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Trigger tools and adverse drug events at a large general hospital in São Paulo/SP, Brazil

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ABSTRACT

OBJECTIVE

The aim of this study was to identify the main adverse drug events (ADEs), and its severity in patients of a large public hospital in São Paulo city using trigger tools and to evaluate its performance.

METHODS

This is a prospective study with adults hospitalized in the units of Surgical Center, Medical Clinic, Intensive Care Unit, Adult Emergency Room and Obstetrics, during a period of two months (May to June 2021). Clinical records were reviewed using eleven different trigger tools selected from the Global Trigger Tools of the Institute of Healthcare and adapted to the Hospital reality. Only trigger medications were used. The active search was performed using Hospital's computerized system and when the prescription of a trigger drug was identified, the pharmacist analyzed the patient's medical record.

RESULTS

There were identified 183 patients with trigger medication prescription. Of these 14,7% presented adverse drug event and were admitted at Medical Clinic (48%). The ADEs identified were pruritus/ skin rash, coumarin poisoning/bleeding, anaphylaxis, excessive sedation, and headache. Considering the severity, 93,6% were moderate and 3,7% severe. The drugs with highest incidence of ADEs were morphine and warfarin. The best performing trigger tools were protamine and flumazenil, and the lowest performing were loperamide and promethazine.

CONCLUSIONS

Trigger tools can be used to identify adverse drug reactions. Its use in hospitals improve patients' medication safety.

DESCRIPTORS

Trigger tools, Medication safety, Adverse drug events.

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INTRODUCTION

Drugs are the main therapeutic approach for the recovery and maintenance of people health conditions. Brazil approved the National Drugs Policy (Politica nacional de medicamentos) by ordinance 3916/1998. The aim is to ensure safety, efficacy, and quality of pharmaceutical products, as well as to promote the rational use and the access to essential medicines[1].

The World Health Organization (WHO) defines pharmacovigilance as the science and activities related to the detection, assessment, understanding and prevention of adverse effects or any drug-related problems. Its main objective is to ensure patient safety and the rational use of the same2.

Pharmacovigilance system is an essential part of drug regulation policies and pharmacogovernance, which is understood as the government structures, public policy, regulations, norms, and institutional authority managed in a way that promotes the interests of society in relation to patients' safety regarding protection from Adverse Drug Events (ADEs) [3,4].

Adverse drug events (ADEs) are any type of injury resulting from the use of drug therapy. Adverse drug events can be of two types: Medication Errors and Adverse Drug Reactions[5].

Adverse drug reactions (ADRs) are any harmful or unwanted effect that occurs after administration of doses of drugs normally used in humans for prophylaxis, diagnosis, or therapy of disease for the modification of physiologic function. Adverse drug reaction is a harm directly caused by the drug at normal doses, during normal use[2].

Medication errors (ME) are preventable adverse drug events that can lead to inappropriate drug use or harm to the patient. Drug-related errors occur at all stages, prescription, transcribing, dispensing, administration, adherence or monitoring of drugs[2,6].

There are several factors that can result in adverse drug events, prescription errors, incorrect dose intake, missed drug dose, unspecified route of administration, error in administration time and others. Many important adverse drug events are unexpected, and no single methodological approach can successfully identify the problem entirely. ADEs are related to disabilities, morbidities, and patients prolonged hospital stay[7,8].

Current system to identify ADEs is voluntary reporting. In this system healthcare professionals fill out an adverse drug event notification form provided by the national regulatory authority[7,8]. This system fail to record all adverse reactions mainly because of unreported cases. It is estimated that this method detects only one in every twenty ADEs[8].

Healthcare institutions have difficulties to identify and monitor ADEs, voluntary reporting and chart reviews are not efficient. Thus, due to low notification, other strategies were created to identify, quantify, and monitor ADEs. One of these alternative methods is active search for notifications. In this system, medical records are reviewed and interviews with patients and/or prescribers are carried out, being widely used in some programs involving hospitalized patients[7].

Researchers from the Institute of Healthcare Improvement (IHI) developed a method of reviewing medical records, the use of Trigger Tools. These triggers can be laboratory tests, signs or symptoms and medications. They created a basic list of triggers called "Global Trigger Tools" with 53 items divided into six categories: care module, surgical module, intensive care module, medication module, perinatal module, and emergency department module. The presence of a trigger could signify the occurrence of an adverse drug event. In a second step the records are reviewed to determine whether an adverse drug event occurred or not. Today trigger tools are in widespread use in quality improvement and pharmacosurveillance[8,9,10].

The aim of this study was to identify the main adverse drug events (ADEs) and its severity using trigger tools in patients of a large Public Hospital in São Paulo, Brazil. The trigger tools causality and performance were also evaluated. Active search of ADEs should be present in clinical practice. Careful and responsible monitoring of medication use tends to make patient care, recovery and especially safety effective.

METHODS

This is a prospective observational study conducted in a large General Hospital in the South region of São Paulo, Brazil. Patients 18 years or older interned at Surgical center, Medical Clinic, Intensive care unit, Emergency and Obstetrics who have been prescribed a trigger tool during the period from May 2021 to June 2021 were included in the study.

