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Incidência de Interações Medicamentosas e Avaliação Clínica nos Pacientes de um Hospital Público Brasileiro

Incidence of Drug-Drug Interactions and Clinical Evaluation in Patients of a Brazilian Public Hospital

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Abstract

Drug-drug interactions (DDIs) are responsible for therapeutic problems and the main causes of adverse drug reactions that require hospitalization. The aim of this study was to analyze the incidence of DDIs in patients admitted in a Public Hospital in Brazil, in 2015.
In a cross-sectional study, DDIs were screened in 351 patients, using Micromedex® database, that classify interactions according to severity and documentary evidence. Potential DDIs were assessed at the daily pharmacotherapeutic follow-up through pharmaceutical anamnesis and analysis of laboratory tests were performed. A total of 2,937 potential DDIs were identified and 28.42% of these had confirmed signs and symptoms clinical in 87 patients (29%). Among the patients that presented interactions, 62.07% were older than 60 years. In this age group, 61.27% of all signs and symptoms clinical observed in the study were also identified, demonstrating a positive association between the occurrence of clinical interactions and age. In addition, a positive correlation between the number of drugs prescribed and the occurrence of signs clinicals was also observed. Most DDIs observed were of moderate severity and were related to imbalance of blood pressure and glycemic levels. This study demonstrated that DDIs are directly related to the age and number of drugs prescribed. And the greater frequency of DDIs with fair documentary evidence alerts to the need to consider all the possible interactions. Thereafter, this study showed that potential DDIs and sign and clinical symptoms are significant in patients and reinforce the need to support Clinical Pharmacy.

Keywords: Drug-Drug Interaction (DDI). Inpatients. Pharmacotherapy. Poly Pharmacy. Sign and Symptom.

Resumo

Interações droga-droga (IDDs) são responsáveis por problemas terapêuticos e as principais causas de reações adversas a medicamentos que levam a hospitalização. O objetivo do trabalho foi analisar a incidência de IDDs em pacientes admitidos em hospital público no Brasil, em 2015. Em um estudo transversal, 351pacientes foram selecionados com IDDs utilizando-se o banco de dados da Micromedex®, e as interações foram classificadas de acordo com a severidade e documentação. Os potenciais IDDs foram avaliados durante o acompanhamento farmacoterapêutico diário por anamnese farmacêutica e a análise dos exames laboratoriais foi realizada. Um total de 2.937 potenciais IDDs foram identificados e 28,42% deles tinham sinais e sintomas clínicos confirmados em 87 pacientes (29%). Entre os pacientes que apresentaram interações, 62,07% tinham mais que 60 anos. Neste grupo de idade, 61,27% de todos os sinais e sintomas clínicos observados foram também identificados, demonstrando uma associação positiva entre interações clínicas e idade. Além disso, uma correlação positiva entre o número de drogas prescritas e a ocorrência de sinais clínicos também foram observados. Muitos IDDs observados foram de severidade moderada e estavam relacionados a alterações das pressões arteriais e níveis glicêmicos. Este estudo demonstrou que IDDs estão diretamente relacionados a idade e número de drogas prescritas. E a grande frequência de IDDs com documentação fraca alertam para a necessidade de se analisar esse tipo de interação. Sendo assim, este estudo mostrou que potenciais IDDs e sinais e sintomas clínicos significantes em pacientes só reforçam a necessidade de se apoiar a farmácia clínica.

Palavras-chave: *Interação Droga-Droga (IDD). Pacientes Internados. Farmacoterapia, Poli Farmácia. Sinais e Sintomas.*

1 Introduction

Studies show that drug-drug interactions (DDI) are responsible for therapeutic problems and are one of the main causes of adverse drug reactions which frequently require hospitalization (MIGUEL *et al*., 2012; MARENGONI *et al*., 2014). Nevertheless, the risk of interactions increases due to the use and/or addition of multiple drugs during hospitalization (DOAN *et al*., 2013; SHARMA *et al*., 2014; MORIVAL *et al*., 2018). Although some problems caused by drug use develop unexpectedly and cannot be predicted, many are related to known pharmacological actions and may possibly be anticipated. However, as drug therapy becomes more complex and many patients are treated with two or more drugs, the ability to predict the magnitude of a specific action of any prescribed drug diminishes (HUSSAR, 2000).

