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Article

Analysis of potential drug interactions in medical clinic sector in a Hospital of João Pessoa – PB

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The objective of this study was to evaluate drug interactions based on medical records of patients hospitalized in University Hospital Lauro Wanderley (UHLW) in João Pessoa-PB, Brazil. This was a quantitative, descriptive study with a cross-sectional design. This research was conducted in the medical clinic of the above hospital by analyzing pharmaceutical intervention in medical records. The investigated samples consisted of all medical profiles with drug interaction information of patients hospitalized from June 2016 to June 2017. Most of these drug interactions were determined and classified by Micromedex® Solutions database. This research was approved by the Ethics Committee in Institutional Human Research, protocol number 2.460.206. In total, 331 drug interactions were found in 131 medical profiles. Dipyrone, enoxaparin, sertraline, ondansetron, quetiapine, tramadol, bromopride, amitriptyline, and simvastatin were medications that showed highest interactions. According to Anatomical Therapy Classification (ATC), drugs that act on the central nervous system result in more interactions. The most prevalent interaction was between dipyrone and enoxaparin. Some limitations of this study are the lack of notifications and data on drug interactions.

Keywords: Drug interaction. Pharmaceutical intervention. Medical clinic.

INTRODUCTION

The prescription of multiple drugs to the same patient is common in clinical practice. The use of polytherapy is justified when there is a necessity to increase effectiveness of treatment with synergic effects, or the patient has more than one disease.

Polypharmacy, defined as "chronic co-prescription of many medications", is prevalent among elderly patients who already have age-related diseases (Passos *et al*., 2012; Marengoni, Graziano, 2015; Mizokami *et al*., 2012).

When different drugs are combined into one therapy, undesirable events arise, especially in hospitals. Patients receive several medications simultaneously during hospitalization, leading to the development a possible adverse drug event (ADE) which increases hospital admissions, length of stay, hospital expenses, and risk of death (Cedraz, Santos Junior, 2014; Hajjar, Cafiero, Hanlon, 2007; Classen *et al*., 1997).

Studies carried out in several hospitals have shown that ADE from polytherapy is considered a new public

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health problem. Some of these ADEs are unpredictable, for example, in case of anaphylaxis, while ADEs in case of drug-drug interactions (DDI) can be prevented. Drug-drug interactions are responsible for most of the ADEs (Calderon-Larranaga *et al*., 2012; Marengoni *et al*., 2014; Silva *et al.,* 2010) and are regarded as a clinical event that alter the effect of a drug due to concomitant use of another drug, food, or other agent. Usually, drugs are employed to obtain a better therapeutic response or increase treatment efficiency (Reis *et al*., 2013; Couto *et al*., 2013). In case of combinatorial drug treatment, a synergistic effect is expected with consequent therapeutic benefits. However, these benefits may decrease with patient morbidity and mortality (Askari *et al*., 2013).

The incidence of drug interaction is related to risk factors associated with patients, medications, and medical prescriptions. With regard to patient risk factors, some people are more susceptible to drug interactions such as elderly, post-operative, intensive care unit, and immunosuppressed patients. In relation to medicines, therapeutic margin of drugs and their potential induction or inhibition of enzymes should be considered before prescribing medicines. The factors associated with prescription are related to patient's clinical condition and drug dose (Scherer *et al*., 2013; Almeida, Lima, 2010). Certain measures could be taken to reduce drug interaction such as computerized prescription and potential DDI verification (Walsh *et al*., 2008).

The DDIs can be classified by time to onset of effect, severity, and mechanism of action (Santos, Torriani, Barros, 2013). **Time to onset of effect**: Rapid onset DDIs includes DDIs in which clinical or adverse effects occur within 24 hours after drug administration. Late onset DDIs are those in which the effect is evidenced after days or weeks (Couto *et al*., 2013). **Severity**: Contraindicated drugs are those that cannot be concomitantly administered in any case. Serious DDIs occur when the drug interaction may endanger the patient's life and may require medical intervention to minimize or prevent adverse reactions. Moderate drug interactions may worsen clinical symptoms and thereby require change of therapy. Minimum drug interactions may have limited clinical implications and do not require changes in therapy (MICROMEDEX, 2017). Mechanism of action: Pharmacokinetic drug interactions occur when one drug modifies the absorption, distribution, metabolism, and excretion of another drug at its site of action (Brunton, Hilal-Dandan*,* 2010). Pharmacodynamic drug interactions occur when the drug shows agonistic effects by increasing the affinity of its cellular receptor or by inhibiting enzymes that inactivate it. Also, the drug may decrease the effect through a competitive antagonist with higher affinity or develop a different response than expected (idiosyncrasy) (Lisboa, 2011). Physical-chemical interactions occur when two or more drugs interact with each other through purely physical and chemical mechanisms (Brunton, Hilal-Dandan, 2010).

