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ANALYSIS OF ADVERSE REACTIONS OF ORTHOPEDIC PATIENTS WHILE TAKING ANTICOAGULANTS: Perspective on the management of quality and safety in healthcare

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ABSTRACT

This study addresses the adverse reactions associated with the use of anticoagulants occurring in an orthopedic hospital in Rio de Janeiro. This is an observational descriptive series of case studies. The data from 20 adult patients were analyzed who have adverse drug reaction (ADR) in the year 2012. The prevalence of adverse reactions was 10%. Regarding the causality of ADR and the use of anticoagulants, 50% were considered possible, regarding the severity, 62.16% were classified as moderate and, in terms of predictability, 100% could have been avoided. It is believed that health professionals are not trained to detect ADRs and thereby minimize risks/damages to patients. Healthcare institutions must invest in management strategies for quality of healthcare and patient safety as a way of minimizing inherent risks in drug therapy, therefore, decreasing expenses and hospital providing a safer and more economical hospital practice.

Keywords: *Healthcare; anticoagulants; adverse reactions; quality; safety.*

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1. INTRODUCTION

Pharmacovigilance is one of the areas where the national health surveillance Agency (ANVISA) provides for carrying out activities relating to the identification, assessment, understanding and prevention of adverse events or any possible problem related to medicines, according to Brasil (2011).

In Brazil, the field of pharmacovigilance was structured in the 70's as one of the pillars in the quality of healthcare. Since then, studies have been useful for the better understanding of the use of medicines. According to Menezes (2010), it has a preventive nature in evaluating the safety of the treatments and the risks related to exposure to them, detecting adverse reactions often not revealed in the pre marketing clinical trials, and probably by reducing morbidity and mortality from drug use.

The hospital where the study is a collaborator of the Sentinel Network and owner of maximum quality certification for hospitals and medical clinics given by the Joint Commission International (JCI),since 2006. It has a service called Risk Management (GRISC), which is responsible for the areas of pharmacovigilance, technical surveillance, hemo-surveillance and sanitizing surveillance, conducting ongoing activities for the evaluation of healthcare technologies, hospital quality, patient safety and rational use of medicines.

Santos (2010), states that drugs have the potential to solve various health problems, increasing life expectancy, eradicating certain diseases and minimizing the suffering of individuals. However, they can also contribute to increasing health costs if used inappropriately or without proper control and/or lead to the occurrence of adverse events, including adverse reactions to medications (ADRs).

ADRs are the sixth cause of death II, preceded by heart diseases, cancer, cerebrovascular accidents, respiratory illnesses and accidents (Tin, 2004). The study at the Helsinki University Central Hospital identified that the mortality rate related to the ADRs was 5% in the year 2010. Meta-analysis for the studies conducted in the hospital environment suggests that 106,000 deaths occurred due to ADR in 1994, representing 4.6% of deaths from all causes. The ADRs are responsible for 0.15% of the causes of death in British hospitals and occupying 4% of the hospital bed capacity (Phirmohamed, 2004).

At the institution where this study took place in 2012 it was identified through the spontaneous reports and by monitoring patients a total of 364 events related to medication use, ADRs accounting for more than half (51%) .

Adverse Drug Reaction is a harmful, undesirable or unintentional effect, which is present after drug administration at doses normally used in man for the prophylaxis, diagnosis or treatment of an illness. Thus, adverse reactions are not considered to drugs that appear after higher doses than usual (accidental or intentional), as affirmed by the National Coordinating Council for Medication Error Reporting and Prevention (2001).

ADRs cause increased hospital expenses, because they represent additional costs as a result of specific treatments or research and a prolonged hospital stay. The study showed that the ADRs were associated with an increase in cost of $ 2,200 per hospitalization (Classen, 1997). In developed countries, 35% of hospitalized patients with ADRs (Ramesh, 2003), which constitute a healthcare services, increasing the length of stay in 2 to 4 days and costs (Heit, 2002). The economic impact is directly linked to the severity of the ADRs, and may vary from U$ 0.06 to U$ 144.80.

Whereas drug therapy with anticoagulants (ATG) is used as a form for the treatment and prophylaxis in orthopedic clients, identification of ADRs associated with the use of this drug class is highlighted in the pursuit of safety and quality of healthcare. Thus, the objectives of this study were to characterize the profile of patients submitted to treatment with anticoagulants who presented ADR, verifying the prevalence of ADR associated with the use of anticoagulants and analyze the ADRs associated with the use of anticoagulants, during the year of 2012, in orthopedic patients.

2. METHODOLOGY

This is a descriptive observational, prospective case study with a quantitative approach (Pereira, 1995).

