Are drug-drug interactions a real clinical concern?

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Abstract

Aim: Although drug-drug interactions (DDIs) cause major adverse drug reactions (ADRs) in patients under polypharmacy, the risk of some specific DDIs may be overrated in literature and different software. This study was conducted to determine the frequency and type of potential and clinically significant DDIs among inpatients admitted in a tertiary care hospital in South India.

Materials and Methods: This longitudinal study was conducted for 30 days. Preformatted forms were used to collect data on the second day of admission. "Medscape Drug Interaction Checker" was used to evaluate and grade the DDIs. All the potential serious DDIs were intimated to the treating physicians and their responses in the prescriptions were noted. The same patients were followed up to evaluate the occurrence of any clinically significant DDIs.

Results: A total of 763 drugs with 125 discrete types were prescribed in 155 patients with an average of 4.9 drugs per patient. One hundred and eight minor, 169 significant, and 24 serious potential DDIs were identified. Patient's age did not correlate, but number of drugs prescribed strongly correlated ($P < 0.001$) with the incidence of different types of DDIs. The prescription was modified in only 6 (25%) cases where potential serious DDIs were reported. Interestingly, no ADRs or impaired efficacy was observed due to the potential serious DDIs.

Conclusion: There was a disparity between the potential and clinically relevant DDIs. Hence, clinical prudency is required before changing prescription due to potential DDIs reported by different software.

Keywords: Adverse drug reactions, drug-drug interactions, inpatients, Medscape Drug Interaction Checker, polypharmacy

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INTRODUCTION

Drug-drug interactions (DDIs) are defined as "two or more drugs interacting in such a manner that the effectiveness or toxicity of one or more drugs is altered."[1,2] DDIs contribute to a major part of adverse drug reactions (ADRs), especially in elderly patients and in patients under polypharmacy.[3] ADRs are a major cause of hospital admissions leading to significant medical and economic problems. In general, the prevalence of clinically relevant drug interactions is about 6% in patients taking 2–4 medications, 50% in those taking 5, and almost 100% in those taking 10 medications.[4]

Apart from ADRs, DDIs can cause impaired therapeutic effect or may also lead to dose adjustment.[5] The Boston

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Collaborative Drug Surveillance Program reported 83,200 drug exposures in almost 10,000 patients and found 3600 ADRs, of which 6.5% resulted from drug interactions.[6] In Harvard Medical Practice Study of adverse events, 20% of events in an acute hospital inpatient setting were drug related, and of these, 8% were considered to be due to DDIs.[5] These can occur either by pharmacokinetic or pharmacodynamic mechanisms.[3,5]

Approximately 37%–60% of patients admitted to the hospital may have one or more potentially interacting drug combinations at admission.[7] The proportion of hospital admissions due to DDIs can range up to 3.8%.[8,9] In inpatients, the risk of having potentially interacting drug combinations can additionally increase because new drugs are often added to the existing drug therapy.[10] Recent studies could show that 2.2%–65.0% of inpatients may have one or more potential DDIs.[10] Another review estimates that 17% of all preventable ADRs in hospitalized patients are caused by DDIs and that ~1% of patients experience an ADR during hospitalization due to a DDI.[11] Various studies in India have also shown significant DDIs resulting in increased morbidity among patients admitted in various tertiary care hospitals.[12] Interestingly, around half of the ADRs resulting from DDIs are predictable and preventable.[13]

However, the incidence of actual occurrence of drug interactions has been reported to be much smaller, ranging from 0% to 1.3%.[14,15] It is also to be borne in mind that many of the "theoretical" or potential DDIs might not be important "clinically" for a change in treatment decision in the real world setting. The risk of some specific DDIs may be overrated in literature and different software as well.[16] Thus, it is required to estimate the potential as well as clinically significant DDIs among the inpatients on polypharmacy. With this background, this study was conducted to determine the frequency and type of potential and clinically significant DDIs among inpatients admitted in a tertiary care hospital in South India.