Data collection procedures proceeded after approval of Universidade Santo Amaro research ethics committee (014079/2021), and in Hospital Geral do Grajaú research ethics committee (4,682,027).

Trigger tools were selected from the "Global Trigger Tools" of the Institute of Healthcare Improvement[10] and adapted to the hospital reality. Only drug triggers were considered, resulting in eleven trigger tools.

The following medications were used as trigger tools: antihistamines and anti-allergy medications that could indicate drug related allergic reactions: desloratadine, dexchlorpheniramine, diphenhydramine, hydroxyzine, hydrocortisone and promethazine, drugs that can reverse the action of other drugs like phytomenadione used to reverse the action of oral anticoagulants as warfarin, naloxone used to reverse the action of opioids, flumazenil used to reverse the action of benzodiazepines, antidiarrheics like loperamide that could indicate diarrhea associated to medication use and protamine that reacts to the use of anticoagulants[11, 12].

The active search of trigger tools in prescriptions was performed using Hospital's computerized system and when the prescription of a trigger drug was identified, the pharmacist analyzed the patient's medical record to justify the prescription of the trigger drug. When the justification was not found, the possible adverse event to the drug was recorded and the occurrence of an adverse drug event was verified.

Once the occurrence of adverse drug event was identified, it was characterized, and classified by severity using the Pan American Health Organization classification[14].

The causality was assessed using the Naranjo scale, which allows the identification of the causal relationship between drugs and Adverse drugs reactions[12,13]. Trigger drugs performance was evaluated according to the proposal by Giordani[8].

RESULTS

The active search resulted in 183 medical records with trigger tool prescription mainly patients between 60 and 65 years old, 61.2% male and 38.8% female. From these records 27 (14,75%) presented adverse drug events, corresponding to patients under 50 years old, 70.37% female and 29.63% male. (Table 1).

Table 1. Characteristics of included patients who were prescribed with a trigger tool.

Characteristics	All patients prescribed with a trigger tool (n = 183)	Patients without evidence of ADEs (n = 156)	Patients with evidence of ADEs (n = 27)
Age (years)			
18 - 50	66 (36.06%)	54 (34.62%)	12 (44.45%)
51 - 59	20 (10.93%)	17 (10.9%)	3 (11.12%)
60 - 75	68 (37.16%)	63 (40.38%)	5 (18.52%)
76 - 95	29 (15.85%)	22 (14.10%)	7 (25.93%)
Total	183 (100%)	156 (100%)	27 (100%)
Gender			
Female	71 (38.80%)	52 (33.34%)	19 (70.37%)
Male	112 (61.20%)	104 (66.67%)	8 (29.63%)
Total	183	156	27

The most prescribed trigger drugs were hydrocortisone (45.53%) and promethazine (28.45%), and the less prescribed were protamine and flumazenil with only one prescription. Evaluating performance, the best trigger tools were promethazine and flumazenil with relative yield of 100% and naloxone 62.5%. The trigger tools with worst performance were loperamide (0%), promethazine (7.5%), diphenhydramine (10.2%) and hydrocortisone (10.88%) as presented in table 2.

Table 2. Trigger tools for active search. Its frequency of prescription and adverse drug events.

Group	Trigger drug	Frequency of trigger drug prescription (n = 232)	Incidence of adverse drug events (n= 36)	Performance Relative Yield*
Anti-allergy	Desloratadine	6 (2.59%)	3 (8.34%)	50.00%
	Dexchlorpheniramine	4 (1.72%	1 (2.78%)	23.80%
	Diphenydramine	9 (3.88%)	1 (2.78%)	10.20%
	Hydroxyzine	13 (5.6%)	4 (11.12%)	29.57%
	Hydrocortisone	101 (43,53%)	11 (30.56%)	10.88%
	Promethazine	66 (28.45%)	5 (13.89%)	7.50%
	Total	199 (85.76%)	25 (69.45%)	
Bleeding disorders	Phytomenadione	23 (9.91%)	7 (19.45%)	30.40%
	Protamine	1 (0.43%)	1 (2.78%)	100.00%
	Total	24 (10.34%	8 (22.23%)	
Antidiarrheic	Loperamide	5 (2.16%)	0 (0%)	0.00%
Opioid antagonist	Naloxone	3 (1.30%	2 (5.56%)	62.50%
Benzodiazepine antagonist	Flumazenil	1 (0.43%	1 (2.78%)	100.00%

* Performance of trigger tools calculated as relative yield.

The impatient unit with more adverse drug event identified was medical clinic with 48.15% of ADEs, Surgical center presented 22.22%, Obstetrics 18.52%, Emergency, 7.41% and Intensive Care Unit 3.7% (Table 3).

Table 3. Frequency of adverse drug events identified using trigger tools in inpatients units.

Inpatient Unit	Patients with Adverse drug events (n = 27)
Medical Clinic	13 (48.15%)
Surgical center	06 (22.22%)
Obstetric	05 (18.52%)
Emergency	02 (7.41%)
Intensive care unit	01 (3.70%)
TOTAL	27

Adverse Drug Events identified in this study were pruritus/skin rash (37.4%), coumarin poisoning/bleeding (29.63%), excessive sedation (14.81%), headache (11.11%) and anaphylaxis (7.41%). Regarding severity, 96.3% (26) were considered moderate and 3.7% (1) were considered severe (Table 4).

