Prevalence of Drug-Drug Interaction in Hospitalized Patient in Basrah City; Southern of Iraq

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Abstract

Objectives: Although multiple drugs administrationmostly increase therapeutic effect, some combinations lead to adverse drug-drug interactions and increased morbidity. This study was designed to identify the types,frequency, severity, and significance of drug–drug interactions (DDIs)

Methods: This retrospective cross-sectional study was conducted from September 2018 to February 2019 in Al-Fayha'a teaching hospital in Basrah, Iraq.The data of 186 patients were collected from hospital patients case sheets. The type and significance of DDIs were analyzed using "Medscape drug Interaction Checker.

Results: At least one to two DDI are noticed in about three quarters of the patients, about 30% cases have three to nine DDIs and 15% of them have ten or more DDIs. According to their severity, there are 85 (11.5%) of serious or potent DDIs. The largest percentage of reported interactions 544 (73.5%) were moderate were close monitoring required. Out of 740documented DDIs,65.1% were pharmacodynamics and 19.5% were Pharmacokinetic interactions, in addition, there were 15.4%of DDIs due to Unknown mechanisms. Most of the major potential DDIs occur with the antibiotic ceftriaxone and blood thinning medications (heparin and warfarin).

Conclusion: The findings of this study revealed a high prevalence of drug-drug interactions in hospitalized patients particularly in patients withcardiovascular disease. Potential DDIs in this study sufficiently high to alert health care providers to pay more attentions in order to prevent or decrease their adverse effects on patients.

Keywords: *Drug interactions; pharmacokinetics drug interactions, pharmacodynamic drug interaction*

Introduction

Drug-drug interactions (DDIs) widely occur in hospitalized patient especially in patients use long list of medications.A drug interaction occurs when the pharmacological effects of the one medication alters the intensity of the other concomitant drug. When two or more medications are taken together, there is a chance of an interaction among the drugs that could be manifested as an increase or decrease in the therapeutic effects or lead to serious unwanted effects which may change the clinical outcome of the patients [1]. Polypharmacyand increased age are significant risk factor for these interactions [2,3]. DDIs generally classified as pharmacodynamic and pharmacokinetic interactions that sub-classified according to mechanism of interactions into absorption, distribution, metabolism and elimination [4].Potential DDIs are one of the preventable mechanisms ofadverse drug events and health damage [5]. Frequency of potential DDIs markedly increase in prescriptions for hospitalized patients [6]. The clinical outcome of a possible DDIs is usually unknown [7]. Studies show that the patients may expose to one or more major or moderate DDIs during hospitalization especially in internal medicine wards and the probability these interactions increased when use more than 6 drug items [8-10].Although DDIs are common in the hospitalized patients, but there are few data reporting these interactions clinically. It is difficult to remember all the known important DDIs.

However, knowledge of the vital types of medications that are more likely to be involved will be useful alert while prescribing [11]. Predicted theoretical drug-drug interactions may not lead to noticeable toxicity or therapeutic failure, therefore clinicalintervention do not always needed. However, any clinically significant DDIs should be identified and discussed with health care team and kept under monitoring.Therefore clinicians should have a sufficient knowledge about the potential drug interactions.Product monographs,info graphics, health information technologies and drug interactions software programswould help in alerting healthcare providers about the possible DDIs[12]. In recent years, manyprograms have been developed to detect potential DDIs. Numerous online drug interactions databasesare available which is either free such as "Drugs.com" and "medscape.com" or copyrighteddatabases(e.g., Micromedex)[13]. The use of theseapplications could enhance patient safety by minimizing the incidence of DDIs, and also help in educating trainers [14]. In this study DDIs were checked using Medscape free online application (https://reference.medscape.com/drug-interactionchecker).

