Journal of Pharmaceutical Care
jpc.tums.ac.ir

Prevalence and Severity of Drug Interactions in a Referral Pediatric Hospital: An Observational, Retrospective Study

Farnoosh Moqadam[1*], Bahador Mirrahimi[2], Ramin Abrishami[1]

[1]Department of Clinical Pharmacy, Faculty of Pharmacy, Tehran Medical Sciences, Islamic Azad University, Tehran, Iran.

[2]Department of Clinical Pharmacy, School of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

Received: 2022-09-05, Revised: 2022-09-22, Accepted: 2022-09-25, Published: 2022-09-30

ARTICLE INFO

Article type:
Original article

Keywords:
Children;
Drug Interactions;
Intensive Care Unit

ABSTRACT

Background: Hospitalized infants and children are usually treated with many medications in the hospital. Concurrent use of multiple drugs, known as polypharmacy, is inevitable in critically ill patients. This study aims to investigate the possible interactions as well as their type and number, and their effect on the treatment process plus the duration of hospital stay of patients.

Methods: In this descriptive study, the medical records of 189 patients admitted to the Intensive care unit (ICU) ward of Mofid Children's Educational Hospital in Tehran were prospectively studied over six months from August 2018 to March 2019. The collected data included disease diagnosis, patient medication information, age and gender, and treatment interventions. Interactions between drugs were identified using Up-to-date database, with the results analyzed by SPSS software.

Results: The results revealed that hospitalization increased with an increasing number of drugs. The findings also indicated a direct relationship between the number of drug interactions and the duration of hospital stay. After examining the relationship between ICU outcome and the number of drug items as well as the number of drug interactions, it was found that there is a direct relationship between the two. There was also a direct relationship between Class D plus X interactions and mortality rate along with duration of stay.

Conclusion: This study showed a direct relationship between drug interactions and the duration of hospitalization. In other words, as drug interactions increased, so did the duration of hospital stay.

J Pharm Care 2022; 10(3): 122-127.

► **Please cite this paper as:**
Moqadam F, Mirrahimi B, Abrishami R. Prevalence and Severity of Drug Interactions in a Referral Pediatric Hospital: An Observational, Retrospective Study. J Pharm Care 2022; 10(3): 122-127.

Introduction

Medication errors are prevalent in the health system and are recognized as the seventh leading cause of death (1). Adverse drug events (ADE) are among the leading causes of increased morbidity, mortality, and health costs (2). It is crucial to evaluate adverse drug reactions (ADRs) and drug interactions (DDI) in infants, children, and adolescents. This group is very different in physiology and psychology compared to adults. Because of insufficient information about this age group, these interactions remain unknown. Such information is very scarce in children; this indicates that hospitalized children are at greater risk of drug-related problems for several reasons, including the wide range of ages and weights, limited physiological knowledge, computational error in dose determination, and inability to communicate correctly with health authorities (3). Some causes of drug interactions in intensive care unit (ICU) children may include poly-pharmacy, multiplicity of prescribers, lack of information about rare drugs, determination of weight-dependent doses, lack of an appropriate therapeutic profile, administration of off-label drugs and most importantly, the patient's condition in the Pediatric Intensive Care Unit (PICU) (3).

The combination of several drugs and the occurrence of drug interactions in pediatric intensive care units (PICU) is frequently unavoidable and needed during the patient

*Corresponding Author: Dr Farnoosh Moqadam
Address: Department of Clinical Pharmacy, Faculty of Pharmacy, Tehran Medical Sciences, Islamic Azad University, Tehran, Iran.
Email: farnooshmqdm94@gmail.com

stabilization process, diagnosis, and specific treatment, but increases the risk of toxicity and can reduce therapeutics' efficacy (4, 5). One of the sources that classify drug interactions by degree of importance is Drug Interaction Facts. This classification of interactions has four aspects: 1) the significance of interactions, 2) Onset of the interaction effect, 3) Severity of interaction, 4) The amount of interaction documentation.

Methods

In this descriptive-analytical study, a total of 200 patients were enrolled from August 2018 to March 2019. The study population consisted of patients admitted to PICU ward of Mofid Hospital, which is one of the educational hospitals of Shahid Beheshti University of Medical Sciences in Tehran, Iran. Patients were visited twice daily by the ICU physician (morning and evening) and three times a week by a clinical pharmacist. After the patients' visit, the prescription medications were written in Cardex filling system by nurses and placed in the nursing station. At first, patients' data were collected and entered to Excel forms on a daily basis. Then, patients' drug interactions were extracted online by UpToDate tool.

