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Prevalence and Clinical Significance of Potential Drug-Drug Interactions at Ayder Referral Hospital, Northern Ethiopia

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Abstract

Introduction: Clinically significant drug-drug interactions reduce effectiveness of drugs or cause fatal adverse events. Although harmful drug interactions are preventable, clinicians' recognition and detection of drug interactions is not optimal.

Objective: To assess prevalence, clinical significance and factors associated with potential drug-drug interactions at medical ward of Ayder Referral Hospital, Ethiopia.

Methods: A cross-sectional study was conducted to determine potential drug-drug interactions. A total of 204 patients' medical records were analyzed for drug-drug interaction using Micromedex drug interaction software. Data were analyzed using SPSS version 16.

Results: We identified 135 interacting-combinations in a total of 266 potential drug-drug interactions (pDDIs) with a mean of 1.3 pDDIs per patient. Of these, 30.1% and 53.7% of patients had at least one major and one moderate pDDIs respectively. The most common pDDIs involved were concurrent use of clarithromycin with simvastatin, aspirin with heparin and dexamethasone with rifampin which have contraindication, major and moderate severity respectively. There was significant association of occurrence of pDDIs with polypharmacy ($p<0.01$).

Conclusion: Potential drug-drug interactions were common at the medical ward of our hospital.

Keywords: Drug interaction; Pharmacodynamics; Pharmacokinetics

Introduction

Drug interactions alter the intensity of pharmacological effects of drugs given concurrently and hence increase or reduce their therapeutic or toxic effects [1,2]. Clinically significant interactions pose potential harm to patients by reducing effectiveness of drugs or causing potentially dangerous and fatal adverse events. They also increase treatment cost [3-7].

Factors that have shown significant association with occurrence of potential drug-drug interactions (pDDIs) include poly pharmacotherapy, age, gender, genetics, alcohol consumption, smoking, renal and hepatic function, main diagnosis and medication and the number of physicians a patient visits [8-10]. Harmful drug interactions are largely preventable since for most drugs a number of therapeutic alternatives are available. However, clinicians' recognition and detection of drug interactions is not optimal. The continually increasing number of drugs makes it virtually impossible for healthcare practitioners to keep up with new knowledge and heightens the risk that significant drug interactions will be overlooked [11].

A number of studies conducted at different part of the globe [12-23] showed that the prevalence of drug- drug interaction as well as its clinical significance (severity of interaction) varies from place to place depending on the presence of alternative drugs, variation in disease epidemiology and composition and level of health care professionals.

In order to design feasible preventive strategies, it is imperative first to determine the magnitude of the problem and the common drugs implicated in clinically significant DDIs in our context. Because the clinical conditions and types of drugs we use may vary from developed countries it will not be appropriate to extrapolate findings of developed nations to our set up. So, we undertook this study to determine the prevalence, clinical significance and factors associated with pDDI in our hospital.

Methods

The study was conducted at Ayder Referral Hospital (ARH) medical ward, northern Ethiopia from March 14 to April 14, 2014. The hospital has 400 beds and it is used as a teaching hospital for the College of Health Sciences, Mekelle University.

Study design

A cross-sectional study design was used. The sample size was determined using single population proportion formula using estimated prevalence of 23% (22).

Data collection tools and screening of pDDIs

Data were collected from patients' medical records by pharmacists using data abstraction checklist. Then screening for pDDIs was carried out by the authors using drug interaction software, Micromedex® Healthcare Series version 2.0.

Data processing and analysis

Data were analyzed using SPSS version 16. Binary logistic regression was also done to check factors that have association with pDDIs. The significance level was set at P-value less than 0.05.

Ethical considerations

Ethical clearance was obtained from ethical review board of Mekelle University.

Results

General patient characteristics

Of the total 222 admitted patients' medical records during the study period, 18 were excluded due to incomplete information, while the remaining 204 were analyzed for pDDIs. The median number of prescribed medications was 3 per patient with a range of 2-14 (Table 1).

