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SCREENING/ASSESSMENT OF POTENTIAL DRUG-DRUG INTERACTIONS IN NEUROLOGY WARD OF A TERTIARY CARE HOSPITAL, PESHAWAR KHYBER PAKHTUNKHWA: PREVALENCE, TYPES AND THEIR PREDICTORS

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Abstract

In hospitalized patients the issue of drug-drug interactions is prevalent and deserves more attention. In the present study an attempt was made to determine pDDIs in hospitalized patients. This study was conducted by collecting the retrospective data of hospitalized patients. The data was fed to software (Micromedex Drug-Reax) to screen out the potential drug-drug interactions (pDDIs). In our study, total number of interactions identified were 396 out of which 201 were moderate and 153 were major. 90% of the patients had at least one pDDI regardless of severity. Among 396 identifed pDDIs, most were of moderate (50.7%) or major severity (38.6%); good (145%) or fair (183%) type of scientific evidence; and delayed onset (125%). The hospital stay was significantly increased ($P < 0.05$) for patients having at least one pDDI of major severity. To reduce the risk of drug interactions there is a need for improvement in the knowledge of health care providers, the use of computerized screening systems, providing information on patient risk factors and establishment of drug information centers, which may rationalize the use of medications in these set-ups.

Keywords: *Drug-drug interaction, DDIs, pDDIs*

Introduction

Scientific discoveries, technological advancements and recent developments in pharmacotherapy have made a significant impact on improving the patients' quality of life. Due to recent developments in pharmacotherapy, there are number of drugs clinically available and their use is increasing day by day. These drugs are capable of producing a therapeutic effect but on the other hand they are associated with many unwanted effects (Edwards and Aronson, 2000; Striano et al. 2008; Pieri et a. 2011). Among these untoward effects, drug-drug interactions are considered as most important (DDIs). The term DDIs is defined as, if two drugs are administered together, one drug alters or modifies the effect of another drug (Baxter et al. 2010). Harmful drug interactions may lead to adverse drug reactions that can serve enough in lengthening the period of stay in hospital, enormous financial burden and consequently the reason of a significant mortality and morbidity rate in a section of hospitalized admitted patients (Classen et al. 1997). Hospitalized patients usually suffer from severe illnesses, multiple disorders, complex therapeutic regimen and very frequent modifications in therapy, the chances of negative outcomes would be more severe in admitted patients. Every drug interaction caries the risk to cause negative outcomes but are often predictable and therefore avoidable or manageable (Cruciol-Souza and Thomson, 2006).

To the best of our knowledge, no such data is available regarding evaluation of potential drug-drug interactions (pDDIs) in neurology wards. Therefore the purpose of this study was to identify and assess the number of potential DDIs in medication orders of hospitalized patients in a neurology ward in a Pakistani tertiary care hospital. The second aim was to report and highlight the commonly occurring drug-drug interaction combinations in neurology ward, in order to monitor the patients carefully for all potential clinical consequences to be managed accordingly by the health care professionals in near future.

Methods

Study design and settings

This study was conducted in neurology ward of a Northwest General Hospital & Research Center, Peshawar, Khyber Pakhtunkhwa, Pakistan. About 530 patients were admitted during a period of one year from 01st June, 2017 to 30th June, 2018. A random sample of 100 patients was selected for the study. Retrospective study was carried out by using automated medication records of 100 patients on random basis admitted in neurology ward. Incomplete records of patients were excluded from the study.

Data collection and screening of pDDIs

As the study involves human subjects therefore declaration of Helsinki approved by World Medical Association were followed. The ethical committee of the Neurology Ward North West General Hospital, Peshawar, affiliated with World Medical Association, granted approval (NWHP/Eth-H-087/15) for conducting this study. The collected medical records were reviewed and screened retrospectively for pDDIs using drug interaction software, Micromedex Drug-Reax System (MDRS) (Thomson Reuters Healthcare Inc., Greenwood village, Colorado, USA). Micromedex disease & drug information system is USA based software which is the world's most complete and carefully researched clinical decision support system. Micromedex database is based entirely on the clinical evidence and used by 5500 hospitals, healthcare institutes and medical universities in more than 85 countries. This data base is relied upon toxicology contents 100% in USA and major poison control centers worldwide.