One of the most important consequences of DDI is an over-response to one or more agents that are also being handled. In addition, there may also be a decrease or loss of efficacy, which may be misinterpreted with therapeutic failure or disease progression (HUSSAR, 2000). Adverse drug reactions (ADRs) caused by DDIs may compromise the quality of life and, eventually, patient survival. The number of hospitalizations, the length of stay in the hospital,

the consumption of other medications and costs are also increasing (MIGUEL *et al*., 2012). In hospital prescriptions, the frequency of drug interactions is a permanent risk, since many have the potential to cause permanent damage, patient's clinical deterioration, increased hospitalizations and length of stay. Thus , decreasing the number of combinations of potentially harmful drugs and contributing to increase patient safety is the great challenge that has been sought (CASTILHO *et al*., 2018).

Different clinical situations provide opportunities for clinical pharmacists to contribute with the identification and prevention of DDIs and ADRs (MILFRED-LAFOREST *et al*., 2013). Interventions by a pharmacist might significantly reduce the number of patients with potential IDDs (ROBLEK *et al*., 2016). Our study sought to verify the incidence of potential DDI using the Micromedex® database. This study aimed to evaluate clinical signs and symptoms due to interactions through pharmacotherapeutic follow-up in patients hospitalized in a public hospital.

2 Material and Methods

2.1 Study design and ethical approval

This is a descriptive cross-sectional study to verify the occurrence of DDIs and clinical evaluation in patients admitted to the Medical Clinic of a Municipal Hospital, between August 24th to November 26th, 2015. The data analyzed were collected by patient's anamnesis and a pharmacotherapeutic follow-up form. The research protocol was approved by the Ethics Committee (n°1.189.659; http://plataformabrasil.saude.gov.br/login.jsf) and the hospital director approved and agreed with this research.

2.2 Participants

The study participants are patients of both sexes hospitalized in the General Medical Clinic of a Public Hospital in the period from August 24th to November 26th , 2015. The inclusion criteria were patients over 12 years old just admitted to the General Medical Clinic of the Hospital. The exclusion criteria were: patients with a stay lower than 48 hours in the hospitalization sector; with mental problems or incapacitated patients (all those that due to illness or mental deficiency do not have the necessary discernment to answer the questions); and patients who were already hospitalized at the beginning of the study.

2.3 Procedures

The data were collected using a pharmacotherapeutic follow-up form composed of 3 parts (A, B e C). Part A was completed from the first day of hospitalization and contains patient's identification information; medical diagnoses and clinical conditions; record of adverse drug reactions (allergies); and intercurrences during hospitalization. In Part B, information about the medicines used was taken, the route of administration, the dosage, the time of administration, the potential drug interactions, the symptoms and possible ways of evaluating them. This generated database were recorded at Micromedex®. Part C was used to record DDIs observed or reported by the patient; in addition, signs, symptoms and laboratory tests were evaluated to verify the occurrence of drug interactions.

Daily, the nursing team registered vital signs: blood pressure, heart rate, respiratory rate and temperature in a card attached to each patient form. Some additional tests such as: electrocardiogram; urea, creatinine, sodium, potassium, glycemia, lipidogram levels; blood count; prothrombin time; partially activated thromboplastin time; aspartate aminotransferase and alanine aminotransferase were asked by medical team for better clarification of the clinical interactions.

2.4 DDIs definition

The verification and classification of DDIs was performed using Micromedex database. The DDIs are classified on basis of severity-levels and documentation-levels as follows:

- *Contraindications*: totally contraindicated.
- *Major*: potentially lethal interaction requiring medical intervention to minimize or prevent serious adverse effects.
- *Moderate*: the interaction may aggravate the patient's conditions and/or require change in therapy.
- *Minimum*: interaction may increase the frequency or severity of side effects and limit clinical effects but requires no change in the therapy.
- *Excellent*: controlled studies have clearly demonstrated the existence of the interaction.
- *Good*: Consistent documentation suggests that interaction exists, but controlled studies are lacking.
- *Fair*: the available documentation is weak evidence, but pharmacological considerations lead one to suspect that the interaction exists.
- *Unknown*: there is no documentation about the interaction.