Inclusion criteria were: hospital stay of more than 48 hours, age younger than 15 years, and more than three drugs in the file. Exclusion criteria included patients or caregivers not willing to participate.

Each patient's daily drug interactions were extracted online through the UpToDate site. These interactions were collected in Excel. The classification of the interactions in UpToDate Online is as follows: Grade A: The data showed no pharmacokinetic and pharmacodynamics interactions. Grade B: Data have shown that these factors can work together, but there is almost no evidence of concern about the clinical consequences of the two drugs being used concomitantly, so no unique action is needed. Grade C: Data have shown that these drugs can interact with each other which is clinically significant. The benefits of using these two drugs at once outweigh the risks. A specific monitoring program can identify potential hazards. Dose adjustment for either or both drugs may be necessary for a small number of patients. Grade D: The data show that they have clinically significant interactions. The patient's condition must be considered to determine if the benefits of the concomitant use override its risks. Specific measures should be taken to identify the benefits and reduce the toxicity of the concomitant use of these two drugs. These include monitoring, empirically changing the dosage of drugs, and choosing alternatives. Grade X: The data show clinically significant interaction. The risks of concomitant use outweigh the benefits. Concomitant use of these drugs is contraindicated.

We used Statistical Package for the Social Sciences (SPSS) software version 22 to analyze the results. Descriptive statistics of variables were prepared using SPSS software. Qualitative variables were given percentages, and quantitative variables with Mean ± Standard Deviation. Differences and possible correlations between variables were then investigated using the Mann-Whitney U test or independent t-test, and the relevant reports were extracted.

Results

We studied 200 patients, of whom 188 were included and 12 of them were excluded due to lack of willingness to participate. The most common causes of admission to the PICU were respiratory distress, pneumonia, seizures, brain tumors, metabolic syndrome, acute lymphoblastic leukemia, hydrocephalus, etc. (Figure 1).

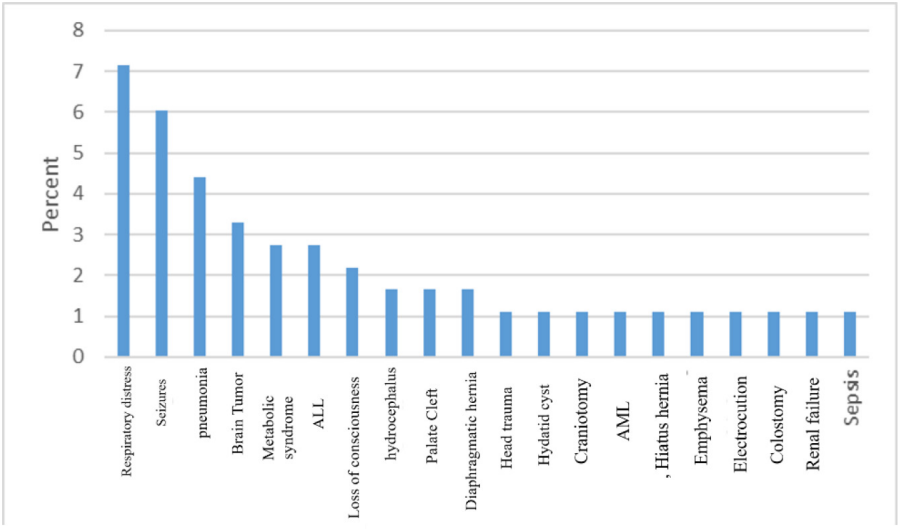

Figure 1. Causes of hospitalization.

Table 1 reports the results of patients' age, sex distribution, and status of patients after discharge. The mean age of patients was 40±46 months (3 years). The results also showed that 101 (53.7%) patients were male and 87 (46.3%) were female. A total of 140 (74.5%) patients were discharged and 48 (25.5%) were expired According to the results, the average number of drugs used per patient was 20.7. The average number of days admitted to the ward was 20.72 days (Table 1).

Table 1. Age of patients, sex distribution and status of patients after discharge

Patient numbers	188
Male	101
Female	87
Age,Mean	3 months
Range	3 days-10 years
Patient status	
Discharged	140
Expired	48
Total number of prescribed drug	2360
The ratio of drug-patient	12.5%
Number of days admitted to the ward	20.72
The average number of drugs used per patient	20.69

The results revealed that out of 2360 drug items, 1566 interactions were identified. The results of the study of patients' records showed that in the medical records of patients, there were 4 (1.2%) interactions of class A, 165 (10.5%) of class B, 947 (60.58%) of class C, 422 (26.99%) of class D and 25 (1.59%) of class X. (Figure 2)

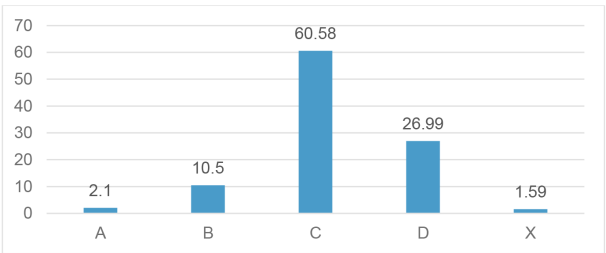

Figure 2. Frequency of interactions in each class.