This survey was conducted in a national reference hospital in Traumatology and orthopedics, and public education, consisting of 299 beds, located in the municipality of Rio de Janeiro. In this institution, the pharmacovigilance team performs active monitoring of patients about the ADRs and examines notifications of events associated with the medicines.

There were 20 patients that participated in the study who showed a sign/symptom and/or alteration of laboratory tests compatible with ADRs to ATG in the year 2012. For the identification of these patients used the database of the pharmacovigilance service of the institution. It is important to remember that these are data from spontaneous or active monitoring notifications.

Data collection was performed using previously developed instrument called "Schedule of patients who underwent therapy with ATG and presented ADRs". These sheets were supplied through information contained in a spreadsheet controlled by the institution GRISC, post signs and symptoms of the study subjects were considered as ADRs.

A descriptive analysis was carried out by constructing, quantitative variables, tables with averages, medians, standard deviations, minimum and maximum values, and for the qualitative variables, tables with frequency distributions and percentages. The information collected was organized into elaborate database in Microsoft Excel version XP ®.

It is important to emphasize here that the most commonly used Algorithm for determining causality of a ADR is the Naranjo algorithm et al. (1981), internationally validated and composed of ten questions, whose answers are objective, with two options (Yes or no), and aims to seek information about the ADRs. For each response, are awarded points, which, through the sum *scores*, it becomes possible to classify the ADRs in probability categories: defined, likely, possible, or doubtful.

The ADRs can be classified into preventable or not, according to the criteria established by Schumock and Tohornton (1992). An ADR is considered predictable before an option to reply "no" to one or more of the questions listed in specific instrument validated by the authors.

In addition, ADRs can be classified as to their severity, according to criteria established by the World Health Organization (2002) in: Light-reaction of small clinical importance and of short duration, and may require treatment, not substantially affecting the patient's life; Moderate – reaction changes the usual activities of the patient, resulting in temporary incapacity without sequelae, causing lack to work or to school and may require attendance in health services; Serious-reaction that threatens directly the patient's life causes hospitalization and can cause permanent sequelae; Lethal - reaction resulting in death.

The exploratory analysis of data was done by means of descriptive statistics, with calculations of measures of position (average, median) and variability (standard deviation).

3. PRESENTATION OF RESULTS AND DISCUSSION

The study was characterized as where prevalence was observed in the following points:

-The prevalence of ADRs associated with the use for the ATG front of all drug adverse events reported or monitored by GRISC in 2012 was 5%;

- However, the prevalence of ADRs associated with the use for the ATG given all of the reported ADRs or monitored by GRISC in 2012 was 10%.

3.1 Client characteristics

According to table 1, 60% of patients who presented the ADR in the year 2012 ATG were female while 40% were male. 50% belonged to the hip Specialized Care Center (SCC), 30% to the trauma SCC, 10% to the knee SCC, 5% to the spinal SCC and another 5% to the medical clinic.

Still according to table 1, 30% of the patients presented co-morbidities and 15% had allergies to medicine or some substance. 20% of patients have made use of more than 5 medicines during the same period that used the antithrombotic.

Studies have emphasized different prevalence of ADRs in hospitals, ranging between 2.2 and 23% (Bordet, 2001). Such reactions are responsible or have direct participation in 6.6% of hospitalizations and feature between the 4th and 6th biggest causes of mortality in the USA (Pffafenbach, 2002).

Most studies show that women are more susceptible to develop ADR due to factors such as differences in body weight, hormone levels, among others (Magellan, 2001). The data revealed in this study supports this assertion, since most patients who had ADR were female. It is believed that men do not seek so often health services and therefore usually not present a previous report of ADR as much as women present.

Polypharmacy is using five or more medications simultaneously. This practice has increased significantly in recent years and began to configure a problem regarding safety related to the use of drugs. Chronic diseases, signs, and symptoms arising from the aging, stand out as the main elements. Polypharmacy is associated with increased risk and the severity of the ADR. The risk of a patient presenting ADR when subjected to polypharmacy increases three to four times (Battes, 1999).

Patients with clinical conditions associated with higher risk of ADR. There are specific clinical situations, such as the acquired immunodeficiency syndrome, which increase the incidence of ADRs. However, this relationship for the comorbidity and ADRs was not observed in this study.

It is known that patients who have ADRs history are more likely to present them when undergoing medical treatment. However, in this study, the patients did not have this relationship from previous reports for the allergy and ADR to ATG (Menon, 2005).

