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ORIGINAL ARTICLE / ÖZGÜN MAKALE

DETERMINATION OF POTENTIAL DRUG-DRUG INTERACTIONS IN GENERAL PEDIATRIC WARD PATIENTS: A CROSS-SECTIONAL STUDY

GENEL PEDİYATRI SERVİSİ HASTALARINDA POTANSİYEL İLAÇ-İLAÇ ETKİLEŞİMLERİNİN SAPTANMASI: BİR KESİTSEL ÇALIŞMA

Hasan MEMİŞ[1], Ahmet ÇAKIR[1]*, Nesligül ÖZDEMİR[1], Zeynep Ülkü GÜN[1]

[1]Inonu University, Faculty of Pharmacy, Department of Clinical Pharmacy, 44210, Malatya, Türkiye

ABSTRACT

Objective: *This study seeks to identify potential drug-drug interactions (pDDIs) in hospitalized patients and compare two commercial drug interaction databases.*
Material and Method: *This prospective cross-sectional study was conducted between February and May 2022 in a tertiary care hospital's general pediatric ward. UpToDate® and Micromedex® Drug Interaction databases were used to determine pDDIs.*
Result and Discussion: *In total, 267 pDDIs were found in 51 pediatric patients' medication lists (181 via UpToDate® and 86 via Micromedex®). The use of at least five different systemic drugs concurrently was statistically significant between groups of patients who experienced at least one pDDI and those who did not. The binary logistic regression analysis showed that a one-drug increase in the total number of drugs a patient received during hospitalization increased the probability of pDDIs by 2.12-fold (CI: 1.321-3.417, p=0.002). The concordance rate between UpToDate® and Micromedex® databases for pDDI determination was 84.31% (kappa coefficient=0.676, standard error=0.102, (p ≤ 0.001)). When the UpToDate® database was assumed as a reference database, the Micromedex® database's sensitivity, specificity, positive predictive value, negative predictive value, and accuracy in determining pDDIs were 79.41%, 94.12%, 96.43%, 69.56%, and 84.5%. To avoid missing pDDIs, utilizing multiple drug interaction databases may be of benefit.*
Keywords: *Children, clinical pharmacist, drug interactions, pediatric patients*

ÖZ

Amaç: *Bu çalışma, hastanede yatan hastalarda potansiyel ilaç-ilaç etkileşimlerini (pDDI'ler) belirlemeyi ve iki ticari ilaç etkileşimi veri tabanını karşılaştırmayı amaçlamaktadır.*

* **Corresponding Author / Sorumlu Yazar:** Ahmet Çakır
e-mail / e-posta: eczahmetcakir@hotmail.com, **Phone / Tel.:** +905309343904

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Gereç ve Yöntem: *Bu prospektif kesitsel çalışma, Şubat ve Mayıs 2022 tarihleri arasında üçüncü basamak bir hastanenin genel pediyatri servisinde yürütülmüştür. pDDI'leri belirlemek için UpToDate® ve Micromedex® İlaç Etkileşimi veritabanları kullanılmıştır.*

Sonuç ve Tartışma: *Elli bir pediatrik hastanın ilaç listesinde toplam 267 pDDI bulunmuştur (UpToDate® aracılığıyla 181 ve Micromedex® aracılığıyla 86). En az beş farklı sistemik ilacın aynı anda kullanımı, en az bir pDDI saptanmış ve saptanmamış hasta grupları arasında istatistiksel olarak anlamlıydı. İkili lojistik regresyon analizi, bir hastanın hastanede yatışı sırasında aldığı toplam ilaç sayısındaki bir ilaç artışının, pDDI olasılığını 2.12 kat artırdığını göstermiştir (GA: 1.321-3.417, p=0.002). pDDI saptnmasında UpToDate® ve Micromedex® veritabanları arasındaki uyum oranı %84.31 olarak bulunmuştur (kappa katsayısı=0.676, standart hata=0.102, ($p \leq 0.001$)). UpToDate® veri tabanı referans veri tabanı olarak kabul edildiğinde, Micromedex® veri tabanının pDDI'leri belirlemedeki hassasiyeti, özgüllüğü, pozitif prediktif değeri, negatif prediktif değeri ve doğruluğu %79.41, %94.12, %96.43, %69.56 ve %84.5 idi. Bir pDDI'yı atlamaktan kaçınmak için çoklu ilaç etkileşimi veritabanlarının kullanılması faydalı olabilir.*

