risk classification and degree of the harm are noted down. Another specific form ("Investigation Form for Suspected Adverse Drug Reactions [ADRs]") is filled out by the pharmacovigilance team with data specific to the pharmaceutical investigation of the ADR, such as the medications used during the reaction period, laboratory evidence and the Naranjo causality algorithm[31].

The active search consists of a daily analysis of the triggers by means of the TASY® computerized system and visits to the hospital wards by residents in Hospital Pharmacy working in the sector, pharmacists and interns, where suspicion of an ADR is verified with the Nursing team.

As for sensitivity, the triggers were analyzed separately according to PPV, calculated as the number of times the trigger detected an ADE, divided by the number of times it was identified or notified[2], either by AS or by SN.

The key terms currently used by Pharmacovigilance in the active search are the following: RM1 – antiallergics (dexchlorpheniramine, loratadine and promethazine); RM2 – Anticoagulant antidotes (phytomenadione and protamine); RM5 – Opioid antagonist (naloxone); RM6 – Antidiarrheal (loperamide); RE9 – Positive test for *Clostridium difficile*; RME7 - Use of Ion exchange resin (calcium polystyrenesulfonate/ Sorcal); RME17 – Use of digoxin + clinic (arrhythmia, bradycardia, nausea, vomiting, anorexia, visual changes – suggestive of digitalis intoxications) and RP19 – Skin Rash/ Cutaneous eruptions.

The "Others" category in Table 2 corresponds to specific signs and symptoms reported by the Nursing team, which are extremely specific to be considered as possible triggers in the pharmacovigilance service; in addition, they would depend on the search for specific words and signs in the medical records. Within this category we have akathisia, headache after spinal anesthesia, extrapyramidal syndrome, fever, malaise and nausea/vomiting.

It is indispensable to note the difference between active search and spontaneous notification in our service. If we consider only the RM1 trigger by active search, for example, what the service does is evaluate all the medication outputs corresponding to the pharmacy trigger on a daily basis and, from there, assess whether any of them was dispensed for a patient with ADR signs and symptoms. In this way, we were able to screen all the hospital wards for a few suspicious patients per day. It is for this reason that the AS notification numbers are high. In turn, the starting point for spontaneous notifications is the detection of a potential ADR, especially by the Nursing team but also by the patient, companions and the Medical team. Consequently, even if SNs appear in lower numbers, they are generally more predictive than AS.

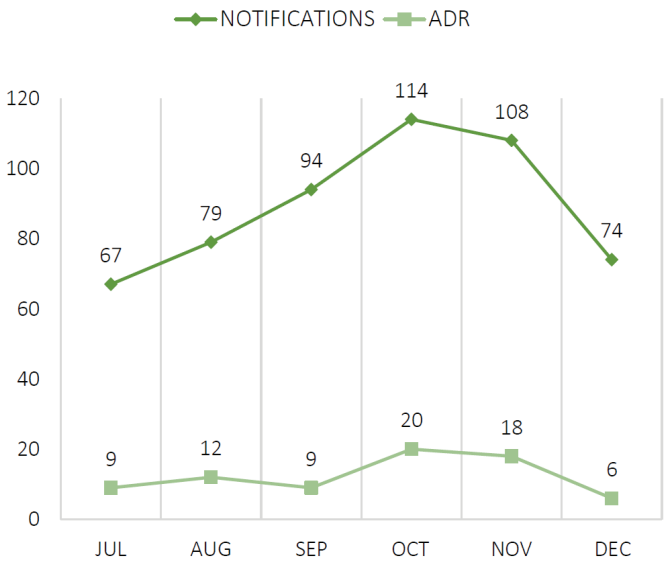
The type of notification was divided into AS, performed by the team of pharmacists from the pharmacovigilance service, and the SNs were classified according to the notifying professional in "Nursing Team", "Medical Team", "Clinical Pharmacy", "Patient" or "Companion".

The data were incorporated into a Microsoft Office Excel® spreadsheet, where descriptive statistical inferences of absolute and relative frequencies for the qualitative variables and graphical representations were developed. The paper was approved by the Research Ethics Committee of the State University of Western Paraná under opinion No. 3,552,940.

Results

In the second half of 2018, 540 notifications to the pharmacovigilance service were identified, of which 536 were related to adverse drug reactions, either by spontaneous notification or by active search. The other notifications comprised three adverse events to materials and one reaction that remained inconclusive. 74 of all 536 suspected ADRs were confirmed (14%). October was the month with the highest number of ADR notifications (Figure 1).

