

Potential Drug–Drug Interactions in the Pediatric Intensive Care Unit of a Tertiary Care Hospital

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Abstract

Aim: To identify and evaluate the potential drug–drug interactions (PDDI) in hospitalized patients in a pediatric intensive care unit (PICU). **Materials and Methods:** In this cross-sectional observational study, we analyzed prescriptions of children aged 1 month–15 years admitted to PICU for PDDIs, and categorized them based on the severity (mild, moderate, and severe), underlying mechanisms, number of concomitant drugs used and potential outcomes of these PDDIs, using a drug interaction checking software. **Results:** Of the 122 prescriptions, we found 175 PDDIs in 77 prescriptions, of which 75.43% were of moderate, 17.71% minor, 6.86% major severity, and none was contraindicated.. The number of PDDIs increased with the number of medications per prescription. The average number of PDDIs per prescription was the highest in those that had >10 drugs (4.29). Pharmacodynamic interactions constituted the majority (73.71%) compared to pharmacokinetic interactions (23.43%). Common PDDIs encountered were between salbutamol and phenylephrine (11.43%), between anti-epileptic drugs (10.86%) and 3rd generation cephalosporins and aminoglycosides (10.29%). The most common potential outcome of these DDIs was hypokalemia (13.71%). **Conclusion:** There is a high prevalence of PDDIs in PICUs, mostly of moderate severity, with a significant relationship with the number of concomitant medications prescribed. Precaution is required while implementing polypharmacy in children.

Keywords: Concomitant medications, pediatric patients, polypharmacy, potential drug–drug interactions, severity

INTRODUCTION

Increase in chronic conditions globally even among the pediatric population, leads to hospitalization and exposure to a wide range of medications, and multiple drugs.^[1] Polypharmacy is a major risk factor for potential drug–drug interactions (PDDIs) resulting in adverse drug reactions, toxicities, reduced treatment efficacy or treatment failure, which not only increases patient morbidity (and mortality) but also healthcare costs.^[2] With increasing polypharmacy among the pediatric population, children are more vulnerable to develop PDDIs, due to different physiology than adults as well as changes in absorption, distribution, metabolism, excretion and reaction to drugs.^[3] Critical patients are at higher risk of developing PDDIs, which is attributed not only to their complex drug prescriptions but also to the physiologic dysfunction arising from their diseases.^[4,5] In addition to polypharmacy, certain other factors can also affect the incidence of PDDIs, such as age, sex, underlying medical condition, prescription from multiple physicians, unlicensed/off-label prescriptions, and prescribing drugs with narrow therapeutic indices.^[6,7]

The prevalence of PDDIs among pediatric population ranges from 3.8% to 75%. The incidence is approximately 40% for patients taking five drugs and exceeds 80% for those taking ≥ 7 medications.^[2,8] Despite high incidence, most of the PDDIs go unnoticed or unassessed in the pediatric intensive care units (PICUs). Lack of consensus among the pediatricians on prescribing medications to children is adding to the existing problem.^[9] Besides, for effective and safe pharmacotherapy in the pediatric population, vast knowledge on the pharmacokinetic parameters (absorption, distribution, metabolism, and excretion) which vary during growth, is necessary.^[10]

PDDI studies on pediatric population are minimal, compared to those in the adult population.^[3] As not all PDDIs will manifest

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Access this article online

Quick Response Code:



Website:
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DOI:
10.4103/jpp.JPP_27_19

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How to cite this article: Rao C, Shenoy V, Udaykumar P. Potential drug–drug interactions in the pediatric intensive care unit of a tertiary care hospital. *J Pharmacol Pharmacother* 2019;10:63-8.

Received: 25-02-2019 **Revised:** 14-05-2019 **Accepted:** 24-06-2019

in the patients, it is quite common to prescribe drugs that can interact. However, it is essential to identify them as they can not only cause adverse effects to the patient but also increase the hospital stay and cost.^[11,12]

We aimed to identify the PDDIs in the PICU of a tertiary care hospital, assess their severity and the possible underlying mechanism.

MATERIALS AND METHODS

This is a cross-sectional observational study conducted for 3 months (September–November 2018), after obtaining approval from the Institutional Ethics Committee. The data was collected from prescriptions of patients admitted in the PICU of a tertiary care hospital of a medical college in southern India.

Information from the prescriptions of patients aged 1 month–15 years admitted to the PICU was collected after obtaining written informed consent from parents and assent from the patients, as applicable. All prescriptions containing two or more drugs were considered for analysis and those with <2 drugs, those for intravenous fluids, blood products, or only supplementary diet were excluded.

