Journal of Pharmacy and Pharmacology 4 (2016) 658-666
doi: 10.17265/2328-2150/2016.12.002

Prevalence of Potential Drug-Drug Interactions in Hospitalized Surgical Patients

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Abstract: The objective of this study is to estimate the prevalence and describe the characteristics of pDDIs (potential drug-drug interactions) in medical prescriptions of hospitalized surgical patients. In this cross-sectional study, we analyzed 370 medical prescriptions from the surgery unit of a Mexican public teaching hospital. The identification and classification of potential drug-drug interactions were performed with the Micromedex 2.0 electronic drug information database. Results were analyzed with descriptive statistics and we estimated OR (odds ratio) to determine associated risk factors. From the study, it was found that the prevalence of potential drug-drug interactions was 45.9%. A total of 385 interactions were identified. Of these, 54.3% were classified as major and 60.5% as pharmacodynamic. Prescriptions for more than seven drugs (OR =7.33, CI (confidence interval) = 4.59~11.71) and advanced age > 60 years, (OR = 1.79, CI = 1.06~2.74) were positively associated with the presence of potential drug-drug interactions. We found a high prevalence of clinically relevant pDDIs in the surgery unit. In view of this outcome, the safety of drug combinations in hospitalized surgical patients should be evaluated during the prescription process in order to prevent adverse events.

Key words: Potential drug-drug interactions, medical prescriptions, concomitant drugs, surgery.

1. Introduction

Prescribing several medications to a patient can cause unexpected consequences. In this regard, the co-administration two or more drugs may represent a risk to patient safety since some of these combinations can cause DDIs (drug-drug interactions). DDIs are defined as the modification of the pharmacological or clinical response to a drug due to the concomitant administration of another drug [1]. This modification is due to alterations in the pharmacokinetic or pharmacodynamic properties of prescribed medications. One of the consequences of the presence of DDIs is the increased or decreased effectiveness of treatment associated with therapeutic failure, as well as an increased toxicity of the prescribed medications [2].

Moreover, DDIs are considered a risk factor for medication safety. As a result, DDIs have become a common concern and an important concept in terms of an appropriate prescription process [3]. Furthermore, the presence of DDIs in hospitalized patients is one of the major causes of adverse events [4, 5]. In ambulatory patients, DDIs represent 0.1% of hospital visits and 1.1% of hospital admissions [6], resulting in increased hospital stay days, as well as higher costs

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associated with healthcare [7, 8]. The risk factors associated with DDIs include age, the number of prescription medications, the presence of comorbidities and the number of hospital stay days [3, 9-11].

The pDDIs (potential drug-drug interactions) are theoretical interactions [12] identified and evaluated at the time of prescription through database information, whereas real DDIs are only detected and evaluated following the administration of the implied medications in case the patient presents an adverse event. Careful identification and monitoring of pDDIs can improve the quality of the prescription process [13] and the safety of drug therapy that patients receive during their hospital stay.

The prevalence of pDDIs in hospitals has been reported between 20% and 91% in various countries [9-11, 14, 15]. Another study, conducted in a referral hospital in Switzerland, reported a pDDI prevalence of 20~24% in hospitalized surgical patient prescriptions [16]; however, studies conducted in hospital surgery units are limited.

The clinical significance of DDIs has been recognized worldwide within the framework of patient safety. In Mexico, studies that focus on the characteristics and frequency of DDIs in order to achieve early detection and timely management are scarce. The objective of this study was to estimate the prevalence and describe the characteristics of pDDIs in medical prescriptions of hospitalized surgical patients from a Mexican public teaching hospital.

2. Materials and Methods

2.1 Study Population and Sample

This cross-sectional, descriptive study was conducted in the surgery unit of a teaching Mexican hospital. We included all the prescriptions with two or more drugs of hospitalized surgical patients. Incomplete prescriptions with missing data were excluded. The sample size was calculated considering the population size of 9,819 (this number corresponds to the number of non-ambulatory surgeries performed in a year) with a power of 20% and a bias of 5%, resulting in a total of 370 medical prescriptions. The study was approved by the Research and Institutional Bioethics Committee with the registration number 011/14HCJM/2014.

