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Original Research Article

Frequency, Levels and Predictors of Potential Drug-Drug Interactions in a Pediatrics Ward of a Teaching Hospital in Pakistan

Mohammad Ismail[1], Zafar Iqbal[1*], Muhammad I Khan[2], Arshad Javaid[3], Hassan Arsalan[4], Farhadullah[4], Faramoz Khan[5], Amir Z Khan[1], Fazli Nasir[1] and Jamshaid A Khan[1]

[1]Department of Pharmacy, University of Peshawar, Peshawar, [2]Ayub Medical College, Abbottabad, Khyber Pakhtunkhwa, [3]Post Graduate Medical Institute, Lady Reading Hospital (LRH), Peshawar, [4]Department of Pharmacy, Sarhad University of Science & Information Technology, Peshawar [5]Medical-B Unit, Khyber Teaching Hospital, Peshawar, Pakistan.

For correspondence:* ***Email:* *zafar_iqbal@upesh.edu.pk;* ***Tel:*** *+92-91-9216750;* ***Fax:*** *+92-91-9218131*

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Abstract

Purpose: *To identify the frequency, levels and predictors of potential drug-drug interactions (pDDIs) in a pediatrics ward of a teaching hospital in Pakistan.*
Methods: *Medication profiles of 400 pediatric patients were evaluated for pDDIs using Micromedex Drug-Reax® software. Logistic regression was used to identify association of pDDIs with hospital-stay, patient's gender, and number of medications.*
Results: *In total, 86 interacting drug-combinations resulting in 260 pDDIs were identified. Overall, 25.8 % patients were exposed to at least one pDDI regardless of severity-type, 10.7 % to at least one major-pDDI, 15.2 % to at least one moderate-pDDI, and 12.5 % to at least one minor-pDDI. Of 260 pDDIs, most were of moderate severity (41.5 %) followed by minor (35.4 %) and major severity (21.9 %); good (76.9 %) or fair (16.5 %) type of scientific evidence; and delayed onset (46.5 %). Some widespread major or moderate interactions included rifampin + pyrazinamide (14 cases), phenobarbital + diazepam (14), dexamethasone + rifampin (8), amikacin + furosemide (7), furosemide + captopril (7), dexamethasone + phenobarbital (6), phenobarbital + divalproex sodium (6), isoniazid + rifampin (5) amikacin + ibuprofen (5), digoxin + furosemide (4), and acetaminophen + phenytoin sodium (4). There was significant association of the occurrence of pDDIs with five or more prescribed medications ($p < 0.001$).*
Conclusion: *PDDIs are less prevalent in the pediatrics ward of the hospital studied. Most of the interactions were of moderate severity. Patients with increased number of prescribed medications were more exposed to these interactions.*

Keywords: *Drug-drug interactions, Prescription screening, Drug related problems.*

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INTRODUCTION

Recent developments in pharmacotherapy have contributed considerably to improve patients' quality of life. As a result of such advancement, the number of available medications and their uses are increasing. Although drugs are used to achieve beneficial therapeutic effects, they can also lead to many undesirable consequences. One of such consequences is the problem of potential drug-drug interactions (pDDIs) that may

lead to alteration of therapeutic response or increase in untoward effects of many drugs [1,2].

A wide variation exists in the prevalence of pDDIs in hospital settings due to differences in the design of research studies. Prevalence of pDDIs has been reported in the range of 19.3 to 88.8 % [3,4]. A study, conducted in two hospitals in England, found that 1225 (6.5 %) hospital-admissions were caused by medicines, of which, 203 (16.6 % of 1225) admission were related to drug-interactions [5]. A review paper analyzed published literature related to drug related problems (DRPs) in hospitals. It was reported that during hospitalization, 17 % of all adverse drug events are caused by drug-drug interactions [6].

Some studies have investigated pDDIs in particular clinical situations or specialties such as cardiology [7], oncology [8], psychiatry [9], intensive care units [10], pulmonology [11], and geriatrics [12]. Most of the aforementioned studies are limited to adult patients. To the best of our knowledge, such data are scarce in pediatrics specialty. It has been pointed out that hospitalized pediatrics patients are at higher risk to drug-induced problems because of many factors such as wide-ranging of patient ages and body-weights, limited physiologic reserve, calculation errors in medications dosing, and incapability to properly communicate with healthcare professionals [13]. In such circumstances, pDDIs are more likely to cause adverse outcomes in pediatrics hospitalized patients. Therefore, studies are obligatory to report data regarding pDDIs in such an important population.