We entered all drugs prescribed to the patients one by one from the time of admission till discharge. Classification of clinically significant identified potential DDIs was done on the basis of following different levels (Micromedex Drug-Reax® System, 2015).

Onset

- ***Rapid:*** The effect of rapid interactions occurs within 24 h of administration and its management requires immediate action.
- ***Delayed:*** The effect occurs when the interacting combination is administered from more than 24 h, i.e., days to weeks.

Severity

- ***Contraindicated:*** The drug combination is contraindicated for concurrent use
- ***Major:*** Such type of interactions may be life-threatening and fatal, required immediate treatment in order to prevent or minimize the serious negative adverse effects.
- ***Moderate:*** Moderate interactions may exacerbate the patient's condition and may require change in therapy.
- ***Minor:*** Limited clinical effects and generally will not require any major change in therapy.

Scientific evidence (documentation)

Excellent: The existence of interaction has been clearly established and documented in well controlled studies.

Good: Documentation strongly suggests the existence of interaction but there is lacking of well controlled studies.

Fair: The availability of evidence is poor but on the basis of pharmacological considerations, the interaction is suspected to exist and data is available from pharmacologically similar drug.

Poor: Documentation is very limited and interaction may occur theoretically such as very few case reports.

Unlikely: Data are very poor and lack of proper pharmacological basis.

Statistical analysis:

Data were analyzed statistically by using GraphPad Prism 5 (GraphPad Software Inc. San Diego CA, USA). The Chi-square test and *t*-test were used to analyze the data. A *P* value < 0.05 was defined as statistically significant.

Results

General patient characteristics

During this study 530 patients were admitted in the neurological ward. A random sampling of 100 patients was selected for this study. Out of 100 patients, 43(43%) were male and 57(57%) were female. The mean age was 47 (Table 1), while mean hospital stay was 04 days (Table 2). The mean number of prescribed medications was 9 (Table 3).

Prevalence of pDDIs

In our study, the total number of interactions identified was 396. Out of 100, 90 patients had at least one pDDIs regardless of type of severity (Table 4).

Moderate pDDIs were most prevalent (201) followed by major pDDIs (153) and minor pDDIs (13). Contraindicated type of pDDIs was rare and recorded only in 29 patients (Table 5).

Levels of pDDIs

The identified pDDIs were categorized according to different levels (**8**). Significant potential drug-drug interactions were observed on the basis of severity, documentation and onset ($P < 0.0001$). Increase incidence of moderate drug-drug interactions (50.7 %) were found followed by interactions of major severity (38.6%). The documentation was fair (46.2%) for majority of drug-drug interactions which was followed by good level of documentation (36.6%). In the majority of cases, the onset of drug-drug interactions was not-specified (46.2%). Moreover, high proportion of delayed onset (31.5%) of potential drug-drug interactions was also observed (Table 6). Additionally, the average stay in the hospital for patients having at least one drug-drug interaction of major severity was found to be significantly higher ($t(98) = 2.024$, $P < 0.05$) that patients having drug interactions of non-major severity.

Commonly interacting combinations

A total of 396 potential interacting drug combinations were identified in this study. There were top 15 frequently occurring interacting drug-pairs, which include 11 major and 4 moderate types of pDDIs. Significant potential drug-drug interactions of major severity ($P < 0.0001$) were observed between aspirin and enoxaparin (20.26%), clopedogril and enoxaparin (7.189%), clopedogril and enoxaparin (6.535%), haloperidol and tramadol (6.535%), enoxaparin and warfarin (6.535%), and valproic acid and meropenem (6.535%). A statistically non-significant moderate drug-drug interaction was noted for aspirin + ramipril (5.472%), aspirin + spironolactone (4.477%) and aspirin + frusemide (3.980%) (Table 7).

