

## Prevalence of Potential Drug-Drug Interactions and its Associated Factors In a Brazilian Teaching Hospital.

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**ABSTRACT – Purpose.** The hazards of prescribing many drugs, including side-effects, drug-drug interactions (DDI) and difficulties of compliance have long been recognized as particular problems when prescribing. This study estimates the rate and factors associated with potential DDI in prescriptions from wards of a Brazilian teaching hospital. **Methods.** Data were retrieved from wards of a teaching hospital (300 beds) handwritten prescription, once a week during a period of 4 months in 2004. Potential DDI were identified using DrugReax® system. Patient's age and gender, number of prescribers; number of drugs and therapeutic drug classes on prescriptions were explored as associated factors to DDI. **Results.** The overall frequency of potential DDI was 49.7%. The frequency of the potentially major DDI was 3.4%, with digoxin-hydrochlorothiazide as the most common interacting pair. The rate of potential DDI was significantly associated to in-patients' gender [woman, Odds ratio (OR)=1.23 (P=0.035)], age  $\geq 55$  years old [OR=1.5 (P=0.0008)], number of therapeutic drug class (ATC code, level 1)  $\geq 4$  [OR=5.5 (P=0.0000), cardiology patients [OR=7.87 (P=0.0000)] hospitalized at weekends [OR=1.24 (P=0.039)] and having digoxin prescribed [OR=16.79 (P=0.0000)]. A positive correlation was found between DDI, patient's age, number of drugs and therapeutic action ATC codes were significant, controlling for gender (Pearson's  $r=0.628$ , P=0.001). **Conclusions.** Cardiology women inpatients, age more than 55 years old, 7 or more drugs prescribed (including digoxin) and hospitalized at weekends should be closely

monitored for adverse outcomes from DDI. A collaborative approach toward drug selection is strongly recommended, as well as electronic prescribing and development of pharmaceutical care in Brazilian hospitals.

## INTRODUCTION

Drug-drug interactions (DDI) in patients receiving multi-drug therapy are of wide concern. Such interactions are an important cause of adverse drug reactions and may lead to an increased risk of hospitalization and higher health care costs (Hamilton, Briceland and Andritz, 1998; Shad, Marsh, Preskorn, 2001; McDonnell and Jacobs, 2002; Wiffen et al 2002; Juurlink 2003). Studies conducted in various countries report rates of potential drug-drug interactions ranging from approximately 1 to 66 (Heininger-Rothbucher et al, 2001; Bjorkman et al, 2002; Geppert et al, 2003; Bobb et al, 2004; Klarin, Wimo and Fastbom, 2005). In Brazil, a number of short-term studies report on potential interactions among selected groups of drugs or patients (Meiners and Bergsten-Mendes, 2001; Miyasaka and Atallah, 2003). These reports suggest rates of 32% for paediatrics patients and 22% for psychiatric ones. The prevalence of drug-drug interactions and the factors associated with it is scarce. The aim of this study was to estimate the prevalence and the factors associated with potential DDI in adult inpatients' prescriptions of wards of a teaching hospital in Brazil.

## MATERIAL AND METHODS

### Study Design

A retrospective case-control study (1:1) was performed using data of the prescriptions held at the pharmacy of a Brazilian teaching hospital. The hospital is a 300-bed teaching public institution, which is also a referral centre for hospital care.

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## Study Population

During a 4-month period, approximately 11,250 adult inpatients received handwritten prescriptions with two or more drugs prescribed at wards. Based on a power calculation including chosen potential predictor with at least 11% of occurrence at controls, desired odds ratio  $OR > 1.5$ ,  $p < 0.05$ , calculated sample was of 1766 prescriptions (883 cases and 883 controls). It was selected random samples of cases (prescriptions with one or more DDI) ( $n=887$ ) and controls (prescriptions without DDI) ( $n=898$ ) were drawn from a source of 11,250 prescriptions (of which 49.7% with DDI). The total amount of prescriptions for further analysis in this study was 1785 prescriptions.

