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POTENTIAL DRUG-DRUG INTERACTIONS IN MEDICAL WARDS OF TIKUR ANBESSA SPECIALIZED HOSPITAL, ETHIOPIA

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ABSTRACT

The aim of this study was to determine the prevalence of potential drug-drug interactions (pDDIs), to identify drugs frequently involved in interaction and to identify factors associated with pDDIs in medical wards of Tikur Anbessa Specialized Hospital (TASH). A prospective crossectional study was conducted on 163 patients admitted in medical wards of TASH. Presence of interaction was cheeked using medscape drug-drug interaction checker. Data was analysed using SPSS version 21. A test of association was done using binary and multiple logistic regressions. The overall prevalence of potential drug-drug interaction was 86.5%. Interactions of major severity account for about one fifth of total pDDIs. The number of drugs taken by the patient was found to be significantly associated with pDDIs. The study highlighted the need to carefully select drugs and implement active pharmaceutical care services in order to prevent harmful effect of these interactions.

Keywords: Drug-drug interaction; Medical wards; Poly-pharmacy; Ethiopia

INTRODUCTION

As the number of patients with multiple co morbidities is increasing the drug therapy also becomes more complex. The use of complex drug regimen in turn will significantly increase the risk of DDI. [1] DDI is a situation in which one drug affects the activity of another when both are administered together. [2] DDIs can be either pharmacokinetic or pharmacodynamic type. Pharmacokinetic interactions are caused by differences in the absorption, transport, distribution, metabolization or excretion of one or both of the drugs compared with the expected behaviour of each drug when taken individually. Pharmacodynamic drug-drug interactions occur when drugs act at the same or interrelated receptor sites, resulting in additive, synergistic, or antagonistic effects of each drug at the target receptor. [3] DDIs may result in increased or decreased efficacy, treatment failure as well as increased toxicity of medications.[4,5] Hospitalized patients are more likely to be affected by these DDIs because of severe and multiple illnesses, co-morbid conditions, chronic therapeutic regimens, poly-pharmacy and frequent modification in therapy.[6]

Assessment and categorization of drug-drug interactions on the basis of severity is very important in order to decide on the risk versus benefit alternatives. On the basis of severity, drug-drug interactions are categorized as minor, moderate and severe. Minor drug interactions do not result in any significant troublesome outcomes. Management of these types of interactions is usually not required. Moderate drug-drug interactions could result in worsening of clinical condition of the patient. Treatment to manage such type of interactions could be considered. Major drug-drug interactions could lead to life threatening condition; therefore it should be considered essential to address such problems as soon as they are identified.

DDIs may cause adverse drug reactions (ADR) which may lead to hospitalization and emergency department visit. The estimated proportion of patients receiving interacting drugs with potential for an ADR or changes in therapeutic effect varies between 0.63% and 56% depending on the study. [7-10] The differences are due to study design, study population and study time periods. One study reported that Among the 156 ADRs with at least one theoretical DDI, 41% could be explained by a DDI. [11] ADR because of DDI also contributes for about 2.8% of hospital admissions per year. [12] Another study showed 1% of all hospital admissions were caused by drug–drug interactions (DDIs), corresponding to 16% of all patients admitted with ADRs. [11] In a geriatric outpatient cohort 21.3% of patients are experiencing at least one ADR as a consequence of a DDI.[9] Prospective study conducted in an internal medicine department in Cluj-Napoca, Romania showed that 25.9% of all validated ADRs were consequences of drug interactions.[13] A study conducted in Switzerland reported that 56.2 % of patients were exposed to one or more major or moderate pDDIs in internal medicine ward.[14] 1.5% of hospitalised patients had a diagnosis related to an ADR. Of these, a DDI was identified in 68% and a severe interaction in 12% respectively.[15] The incidence of DDI related adverse drug reactions is 6% in elderly outpatients. [16]