2.5 Statistical analysis

Descriptive statistics were used to present the demographic data from the study sample. Data were tabulated and analyzed using the Microsoft Excel program and the statistical software Instat, where the means and frequencies of the variables under study were calculated, as well as the Chi-square test. Simple logistic regression analyses were performed to investigate the association among sex, age and hospital length of stay and having at least one potential and clinically significant DDI. The results are presented as odds ratios (ORs) with 95% confidence intervals (CIs). All analyses were conducted using GraphPad Prism 5.0. Values of $p<0.05$ were considered as significant.

3 Results and Discussion

3.1 Study population

From the population sample of 351 individuals recruited, 51 were excluded. Patients were excluded because of low time of hospitalization (<48 hours), presence of a mental problem or inability to answer questions or express their wishes, in addition to patients who were already hospitalized at the beginning of the study. Patients who were on continuous use of drugs for basic diseases maintained their treatment throughout the hospitalization period. The drugs used were included during the analysis of possible DDIs. Patients aged 12 to 95 years, of both sexes, participated in the study. Descriptive statistics of the study population is shown in Table 1.

Table 1 - Descriptive statistics of study population and comparison between people with and without potential and clinical evaluation DDIs

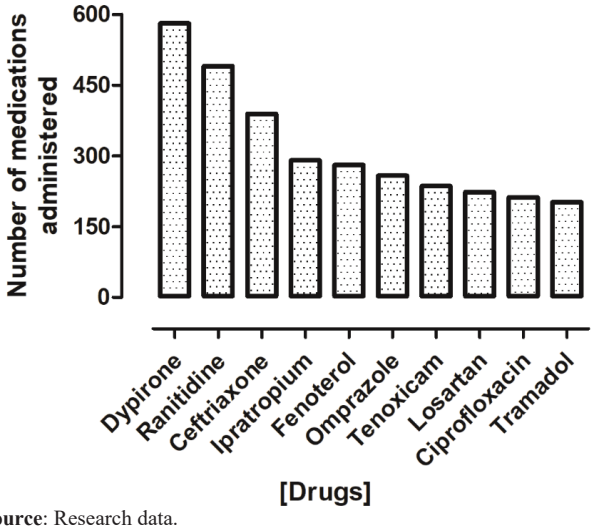
		Potential			Clinical Evaluation		
Characteristics of Study Sample	**Total**	**DDI(s)**	**No DDI**	**OR (95% CI)**	**DDI(s)**	**No DDI**	**OR (95% CI)**
Cases, *n*	300						
Male (%)	n=154 (51.3)	119(51.3)	35(51.5)	0.993 (0.578-1.705)	44(50.6)	110(51.6)	0.958 (0.582-1.578)
Female (%)	n=146 (48.7)	113(48.7)	33(48.5)	Ref.	43(49.4)	103(48.4)	Ref.
Age (years), mean±SD (range)	53.6±20.3 (12-95)	232	68	4.804* (2.633-8.766)	87	213	3.339* (1.920-5.807)
Hospital length of stay (day), mean±SD (range)	4.5±3.5 (2-35)	232	68	4.231* (2-8.952)	87	213	2.170* (1.294-3.639)

* P-value < 0.001. CI – confidence interval, DDI(s) – drug-drug interaction(s), OR – odds ratio, Ref – reference category, SD – standard deviation.
Source: Research data.

The variables sex, age and hospital length of stay were analyzed in relation to potential and clinical evaluation DDIs. Only age and hospital length of stay were associated with DDIs. The adjusted odds ratio (OR) and 95% confidence interval (95%CI) for the variables are shown in Table 1.

