Drug-Drug Interactions Associated with Length of Stay and Cost of Hospitalization

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ABSTRACT

Purpose To evaluate the prevalence of drug-drug interactions (DDI) in hospitalized patients and to identify associated risk factors. **Methods** A retrospective cross-sectional analysis of prescription data and medical records from a public hospital in Brazil was conducted to identify potential DDI. Inappropriate drug combinations were identified and classified with a standard drug interaction source. Primary diagnoses were classified with Charlson Comorbidity Index (CCI). Sex, age, polypharmacy and length of stay, among other variables, were correlated with the frequency of potential DDI. **Results** The study included 589 patients and 3,585 prescriptions. Thirty-seven percent of the patients were exposed to at least one potential interaction during their stay in the hospital. The most frequent interacting pair was Digoxin+Furosemide (11%). In univariate analysis, several variables were associated with DDI, including sex, age, number of prescribed drugs, length and cost of hospitalization and CCI. Multivariate analysis showed that the adjusted odds of being prescribed a potential DDI among patients in polypharmacy was almost five-fold that of patients taking fewer than five drugs. Further, length of stay, CCI and cost of hospitalization were independently associated with DDI. **Conclusion** Analysis of prescription data found that a substantial number of potential DDI were identified. Results of this study indicate that DDI is associated with number of prescribed drugs, increased duration of stay in the hospital and cost, which suggests that DDI are a significant clinical and economic problem. Potential harm to patients could be avoided.

INTRODUCTION

Adverse drug events (ADEs) have become a major public health concern to patients and health care professionals. The economic burden of drug-related morbidity and mortality was estimated to be US$ 177.4 billion in 2001 in the United States (1). Classen *et al.* (1997) showed that ADEs significantly prolong length of hospital stay and cost of treatment, and elevate the risk of death (2). Drug-drug interaction (DDI) is a specific type of adverse drug event; it occurs when the effect of one drug is changed by the presence of another drug, resulting in increased toxicity or reduction in therapeutic efficacy. DDI are significantly more likely to occur in hospital settings, where patients are commonly on multiple drug regimens.

Studies concerning drug-drug interactions have reported potential DDI in medical prescriptions, regardless of whether they lead to adverse clinical consequences. These studies have found rates of potential DDI ranging from approximately 5.4% to 63% (3-7). Differences in methods to classify drug interactions, study periods and target population contribute to these discrepancies.

Despite evidence of deleterious outcomes related to many DDIs, factors associated with such events have not been fully elucidated, and little is known about the characteristics of the patients exposed to DDIs. It has been shown that these events increase with patient age, with the number of drugs prescribed and when multiple physicians are involved in patient care (8-10). By contrast, few studies have addressed the relationship between drug-drug interactions and other important factors, such as length of stay, mortality and cost of hospitalization. Furthermore, previous studies have not evaluated the use of risk-adjustment measures (11) that would allow adjustment for confounders for the above outcomes.

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The present study aimed to assess the prevalence of DDI in hospital prescriptions and DDI's relationship with risk factors, including patient's age, number of prescribed drugs and length and cost of hospitalization.

METHODS

A retrospective cross-sectional study was conducted at the General Hospital of Vitória da Conquista, Brazil. The study population comprised all patients aged 18 years or older admitted to the hospital from January 2007 to March 2007 who had a length of stay greater than 24 hours. The hospital is a 172-bed public institution providing primary and tertiary care to an urban population of approximately 300,000 inhabitants. It also serves as a referral center for the Southwest region of Bahia state, one of the most populous states in Brazil.

Patients transferred to another hospital for possible admission were excluded from the study, as well as patients who died within 48 hours of admission. Patients for whom no information on medical prescription was available were also excluded.

Information on prescription drugs (drug names, dosage, prescription dates, ward) was collected from records of the hospital pharmacy department. All prescription records containing two or more drugs were selected. Hospitalization records, including length of stay, cost, diagnosis on admission (according to ICD-10 classification) and demographic information (age, sex) were retrieved from the national hospital database of the Brazilian Healthcare System (SIH/SUS) using information from the hospitalization authorization form (*AIH*). AIH is a DRG-based hospital payment system that covers almost 70% of all Brazilian hospital admissions and 100% of admissions in the hospital where the study was carried out. The AIH is used exclusively for the payment of hospitalizations that are reimbursed through a prospective payment system. The payment unit in this system is the "procedure;" the value of each procedure is pre-defined at the central level, without distinguishing among different providers (except for university hospitals). Information was also collected from patient medical discharge forms.