MATERIALS AND METHODS

This study was conducted as per "National Ethical Guidelines for Biomedical and Health Research Involving Human Participants," Indian Council of Medical Research.[17] Approval of the Institutional Ethics Committee, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry, was obtained for the same.

Study design
This was a observational and longitudinal study.

Study duration
The duration of this study was 30 days.

Study method
Preformatted forms were used to collect data from the case sheets of all the inpatients admitted in the general ward under the Department of Medicine (Unit 2), JIPMER, Puducherry (a tertiary care hospital), during the study period. Demographic information, working/established diagnosis, and medication details were collected on the second day of admission in the general ward. "Medscape Drug Interaction Checker" was used to evaluate and grade the DDIs.[18] It grades DDIs into three categories: minor (no change required), significant (monitor closely), and serious (use alternative). All the potential serious DDIs were intimated to the treating physicians and their responses in the prescriptions (continue/discontinue/adjust dose/adjust frequency/substitute the particular drug[s]) were noted subsequently. The physician's decisions were not influenced. The same patients were followed up till discharge to evaluate the occurrence of any clinically significant DDIs, i.e., ADRs or impaired efficacy or abnormal concentration of drug(s) in the body fluid resulting from the reported potential serious DDIs.

Sample size estimation
The prevalence of polypharmacy was assumed to be 50%.[19] The hypothesized percentage frequency of outcome factor in the population studied (*P*) is 50%. The confidence limit (L) is taken as 5%. Using the formula, $n = (Z_{1-\alpha/2})^2 \times PQ/L^2$ (where Q = 100- P and $Z_{1-\alpha/2}$ value for 95% confidence interval = 1.96), the required sample size (*n*) came to 96.

Statistical analysis
Descriptive statistics were used for demographic characteristics and types of potential and clinically significant DDIs. Pearson correlation was determined between the incidence of different types of DDIs with age and number of drugs prescribed. *P* < 0.05 was considered as statistically significant. All analyses were done in SPSS (version 19) (IBM, New York, NY, USA).

RESULTS

Demographic characteristics
A total of 155 patients' case sheets were studied. The mean age of the patients was 44 ± 17 years with 51.3% being males. A total of 763 drugs with 125 discrete types were prescribed in all the patients with an average of 4.9 drugs

per patient. The most commonly used drugs are enlisted in Table 1. Of all these drugs, 65% were administered orally, 22.5% intravenously, 5.1% subcutaneously, 3.3% were administered through inhalational route, and 1.4% through intramuscular route.

Commonly used drugs and drug-drug interactions

Using the "Medscape Drug Interaction Checker,"[18] 108 minor, 169 significant, and 24 serious potential DDIs were identified. There were no potential DDIs in 75 (48.4%) patients.

Correlation of drug-drug interactions with other parameters

Patient's age did not correlate, but number of drugs prescribed strongly correlated ($P < 0.001$) with the incidence of different types of DDIs [Table 2].

Steps taken by the treating physicians and outcome

All the 24 serious potential DDIs were intimated to the treating physicians. Prescription was modified in only 6 (25%) cases. Table 3 shows the details of the serious DDIs with steps taken by the treating physicians after reporting. Drug concentration in the body fluid was not measured for any of these patients. Interestingly, no ADRs or impaired efficacy was observed due to the identified potential serious DDIs.

DISCUSSION

In this study, we wanted to evaluate the frequency and type of potential and clinically significant DDIs among inpatients. Polypharmacy is unavoidable as elderly patients usually suffer from many chronic diseases which demand the use of multiple drugs resulting in complex regimen. In these patients, the chances of DDIs increase proportionally. However, studies assessing potential DDIs should be separated from those looking at clinically significant DDIs.[20]

In our study, we have found more potential DDIs (51.6%) when compared to other studies, such as, that of Björkman *et al*.(46%)[21] and Gosney and Tallis (33%).[7] Polypharmacy was also higher (84.5%) in our study than that reported internationally.[22,23] Since there was a strong correlation with frequency of different DDIs and number of drugs prescribed, higher polypharmacy might have attributed to higher DDIs in our study.