Anahtar Kelimeler: *Çocuklar, ilaç etkileşimleri, klinik eczacı, pediyatrik hastalar*

INTRODUCTION

In pediatric patients, treatment regimens with more than one drug may be required to treat diseases and this may lead to potential drug-drug interactions (pDDIs). One of the most significant drug-related problems that make therapy more challenging among pediatric patients is pDDIs. Due to the fact that the pharmacokinetics (PK) and pharmacodynamics (PD) of drugs vary in children, it is much more important to monitor treatment for drug interactions [1]. Even in children, the cytochrome p450 enzyme system, which is responsible for a significant proportion of drug interactions, varies with age [2].

Drug interactions are frequently encountered, especially in patients with polypharmacy and long hospital stay [3]. In a retrospective cohort study using the American Pediatric Health Information System database, it was reported that 75% of the pediatric patients in intensive care unit were exposed to at least one pDDI, and 51.1% of these interactions were major interactions [1]. In another study involving 42 Children's Hospitals, at least one pDDI was found in approximately half of the 498,956 hospitalizations [4].

In pediatric patients, it is vital not only to identify drug interactions but also to manage them. Drug-drug interaction databases, having become widespread in recent years for managing drug interactions, are time-saving facilitator applications for healthcare professionals. However, these databases differ in sensitivity, specificity and accuracy in detecting drug-drug interactions [5,6]. Besides, the results obtained from these databases and clinicians' evaluations show large discrepancies in clinical importance of interactions [7]. Considering both the difference in databases and the pharmacokinetic difference in pediatric patients, drug interaction management in pediatric patients becomes an issue that needs attention.

This study aims to identify pDDIs in patients hospitalized in a general pediatric ward of a tertiary care hospital and to compare the performance of two different drug interaction databases to identify pDDIs.

MATERIAL AND METHOD

This cross-sectional study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the ethics committee of Inonu University (25th January 2022 - No: 2022/3055). The study conducted between February 2022 and May 2022 in the general pediatric ward of a tertiary care hospital in eastern Türkiye, which has a capacity of 14 beds. Patients who were admitted to the general pediatric ward and whose parental consent was obtained were included in the study. All drug-drug interactions of the patients were determined by two clinical pharmacists in the ward. Information about the sex, age and daily medication lists of the patients were obtained from the electronic database of the hospital. Drug-drug interactions were determined using the UpToDate® Drug Interaction and IBM Micromedex® Drug Interaction databases. In the evaluation of the data, descriptive and advanced statistical analyses were performed using SPSS V25.0.

Statistical Analysis

While continuous variables were indicated by median and interquartile range (IQR), categorical variables were presented by number (n) and percentage (%). The results of statistical tests were deemed statistically significant unless the *p* value of the test was greater than 0.05. The Kolmogorov-Smirnov test was used to determine whether the quantitative data is normally distributed or not. Chi-squared and Mann-Whitney U tests were used to compare categorical and continuous data, respectively. The correlation between the two data was determined through Spearman's rho test. If the correlation coefficient falls between 0.01 and 0.29, 0.30 and 0.70, or 0.71 and 0.99, the correlation is judged to be poor, fair, or strong, accordingly. Risk factors having potential to affect the occurrence of pDDIs were determined by binary logistic regression analysis. Cohen's kappa value was used to determine the concordance rate between the UpToDate® and Micromedex® databases in terms of the databases' ability to identify pDDIs, the severity of identified pDDIs, and the documentation rates of identified pDDIs. If Cohen's kappa value was less than zero, it was concluded that the databases did not agree. If Cohen's kappa value was between 0-0.20, 0.21-0.40, 0.41-0.60, 0.61-0.80 or 0.81-1.0; then it was accepted that there was slight agreement, fair agreement, moderate agreement, substantial agreement or almost perfect agreement between the databases, respectively. The UpToDate database categorizes pDDIs into five risk rating categories. These classifications, namely A, B, C, D, and X, indicate: no known interaction, no action needed, monitor therapy, consider therapy modification, and avoid combination, respectively. However, the Micromedex database has no risk rating category classification system. To determine the degree of concordance between the two databases regarding the severity of identified pDDIs, the risk rating categories B, C, D, and X from the UpToDate® database were paired with the minor, moderate, major, and contraindicated severity categories from the Micromedex® database.