## Inclusion Criteria

Prescriptions with two or more drugs prescribed were selected once a week, from January to April 2004. All drug groups were accepted. Patients of both genders and 12 years-old or more were included in this study. Only one prescription from each patient during his/her hospitalization at ward during the study period was included.

## Study Protocol

A total of 1785 prescriptions were selected. The ratio man/woman in the study was preserved as 60/40, according to the hospital's wards ratio. Cases and controls were identified by using a computerized DDI database system (Micromedex® DrugReax® - Klasko, 2004). Case was defined as prescription with one or more potential DDI. To estimate rates, results were expressed as odds ratios. All drugs were classified with Anatomical-Therapeutic-Chemical Classification (ATC code, level one – WHO, 2004).

## Exposure Measures

Study predictors of DDI included and its criteria were: (a) prescriber characteristics [medical specialty; number of prescribers at each prescription; prescribing week day (weekend or no)], (b) patient characteristics [gender, age (more than 55 years old)], (c) drug characteristic [number of drugs, number of therapeutic drug classes

(number of ATC codes), therapeutic drug class, drug].

## STATISTICAL ANALYSIS

Demographic data of patients and other data of prescriptions were presented as media, standard deviation and percentage. Student's  $t$ ,  $\chi^2$  (qui-square) and Fisher's exact tests were performed. Probability (P) values of 0.05 or less were considered statistically significant. Odds ratio with 95% confidence intervals (95% CI) and Pearson's correlation were calculated. All statistical analyses used the statistical package EpiInfo® (Who, 2004).

## RESULTS

From 1785 prescriptions retrieved from hospital pharmacy for data analysis, at least 1089 prescriptions (61%) were of inpatients of male ward. The average age of inpatients was  $52.7 \pm 18.9$  years old (range: 12–98 years old).

Table 1 presents detailed information on all prescriptions that were included in this study.

**Table 1.** Characteristics of sample of prescriptions

CHARACTERISTICS	CASES	CONTROLS
	Range	Range
Patient's age (years old)	12-98	12-97
Number of prescribers	1-4	1-3
Number of drugs	2-20	2-17
Number ATC codes	1-8	1-8
<b>TOTAL</b>	<b>887</b>	<b>898</b>

Age of case patients ( $51.5 \pm 21.4$  years old) was not significantly different ( $p=0.551$ ) from controls ( $50.6 \pm 19.2$  years old). Prevalence of potential DDI was significantly higher for inpatients who were women [52.9%; 368/696;  $OR=1.23$  (95% IC: 1.01-1.50;  $p=0.035$ )] or patients who were 55 years old or more (55.2%; 411/745;  $OR=1.41$  (95% IC: 1.15-1.73;  $p=0.0008$ ).

Medical specialty, number of prescribers and prescription week day presented significant differences in DDI prevalence. Cardiology and ophthalmology, as medical specialties showed the

greatest potential DDI prevalence (87.2%, 123/141 for prescriptions from Cardiology; 85.0%, 17/20 for Ophthalmology). Prevalence of DDI in prescriptions for patients hospitalized at weekends was 53.4% [299/560; OR=1.24 (95% IC: 1.01-1.52, p=0.039)], and these were significantly different. Prevalence of DDI was significantly affected on a linear mode by more than one prescriber [53.2% (327/615), OR=1.25; 95% IC: 1.02-1.53; p=0.031], linear trend of  $\chi^2$  was also significant ( $\chi^2 = 7,374$ ; p=0,006).

The media number of drugs prescribed at case prescriptions ( $9 \pm 3$  against  $5 \pm 3$ ; p=0.0000) and media number of therapeutic drug classes ( $4 \pm 1$  against  $3 \pm 1$ ; p=0.0000) were significantly different from controls. DDI increased with the number of prescribing drugs and also with the number of ATC codes of therapeutic drug classes. Prevalence of DDI was significantly different when 7 or more drugs were present at prescription [58.5% (848/1450)] and when 3 or more therapeutic action codes were involved [64.5% (719/1114)]. DDI increased on a linear mode with the number of drugs prescribed (trend  $\chi^2=506.058$ , p=0.0000) and on a similar way with the number of ATC codes of therapeutic drug classes (trend  $\chi^2=284.353$ , p=0.0000). The top three ATC codes of therapeutic

drug classes associated with potential DDI were: sensory organs [ATC code "S", 80% (32/40), OR=4.16 (95% IC: 1.85-10.51; p=0.0002)], blood [ATC code "B", 67,2% (565/841), OR=3.95 (95% IC: 3.23-4.84; p=0.0000)] and cardiovascular system [ATC code "C", 67,0% (543/811), OR=3.71 (95% IC: 3.03-4.54; p=0.0000)].