Apart from polypharmacy, other drug factors contributing to higher rate of DDI are drugs with narrow therapeutic index and sequence of drug administration.[4] Patient-related factors leading to higher DDI include age,

Table 1: Most commonly used drugs (*n*=763 prescribed drugs)

Name of drug	Percentage
Paracetamol	6.2
Pantoprazole	5.9
Omeprazole	4.9
Insulin	4.2
Calcium carbonate-Vitamin D$_3$	4.1
Furosemide	3.9
Tramadol	3.0
Folic acid	3.0
Amikacin	2.9
Famotidine	2.8
Ceftriaxone	2.6
Atorvastatin	2.5
Ferrous sulfate	2.2
Aspirin	2.2
Ondansetron	2.2
Prednisolone	2.2
Salbutamol	1.9
Vitamin B complex	1.7
Potassium chloride	1.6
Metoclopramide	1.4
Cough syrup	1.3
Lactulose	1.2
Metformin	1.0
Ipratropium	1.0
Other drugs individually	<1.0

Table 2: Correlation of all types of drug-drug interactions with different parameters

Type of DDI	Parameters	Pearson correlation	P
Minor	Age of patient	0.19	0.018
	Number of drugs prescribed	0.992	<0.001
Significant	Age of patient	−0.018	0.829
	Number of drugs prescribed	0.991	<0.001
Serious	Age of patient	0.015	0.857
	Number of drugs prescribed	0.981	<0.001

DDI=Drug-drug interaction

gender, genetics, comorbid condition, concurrent disease affecting drug clearance, and the number of physicians a patient visit.[4]

In our study, we have found that most of the potential DDIs were significant, followed by minor and serious. Although all the potential serious DDIs were intimated to the treating physicians, prescriptions were changed only in 25% of the cases, with clinical justification. However, no ADRs or impaired efficacy was observed due to the potential serious DDIs. Thus, there was a disparity between the potential and clinically relevant DDIs.

Previous authors have also expressed their concern on the usefulness of electronic software in predicting clinically relevant DDIs as these software tend to overalert.[24] Kulkarni *et al*. reported that checks by a pharmacologist agreed with only 11% of DDI alerts from electronic

Table 3: Details of the serious drug-drug interactions with steps taken by the treating physicians after reporting

