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RESEARCH

Evaluation of drug-drug interactions in critically ill pediatric patients

Durumu kritik olan pediatrik hastalarda ilaç-ilaç etkileşimlerinin değerlendirilmesi

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Abstract

Purpose: The aim of this study was to determine the drug-drug interactions that are frequently encountered in critically ill patients and the factors that predict these interactions.

Materials and Methods: All patients who were admitted to the pediatric intensive care unit (13 bed) of a university hospital and used more than one drug in their treatment were included in this prospective and cross-sectional study. Patients' demographics, laboratory findings, and medications included in their treatment were evaluated daily by a clinical pharmacist. The UpToDate® database was used to detect potential drug interactions.

Results: During the study, 797 potential drug-drug interactions were detected in 55 (83.33%) of 66 patients followed. All these interactions were evaluated by the clinical pharmacist and 114 recommendations were made to the physicians following the treatment regarding these potential interactions. Eighty-five (74.56%) of these recommendations were accepted by physicians. Within the scope of the study, each patient was followed up for a median of 9 (2-63) days, and the median value of potential drug interactions detected during this period was calculated as 7 (1-89).

Conclusion: The existence of pDDIs was significantly associated with the number of prescribed medications. Exposure to pDDIs is frequent in critically ill pediatric patients and related to the number of medications. Daily and close cooperation between clinicians and clinical pharmacists is recommended to prevent harmful outcomes of DDIs. In order to minimize this risk, it is recommended to avoid polypharmacy as much as possible and to offer alternatives to inducer and inhibitor drugs in treatment.

Keywords: Critically ill pediatric patient, drug interactions, polypharmacy

Öz

Amaç: Bu çalışmada, kritik çocuk hastalarda sıklıkla karşılaşılan ilaç-ilaç etkileşimlerinin ve bu etkileşimleri tahmin eden faktörlerin tespit edilmesi amaçlanmaktadır.

Gereç ve Yöntem: Prospektif ve kesitsel olan bu çalışmaya bir üniversite hastanesinin çocuk yoğun bakım ünitesine yatışı yapılan ve tedavilerinde birden fazla ilaç kullanılan tüm hastalar dahil edilmiştir. Hastaların demografik özellikleri, laboratuvar bulguları ve tedavilerinde yer alan ilaçlar günlük olarak bir klinik eczacı tarafından değerlendirilmiştir. Potansiyel ilaç etkileşimlerinin tespit edilmesi için UpToDate® veri tabanından yararlanılmıştır.

Bulgular: Çalışma boyunca takip edilen 66 hastanın 55'inde (%83.33) toplam 797 adet potansiyel ilaç-ilaç etkileşimi tespit edilmiştir. Tüm bu etkileşimler klinik eczacı tarafından değerlendirilmiş ve bu potansiyel etkileşimlere yönelik, tedaviyi takip eden hekimlere 114 öneride bulunulmuştur. Bu önerilerin 85'i (%74.56) hekimler tarafından kabul edilmiştir. Çalışma kapsamında her hasta ortanca 9 (2-63) gün takip edilmiş, bu sürede tespit edilen potansiyel ilaç etkileşimlerinin ortanca değeri 7 (1-89) olarak hesaplanmıştır.

Sonuç: Kritik çocuk hastaların tedavilerinde potansiyel ilaç etkileşimi riski yüksektir. Bu riskin azaltılması adına, mümkün olduğu kadar polifarmasiden kaçınılması, tedavide bulunan indüktör ve inhibitör ilaçlara alternatifler sunulması önerilmektedir. Yoğun bakım ünitelerinde uzmanlaşmış eczacıların, multidisipliner ekibe dahil olmasının, potansiyel ilaç etkileşimlerinin yönetimini sağlayarak tedavinin optimizasyonuna katkı sağlayacağı düşünülmektedir.

Anahtar kelimeler: Kritik çocuk hasta, ilaç etkileşimleri, polifarmasi

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INTRODUCTION

Adverse drug events are among the primary causes that increase morbidity, mortality, and health costs [1]. Polypharmacy is an important known risk factor for adverse drug reactions [2]. Polypharmacy is defined as the use of many drugs to treat a single or multiple diseases at the same time, or the use of multiple drugs having the same mechanism of action to treat a single condition [3]. Drug interactions are a significant effect of polypharmacy. It was reported that, drug-drug interactions developed in 13% of patients taking 2 drugs; This rate approaches 40% in patients taking 5 drugs and exceeds 80% in patients taking 7 or more drugs [4]. These rates do not differ between adults and pediatric patients.