DDI in each prescription was assessed using Lexicomp drug interaction software^[13] and categorized based on their severity using the Lexicomp severity scale–

- Minor (cause minimal effects that are usually tolerable–do not require medical intervention),
- Moderate (possibility of significant interaction, but do not meet the criteria for major–generally require monitoring of therapy, may require medical intervention in few),
- Major (potential for serious interaction – typically requires medical intervention and/or close monitoring) and contraindicated (drugs which should never be used together because of severe, life-threatening interactions).^[3,14]

The PDDIs were also categorized based on their underlying mechanisms as pharmacokinetic and pharmacodynamic interactions. The pharmacokinetic interactions were further subdivided into those related to absorption, distribution, metabolism, and elimination. The association between the potential for DDIs and number of drugs prescribed, as well as the age of the patient, was also assessed.

Statistical analysis

The sample size was calculated using the following formula,

$$n = \frac{Z_{\alpha}^2 p(1-p)}{e^2}$$

where,

n = number of prescriptions

Z_{α} = value under standard normal table for the given value of confidence interval (CI), i.e., 1.96 at 95% CI

p = proportion of the sample population with CI of 95%, i.e., 8.7%^[14]

e = margin of error, i.e., 5%

The sample size of 122 prescriptions was taken.

Data was captured on the MS Excel worksheets (2007), analyzed as mean, frequency, and the percentage using the Statistical Package for the Social Sciences (SPSS) software version 23.0 (developer - IBM Corporation) and results were expressed using descriptive statistics. Fisher's test and Chi-square test were used. Tables and figures were used as appropriate.

RESULTS

Of 122 prescriptions evaluated, there were 175 PDDIs in 77 prescriptions (2.27 PDDIs per prescription). These prescriptions were of 97 patients with a mean age of 3.9 years, ranging 1 month–14 years. Table 1 tabulates the demographic characteristics of the study population.

Males had more PDDIs ($n = 105$, 60.0%) compared to females ($n = 70$, 40.0%). Prescriptions for the age group <5 years ($n = 132$; 75.43%) had more PDDIs; of this, those aged <1 year comprised 44.0% ($n = 77$, 44%). Thereafter, there was a decline in number as the age increased. We noted that 63.11% in this study had at least one PDDI.

Of 175 PDDIs, 132 (75.43%) were “moderate” in severity, followed by minor PDDIs ($n = 31$, 17.71%), and major PDDIs ($n = 12$, 6.86%); none were contraindicated.

The highest number of PDDIs were found in those prescriptions that had 6–10 drugs ($n = 83$; 47.43%); however, the average number of PDDIs per prescription was highest in those that had >10 drugs (4.29) [Table 2].

There were 129 (73.71%) pharmacodynamic interactions, of which interactions involving synergism or drugs which enhance each other's adverse effect were more common ($n = 118$, 67.43%) [Figure 1]. Among pharmacokinetic interactions ($n = 41$, 23.43%), the reactions involving an alteration in the metabolism of one drug by the other ($n = 28$, 16%) were common.

Table 1: Correlation of patients age- and gender-wise and potential drug-drug interactions

Parameters	Number of patients		Total (%)	χ^2	P
	With PDDI (%)	Without PDDI (%)			
Age group (years)					
<1	18 (18.56)	8 (8.24)	26 (26.80)	0.931	0.818
1-5	24 (24.74)	17 (17.53)	41 (42.27)		
6-10	14 (14.43)	7 (7.22)	21 (21.65)		
11-15	6 (6.19)	3 (3.02)	9 (9.28)		
Gender					
Males	40 (41.24)	22 (22.68)	62 (63.92)	0.027	0.870
Females	22 (22.68)	13 (13.40)	35 (36.08)		

PDDI=Potential drug-drug interactions

The most common drug involved in the interaction was salbutamol ($n = 54$, 30.86%), followed by antibiotics (3rd generation cephalosporins and aminoglycosides ($n = 36$; 20.57%), and paracetamol ($n = 33$, 18.86%) [Figure 2].

The most common potential outcome was hypokalemia ($n = 24$, 13.71%), observed with the coadministration of a β_2 agonist (salbutamol) and a glucocorticoid ($n = 18$, 10.29%), followed by sympathomimetic adverse effects ($n = 20$, 11.43%) and therapeutic failure of anticonvulsants induced by the other drugs (enzyme inducing anti-epileptic drugs) due to enzyme induction ($n = 19$, 10.86%) [Table 3]. Table 4 tabulates the drug combinations and severity of PDDIs.

Of 175 PDDIs, four PDDIs (1 major, 1 moderate, and 2 minor) based on the symptoms/laboratory reports were noted [Table 5].

