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RESEARCH ARTICLE

Evaluation of drug–drug interaction screening software combined with pharmacist intervention

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Abstract *Background* Drug-drug interactions (DDI) in hospitalized patients are highly prevalent and an important source of adverse drug reactions. DI computerized screening system can prevent the occurrence of some of these events. *Objective* To evaluate the impact of drug–drug interaction (DDI) screening software combined with active intervention in preventing drug interactions. *Setting* The study was conducted at General Hospital of Vitória da Conquista (HGVC), Brazil. *Method* A quasi-experimental study was used to evaluate the impact of IM-Pharma, a locally developed drug–drug interaction screening system, coupled with pharmacist intervention on adverse drug events in the hospital setting. *Main outcome measure* The proportion of patients co-prescribed two interacting drugs were measured in two phases, prior the implementation of IM-Pharma and during the intervention period. DDI rates per 100 patient days were calculated before and after implementation. Risk ratios were estimated by Poisson regression models. *Results* A total of 6,834 instances of drug–drug interactions were identified; there was an average of 3.3 DDIs per patient in phase one and 2.5 in phase two, a reduction of 24 % ($P = 0.03$). There was a 71 % reduction in high-severity drug–drug interaction ($P < 0.01$). The risk for all DDIs decreased 50 % after the implementation of IM-Pharma ($P < 0.01$), and for those with high-severity, the reduction was 81 % ($P < 0.01$). *Conclusion* The performance of IM-Pharma combined with pharmacist intervention was positive with an expressive reduction in the risk of DDIs.

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Impact of findings on practice:

- Computerized drug–drug interaction screening software can reduce the occurrences of adverse drug events.
- For optimal results, the use of drug–drug interaction screening tools should be combined with active interventions in the prescribing and dispensing process.

Introduction

Adverse drug events (ADEs) have become a major public health issue and represent a concern for patients and health care professionals. The economic burden of drug-related morbidity and mortality was estimated to cost US$ 177.4 billion in 2001 in the United States [1] and €434 million per year in Germany [2]. Classen et al. [3] showed that ADEs significantly prolong the length of hospital stay, increase the cost of treatment and elevate the risk of death. Drug–drug interaction (DDI) is a specific type of adverse drug event that occurs when the effect of one drug is changed by the presence of another drug, resulting in increased toxicity or reduction in therapeutic efficacy. DDIs are significantly more likely to occur in hospital settings, where patients are commonly on multiple drug regimens.

Studies concerning drug–drug interactions mainly report potential DDIs in medical prescriptions, regardless of whether they actually lead to adverse clinical consequences. These studies have found rates of potential DDIs ranging from approximately 5.4–63 % [4–7]. Differences in methods for classifying drug interactions, study periods and target populations contribute to these discrepancies.

It has been demonstrated that computerized drug–drug interaction screening software can prevent the occurrence of some of these events [8–10]. Most screening systems are integrated with computerized physician order entry (CPOE). CPOE integrated with screening software incorporates clinical decision support into daily practice and allows physicians to check for drug interactions while directly entering orders into the computer. However, studies indicate that current use of these tools is sub-optimal, resulting in the failure to identify important interactions and false identification of clinically irrelevant interactions [11, 12]. A large volume of clinically insignificant alerts generated too frequently or with low credibility can result in "alert fatigue," and clinically significant alerts may be overridden [13].

To minimize the risk of ignoring significant alerts, electronic screening should be combined with active intervention to prevent the dispensing of drug combinations that have the potential for serious adverse interactions [14]. Pharmacists can play an important role in this matter, as they are trained to recognize medication-related problems and have the opportunity to review the medication profiles in the inpatient setting before medications are dispensed [15]. They can discuss and collaborate closely with prescribers when drug interactions are found and also recommend alternative therapies.

Aim of the study

The present study aimed to evaluate the impact of drug–drug interaction screening software associated with active pharmacist intervention in preventing drug interactions. The main hypothesis is that, compared with the pre-intervention period, the rate of co-dispensing drugs with potential interactions would be lower after the introduction of a critical drug interaction program.