Critically ill children may be more affected by the effects of drug interactions due to pharmacokinetic differences caused by the various developmental stages of pediatric patients and the physiopathology of critical illness (organ dysfunctions, changes in the distribution and excretion of extracorporeal supports) affecting pharmacokinetics [1,5,6]. Adult data cannot be used to create an accurate approximation for the pediatric patient group. As a result, it is significantly harder to anticipate the clinical outcome of interactions in the young patient population than it is in the adult patient group. The clinical significance of potential drug-drug interactions (pDDIs) should be made clearer to this patient group, and they should be closely monitored [7,8].

Knowledge about potential drug interactions in child health care may contribute to monitoring and minimizing adverse drug reactions and treatment failures[1]. The lack of pediatric pharmacoepidemiological studies in the literature, particularly in our countries, led to the investigation of pDDIs prevalence in a pediatric intensive care unit (PICU) at a university hospital in Türkiye. Prevalence and prediction studies like this will help clinicians to prevent the development of DDIs in their day-to-day practice and improve patient safety, especially in areas there is no access to clinical pharmacy services[9,10].

The aim of this study was to identify potential drug-drug interactions (pDDIs) and characteristics that predict interactions in critically ill pediatric patients who take multiple drugs.

MATERIALS AND METHODS

Study design

This prospective, cross-sectional, and descriptive study was carried out at the Balcalı Hospital of the Çukurova University Faculty of Medicine. The research was conducted in collaboration with the Department of Pediatric Intensive Care at Çukurova University. The PICU includes 13 beds, and patients are seen by physicians and nurses on a daily basis for therapy. A clinical pharmacist (PhD) and an intern pharmacist from Faculty of Pharmacy were included in the critical care team throughout the study, attended daily visits, and examined all patients' treatments for pDDIs. The research was carried out as part of the intern pharmacist's graduation project. This study was approved by Non-Invasive Clinical Research Ethics Committee of Çukurova University Faculty of Medicine for the study (Decision No: 117/52). The study was started after the approval of the ethics committee and was completed within the time specified for the graduation project (between 6 December 2021 and 1 April 2022).

Sample

The study's population consists of patients admitted to the PICU. Patients who are still being treated in the PICU and who are taking at least two different drugs are eligible for the study, which will take place from December 6, 2021 through April 1, 2022. The study's sample size was set at 60 people, with 80% power and a type 1 error level of 0.05.

Data collection

Patients included in the study demographic and clinical data were obtained prospectively. Height, weight, body mass index, laboratory findings, and treatment information can be obtained from patient records and, when necessary, from the hospital information systems (Enlil-HBYS 2015) was reached and recorded in the 'Data Collection Form' used within the scope of the study. In addition, physicians calculated and recorded Pediatric Risk of Mortality Score III (PRISM 3) scores, one of the most extensively used mortality scoring systems in PICU.

Intervention

The UpToDate® database was used to assess pDDIs in treatments. Table 1 shows the risk rating of pDDIs detected. As a consequence of the clinical pharmacist's review, recommendations for the management of pDDIs were provided to physicians, depending on the risk level of the interactions and whether they were clinically significant for the patient's therapy. The physicians' responses to these recommendations were documented. Without the physicians' knowledge, no treatment recommendations were made for the patients.

Table 1. Risk category of drug interactions [14]

Risk category	Action	Description
A	No known interactions	Data have not demonstrated pharmacodynamic and pharmacokinetic interactions between the indicated drugs.
B	No action needed	Data demonstrate that the indicated drugs may interact with each other, but there is little or no evidence of clinical concern from their concomitant use.
C	Treatment monitoring	Data demonstrate that the indicated drugs may interact with each other in a clinically meaningful way. The benefits of using these two drugs together often outweigh the risks. An appropriate monitoring plan should be implemented to identify potential adverse effects. A dose adjustment of one or both drugs may be required in a minority of patients.
D	Consider therapy modification	Data demonstrate that the 2 drugs can interact with each other in a clinically meaningful way. A patient-specific assessment should be made to determine whether the benefits of concomitant therapy outweigh the risks. Special precautions should be taken to realize the benefits and/or minimize toxicity resulting from the concomitant use of drugs. These actions may include aggressive monitoring, empirical dosage changes, and selection of alternative medications.
X	Avoid combination	Data demonstrate that the indicated drugs may interact with each other in a clinically meaningful way. The risks associated with the concomitant use of these drugs often outweigh the benefits and are generally considered contraindicated.

Stattitical analysis

Frequency percentage values were used for descriptive statistics of the study data, and mean (standard deviation) and median values were used for continuous data. The normality assumptions of the data were checked by taking into account the skewness and kurtosis coefficients and it was determined that the assumptions were satisfied. While examining the variables predicting pDDIs, simple linear regression analysis was performed for each variable to see the effect of each variable. Statistical analyzes of the data were carried out with the SPSS 20.0 program. The significance level for all values was determined as 0.05.

RESULTS

Sixty-six patients treated in the PICU during the study period were included in the study. Thirty-six (54.55%) of these patients were male, with a median age of 7 years (4 months-17 years) and a median PRISM III score of 2 (0.3-97).