Performance of pDDI screening programs was assessed through calculating sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) [8] and their definitions were given in Table 1.

Table 1. Definition of sensitivity, specificity, negative and predictive value in the setting of pDDIs.

Parameter	Definition	Calculation
Sensitivity	The ability to detect clinically important drug-drug interactions.	number of true-positives / (number of true-positives + number of false-negatives)
Specificity	The ability to ignore clinically unimportant drug-drug interactions.	number of true-negatives / (number of true-negatives + number of false-positives)
Positive predictive value (PPV)	When a drug-drug interaction is found, the probability that the drug-drug interaction is clinically important.	number of true-positives / (number of true-positives + number of false-positives)
Negative predictive value (NPV)	When a drug-drug interaction is ignored, the probability that the drug-drug interaction is clinically unimportant.	number of true-negatives / (number of true-negatives + number of false-negatives)

True-positives: at least 1 pDDI was determined by both of the databases
True-negatives: no pDDI was determined by both of the databases
False-positives: at least 1 pDDI was determined by the Micromedex® database while no pDDI was determined by the UpToDate® database
False-negatives: no pDDI was determined by the Micromedex® database while at least 1 pDDI was determined by the UpToDate® database

RESULT AND DISCUSSION

The study comprised a total of 51 pediatric patients, 49% of whom were male. The median (IQR) value of the patients' age was 18 (8-96) months. The median (IQR) length of hospitalization for patients was 7 (5-11) days. The median (IQR) number of different systemic drugs utilized per hospitalized patient

was 6 (3-7). Table 2 lists the admission diagnoses of patients classified by the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10).

Table 2. The diagnoses made at the time of the patients' admission

ICD-10 Code	Number (%)
J00-J99 Diseases of the respiratory system	30 (58.82)
A00-B99 Certain infectious and parasitic diseases	8 (15.69)
R00-R99 Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	5 (9.80)
Q00-Q99 Congenital malformations, deformations and chromosomal abnormalities	3 (5.88)
U00-U85 Codes for special purposes	1 (1.96)
L00-L99 Diseases of the skin and subcutaneous tissue	1 (1.96)
K00-K93 Diseases of the digestive system	1 (1.96)
H00-H59 Diseases of the eye and adnexa	1 (1.96)
D50-D89 Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	1 (1.96)

According to the UpToDate® and Micromedex databases, the number of patients having at least one pDDI identified was 34 (66.7%) and 28 (54.9%), respectively. The number of patients with at least one pDDI determined using any of the two databases was 35 (68.6%).

In total, 267 pDDIs were detected on 473 daily medication lists. 181 (67.79%) of the pDDIs were identified using the UpToDate® database, whereas 86 (32.21%) were identified using the Micromedex database. These 267 pDDIs were identified in 129 drug pairings, 50 of which (38.76%) were detected using the Micromedex® database and 79 (61.24%) using the UpToDate® database. Once the overlapping drug pairings between the databases were excluded, 88 different drug pairings remained. Again, once the overlapping pDDIs between the databases were excluded, 195 different pDDIs remained. According to the data obtained from the UpToDate® and Micromedex® databases, the number of pDDIs per daily medication list was found to be 0.38 and 0.18, respectively. According to the UpToDate® database, the following pDDI mechanism-specific distribution rates were determined: 35.91% were pharmacokinetic, 51.93% were pharmacodynamic, and 12.15% were unknown. In addition, the Micromedex® database revealed the following distribution rates for pDDIs in terms of their mechanisms: 63.95 percent of them were pharmacokinetic, 19.77 percent were pharmacodynamic, and 16.28 percent of them were unknown.