The hospital where the study was conducted is a teaching hospital of second and third level of medical care with 501 beds and the following areas: pediatrics, OB/GYN (obstetrics and gynecology), internal medicine and surgery. Surgery has 90 beds and includes the following surgical specialties: general surgery, neurosurgery, thorax and cardiovascular, orthopedics and traumatology, maxillofacial surgery, urology, oncosurgery, bariatric, colon and rectal surgery, laparoscopic surgery, plastic surgery, head and neck, and ophthalmology.

2.2 Procedure

Patient demographic information (age and gender), specialty area and pharmacotherapy were registered with a specific format designed for this purpose by our study group. During the data collection, 12 prescriptions were excluded due to incomplete prescriptions. The evaluation period continued until we obtained the calculated sample size which culminated in five months.

2.3 Identification and Analysis of pDDI

Micromedex 2.0 electronic database was used for pDDI identification and analysis. The names of the drugs prescribed were introduced in the Drug-Reax system [17], and after the detection of pDDIs, these were classified according to severity and quality of the documentation as provided by the electronic database (Table 1). Also, the information of the possible clinical implications derived from the pDDIs was classified into seven categories (Table 2). The production mechanism was classified as: pharmacodynamic, pharmacokinetic or unknown, and the observed time of onset of the adverse event was classified as: rapid, delayed or not specified.

Table 1 Classification criteria for the severity and quality of the documentation of potential drug-drug interactions according to Micromedex 2.0 database.

Items	Classification	
Severity	Contraindicated	When the drugs are contraindicated for their concomitant use
	Major	The interaction is life threatening and or requires medical treatment or intervention to minimize or prevent severe adverse effects
	Moderate	The interaction may result in exacerbation of the disease and/or change in therapy
	Minor	The interaction would limit the clinical effects. The manifestations may include an increase in frequency or severity of adverse effects, but usually they do not require change in therapy
Quality of the documentation	Excellent	There are controlled studies that have clearly established the presence of the interaction
	Good	The documentation suggests an interaction, but lacks documented evidence from controlled trials
	Fair	The available documentation is considered poor, but pharmacological data suggests that an interaction is present or the documentation is good for a pharmacologically similar drug

Table 2 Categories of the possible clinical implications of potential drug-drug interactions established from the information of Micromedex 2.0 according to its adverse event.

Category	Possible adverse event of the pDDIs
Metabolic alterations	Hypoglycemia, hyperglycemia, increased level thyroid-stimulating hormone
Decreased therapeutic efficacy	Decreased therapeutic efficacy of the one the drug implicated in the interaction
Toxicity CNS (central nervous system)	Ataxia, hyperreflexia, nystagmus, tremor, seizure, syncope, serotonin syndrome, CNS depression, and sedation
Cardiovascular system alterations	QT-interval prolongation, arrhythmia, hypotension and bradycardia
Risk of bleeding	Bleeding
Gastrointestinal tract adverse events	Gastrointestinal hemorrhage, ulceration, bleeding, perforation, nausea, vomiting and diarrhea
Others	Adverse events in isolation: hyperkalemia, hepatotoxicity, ototoxicity, tendon rupture, nephrotoxicity, thrombosis, and respiratory depression

We considered all identified potential interactions by the Drug-Reax system, independently of the severity and quality of the documentation.

Even though patients were prescribed several medications, in this study we only considered those medications that were actually administered according to prescription records. Furthermore, the route of administration of a particular medication determines the presence of a specific interaction as described in the literature, so in this study we only included those pDDIs whose administration route corresponded to the possible mechanism of production in accordance to data described by Micromedex 2.0.

2.4 Statistical Analysis

Qualitative data were presented as frequencies and percentages. Quantitative data were presented as median and range. We estimated the OR (odds ratio) and CI (confidence interval) for the number of drugs prescribed and age. Statistical significance was considered at a p value of ≤ 0.05. All data were analyzed with the SSPS V. 20 program.

Prevalence was calculated with the following formula:

$$\text{Prevalence} = \frac{\text{Number of medical prescriptions with at least one pDDI}}{\text{Total number of analyzed prescriptions}} \times 100$$

3. Results

Of the total prescriptions (n = 370), 52% were from female patients and 48% from males and the median age was 46 years with a range of 14~96 years. The number of drugs per prescription was 2~16, with a median of seven drugs. Medical prescriptions included in the study were mainly from general surgery (52.2%), neurosurgery (11.6%), orthopedics and traumatology (8.4%), thorax and cardiovascular (8.1%) and the

remainder other specialties (19.7%). We detected at least one pDDI in 170 medical prescriptions from the total number of prescriptions included in this study (n = 370). As a result, the estimated prevalence of pDDI prescriptions was 45.9% (170/370), with a median of two interactions and a range of 1~12 pDDIs per medical prescription.