DISCUSSION

The concept of PDDIs in the adult population has been studied decades, but the same in the pediatric population is gaining momentum now. It has been observed that ~50% of children who receive medications are prone to develop adverse effects due to drug interactions.^[15] Patients in the pediatric intensive care unit receive many drugs due to the associated clinical conditions. However, there are limited data on these drug interactions in patients in PICU. We assessed 122 prescriptions of pediatric patients in the PICU, for PDDIs as this is a

commonly encountered, but under evaluated problem, due to the high prevalence of polypharmacy in these patients.

We noted a high prevalence of polypharmacy in the study population. Many studies have considered polypharmacy to be the concurrent use of 5 or more drugs,^[16,17] while extensive polypharmacy is deemed to be the use of 10 or more in adults.^[18] The definition of polypharmacy about the pediatric population has not quite been established. However, in our study, all patients receiving >2 drugs were analyzed for drug interactions.

There is a varied prevalence rate of PDDI in the pediatric population, ranging between (3.8%–75%).^[8,19,20] We noted that 63.11% in this study had at least one PDDI (average of 2.27 PDDIs/prescription), which gives the prevalence estimate of these interactions in this population, comparable to Morales-Ríos *et al.*^[3] (61%) prevalence of PDDIs.

PDDs are common among patients aged 2–6 years.^[21] In this study, PDDIs were more common among patients aged <5 years (75.43%). However, our observation is in contrast to the reports of Ismail *et al.*^[22] where the odds of exposure to major PDDIs were significantly higher in 6–12 age group ($P = 0.008$). Of the prescriptions analyzed, 60% were of male patients which could be attributed to the fact that more number of male patients were admitted to PICU at the time of the study.

The severity assessment of the PDDIs (using Lexicomp drug interaction software) showed that majority were of moderate severity (75.43%), followed by minor (17.71%) and major (6.86%) interactions. This sequence is comparable to most of the drug interaction studies that have been done in this population.^[3,10,21,23] Dai *et al.*^[2] reported that 70% of the interactions in their study were either major or contraindicated. We did not find any interaction

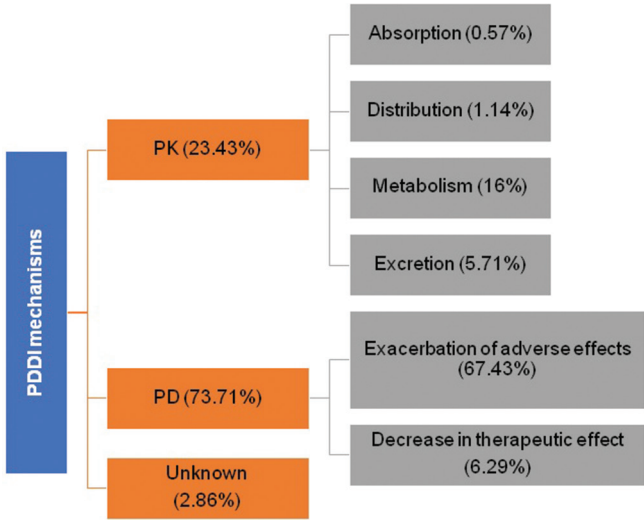


Figure 1: Potential drug–drug interaction distribution based on their underlying mechanism

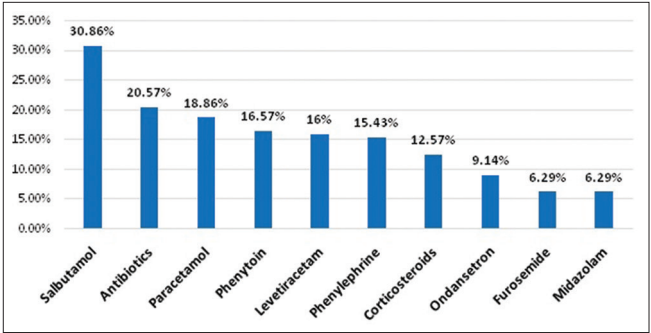


Figure 2: Commonly used drugs classes in the potential drug–drug interactions

Table 2: Number of potential drug-drug interactions and the number of concomitant medications per prescription			
Number of concomitant medications	Number of prescriptions ($n=122$)	Number of PDDIs ($n=175$) (%)	Average number of PDDIs/prescription
2-5	85	62 (35.43)	0.73
6-10	30	83 (47.43)	2.77
>10	7	30 (17.14)	4.29

PDDI=Potential drug-drug interactions

Table 3: Severity of common potential outcomes of the potential drug-drug interactions

