Original Article

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A retrospective and cross-sectional study to evaluate potential drug–drug interaction in hospitalized pediatrics, Bandar Abbas, Iran

Motahareh Ahmadi[1], Abd Nazemi[2], Seyedeh Fatemeh Davoodpour[3], Fahimeh Gharaie Pour[1], Maryam Montaseri[4], Omid Safa[1,*]

[1]Department of Clinical Pharmacy, Faculty of Pharmacy, Hormozgan University of Medical Sciences, Bandar Abbas, Iran.

[2]Pediatric Hospital, Hormozgan University of Medical Sciences, Bandar Abbas , Iran.

[3]Faculty of Pharmacy , Hormozgan University of Medical Sciences, Bandar Abbas , Iran.

[4]Department of Public Health, Faculty of Health, Hormozgan University of Medical Sciences, Bandar Abbas, Iran.

Abstract

The incidence of drug interactions in hospitalized patients is common due to the administration of various drugs, lack of proper monitoring, and sometimes multiple patient's co-morbidities. This study aims to evaluate potential drug-drug interactions (PDDIs) in pediatrics hospitalized in an educational pediatric hospital. The present study is a retrospective cross-sectional study. The study population included patients hospitalized in different parts of Bandar Abbas Pediatrics Hospital. A total of 400 medical records were assessed. PDDIs were evaluated by Lexi-Comp drug interaction. SPSS software was used for data analysis. Based on the results, PDDIs were observed in 133 cases (33.25%). The mean ± SD of PDDIs per prescription was 1.97±1.56. The majority of the interactions were moderate (79.1%) with risk rating C (45.7%). Salbutamol, phenytoin, phenobarbital, and clarithromycin were responsible for most of the interactions with 95, 40, 25, and 17 PDDIs, respectively. Drug interactions with risk-rating X were observed in five cases. The number of drugs per prescription was significantly associated with PDDIs (P=0.000). Although the prevalence rate of PDDIs in this study was lower than that reported by recent studies, careful evaluation of drug charts and the implantation of educational programs for the medical staff should be considered.

Keywords: Drug, drug-drug interaction, Pediatric Hospital.

1. Introduction

When at least two drugs are taken concomitantly, there is a potential for drug interactions. In such situation, the effect of a drug may be altered by another drug (1). This event can lead to harmful or beneficial effects. Adverse clinical interactions can lead to non-response to treatment, serious complications, and even death (2-3).

A series of patient-dependent and prescription-dependent factors are involved in drug interactions. Age, acute medical condition, underlying co-morbidity, number of prescriptions and groups of drug administered are among them (4).

Medication prescription to pediatrics is difficult due to weight-based drug dosing, poor compliance in administration, variability of pharmacokinetic parameters, and finally their sensitive nature (5). The prevalence of drug interactions in the pediatric population is estimated to be 3.8% -75% (6-12). It becomes more challenging in hospitalized pediatrics, especially in the educational settings due to the variety of referrers, different un-

Corresponding Author: Omid Safa, Department of Clinical Pharmacy, Faculty of Pharmacy , Hormozgan University of Medical Sciences, Bandar Abbas , Iran
Email: Odsafa@yahoo.com

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derlying problems of patients, high rates of visits, and visits by interns and medical assistants (13-14).

It would results in an increase in the length of hospitalization, treatment costs, and the rate of morbidity and mortality, if drug interactions are not timely identified (14). No studies have evaluated drug interactions in the hospitalized children in Bandar Abbas. We decided to do such investigation in an educational and referral pediatric center.

2. Material and methods

2.1. Study design

This study was a retrospective cross-sectional study, conducted in pediatric hospital; a large referral educational hospital in the south of Iran, Bandar Abbas, Hormozgan. We investigated potential drug-drug interactions (PDDIs) in all patients hospitalized in different wards of this hospital in a three month period, October to December 2017.

2.2. Data collection

During the study period, all patients hospitalized in different parts of the hospital were enrolled according to the inclusion and exclusion criteria. We extracted the required information from the medical sheets and drug charts and recorded them in a data collector form. This three-part form contained: 1. patient's personal information (patients coding, gender, age, weight, hospital ward, cause of hospitalization, and treatment service), 2. Drug chart or prescriptions (number of drugs, pharmaceutical form, and the date of start /stop of medication order), and 3. Potential drug-drug interaction (occurrence, number of interaction per prescription, severity, risk rating, and mechanisms and the outcome of the PDDIs).

2.3. Evaluation of interactions

Occurrence, severity, and risk rating of drug- drug interactions were assessed via Up to date drug interaction checker (https://lib.utdo.ir:2057), which is an online reference database in medical and pharmaceutical sciences. Risk rating of drug interactions based on up to date reference, is classified to five categories; A: No known interaction, B: No action needed, C: Monitor therapy, D: Consider therapy modification and X: Avoid combination. Such as other references, severity of interactions classified to minor, moderate and major (15).