All drugs were classified according to the Anatomical Therapeutic Chemical Classification (ATC). In case of fixed drug combinations, each active compound was treated separately. As a result, for every patient, a list of all possible drug pairs was generated. Potential DDI were identified on this list and classified using a standard drug interaction source (12). The source classifies pairs of drugs with potential interactions according to a 5-level clinical significance rating based on the severity (i.e., major, moderate, minor) and extent of documentation (i.e., established, probable, suspected, possible, unlikely). Only DDI with significance level 1 (severity: major, documentation: suspected or higher) or 2 (severity: moderate, documentation: suspected or higher) were identified.

The frequency of potential drug interactions was analyzed, rather than the frequency of diagnosed drug interactions. Age, sex, admission to intensive care unit (yes or no), blood transfusion (yes or no), death, cost (in US$), length of stay (in days) and polypharmacy (yes or no) were associated to the frequency of potential drug interactions. A patient taking an average of five or more medications per day was considered to be a polypharmacy patient. Clinical conditions were classified with a modified version of the Charlson Comorbidity Index (CCI) on the basis of hospital discharge International Classification Disease 10^{th} version (ICD-10) codes. This Charlson-like index uses a single hospital diagnosis based on ICD-10 for risk adjustment (13). The modified CCI was dichotomized (low morbidity = 0, high = 1).

Descriptive statistics were expressed as proportion, mean (±SD) or median with the corresponding range. Univariate analyses were performed using logistic regression models to estimate the effect of covariates on the occurrence of potential drug interactions. In multiple logistic regressions, variables considered for adjustment were those associated with DDI at $p<0.20$ in univariate analysis. For these analyses, continuous variables (cost and length of stay) were dichotomized at the median value. Modeling began with all variables, followed by sequential deletion according to statistical significance. Models were compared using the likelihood ratio test. Odds ratios and 95% confidence intervals (95% CI) were derived from the β coefficients and their respective standard errors. All statistical analysis was performed with R for Windows® version 2.6.2.

The research project was approved by the local ethics committee and registered in the National System of Information on Ethics in Research (SISNEP).

RESULTS

Overall, 763 patients were identified for this study. Of these, 159 were excluded due to incomplete information regarding medical prescriptions, and 15 were excluded due to death within 48 hours following admission. Both groups of patients, selected and non-selected, were similar with respect to age (mean: 50.5 versus 50.7 years, respectively; $p = 0.90$) and gender (female:male, 305:284 versus 104:70, respectively; $p = 0.08$).

The selected population comprised 589 patients (284 males and 305 females) and 3,585 prescriptions. The average age of the patients was 51±22 years (range 18-99) and the median length of hospital stay was 6 days. The total median cost per hospitalization was US$ 192.10. The most common causes of hospital admission, according to ICD-10 Classification, were: S06.0 - Concussion (7.3%); G45.9 - Transient cerebral ischemic attack unspecified (7.0%) and I50.9 Cardiac, heart or myocardial failure NOS (7.0%). Prescription size ranged from 2 to 11 and median of 5.3.

A total of 1,282 potential DDI were identified in 816 (23%) prescriptions, 220 (37%) patients were exposed to at least one potential interaction during their stay in the hospital. Among the 816, 504 had one potential drug interaction (62%), while 312 (38%) had more than one. Potential drug interaction detected expressed as the number of drug pairs within a single prescription at each level of severity and evidence are shown in Table 1. Those of major severity level accounted for 22%, and 67% of them were supported by levels 1 or 2 of evidence, i.e., evidence to suggest that adverse effects were probable. The most frequent interacting drug pairs were Digoxin+Furosemide, Amitriptilin+Phenytoin, Amikacin+Ketoprofen, Captopril + Spironolactone, Phenytoin+ Dexamethasone and (Table 2).

Table 1. Drug interactions by level of severity and evidence

Severity	
Level	Frequency % (n)
Major	22 (278)
Moderate	78 (1004)
Evidence	
Level	Frequency % (n)
Established	16 (206)
Probable	37 (479)
Suspected	47 (597)

Table 2. The five most common potential drug-drug interactions

Drug Interaction Pair (n)	Potential adverse event	Severity	Evidence
Digoxin+furosemide (145)	Digitalis-induced arrhythmias	Major	Probable
Amitriptilin+phenytoin (104)	Increased phenytoin effects	Moderate	Possible
Amikacin+ketoprofen (101)	Increased amikacin accumulation	Moderate	Suspected
Captopril+spironolactone (96)	Increased serum potassium concentrations	Major	Probable
Phenytoin+dexamethasone (96)	Decreased dexamethasone effects	Moderate	Established