Medications identified as the probable cause of these adverse drug reactions in the 27 patients are Morphine (40.74%), Warfarin (18.52%), Ceftriaxone (11.12%), Fentanyl (7.41%), Unfractioned heparin (3.70%), Amiodarone 3.70%, Rivaroxaban 3.70%, Enoxaparin 3.70%, Clonazepam (3.70%) and Losartan (3.70%) (Table 4).

Naranjo scale indicates the probability of an adverse drug event. Applying this scale main of the ADEs were probable (59.26%) and 40.74% were definitive as presented in table 4. There were not reactions classified as possible or fatal.

Table 4. Characteristics of 27 adverse drug events identified using trigger tools

Characteristics	Adverse drug event
Adverse drug events identified	(%)
pruritus/skin rash	37.4%
coumarin poisoning/bleeding	29.63%
excessive sedation	14.81%
Headache	11.11%
and anaphylaxis	7.41%
ADEs culprit medications	
Morphine	40.74%
Warfarin	18.52%
Ceftriaxone	11.12%
Fentanyl	7.41%
Unfractioned heparin	3.70%
Amiodarone	3.70%
Rivaroxaban	3.70%
Enoxaparin	3.70%
Clonazepam	3.70%
Losartan	3.70%
Naranjo scale of causality	
Definitive	40.74%
Probable	59.26%
Possible	0%
Doubtful	0%
Severity	
Severe	3.70%
Moderate	96.3%
Mild	0%

DISCUSSION

The use of trigger tools identified 27 patients that presented adverse drug reactions corresponding to 14,75% of patients with prescription of trigger medications. Most of these patients were women under 50 years old as can be verified in table 1. This profile with more ADEs in female gender coincides with other studies[8,15,16]. Varallo's study[17] however, presented more men with ADEs (55.9%). Some authors affirm that elderly is more vulnerable to adverse events. Salazar[11], however, establishes that the greatest vulnerability could be related to the amount of medication in the treatment and not the age.

A trigger drug prescription does not mean necessarily the presence of an adverse drug event[9,12]. In this study the most prescribed trigger drug was Hydrocortisone with 45,53% of total trigger drugs prescriptions, if we consider all the 27 ADEs it was responsible for 30,56% ADEs, but if we consider performance, it was of only 10.89% relative yield. Promethazine corresponded to 28.45% of total prescriptions with a performance of 7.57% relative yield and phytomenadione was present in only 9.91% of total prescriptions but presented a performance of 30.43% rela- tive yield (table 2). Research in Rio de Janeiro's large hospital[19] presented similar results.

As we can see in table 2, Phytomenadione was less prescribed than hydrocortisone but had a better performance, this drug was prescribed to 23 patients resulting in the identification of 7 ADEs (30.43% relative yield). Medications such as protamine and flumazenil were prescribed only once, and this single prescription was related to an adverse drug event with a performance of 100% relative yield. The low performance of Hydrocortisone and promethazine as trigger tools could be explained because they are used in the hospital for other purposes such as treatment of shock and agitation respectively. Trigger drugs like protamine (bleeding disorders), and flumazenil (benzodiazepine antagonist) are used mainly as antidote which increases its performance as trigger tools.

The large number of adverse drug events were in Medical

Clinic (48.15%) and Intensive Care Unit had the lowest incidence with only one adverse drug event (3.70%). Salazar research resulted in 37.9% ADEs in Medical Clinic. Francisconi et.al.[15] realized a study in Paraná's hospital resulting in 48% of adverse drug events in Intensive care unit and 6% in emergency. This discrepancy in the results can be explained by the fact that the Clinical Medical patients stay for a longer time in the hospital if compared to Intensive care unit[11].

Adverse drug events severity is not easy to compare because of the different realities, different hospital units, in Salazar work[11] most reactions were classified as moderate (89.1%), in a Helsinky's hospital[16] 83.1% were severe. In this study most of the ADEs were classified as moderate (96.3%).

The most frequent adverse drug events were cutaneous pruritus/rush (37.04%) and bleeding (29.63%) similar results were obtained in a teaching hospital in Jordan[21]. Cutaneous pruritus is a moderate adverse drug reaction, but it can affect the patient's quality of life. Despite its severity ADEs affect patient quality of life and security. Naranjo algorithm classified 59,26% of ADEs as probable.

Finally, no spontaneous notification was related for any health professional at the hospital to the pharmacovigilance. All the notification were realized through this active search.

CONCLUSION

The application of active search using trigger tools permitted identify adverse drug events, their incidence and severity. It was evaluated the suspicious drugs responsible for the ADEs and the trigger tool performance. Flumazenil and Protamine were the trigger drugs with best performance and Loperamide had the worst performance, followed by Promethazine. Cutaneous rush and bleeding were the adverse drug events with more incidence. Trigger tools can be used to identify adverse drug reactions. Its use in hospitals improve patients' medication safety.

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