The results did not find an association between sex and the presence of DDIs in the clinical evaluation of signs and symptoms. This result is consistent with other studies stating the same result, although different methodologies have been applied (ASTRAND *et al*., 2006; HOSIA-RANDELL; MUURINEN; PITKÄLÄ, 2008). It was also found that 29% of the patients (n=87) had at least one DDI. (ASTRAND et al., 2006; HOSIA-RANDELL; MUURINEN; PITKÄLÄ, 2008). Among the potential DDIs analyzed, 28.42% (n=759) had drug interactions with clinical evaluation. Gosney and Tallis (1984) evaluated 573 elderly inpatients and found that 23.7% had at least one clinically significant drug interaction during the hospitalization period. Similarly, other studies show that one quarter of patients presented DDI in the USA and Asia (PENG et al., 2003; JANCHAWEE et al., 2005; LAFATA et al., 2006). Dallenbach *et al*. (2007) found 23% prevalence of clinically significant DDIs in Switzerland. Lopez-Picazo *et al.* (2011) reported 20.6% prevalence of potential DDIs among primary care patients in Spain. Lin *et al*. (2011) exhibit that the prevalence of potential DDIs was 25.6% in Taiwan. Recently, the study carried out by Jazbar *et al*. (2018) also shows that approximately one quarter of the Slovenian population is exposed to potential DDIs and 15.6% were clinically significant DDIs. Total of 1,325 medical prescriptions were evaluated, in which 158 were different active. However, only 149 drugs were effectively administered during the study period. The most prevalent drugs administered were dipyrone (8.03%), ranitidine (6.77%) and ceftriaxone (5.37%), as shown in the Figure 1.

Figure 1 - Total number of the ten most commonly administered drugs in the patients in this study



Source: Research data.

The mean age of the patients was 53.6 years, ranging from 12 to 95 years. Most individuals were between 24 and 60 years old, however, of the patients who presented at least one interaction, 62.07% (n=54) were older than 60 years (Table 2). The results found an association between age and the presence of DDIs with signs and symptoms clinical. Similar data were also shown by Sönerstam *et al.* (2018). with people older than 65 years with dementia in Northern Sweden, 43.2% of the study population presented clinically significant DDIs. These results may be better clarified when one looks at potential interactions, such as Reimche *et al.* (2011), who found that

the factor with the greatest influence on the incidence of drug interaction is age (adjusted rate ratio patient >75 years *vs* <30 years, 2.25; 95%IC 2.15:2.35). Other studies showed that age was also an important factor in the incidence of potential interactions, possibly due to the existence of comorbidities or hepatic and renal disfunction, leading to the prescription of a greater number of medications NABOVATI *et al*., 2014; KANNAN *et al*., 2011). Another factor associated with the elderly is the poli pharmacy, since the number of drugs prescribed has a positive correlation with the drug interaction as observed in the present study, in which 70% of the patients who had more than 11 prescription drugs had at least one drug interaction (TATUM *et al*., 2019). These data are corroborated in other studies that determined that the number of drugs is a r risk factor for the incidence of potential interactions (REIMCHE; FORSTER; WALRAVEN, 2011; KANNAN *et al*., 2011; DAI *et al*., 2016).

Table 2 - Patients who presented clinically relevant DDIs according to the age group

Patients ages (years)	Total number of patients	Number of DDIs patients
12|-- 24	9.00 % (n = 27)	1.15 % (n=1)
24|-- 60	48.33 % (n = 145)	36.78 % (n=32)
60|--| 95	42.67 % (n=128)	62.07 % (n=54)
Total	300	87

* p<0.05, Chi-square.

Our results also demonstrated that the hospital length of stay was associated with potential (OR:4.231) and clinical evaluation (OR:2.170) DDIs. Moura *et al*. (2009) also found similar results (OR:4.38; 95%CI 3.03:6.41) showing that DDI is associated with number of prescribed drugs, increased duration of stay in the hospital and cost. Other studies found a positive association between hospital length of stay with DDI (RIECHELMANN *et al*., 2005; TERLEIRA *et al*., 2007). With these data, it can be suggested that with increased hospital stay, more drugs can be used, resulting in an increased likelihood of DDIs.