Materials and Method

The present study held in Al-Fayha'a teaching hospital based in Basrah, southern of Iraq. This hospital provides medical services for large number of population in Basrah city and receive both in- and outpatients from all age groups. The study designs as retrospective cross-sectional study was conducted from September 2018 to February 2019.This study was approved by the ethical committee of the collegeof pharmacy/ university of Basrah. Patients admitted with different diagnosis wereincludedin this study. Hospital permission was obtained to access the patient's medical files during hospital stay for research purpose. Medications prescribed during the hospital admission were allocated from medical reports. Patient's age, sex, length of hospitalization period, causes of admission, morbidities and associated comorbidities, and details of medication therapy collected from hospital patients case sheets. The type and significance of DDIs were evaluated using "Medscape Drug Interaction Checker". It grades DDIs into three categories: minor (no change required), moderate (monitor closely),and potent DDIs (use alternative). Data analysis performed by Medcalc® software v12.

Results

Demographic Data

Demographic characteristics had shown in Table1, A total of 186 patients' case sheets were studied. The mean age of the patients was 56.4 ± 19 years, most patients were in age range of 60-80 years. With51% beingmales. Most patients were received more than 3 medications. The length of stay was at least one week for most patients, few percentage stay more than seven days.Table 1 also showed the medical conditions and comorbidity of the patients included in the study.

Table 1: Demographic data of patients included in the study

Criteria	Frequency: N (%)	P values
Age	56.4 ± 19	
Age range		
<20	7(3.8%)	<0.0001
20-40	24(12.9%)	
40-60	59(31.7%)	
60-80	77(41.4%)	
>80	19(10.2%)	

Cont... **Table 1: Demographic data of patients included in the study**

Gender		
Male	95 (51.1%)	0.77
Female	91(48.9%)	
No of comorbidities		
No comorbidity	68(36.6%)	<0.0001
1	57(30.6%)	
2	42(22.6%)	
3	15(8.1%)	
>3	4(2.2%)	
Length of hospital Stay (days)		
< 3	62(33.3%)	<0.0001
3-7	111(59.7%)	
≥7	13(7%)	
No. of prescribed Medications		
< 3	9(4.8%)	<0.0001
3-6	82(44.1%)	
6-10	73(39.2%)	
≥ 10	22(11.8%)	
Hospital ward used		
1	180(96.8%)	<0.0001
2	4(2.2%)	
3	2(1.1%)	
Type of morbidities		
Cardiovascular system	93(50%)	<0.0001
Diabetes & endocrine (other than Diabetes)	11(5.9%)	
Pulmonary system	29(15.6%)	
Gastro-intestinal tract	24(12.9%)	
Hepatic &biliary	8(4.3%)	
renal system	7(3.8%)	
hematology	5(2.7%)	
Obstetrics & gynecology	3(1.6%)	
Miscellaneous	6(3.2%)	

Types of drug-drug interactions (DDIs)

Details of the DDIs were reported in Table 2. At least one to two DDI are noticed in about three quarters of the patients. About 30% cases have three to nine DDIs and 15% of them have ten or more DDIs. According to their severity, there are 85 (11.5%) of serious or potent DDIs. The largest percentage of reported interactions 544 (73.5%) were moderate were close monitoring required.

The documented DDIs were mostly pharmacodynamics482 (65.1%) (increase or decrease effects of medications). Pharmacokinetic interaction about144(19.5%) with most of them were due to change in metabolism (enzyme induction or inhibition). In addition, there were 114 (15.4%) of DDIs due to Unknown mechanisms.

Table 2: Documentation, severity and type of drug interaction reported

Possible Drug -drug interactions /patient n=186	Frequency	P value
None	48(25.8%)	<0.0428
1-2	45(24.2%)	
3-5	38(20.4%)	
6-9	27(14.5%)	
≥10	28(15.1%)	
Types of DDIs according to their potencyn=740		
Minor	111 (15%)	<0.0001
Moderate	544 (73.5%)	
Serious	85 (11.5%)	
Type of interaction according to mechanism n=740		
Unknown mechanism	114 (15.4%)	<0.0001
Pharmacodynamics	482 (65.1%)	
Pharmacokinetic interaction	144(19.5)	
Types of Pharmacokinetic interactions n=144		
1-Absorption	33 (4.5%)	<0.0001
2-Metabolism	86 (11.6%)	
3-Elimination	25 (3.4%)	