The prophylaxis and treatment protocol for Deep Vein Thrombosis (DVT) and Pulmonary Embolism thrombus (PET) of the institution investigated classified as very high risk, those patients with multiple trauma, especially of the lower limbs, spinal trauma, arthroplasty or hip fracture and knee arthroplasty. The institutional protocol also States that DVT can occur in up to 50% of total hip arthroplasties and by up to 70% of knee replacements if not carried out in the chemoprophylactic standardization indicated. Considering the start of the low molecular weight heparin 12 hours before the surgical procedure or depending on the case, after 12h. Can range from 10 to 35 days after surgery (Brasil, 2012).

IT draws attention to the fact that 50% of patients who presented ADR were from hip SCCs. Seeking support in the literature, can be correlated to the fact that the hip surgeries are more frequent than of the spine, for example, and to be a postoperative complication of potential greater than the postoperative knee arthroplasty. Thus, the increase in the number of days of therapy may increase and cause, therefore, the increased likelihood of occurrence of an ADR (Sizínio, 2009).

Table 2 shows that the average age of the patients was 45.7 years (standard deviation = 15.88). The hospitalization period was on average of 28.9 days (standard deviation = 21.75) and the average time used anticoagulant was 31.05 days (standard deviation = 21.43).

The time use of DVT prophylaxis with institutional protocol is 10 to 35 days, depending on each specific case for the high-risk groups of developing the disease. Most of the patients are discharged from the hospital and continues to take the medication at home, which explains the average time that the antithrombotic used was greater than the average hospital stay (Brasil, 2012).

It is important to note that the average of 31.05 days of full use of the drug in the study, consistent with the institutional protocol of DVT prophylaxis. There are exceptions in the case of 7 patients who remained in the hospital for orthopedic complications and to prevent the occurrence of DVT, had more than 35 days of low molecular weight heparin, which is not recommended (Brasil, 2012).

An international reference on pharmaceuticals, says that for prophylaxis, the ideal is to achieve 40 mg of low molecular weight heparin, 1 time a day for 6 to 11 days, no more than14 days. Taking into consideration the information of Drugs (Drug Information Online, 2014) and the institutional protocol itself, it is observed that some patients were exposed to prolonged therapy, even though all were within the recommended dosages, i.e. 40 mg 1 time per day, subcutaneous tissue (Sizínio, 2009).

Of the 20 patients, 3 of them were undergoing DVT treatment in a longer delayed post-operative. The institutional protocol for DVT treatment, which consists of using oral anticoagulants, in the case of the place of study, warfarin (starting with 5 mg day and, subsequently, adjusting as INR of the patient for 3 months or more and can combine low weight heparin until 5 days) was followed correctly in relation to warfarin. On the other hand, 1 patient had association with low molecular weight heparin, at the dosage indicated, but for an extended period (29 days).

The study suggests DVT treatment with a dosage of 2 to 5 mg a day for the first two days and after, adjusting dosages with the INR or PTT results and using the medicine for a period of 3 to 12 months, always performing the laboratory examinations regularly (Sizínio, 2009).

3.2 Adverse reactions associated with the use of anticoagulants

The ADRs observed were divided by systems such as: gastrointestinal, skin changes, urinary changes, respiratory changes and investigations. In total 15 different types of ADRs were identified.

They had a higher nausea and vomiting expression with 20% incidence, peripheral edema with 20%, hematoma with 20%, and dark urine with 25% and epigastric pain with 15%. In a smaller number still emerged PTT and INR, melena (highly severe), ecchymosis, epistaxis, hematuria and anemia, each with 10% incidence and thrombocytopenia, elevation of TAP and oral bleeding with 5%.

According to the label of enoxaparin and warfarin in Drugs, most ADRs confirm this as possible to happen with continued therapy, however, vomiting, oral bleeding, epistaxis, dark urine, melena and changes of the TAP are not reported.

The labeling for Clexane® released by ANVISA is more restricted when compared with the drugs, however, presents some reactions not mentioned above, such as allergic manifestations and fever, also presented on the Marevan® label.

None of the labels indicated melena as an ADR, which suggests that there may have been an incongruity in control of laboratory tests and proper adjustment of dosages in two cases found in the study. One of them came in a patient who had prophylaxis with enoxaparin and the other with patient who was receiving DVT treatment with warfarin (Diogo, 2009).

When applying the Naranjo algorithm for determining the probability of causation, failed to qualify any ADR as defined. Most of the ADRs were classified as possible. It is important to remember that in Brazil it is recommended that after the completion of the questions and determining if, the reaction has definite or probable causality; such a reaction should have priority for immediate action as the ban of one or more lots, the dissemination of warnings and sending notifications to the National Health Surveillance Agency. That reaction defined as possible or doubtful, too, will need stimulus actions to obtain greater number of notifications, as disclosure, alerts in order to strengthen the hypothesis (Capucho, 2011).