The distribution of the pDDIs as regards their severity and documentation rates were given in Table 3.

The UpToDate® database indicated that 64 (35.36%) of the pDDIs did not necessitate any action, 79 (43.64%) required therapy monitoring, 35 (19.34%) required therapy modification, and 3 (1.66%) required avoidance of combination.

According to the UpToDate® database, the top three drug pairs that probably caused at least one pDDI (n, %) were budesonide-clarithromycin (21, 11.6), albuterol-budesonide (20, 11.05), and albuterol-clarithromycin (19, 10.50). Moreover, according to the Micromedex® database, the first three drug pairs that most commonly probably caused at least one pDDI (n, percent) were budesonide-clarithromycin (21, 24.42), clarithromycin-methylprednisolone (10, 11.7), and epinephrine-linezolid (3, 3.49). When the two databases were analyzed together, the first three drug pairs that probably caused at

least one pDDI the most frequently (n, percent) were budesonide-clarithromycin (42, 15.73), clarithromycin-methylprednisolone (21, 7.83), and albuterol-clarithromycin (20, 7.49).

Table 3. The distribution of pDDIs according to severity and documentation rates of two databases

Factor	Rate	UpToDate® n (%)	Micromedex® n (%)
Severity	Minor	35 (19.34)	3 (3.49)
	Moderate	134 (74.03)	53 (61.63)
	Major	12 (6.63)	26 (30.23)
	Contraindicated	NA	4 (4.65)
Documentation	Fair	99 (54.70)	55 (63.95)
	Good	58 (32.04)	28 (32.56)
	Excellent	24 (13.26)	3 (3.49)

NA: not applicable

Table 4 shows the ten most frequently observed pDDIs. The classification of the drug groups associated with pDDIs frequently is given in Table 5. The Anatomical-Chemical Classification System (ATC) was used to classify the drugs.

It was determined that there was a positive-oriented fair association between concomitant usage of at least 5 different systemic drugs and number of pDDIs (correlation coefficient=0.644, $p<0.001$ for the UpToDate® database; correlation coefficient=0.572, $p<0.001$ for the Micromedex® database).

It was observed that there was a positive-oriented strong association between the total number of different systemic drugs administered during hospitalization and number of pDDIs (correlation coefficient=0.738, $p<0.001$ for the UpToDate® database; correlation coefficient=0.710, $p<0.001$ for the Micromedex® database).

Statistically, the number of pDDIs categorized according to the risk categories of the UpToDate® database is not affected by sex ($p>0.05$). The effect of concomitant usage of at least five different systemic drugs on the number of pDDIs is statistically significant for risk rating categories B, C, and D ($p \leq 0.001$), but not for group X ($p>0.05$).

It was found that sex has no statistically significant effect on the number of pDDIs detected regarding their degree of importance in the UpToDate® database ($p>0.05$). The concomitant usage of at least 5 different drugs was however found to has statistically significant effect on the distribution of pDDIs according to risk rating categories of UpToDate® database except for X category (p values for A, B, C, D, and X categories is NA, <0.001, <0.001, =0.001, and >0.05, respectively).

Sex of the patient has no statistically significant effect on severity of pDDIs according to both UpToDate® and Micromedex® databases ($p>0.05$). The concomitant usage of at least 5 different systemic drugs has statistically significant effect over the number of pDDIs according to severity categories of the UpToDate® which consists of minor, moderate, and major (p values for minor, moderate, and major severity were <0.001, <0.001, and =0.039, respectively). The effect of concomitant usage of at least 5 different systemic drugs was statistically significant only for the number of pDDIs whose severities were moderate according to the Micromedex® database ($p \leq 0.001$).

A binary logistic regression analysis was performed to determine the factors that could potentially affect the occurrence risk of pDDIs. In the analysis, the effects of the length of hospitalization and the total number of drugs to which the patient was exposed were examined. Increasing the total number of drugs a patient received during hospitalization by one could increase the odds of identifying the risk of pDDIs by 2.12-fold (95% confidence interval [CI]: 1.321-3.417, p=0.002).