Studies show that DDI frequency ranges from 3% to 5% in patients who consume less medications, while the frequency increases up to 20% for those who take 10 to 20 drugs (Almeida, Lima, 2010). According to Dechanont *et al.* (2014), higher the drug prescription number, higher is the probability of drug-drug interaction. Therefore, the risk of drug interactions is always present in hospitals, since patients are exposed to several medications for a long period. Many drug-related problems are due to drug interactions, however, they are easily preventable adverse events (Moura, Acurcio, Belo, 2009; Reis *et al*., 2013).

Clinical pharmacists can reduce drug-related problems, such as DDIs, through pharmacotherapy evaluation and optimization. Detection of DDIs will lead to reduction in a patient's hospital stay, decrease readmission and result in better control of biomarkers (lipids, anticoagulant levels and blood pressure) (Hanlon *et al*., 1996; Viktil, Blix, 2008). Despite the importance of these interventions, there are few reports in this area of study (Nunes, 2008). Therefore, the present study aims to evaluate drug interactions in medical records of patients hospitalized in University Hospital Lauro Wanderley (UHLW) in João Pessoa-PB.

MATERIAL AND METHODS

Study design

This was a quantitative, descriptive study with a cross-sectional design carried out in University Hospital Lauro Wanderley (UHLW) on potential drug interactions

via analysis of medical records of patients hospitalized in the Medical Clinic sector. This research was done according to resolution number 466/2012 and was approved by the Ethics Committee in Institutional Human Research by the protocol number 2.460.206.

The UHLW is a college hospital of the Federal University of Paraíba with approximately 220 beds and 80 doctor's offices, and 20,000 appointments and 250 surgeries are performed every month. The Medical Clinic sector has 70 beds to treat patients with chronic diseases such as hypertension, diabetes, heart disease, among others.

Identification of Study Population

The medical records constituted the population of the study. The investigated sample consisted of patients' medical profiles with drug interactions, hospitalized in the Medical Clinic sector of UHLW from June 2016 to June 2017.

Inclusion criteria

The medical records of patients hospitalized in the Medical Clinic sector, presenting DDI, were included in the study.

Data Management

The data of the subjects were collected from medical records of patients in the Medical Clinic: month of admission, patient identification (age and gender), and information about prescribed medications.

Clinical pharmacists analyzed all patients' prescriptions indicating pharmaceutical intervention and checked for DDIs. In case of unreadable prescriptions, the prescribing professional was consulted.

The data obtained from medical profiles were recorded in Microsoft Excel® for later analysis and mean and standard deviation was calculated.

The DDIs were determined by a tool available in Capes Portal - Ministry of Education, Micromedex® Solutions database (Micromedex HealthCare Solutions), and classified according to severity (contraindicated, superior, moderate and minor), time to onset of action (fast, late or unspecified) and documented data (excellent, good, reasonable and unknown). The Anatomical Therapy Classification (ATC) system was used to classify drugs with potential drug interactions. This classification divides drugs into groups and subgroups (levels) according to the site of action, chemical, pharmacological, and therapeutic properties.

RESULTS AND DISCUSSION

During the study period, 1,085 pharmaceutical interventions were randomly documented from 131 patients hospitalized in the UHLW Medical Clinic. This constituted 27.7% of total interventions in this period wherein 331 DDIs were observed. The mean age of these 131 patients with DDI in prescriptions was 58 ± 16.62 years (range: 22−92).