It was found a positive correlation between total DDI and some predictors: patient's age, number of drugs and number of therapeutic areas, controlling for gender. Pearson's correlation was 0.628 (p=0.001).

At least 653 (73.6%) prescriptions presented more than one DDI with different adverse drug reactions, while 234 (26.4%) presented one. Prevalence of major DDI was 3.4% of 887. Some specific drugs were strongly associated with major DDI. Prescription of digoxin, aminophyllin, amiodarone, fluoxetine, metoprolol or warfarin led to potential DDI in approximately 95% of the times. Chances of DDI with one of these drugs were on average 13 times bigger than with other drugs. Table 2 presents the significant findings of the analysis.

**Table 2.** Prescription factors associated with drug interactions

<b>PREDICTOR FACTOR</b>	<b>OR</b>	<b>IC (95%)</b>	<b>P</b>
<b>PATIENT CHARACTERISTICS:</b>			
Age $\geq$ 55 years old	1.41	1.15-1.73	0.0008
Gender = Woman	1.23	1.01-1.50	0.0350
Number of drugs $\geq$ 7	9.91	7.92-12.39	0.0000
Number of therapeutic codes $\geq$ 3	9.91	7.92-12.39	0.0000
<b>PRESCRIBER CHARACTERISTICS:</b>			
More than one prescriber	1.25	1.02-1.53	0.0310
Medical Specialities: Cardiology	7.87	4.72-13.84	0.0000
Ophthalmology	5.83	1.68-31.13	0.0030
Prescription for weekend hospitalizations	1.24	1.01-1.52	0.0390
<b>DRUG CHARACTERISTICS:</b>			
ATC code "B"	3.95	3.23-4.84	0.0000

ATC code "C"	3.71	3.03-4.54	0.0000
ATC code "S"	4.16	1.85-10.51	0.0002
ATC code "J"	2.17	1.79-2.64	0.0000
Digoxin	16.79	7.35-47.17	0.0000
Metoprolol	16.79	7.35-47.17	0.0000
Aminophylin	14.60	3.66-126.75	0.0000
Amiodarone	7.42	3.64-17.09	0.0000
Fluoxetine	10.83	3.89-41.77	0.0000
Warfarin	indef	57.55	0.0000

## DISCUSSION

This study revealed that the overall prevalence of potential DDI in Brazilian teaching hospital prescriptions was 49.7%, prevalence of major DDI was 3.4% and which factors were associated with it. Prevalence of DDI was on the expected range of 1 to 66 reported before by other authors (Heininger-Rothbucher et al, 2001; Bjorkman et al, 2002; Geppert et al, 2003; Bobb et al, 2004; Klarin, Wimo and Fastbom, 2005). In Brazil, there are few studies about it. However, our values cannot be directly compared with Brazilian authors who had reported previously (Meiners and Bergsten-Mendes, 2001; Miyasaka and Atallah, 2003) because of the differences in the study design and population.

Our findings revealed also that the prevalence of potential DDI was positively associated with the patient's gender and age. A higher rate of DDI was present between woman and patients who were 55 years old or more. This corresponds to other studies reporting that potential drug interactions were common in elderly people who were on multi-drug regimen (Hamilton, Briceland and Andritz, 1998; Bjorkman et al, 2002). Our study shows that the odds ratio of having a potential DDI was twice greater than that of ages less than 55 years old. The higher rate of potential drug interactions in old age in this study was probably because of the higher number of prescribed medications to this population. Results from Kohler et al (2000) indicated that the percentage of elderly patients with potentially interacting drug combinations prescribed increased greatly with the number of medications given.