Table 4. The first 10 of the most commonly encountered pDDIs determined through the UpToDate® and the Micromedex® databases

UpToDate®				Micromedex®			
Drug pair	**Risk Category/ Severity**	**Docume-ntation Rate**	**Comment**	**Drug Pair**	**Severity**	**Docume-ntation Rate**	**Comment**
Budesonide (inh)-clarithromycin (iv)	D/Moderate	Good	Clarithromycin can increase the serum level of budesonide.	Budesonide (inh) -clarithromycin (iv)	Moderate	Fair	Clarithromycin can increase the serum level of budesonide.
Albuterol (inh)-budesonide (inh)	B/Moderate	Fair	Budesonide can increase the hypokalemic effect of albuterol.	Clarithromycin (iv)-methylprednisolone (iv)	Moderate	Good	Clarithromycin can increase the side effects of methylprednisolone.
Albuterol (inh)-clarithromycin (iv)	B/Minor	Fair	The QT prolongation risk can increase with concomitant usage	Epinephrine (nasal)-linezolid (iv)	Contrain dicated	Fair	Increased hypertensive effect can be seen with concomitant usage.
Albuterol (inh)-epinephrine (nasal)	C/Moderate	Fair	Sympathomimetics can increase adverse/toxic effects of the other sympathomimetics.	Clarithromycin (iv)-valproate (iv)	Moderate	Fair	Increased levels of valproate can be seen with concomitant usage.
Albuterol (inh)-methylprednisolone (iv)	B/Moderate	Fair	Methylprednisolone can increase the hypokalemic effect of albuterol.	Amikacin (iv)-ibuprofen (po)	Moderate	Good	Increase in exposure of amikacin can be seen with concomitant usage.
Clarithromycin (iv)-methylprednisolone (iv)	C/Moderate	Excellent	Clarithromycin can increase the serum level of methylprednisolo-ne.	Budesonide (inh)-ibuprofen (po)	Major	Fair	Increase in the risk of gastrointestinal system bleeding and ulcer can be seen.
Amikacin (iv)-ceftriaxone (iv)	C/Moderate	Excellent	Cephalosporins can decrease the serum levels of aminoglycosides. Cephalosporins can increase nephrotoxic effects of aminoglycosides.	Clarithromycin (iv)-clonazepam (po)	Major	Fair	Clarithromycin increases the toxicity of clonazepam.
Albuterol (inh)-linezolid (iv)	D/Major	Fair	Linezolid can increase hypertensive effect of albuterol.	Albuterol (inh)-digoxin (po)	Moderate	Good	Concomitantly use of the two decreases serum digoxin levels.
Epinephrine (nasal) -linezolid (iv)	X/Major	Fair	Linezolid can increase hypertensive effect of epinephrine.	Albuterol (inh)-furosemide (iv)	Moderate	Fair	Concomitantly use of the two can result in hypokalemia and ECG changes.
Albuterol (inh)-azithromycin (iv)	B/Minor	Fair	The QT prolongation risk can increase with concomitant usage	Amikacin (iv)-piperacillin/tazobactam (iv)	Minor	Good	Decrease in the efficacy of amikacin can be seen with concomitant usage.

inh: per inhalation, iv: intravenous, po: per oral

Table 5. The ATC groups of the drugs the most commonly caused pDDIs

UpToDate®		Micromedex®	
Drug Group (ATC)	**n (%)**	**Drug Group (ATC)**	**n (%)**
Drugs for Obstructive Airway Diseases	112 (30.94)	Antibacterials for systemic use	68 (39.53)
Antibacterials for Systemic Use	101 (27.90)	Antiepileptics	25 (14.53)
Antiepileptics	49 (13.54)	Drugs for obstructive airway diseases	25 (14.53)
Corticosteroids	25 (6.91)	Corticosteroids	13 (7.56)
Nasal Preparations	17 (4.70)	Cardiac glycosides	6 (3.49)
Psycholeptics	10 (2.76)	Anti-inflammatory and antirheumatic products	5 (2.91)
Analgesics	9 (2.49)	Nasal preparations	4 (2.33)
Drugs for Functional Gastrointestinal Disorders	7 (1.93)	Psycholeptics	4 (2.33)

Table 6 lists factors that may be related with the presence of pDDIs.