Chart 1. Total number of notifications and adverse reactions in the second semester of 2018 at HUOP



The reformulated service was establishing itself in the first months analyzed. In the graph we can see a slight variation from October to November, but an abrupt drop in December. This drop can be linked to the lower actual occurrence of ADRs in that month or to greater underreporting due to the vacation period and different routines of the professionals within the hospital, which favored the reduction in the numbers.

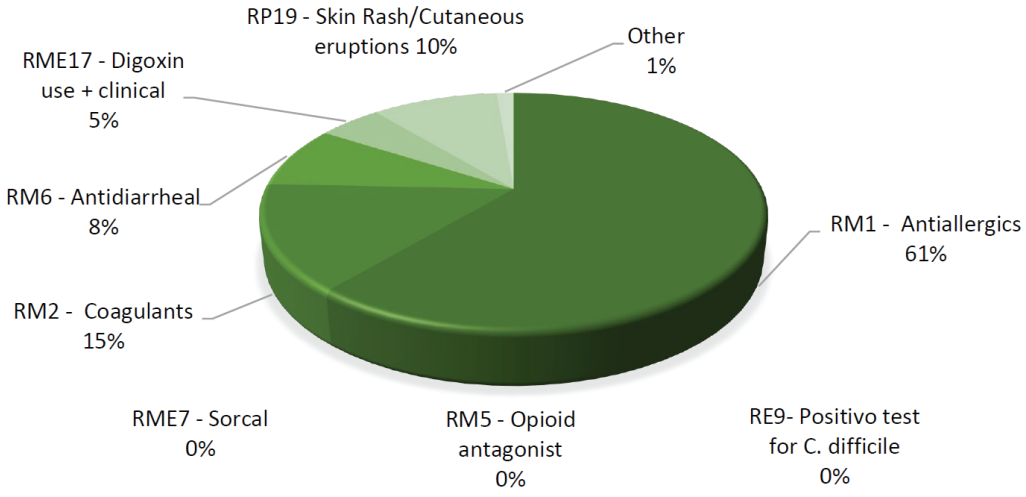
In Table 1 we can see the profile of notifications and ADRs by hospital ward. The Emergency Room (ER) was the ward with the highest number of notifications (215), mainly due to the use of triggers, but had only 10 confirmed reactions, 4 of which were not reported by AS, but by notifications from the Nursing team.

Table 1. Notification profile by hospital wards in quantity, notification type, and how many of these notifications turned into adverse reactions (ram).

Wards	Total ADR (%)	Total Notifications	Notifications type	Notifications/ADR
Ambulatory	0 (0)	4	Active Search	0/4
CC/CO	0 (0)	11	Active Search	0/11
CO-Hospitalization	0 (0)	4	Active Search	0/4
F2	9 (12,3)	73	Active Search	4/68
			Nursing Team	5/5
F3	9 (25,7)	35	Active Search	7/32
			Nursing Team	2/3
G1	10 (23,8)	42	Active Search	4/34
			Nursing Team	5/7
			Medical Team	1/1
G2	21 (39,6)	53	Active Search	8/33
			Nursing Team	13/18
			Clinical pharmacists	1/1
			Patient	1/1
G3	15 (31,9)	47	Active Search	2/25
			Nursing Team	13/20
			Medical Team	0/1
			Patient's caregiver	0/1
PS	10 (4,7)	215	Active Searchz	6/210
			Nursing Team	4/5
ICU	0 (0)	1	Active Search	0/1
General ICU	0 (0)	47	Active Search	0/47

With regard to the triggers, what was most found in our notifications was RM1 (antiallergics - dexchlorpheniramine, loratadine and promethazine), with 61% of all notifications. Then we have RM2, corresponding to anticoagulant antidotes (phytomenadione and protamine), with 15%. The third sign and symptom that most appeared during the notifications was rash and itching (RP19), with 10%, which are not part of the pharmacovigilance triggers and were identified almost exclusively by spontaneous notification. RE7 (Ion exchange resin/Sorcal), RE9 (Positive test for *C. difficile* in feces) and RME 5 (Naloxone) were either not notified or did not find any ADE during the period (Figure 2).