Potential outcome	n (%)	Severity
Hypokalemia	24 (13.71)	Minor
Sympathomimetic adverse effects	20 (11.43)	Moderate
Therapeutic failure of anticonvulsant	19 (10.86)	
Antibiotic-induced nephrotoxicity	18 (10.29)	
CNS depression	16 (9.14)	
QTc prolongation	16 (9.14)	

CNS=Central nervous system, QTc=Corrected QT Interval

Table 4: Common drug interactions encountered in the pediatric intensive care unit

Severity	Combination of drugs	n (%)
Major	Linezolid + salbutamol	2 (1.14)
	Deferoxamine + ascorbic acid	1 (0.57)
	Colistin + vancomycin	1 (0.57)
	Ofloxacin + zinc salts	1 (0.57)
	Phenylephrine + tramadol	1 (0.57)
Moderate	Phenylephrine + salbutamol	20 (11.43)
	Aminoglycoside + 3 rd generation cephalosporin	18 (10.29)
	Paracetamol + phenylephrine	12 (6.86)
	Phenytoin/fosphenytoin + paracetamol	10 (5.71)
	Phenytoin/fosphenytoin + levetiracetam	8 (4.57)
	Levetiracetam + midazolam	7 (4)
	Salbutamol + furosemide	6 (3.43)
	Chlorpheniramine + ipratropiumphenytoin/fosphenytoin + valproate	3 (1.71)
	Phenytoin/Fosphenytoin + Valproate	2 (1.14)
	Salbutamol + ondansetron	2 (1.14)
Minor	Salbutamol + corticosteroid	18 (10.29)
	Paracetamol + ondansetron	10 (5.71)

that is “contraindicated,” as opposed to the studies of Hassanzad *et al.*^[23] and Dai *et al.*^[2] which had 0.5% and 0.8% contraindicated PDDIs, respectively. The high level of PDDI prevalence in our study could be due to several factors such as the underlying medical condition, the presence of extensive polypharmacy, and long duration of hospital stay, to name a few.^[24,25]

An important finding in this study was the relationship between the number of drugs prescribed to a patient and the incidence of PDDIs. Although the interactions were more in prescriptions that had 6–10 drugs, the average PDDI per prescription were the highest in those that had >10 drugs (4.29/prescription). Similar findings were reported by Sherin and Udaykumar^[26] where the average number of PDDI per prescription increased with an increase in the number of concomitant medications. This suggests that an increase in polypharmacy is linked to an increase in the number of PDDIs which have been established in several other studies as well.^[27-29]

On analysing the underlying pharmacological mechanisms associated with these interactions, we found that $\approx 3/4^{\text{th}}$ were pharmacodynamic interaction (73.71%) and $1/4^{\text{th}}$ were pharmacokinetic (23.43%). Similar findings were

reported by previous studies (65% Pharmacodynamic vs. 35% Pharmacokinetic interactions).^[10]

The drug most commonly involved in PDDIs was salbutamol, which could be attributed to a large number of pediatric patients being admitted with respiratory complaints to the PICU of our hospital. Forty of 122 prescriptions (32.78%) in this study belonged to patients with a respiratory diagnosis. The most common interaction of salbutamol was found with phenylephrine (11.43%, moderate severity), another sympathomimetic drug with antihistaminic and nasal decongestant properties. This drug duo could increase the risk of sympathomimetic side effects, which will require close monitoring. A less severe interaction of salbutamol was found with glucocorticoids ($n = 18$; 10.29%, minor severity). Both salbutamol and glucocorticoids reduce serum potassium levels (β_2 agonists shift potassium into the intracellular space, while corticosteroids increase potassium excretion). However, conflicting evidence exists on whether their concomitant use can increase the risk of hypokalemia.^[30,31] It usually does not warrant medical intervention and can be managed by monitoring the serum potassium levels. Salbutamol prolongs QTc, which showed interactions (of mild-moderate severity) with other QTc prolonging agents such as phenytoin/fosphenytoin (antiepileptic drug) and ondansetron (anti-emetic) in our study that could potentially harm the patients. Another common potential interaction encountered was among anti-epileptic drugs (10.86%, moderate severity), particularly between phenytoin/fosphenytoin and levetiracetam, which could potentially result in therapeutic failure of one drug due to enzyme induction by the other (usually phenytoin, as it is a strong CYP enzyme inducer). Antibiotic interactions were also common (10.29%, moderate severity), particularly between a 3rd generation cephalosporin and an aminoglycoside, where one drug enhances the nephrotoxic effects of the other. Few studies have found that opioids (fentanyl) and benzodiazepines (midazolam) constituted the most common PDDIs.^[2,25,32] In our study, benzodiazepines were among the commonly involved drugs in PDDIs ($n = 15$; 8.57%, moderate severity), particularly midazolam; opioids (fentanyl) was involved only in one interaction. However, the most common DDIs may not always pose the greatest risk; instead, PDDIs arising from drugs that are less commonly used may be more dangerous, as clinicians would not be as vigilant toward them.