Table 6. The relationship between various factors and the determination of pDDIs

Factors	**The roup that at least one pDDI was encountered (n=35)**	**The group that no pDDI was encountered (n=16)**	***p* value**
Age (months) [median (min-max)]	18.00 (8.00 – 43.50)	72.00 (9.50 – 99.00)	0.324[a]
Sex n (%)			0.485[b]
Male	16 (45.71)	9 (56.25)	
Female	19 (54.29)	7 (43.75)	
The duration of hospitalization (days) [median (min-max)]	7.00 (5.50 – 11.50)	6.50 (5.00 – 8.00)	0.194[a]
Concomitant usage of at least 5 different systemic drugs n (%)	28 (80.00)	3 (18.75)	<0.001[b]

[a]Mann-Whitney U test [b]Chi-squared test

The concordance rate between the UpToDate® and Micromedex® databases was 84.31% in terms of their ability to identify pDDIs (kappa coefficient=0.676, standard error=0.102, ($p \leq 0.001$).

The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of the Micromedex® database in determining pDDIs were calculated to be 79.41%, 94.12%, 96.43%, 69.56%, and 84.31% when the UpToDate® database was assumed as the reference database. The main reason we assume the UpToDate® database as a reference is that it categorizes drug interactions into risk rating categories and gives a higher number of drug interactions compared to the Micromedex® database.

The concordance rates between the drug interactions databases were given in Table 7.

Drug-drug interactions are major issues that require attention, as they result in prolonged hospitalizations, increased health care expenses, severe drug responses, and treatment failure. Inappropriate drug use is an important risk factor for the development of adverse reactions [9]. For this reason, pDDIs are issues that should be considered by healthcare professionals for the well-being of the patient.

In a previously conducted study, Hassanzad et al. [10] found 845 pDDIs via the Lexi-Interact® database among 176 prescriptions obtained from 176 pediatric patients. In our study, the number of pDDIs was 181 out of 473 daily medication lists obtained from 51 pediatric patients via the UpToDate® database, which was quite different from those of Hassanzad et al. The explanation of this could be our relatively small sample size. In addition, while Hassanzad et al. evaluated the prescriptions of the patients only on the second day of hospitalization, we evaluated the daily medication lists of the patients

on each day of their hospitalization. Maybe in our case, interday drug variability was lower than those of Hassanzad et al.

Table 7. The concordance rates between the UpToDate® and the Micromedex® databases in terms of the severities and documentation rates of the determined pDDIs

Parameter	Degree	Concordance Rate (%)	Kappa Coefficient	Standard Error	*p* value
The Severity of the Interaction	Minor	54.90	-0.026	0.072	0.724
	Moderate	84.31	0.689	0.098	< 0.001
	Major	74.51	0.485	0.106	< 0.001
	Contraindicated	96.08	0.646	0.233	< 0.001
Documentation Rate	Fair	88.24	0.765	0.090	< 0.001
	Good	78.43	0.571	0.107	< 0.001
	Excellent	60.78	0.071	0.082	0.355

A study which was conducted among 384 pediatric patients in a university hospital, the frequency rate of pDDIs was found as 45.8% according to the Micromedex® database [11]. In another study that employed the Micromedex® database and included all patients younger than 21 years of age hospitalized between January 2011 and December 2011 in U.S. children's hospitals, the rate of pDDIs was 49%. [4]. In our study, the frequency of pDDIs in our analysis of 51 pediatric patients was 54.9% (n=86) according to the Micromedex® database.

Getachew et al. [11] categorized pDDIs based on their mechanisms and found that the biggest proportion (50%) belonged to the pharmacokinetic group, as did our study (63.95%) according to the Micromedex® database. Tavousi et al. [12] categorised pDDIs based on their mechanisms and found that the biggest proportion belonged to the pharmacodynamic category (56.1%), as did our analysis (51.93%) according to the UpToDate® database.