A total of 385 pDDIs were identified and classified based on their severity, production mechanism, time of onset of the adverse event, and the quality of documentation provided by Micromedex 2.0. Of these, 53.4% were classified as major and 65.5% of pharmacodynamic. In terms of the quality of the documentation, 51.9% corresponded to the fair category and for 57.7%; the time of onset was classified as not specified (Table 3).

The possible clinical implications derived from pDDIs were classified in seven categories according to information provided by Micromedex 2.0, where 23.4% of pDDIs could cause cardiovascular system alterations followed by decreased therapeutic efficacy (19%) (Table 3).

The most frequent potential drug-drug interactions identified were: metronidazole/fluoroquinolones, ondansetron or octreotide (15.8%), enoxaparin/NSAID (nonsteroidal anti-inflammatory drug) (14.3%), and NSAID/NSAID (6.7%) (Table 4).

NSAIDs (nonsteroidal anti-inflammatory drugs) were most often associated with pDDIs, followed by fluoroquinolones and nitroimidazoles (Table 5).

Lastly, the number of drugs (OR = 7.33, CI = 4.59~11.71) and older age (OR = 1.79, CI = 1.06~2.74) were positively associated with the presence of potential drug-drug interactions (Table 6).

4. Discussion

The prevalence of pDDIs in the surgery unit was found to be 45.9%. Of these, most were considered major in terms of severity (54.3%) and 60.5 % of pharmacodynamic origin according to the Micromedex 2.0 classification. Our results differ with those reported by Kulkarni et al. [10], who found a prevalence of pDDIs in medical prescriptions up to 91% where most mainly were moderate (70%) and of pharmacokinetic

Table 3 Characteristics of potential drug-drug interactions in the surgery unit according to Micromedex 2.0 database.

Characteristics of potential drug-drug interactions		Number of pDDIs n = 385	Percentage (%)
Severity	Contraindicated	29	7.5
	Major	209	54.3
	Moderate	141	36.6
	Mild	6	1.6
Production mechanism	Pharmacodynamic	233	60.5
	Pharmacokinetic	63	16.4
	Unknown	89	23.1
Time of onset of the adverse event	Not specified	222	57.7
	Rapid	115	29.9
	Delayed	48	12.5
Quality of the documentation	Fair	200	51.9
	Good	127	33.0
	Excellent	58	15.1
Possible clinical implications	Cardiovascular system alterations	90	23.4
	Decreased therapeutic efficacy	73	19.0
	Risk of hemorrhage	58	15.0
	Toxicity CNS (central nervous system)	55	14.3
	Metabolic alterations	49	12.7
	Gastrointestinal tract adverse events	38	9.9
	Others	22	5.7

Table 4 Characteristics of most frequent potential drug-drug interactions in hospitalized surgical patients.

Drug pairs with most frequent potential drug-drug interactions	Number of pDDIs (%)	Severity/quality of the documentation	Description of the potential interaction	
Metronidazole + (Fluoroquinolone, ondansetron, octreotide)	61 (15.8%)	Major/fair	Mechanism	Pharmacodynamic, additive effects on QT-interval prolongation
			Possible clinical implications	Increased risk of arrhythmias and QT interval prolongation
			Clinical management	Close monitoring of ECG[a]
Enoxaparin + NSAID[b]	55 (14.3%)	Major/good	Mechanism	Pharmacodynamic, decreased platelet function and coagulation
			Possible clinical implications	Increased risk of hemorrhage
			Clinical management	Discontinue NSAID[b] use before administering enoxaparin, whenever possible; otherwise monitor the patient for bleeding signs and symptoms
NSAID[b] + NSAID[b]	26 (6.7%)	Contraindicated/fair	Mechanism	Pharmacodynamic, additive effects on gastrointestinal irritation
			Possible clinical implications	Increased of serious gastrointestinal adverse effects (ulceration, bleeding and perforation)
			Clinical management	Avoid combinations completely
NSAID[b] + ACE[c] inhibitors	22 (5.7%)	Moderate/excellent	Mechanism	Pharmacodynamic, decreased production of renal prostaglandins
			Possible clinical implications	Renal dysfunction and decreased antihypertensive efficacy
			Clinical management	Monitor the antihypertensive efficacy and renal function periodically
Fluoroquinolone + Antidiabetic drug	20 (5.2%)	Major/excellent	Mechanism	Unknown
			Possible clinical implications	Increased risk of hyperglycemia or hypoglycemia
			Clinical management	Close monitoring of blood glucose levels and adjust the dose of the antidiabetic agent indicated
Omeprazole + Phenytoin	19 (4.9%)	Moderate/fair	Mechanism	Unknown[d]
			Possible clinical implication	Increased risk of phenytoin toxicity (ataxia, hyperreflexia, nystagmus, tremor)
			Clinical management	Patient monitoring of phenytoin serum levels and dose adjustment
Metoclopramide + Tramadol	16 (4.2%)	Major/fair	Mechanism	Unknown
			Possible clinical implications	Increased risk of seizures
			Clinical management	Not provided[e]
NSAID[b] + Calcium channel blocker	13 (3.4%)	Moderate/good	Mechanism	Pharmacodynamic, additive effects, and decreased renal prostaglandin production
			Possible clinical implications	Increased risk of gastrointestinal bleeding
			Clinical management	Monitor signs and symptoms of gastrointestinal bleeding such as nausea and blood in stool