Of 175 PDDIs, four PDDIs (1 major, 1 moderate, and 2 minor), which may have manifested in the patients, based on the symptoms/laboratory reports (which may not be attributed to their disease *per se* or any other comorbidities). However, we cannot confirm it completely as all patients have been discharged.

The most common potential outcome in our study was found to be hypokalemia (13.71%) contributed mainly by an interaction between salbutamol and corticosteroid. As mentioned earlier, this is generally of minor severity and requires only monitoring. In a study conducted by Baniyadi *et al.*, prolongation of QTc interval was found to be the most

Table 5: Potential drug-drug interactions based on symptoms/laboratory reports

Patient details	Diagnosis	PDDI	Severity	Observation
Female, 2-year 8 months	T cell all and sepsis	Colistin and vancomycin (increased risk of nephrotoxicity)	Major	During the period of administration of these drugs, mild transient elevation of BUN levels (observed value 55-59 mg/dl, normal range: 10-50 mg/dl) and transient decrease in urine output was noted. However, they reverted to normal
Female, 5 months	Cytomegalovirus infection and bronchopneumonia	Salbutamol and furosemide (increased risk of hypokalemia)	Moderate	Potassium levels showed a declining trend until it reached up to 2.82 mEq/L (normal range: 3.5-5 mEq/L), following which it kept fluctuating. No intervention was done
Male, 4 months	Lower respiratory tract infection	Salbutamol and hydrocortisone (increased risk of hypokalemia)	Minor	Potassium levels declined from 5.69 to 2, 8 mEq/L, following which it fluctuated between low to normal. No intervention was done
Male, 7 years	Wheeze associated lower respiratory tract infection, Grade 1 Protein-energy malnutrition	Salbutamol and hydrocortisone (increased risk of hypokalemia)	Minor	Potassium level transiently reduced to 3.19 mEq/L. No intervention was done

BUN=Blood urea nitrogen, PDDI=Potential drug-drug interactions

common potential outcome.^[14] Concerning this, we found a few potential instances of QTc prolongation (9.14%) in our study as well.

The strength of our study lies in the fact that drug-drug interaction studies are minimal among the pediatric population. Hence, information from our research can improve the understanding of prescription pattern in critically ill pediatric patients as well as encourage physicians to prescribe certain medications with caution to these patients. Apart from this, our study can provide a framework for future pharmacotherapeutic studies.

This was a single-center study, with small sample size. Hence, the findings of this study cannot be generalized. The interactions identified by Lexicomp software were all potential DDIs, and we did not assess whether they manifested in the patients or not, which is a major limitation. Although Lexicomp drug interaction checker is very reliable (supported by Wolters Kluwer Health) and commonly used system for identifying PDDIs, discrepancies have been found in the identification and grading of PDDIs severity between different systems.^[33,34] Hence, the results of this study may not correlate well with those of other similar studies that have used different PDDI-checking system.

Furthermore, discrepancies have been reported between the number of PDDIs detected with electronic systems and those evaluated by doctors as clinically relevant,^[35] which could be a potential limitation to our study.

Pediatric population with immature systems to handle the drug load is more prone to drug toxicities and adverse effects. Hence, a more focused approach is needed to identify and manage drug interactions. It is essential to check the possible drug interactions in this population and the necessary steps to be taken to avoid these unwanted reactions. All practicing pediatricians must be trained to recognize these interactions and updated periodically. Incorporating the drug interaction software into the computer system that is used for computerized

prescriptions that evoke alarm when these possible interactions are predicted will prove its worth in preventing the major interactions from occurring. However, the clinical correlation of the prediction lies in the skill of the treating pediatrician. Further research is required in incorporating the software and standardizing the same for our setups.

CONCLUSION

It is evident that PDDIs are currently on the rise with an increase in polypharmacy. The prevalence in our study was high and a majority of them were of moderate severity. Precautions need to be taken while prescribing medications to this vulnerable population including timely identification of possible interactions, minimizing risks, and close monitoring of clinically relevant parameters.

Acknowledgments

We acknowledge the nursing staff posted in PICU of Father Muller Medical College and Hospital, Mangalore, who lent their support. We also acknowledge the support of Dr. M. S. Latha in proofreading this article.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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