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Prevalence, Types and Predictors of Potential Drug-Drug Interactions in an Internal Medicine Ward of The Mardan Medical Complex, Mardan,Kpk, Pakistan

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Abstract – The aim of this study was to determine the prevalence, types and predictors of potential drug-drug interactions (pDDIs). In this retrospective study, medication records of 40 patients were randomly selected from the internal medicine ward and analyzed for pDDIs. A total of 30 interacting drug pairs resulted into 53 pDDIs. Overall 52.50% patients have at least 1 pDDI regardless of the type of severity; 12.50%, 25% and 42.50% patients have at least one major, moderate and minor pDDI. Out of 53 pDDI the basis of severity 58.49%, 26.41% and 15.41% were of minor, moderate and major types respectively; 96.30% were of delayed onset; whereas those with probable and suspected scientific evidences were 37.73% each. pDDIs were more prevalent in the internal medicine ward, majority of which were of minor type of severity. Patients prescribed with more than 7 number of medication were at high risk of occurrence of pDDIs.

Keywords – Potential Drug-Drug Interactions, Prevalence, Types, Predictors, Scientific Evidence.

1. Introduction

Drug interactions are increasing day by day leading to major manifestations of health care issues [1].The term drug-drug interaction refers to alteration in the pharmacokinetics or effects of a drug by the presence of another drug [2]. Drug-drug interactions (DDIs) can lead to increased toxicity and untoward effects of many drugs [3]. DDIs can also affect the therapeutic response e.g. rifampin reduces antimicrobial effects of clarithromycin[4]. Sometimes reduction and increase in efficacy may be same harmful e.g. dose of warfarin need to be increased when given concomitantly with rifampicin [5], while patients on tetracycline antibacterial should not use (or separate their ingestion) substances containing multivalent cations and milky foods [6], [7].

Pharmacokinetic mechanisms for drug-drug interactions include drugs absorption, drugs distribu-tion, drugs metabolism and excretion of drugs. While the pharmacodynamic type of mechanisms include additive, synergistic and antagonistic interactions at receptor site [2]. In many studies it has been demonstrated that old age, polypharmacy, gender and long hospital stay are the com-mon predictors of pDDIs [8-13]. Beside these other factors may also be consi-dered in hospitalized patients for the issue of DDIs including the severity of disease, complex therapeutic regime, chronic diseases and co-morbid conditions [14].

Aim of this study was to determine the prevalence, types and predictors of pDDIs in an internal medicine ward in our part of the world.

2. Materials and Methods

2.1. Study design and Settings

This retrospective cross sectional study was conducted in an internal medicine ward (Medical-A) of the Mardan Medical Complex (MMC), Mardan, Kyber Pukhtoon Khwa, Pakistan. MMC is a 450 bed tertiary care, teaching hospital that provides health care services to the residents of districts Mardan, Sawabi, Nawshehra, Charsadda and many other areas. MMC have general medical, general surgical and obstetrics/ gynecology wards (two each), cardiology/CCU, orthopedics, pediatrics, ENT, skin/psychiatry/dengue fever ward (one ward each), an ICU and an accident and emergency department.

2.2. Sample size and data collection

Medication records, of 40 patients admitted to the ward during 15th August to 15th September 2015, were randomly selected. For this purpose a specially designed performa was used. Data collected from the medication records included the patient's demography, weight, height, admission date, discharge date, chief complaints, history of present illness, past medical history, past surgical history, social history, family history, allergies, results of relevant laboratory tests, final diagnosis and detail of medication including dosage form, brand (generic), dose, frequency and duration of drugs.

2.3. Analysis of data and classification of pDDIs

Medication charts of the patients were analyzed for pDDIs using a drug interactions software, Drug Interactions Facts ^{TM} 2009 [15], Following [14] all regular and Pro Re Nata medication used by the patients in hospital, that is, from the time of admission till discharge were included, however,

IV fluids (N/S, R/L, D/W of different conc.) and topical products such as eye drops, otics, creams, ointments and lotions etc. were excluded from the study. The software Drug Interactions Facts ™ 2009 [15] tells all about a drug's interactions including its common trade name, significance, onset, severity, documentation, effects, mechanism, management and discussion on it.

According to the software the pDDIs are classified into the following types.

2.3.1 Onset of effects:

1) Rapid: The effect of interaction can be seen within 24 hours of drugs administration.
2) Delayed: The effect of the interacting drugs delays to week.

2.3.2. Severity

1) Major: The interaction results in life threatening or permanent damage. An altered pharmacokinetic and a pharmacodynamic effect has been demonstrated in well controlled human studies.
2) Moderate: in this type of interaction health status of the patients is deteriorated.
3) Minor: This type of interaction is of little effect.