The rate of potential DDI was also associated with prescription size. This result was similar to that found by Bjerrum (2003), who noted that 15% of the population exposed to polypharmacy was exposed to drugs carrying a risk of harmful interaction. Results from other studies indirectly support this finding. Our study showed that the odds ratio of having potential drug interactions increased in a linear mode when the number of prescribed drug increased by one.

Also, Pearson's correlation showed positive association between total DDI and patient age, prescription size and number of therapeutic areas of drugs prescribed. Our data suggests that along with prescription size, medical specialty and number of prescribers are also clear predictors of potential DDI.

Fijn et al (2002) had found a highest rate for Orthopaedists while we do found a highest prevalence for Cardiologists. In our study, the chance of interacting drug pairs per prescription was 8 times higher for Cardiology patients than to ones from other medical specialities. These differences suggest that the pattern of hospital drug prescribing and patients are not similar around the world.

According to prescription data retrieved, it was not possible to estimate the duration of drug treatment. However, assuming that a patient had been taking any drug continuously prior to receiving another drug in the next period, we have shown that the rate of drug interactions was higher and dependent on the day of the week.

This study also revealed the prevalence of the potentially major drug interactions in Brazilian

teaching hospital adult wards. Langdorf et al (2000) had found 25% of prevalence of DDI at California. The major DDI included the commonly cardiovascular prescribed combination regimen of digoxin and hydrochlorothiazide. The risk of digitalis toxicity is increased in patients receiving these drugs concomitantly. Patients given diuretics with digitalis should be told to add rich sources of potassium to their diet or they should be given potassium supplements, even though their serum potassium level is normal (Klasco, 2004). Twenty-four percent of 144 patients on combination therapy of digoxin plus diuretic experienced digoxin toxicity, compared to only 9% of 53 patients on digoxin alone (Hurwitz & Wade, 1969). If a digitalis glycoside and a thiazide diuretic are used concurrently, the patient should be monitored for ECG signs of potassium depletion (Jorgensen & Sorensen, 1970). The clinical significance of such interactions depends on many factors such as drug dosage, period of concurrent drug use and extent of patient monitoring by physicians. These parameters were not the scope of this work, but are under investigation by now.

We had found 10% of prevalence of major DDI and that is of great concern. We cannot quantify how many of these DDI were known by the prescribing physicians but we assume that they were possibly unaware of the potential risk associated with certain combinations. We suppose that pharmacy staff had also failed to mediate this information to physicians. The process of prescribing and dispensing drugs at Brazilian hospitals should be reengineered.

The limitations of this study were most due to the retrospective design of it. To better quantify the clinical relevance of potential interacting drug combinations during hospital stay, a prospective design would be necessary, including a follow-up long enough after discharge to assess the outcome of DDI with a delayed onset too. More over, the clinical relevance of a DDI is often categorised along two dimensions (Roberts et al., 1996), the expected 'severity' of a patient's physical reaction to a DDI and the 'documentation', i.e. the amount and quality of research that suggests whether a particular DDI will indeed occur in humans. The clinical effects of any DDI, regardless of how well documented, do not occur in every patient or to the same degree of intensity. They depend on patient-related factors that usually require individual

assessment (Jankel and Fitterman, 1993). Besides, an additional drug prescribed may sometimes counteract the potential adverse clinical consequences resulting from a specific interacting drug combination. Generally, drug interactions programs do not consider this. Moreover, the sequence of drug administration and patient-related factors may be crucial for the occurrence of adverse effects and they were not part of the computerised check for DDI because patients' charts were not online.

The potentially major drug interacting combinations can be associated with clinically relevant adverse reactions. This does not preclude from closely monitoring the drug prescriptions to minimize the patient's risk of drug-related problems. A computerised drug-interaction program may be a valuable and helpful tool to check for DDI, but it has to combine with clinical pharmacological experience and expertise as well as the knowledge of relevant patient-related factors (Bond et al., 2001; Gray and Felkey, 2004). This also implies that computer programs should emphasize more on the practical importance of a drug interaction.