Table 3: Ratios of prescribed medication, DDI per system case and DDI per prescribed medication

	Cases	Ratio of Prescribed medications / system case	ratio of DDI /system case	DDI/Prescribed medication
Cardiovascular system	93	7	5.5	0.8
Diabetes & endocrine (other than Diabetes)	11	5.8	3.7	0.6
Pulmonary system	29	7.2	4	0.6
Gastro-intestinal tract	24	3.5	1.8	0.5
Hepatic &biliary	8	4.3	2.1	0.5
Renal system	7	3.3	0.9	0.3
Hematology	5	6	3.4	0.6
Obstetrics & gynecology	3	4	1.7	0.4
Miscellaneous	6	5.2	4.2	0.8
P-value		0.0845	0.0464	0.5632

Data analyzed using t test

Table 4: Associated comorbiditiesthat recorded in the study

	No. of comorbidities	**medication /co-morbidity**	**interaction /co-morbidity**
Cardiovascular system	133	2.9	2.3
Diabetes & endocrine (other than Diabetes)	13	2.7	1.7
Pulmonary system	29	3.6	2
Gastro-intestinal tract	5	2.9	1.4
Hepatic & biliary	6	2.4	1.2
Renal system	7	1.6	0.4
Hematology	5	3	1.7
Obstetrics & gynecology	0	4	1.7
Miscellaneous	4	3.1	2.5
P values		0.0322	0.0146

Potential interactions (alternative medications should be tried)

The serious interactions are about 85 (11.5%) of total interactions (780). The frequencies and potential risk of these interactions are shown in table 5. The most common interaction has been seen with ceftriaxone-heparin and ceftriaxone-calcium (19, 9) respectively. The potential interactions with blood thinning drugs like heparin, warfarin, aspirin and clopidogrel also frequently seen in this study.

Table 5: Frequencies of serious drug-drug Interactions and their potential risk.

Drug-Drug	Frequency	Risk of Potential Events
Ceftriaxone- Heparin	19	Increase risk of bleeding
Ceftriaxone-Calcium	9	Potentially risk of particulate precipitation in lungs and kidneys.
Omeprazole-Clopidogrel	7	Decrease anticoagulant effect of clopidogrel
Aspirin-Captopril	6	Risk of decrease in renal function.
Heparin-Azithromycin	4	Increase risk of bleeding
Hydrocortisone-simvastatin	3	Decrease effect of Simvastatin
Hydrocortisone-simvastatin	4	Decrease effect of Simvastatin
Amikacin-Lasix	2	Increased risk of ototoxicity and nephrotoxicity
Omeprazole-Digoxin	2	Increase effects of digoxin
Digoxin-Bisoprolol	1	Increase risk of bradycardia
Ceftriaxone-Warfarin	2	Increase bleeding risk
Heparin-Warfarin	1	Increase risk of bleeding
Azithromycin-Digoxin	1	Increase digoxin effect
Asprin-Lisnopril	1	Risk of decrease in renal function.
L-Thyroxin-Heparin	1	Increase risk of bleeding
Azithromycin-Heparin	1	Increase risk of bleeding
Clarthromycin-Ondasteron	1	Increase risk of arrhythmias
Metoprolol-Digoxin	1	Increase risk of bradycardia
Hydrocortisone-simvastatin	3	Decrease effect of Simvastatin
Aldactone-potassium	1	Increase risk of hyperkalemia
Simvastatin-amiodarone	1	Increases toxicity of simvastatin
Carbamazepine-Omeprazole	1	Decrease the level or effect of omeprazole
Azithromycin-Warfarin	1	Increase risk of bleeding
Carbamazepine-Atorvastatin	1	Decrease effect of Atorvastatin
Amiodarone-Simvastatin	1	increases toxicity of simvastatin
Metronidazole-Simvastatin	1	increase effect of simvastatin

Discussion

Drug-drug interactions are common preventable health risk. The present retrospective study analyzes the type and number of DDIs in hospitalized patients using data from 186 patients case sheets in Al-Fayhaa Teaching Hospital in Basra- Iraq. There are various methods for identification of DDIs. In this study *Medscape drug interaction* checker program is used.