3.2 Potential and clinical evaluation DDIs

After excluding drugs that were not administered, 2,937 potential drug interactions were identified (Table 3). Of these, 9.06% (n=266) could not be evaluated because of the need for unavailable diagnostic tests, such as the determination of certain drugs in the plasma. Thus, 2,671 potential interactions were evaluated and 28.42% (n=759) of the interactions were observed in 87 patients (29%), with a mean of 8.72 interactions/patient, during the hospitalization period. It was observed 105 different interactions, which were repeated 759 times.

Table 3 - Classification of potential and clinical evaluated DDIs.

Severity/ documentation	Potential DDIs (%)	Clinical evaluated DDIs (%)
Contraindicated	0.44 % (n = 13)	0
Excellent	0	0
Good	0	0
Fair	0.44 %	0
Major	26.69 % (n = 784)	12.52 % (n = 95)
Excellent	4.56 %	2.24 %
Good	7.12 %	0.40 %
Fair	15.01 %	9.88 %
Moderate	67.35 % (n =1978)	86.56 % (n = 657)
Excellent	9.67 %	16.21 %
Good	29.45 %	37.15 %
Fair	28.23 %	33.20 %
Minimum	5.52 % (n = 162)	0.92 % (n = 7)
Excellent	2.01 %	0
Good	3.24 %	0.92 %
Fair	0.27 %	0
Total	2,937	759

In Table 3, it was also verified that of the interactions that occurred, 12.52% are of higher severity, 86.56% moderate, 0.92% minimum. No contraindicated severity DDI was observed. The drug interactions after evaluation of signs and symptoms clinical were: moderate severity, 37.15% had good documentation, 33.20% fair and 16.21% excellent documentation. Most patients who presented DDI and had sign and symptoms evaluated were diagnosed with diseases of the circulatory system (22.99%). And, a higher proportion of clinically significant DDIs per patient were observed in those diagnosed with infectious, parasitic and circulatory diseases, concomitantly (Table 4).

Table 4 - Ten higher prevalence diagnosis

	Diagnosis	Patients (n)	Patients with DDIs and Clinical Evaluation
1	Circulatory system diseases	50	22.99 % (n = 20)
2	Respiratory system diseases	45	10.34 % (n = 9)
3	Injury, poisoning and other consequences of external causes	38	16.09 % (n = 14)
4	Neoplasms	21	9.20 % (n = 8)
5	Infectious and parasitic diseases	14	3.45 % (n = 3)
6	Genitourinary system diseases / Circulatory system diseases	8	3.45 % (n = 3)
7	Endocrine, nutritional and metabolic diseases / Circulatory system diseases	3	3.45 % (n = 3)
8	Infectious and parasitic diseases / Circulatory system diseases	2	1.15 % (n = 1)
9	Respiratory system diseases / Blood and hematopoietic diseases and immune disorders	1	1.15 % (n = 4)
10	Respiratory system diseases / circulatory / genitourinary	1	1.15 % (n = 1)

Source: Research data.

Although the relationship between the drug interactions and the diagnoses presented by the patients was not statistically significant, 22.9% (n=20) of the DDIs with clinical evaluation were found in patients with circulatory system disorders. Similar data were demonstrated in the study by Lima and Cassiani (2009), which 26.6% of the potential drug interactions found in patients admitted to the intensive care unit were related to circulatory system pathology. Another important finding in the present study was the presence of 105 DDIs with signs and symptoms clinical evaluated that repeated 759 times. Among them, 86.56% were of moderate severity and 12.52% greater severity. Moura *et al.* (2009) also observed a similar result when performed a study in a Brazilian General Hospital and found that 78% of the potential drug interactions were moderate severity. The ten most frequently observed DDIs (in a total of 759 interactions) in the present study are described in Table 5. Most of the interactions were of moderate severity and an example observed among the interactions with excellent documentation was between dipyrone and captopril. In most patients that used captopril and who used dipyrone concomitantly, blood pressure levels were elevated. In this study some drug interactions observed presented an excellent documentation, others good documentation and two of the interaction presented fair documentation. These two interactions occur at a relative high frequency, (6.59% and 2.77%), demonstrating that these studies could detect an unanticipated DDI with moderate and major severity.