One common problem in the study of prevalence of DDI in prescriptions is that there are little agreement among commonly used drug interaction compendia and the absence of a gold standard reference (Abarca et al, 2004). In spite of that, DrugReax® has been considered the most complete one (Malone et al, 2004). In fact, we have used in this study the one that lists the majority of known interactions and this could have overestimated DDI in our sample. One problem for this kind of research at developing countries is the affordability to appropriate drug databases and drug interaction computer prescribing software. Besides, analysis of great number of handwritten prescriptions is time consuming without electronic prescribing.

All these points could have overestimated the risk of DDI. For better assess of the clinical relevance of a DDI it would be of great interest to know how often a DDI indeed manifests at prescriptions. This is the major contribution of this study. These numbers are generally lacking because drug interaction studies are focused on the mechanisms, pharmacokinetic studies, or from single case reports or case series that give no information on the denominator of patients exposed

to this drug combination (Koh, 2001; McCabe, 2004). Besides, DDI' studies of clinical relevance are often performed in a small group of volunteers or derive from case series with specific patients or drugs.

## CONCLUSIONS

Potential drug interactions are frequent among inpatients prescribed multiple medications. Prevalence of drug interactions increases by a linear mode according to number of drugs prescribed, number of therapeutic drug classes, patients' gender and age. Our findings revealed a positive Pearson's correlation between total DDI and patient age, number of prescribers, cardiology patients and hospitalization on weekends. Cardiology patients with comorbidity, age more than 55 years old, who had seven or more drugs prescribed (including digoxin) and hospitalized at weekends should be close monitored for adverse outcomes from DDI, to avoid clinically important consequences.

Electronic prescriptions, bar codes identification of patients and drugs, accurate system of drug news inside the hospital and prescription of less than seven drugs, as well as careful selection of drugs and active pharmaceutical care practices are some of the suggestions strongly recommended to Brazilian hospital physicians and pharmacists. More integrative relationship between health professionals and ways to improve hospital care are also recommended.

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## REFERENCES

- [1]. Abarca J, Malone DC, Armstrong EP, Grizzle AJ, Hansten PD, Van Bergen RC, et al. Concordance of severity ratings provided in four drug interaction compendia. *J Am Pharm Assoc (Wash DC)* 2004; 44(2): 136-41.
- [2]. Bjerrum L, Andersen M, Petersen G, Kragstrup J. Exposure to potential drug interactions in primary health care. *Scand J Prim Health Care* 2003; 21(3):153-8.
- [3]. Bjorkman IK, Fastbom J, Schmidt IK, Bernsten CB. Drug-drug interactions in the elderly. *Ann Pharmacother* 2002; 36(11):1675-81.
- [4]. Bobb A, Gleason K, Husch M, Feinlass J, Yarnold P, Noskin G. The Epidemiology of Prescribing Errors: The Potential Impact of Computerized Prescriber Order Entry. *Arch Intern Med* 2004; 164(7):785-792.
- [5]. Bond CA, Raehl CL, Franke T. Medication errors in the United States Hospitals. *Pharmacotherapy*. 2001; 9: 1023-1036.
- [6]. Fijn R, Van den Bemt PMLA, Chow M, De Blaey CJ, De Jong-Van den Berg LTW, Brouwers JRBJ. Hospital prescribing errors: epidemiological assessment of predictors. *Br J Clin Pharmacol* 2002; 53:326-31.
- [7]. Geppert U, Beindl W, Hawranek T, Hintner H. [Drug interactions in clinical practice. A pilot project for quality assurance in prescribing]. *Hautarzt* 2003; 54(1):53-7.
- [8]. Gray MD and Felkey BG. Computerized prescriber order-entry systems: evaluation, selection and implementation. *Am. J. Health-Syst Pharm*. 2004; 61:190-7.
- [9]. Hamilton RA, Briceland LL, Andritz MH. Frequency of hospitalization after exposure to known drug-drug interactions in a Medicaid population. *Pharmacotherapy* 1998; 18(5):1112-20.
- [10]. Heining-Rothbucher D, Bischinger S, Ulmer H, Pechlaner C, Speer G, Wiedermann C. Incidence and risk of potential adverse drug interactions in the emergency room. *Resuscitation* 2001; 49(3):283-8.
- [11]. Hollifield JW. Thiazide treatment of hypertension. Effects of thiazide diuretics on serum potassium, magnesium and ventricular ectopy. *American Journal of Medicine* 1986; 80:8-12.
- [12]. Hurwitz N, Wade OL: Intensive hospital monitoring of adverse reactions to drugs. *Br Med J* 1969; 1:531-536.
- [13]. Jankel CA and Fitterman LK. Epidemiology of drug-drug interactions as a cause of hospital admissions. *Drug Safety* 1993; 9:51 -59.