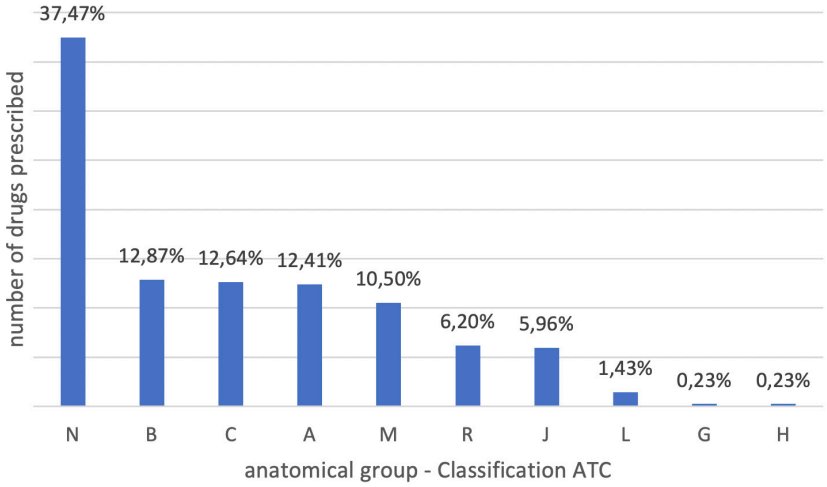
A study by Pivatto Junior *et al*. (2009), at a university hospital in Porto, corroborates this result as it associates age with risk of drug interactions. The authors state that population over 50 years is more vulnerable to drug interactions risk, probably due to a higher prevalence of chronic diseases and consequently a higher medication quantity along with natural physiological changes that are accompanied with age.

The sample population consisted of 73 female (55.7%) and 58 males (44.3%) patients. Balen *et al*. (2017) identified a higher probability of potential drug interactions in female patients (62. 1%). However, Cedraz, Santos Junior (2014) identified and characterized drug interactions in medical records of the Intensive Care Unit in a public hospital in Feira de Santana, Bahia and found a higher correlation with male patients (57.14%). According to this study, women were deemed stronger for biological reasons and also due to the fact that men are more exposed to violence and require longer hospitalization for recovery, thereby making them more susceptible to drug interactions. Studies like Gomes *et al.* (2010) and Yunes, Coelho, Almeida (2011) show that several interactions can occur in drugs prescribed in hospitals, corroborating results obtained in the present study. According to Micromedex® database, we found 301 interactions among the 94 medicines prescribed for

patients in Medical Clinic, UHLW. Dipyrone (20.9%), enoxaparin (16.6%), sertraline (10.2%), ondansetron (9.6%), quetiapine (8.6%), tramadol (8.0%), bromopride (6.3%), amitriptyline (6.0%), and simvastatin (5.3%) were the drugs with the highest interaction.

In this study, medical prescriptions had 419 drugs involved in adverse events. These drugs were classified into 10 different anatomical groups by ATC.

Graphic I shows drugs distribution according to ATC classification (Level 1).



GRAPHIC I - Distribution of drugs (%) prescribed, according to level 1, of the ATC classification.

Anatomical Therapy Classification (ATC): This classification divides the drugs into groups and subgroups (levels), according to the body or system on which they act, taking into account its chemical properties, pharmacological and therapies
N – Central Nervous System; B – Blood and Hematopoietic Organs; C – Cardiovascular System; A – Digestive system and Metabolism; M – Musculoskeletal System; R – Respiratory system; J – General antiinfectives for systemic use; L – Antineoplastic and immunomodulatory agents; G – Genitourinary system and sex hormones; H – Systemic Hormone Preparations, excluding sex hormones and insulins.

This classification divides drugs into groups and subgroups (levels) according to target organ or system as well as its chemical, pharmacological, and therapeutic properties. According to this classification, drugs that act on the central nervous system appear more frequently. Second in line were drugs that act on blood and hematopoietic organs, followed by those that act on cardiovascular system for treatment of hypertension. The most frequent groups in this study, N, B, C and A, coincide with results of a previous study in the Intensive Care Unit of a university hospital in Ceará that shows a (Lima, Cassiani, 2009)

Higher prevalence of degenerative diseases in elderly population (Parkinson's, Alzheimer's, cardiovascular disease and hypertension) and subsequent high chronic drug usage results in drug interactions.