Table 5 - Ten most frequent drug interactions with sign and symptoms clinical evaluated in the study

DDI interactions (frequency)	Severity	Documentation	Clinical Consequence
Fenoterol + Regular Insulin (50 – 6.59%)	Moderate	Fair	- The addition of fenoterol in patients who used regular insulin increased glycemic levels in most of them.
Dipyrone – Captopril (42 – 5.53%)	Moderate	Excellent	- In most patients who used captopril and who used dipyrone concomitantly, blood pressure levels were elevated (especially in those with renal impairment).
Dipyrone – Losartan (30 – 3.95%)	Moderate	Good	- Patients who used losartan and who started to use dipyrone showed increased blood pressure levels.
ASA -Furosemide (26 – 4.42%)	Moderate	Good	- Patients who used concomitant ASA and furosemide increased blood pressure levels.
Tenoxicam -Captopril (24 – 3.16%)	Moderate	Excellent	- The addition of nonsteroidal anti-inflammatory drugs in a patient using captopril decreased the antihypertensive effect of the angiotensin converting enzyme inhibitor in most of them.
Ciprofloxacin - Regular Insulin (21 – 2.77%)	Major	Fair	- All patients who used regular insulin concomitantly with ciprofloxacin had increased glycemic levels.
ASA – Enalapril (21 – 2.77%)	Moderate	Excellent	- Most patients who used concomitant ASA and enalapril had increased blood pressure levels.
ASA - Captopril (20 – 2.63%)	Moderate	Excellent	- Most patients who used concomitant ASA and captopril had increased blood pressure levels.
Dipyrone - Furosemide (19 – 2.5%)	Moderate	Good	- In patients who used furosemide and who started using dipyrone, there was an increase in blood pressure levels.
ASA - Carvedilol (18 – 2.37%)	Moderate	Good	- In most patients who used concomitant carvedilol (beta-adrenergic blocker) and ASA, blood pressure levels were increased.

Source: Research data.

No patient had contraindicated interactions, even though this study detected four potential drug interactions of contraindicated severity but with poor documentation. Of the nine potential drug interactions of major severity and excellent documentation, only two occurred, among them: losartan and captopril; and losartan and enalapril (Table 6). These interactions are associated with the patient difficulty controlling blood pressure in many cases. Among the ten potential drug interactions of major severity and good documentation, only the interaction between nifedipine and prednisone was observed in this study. The others

interactions who had sign and symptoms evaluated of major severity detected in this study were qualified as with fair documentation. Data showed in Table 6.

Table 6 - DDIs with sign and symptoms evaluated of major severity detected in the study