Considering reliability rating of interactions, the results showed that 1025 (60.57%) were fair, 424 (27.12%) were good, 91 (5.82%) were excellent, and 23 (1.47%) were poor (Figure 3). Table 2 reports the most common interactions in each class A B C D X.

Figure 3. Frequency of documentation of interactions in each class.

Table 2. The most common interactions in each class A B C D X.

Category X	Cotrimoxazol + Metronidazole	0.19%
Category X	Salbutamol + labetolol	0.19%
Category X	Diazepam + Metronidazol	0.12%
Category D	Fentanyl + Midazolam	3%
Category D	Midazolam + Phenobarbital	1.14%
Category D	Diazepam + Phenobarbital	0.9%
Category D	Diazepam + Phenytoin	0.89%
Category D	Fentanyl + Phenobarbital	0.89%
Category C	Acetaminophen + Phenytoin	1.5%
Category C	Furosemide + Fentanyl	1.5%
Category C	Captopril + Furosemide	0.89%
Category C	Acetaminophen + Phenobarbital	1.2 %
Category C	Propofol + Midazolam	0.63%
Category B	Acetaminophen + Fentanyl	2.4%
Category B	Acetaminophen + Pethidine	0.7%
Category B	Acetaminophen + Ondansetron	0.63%
Category B	Acetaminophen + Morphine	0.56%
Category B	Salbutamol + Dexamethasone	0.44%
Category A	Levetiracetam + Valproic acid	0.19%
Category A	Fluconazole + Ranitidine	0.19%

The results showed that the number of drug interactions increased with increasing number of prescribed medications. The results indicated that there was a relationship between the number of medications and the duration of hospital stay. This means that as the number of medications per patient increased, so did the duration of hospital stay (P<0.064). There was a direct relationship between the duration of hospitalization and the number of drug interactions, but this relationship was not significant (P<0.1).

The results revealed a significant relationship between the number of medications prescribed for each patient and ICU outcome. This means that expired patients had more drugs in their medical records (P <0.01). There was no significant relationship between the number of drug interactions and the ICU outcome, but more interactions were found (P <0.2) in the expired patients' drug records.

Based on the results, there was no significant relationship between D plus X interactions and the duration of hospitalization, but there were more cases of D plus X interactions in drug records of patients who had been hospitalized longer (P<0.09).

The results also showed a significant and positive relationship between D plus X interaction and mortality (P<0.03). Specifically, the number of Class X interactions was higher than D in those expired.

Discussion

This study has provided relevant data about the occurrence of pDDIs in hospitalized children. In this study, we characterized PDDIs according to their severity and reliability as well as the association with the secondary outcomes. To date, there have been only a few studies on the prevalence, common drug combinations, and risk factors of PDDIs in critically ill children (2, 5-7).

There were 1566 potential drug interactions out of 2360 prescribed drugs. Severe pDDIs showed association with the PICU length of stay. The mean length of hospital stays of children in the ICU (72 days) was far longer than that observed in other studies, which ranged from 5.5 to 10.6 days (8, 9).

The length of stay in intensive care can differ due to clinical and social factors. However, institutional factors (practice patterns of physicians, clinical protocols, the proportion of nurses by patients, availability of intermediary care, for example) are the likely primary cause of much of the variability in PICU length of stay which need to be further investigated in other studies (10).Studies on adult critical care units have indicated a variation of 44.3%–87.9% in the frequency of pDDIs observed (11-13).

The incidence observed in this study (66.35%) was nearly similar to other study findings. Other studies found lower frequencies in Indian (63%), Pakistani (59.4%), Mexican (42%), and Chilean (41%) PICUs (6, 14). In pediatrics, analysis of prescriptions in the wards of a Brazilian teaching hospital (excluding the PICU, oncology, and emergency) identified seven pDDIs per patient at average, which was slightly lower than the value found in the exclusive PICU analysis conducted in this study (8.32 ± 0.08).