During the study, 797 pDDIs were detected in 55 (83.33%) of the patients. Of these interactions, 10 (1.25%) were detected as level A, 72 (9.03%) as level B, 489 (61.4%) as level C, 209 (26.2%) as level D, and 17 (2.13%) as level X. Clinical significance of all these pDDI were evaluated by the clinical pharmacist and 114 recommendations were made to physicians. Eighty-five (74.56%) recommendations were accepted and implemented. In order to manage the drug interactions, these recommendations were classified into 4 groups; dose change, medication change (withdrawal from treatment or alternative medicine recommendation), changes in drug administration times and monitoring (drug blood level, monitoring of hematological and cardiac findings, etc.) (Table 2).

Table 2. Recommendations (n=114) for potential drug interactions identified

	Recommendations n(%)	Accepted n(%)
Dose adjustment	16 (14.04)	9 (7.89)
Drug change	17 (14.91)	3 (2.63)
Changes to medication administration times	6 (5.26)	4 (3.51)
Monitoring	75 (65.79)	69 (60.52)

Each patient was followed up on for an average of 9 (2-63) days during the period of the study, and the median (min-max) value of pDDIs detected during this time was calculated as 7 (1-89). Only the minimum (p=0.361) and maximum (p=0.202) number of drugs showed normal distribution in the variables. Other variables did not show normal distribution (p<0.001) (Table 3). Age, minimum and maximum number of drugs, number of inducer and inhibitor drugs, and number of days followed all predicted pDDIs statistically significantly (p<0.05). PRISM ratings do not predict pDDIs significantly (p>0.05) (Table 4).

Table 3. Data of drugs used and interactions detected during hospitalization of patients

	Median (min-max)	Mean (± sd)
Minimum number of drugs	8(1-18)	7.62±0.47
Maximum number of drugs	10(2-23)	10.87±0.66
Number of inhibitor drugs	1(0-5)	1.07±0.15
Number of inducer drugs	1(0-5)	1.18±0.15
Number of potential drug interactions	7(1-89)	14.49±2.44
Recommendations	1(0-13)	2.04±0.36

Min-max: minimum-maximum, sd: standart deviation

Table 4. Variables that predict potential drug interactions

Variables	β	t	p
Age	0.279	2.051	0.041*
PRISM III score	-0.015	-0.106	0.916
Minimum number of drugs	0.354	2.753	0.008*
Maximum number of drugs	0.769	8.760	0.000*
Number of inhibitor drugs	0.591	5.331	0.000*
Number of inducer drugs	0.718	7.499	0.000*
Number of days followed	0.729	7.753	0.000*

*p<0.05, PRISM: Pediatric Risk of Mortality

DISCUSSION

Unlike many research on pDDIs in adult critically ill patients, the number of studies conducted in PICU is limited. The aim of this study is to contribute to clinical practice and the literature by detecting pDDIs in PICU.

Throughout the study, there were 797 pDDIs detected, with 209 (26.23%) interactions categorised as degree D and 17 (2.13%) classified as level X. Furthermore, in our study, the median number of pDDIs was found to be 7 (1-89). Costa Lima et al. followed up pDDIs for each patient, a ratio close to our result 14 (1.25%) of the identified interactions were contraindicated, with 631 (56.19%) having a severe severity[1]. Of the detected interactions, 14 (1.25%) were contraindicated, 631 (56.19%) high severity. In the study of Baniasadi et al. that lasted for 4 months, it was shown that the pDDIs rate was 485.9 interactions/100 patients. In terms of interaction severity, it was reported that 8.7% of interactions were considered major, and 0.5% contraindicated [10]. Choi et al. reported that 115 patients (72.3%) were exposed to a total of 592 pDDIs caused by 258 drug pairs. It has been reported that 2.6% of 592 pDDIs were classified as contraindicated and 56.2% as major according to the

severity of the interaction [11]. It is seen that the average number of interactions and pDDIs at the contraindicated level are similar to the results of this study. pDDIs identified within the scope of the study were evaluated daily by a clinical pharmacist, and 114 recommendations for clinically significant ones were presented to the physicians responsible for treatment. Eighty-five (74.56%) of these recommendations were accepted and implemented. It was determined that the median value of the number of recommendations made for each patient was 1 (0-13). Parallel to this, in the study of Malfara et al., it was reported that the total number of interventions performed by the clinical pharmacist was 197, and 97% of them (n=191) were accepted by the intensive care team [12]. In the study of Krupicka et al., it was stated that the median value of the number of recommendations per patient was 1 [13]. It is seen that the average number of interactions and drug interactions at the contraindicated level are similar to the results of this study.