Chart 2. Contribution of each tracker to the total number of notifications received



The PPV values[11], which correspond to the number of confirmed ADRs among the suspected ones found by the trigger, can be seen in Table 2. An interesting fact can be observed: as it is not possible to search for specific words within one or several medical records in the TASY® electronic system, the RP19 trigger cannot be used within our AS since, as this service comprises all hospital wards, reading all the medical charts on a daily basis is inconceivable. Consequently, most of the times when rash or cutaneous eruptions were found in our notifications were via SNs, especially by the Nursing team. The PPV for this trigger was 73%, representing the most sensitive parameter among those analyzed.

The trigger that seeks to superimpose the data found by RP19 is RM1, on the premise that once the patient has skin reactions, antiallergics will be prescribed to relieve these symptoms. However, although onset of the reaction logically occurs before prescribing the antiallergic, there was no spontaneous notification of these cases, and the patients only arrived at the pharmacovigilance service due to AS. Despite the high number of reports, only 30 of the 327 RM1 notifications were considered ADRs, which lowered the trigger's PPV to 9%. Although low, this value is considered satisfactory, as it was the second highest source (41%) of the ADRs found in the service.

Thus, it was evaluated that morphine (17%) and dipyrone (10%) were the medications that most appeared as possible causes of ADRs during the period; followed by vancomycin and cefazolin, both with 6%, and by tramadol with 5%.

The most frequent symptoms in morphine-associated reactions were pruritus (70%) of varying intensity, erythema and rash (17%), nausea/vomiting (12%): malaise, "chest discomfort", hypotension and sweating were also observed. All reported symptoms are in the package insert with unknown frequency, and the reactions therein reported as very common (>10%) are as follows: difficulty breathing, shortness of breath or slow and shallow breathing, and pale or blue lips, nails or skin[33]. In turn, the symptoms related to dipyrone were also rash/erythema (78%) and pruritus (57%), difficulty breathing, intense sweating, tingling, emesis and syncope; erythematous macules were also reported.

Table 2. Contribution of trackers to the number of notifications and adverse reactions, and Positive Predictive Value (PPV) in the second semester of 2018.

Tracker	Number of Notifications (%)	Number of ADR's	% of Total ADRs	PPV	PPV (%)
RM1 - Antiallergics	327 (61)	30	41	0,092	9,174
RM2 - Coagulants	78 (14,6)	2	3	0,026	2,564
RM5 - Opioid Antagonist	1(<1)	0	0,0	0,000	0,000
RM6 - Antidiarrheal	45 (8,4)	0	0,0	0,000	0,000
RE9 - Positive C. difficile Test	4 (<1)	0	0,0	0,000	0,000
RME7 - Sorcal	0 (0)	0	0,0	0,000	0,000
RME17 - Digoxin Use + Clinical	26 (4,9)	0	0,0	0,000	0,000
RP19 - Skin Rash/Cutaneous Eruptions	52 (9,7)	38	51	0,731	73,077
Others	7 (1,3)	5	7	0,714	71,429

Discussion

It is important to point out that an ADR cannot always be suspected or attributed to a specific medication, as the patient oftentimes uses more than one drug that can cause the ADR in question. Thus, even if one of them is the most likely to cause it, either by statistics or time causality, it cannot be ignored that the other medications are at least contributing to onset or maintenance of the symptom(s) presented. This reflects in the profile of the medications that cause reactions, as we can have one or several suspected drugs in a single notification.

Another paper published by the Pharmacovigilance Service of the hospital in question, in 2015, observed the notification of 58 suspected ADR cases between January 2012 and December 2013[8]. With this comparison we can observe the significant improvement in the notification system. If we only consider the spontaneous notifications, we would only have 63 reports and 45 confirmed ADRs, and if we add the active search, we were able to screen 74 cases of adverse reactions in the hospital in 25% of the previously studied period.

These data do not show worsening of the service or the appearance of rampant adverse reactions, but rather an improvement in the notification system, perhaps due to a more active pharmacovigilance service in recent years and/or greater knowledge of the reporting professionals, helping to reduce underreporting in our hospital. It is established that teams with greater preparation, awareness of possible problems and the importance of the service, report more[5,34].

A study carried out in a maternal and child hospital from the state of Pará found 621 notifications related to the pharmacovigilance service in a two-year period, in which the number of SNs reached 25.88% of all notifications in 2015, but dropped to 5.04% in 2016. In this way, we can see that the concern to spread the importance of this tool is essential, even when notifications reach a favorable number[6].