Reports of similar studies are common world-wide. However to the best of my knowledge there are few studies about drug-drug interaction and associated factors among hospitalized patients in Ethiopia. The increasing complexity of medication regimens of the patients, as well as the fragmented health care system in Ethiopia, with multiple prescribers for one patient are important elements that might lead to DDIs. Since DDIs are important causes for increase in morbidity and mortality rates in hospitalised patients,[17] it is imperative to assess the insight of pDDIs in hospitalised patients. Hence, the present study was undertaken to determine the prevalence of potential drug-drug interactions, to identify drugs frequently involved in interaction and to identify factors associated with pDDIs among hospitalized patients in medical wards of Tikur Anbessa Specialized Hospital.

METHODS

Study area and design: This prospective cross-sectional study was conducted in the medical wards of Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia for a period of 3 months (June - August, 2014). The hospital has more than 600 beds and gives diagnostic and treatment service for about 370,000-400,000 patients per year.[18] one hundred sixty three patients were included in the study by using simple random sampling method.

Study subjects: Patients admitted consecutively to Internal medicine wards were included in the study. Demographic information (age and sex), length of hospital stay, main diagnosis, number of drugs and details of co-morbidities were obtained from the clinical records. Subjects who were included in the study were those with age greater than 14 years, hospital stay of 24 hr and above and patients prescribed with at least two medications.

Data collection and analysis: The data collection process was supervised; all filled data abstraction formats were reviewed and cheeked for their completeness every day. All medications that were prescribed were screened for potential DDIs. Taking more than 5 drugs /day was considered as poly pharmacy.[19,20] Potential DDIs were detected using medscape Drug Interactions Checker. All drugs in a patient's medication profile were entered one by one into the software. The software displays all interacting combination(s) present in the medication profile. It also provides information about the mechanism and potential adverse outcomes of an interaction. All identified-pDDIs were categorized on the basis of their levels of severity and mechanism of interaction.

On the basis of severity medscape drug interaction checker categorizes DDIs as minor, moderate and major. Those interactions that may potentially result in life-threatening outcomes and need medical interventions are considered as major DDIs. Moderate DDIs cause potential deterioration of clinical condition and may require a change in therapy. Minor DDIs usually result in mild effects and may not necessitate therapeutic changes.

After data was checked for completeness, it was edited, cleaned and analysed. The collected data was entered into Epi Info 7 software version 7.1.4 (Centers for Disease Control and prevention, Atlanta, GA) and analysed using IBM SPSS statistics for Windows version 21.0.0.0 (IBM Corp. Released 2012, Armonk, NY: IBM Corp). Cross tabulation was used in bivariate analysis. A test of association was done using binary and multiple logistic regressions. *P* value < 0.05 was considered significant. Descriptive statistics was used to characterize drug-drug interaction. Results of the study were organized in the form of frequencies and percentages.

Ethical clearance: Letter of ethical clearance was obtained from the ethical review committee of Addis Ababa University, school of pharmacy. Verbal consent from a patient was requested to extract data from medication charts. Privacy and confidentiality was ensured throughout the study. Thus, name and address of the patient was not recorded in the data abstraction forms.

RESULTS

Characteristics of study population: A total of 163 patients were included in the study, of which 83 (51.9%) were females. The mean age was 37.7 years with the maximum number of patients (36.2%) being in the age group of 20-34 years. Majority of patients (54%) were found to have one to two co-morbidities. About one third of patients stay in the hospital a week or more. A total of 1202 medications were prescribed. Average number of drugs prescribed for a patient was 7.4 (SD=3.8). Majority of the study subjects (120 cases, 73.6%) received more than 5 drugs. The average number of diseases per patient was 3.1. The disease distribution of the study subjects showed a higher incidence of infections (73.6%) followed by cardiovascular diseases (47.2%), hematologic disorder (26.4%), electrolyte abnormalities (21.5%), gastrointestinal disorders (15.3%) and others (52.8%). The details of demographic and clinical characteristics of the study subjects are shown in Table 1.