Variable		Patient, n (%)
Gender	Male Female	117(57.4) 87(42.6)
Age category (years)	15-45 46-65 ≥ 66	127(62.2) 54(26.5) 23(11.3)
Co-morbidity	Present Absent	155(76) 49(24)
Number of prescribed medications per patient	≤ 4 5-7 ≥ 8	113(55.4) 67(32.8) 24(11.8)

Table 1: Characteristics of patients admitted at ARH medical ward, 2014.

Prevalence of pDDIs

Overall, 109 (53.4%) patients had at least one pDDIs regardless of type of severity (Table 2).

Number of pDDIs per patient	Patients: n (%)
1	54(49.5)
2	27(24.8)
3	7(6.4)
4	7(6.4)
5	4(3.7)
>5	10(9.1)

Table 2: Prevalence of pDDIs at ARH medical ward, 2014.

Characterization of pDDIs

Among the 266 pDDIs identified, most were of moderate (143; 53.7%) in severity; good (132; 49.6%) in scientific evidence; delayed onset (123; 46.2%) and were pharmacokinetic in mechanism (142: 53.4%) (Table 3).

Characteristics	Frequency (in 266 pDDIs) n (%)
Severity Contraindicated Major Moderate Minor	7(2.6) 80(30.1) 143(53.7) 36(13.5)
Documentation Excellent Good Fair	31(11.6) 132(49.6) 103(38.8)
Onset Rapid Delayed Non-specified	35(13.2) 123(46.2) 108(40.6)
Mechanism Pharmacokinetic Pharmacodynamic Unknown	142(53.4) 78(29.3) 46(17.3)

Table 3: Characterization of pDDIs at ARH medical ward, 2014.

Common interacting drug-combinations

Severity of common drug-drug interactions along with their frequencies, onset, mechanism and documentation are shown below (Table 4).

Drug interactions	Frequency	Onset	Severity	Documentation	Mechanism
Clarithromycin+Simvastatin	3	Not specified	Contraindicated	Good	PK
Chlorpromazine+Metoclopramide	1	Not specified	Contraindicated	Fair	Unknown
Aspirin+Heparin	6	Not specified	Major	Fair	PD
Clopidogrel+Heparin	5	Not specified	Major	Fair	PD
Cimetidine+Clopidogrel	4	Not specified	Major	Fair	PK

Aspirin+Clopidogrel	4	Not specified	Major	Fair	PD
Dexamethasone+Rifampin	10	Delayed	Moderate	Good	PK
Furosemide+Propranolol	8	Rapid	Moderate	Fair	Unknown
Clarithromycin+Rifampin	5	Not specified	Moderate	Excellent	PK

Table 4: Common interacting drug-combinations at ARH medical ward, 2014. PK=pharmacokinetic, PD=pharmacodynamic.

Risk factors for potential drug interactions

In binary logistic regression analysis, there was significant association between the occurrence of pDDIs with polypharmacy (p<0.001) (Table 5).

Variables	Drug-drug interaction		AOR (95% CI)	P value
	Present	Absent		
Gender Male Female	64(54.7%) 45(51.7%)	53(45.3%) 42(48.3%)	Reference 0.887(0.509-1.547)	0.673
Age category 15-45 46-65 ≥ 66	66(52.0%) 30(55.6%) 13(56.5%)	61(48.0%) 24(44.4%) 10(43.5%)	Reference 1.202(0.491-2.940) 1.040(0.389-2.781)	0.688 0.938
No. of medications per patient ≤ 4 5-7 ≥ 8	36(31.8%) 50(74.6%) 23(95.8%)	77(68.2%) 17(25.4%) 1(4.2%)	Reference 49.194(6.39-378.685) 7.820(0.981-62.368)	<0.001* 0.052
Co-morbidities Present Absent	88(56.8%) 21(42.8%)	67(43.2%) 28(57.2%)	Reference 0.571(0.298-1.093)	0.091

Table 5: Factors associated with pDDIs at ARH medical ward, 2014. *P<0.05, AOR=adjusted odds ratio.