- [14]. Jorgensen AW, Sorensen OH: Digitalis intoxication: A comparative study on the incidence of digitalis intoxication during the periods 1950-52 and 1964-66. *Acta Med Scand* 1970; 188:179-183.
- [15]. Juurlink DN, Mamdani M, Kopp A, Laupacis A, Redelmeier DA. Drug-drug interactions among elderly patients hospitalized for drug toxicity. *JAMA* 2003; 289(13):1652-8.
- [16]. Klarin I, Wimo A, Fastbom J. The Association of Inappropriate Drug Use with Hospitalisation and Mortality: A Population-Based Study of the Very Old. *Drugs Aging* 2005; 22(1):69-82.
- [17]. Klasco R. MICROMEDEX. Drug-Reax System [CD-ROM]. In. Version 2004/2005. ed. Greenwood Village, Colorado: THOMSON MICROMEDEX; 2004.
- [18]. Koh T. Risk of torsades de pointes from oral erythromycin with concomitant carbimazole (methimazole) administration. *Pacing Clin Electrophysiol* 2001; 24 (10):1575-6.
- [19]. Kohler G, Bode-Boger S, Busse R, Hoopmann M, Welte T, Boger R. Drug-drug interactions in medical patients: effects of in-hospital treatment and relation to multiple drug use. *Int J Clin Pharmacol Ther* 2000; 38(11):504-13.
- [20]. Langdorf M, Fox J, Marwah R, Montague B, Hart M. Physician versus computer knowledge of potential drug interactions in the emergency department. *Acad Emerg Med* 2000; 7(11):1321-9.
- [21]. Leary WP, Reyes AJ. Diuretic-induced magnesium losses. *Drugs* 1984; 28(Suppl. 1):182-7.
- [22]. Malone DC, Abarca J, Hansten PD, Grizzle AJ, Armstrong EP, Van Bergen RC, et al. Identification of serious drug-drug interactions: results of the partnership to prevent drug-drug interactions. *J Am Pharm Assoc (Wash DC)* 2004; 44(2):142-51.
- [23]. McCabe BJ. Prevention of food-drug interactions with special emphasis on older adults. *Curr Opin Clin Nutr Metab Care* 2004. Jan; 7 (1):21-6.
- [24]. McDonnell PJ, Jacobs MR. Hospital admissions resulting from preventable adverse drug reactions. *The Annals of Pharmacotherapy* 2002; 36:1331-6.
- [25]. Meiners M, Bergsten-Mendes G. Prescrição de medicamentos para crianças hospitalizadas: Como avaliar a qualidade? *Rev Assoc Med Bras* 2001; 47:332-7.
- [26]. Miyasaka L, Atallah A. Risk of drug interaction: combination of antidepressants and other drugs. *Rev Saúde Pública* 2003; 37(2):212-5.
- [27]. Roberts JS, Watrous ML, Schulz RM, et al. Quantifying the clinical significance of drug-drug interactions: scaling pharmacists' perceptions of a common interaction classification scheme. *Ann Pharmacother* 1996; 30:926-934.
- [28]. Shad MU, Marsh C, Preskorn SH. The economic consequences of a drug-drug interaction. *J. Clin Psychopharmacology* 2001; 21:119-20.
- [29]. WHO. World Health Organization. Anatomical-Therapeutic-Chemical Classification - ATC 2004. In: <http://www.whocc.no/atcddd>; 2004.
- [30]. Wiffen P, Gill M, Edwards J, Moore A. Adverse drug reactions in hospital patients: A systematic review of the prospective and retrospective studies. *Bandolier* 2002; Extra (June):1-15.