The present study aimed to find prevalence and levels of pDDIs in a pediatrics ward; their association with length of hospital-stay, patients' gender, and number of prescribed medications; and to determine widespread interacting drug-combinations.

METHODS

This study was carried out in pediatrics ward of Khyber Teaching Hospital, Peshawar, Pakistan, which is a 1200-bed teaching hospital. The hospital is a busy health care center along with referral services. It serves a population of about 350 thousand inhabitants of Jamrud Road and adjacent areas of Peshawar district.

The study was approved by Ethical Committee of the Department of Pharmacy, University of Peshawar. A cross-sectional design was used which involved evaluation of medical records of 400 patients admitted during the month of May - July 2011. Hospitalized patients, < 18 years old, suffering from any type of disease, and both males and females were included in this study. Permission was obtained from hospital administration to carry out this study in hospital. The following information items were collected: patient's age, gender, date of admission, date of discharge, diagnosis and detail of medication therapy provided in the hospital. All regular and PRN (pro-re-nata, means as required) medications were included, however, topical products such as creams, ointments, eye drops and ear drops were excluded from analysis.

Micromedex Drug-Reax® Software (Thomson Reuters Healthcare Inc., Greenwood Village, Colorado, United States) [14], was used to screen patients' medication profiles for pDDIs. The software displays all drug-interactions present in the patient's profile. As per classification of Micromedex Drug-Reax® System [14], all identified-pDDIs were categorized on the basis of their levels of severity, onset, and scientific evidence as follows:

Onset

- *Rapid*: The effect of interaction occurs within 24 hours of administration.
- *Delayed*: The effect occurs if the interacting combination is administered for more than 24 h, i.e., days to week(s).

Severity

- *Contraindicated:* The drug-combination is contraindicated for concurrent use.
- *Major:* There is risk of death and/or medical intervention is required to prevent or minimize serious negative outcomes.
- *Moderate:* The effect of interaction can deteriorate patient's condition and may require alteration of therapy.
- *Minor:* Little effects are produced that don't impair therapeutic outcome and there is no need of any major change in therapy

Scientific evidence (Documentation)

- *Excellent:* The interaction has been clearly demonstrated in well-controlled studies.
- *Good:* Studies strongly suggest that the interaction exists except proof of well-controlled studies.
- *Fair:* Available evidences are poor, but the interaction is suspected on the basis of pharmacologic considerations; or, evidences are good for an interaction of pharmacologically similar drug.
- *Poor:* Theoretically, the interaction may occur but reports are very limited, such as few case reports.

- *Unlikely:* Data are very poor and lack a proper pharmacologic basis.

Prevalence of pDDIs, belong to any of the severity-levels (overall-prevalence), was identified. Likewise, number of patients exposed to different types of pDDIs such as contraindicated-pDDIs, major-pDDIs, moderate-pDDIs and minor-pDDIs, were determined. All identified pDDIs were categorized on the basis of their levels of severity, onset, and scientific evidence.

Statistical analyses

Quantitative variables such as age, hospital stay and number of prescribed medications are presented as median and ranges. Categorical variables such as gender, prevalence and levels of pDDIs are presented as frequencies and percentages. Logistic regression technique was used to determine the association of occurrence of one or more pDDIs with length of hospital stay, patients' gender, and number of prescribed medications. In the model, exposure to potential drug-drug interactions (pDDIs) was the dependent variable (0 = absent, 1 = present). Whereas, the following variables were included as predictors of pDDIs: length of hospital stay (1 = less than 5 days, 2 = 5 days or above), patient's gender (1 = female, 2 = male), and number of prescribed medications (1 = less than 5, 2 = 5 or above). Initially a univariate analysis was performed followed by multivariate analysis, in which, variables with univariate *p*-values < 0.1 were included. The Hosmer–Lemeshow test was used to assess goodness-of-fit of the logistic regression model. *P*-value of 0.05 or less was considered statistically significant. SPSS for Windows version 16 (SPSS, Inc., Chicago, IL, USA) was used for all statistical analyses.

RESULTS

Of the total 400 patients, 254 (63.5 %) were males and 146 (36.5 %) were females. Median age was 1.5 years, median hospital stay was four days and median number of prescribed medications were four (Table 1). One hundred and three (25.8 %) had at least one pDDI regardless of type of severity (Table 2). As far as prevalence of pDDIs on the basis of severity was concerned, moderate pDDIs were most prevalent and recorded in 15.2 % patients followed by minor pDDIs (12.5 %).