Offending drugs	Mechanism of serious DDI	Frequency	Steps taken by the treating physicians and explanations
Furosemide and amikacin	Each increases toxicity (ototoxicity and nephrotoxicity) of the other by pharmacodynamic synergism	5	Furosemide was stopped in 3 patients with chronic kidney disease and sepsis In 2 patients with pulmonary edema and sepsis, no modification of prescription was done, without further decline in renal function Ototoxicity was not evaluated
Rifampin and dexamethasone	Rifampin decreases the level or effect of dexamethasone by affecting hepatic/intestinal enzyme CYP3A4 metabolism	3	No modification of prescription was done Dexamethasone was continued as all were cases of tubercular meningitis
Enoxaparin and warfarin	Both increase anticoagulation	2	No modification of prescription was done as both were cases of peripheral venous thrombosis requiring anticoagulant therapy INR was monitored routinely
Omeprazole and digoxin	Omeprazole increases the level or effect of digoxin by increasing gastric pH	1	Omeprazole and digoxin were dosed 12 h apart
Omeprazole and clopidogrel	Omeprazole decreases effects of clopidogrel by affecting hepatic enzyme CYP2C19 metabolism	1	Omeprazole was stopped
Tramadol and codeine	Both may reinitiate opiate dependence in patients previously addicted to other opiates and may also provoke withdrawal in opiate-dependent patients	1	Codeine-containing cough syrup was stopped
Azithromycin and digoxin	Azithromycin increases the level or effect of digoxin by altering intestinal flora	1	No modification of prescription was done Azithromycin was stopped after 3 days
Artesunate and ondansetron	Both increase QTc interval	1	No modification of prescription was done Periodic ECG showed no abnormality
Rifampin and hydrocortisone	Rifampin decreases the level or effect of hydrocortisone by affecting hepatic/intestinal enzyme CYP3A4 metabolism	1	No modification of prescription was done Hydrocortisone was continued as it was a case of tubercular meningitis
Heparin and warfarin	Both increase anticoagulation	1	No modification of prescription was done in this patient with cerebrovascular accident INR was monitored routinely
Aspirin and enalapril	Both cause pharmacodynamic antagonism which can result in a significant decrease in renal function. Aspirin reduces the synthesis of vasodilating renal prostaglandins and thus diminishes the antihypertensive effect of enalapril	1	No modification of prescription was done Both the drugs were indicated in this case of coronary arterial disease with hypertension
Piperacillin and heparin	Piperacillin increases the level or effect of heparin by anticoagulation; piperacillin can inhibit platelet aggregation	1	No modification of prescription was done Both the drugs were indicated in this case of ventilator-associated pneumonia with venous thrombosis
Carbamazepine and dexamethasone	Carbamazepine decreases the level or effect of dexamethasone by affecting hepatic/intestinal enzyme CYP3A4 metabolism	1	No modification of prescription was done
Carbamazepine and atorvastatin	Carbamazepine decreases the level or effect of atorvastatin by affecting hepatic/intestinal enzyme CYP3A4 metabolism	1	No modification of prescription was done
Ceftriaxone and calcium gluconate	Both increase the risk of potentially fatal particulate precipitation in lungs and kidneys	1	No modification of prescription was done
Calcium gluconate and doxycycline	Both decrease levels of the other by inhibition of GI absorption	1	No modification of prescription was done
Ritonavir and atorvastatin	Ritonavir increases toxicity of atorvastatin, OATP1B1 inhibitors may increase risk of myopathy	1	No modification of prescription was done

CYP=Cytochrome P450 enzyme, DDIs=Drug-drug interactions, ECG=Electrocardiogram, INR=International normalized ratio, OATP=Organic anion-transporting polypeptide, GI=Gastrointestinal

software, and the remaining 89% were thought to be of not clinically relevant.[25]

It is thus important to monitor and evaluate the clinically significant DDIs and distinguish them from the "theoretical" or potential ones in each setting. Physicians remember common and clinically significant DDIs and it is impracticable for them to remember all the potential DDIs as available from literature or drug interaction software. It might not be also possible in real practice to change prescription for each and every potential DDIs. The potential benefits of drug combinations should be weighed against the seriousness of the DDI, taking into account of the availability of alternatives. If the benefit of treatment is of such importance that it outweighs the potential risks and no safer alternatives are apparent, then the risks of a potential DDI may be tolerated and treatment can be continued with appropriate monitoring.[26]

Our study was conducted for a short duration with a small number of patients in a selected ward and unit, which might not reflect the actual scenario in the entire hospital. It is also noteworthy to mention here that several studies testing the performance of drug interaction software found low levels of sensitivity and specificity, but more recent studies indicate that sensitivity and specificity have improved.[27] Using "Medscape Drug Interaction Checker"[18] should be coupled with considering the real clinical scenarios (where some DDIs might be therapeutically warranted) on a case-to-case basis to arrive at a clinical decision.

CONCLUSION

Twenty-four serious potential DDIs were identified among 155 patients. Prescription was modified in only 6 (25%) of these cases. No ADRs or impaired efficacy was observed due to the identified potential serious DDIs. Thus, there is a disparity between the potential and clinically relevant DDIs. Clinical prudency is required before changing prescription due to potential DDI reported by different software.

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Conflicts of interest
There are no conflicts of interest.

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