DDI (frequency)	Severity	Documentation	Clinical consequence
Ciprofloxacin - Regular insulin (21 – 22.1%)	Major	Fair	- All patients using regular insulin concomitantly with ciprofloxacin showed elevated glycemic levels.
Ciprofloxacin - Metformin (17 – 17.89%)	Major	Fair	- Patients who used concomitant fluoroquinolones and antidiabetics showed elevations in glycemic levels.
Ciprofloxacin - NPH insulin (16 – 16.84%)	Major	Fair	- Patients who used concomitant fluoroquinolones and antidiabetics showed elevations in glycemic levels.
Captopril - Losartan (10 -10.52%)	Major	Excellent	- Concomitant use of angiotensin converting enzyme inhibitors and angiotensin II receptor blockers has resulted in changes in renal function (elevation of sodium, potassium, urea and/or creatinine), especially in patients with renal impairment.
Enalapril - Losartan (7 – 7.37%)	Major	Excellent	- Concomitant use of angiotensin converting enzyme inhibitors and angiotensin II receptor blockers has resulted in changes in renal function (elevation of sodium, potassium, urea and/or creatinine), especially in patients with renal impairment.
Ciprofloxacin - Glibenclamide (5 – 5.26%)	Major	Fair	- Patients who used concomitant fluoroquinolones and antidiabetics showed elevations in glycemic levels.
Ciprofloxacin - Glimepiride (4 – 4.21%)	Major	Fair	- Patients who used concomitant fluoroquinolones and antidiabetics showed elevations in glycemic levels.
Metronidazole - Ondansetron (4 – 4.21%)	Major	Fair	- In a patient who used metronidazole and who started using ondansetron there was prolongation of the QT interval on the electrocardiogram.
Nifedipine - Prednisone (3 – 3.16%)	Major	Good	- In a patient who used nifedipine concomitantly with prednisone had elevated blood pressure levels.
Pethidine - Tramadol (2 – 2.21%)	Major	Fair	- Concomitant use may lead to serotonergic syndrome with symptoms of hypertension, hyperthermia, changes in mental status.
Amiodarone - Ranitidine (2 – 2.21%)	Major	Fair	- In a patient who used amiodarone and ranitidine had bradycardia (increased exposure to amiodarone).
Fenoterol + Propranolol (1 – 1%)	Major	Fair	- In a patient who used propranolol and fenoterol had bronchospasm (pharmacological antagonism).
Amitriptyline - Tramadol (1 – 1%)	Major	Fair	- Concomitant use of amitriptyline and tramadol resulted in serotonergic syndrome (hypertension, hyperthermia, altered mental status).
Morphine - Tramadol (1 – 1%)	Major	Fair	- A patient with prolonged use Tramadol had CNS depression after addition of morphine.
Regular Insulin - Levofloxacin (1 – 1%)	Major	Fair	- Concomitant use of fluoroquinolone (levofloxacin) and regular insulin resulted in changes glycemic levels.

Source: Research data.

The interaction between fenoterol and regular insulin was the most frequent in our study, and it is associated with severe bronchospasm and the decrease in the efficacy of β-2 agonists. The concomitant use of a β-adrenergic antagonist and a β-2 agonist may interfere in the efficacy of both agents due to pharmacological antagonism (LING; SALEEM; SHEE, 2008). However, among the ten most prevalent DDIs with signs and symptoms clinical evaluated are those of moderate severity related to imbalance of blood pressure and glycemic levels. These changes were also reported by Cruciol-Souza and Thomson (2006) who evaluated potential interactions in a Brazilian University Hospital and concluded that 19.2% and 3.4% of adverse reactions from drug interactions were related to hypertension and hypoglycemia, respectively.

Some of the interactions in the present study required dose adjustment or monitoring in order to prevent adverse drug reactions (moderate severity). Angiotensin-converting enzyme (ACE) inhibitors were among the drugs that had been adjusted. According to Jackson nonsteroidal anti-inflammatory drugs (NSAIDs), including acetylsalicylic acid, may decrease the antihypertensive response of ACE inhibitors (JACKSON, 2006a). Potassium-sparing diuretics and potassium supplements may increase hyperkalemia induced by ACE inhibitors and angiotensin II receptor antagonists, as well as the presence of renal failure. ACE inhibitors may also increase plasma levels of digoxin and lithium, as well as trigger hypersensitivity reactions to allopurinol. In addition, its bioavailability may be reduced with the use of antacids (JACKSON, 2006a). In addition, loop diuretics, also present in the ten most frequent interactions, interact with NSAIDs, and may also interact with several medications (JACKSON, 2006a). According to the same author, as well as loop diuretics, thiazides can decrease glucose tolerance, and precipitate latent Diabetes mellitus, probably by reducing insulin secretion, as well as changes in glucose metabolism.

Hyperglycemia seems to be related to potassium depletion, which in turn also compromises the antihypertensive effect and cardiovascular protection afforded by thiazides in hypertensives. Thiazide diuretics may reduce the activity of some drugs (HAMMAND *et al*., 2017; RHEE *et al*., 2018).