During the period under study, only 4% of the notifications were via SNs. However, we must take into account that, even so, SNs are more assertive in identifying ADRs than AS, represent the classic method of identifying these problems and are extremely relevant for effective patient safety[4,7,11,12,22,26,30,35].

Allied to this, using triggers significantly assisted in improving the service. If we consider the results herein presented, 29 ADRs would not have been reported if they had not been found via AS.

In this period, 2 pharmacovigilance triggers stood out, RM1 (anti-allergy) and RM2 (anticoagulant antidotes), with PVVs of 9% and 3%, respectively. A study with ADR triggers in pediatric patients[11] showed higher predictability of antiallergics (dexchlorpheniramine, loratadine and promethazine) with a 38% PPV index. The use of anticoagulant antidotes (protamine and Vitamin K) as triggers was also reported as an important ADR trigger with a relative yield of 12.5% in a general hospital[4] and 30.4% in another one specialized in Cardiology[29].

The very low presence of other professionals in the SNs is worrying, especially the lack of notifications by professionals closely linked to the medications and trained to identify potential ADRs. If we also consider that the PNSP states that the reporting practice is desirable for health professionals and assists in patient safety, a hospital linked to the university plays a crucial role, as it can stimulate this culture both in an educational and professional environment, training professionals even more qualified and focused on patient safety.

Regarding the medications, we can see in the literature that analgesics and antibiotics are among the most involved in ADRs[4,33]. In this case, morphine, an opioid analgesic and part of the Potentially Dangerous Medications (PDMs), was suspected in 17% of the ADRs during the period, whereas in the previous study carried out here, for example, the drug most involved in reactions was vancomycin with 8.7%, which today ranks 3rd with 6%[8].

It is important to state that the change in the profile might be due both to greater awareness of the risk imposed by the antimicrobial class and professional caution, and to the suggestion that the 6-month period was not enough for us to have a complete view of the profile of medications that caused the reaction.

A study conducted in Brazil showed that PDM control and the prevention of adverse events are less used measures for patient safety[5]. In the current study, we were able to notice that, in addition to the medication most involved with the reactions being a PDM, we have an ADR and SN tracking network, which, although improved in recent years, still has a lot to grow.

It is fundamental to note that the half-yearly analysis was a limitation of our study and that, perhaps, an analysis in 1 or 2 years would allow more robust data collection for analysis. In addition to that, a longer period of time would allow for an actual evaluation of the triggers, allowing to evaluate the inclusion or exclusion of some of them. The annual analysis would still allow, for example, evaluating in which months we have fewer notifications, making it possible to act more intensely with training with the hospital staff in these periods.

Conclusion

The results also show that using triggers and the active search make it possible to identify and act on ADRs when SNs fail, improving safety and effectiveness of the service, in addition to generating data that evaluate the management and measures taken by the team to reduce the number of events. The most effective triggers in our service were for antiallergics and anticoagulant antidotes, and we noticed that, although the appearance of rash and skin eruptions is highly predictive of the onset of ADRs, the absence of a word-specific search tool in medical records precludes their use as a trigger. A software update that allows this action would significantly help in the service.

It is concluded that spontaneous notification continues to be the most assertive way of gaining knowledge about ADRs, with a much higher PVV value than AS and that hey notably carried out by the Nursing team. In addition to that, SNs play an important role in preventing problems arising from the reactions, appearing before prescribing antidotes or symptomatic drugs, that is, before we can track them by active search, which eases early decision-making.

Finally, it is important to emphasize that adverse drug reactions should be considered events that can be monitored and followed-up, in order to discover how and why they occur, enabling measures that minimize the risk of an adverse events or that allow the team to take care of the most frequent reactions, seeking excellence in service and patient safety. Actions that seek to contribute knowledge about ADRs and the pharmacovigilance service to all hospital professionals increase visibility of the sector and encourage the collaboration of other professionals, as well as taking this knowledge to the different health courses within the university where the hospital is linked can assist in conferring greater visibility to the theme.

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Collaborators

Candido, KL: data collection; interpretation of the study; writing of the article. Groll, SV: relevant critical review of the intellectual content and structural organization; data analysis and interpretation; approval of the final version. Caldeira, LF and Sanches, AC: relevant review of the intellectual content and approval of the final version.

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Declaration of conflict of interests

The authors declare that there is no conflict of interest in relation to this article.

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