In order to explore factors associated with potential DDI, several variables were considered in univariate analysis. The odds ratio (OR) for each variable is presented in Table 3. The proportion of DDI was higher among male patients (OR: 1.90, 95% IC: 1.36-2.67) and patients aged 60 years or older (OR: 1.58, 95% IC: 1.12-2.23). The odds of being prescribed a potentially interacting drug combination were seven times greater among those patients with polypharmacy, that is, those with an average of five or more drugs per prescription. Patients with length of stay = 6 days or higher were more likely to be exposed to at least one potential drug

interaction (OR: 4.38, 95% IC: 3.03-6.41). The average (mean) length of stay for patients with drug-drug interactions was 15 days (95% CI 13-17) and 8 days (95% CI 7-9) for patients not exposed to DDI (Figure 1). Furthermore, high cost of hospitalization (US$ 192 or higher) was positively associated with DDI (OR: 3.10, 95% IC: 2.19-4.42). Patients admitted to intensive care unit, those who died during the hospitalization, patients with CCI ≥ 1 and patients receiving blood transfusions were also associated with potential DDI.

All variables that were found to have a significant relationship with drug-drug interaction in univariate analysis were included in multiple logistic regression. The adjusted OR and 95% confidence intervals for the variables included in the final model are shown in Table 3. Only CCI (odds ratio [OR] = 1.81; 95% CI = 1.29-2.74; P<0.004), length of stay (OR = 2.98; CI = 1.98-4.51; P<0.000), cost (OR = 1.79; CI = 1.19-2.68; P<0.005) and number of drugs (OR = 4.74; CI = 3.02-7.64; P<0.000) were independently associated with potential drug interactions in the final multivariate model.

DISCUSSION

In the present study, the rate of potential drug interactions in patients admitted to the hospital was 37% overall, 12% for major severity and 67% were supported by levels 1 or 2 of evidence. These numbers raise concerns of potential harm to the patients that could be avoided.

Despite different methods used to classify drug interactions, which make comparisons among studies difficult, these findings are similar to others reported for hospital-based studies evaluating clinical drug interaction (5, 14, 15). Egger *et al* (2003), using the Micromedex information system as a source of evidence, retrospectively screened medication records for potential DDI at hospital admission and discharge (14). Characteristics of the patients as well as prescription data were similar to the present study. The authors found that 60% of the patients had a potentially interacting drug combination on their prescription record at hospital discharge. Vonbach *et al* (2008) studied the prevalence of potential DDI during the hospital stay and at discharge (15). Similar to the present study, the authors considered only major and moderate DDI, and the frequency of patients with at least one DDI during the hospital stay was 56%.

Despite the high prevalence of potential drug-drug interaction, adverse clinical consequences resulting from a specific interacting drug combination may sometimes be counteracted by prescribing an additional drug. For instance, in this study the most frequent interacting drug pair was digoxin and furosemide. This combination may precipitate or contribute to the development of arrhythmias, especially in patients with preexisting cardiac abnormalities, but these effects can be prevented by dietary sodium restriction or addition of potassium-sparing diuretics. Due to the retrospective design of this study, it was not possible to assess whether these measures were taken.

Consistent with earlier studies, gender, age and polypharmacy were found to be associated with drug-drug interactions (5, 9, 10, 16). In addition to these factors, death, admission to ICU, CCI, blood transfusion, length of stay and cost were also associated with this outcome. Cruciol-Souza *et al.* (2006), in a case-control study, found an OR of 1.41 in older patients (age ≥ 55 years), and the odds of potential DDI among those patients on multiple drug regimen (7 or more) was nine-fold. In our study, the higher prevalence of DDI in older patients compared with younger ones could be partly explained by the high number of co-morbidities and pharmacologically active substances prescribed. In fact, association between potential interactions and patient age did not remain significant after adjusting for polypharmacy and other factors. Unlike our study, Cruciol-Souza *et al.* found that the odds of exposure were higher among females than males (OR: 1.23). By contrast, Gagne *et al.* (2008), in a prevalence study using an outpatient prescription database, also found an association between drug-drug interactions and age (OR:2.11) and, consistent with our results, the odds in females compared to males was lower (OR: 0.77) (10). Differences in these findings could stem from a number of factors, including prescribing habits and patient profiles; drug interaction screening databases used in both studies were different from ours. In fact, there are various DDI studies found in the literature and little agreement among them with respect to severity and clinical importance of interactions (17). Regarding this issue, Drug Interaction Facts is considered one of the most accurate compared to other sources of information on DDI, with both a sensitivity and specificity of 97% (18).