2.3.3. On the basis of confidence that an interaction can occur (documentation)

1) Established interactions: Those interactions which have strong evidence of occurrence.
2) Probable: Those interactions which are very likely to occur, but not proven clinically.
3) Suspected:Interactions which are suspicious; have some good data but needs more study.
4) Possible: pDDIs that could occur, but the data which proves its occurrence is very limited.
5) Unlikely: Interactions which are doubtful, having no good evidence of an altered clinical effect.

2.4. Statistical analysis

The data has quantitative and qualitative variables. Age of the patients, stay at hospital and the number of prescribed medicines were classified as quantitative variables which were described as median and ranges. Gender of patients, prevalence, types and predictors of pDDIs considered to be categorical variables were represented as percentages. A binary logistic regression analyses was conducted to predict exposure of patient to pDDIs. Odds ratios were calculated for specific risk factors including age, hospital stay and number of drugs per patient. Exposure to pDDIs (0=absent, 1=present) was considered as dependent variable while the others including gender (male=2, female=1), age (< 55 years=1, ≥55 years=2), hospital stay (< 5 days=1, ≥5=2) and number of medication per patient (< 7=1, ≥7=2) were considered as covariates or independent variables in the model. We used Hosmer-Lemeshow test to check goodness of fit of the model. The method used as Enter method. For statistical analyses SPSS version 16® was used.

3. Results and Discussion

3.1. General characteristics of patients

Out of the total 40 patients 24 (60%) patients were male and 16 (40%) patients were female. Age of the patients ranged from 13 to 85 (years) with a median age of 46 years. Duration of patients stay at the hospital was ranged from 2 to 12 (days) with a median of 3days. These characteristics are given in table 1.

Table 1. General characteristics of patients

Gender	**Patients: number**	**(%)**
Male	24	60
Female	16	40
Age (years)	**Patients: number**	**(%)**
≤15	1	2.5
16_30	12	30
31_45	7	17.5
46_60	5	12.5
61_70	11	27.5
≥76	2	5
	Years	
Median	46	
Range	13-85	
Hospital stay	**Patients: number**	**(%)**
≤ 2	6	10
3_4	29	72.5
5_6	5	12.5
≥7	2	5
	Days	
Median	3	
Range	2-12	
Medication prescribed per patient	**Patients: number**	**(%)**
≤ 2	1	2.5
3_4	6	15
5_6	1	45
7_8	9	22.5
9_10	5	12.5
≥11	1	2.5
	Drugs	
Median	5.5	
Range	2-11	

3.2. Prevalence of pDDIs

In this study a total of 53 potential drug-drug interactions and 30 types of interacting drug combinations were determined. Overall, 21 (52.50%) patients had at least 1 pDDI regardless of the type of severity; 17(42.50%), 10(25%) and 5(12.50%) patients had at least one minor, moderate and major types of interactions respectively, which shows that minor type of interactions were more prevalent as shown in (Table 1). Important to be noted that 19(47.50%) of patient's prescriptions were free of even a single interaction.

The number of pDDIs per patient ranged from 1 to 7, where 7(33.24%), 4(19.04%), 4(19.04%), 3(14.20%), 2(9.5%), 3(14.2%) and 1(0.04%) patients had ≤2, 3, 4, 5, 6 and 7 pDDIs in their prescriptions, whereas 1 was determined to be the median (Table-2).

Table 2. Prevalence of pDDIs

Types of pDDIs	**Patients: number (%)**
Overall	21 52.50
Major	5 12.50
Moderate	10 25.00
Minor	17 42.50
Number of pDDIs per patient	**Patients: number (%)**
≤2	7 33.24
3	4 19.04
4	4 19.04
5	2 09.50
6	3 14.20
≥7	1 00.04
	pDDIs (n=53)
Median	1
Range	1-7

3.3. Types of pDDIs

Since all the identified pDDIs were classified on the basis of their onset, levels of severity and documentation into different types as described in the previous chapter. Table 4.3 describes these types for the 53 pDDIs, out of which 2(3.7%) and 51(96.3%) were of rapid and delayed onset respectively. Interactions on the basis of severity included 8(15.9%) major, 14(26.41%) moderate and 31(58.49%) minor types of pDDIs.While pDDIs on the basis of documentation were 2(3.77%) established, 11(20.7%) probable, 20(37.73%) suspected, 12(37.73%) possible and 8(15.09%) unlikely, as shown in table 3.