Methods

The IM-Pharma is a locally developed drug–drug interaction screening system previously validated [16]. This tool, developed in Microsoft Visual Basic® 6.0 and Microsoft Access® 2007, was designed to provide pharmacists with relevant information on drug–drug interactions. The prototype was fitted into the workflow of pharmacists, allowing them intercept drug interactions before the medication was dispensed. The IM-Pharma database was updated with a list of potential DDIs, based on the *Drug Interaction Facts* (DIF) publication [17]. The application produces combinations of two drugs for each prescription filled, compares them with the list of potential DDIs and detects if there are any combinations coinciding with the pre-selected pairs. The system classifies pairs of drugs with potential interactions according to a 5-level clinical significance rating based on the severity (high, medium, low) and the extent of documentation or level of evidence (established, probable, suspected, possible, unlikely). Only DDIs with a significance level of 1 (severity: high; documentation: suspected, probable or established) or 2 (severity: medium; documentation: suspected, probable or established) were identified.

The study was conducted at General Hospital of Vitória da Conquista (HGVC), 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, one of the most populous states in Brazil. A quasi-experimental study was used to evaluate the impact of the IM-Pharma intervention. In phase one, the pre-intervention period (prior the implementation of IM-Pharma), a retrospective cohort study was conducted at HGVC from January 2007 to December 2007. All the existing paper-based prescriptions stored in the hospital pharmacy department were entered into the computer system to check for drug interactions. In phase two, the intervention period, a prospective cohort study was conducted in the same wards of the hospital from November 2009 to March 2010. During this period, physicians continued to write medication orders on paper and to send them to the pharmacy department. However, in this phase the screening software, coupled with active intervention, was used to prospectively check for drug interactions: pharmacists were required to revise drug alerts and consult with the prescriber prior to dispensing prescriptions with high-severity drug–drug interactions. After making adjustment, if needed, pharmacists entered the order into IM-Pharma. Data on phase 2 were directly collected from the system database.

The study population was comprised of all adults patients ($\geq$18 years) admitted to the hospital. Patients transferred to another hospital for possible admission were excluded, as well as those who died within 48 h of admission. Patients with no information on medical prescriptions were also excluded. The total number of patient-days and discharges was obtained 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 nearly 70 % of all Brazilian hospital admissions and 100 % of admissions in the study hospital. 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 predefined at the central level, without distinguishing among different

providers (except for university hospitals). Information was also collected from patient medical discharge forms. Hospitalization records also provided information on the diagnosis at admission (according to ICD-10 classification) and demographic data (age, sex).

Information on prescriptions (drug names, dosage, prescription dates, ward) was collected from the records of the hospital pharmacy department. All prescriptions involving two or more drugs were selected.

The primary outcome measure used to evaluate the software's impact was the proportion of patients co-prescribed two interacting drugs. Co-prescribing was defined as the issuing of two or more drugs on the same prescription note [18]. All interaction episodes were counted, including the prescription those drug combinations dispensed to the same patient on multiple occasions.

Statistics analysis

Descriptive statistics were expressed as proportions or as the means (± SD) or medians with the corresponding ranges. The Chi-squared test and the Student's *t* test were used to identify statistical differences in patient characteristics in phases one and two. Incidence rates and risk ratios (RRs) of DDIs before and after IM-Pharma implementation per 100 patient-days were computed; 95 % confidence intervals (95 % CI) were calculated under the assumption that the number of events per 100 patient days followed a Poisson distribution. To evaluate the impact of introducing IM-Pharma, risk ratios for the counts of DDI, adjusted for potential confounders (age, sex and number of medications taken), were calculated for both phases using multivariate Poisson regression models. The significance level was set at $P < 0.05$. All statistical analyses were performed using R for Windows® version 2.6.2.

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

Results

During the study period, there were 2,147 discharges and 27,426 patient days. The mean age ± SD was 52.8 ± 20.9 years, and 53 % of the patients were male. The most common diagnoses were circulatory diseases (17.8 %), injury from external causes (16.2 %), respiratory system diseases (13.0 %) and nervous system diseases (11.5 %). Both groups, pre-intervention and intervention, were similar in age and average number of medications received during the stay, but those in phase two were more likely to be female (Table 1).