2.4. Inclusion and exclusion criteria

All patients who had at least 48 h of hospitalization in any part of the hospital and received at least two concomitant drugs. Patients were excluded if any of the following conditions existed: discharged without a specific therapeutic treatment, those who were only receiving serum therapy or supplements, or those who were only admitted to receive blood products.

2.5. Statistical method

Data were analyzed using IBM SPSS software version 24.0. Mean±standard deviations, number and percentages for descriptive analysis were reported. The association between risk factors and occurrence of PDDIs was assessed by binary logistic regression. Univariate and multi-variate analyses were performed to compute adjusted odds ratio (AOR). The significance level was considered as P-value <0.05.

2.6. Ethical approval

This study was approved by the Ethics Committee of Hormozgan University of Medical Science (ethic code: IR.HUMS.REC1397.077)

3. Results

3.1. Patient's demographic, clinical, and prescription data

Of 400 patients involved in this study, 194 were boys, and the rest were girls with an age range from 1 day to 16 years. 73% of patients were in the age group less than two years old. Infectious disease (60.8%) followed by gastrointestinal problems (59%), sepsis (6.25%), and seizure (6.25%) were the most common causes of hospitalization. The majority of patients were admitted in pediatric ward (83.7%). Pediatricians (38.4%) visited patients more than other specialists (Table 1).

In our study, a total of 2608 drugs were prescribed. The minimum number of drugs administered concomitantly, was 4 and the maximum

Table 1. Demographic and clinical data of patients (n=400).

Variable	Results
Gender, n(percent)	Boy= 194 (48.5 %), Girl= 206 (51.5 %)
Age groups(years), n(percent)	0-2 = 292 (73 %), 2-4 = 36 (9 %) 4-6 =36 (9 %), 6-8 = 22(5.5 %) 8-10 = 7 (1.75 %), 10-12= 5 (1.25 %), 12-16= 2 (0.5 %)
Cause of administration, n(percent)	Infections disease = 243 (60.8 %), Gastrointestinal problems = 59 (14.8 %) Sepsis= 25 (6.25 %), Seizure =25 (6.25 %) Fever = 16 (4 %), Asthma = 6 (1.5 %) Other causes= 26 (6.5 %)
Hospital ward, n(percent)	Pediatric= 335(83.7 %), NICU= 32 (8 %) PICU= 9 (2.3 %), Surgery = 24 (6 %)
Treatment service, n(percent)	Pediatrics = 154 (38.4 %), Nephrology= 31(7.8 %) Immunology= 54 (13.5 %), Infectious= 81 (20.2 %) Gastroenterology= 23 (5.8 %), Neurology= 11(2.8 %) Cardiac= 22 (5.5 %), ndocrine= 24 (6 %)

NICU: Neonatal Intensive Care Unit, PICU: Pediatric Intensive Care Unit.

was 21(6.5±2.48). In 43.7% of patients, 4 to 6 drugs, were received concomitantly (Table 1).

3.2. Prevalence and severity of potential drug interactions

The prevalence rate of potential drug-drug interaction in our investigation was estimated as 33.25%; at least one PDDI in 133 prescription (n=400). The mean of interaction per prescription was 1.97±1.56. Based on Up to date database references, the majority of potential interactions was moderate (79.1%) and monitor therapy was needed (risk rating C, 45.7%) (Table 2).

Salbutamol was responsible for most of the potential drug interactions with moderate severity (36.8%). Potential major interactions were

Table 2. Prescription data, prevalence, and severity of potential drug interaction.

Variable	Results
Number of drug, n(percent)	≤4 = 73 (18.25 %) , 5-6= 169 (42.25 %) 7-8= 91 (22.75 %), 9-10= 41 (10.25 %) >10= 26 (6.5 %) Mean± SD (per prescription)= 6.5 ± 2.1
Potential drug interaction	Yes = 133 (33.25 %) No= 267 (66.75 %)
Interaction per prescription(mean ± SD) n=258	1.97 ± 1.56
Severity, n(percent) n=258	Minor = 15 (5.8%), Moderate = 204 (79.1 %) Major = 39 (15.1 %)
Risk rating, n(percent) n=258	B = 93 (36.05 %), C= 118 (45.7 %) D= 42 (16.28 %), X= 5 (1.93 %)

A: No known interaction, B: No action needed, C: Monitor therapy, D: Consider therapy modification, X: Avoid combination

Table 3. Responsible drugs for potential drug interaction with severity and risk rating.