The prevalence of pDDIs with major (22%) and moderate (68%) severity observed was lower and higher than that obtained in a cohort with 498,956 American inpatients under 21 years of age from pediatric beds (41% and 28%, respectively) (6, 15).

The common drug combinations associated with PDDIs also differ between PICUs and adult ICUs. For example, despite the heterogeneity of patients included in the studies, aspirin, insulin, and clopidogrel are the most common drugs implicated in DDIs in adult ICUs (16) ,whereas these drugs are not commonly used in pediatric patients. Furthermore, even among pediatric patients, frequent drug combinations related to PDDIs differ among hospitals (5, 17).

This is presumed to be due to differences in the composition of critically ill patients, drug preferences of intensivists, and drug permits in each country. Some frequent pDDIs pairs observed in this study have also been described in other studies; for example, the midazolam and fentanyl pair has been reported in both studies (14). Studies on pDDIs, with different methodologies and scenarios, also show that the combination of midazolam and fentanyl was associated with the most frequent pDDI (8). intensive care, this pDDI has less clinical relevance due to continuous multi parametric and multimodal monetarization of the patients, including possible signs of abstinence from weaning. Further, prescription of ranitidine or omeprazole is related to the stress ulcer prophylaxis protocol adopted by the PICU. In a prospective, cross-sectional, observational study in five PICUs in Porto Alegre, ranitidine was also the most commonly used drug for this prophylaxis. Similarly in this study ranitidine was one of the reported drugs contributing to common interactions (18). Excessive polypharmacy (more than ten drugs) is commonly required in critically ill patients, and it is a risk factor for adverse drug reactions as well as medication errors in children (18).

The relationship between the number of drugs prescribed and pDDI occurrence, observed in this study, is well known, and both are related to a longer length of stay of adults and children in ICUs (13, 19).

Severe pDDIs may have greater clinical relevance, though the pDDIs severity differences have been rarely investigated in studies, notably those involving pediatric patients. It is the main contribution of this investigation. Meanwhile, our findings noted the association of pDDI with X and D grade and the increase of PICU length of stay (P<0.09) as well as the ICU outcomes (death) (P<0.02). It showed that there is a direct relationship between the number of DDI and X plus

D grade as well as increased hospitalization and death.

According to a report by Dai et al., exposure to the most common pDDIs may not pose a high risk for patients as clinicians may be familiar with and prepared to manage the DDIs (13).

Furthermore, it was found that most potential ADRs could be detected early or prevented by routine intensive care in PICU. For example, most of the common PDDIs can be actively monitored by frequently checking vital signs, performing blood tests which include drug level analysis, controlling the hourly urine output, and regularly assessing the sedation depth, which will ensure the detection of actual ADRs (2, 20).

Nevertheless, intensivists cannot avoid prescribing these high-risk medications as they are essential for managing and treating diseases requiring intensive care. Thus, in this special context, the basic management in ICUs can play an important role in monitoring PDDIs. Furthermore, it is presumed that the level of care in PICUs can ultimately affect CR-PDDIs. The identification of pDDIs, especially those that offer more significant risk to the patient, was one of the strategic actions of clinical pharmacists in the investigated PICU. However, there was physician resistance to adjust the prescription. The observation of increased length of hospital stay for patients with major and contraindicated pDDI may contribute to changes in the team's practices. We believe these results could be generalized to similar settings (21).

The occurrence of pDDI laboratory and clinical manifestations also cannot be verified. However, the findings presented may support new observational studies in pediatric patients that relate mainly to the pDDI mechanism for the patients' clinical evaluation. There is also a need to identify and deprescribe (when possible) medicines that have potential contraindications or more severe pDDIs in critically ill pediatric patients until new evidence is found to substantiate the risk analysis and the possible benefit of keeping the association of certain medications. It is suggested to: 1) discuss the available pharmacotherapeutic alternatives and the possibility of replacing one drug with another of the same pharmacological group for risk and benefit assessment by the healthcare team; 2) monitor the serum level of drugs that may change in the presence of interactions; and 3) investigate the correlation between some clinical manifestations and the presence of potential DDIs.