Table 1 Patients characteristics and occurrence of drug–drug interactions for the pre-intervention and intervention periods

Variable	Phase one	Phase two
No of patients	1,852	295
Patient-days	21,948	5,817
Age, mean (± SD), in years	52.7 (± 20.9)	53.4 (± 21.3)
Male, No, %*	1,032 (56 %)	105 (36 %)
Main diagnosis group, No, %		
Diseases of the circulatory system	324 (17.5)	59 (20.0)
Injury, poisoning and certain other consequences of external causes	290 (15.7)	57 (19.3)
Diseases of the respiratory system	245 (13.2)	35 (11.9)
Diseases of the nervous system*	234 (12.6)	12 (4.1)
Mortality rate (%)	16.3 %	18.3 %
Number of medications, mean (± SD)	13.0 (± 8.0)	13.3 (± 8.6)
No of DDIs (average per patient)*	6,038 (3.3)	722 (2.4)
No of high-severity DDIs (average per patient)*	1,800 (0.97)	75 (0.25)

* $P < 0.05$

A total of 6,760 DDIs were identified in the entire study, yielding an average of 3.15 DDIs per patient. Of these, 6,038 instances of co-dispensing of interacting drugs were observed in 1,852 subjects in the pre-intervention period, yielding an average of 3.3 DDIs per patient. In the intervention period, 722 instances of DDI were observed in 295 subjects, yielding an average of 2.4 DDIs per patient, which was a significant reduction of 25 % ($P = 0.03$) (Table 1). High-severity DDIs accounted for 28 % of all DDIs (or 1,875 instances); the average occurrence of these events in the pre-intervention period was 0.97 DDIs per patient, compared to 0.25 events per patient in the intervention period, representing a relative decrease of 73 % ($P < 0.01$).

Incidence rates and adjusted risk ratios (RRs) comparing the pre-intervention and intervention period are listed in Table 2. The rate of DDIs was 27.5/100 patient days in phase 1 and 13.2/100 patient days in phase two. Compared with the pre-intervention period, the risk of drug–drug interactions in the intervention period decreased 52 % when compared with the pre-intervention period ($P < 0.01$; RR = 0.48; 95 % CI = 0.44-0.52). There was a significant reduction of 83 % in the risk of high-severity drug–drug interactions in phase two compared with phase one ($P < 0.01$; RR = 0.17; 95 % CI = 0.13-0.21).

Specific high-severity DDI pair incidence rates (per 1,000 patient-days) and risk ratios (RRs) for phases one and two are displayed in Table 3. Among those, the highest

Table 2 Risk ratio and rate of ratios of drug–drug interactions for the pre-intervention and intervention periods

	Incidence Rate (95 % CI)—per 1,000 patient days		RR (95 % IC)*
	Pre-intervention	Intervention	
All DDIs	27.5 (26.8–28.2)	13.2 (12.2–14.2)	0.48 (0.44–0.52)
High-severity DDIs	8.20 (7.83–8.59)	1.36 (1.08–1.72)	0.17 (0.13–0.21)

* Adjusted for sex, age and number of medications

Table 3 Drug–drug interactions rates in the pre-intervention and intervention periods for high-severity DDI pairs

DDI pair	Incidence Rate (per 1,000 patient-days)		*P* value*
	Pre-intervention	Intervention	
Aminoglycoside (Amikacin) × Furosemide	2.60	0	< 0.01
Aminoglycoside (Amikacin) × Nondepolarizing muscle relaxants (Pancuronium)	0.27	0	0.61
Captopril × Spironolactone	26.1	2.56	<0.01
Amiodarone × Digoxin	2.64	0.73	0.01
Amiodarone × Fentanyl	0.36	0.18	0.99
Amiodarone × Quinolones (moxifloxacin)	0.14	0	0.99
Amiodarone × Warfarin	0.50	0.37	0.99
Aspirin × Warfarin	0.27	0.73	0.12
Beta-blockers (Propranolol) × Chlorpromazine	1.09	0	0.01
Corticosteroids (dexamethasone) × Rifampin	0.50	0	0.14
Digoxin × Diuretics (hydrochlorothiazide)	3.37	1.10	0.03
Digoxin × Furosemide	32.5	5.84	<0.01

* Estimated by Poisson test

rate of co-dispensing occurred with the digoxin-furosemide drug pair in both phases one and two, with a pre-intervention rate of 32.5 instances per 1,000 patient-days and an intervention period rate of 5.84 events per 1,000 patient days ($P < 0.01$). The greatest improvement in the co-dispensing rate occurred with the Captopril-Spironolactone pair, with an initial rate of 26.1 instances per 1,000 patient days that decreased to an intervention rate of 2.56 instances per patient days (significant reduction of 90 %—$P < 0.01$).