Discussion

The present study highlights the detection of potential drug-drug interactions (pDDI) using a computer program to check the medication orders of inpatients in tertiary care hospital. This study-was conducted-in neurology ward of a private hospital set-up. 396 drug interactions were identified in clinical records of 100 hospitalized patients admitted in neurology ward. In this study, most of pDDIs were moderate (50.7%) or major severity (38.63%). Moderate-pDDIs are of special concern, as they are more common in the-present-study. In this study, our 90% patients had at least one potentially interaction drug combination during hospitalization. Harmful drug interactions may lead to adverse drug reactions that can serve enough in lengthening the period of stay in hospital, implement enormous financial burden and consequently the reason of a significant mortality and morbidity rate in section of hospitalized admitted patients. Study was conducted in LDS tertiary care hospital (Salt Lake City Utah) from Jan 1990 to Dec 1993 to identify the root causes of adverse drug events. 50% of all ADEs (adverse drug events) were potentially preventable. Excessive dosage of a drug for patient weight and calculated renal accounted for 42%. Drug interactions accounted for 4.6%, known drug allergies accounted for 1.5% and medication errors for 1% for all ADEs (5). In our study, we cannot quantify how many of the identified DDIs were known by the physician but we assume that they were possibly unaware of the potential risk associated with certain combination. To better quantify the clinical relevance of potential interacting drug combinations during hospital stay, a prospective design would be necessary in order to minimize the chances of prolong stay, increased economical burden and drug related morbidity and mortality rate, which has been estimated to cost more than $136 billion a year in the United states (4, 5). It is well documented fact that the incidence of DDIs in different countries varies from 6% to 70% due to variability in methodologies and settings, such as design of research studies, locations of study (e.g., hospitals, emergency rooms, community settings, nursing homes), population's characteristics (e.g., elderly, adults), availability of advanced clinical pharmacy services and most important, accessibility and use of electronic DDIs, screening programs (Cruciol-Souza and Thomson, 2006). Nature and frequency of DDIs in community and outdoor patients have been investigated. In Taiwan medical center, the pDDIs were identified in medications of almost 25.6% outpatients' prescriptions (Burke et al. 2008). Another study was conducted, in which medical records of ambulatory patients was evaluated. Patients aged more than 50 years, 80% of them were having one or more pDDIs (Burke et al. 2008; Hepler and Strand, 1990). There are many drug interactions compendia which have classified the drug interactions on the basis of their levels of severity, onset, evidence based scientific literatures, management-options-or-their-combinations (Tatro, 2000; Merlo et al. 2001; Hansten and Horn, 2007). Hospitalized patients usually suffer from severe illnesses and multiple disorders as compared to community and outpatient settings. Due to this reason, DDIs are less likely to occur in outdoor patients or community setups as compared to hospitalized patients. Therefore, their negative outcomes would be more severe in admitted patients. As large number of medications are prescribed and due to complex therapeutic regimens, DDIs needs more attention in hospitalized patients. Now a days' advance computer software systems are available and with the help of these software systems, pDDIs can be easily identified. These can be either manageable by substituting another drug, by adjusting the dose or by close monitoring of clinical symptoms and laboratory test results (Hepler and Strand, 1990; Tatro, 2000; Merlo et al, 2001; Cruciol-Souza and Thomson, 2006; Hansten and Horn, 2007; Burke et al. 2008). Pharmacists can optimize the pharmacotherapy by applying their professional knowledge, skills and using the computerized scientific evidence based software programs, which can be helpful to minimize or prevent the serious negative consequences of DDIs (WHO, 2013). The combination of aspirin and enoxaparin is associated with a risk of developing an epidural or spinal-hematoma during low molecular-weight-heparin (LMWH) in those patients who are receiving neuraxial-anesthesia or spinal-puncture, (Martindale et al. 1999). Caution should be exercised while taking haloperidol with tramadol, as this combination reduces the seizure threshold and

therefore precipitate dangerous seizures (Gardner et al. 2000). Similarly, coadministration with carbapenem antibiotics may substantially decrease the serum concentrations of valproic acid. Concomitant use of valproic acid with carbapenem antibiotics is generally not recommended (Coves-Orts et al, 2005). These results suggest that patients are at higher risk to negative consequences of these identified drug interactions, which necessitates close monitoring of patients' clinical conditions.