These interactions alert us to the need for constant clinical and laboratory monitoring of these patients, which may require dose adjustments and/or change in therapy. In the present study, dipyrone was the drug with the highest frequency of administration and responsible for 03 of the 10 drug interactions of moderate severity, all related to difficult blood pressure control. In other studies dipyrone was also the most frequent medication in prescriptions on potential interactions in hospitalized patients (DE OLIVEIRA; SCHUELTER-TREVISOL; TREVISOL, 2014; ANDRADE; LOBO; DA SILVA, 2017; BURKE; SMYTH; FITZGERALD, 2006).

Concerning the interactions of greater severity with good documentary evidence, the interaction between prednisone and nifedipine was observed. Prednisone is a cytochrome inducer (CYP 3A4) and therefore decreases blood levels of nifedipine (FDA, 2013a). According to Bahar *et al.* (2017), CYP enzymes are also inducers of hepatic CYPs.

Of the 15 interactions of major severity observed in our results, 06 were in relation to the quinolone group (05 with ciprofloxacin and 01 with levofloxacin) with antihyperglycemics. The prevailing symptom was hyperglycemia, which despite having an unknown mechanism. Studies show that the quinolone group itself can raise blood glucose levels (FDA, 2013b). Jain *et al*. (2017) reported that various drugs may alter the response of diabetic patients to their therapeutic regimens, and cause hypoglycemia or hyperglycemia. Conversely, other drugs such as epinephrine and clonidine may cause hyperglycemia in normal patients or compromise metabolic control in diabetics (DOYLE; EGAN, 2003).

Clinically significant drug interactions between captopril and losartan, and between enalapril and losartan (have excellent documentation) are also among the ten major severity interactions. The double-blocking of the renin-angiotensin-aldosterone system, caused by the concomitant use of an angiotensin converting enzyme inhibitor and an angiotensin II receptor antagonist, is related to the increased incidence of adverse effects, such as hypotension, syncope, hypercalcemia, and changes in renal function (MICROMEDEX, 2016).

In this study, 184 patients (54.67%) presented drug interactions with clinical evaluation by taking 5 or more medications, and the results demonstrated that with the use of Micromedex® databases it was possible to prevent some signals and symptoms caused by the medicines. Keine *et al*. (2019) used uMETHOD Health, a software platform,to enhance medication management in elderly population and showed that this system was able to identify various polypharmacy problems that individuals have been currently facing, avoiding drug interactions and monitoring patients for expected reactions. The use of electronic medical records must be prevalent in hospitals because many especially elderly patient (42.67% in this study), use many drugs per day. Keine *et al*. (2019) report in their studies that physicians do not take more actions to prevent drug interactions in their patients, and Phansalkar *et al*. (2012) showed that between 33% and 96% of medication-related electronic medical records alerts are overridden by physicians. This is mentioned as “alert fatigue” - even clinically expressive alerts that have been ignored (PHANSALKAR *et al*., 2012; PATERNO *et al*., 2009). Computational approaches provide information to discover potential DDIs on a large scale for further screening and have gained recently a lot of attention from academy and industry (ZHOU *et al*., 2016). There are many available systems to detect DDIs and also drug-protein interaction which play important roles in pharmacodynamic and pharmacokinetic steps of drugs (SHI *et al*., 2019). These systems, as demonstrated in this study, must be a common alternative for hospitals and drugstores to prevent many

effects from DDIs in hospitalized patients, and also to reduce public costs.

4 Conclusion

The results of the present study demonstrated that drug interactions are directly related to the age and number of prescribed drugs. Dipyrone was the drug of greater frequency of administration. Most DDIs observed were of moderate severity and were related to imbalance of blood pressure and glycemic levels, which generally require dose-adjusting medical intervention to reduce the adverse reactions resulting from these interactions. And the greater frequency of drug interactions with fair documentary evidence alerts to the need to consider all the possible interactions. Taken together, this study showed potential DDIs and sign and symptoms clinicals significant in patients and reinforces the need to support Clinical Pharmacy.

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