In the study, the following variables predicted pDDIs actions in a statistically significant way: age, the minimum and maximum number of drugs, the number of inducer and inhibitor drugs, and the number of days followed ($p<0.05$). There was no statistically significant difference between the gender and age of the patients and the possibility of pDDIs in the investigations of Costa Lima et al, and the average length of stay in the intensive care unit was provided as 11.3 ± 15.5 day[1]. Patients who received 6-7 (odds 5.6, 95% CI 1.6-19.1, $p = 0.006$) and >8 drugs per day were more likely to be exposed to pDDIs than patients who received an average of 5 drugs per day, and those who stayed for 1-2 weeks were five times more likely to be exposed to pDDIs than patients who stayed for 1 week in the PICU. They were found to have a chance of being exposed to pDDIs ($p = 0.035$), and those staying longer than two weeks had an eight-fold higher chance ($p = 0.049$)[12]. This study, which was conducted in conjunction with the previous investigations, demonstrates that the risk of pDDIs between medications increases as the number of drugs in therapy increases.

This study has some limitations The first is the short period of study. Because this study was designed as a graduation project, the target sample size could not be reached in a restricted amount of time. Due to the short period of study, it could not be evaluated as one of the factors predicting some clinical outcomes of the patients. Furthermore, because there was an absence of specific kits at the hospital laboratory during the research period, the recommendations for monitoring the levels of certain pharmaceuticals were acknowledged but not executed.

As a result, the existence of pDDIs was significantly associated with the number of prescribed medications. Exposure to pDDIs is frequent in critically ill pediatric patients and related to the number of medications. Daily and close cooperation between clinicians and clinical pharmacists is recommended to prevent harmful outcomes of DDIs. In order to minimize this risk, it is recommended to avoid polypharmacy as much as possible and to offer alternatives to inducer and inhibitor drugs in treatment. In addition, the development of predictive applications that include risk factors in drug-drug interactions checker databases will provide convenience to clinicians and patient safety in intensive care units.

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REFERENCES

1. Costa Lima E, Camarinha BD, Bezerra NCF, Panisset AG, Souza, RB etal. Severe potential drug-drug interactions and the increased length of stay of children in intensive care unit. Front Pharmacol. 2020;11:555407.
2. Nguyen JK, Fouts MM, Kotabe SE, Lo E. Polypharmacy as a risk factor for adverse drug reactions in geriatric nursing home residents. Am J Geriatr Psychiatry. 2006;4:36-41.
3. Bhatt-Mehta V. "Potential" drug-drug interactions and the PICU: Should we worry about ICU polypharmacy? Pediatr Crit Care Med. 2016;17:470-2.
4. Sharifi H, Hasanloei MAV, Mahmoudi J. Polypharmacy-induced drug-drug interactions; threats to patient safety. Drug Res. 2014;64:633-7.
5. Ismail M, Aziz S, Noor S, Haider I, Shams F 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;40:243-50.

6. Kunac DL, Kennedy J, Austin NC, Reith D. incidence, preventability, and impact of adverse drug events (ADEs) and potential ADEs in hospitalized children in New Zealand. Paediatr Drugs. 2009;11:153-60.
7. Silva DCB, Araujo OR, Arduini RG, Alonso CFR, Shibata AO et al. Adverse drug events in a paediatric intensive care unit: a prospective cohort. BMJ Open. 2013;3:e001868.
8. Salem F, Rostami-Hodjegan A, Johnson T. Do children have the same vulnerability to metabolic drug-drug interactions as adults? A critical analysis of the literature. J Clin Pharmacol. 2013;53:559-66.
9. Hassanzad M, Nejad ST, Mahboobipour A, Salem F, Baniasadi S. Potential drug-drug interactions in hospitalized pediatric patients with respiratory disorders: a retrospective review of clinically important interactions. Drug Metab Pers Ther. 2020;35:20190012.
10. Baniasadi S, Hassanzad M, Alehashem M. Potential drug-drug interactions in the pediatric intensive care unit of a pulmonary teaching hospital. Eur Respir J. 2016;48:1301.
11. Choi YH, Lee IH, Yang M, Cho YS, Jo YH etal. Clinical significance of potential drug–drug interactions in a pediatric intensive care unit: A single-center retrospective study. Plos One. 2021;16:e0246754.
12. Malfara M, Pernassi M, Aragon D, Carlotti A. Impact of the clinical pharmacist interventions on prevention of pharmacotherapy related problems in the paediatric intensive care unit. Int J Clin Pharm. 2018;40:513-9.
13. Krupicka M, Bratton SL, Sonnenthal K, Goldstein B. Impact of a pediatric clinical pharmacist in the pediatric intensive care unit. Crit Care Med. 2002;30:919-21.
14. Lexicomp® Drug Interactions. https://www.uptodate.com/drug-interactions/?source=responsive_home#di-druglist. (accessed Dec 2021).