The levels of onset, severity and scientific evidence (documentation) for the identified pDDIs are given in Table 3. Of 260 pDDIs, most were of moderate severity (41.5%) followed by minor (35.4%) and major severity (21.9%); good (76.9%) or fair (16.5%) type of scientific evidence; and delayed onset (46.5%).

Table 1: General characteristics of patients in the pediatric ward

Characteristic	***Patients: n (%)***
Gender	
Male	254 (63.5)
Female	146 (36.5)
Age **(**years**)**	
< 01	136 (34)
01-04	149 (37.2)
05-09	70 (17.5)
≥10	45 (11.2)
Median - 1.5 years	
Range - 1 month-17 years	
Hospital stay (days)	
≤3	186 (46.5)
4-6	166 (41.5)
≥7	48 (12)
Median - 4	
Range - 1-18	
Prescribed medications per patient	
≤3	154 (38.5)
4-6	163 (40.7)
≥7	83 (20.7)
Median - 4	
Range - 1-15	

Table 2: Prevalence of potential drug-drug interactions in a pediatric ward

Type of prevalence	***Patients: n (%)***
Severity of pDDIs	
Overall*	103 (25.8)
Contraindicated	2 (0.5)
Major	43 (10.7)
Moderate	61 (15.2)
Minor	50 (12.5)
Number of pDDIs per patient	
1-2	71 (17.7)
3-4	20 (5)
≥5	12 (3)
Median - 1	
Range - 1-12	

- PDDIs **=** Potential drug-drug interactions
-* Overall prevalence means presence of at least one pDDIs regardless of severity-type

Table 3: Levels of potential drug-drug interactions in a pediatric ward

Level	Frequency in 86 interacting drug-pairs*	Frequency in 260 pDDIs*
	n (%)	n (%)
Severity		
Contraindicated	2 (2.3)	3 (1.2)
Major	15 (17.4)	57 (21.9)
Moderate	53 (61.6)	108 (41.5)
Minor	16 (18.6)	92 (35.4)
Documentation		
Excellent	11 (12.8)	17 (6.5)
Good	49 (57)	200 (76.9)
Fair	26 (30.2)	43 (16.5)
Onset		
Rapid	23 (26.7)	112 (43.1)
Delayed	53 (61.6)	121 (46.5)
Not specified	10 (11.6)	27 (10.4)

- PDDIs = Potential drug-drug interactions
- In pediatric ward, 86 interacting drug-combinations were identified that encountered in total number of 260 pDDIs.*

In this study, 86 potential interacting drug-combinations were identified. The top 14 frequently occurring interacting drug-pairs included four major, seven moderate and three minor types of pDDIs. These 14 interacting drug-pairs encountered in 155 pDDIs (59.6% of 260), while rest of 72 interacting drug-pairs presented in the remaining 40.3% pDDIs. Frequencies of some widespread interacting drug-combinations are given in Table 4.

In univariate logistic regression analysis (Table 5), there was significant association of the occurrence of pDDIs with hospital stay of five days or longer (OR = 1.92; 95 % CI = 1.21-3.04; $p < 0.01$), female gender (OR for male = 0.63; 95 % CI = 0.39-0.99; $p = 0.047$), and five or more number of prescribed medications (OR = 7.34; 95 % CI = 4.37-12.32; $p < 0.001$). In multivariate analysis (Table 5), association was significant only in case of five or more number of prescribed medications (OR = 6.82; 95 % CI = 4.0-11.59; $p < 0.001$).

DISCUSSION

In the present study, prevalence and nature of pDDIs have been reported in 400 pediatric hospitalized patients. Total 86 interacting drug-combinations were identified that encountered in 260 pDDIs. Overall, 25.8 % patients were exposed to at least one pDDI regardless of severity-types, 10.75 % to at least one major pDDI, 15.25 % to at least one moderate pDDI, and 12.5 % to at least one minor pDDI. In comparison to other clinical settings, overall prevalence of pDDIs in pediatrics (25.8 %) was lower than that reported by many other studies ranging from 37 % to 50% in whole hospital settings [15,16]; 77.5 % in cardiology [7], 48 % in internal medicine [17], 58 % in oncology [8], 64.8 % in psychiatry [9], 70 % in intensive care units [10], and 45 % in pulmonology [11]. Results of the present study suggest that pDDIs are less prevalent in pediatrics ward as compared with other wards and specialties such as cardiology, internal medicine, oncology, psychiatry, intensive care units and pulmonology.