Potential drug-drug interactions: From 163 patients included in the study 141 had at least one pDDI. A total of 885 pDDIs, which were comprised of 258 types of interacting combinations, were identified. The overall prevalence of potential drug-drug interaction was 86.5%. The number of pDDIs per patient vary from 1 to 29. On average 5.4 pDDIs occur per a single patient. Large proportion of patients (54 [33.1%]) were found to have more than 6 interacting combination. Patients without any DDI were only 22 (13.5%). Larger proportion of pDDIs identified was of moderate severity (51.3%) while just 19.9% were of major severity. As compared to pharmacokinetic type of interaction the pharmacodynamic type was found to be more common (53.8%). The frequency of interaction interms of severity and mechanism is mentioned in table 2.

Drugs involved in interaction

When specific drugs involved in any type of interaction were analysed cimetidine (85) was found at the top followed by heparin (55), warfarin (51), spironolacton (42), tramadol (37), digoxin (36) and furosemide (36). Drug pairs frequently involved in major DDI were cimetidine/tramadol (22 [12.5%]), warfarin/heparin (15 [8.5%]), ceftriaxon/heparin (13 [7.4%]), cimetidine/prednisolone (9 [5.1%]), isoniazide/rifampin (8 [4.5%]) and sulfamethoxazole/heparin (7 [4%]). The commonly encountered interactions of significant severity were spironolacton/furosemide (11), furosemide/digoxin (10), spironolacton/digoxin (7) and sulfametoxazole/fluconazole (7). The top 10 interacting pairs of major or moderate severity along with their potential adverse outcome are listed in table 3.

Risk factors: Age, sex, duration of hospital stay, disease type, number of drugs and number of co morbidity were studied to determine whether they have association with the likelihood of occurrence of pDDIs or not. Among these factors only number of drugs taken by the patient was found to be significantly associated with pDDIs. Multiple logistic regression showed that patients who took 5 or more drugs are 15.75 times more likely to have at least one PDDI as compared to those taking less than 5 drugs [Table-4].

DISCUSSION

The present study revealed that the overall incidence of potential DDIs were 86.5% which is high as compared to other studies which encountered pDDIs of 21.3 % - 56.2%.[21-28] This very high incidence of pDDI may be because the study was conducted in a hospital serving referred patients who have severe illnesses and more co morbidities and receive multiple drugs which is evidenced by the presence of more than 90 % study subjects with at least 1 co-morbidity, a hospital stay of more than a week for about two-third of the patient and average number of drug per patient of more than 7.

The number of pDDIs per patient was also high (5.4) as compared to studies conducted in Ethiopia as well as outside Ethiopia.[27,29] Majority of patients (54 [33.1%]) were found to have more than 6 interacting combination. In contrast to this the study in Pakistan found that only10 % of study subjects experience more than 6 pDDIs.[27] The result of this study indicated that majority of the pDDIs were of moderate severity. This is in line with the results of many other studies.[21,24,27,30] About one-fifth of pDDIs in this study were of major severity. This is a similar finding with the result of other studies which report 18.3%, 21.2% and 16% of pDDIs to be of major severity. [23,27,30]

Some of the specific drugs commonly involved in pDDI were cimetidine, heparin, warfarin, spironolacton, tramadol, digoxin and furosemide. Other studies also mention some of these drugs as commonly involved drugs in pDDI. For example study done in Western Nepal mentions digoxin, furosemide and warfarin were drugs frequently involved in interaction.[21] The study done by Akshaya S. et al and Camelia B. et al mentioned in their list of commonly involved drugs in interaction furosemide and spironolacton respectively.[29, 31] Cimetidine was frequently involved in interaction with various drugs like tramadol, prednisolone, dexamethason, warfarin, fluconazole, cotrimoxazole, pethidine, hydrocortisone, diazepam, codeine, nimodipine, simvastatin and digoxin. The mechanism of interaction of cimetidine with these drugs was either by inhibiting CYP 450 enzyme or by increasing gastric PH. Heparin and warfarin were also interact with many other drugs like sulfametoxazole, cimetidine, ceftriaxon, fluconazole, azithromycin, acetyl salsylic acid which necessitates strict blood cogulation monitoring, dose adjustment or drug discontinuation based on the outcome of interaction.