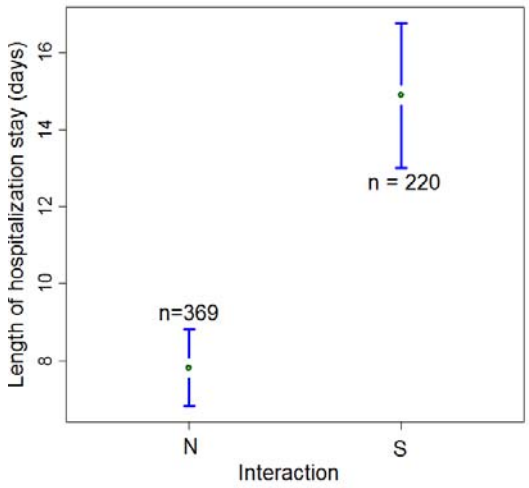

Figure 1. Length of hospital stay, in days, for patients with (S) and without (N) drug-drug interaction (mean and 95% confidence interval).

Our results also demonstrated that length of stay (OR: 4.38) and cost (OR: 1.79) of hospitalization were associated with DDI. Riechelmann *et al.* (2005) in a study of hospitalized cancer patients also found a positive association between length of stay and potential drug-drug interactions (19). Terleira *et al* (2007) found that interactions between drugs and laboratory tests produced an increase in the duration of hospital stay (20). These results may be explained by the fact that more drugs were administered to patients with a longer stay, resulting in a higher probability of drug-drug interactions. However, this possibility could be controlled, since the estimation was adjusted by the average number of drugs received per day. Thus, this association may be confounded by the severity of illness. Once more, patients with a higher severity of illness are more likely to have been prescribed more drugs so they are more likely to experience DDI. However, variables that quantify severity (CCI, blood transfusion and admission to ICU) were included in the multiple logistic model. It is therefore reasonable to believe that the increase in both length of hospital stay and cost of hospitalization could be related to possible adverse events resulting from drug interactions. For instance, a drug-related problem may demand extra lab tests or a symptomatic treatment that could lead to a prolongation of hospital stay and increased cost. However, this association must be interpreted with caution, since clinical manifestation of drug-drug interaction was not assessed.

Limitations of this study include its retrospective design and the use of an administrative claims database as source of patient information. For this reason, bias due to incomplete medical record documentation has to be considered. Moreover, this study was concerned with potential drug interactions on prescriptions, and no attempt was made to determine whether the patients actually ingested the medication or whether the interaction resulted in an adverse drug event. However, researchers have found various adverse patient outcomes as a result of DDI (21), including emergency department visits (22), hospital admission (23) or re-hospitalization (14). Therefore, future studies are needed to assess drug interactions and other drug-related problems that may appear clinically.

CONCLUSION

This study shows that potential drug-drug interactions are frequent among hospitalized patients. This work contributes to the epidemiologic data on the prevalence of these events and factors associated with them. The rate is directly related to number of prescribed drugs and length of hospital stay and cost, among other factors. Thus, development and implementation of cautionary guidelines and computer-based screening could help physicians and pharmacists prevent potentially dangerous drug interactions in order to avoid harming patients.

Table 3. Univariate and Multivariate analysis for factors associated with drug interactions

Variable	N(%)		Odds Ratio (95% CI)		*P* value	
	With Interaction	Without Interaction	Unadjusted	Adjusted	Unadjusted	Adjusted
Sex						
Male	128 (45)	156 (55)	1.90 (1.36-2.67)		< 0.000	
Female	92 (30)	213 (70)				
Age (years)						
≥ 60	95 (44)	120 (56)	1.58 (1.12-2.23)		0.010	
< 60	125 (33)	249 (67)				
Death						
Yes	39 (53)	34 (47)	2.12 (1.30-3.49)		0.003	
No	181 (35)	335 (65)				
Admission to ICU						
Yes	28 (62)	17 (38)	3.02 (1.63-5.76)		0.001	
No	192 (35)	352 (65)				
Department						
Surgical	31 (43)	41 (57)	1.31 (0.79-2.16)		0.290	
Clinical	189 (37)	328 (63)				
CCI						
≥ 1	101 (53)	91 (47)	2.59 (1.82-3.71)	1.81 (1.20-2.74)	< 0.000	0.004
= 0	119 (30)	278 (70)				
Blood transfusion						
Yes	36 (51)	35 (49)	1.87 (1.13-3.08)		0.010	
No	184 (36)	334 (64)				
length of stay (in days)	169 (52)	159 (48)	4.38 (3.03-6.41)	2.98 (1.98-4,51)	< 0.000	< 0.000
≥ 6	51 (20)	210 (80)				
< 6						
Cost (US$)						
≥ 192.10	149 (50)	149 (50)	3.10 (2.19-4.42)	1.79 (1.19-2.68)	< 0.001	0.005
< 192.10	71 (24)	220 (76)				
Polypharmacy						
Yes	191 (52)	179 (48)	6.99 (4.56-11.04)	4.74 (3.02-7.64)	< 0.000	< 0.000
No	29 (13)	190 (87)				

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