Discussion

In this study the prevalence of pDDIs was 53.4% per 100 hospitalization episodes. This is a relatively high figure that highlights the importance of this previously unstudied problem in our hospital. Although our methodology and definitions might be different from those used in other studies, the result were similar to previously cited studies [16,23] in hospitalized pediatric patients (52.17% to 66%). Studies that have looked at prevalence of DDIs among hospitalized adult patients have yielded similar results. A prospective study conducted in India has shown that 52.17% (n=230) of hospitalized patients were exposed to 330 pDDIs [16]. This result is almost similar to our findings although the clinically relevant DDIs were low compared to our study. While another study done in the same country found 66% (n=250) pDDIs [23]. The prevalence of contraindicated, major, moderate and minor DDIs were 7 (2.6%), 80 (30.1%), 143 (53.7%) and 36 (13.5%) respectively. Findings from India for major, moderate and minor DDIs were 24.85%, 53.33% and 21.82% respectively [16]. The difference could be explained by lack of availability of alternative drugs in our setup and variation in disease pattern.

The clinical significance of pDDIs in our hospital was also higher than the findings from Brazilian teaching hospital which revealed 3.4% of major DDIs from a total 887 interacting combinations [14]. Similarly, the clinical significance of DDIs was much higher than a study conducted in Indian tertiary care hospital which reported 0.14%, 3.6%, and 27.9% of contraindicated, major and moderate level of clinical significance respectively [15]. But it is similar to findings from another Indian study where the major and moderate DDIs were 24.85%, and 53.33% respectively [16]. This high result could be due to the limited availability of alternative drug in our hospital in addition to the lack of strong ward pharmacist involvement in drug therapy and pharmaceutical care.

Common interacting drug-combinations of contraindicated, major and moderate severity are very important for practitioners because these pDDIs are more likely to produce negative outcomes. In our study, the most common potential DDI involved were concurrent use of Clarithromycin with Simvastatin, Aspirin with Heparin and

Dexamethasone with Rifampin, with contraindicated, major and moderate severity respectively. This result is different from the Indian finding where the most common interactions reported were with furosemide and theophylline followed by paracetamol and furosemide and azithromycin with ondansetron [16]. The variation might be explained by differences in disease prevalence, treatment protocol followed, and level of prescriber or available treatment options.

The co-administration of clarithromycin with simvastatin has resulted in increased simvastatin plasma concentrations and rare reports of rhabdomyolysis. Therefore, if clarithromycin therapy is necessary, holding simvastatin during the course of treatment is recommended [24].

The second most common interaction identified in our study was between aspirin and heparin. Concomitant use of heparin and aspirin increases the risk of gastrointestinal bleeding due to the potential for decreased platelet function and decreased coagulation. Thus, cautious use with closely monitoring patients for gastrointestinal bleeding is recommended. The potential interaction between dexamethasone and rifampin was also identified. Concurrent use of rifampin and dexamethasone has resulted in enhanced metabolism of the corticosteroid and decreased effect [24].

In our study 142(53.4%) of the DDIs were pharmacokinetic while 78(29.3%) were pharmacodynamic in nature. Indian study reported 19.14% of pharmacokinetic and 80.86% pharmacodynamic mechanism [16]. This difference could be due to differences in the type of drugs used in the two countries. Detection of the most common and clinically significant interacting drug combination could lead to use of other alternative if possible or alteration of dose of the medication with careful monitoring so as to minimize their negative health outcomes.

Co-morbid condition independently increased the odds of potential DDIs almost 2-folds. This is not surprising as drugs prescribed for co-morbid diseases condition are often used in combination. Poly pharmacotherapy was also associated with pDDIs. But there was no association between age of patient and gender with the occurrence of DDIs which is different from the Brazilian finding where they reported a higher rate of DDIs among woman and patients who were 55 years old or more [14].

Conclusion

Potential DDIs were common at the medical ward of ARH. Our findings revealed a significant association between DDI and number of medications prescribed per patient. Nearly one third of pDDIs were clinically significant. These DDIs have a potential to increase or decrease the therapeutic effect or to increase the risk of adverse drug reactions. So increasing awareness of pDDIs, rational prescribing of drugs and close monitoring of patients in whom these drugs are prescribed, participation of pharmacists in the multidisciplinary team round is recommended.

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Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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