Drug-pairs that could give rise to potentially severe interactions were identified. The judgment here is based on theoretical consideration. In clinical practice, some of these combinations may still be used, but the patient should be closely monitored for manifestations such as lack of therapeutic efficacy or toxicity, especially for drugs whose therapeutic effects may be diminished or augmented when used in those combinations.

In the attempt to identify risk factors, the result of this study supported published findings that the number of drugs taken by a patient is an important risk factor for pDDI. Number of drugs used was found to be a risk factor for increasing DDIs by a number of studies.[21,24,27,29,32] However sex, age, length of hospital stay, type of diagnosis and number of comorbidity were not found to affect pDDIs. Similar studies also found sex and age are not significant factors.[21,29,33] Eventhough some studies report in contrast to the present study that length of hospital stay [21,27,32] and number of comorbidity [21,24,32] are significant factors for pDDI there are some studies [29, 33] which also report a similar finding with the present study.

Drug interaction is a major factor that might cause therapeutic failure or adverse drug reaction to patients.[34] As drug interactions can negatively affect patient's clinical outcome, quality of life, as well as contribute to unnecessary health care cost, the high prevalence rate (86.5%) in this study would make this an important area requiring future pharmacists to focus on. Identification and prevention of potentially harmful DDIs is a critical component in the task of clinical pharmacists. So they must remain active in their monitoring of pDDIs and make appropriate interventions based on the type and severity of identified DDIs. Careful selection of drugs, appropriate dose adjustments and close patient monitoring through active pharmaceutical care service is encouraged in order to avoid the negative consequences of drug-drug interactions.

The findings of this study may not be generalized because it is a single centred study conducted at one tertiary care teaching hospital where patients with multiple co- morbidity and more advanced disease states are seen. It did not also include patients from other wards of the hospital where the incidence and pattern of DDIs may be different.

CONCLUSION

The present study has showed a high prevalence of pDDIs in internal medicine wards. Patients with increased number of prescribed medications were at higher risk. The study highlighted the need to carefully select drugs and implement active pharmaceutical care services in order to prevent harmful effect of these interactions.

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Table 1: Demographic details and clinical characteristics of the study subjects

Demographic and clinical characteristics of patients	Category	Number (%)	Mean ± SD (Range)
Sex	Male	80 (49.1)	
	Female	83 (50.9)	
Age group (years)	<20	20 (12.3)	37.7 ± 17.6
	20-34	59 (36.2)	(14-85)
	35-49	45 (27.6)	
	50-64	19 (11.7)	
	>65	20 (12.3)	
Hospital stay (days)	< 7	57 (35)	11.1 ± 7.4
	≥ 7	106(65)	(2-36)
Number of co-morbidities	0	16 (9.8)	2.1 ± 1.3
	1-2	88 (54)	(0-8)
	3-4	53 (32.5)	
	≥ 5	6 (3.7)	
number of drugs prescribed	< 5	43 (26.4)	7.4 ± 3.8
	≥ 5	120 (73.6)	(2-21)
Diagnosis	GI disorders	25 (15.3%)	
	Cardiovascular disease	77 (47.2%)	
	Hematologic disorders	43 (26.4%)	
	Electrolyte abnormality	35 (21.5%)	
	Infectious disease	120(73.6%)	
	others	46 (52.8%)	

SD: Standard deviation
GI: Gastrointestinal

Table 2: Types of drug-drug interaction identified

Drug-drug interaction (DDI) classification method	Category	No of patients with at least one interacting combination (%) N=163	Number of DDIs (%) N= 885
Mechanism of interaction	pharmacokinetics	94 (57.7)	385 (43.5)
	pharmacodynamics	135 (82.8)	476 (53.8)
	unknown	6 (3.7)	24 (2.7)
Level of severity	serious	90 (55.2)	176 (19.9)
	significant	110 (67.5)	454 (51.3)
	minor	102 (62.6)	255 (28.8)