[a] ECG: electrocardiogram;

[b] NSAID: nonsteroidal anti-inflammatory drug;

[c] ACE: angiotensin converting enzyme;

[d] Possible mechanism: inhibition of phenytoin metabolism;

[e] The box with the words "Not provided" is because the Micromedex 2.0 information clinical management was not found.

(Table 4 continued)

Drug pairs with most frequent potential drug-drug interactions	Number of pDDIs (%)	Severity/quality of the documentation	Description of the potential interaction	
NSAID + Angiotensin II receptor blocker	9 (2.3%)	Moderate/good	Mechanism	Pharmacodynamic, interference in the production of vasodilator and natriuretic prostaglandins
			Possible clinical implications	Decreased antihypertensive efficacy and increased risk of renal insufficiency
			Clinical management	Monitor renal function
ACE Inhibitor + Antidiabetic drug	9 (2.3%)	Moderate/fair	Mechanism	Unknown
			Possible clinical implications	Increased risk of hypoglycemia
			Clinical management	Monitor glucose more frequently during concomitant use and after the withdrawal of any of the drugs

[a] ECG: electrocardiogram;

[b] NSAID: nonsteroidal anti-inflammatory drug;

[c] ACE: angiotensin converting enzyme;

[d] Possible mechanism: inhibition of phenytoin metabolism;

[e] The box with the words "Not provided" is because the Micromedex 2.0 information clinical management was not found.

Table 5 Most frequent drug groups involved in potential drug-drug interactions.

Pharmacological classification of drugs	Percentage (%) (n = 770)
Nonsteroidal anti-inflammatory drugs	23.1
Fluoroquinolones	11.4
Nitroimidazoles (metronidazole)	8.8
Anticoagulants	7.1
Anticonvulsants	6.4
Antiemetics	4.9
Angiotensin converting enzyme inhibitors	4.5
Beta-adrenergic blockers	3.2
Opiod analgesics	3.1
Others	27.5

Data are expressed as percentages of the total drugs involved in pDDIs.

Table 6 Association between age and the number of drugs prescribed in the presence of a potential drug-drug interaction.

Variable		Potential drug-drug interaction		p value[a]	OR[b] (95% CI)
		Presence (n(%))	Absence (n(%))		
Number of drugs	≤ 7	60(27.3%)	160(72.7%)	Reference	
	≥ 8	110(73.3%)	40(26.7%)	<0.001	7.33 (4.59~11.71)
Age	≤ 60	118(42.6%)	159(57.4%)	Reference	
	≥ 61	52(55.9%)	41(44.1%)	0.026	1.79 (1.06~2.74)

[a] The p value is calculated by Chi2. Statistical significance was considered at $p \leq 0.05$.