Table 4: Frequencies of interacting drug-combinations

Interaction	Frequency
Major interactions	
Rifampin + pyrazinamide	14
Phenobarbital + diazepam	14
Amikacin + furosemide	7
Isoniazid + rifampin	5
Quinine + rifampin	3
Artemether/lumefantrine + quinine	3
Calcium carbonate + digoxin	2
Theophylline + ciprofloxacin	2
Moderate interactions	
Dexamethasone + rifampin	8
Furosemide + captopril	7
Phenobarbital + divalproex sodium	6
Dexamethasone + phenobarbital	6
Amikacin + ibuprofen	5
Digoxin + furosemide	4
Acetaminophen + phenytoin sodium	4
Phenytoin sodium + diazepam	3
Furosemide + ibuprofen	3
Dexamethasone + phenytoin sodium	3
Ciprofloxacin + zinc	3
Rifampin + divalproex sodium	3
Minor interactions	
Amikacin + cloxacillin sodium	35
Amikacin + ampicillin	35
Phenytoin sodium + phenobarbital	5
Iron + antacid	3

Table 5: Logistic regression analysis

Variable	Patients: *n*		Univariate		Multivariate	
	Interaction present (*n* = 103)	Interaction absent (*n* = 297)	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Hospital stay (days)						
< 5	57	209	1.92 (1.21-3.04)	<0.01	1.25 (0.75-2.08)	0.396
≥ 5	46	88				
Gender						
Female	46	100	0.63 (0.39-0.99)	0.047	0.74 (0.45-1.23)	0.246
Male	57	197				
Number of drugs						
< 5	24	205	7.34 (4.37-12.32)	<0.001	6.82 (4.0-11.59)	<0.001
≥ 5	79	92				

-OR = Odds ratio; CI = Confidence interval.

- Exposure to potential drug-drug interactions (pDDIs) was the dependent variable in the model (0 = absent, 1 = present). The following variables were included in the model as predictors of pDDIs: hospital stay (1 = less than 5 days, 2 = 5 days or above), patient's gender (1 = female, 2 = male), and number of drugs (1 = less than 5, 2 = 5 or above).

-Hosmer–Lemeshow goodness-of-fit test: $p = 0.87$

As far as levels of pDDIs are concerned, our study shows that most of the interactions were of moderate severity (41.5 %) followed by minor (35.4 %) and major severity (21.9 %); good (76.9 %) or fair (16.5 %) type of scientific evidence; and delayed onset (46.5%). Similar findings have been reported by other studies, conducted in other wards or specialties [17,18]. A study identified total 402 pDDIs in clinical records of 500 patients, of which, most were of moderate severity (70 %), good scientific evidences (69.4 %) and delayed onset (89.8 %) [17].

Clinical records of 407 patients were evaluated for pDDIs. Total 276 pDDIs were identified, of which, most pDDIs were having moderate severity (77 %) and good scientific evidences (40 %) [18]. The aforementioned discussion shows that results of our study are consistent with published literature. Moreover, the list of interacting drug-combinations, particularly widespread major and moderate interactions, will be helpful for health care professionals to screen patients' profiles for pDDIs. This will improve practice regarding the management of pDDIs in clinical settings.

The results of this study show that patients with five or more number of prescribed medications were found to be more exposed to pDDIs (OR = 6.82; 95 % CI = 4.0-11.59; $p < 0.001$). These results are in agreement with many other published reports [3,8,10,12,15,18]. It is recommended that patients with increased number of medications should be properly monitored for pDDIs in order to prevent and minimize the negative consequences of these interactions.

Limitations of the study

In the present study, only potential drug-drug interactions were investigated. Further work will be required to identify the actual effects of these interactions. This study was conducted in a tertiary care hospital of Khyber Pakhtunkhwa province of Pakistan. Therefore, the findings may not be generalizable to hospitals elsewhere in Pakistan. However, we expect a similar pattern in pediatric wards of other tertiary care hospitals.

CONCLUSION

PDDIs were less prevalent in pediatrics ward. Most of the interactions were of moderate severity. Patients with increased number of prescribed medications were more exposed to these interactions. Due to sensitive nature of pediatric population, close monitoring is recommended for detection and management of pDDIs.

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