References

1. Sepehri G, Khazaelli P, Dahooie FA, Sepehri E, Dehghani MR. Prevalence of potential drug interactions in an Iranian general hospital. Indian J Pharm Sci. 2012;74(1):75-9.
2. Dai D, Feinstein JA, Morrison W, Zuppa AF, Feudtner C. Epidemiology of Polypharmacy and Potential Drug-Drug Interactions Among Pediatric Patients in ICUs of U.S. Children's Hospitals. Pediatr Crit Care Med. 2016;17(5):e218-28.
3. Yeh ML, Chang YJ, Yeh SJ, et al. Potential drug-drug interactions in pediatric outpatient prescriptions for newborns and infants. Comput Methods Programs Biomed. 2014;113(1):15-22.
4. Hasnain H, Ali H, Zafar F, et al. Drug-drug interaction; facts and comparisons with national and international bentch marks. a threat more than a challenge for patient safety in clinical and economic scenario. The Professional Medical Journal. 2017;24:357-365.
5. Hassanzad M, Arenas-Lopez S, Baniasadi S. Potential Drug-Drug Interactions Among Critically Ill Pediatric Patients in a Tertiary Pulmonary Center. J Clin Pharmacol. 2018;58(2):221-227.
6. Ismail M, Aziz S, Noor S, et al. Potential drug-drug interactions in pediatric patients admitted to intensive care unit of Khyber Teaching Hospital, Peshawar, Pakistan: A cross-sectional study. J Crit Care. 2017;40:243-250.
7. Rosen K, Wiesen MH, Oberthür A, et al. Drug-drug interactions in Neonatal Intensive Care Units: how to overcome a challenge. Minerva Pediatr (Torino). 2021;73(2):188-197.
8. Lima RE, De Bortoli Cassiani SH. Potential drug interactions in intensive care patients at a teaching hospital. Rev Lat Am Enfermagem. 2009;17(2):222-7.
9. Gonçalves MG, Heineck I. Frequência de prescrições de medicamentos off label e não licenciados para pediatria na atenção primária à saúde em município do sul do Brasil [Frequency of prescriptions of off-label drugs and drugs not approved for pediatric use in primary health care in a southern municipality of Brazil]. Rev Paul Pediatr. 2016;34(1):11-7.
10. Pollack MM, Holubkov R, Reeder R, et al, Eunice Kennedy Shriver National Institute of Child Health and Human Development Collaborative Pediatric Critical Care Research Network (CPCCRN). PICU Length of Stay: Factors Associated With Bed Utilization and Development of a Benchmarking Model. Pediatr Crit Care Med. 2018;19(3):196-203.
11. Hammes JA, Pfuetzenreiter F, Silveira Fd, Koenig A, Westphal GA. Potential drug interactions prevalence in intensive care units. Rev Bras Ter Intensiva. 2008;20(4):349-54.
12. Spriet I, Meersseman W, de Hoon J, von Winckelmann S, Wilmer A, Willems L. Mini-series: II. clinical aspects. clinically relevant CYP450-mediated drug interactions in the ICU. Intensive Care Med. 2009;35(4):603-12.
13. Reis AM, Cassiani SH. Prevalence of potential drug interactions in patients in an intensive care unit of a university hospital in Brazil. Clinics (Sao Paulo). 2011;66(1):9-15.
14. Santibáñez C, Roque J, Morales G, Corrales R. Características de las interacciones farmacológicas en una unidad de cuidados intensivos de pediatría [Characteristics of drug interactions in a pediatric intensive care unit]. Rev Chil Pediatr. 2014;85(5):546-53. Spanish.
15. Feinstein J, Dai D, Zhong W, Freedman J, Feudtner C. Potential drug-drug interactions in infant, child, and adolescent patients in children's hospitals. Pediatrics. 2015;135(1):e99-108.
16. Fitzmaurice MG, Wong A, Akerberg H, et al. Evaluation of Potential Drug-Drug Interactions in Adults in the Intensive Care Unit: A Systematic Review and Meta-Analysis. Drug Saf. 2019;42(9):1035-1044.
17. Dai D, Feinstein JA, Morrison W, Zuppa AF, Feudtner C. Epidemiology of Polypharmacy and Potential Drug-Drug Interactions Among Pediatric Patients in ICUs of U.S. Children's Hospitals. Pediatr Crit Care Med. 2016;17(5):e218-28.

18. Araujo TE, Vieira SM, Carvalho PR. Stress ulcer prophylaxis in pediatric intensive care units. J Pediatr (Rio J). 2010;86(6):525-30.
19. Moura C, Prado N, Acurcio F. Potential drug-drug interactions associated with prolonged stays in the intensive care unit: a retrospective cohort study. Clin Drug Investig. 2011;31(5):309-16.
20. Uijtendaal EV, van Harssel LL, Hugenholtz GW, et al. Analysis of potential drug-drug interactions in medical intensive care unit patients. Pharmacotherapy. 2014;34(3):213-9.
21. Camm AJ, Fox KAA. Strengths and weaknesses of 'real-world' studies involving non-vitamin K antagonist oral anticoagulants. Open Heart. 2018;5(1):e000788.