[b] Risk factors for OR values with their respective confidence intervals are: number of drugs prescribed and age.

origin (42%) [10]. This discrepancy could be the result of the differences within drug profiles of medications prescribed in the surgery unit. Moreover, in a teaching hospital in Ethiopia, the prevalence of pDDIs was found to be 32.61% and only 9.59% of these were considered major. In comparison with our results, the difference in the prevalence of pDDIs could be due to the distinct databases that were used in each study, as well as by the methodology implemented to classify pDDIs [18]. On the other hand, a study performed in a teaching hospital in Brazil reported a pDDI prevalence in adult hospitalized patients of 49.2% which was

similar to our findings [11]. Even though this study was not conducted in the surgery unit, the similarity found may be due to the comparable ages of patients in both studies (12~96 years compared to 14~96 years of our study), and by use of the same database.

In regards to other reported findings in the international literature in terms of the prevalence and nature of pDDIs in hospitalized surgical patients, these are scarce. A study performed in Reference Hospitals of Switzerland, medical prescriptions of three different departments where analyzed, including the surgery unit where a lower pDDI prevalence of 20~24% was found in hospitalized surgical patients [16], compared to the 45.9 % prevalence of our study group. Considering pDDI severity, the majority were classified as moderate and mild [16], compared to the severe classification of most pDDIs in our study. This variability between the prevalence and pDDI profiles, in spite of being conducted in the same hospital area (surgery unit), could be attributed to the differences between the database used for pDDI identification and classification.

In our study, the most frequent interaction was the concomitant use of two drugs which favors an increased risk of QT-interval prolongation. Previous studies involving the prevalence and clinical significance of this interaction have been performed in ICUs (intensive care units). In hospitalized ICU patients who received at least two medications that prolong QT-interval, we identified the presence of DDIs derived from this combination as a cause of QT prolongation. The medications which were most frequently associated to interactions were: ondansetron, amiodarone, metronidazole and haloperidol [19]. Although this study was not conducted in an ICU, the drug combinations that prolong the QT-interval are common and this practice could have a negative impact on patient safety. Meanwhile, the risk of arrhythmia with medications not used for heart disease is small (0.01~0.1%) [20]; however, the concomitant use of two or more medications from this drug group, and the presence of pDDIs, could significantly increase this risk, and thus, the probability of a serious adverse event is more likely.

Patients included in this study were either in a pre or post-operative period and pain is one of the most common symptoms that these patients report, so the use of analgesics is common. NSAIDs were most often associated with pDDIs. In accordance with our results, NSAIDs have been identified as one of the groups most often associated with DDIs in hospitals [21]. However, it is important to mention that this outcome is also associated to the frequency of prescription since a high percentage (73.4%) of medical prescriptions included at least one NSAID. Previous studies which have included different hospital areas or patient groups, the drug groups associated with an increased pDDI frequency were different to our findings. A study which included pDDIs in medical prescriptions of patients with hypertension, atenolol and acetylsalicylic acid were the most frequent medications (25.9%) associated to pDDIs [22]. Furthermore, in hospitalized patients from a cardiovascular unit, atorvastatin was the drug most often associated with pDDIs (33.3%) and one of the most commonly prescribed (14.7%) [23].

The association between the number of drugs (> 7) and advanced age (> 60 years) was estimated in this study, where both factors were positively associated with the presence of pDDIs. These factors, as well as the presence of comorbidities, and length of hospital stay in days have already been considered in the literature as important risk factors for the presence of potential drug-drug interactions [9, 11, 14, 15, 21].

Among the weaknesses of the study is the possibility of selection bias since the sampling method was not established; however, we included all prescriptions that met the selection criteria during the length of the study. In the study's limitations, the lack of inclusion of other risk factors for the presence of drug-drug interactions, as well as the length of hospital stay and the presence of other comorbidities were not considered in this study. Future follow-up studies could be useful for assessing

the safety of drugs most commonly prescribed in the surgery unit where clinically significant pDDIs where identified with the main objective of establishing strategies to avoid adverse events in patients.

5. Conclusions

The high prevalence and profile of pDDIs found in this study show that the combination of certain medications during the prescription process in hospitalized surgical patients is a common practice and thus, represents a latent risk factor for patient safety. Timely detection and evaluation of pDDIs could be key for ensuring the efficacy and safety of the drug treatment patients receive during their hospital stay.

We suggest future follow-up studies in hospitalized surgical patients in order to assess the clinical manifestations, possible risk factors, and determine strategies aimed at preventing adverse events, associated with the pDDIs identified in this study.

Acknowledgments

The authors wish to thank the PRODEP (Teacher Professional Development Program) for the financial resources granted and the institution for providing support and granting the necessary authorizations for the study.

Conflict of interest

There are no conflicts of interest to declare.

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