Table 3. types of pDDIs

Types	**Frequency (in 53 pDDIs)**	**%**
Onset		
Rapid	02	03.70
Delayed	51	96.30
Severity		
Major	08	15.09
Moderate	14	26.41
Minor	31	58.49
Documentation		
Established	02	03.77
Probable	11	20.70
Suspected	20	37.73
Possible	12	37.73
Unlikely	08	15.09

3.4. Predictors of pDDIs

Predictors of pDDIs, were determined by SPSS version 16.0 for windows, given in table 4. where for each variable like gender, age, hospital stay and number of drugs per prescription, EXP(B) values were 0.956, 2.315, 0.676 and 12.727 respectively. Out of these variables first thevariable "number of drugs per patient" got the highest value of 12.727, this value indicates that when the number of drugs per prescription is raised by one unit (one drug) the odds ratio is 12.727 times as large and therefore patients are 12.727 times more likely exposed to pDDIs.

In the logistic regression analysis (table 3) there was significant association of the occurrence of pDDIs with 7 or more drugs prescribed per patient (Sig.0.007) compared to the hospital stay 5 days or more (Sig. 0.716), age 55 years or more (Sig. 0.276) and gender male (Sig. 0.954). Important to be noted, Sig. refers to the P-value of statistics.

Table 4 commonly interacting drugs

Names of interacting drugs	**Frequency**
Major	
Isoniazid + rifampin	**3**
Clarithromycin + digoxin, Digoxin + furosemide	**2 each**
Moderate	
Dexamethasone + aspirin……	**5**
Rifampin + paracetamol, Aspirin + bisprolol, Omeprazole + digoxin, Diazepam + digoxin, Carvidolol + aspirin, Ceftriaxone + heparin, Glimipride + aspirin, Valproic acid + alprazolam, Valproic acid + carbamazapine, Alprazolam + carbamazapine.	**1 each**
Minor	
(Omeprazole + aspirin)……..	**6**
(Aspirin + furosemide)……	**4**
(Rifampin + pyrazinamide)……	**3**
Alprazolam + omeprazole, GTN + aspirin, Omeprazole + clarithromycin	**2 each**
Quinine + cimetidine, Glimipride + rosuvastatin , Diclofenac sodium + furosemide Dexamethasone + telmesertan, Ceftriaxone + clrithromycin, Omeprazole + diazepam, Omeprazole + nifidipine, Paracetamol + furosemide, Clarithromycin + dextrometherphan, Clarithromycin + aspirin.	**1 each**

3.5. Commonly interacting drugs

In a total of 53 interactions 30 types of interacting drug combinations were identified. These interactions are given in the (table 4) with names of interacting drugs and there frequencies of occurrence.

This retrospective cross sectional study was conducted in the internal medicine ward (Medical A ward) of Mardan Medical Complex (MMC), Mardan, KPK; Pakistan. Where the patients medication records were randomly selected during the hospital stay of the patients from 15th August to 15th September 2015. Data related to the patient's demographics, diagnosed conditions, number of medication prescribed and duration of stay at hospital was recorded. This data was recorded because it made easy the study to be conducted whereas purpose of this study to be retrospective was to detect the pDDIs to judge the medication practices in the medical ward in the absence of a pharmacist. Results regarding the prevalence, types and predictors or the risk factors of pDDIs , proving this study to be the first study of its kind conducted in the hospital and district Mardan.

In this study we included 40 case histories of the patients. Out of these 24 (60%) patients were male and 16 (40%) patients were female, which shows that sample contained greater number of male patients. Age of the patients ranged

from 13 to 85 (years) with a median age of 46 years. Duration of patients' stay at the hospital ranged from 2 to 12 (days) with a median of 3 days. A total of 243 active drugs were prescribed to the 40 patients, medication prescribed per patient ranged from 2-11 with a median of 5.5. Variation in these parameters was dependent on the clinically diagnosed conditions as well as on the improvement of health status of the patients.

The overall prevalence of pDDIs was 52% regardless of the type of severity. On the basis of severity of pDDIs 12.5% of patients were exposed to at least 1 major, 35% to at least 1 moderate and 42.5% to at least 1 minor type of pDDIs which shows that patients having major interactions were of average prevalence whereas those having moderate and minor types of interactions were more prevalent comparatively. Prevalence with respect to pDDIs per patient was with an average of 1.08, median of 01 and range of 1-7 where 7(33.24%), 4(19.04%), 4(19.04%), 3(14.20%), 2(9.5%), 3(14.2%) and 1(0.04%) patients had ≤2, 3, 4, 5, 6 and 7 pDDIs in their prescriptions, which shows that ≤2, 3, 4, 5 pDDIs per patient were more prevalent compared to 6 and 7 pDDIs per patient.