Drug	Severity			Risk rating				Number	Percent %
	minor	moderate	major	B	C	D	X		
Salbutamol	0	95	0	78	17	0	0	95	36.8
Phenytoin	0	22	18	0	22	18	0	40	15.5
Phenobarbital	0	18	7	0	12	13	0	25	9.68
Clarithromycin	2	8	7	2	6	7	2	17	6.59
Azithromycin	0	11	0	0	11	0	0	11	4.26
Aspirin	0	10	1	0	10	1	0	11	4.26
Vancomycin	0	11	0	0	11	0	0	11	4.26
Acetaminophen	9	0	0	9	0	0	0	9	3.5
Gentamicin	0	6	0	0	6	0	0	6	2.32
Sodium Valproate	3	0	1	3	0	1	0	4	1.55
Amikacin	0	4	0	0	4	0	0	4	1.55
Warfarin	0	4	0	0	4	0	0	4	1.55
Clonazepam	0	3	0	0	3	0	0	3	1.16
Captopril	0	3	0	0	3	0	0	3	1.16
Midazolam	0	3	0	0	3	0	0	3	1.16
Itraconazole	0	0	2	0	0	1	1	2	0.78
Diazepam	0	2	0	0	2	0	0	2	0.78
Methyl-prednisolone	0	1	0	0	1	0	0	1	0.39
Enoxaparin	0	1	0	0	1	0	0	1	0.39
Ipratropium bromide	0	0	1	0	0	0	1	1	0.39
Cholestyramine	0	1	0	0	1	0	0	1	0.39
Pancralipase	1	0	0	1	0	0	0	1	0.39
Ketorolac	0	1	0	0	1	0	0	1	0.39
Pantoprazole	0	0	1	0	0	1	0	1	0.39
Somatostatin	0	0	1	0	0	0	1	1	0.39
Sum	15	204	39	93	118	42	5	258	100

A: No known interaction, B: No action needed, C: Monitor therapy, D: Consider therapy modification, X: Avoid combination.

observed with phenytoin, phenobarbital, and clarithromycin, respectively with 18, 7, and 7 numbers. Moreover, the majority of interaction with risk rating D, was related to phenytoin (n=18) and phenobarbital (n=13). Contraindicated interactions or interactions with risk rating X, were reported with somatostatin (n=1), clarithromycin (n=2), ipratropium bromide (n=1), and itraconazole (n=1) (Table 3).

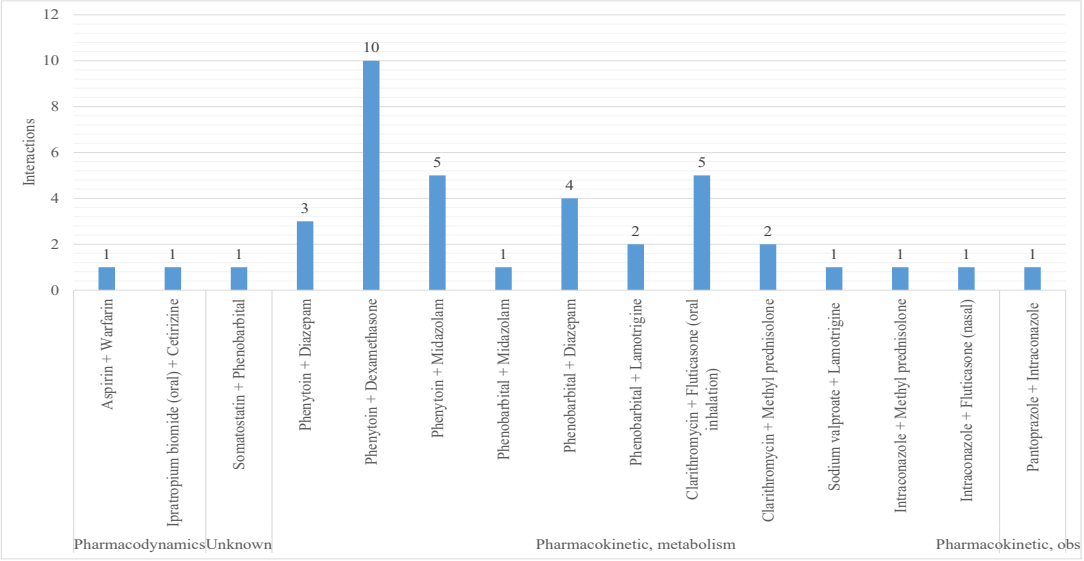
We determined 75 types of drug- pair for PDDIs. Graph 1 shows, 15 drug-pair contributing in major interactions with the mechanism and outcome of interactions.

3.3. Association with patient's and prescription factors

Association between sex (P=0.383) and age (P=0.671) with PDDIs; in our study was absent (Table 4). The number of drugs per prescription was significantly associated with the occurrence of PDDIs (P=0.000).