Discussion

This study showed that the implementation of drug–drug interaction screening software integrated with active pharmacist intervention decreases the co-dispensing of interacting drugs. It is an important achievement because drug–drug interactions can lead to adverse drug events, which account for 4 % of all medication errors related to physician ordering [19–21]. A decrease of approximately 50 % was observed in the average number of DDIs per patient and in the DDI rate after IM-Pharma implementation. A remarkable risk reduction of 83 % was noted for high-severity drug–drug interactions in the intervention period. These findings are consistent with previous investigations that have demonstrated that computerized drug–drug interaction screening software can prevent the occurrence of DDIs in both ambulatory and hospital settings [8, 14].

The identification of patients at risk and the accurate management of their drug therapies are important challenges for health care professionals. Currently, many existing CPOE systems are integrated with screening software to alert prescribers of DDIs; however, studies have indicated that physicians override 89.4 % of drug interaction alerts [22]. Thus, creating a system that only triggers clinically important drug interaction alerts or that differentiates them by level of severity has been recognized as an effective method to reduce alert fatigue [23]. Furthermore, adequate management of drug interactions can be obtained through a multi-dimensional approach [24]. In this study, these elements were combined with an intervention: electronic alerts were limited to drug–drug interactions that were considered critical, and pharmacists were required to revise drug alerts and consult with the prescriber prior to dispensing prescriptions with high-severity drug–drug interactions. These factors may have contributed to the positive effects obtained by the intervention.

Data from Table 3 indicates that for some high-severity DDI pairs, there were no differences in the rates between

phases one and two. There are several factors that can explain these findings, including the particularities of the patient's drug regimen, clinical status and drug administration. Also, other medications could be added to the patient's pharmacotherapy to treat a possible drug adverse event. For example, adverse effects of an amiodarone and fentanyl combination, including atrioventricular blockade with bradycardia and hypotension, may not be observed during short-term therapy [25]. In most cases, administrating these two medications together is accomplished without complications. Another example is the management of the aspirin and warfarin interaction, a combination that can lead to an increased risk of bleeding. However in some cases, depending on the aspirin dose, the potential benefit in decreasing thromboembolic events outweighs the risks [26].

This study has some limitations. First, it is a non-randomized study using a before and after design, which is subject to misclassification and confounding bias. For example, the number of DDIs during the intervention period could have been different than the pre-intervention period because of the presence of background factors or changes in the hospital's prescription protocols. These factors could not be assessed by the authors. Although impossible to eliminate completely, experimenter bias was avoided by using independent researchers and allied health personnel for data collection, who were not involved in the design and analysis of this study. Thus, a temporal trend or a seasonal bias could have caused some of differences seen as before and after assessments were performed in different periods of the year. Univariate analyses were conducted to evaluate for selection bias by comparing patient characteristics of the pre-intervention and intervention groups. Age and average number of medications received during the stay, two well-known factors that increase the risk of DDIs, were similar in both groups. Subjects in phase two were more likely to be female, but this gender difference does not seem to be clinically relevant. At best, the potential effect of this bias was minimized through multivariate analysis. Another point to consider is that the current study only examined the frequency of potential DDIs in prescriptions, whereas other researchers have identified and reported ADEs resulting from DDIs, such as an increased number of hospital admissions [27] or re-hospitalizations [28]. Decreases in co-dispensing rates should translate into improved healthcare for patients. It would be expected that the use of the system by pharmacists and how well guidelines were accepted by prescribers would vary over time. For example, pharmacists would be more enthusiastic in using this new technology just after implementation while prescribers would be less prone to accept pharmacist's suggestions at the first. The initial positive effects observed immediately after the implementation of IM-Pharma can be viewed as the first-stage benefits of this strategy. Furthermore, it is hoped that the sharing of this information would result in increased acceptance by the hospital staff.

Conclusion

The performance of drug–drug interaction screening software accompanied by active pharmacist intervention appears to decrease the average number of events per patient and the risk of co-dispensing interacting drugs.

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