In the previously published studies different criteria have been used to define drug-drug interactions which make it difficult to give an accurate estimate of the incidence of drug interaction, more will be true in distinguishing between the clinically significant and non-significant drug-drug interactions[16]. In many studies pDDIs are classified on the basis of onset, severity and evidence of occurrence[14] [17, 18].In our study we also classified pDDIs on the basis of onset, severity and evidence of occurrence. we obtained pDDIs of 03.70% rapid, 96.30% delayed; on the basis of onset, 15.09% major, 26.41% moderate, 58.41% minor; on the basis of severity and 03.77% established, 20.70% probable, 37.73% suspected, 37.73% possible and 15.09% unlikely; on the basis of documentation. Results of this study shows that delayed type of pDDIs on the basis onset, minor type of pDDIs on the basis of severity and other including suspected and possible types of pDDIs on basis of documentation were greater in number compared to the others.

The results are not compared to the former studies because of variation in the sample size.

Studies have demonstrated that old age, taking increased number of medications, long hospital stay and gender are common predictors of DDIs [8, 10, 11] [9, 12-14, 17]. In our study there was a significant association of pDDIs with patients having number of drugs equal to 7 or more for which the P-value (Sig.) was 0.007 with an odds ratio of 12.727, for hospital stay of 5 days or more P-value and odds ratio were 0.716 and 0.676 respectively, for age 55 years or more P-value and odds ratio were 0.276 and 2.315 respectively. From this discussion it is clear that patients prescribed with number of medications equal to seven or more were at high risk of developing pDDIs compared to the other variables.

Practitioners must have knowledge about the commonly occurring major and moderate interactions because they are more likely to produce negative outcomes [14]. Overall 30 types of interacting drug combinations were observed out of 53 pDDIs (table 4), those which were more frequent with known mechanism of action are described as major, moderate and minor pDDIs in the following three subsequent paragraphs respectively.

Major interactions included concurrent administration of furosemide with digoxin which will result in an increase urinary excretion of potassium and magnesium, these electrolyte abnormalities may lead to hypokalemia and hypomagnesemia which is a precipitating or contributing factor for the development of cardiac arrhythmias, especially in cardiac patients who are receiving digitalis glycosides .[19]Digoxin toxicity has been reported in another case after clarithromycin administration,[20] Macrolides and related antibiotics may inhibit renal tubular P-glycoprotein excretion of digoxin .[21]Increased plasma digoxin levels and symptoms of toxicity should be monitored; decrease the dose of digoxin if necessary.[15] Hepatotoxicity may occur at a rate higher using isoniazid with rifampin than with either agent alone. Possibly an alteration in the metabolism of isoniazid is caused by rifampin. If alterations in liver function tests occur, discontinuation of one or both of these agents should be considered [15].

Therapeutic effect of aspirin may be reduced when administered along Dexamethasone this is due to decrease in the serum concentration of aspirin.[22] This is because Dexamethasone increases renal elimination of aspirin and may also stimulate liver metabolism of salicylates [15].

The pharmacologic effects of certain Benzodiazepine may be decreased when administered along carbamazepine [23]. This is because of Induction of Benzodiazepine metabolism (CYP3A4) by carbamazapine. Monitor for a decrease in benzodiazepine clinical response during coadministration of carbamazapine. If an interaction is suspected, consider using a higher dose of the Benzodiazepine [15].

Administration of quinine with cimetidine may reduce the oral clearance of quinine, and the mean elimination half-life may be increased.[24] This is because Cimetidine may reduce the hepatic microsomal mixed function-oxidase enzyme metabolism of quinine. Dose-dependent toxicitysuch as cinchonism should be monitored if using cimetidine along quinine, particularly in patients receiving antimalarial doses of quinine [15].

Pyrazinamide administered in combination with rifamycins will lead to decreased Serum rifampin levels, possibly reducing the clinical effects of rifampin [25]. No action is required. If an interaction is suspected, consider increasing the dose of rifampin.[15]When aspirin is administered with furosemide in patients with cirrhosis and ascites, the diuretic response to loop diuretics may be impaired [26]. No clinical interventions are generally required. For patients with cirrhosis and ascites requiring furosemide, aspirin should be used with caution [15].

4. Conclusion

A high prevalence rate of pDDIs was recorded in the internal medicine ward, out of which first minor and then moderate types were more prevalent, same was the case with the types of pDDIs where first minor and then moderate were more frequent on the basis of severity. Almost all types of pDDIs were of delayed onset and on the basis of documentation those having suspected and possible evidences were more frequent. Patients prescribed with increased number of medication were more exposed to pDDIs.

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