DDI: Drug-drug interaction

Table 3: Top 10 interacting pairs of major or moderate severity along with their potential adverse outcome

Interacting pairs	frequency	severity	Potential adverse outcome
Cimetidine/tramadol	22	major	Increase the risk of tramadol side effects
Warfarin/heparin	15	major	Increase bleeding risk
Ceftriaxon/heparin	13	major	Increase bleeding risk
spironolacton/furosemide	11	Moderate	May cause hypo/hyperkalemia
furosemide/digoxin	10	Moderate	Increase the risk of digoxin toxicity
Cimetidine/prednisolone	9	major	May increase prednisolone side effect
Isoniazide/rifampin	8	major	Increase risk of hepatotoxicity
sulfamethoxazole/heparin	7	major	Increase bleeding risk
spironolacton/digoxin	7	Moderate	Increase the risk of digoxin toxicity Increase risk of hyperkalemia
sulfametoxazole/fluconazole	7	Moderate	Increase QTc interval

Table 4: Associated factors for the presence of potential drug-drug interaction

Variables	Category	Drug-drug interaction (%)		COR (95% CI)	AOR (95% CI)
		No	Yes		
Sex	Male	12(15)	68(85)	1.00	1.00
	Female	10 (12)	73(88)	1.28 (0.52-3.18)	1.16 (0.37-3.63)
Age	<20	3 (15)	17(85)	1.00	1.00
	20-34	8(13.6)	51(86.4)	1.13 (0.27-4.73)	0.58 (0.10-3.41)
	35-49	7(15.6)	38 (84.4)	0.96(0.22-4.16)	0.48 (0.07-3.41)
	50-64	2 (0.0)	17 (100)	1.32 (0.41-6.27)	0.64 (0.20-4.55)
	>=65	4 (20)	16 (80)	0.71(0.14-3.66)	0.92 (0.11-7.96)
Hospital stay	< 7 days	12 (21.1)	45 (78.9)	1.00	1.00
	≥ 7 days	10 (9.4)	96 (90.6)	2.56 (1.03-6.37)	2.09 (0.64-6.90)
Number of comorbidities	0	5 (31.3)	11 (68.8)	1.00	1.00
	1-2	9 (10.2)	79 (89.8)	3.99(1.12-14.10)	1.49 (0.32-6.93)
	3-4	7 (13.2)	46 (86.8)	2.99(0.80-11.21)	0.37 (0.05-2.69)
	≥ 5	1 (16.7)	5 (83.3)	2.28 (0.21-24.89)	0.14 (0.00-2.06)
Number of drugs	< 5	17 (39.5)	26 (60.5)	1.00	1.00
	≥5	5 (4.2)	115(95.8)	9.55(3.20-28.48)*	15.75(3.90-63.59)*
Disease state	GI disorders	6 (24)	19 (76)	0.67 (0.24-2.37)	0.45 (0.15-1.36)
	Cardiovascular disease	9 (11.7)	68 (88.3)	1.50 (0.56-5.98)	1.79 (0.61-5.22)
	Hematologic disorders	5 (11.6)	38 (88.4)	2.11 (0.82-7.65)	1.78 (0.55-5.78)
	Electrolyte abnormality	4 (11.4)	31 (88.6)	1.43 (0.40-4.37)	1.33 (0.39-4.53)
	Infectious disease	13 (10.8)	107 (89.2)	1.93 (0.69-6.81)	2.24 (0.79-6.35)
	others	10 (21.7)	36 (78.3)	1.00	1.00

** Statistically significant.*
COR: crude odds ratio; AOR: adjusted odds ratio; CI: confidence interval.
GI: Gastrointestinal pDDIs: Potential Drug-Drug Interactions

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