Enoxaparin + dipyrone (n=19; 6.31%), enoxaparin + sertraline (n=11; 3.6%), dipyrone + sertraline (n=6; 2%) amlodipine + simvastatin (n=6; 2%) were most frequently involved in drug interactions.

Among the 301 DDIs identified, dipyrone in combination with enoxaparin was the most prevalent interaction with higher severity; a well-documented interaction with a lack of adequate studies. Regarding onset of effect, dipyrone + enoxaparin and other prevalent interactions (amlodipine + simvastatin) have a rapid onset. In other words, adverse effects occur in less than 24 hours after drug administration and require agile professionals to identify and reduce undesirable effects.

Our results are consistent with those obtained by Okuno *et al.* (2013) that demonstrate that dipyrone is responsible for most drug interactions.

The third most frequent drug interaction involved increased bleeding as the main adverse effect. Teles *et al*. (2011) showed that among drugs, anticoagulants

interact more with other medications. Mazzola *et al*. (2011) also indicated that frequent use of enoxaparin in combination with dipyrone has clinical relevance as it increases bleeding risk. This can affect surgical procedures and demand strict patient monitoring to avoid any undesirable symptoms.

Patients concomitantly treated with amlodipine and simvastatin should not exceed 20 mg of simvastatin per day. This may elevate serum levels of simvastatin and increase risk of myopathy, including rhabdomyolysis (Micromedex, 2017).

In regard to severity, 253 DDIs (84%) were considered high severity, in other words, can cause serious damage and require patient follow-up or change in therapy.

Contraindicated drug interactions were also present (7%), although less frequently, demonstrating the importance of drug interactions as an adverse event in clinical practice. This may result in potential hospitalization, readmission, undesirable results for patient, and consequently higher hospital expenses. Among the adverse events caused by contraindicated drug interactions, the most frequent is extrapyramidal effects (68%), particularly with bromopride. This shows that a well-trained multidisciplinary team of health professionals is important to monitor these interactions during hospitalization.

On the subject of clinical management, Micromedex® database recommends patient monitoring to avoid or resolve interactions in 39.2% of the cases, followed by dose adjustment (25%).

A study by Lima, Cassini (2009) corroborate the results in the present study. Their study demonstrated that the most commonly employed mode of clinical management was to sequentially observe the patient's signs and symptoms, monitor therapeutic response and adjust dosage. Monitoring is considered an effective way to prevent adverse events.

In regard to drug interaction profile, pharmacokinetic interactions were more frequent, being responsible for 48% of the total interactions, than pharmacodynamic profile (39%) and those not specified (13%). The same was also found in previous studies by Oliveira Paula (2014) and De Carvalho *et al.* (2013).

The risk of pharmacokinetic drug interactions may lead to positive or negative effects such as decreased enzymatic activities and reduced blood flow. These factors may increase or decrease drug action and lead to dangerous adverse reactions in the patient. In relation to time to onset of adverse effects, the interactions were classified as fast, late, and unspecified. Due to lack of data, 69% of interactions present in the records were not classified, 24% showed a late start, and approximately 7% showed a rapid start.

Drug interactions with a rapid onset require greater attention by professional teams in order to avoid serious damage to the patient's health. Similarly, drug interactions that have a late development also require care and attention as they may appear after hospital discharge.

Pinto *et al*. (2015) emphasized the need for research on DDIs, reporting that lack of data on time to onset of drug interactions is due to the lack of reporting directives on drug-related problems.

CONCLUSION

DDIs are a public health problem that need to be monitored with appropriate intervention by a responsible team as it may risk a patient's health. The present study demonstrates the prevalence of high drug interactions in medical records and highlights the need to monitor treatment and follow-up patients in order to achieve successful therapy. The results also contribute to the elucidation of DDIs and provides perspective to the importance of rational use of medicine in clinical pharmacy.

Some limitations of studies on drug interactions are a lack of data and absence of directives to competent authorities, thereby limiting the availability of information and scientific evidence regarding severity and time to onset of DDIs. Therefore, further studies on this subject are required to reduce the rate of drug interactions.

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