The prevalence ofDDIs is especially high in hospitalized patients, and the incidence of DDIs is usually associated with polypharmacy and patient age [15,16]. The mean age of patients included in this study are [56.4 ± 19] and most of them in age range 60-80 year. This compatible with previous studies that correlate DDIs with age [17]. This result explained by fact that most elderly patients have multiple comorbidities as shown in table [4] that illustrate the significant increase in DDIs with increasing comorbidities especially cardiovascular disease. This agree with other studies which conclude that patients with cardiovascular disease have additional risk for DDIs [18,19]. Additionally, the present of polypharmacy medication in hospitalized patients are very important factor that explain the high rate of DDIs recorded in this study. Table 1 show that most patient take three medications or more and about 22(11.8%) take more than nine medications. Similar conclusion found by Assefa et al who show a higher incidence of potential DDIs in elderly people withpolypharmacy and cardiovascular disease [20]. The length of hospital stays also among the factor that lead to high rate of DDI [21,22]. In the present study most of the studied patients were hospitalized about three to seven days [111(59.7% of cases)] and some of them stay more, as seen in table 1.

In the present study most patients (about 75%) experience at least one interaction during hospitalization. The total number of interactions are 740 DDIs identified from 186 case with average (3.9) interaction per case. Similar studyfound that 78.2% of the cases had at least one potential DDI [23].Lower rate of interactions, about 46% and 26% had been seen in other studies [24,25] respectively. The heterogeneity in the results of various studies may reflect differences in the conditions of the included patients and level of care, as well as the various methodology used, especially the software used to identify these DDIs [26].

Most of DDIs in the present study occur due to pharmacodynamic mechanism482 (65.1%), followed by pharmacokinetic 144(19.5%) and about is occur by unknown mechanism 114 (15.4%). Moderate interactions are frequently found in the present study and 544 (73.5%) respectively. This agree with other studieswhich shows that moderate DDIs were highly incident [27,28].

The mild interaction is about 111 (15%). The mild andmoderate DDIs may not associated with potentially harmful effects, however its need careful monitoring and adequate management. Serious DDIs or X- interactions is about 85 (11.5%) in our study and they are considered high compare with Shetty V. et al study that report 3.02% of X-interaction (19). Unfortunately, these interactions would cause clinically significant adverse effects on patients. Serious interactions reported in the present study include interactions blood thinning drugs with ceftriaxone and/or other medications and in most cases result in increasing the potential risk of bleeding. Another potential interaction seen in this study, is decrease the efficacy of clopidogrel by co-administration with omeprazole.This pharmacokinetic interaction occurs due to enzyme inhibition action of omeprazole on cytochrome p450. Instead of omeprazole, other proton pump inhibitor, pantoprazole not inhibit with the enzyme and not interfere with clopidogrel action.

Many potential interactions preventable adverse effect that need pharmacological knowledge. These DDIs not well documented and many of them unnoticed by health care organizations. Even in developed countries like united states, there is a study shows that DDIs did not recognize and/or adequately treated [30]. Therefore, health care provider in our society, especially clinical pharmacists, should be encourage to use electronic based software for checking DDIs and discuss them with specialists for modification and or monitoring their clinical outcomes.

There are some limitations in the present results including that its retrospective study so the adverse

effects of these DDIs not followed clinically. DDIs are checked and recorded using *Medscape drug interaction checker*to hence its needed identify real clinical interactions from theoretical one. Inaddition, the performance of drug-drug interaction software is different in their sensitivity and specificity.Finally, the data are collected from one hospital and we need further studies in multiple hospitals or health centers to shed light on true percentage of DDIs in our society.

Conclusion

There are many potential drug interactions in hospitalized patients especially who have cardiovascular comorbidities. The serious DDIs were unfortunately high in the studied patients and its sufficiently high to alert health care organization to pay more attention toward these avoidable adverse effects on patients. There is a need to provide health care team and clinical pharmacists with the useful software to check and monitoring the significant drug interactions in order to prevent or at least minimize their adverse effect on patients.

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