Conclusion

We have recorded a high prevalence of potential drug-drug interactions in the neurology ward, most of which were of moderate severity. Our findings indicate that the identified drug-drug interactions have high potential to harm or deteriorate patients' clinical conditions and alter the therapeutic response. Prescriptions should be screen at least for major drug-drug interactions. Clinical pharmacists should regularly analyze the prescriptions that commonly contain major drug-drug interactions prior to drug dispensing and thereof administration. We recommend careful monitoring of patients, use of computerized drug interaction programs which is valuable and helpful tool but it has to be combined with clinical pharmacological experience and expertise as well as establishment of drug information centers, which are some of possible solutions to the current problems in managing prescription drugs.

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List of abbreviations

DDIs: Drug-Drug Interactions
pDDIs: Potential Drug-Drug Interactions
LMWH: Low Molecular-Weight-Heparin
VPA: Valproic-Acid
MDRS: Micromedex Drug-Reax System

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Table 1: Patients Gender

Characteristics of Patient	Frequency
Gender	**Patients: n (%)**
Male	43(43)
Female	57(57)

Table 2: Patient Hospital stay

Stay at Hospital (days)	Patients: n (%)
<3	38(38)
4-6	35(35)
>7	27(27)
Mean	4
Range	1-16

Table 3: Prescribed medications per patient

Prescribed-medications-per-patient	Patients: -n (%)
<4	25(25)
5-10	40(40)
11-14	35(35)
Mean	**9**
Range	**4-14**

Table 4: Total no. of Drug Interactions

Drug Interactions	Frequency
Total Patients	100
Total no. of Interactions Present	396
No interaction found in patients	10

Table 5: Distribution of identified pDDIs on the basis of severity

Drug Interactions on the basis of Severity	Frequency
Total Interactions	396
Contraindicated	29
Major	153
Moderate	201
Minor	13

Table 6: Distribution of identified potential Drug-Drug interactions on the basis of levels

Levels	Frequency (*n*)	Percentage (%)	χ^2	*P* value
Severity				
Contraindicated	29	7.3232	345	< 0.0001***
Major	153	38.636		
Moderate	201	50.757		
Minor	13	3.2828		
Documentation				
Excellent	47	11.868	115.1	< 0.0001***
Good	145	36.616		
Fair	183	46.212		
Onset				
Rapid	67	16.919	78.65	< 0.0001***
Delayed	125	31.565		
Non specified	183	46.212		

Chi-square test was used and $P < 0.05$ was considered as significant
***P = value is significant

Table 7: Common interacting drug-combinations

Drug interactions	Frequency (*n*)	Percentage (%)	χ^2	*P* value
Contraindicated				
Ceftriaxone + Calcium chloride	15	51.72	-	-
Major				
Aspirin + Enoxaparin	31	20.26	65.40	< 0.0001***
Aspirin + Clopedogril	11	7.189		
Clopedogril + Enoxaparin	10	6.535		
Haloperidol + Tramadol	10	6.535		
Enoxaparin + Warfarin	10	6.535		
Valproic acid + Meropenem	10	6.535		
Clopedogril + Omeprazole	8	5.228		
Aspirin + Escitalopram	5	3.267		
Atracurium + Gentamicin	4	2.614		
Tramadol + Valproic acid	4	2.614		
Dexamethasone + Nimodipine	3	1.960		
Moderate				
Aspirin + Ramipril	11	5.472	1.046	0.7902
Aspirin + Spironolactone	9	4.477		
Aspirin + Frusemide	8	3.980		
Dexamethasone + Moxifloxacin	7	3.482		
Minor				
Aspirin + hydrocortisone	7	53.84	-	-

Chi-square test was used and $P < 0.05$ was considered as significant
***P = value is significant