4. Discussion

Taking multiple drugs increases



Graph 1. 15 pair-drug involved in major potential drug interactions

the risk of Drug-Drug Interactions in hospitalized patients (4).DDIs may be clinically important and reduce the efficacy of treatment, leading to adverse drug reactions and

Table 4. Association between risk factors and occurrence of PDDIs.

variable			(Univariate Analyses)				(Multivariate Analyses)			
	PDDIs		Sig. Pvalue	OR	95% C.I.for EXP(B)		Sig. Pvalue	OR	95% C.I. for EXP(B)	
	Present	Absent			L	U			L	U
Sex			.383	.997	.990	1.004	.786	.999	.991	1.007
Male	66	128								
Female	67	139								
Age (year)			.671	1.094	.722	1.660	.993	.998	.633	1.573
0-2	102	190								
2-4	8	28								
4-6	13	23								
6-8	9	13								
8-10	0	7								
10-12	1	4								
12-16	0	2								
Drug number			.000	1.471	1.317	1.643	.000	1.469	1.315	1.642
≤4	5	68								
4-6	34	135								
6-8	52	39								
8-10	25	16								
>10	17	9								

Abbreviations: PDDIs: Potential Drug –Drug Interactions; OR: odds ratio; CI: confidence interval; EXP(B): Exponentiation of the B coefficient; P< 0.05.

even death. However they may not always be harmful (2).

We investigated PDDIs in the pediatric population hospitalized in an educational pediatric hospital in Bandar Abbas. We used Up to date drug interaction checker and reported prevalence, severity, risk rating of PDDIs.

Based on our results, the prevalence rate of PDDIs was 33.25%. The prevalence value of PDDIs in the pediatric population is estimated to be 3.8% -75% (6-12). In Iran, a proportion of 42% was recorded in the Neonatal Intensive Care Unit of Bu Ali hospital, Sari (16). In a recent investigation in pediatric population in Italy, a prevalence value of 61% in 915 patients admitted to Emergency department, was published. They used Medscape drug interaction software (17). This difference in prevalence values may correlated with the use of the different interaction checker softwares

Of the 258 PDDIs in this study, 15.1% were identified as major type. Higher rates have been reported by similar studies in Iran and other countries (8, 16-18). Phenytoin, phenobarbital, clarithromycin were responsible for most of the major interactions (Table 3).

Phenytoin and phenobarbital are still two consuming antiepileptic medicines for control of seizure in hospitals of our country. In addition, phenobarbital is also used to treat neonatal jaundice. Clarithromycin is a macrolide antibiotic, which is over prescribed in some health care settings, due to the increased resistance to azithromycin in recent years. It is important that all three medicines can affect the liver enzymes contributing in metabolism pathway and thus alter (induce/inhibit) metabolism of concomitant drugs.

Graph 1 summarizes 15 pair- drug involved in the major drug interactions with their mechanism and outcome of interactions. The mechanism of drug interaction was dominant in pharmacokinetic type.

Therefore, phenytoin, phenobarbital, clarithromycin should be considered as potentially high risks for DDIs. Antibiotics and anticoagulants had the majority of major interactions in a study carried out in Ethiopia (18).

We suggest a hospital or clinical pharmacist to assess and manage drug interactions. They can identify PDDIs on the patient's drug charts and prevent them via dose adjustment or recommend to use alternative medicines. However, we didn't do any interventions and our study was an observational only.

Up to date drug interaction checker, also, specifies rating risk of drug interactions, which means what type of intervention should be performed (15). Our PDDIs were mostly, risk rating-C, which means monitor therapy. Interactions with risk rating- D, observed by phenytoin and phenobarbital, meant recommendation for considering therapy modification. There were a total of 5 contraindicated (risk rating- X) PDDIs two of which was related to clarithromycin.

Both sex and age had no association with the occurrence of PDDIs, which agrees with a study conducted in a tertiary hospital in Ethiopia (4). However, Morales et. al found that female gender and age were significantly in association with the occurrence of PDDIs in a pediatric population (17).

Number of drugs was significantly associated with the occurrence of PDDIs (P=0.000). Although the concomitant administration of several drugs is likely to be effective to improve the efficacy of treatment, polypharmacy may cause unwanted reactions. The risk of PDDIs in patients who receive five drugs concomitantly, is estimated as 40%, and it is doubled in the administration of seven or more drugs (18). It seems that drugs number per prescription and groups of drugs prescribed have a more important role compared with age and sex.

5. Conclusion

The prevalence of PDDIs in the studied hospital was 33.25%. In terms of severity, the majority of them was moderate with risk rating C. Age and polypharmacy were associated with the occurrence of PDDIs. The real occurrence of DDIs was mot assessed, and this study just focused on the potential occurrence. It is suggested that the effect of preventing drug interactions by clinical or hospital pharmacists on the outcome of patients should be investigated in future interventional studies.

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Conflict of Interest

None declared.

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