From the 20 patients, 65% had more than one sign or symptom. The total of ADRs evaluated was 36. Of these, 21.6% had probable causality, 43.24% had possible causality and 35.13% were doubtful causality. Regarding the severity it is observed that 32.43% of ADRs were presented as mild (not require treatment or prolongation of hospital stay), 62.16% as moderate (requires prolonged treatment or hospitalization for at least 1 day or both) and 5.4% as severe (life-threatening or contributes to the patient's death, is permanently disabling, requires intensive medical care, or takes more than 14 days to recover).

It is important to note that 100% of ADRs were classified as predictable, i.e. preventable.

4. CONCLUSIONS

In this study, 50% of ADRs have a possible causal probability and 62.16%, moderate severity. The signs and symptoms that resurfaced were nausea and vomiting with 20% of incidence, peripheral edema with 20%, with 20% hematoma, darkened urine with 25% and epigastric pain with 15%, causing weakness and patient discomfort and, long-term, and may bring irreversible losses and increased costs with hospitalization.

It is worth mentioning that there are criteria of predictability of the ADRs, so that some conditions are controlled. Dosage, frequency and administration appropriate to age, weight and condition of the patient; therapeutic monitoring and other laboratory tests and interaction with other administered drugs. Based on these parameters, all the ADRs identified in the study were considered predictable.

The consequences of the use of medicines and clinical and economic impacts directly influence quality of care and safety of who uses them. Adverse Drug Reactions are a response to a drug that is harmful, unintentional and which occurs at doses used in humans. By occurring this way, it is difficult to intervene before their occurrence, however, the patient monitoring by the health care team is important for them to act minimizing the damage caused by the ADR.

By the surgical character of the hospital and the public patients being orthopedic and knowing that the institutional protocol standardizes the prophylaxis second risk of each client classification, is of fundamental importance adequate monitoring for the possible signs / symptoms of an ADR by the healthcare team.

It should be considered that many ADRs are not identified as an adverse reaction or else, even if they are witnessed, are not informed, notified by the healthcare team, which may contribute to a negative outcome. The under reporting is still a very common problem, which hinders the correct intervention. The need for continuing education in noted for health professionals, with the objective of guidance on the identification of ADR and its proper notification (Abrhiem, 2013).

As mentioned above, one of the main methods used for pharmacovigilance for identification of adverse reaction is suspected, reporting made by health professionals. The spontaneous reporting system can generate signs of relationship between the use of the medicine and the development of ADR and its success or failure depends on the active participation of the notifiers. Thus, the reporting of ADR is crucial to accurate description of the event, whereas including the clinical terms.

Considering that drug therapy is widely used as a treatment modality for customers with several health changes, the identification of the adverse event related to medicines gain prominence in search of the management of safety and quality in healthcare. The attitude of constant vigilance to identify faults that occur becomes a concern of professionals involved in the care management system in healthcare, the users and institutions to increasingly minimize possible damage to the patient and reduce the costs with complications of hospitalization.

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APPENDICES

Tables

Table 1 – Characteristics of patients undergoing ATG therapy according to the occurrence of ADRs. Rio de Janeiro, 2014.

Variables	ADR (n)
Gender	
Female	12
Male	8
Center of Origin	
Hip	10
Spinal Column	1
Trauma	6
Knee	2
Medical Clinic	1
Comorbidity	
Yes	6
No	14
Allergies	
Yes	3
No	17
Polypharmacy (> 4 medicines)	
Yes	4
No	16

Table 2 - Distribution of orthopedic adult patients using ATG that presented ADRs according to quantitative variables. Rio de Janeiro, 2014.

Variables	Average	Median	Standard Deviation	Minimum	Maximum
Age	45.7	65.0	15.88	20.0	79.0
Length of hospitalization	28.9	21.0	21.75	4.00	76.0
Total time using ATG	31.05	29.5	21.43	5.00	75.0
Number of drugs prescribed (total)	3.95	3.00	2.72	1.00	12.0

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Table 3 - Frequency of ADRs to ATG in adult orthopedic patients. Rio de Janeiro, 2014.

Adverse reaction	Patients (n = 20)	%
Gastrointestinal Changes		
Epigastric pain	3	15
Nausea and vomiting	4	20
Oral bleeding	1	5
Melena	2	10
Investigations		
Elevation of TAP	1	5
Elevation of PTT	2	10
INR Elevation	2	10
Anemia	2	10
Peripheral edema	4	20
Thrombocytopenia	1	5
Skin changes		
Hematoma	4	20
Ecchymosis	2	10
Urinary Changes		
Darkened urine	5	25
Hematuria	2	10
Respiratory Changes		
Epistaxis	2	10