In a study done by Bebitoglu et al. [12], a total of 634 pDDIs were identified in hospitalized pediatric patients over the course of one year by using Lexi-Interact database. The following were the rates of interactions based on risk rating categories: 42.7% of the interactions were in category A, 44.8% were in category B, 8.4% were in category C, and 4.1% were in category D. We found 181 pDDIs using UpToDate®. None were A, 35.36% B, 43.65% C, 19.34% D, and 1.66% X risk rating category. We observed fewer interactions than Bebitoglu et al. [13] since duration of our study was shorter.

Getachew et al. [11] found that the proportion of pDDIs with minor, moderate, and severe severity was 39%, 51%, and 10%, respectively, out of a total of 393 pDDIs according to the Micromedex® database. Ismail et al. [12] was found the minor, moderate, major and contraindicated severity rates of pDDIs as 35.4%, 41.5%, 21.9%, and 1.2%, respectively according to Micromedex® database among 260 pDDIs in pediatric patients. However, in our study the minor, moderate, major, and contraindicated severity rates were found as 3.49%, 61.63%, 30.23%, and 4.65% respectively in total 86 pDDIs according to the Micromedex® database. We think that this observed difference in the distribution of interaction severity may be due to the difference in the drugs used in the treatment of the patients and the patient profile.

Choi et al. [14] have conducted a study in 115 pediatric patients and obtained 592 pDDIs according to the Micromedex® database in 258 drug pairs. However, in our study, we found 86 pDDIs in 50 different drug pairs in 51 pediatric patients according to the Micromedex® database. The difference in the number of drug pairs can be explained by the inclusion of different drug pairs in our study.

In a study including 88 pediatric patients, the Micromedex® database identified ampicillin-amikacin as the most common drug pair causing pDDIs [15]. In another study consisting of 115 pediatric oncology patients, according to the Lexi-interact database, aminoglycosides and cephalosporines were found to be the most common drug pair causing pDDIs [16]. In our study, the most common drug pair causing pDDIs was determined as budesonide-clarithromycin according to both databases. When the

two studies are compared, it is seen that antibiotics are the drug pairs that cause the most of the interactions.

In a study including 510 pediatric patients, antimicrobials were identified as the class of drugs that caused the most severe pDDIs [13]. In another study including 124 pediatric patients, the drug groups that the most frequently associated with pDDIs have been found as nervous system drugs and antiinfectives for systemic use [3]. In our study, however, antibacterials for systemic use, antiepileptics, and drugs for obstructive airway diseases were most frequently associated with pDDIs.

The number of pDDIs increases with age and the number of prescribed drugs, especially as the number of antiepileptic and immunosuppressant drugs increases [17]. As being parallel with our study, Getachew et al. [11] found that there was a positive association between total number of drugs and the likelihood of pDDIs [11]. Although the study suggested that age had a substantial effect on the incidence of pDDIs, particularly in the 2–6 year age group [11], this was not the case in our research. Maybe this is because we have not categorized the age further. In another study, the association between the number of drugs and the number of pDDIs was analyzed, and it was shown that an increase in the total daily number of drugs was associated with an increase in the number of pDDIs in both adult and pediatric populations [17]. Also in the same study, the frequency of pDDIs which belongs to risk rating category C and D was highest among prescriptions containing 3-4 drugs [13]. In a prior study done in a pediatric intensive care unit, compared to those with <5 distinct drugs daily, those with 5–9 distinct drugs daily had 5 times higher likelihood of any pDDIs exposure, and those with ≥10 distinct drugs daily had 37 times higher likelihood of any pDDIs exposure [1]. In our study, concomitantly usage of at least 5 different systemic drugs was associated with higher occurrence of pDDIs.

Ismail et al. [12] performed logistic regression analysis to define various factors associated with the occurrence of pDDIs; the relationship between the occurrence of pDDIs and hospitalization lasting longer than five days, female sex, and use of at least five drugs were found to be statistically significant. In the present study, we observed that a one-drug increase in the overall number of drugs a patient received during hospitalization increased the likelihood of identifying pDDIs by 2.12-fold.

While the concomitant usage of at least 5 different systemic drugs was significantly affected the number of pDDIs according to the risk rating category of B, C and D of UpToDate® database; it was observed that concomitant usage of at least 5 different systemic drugs was not significantly associated with risk rating category X. This maybe a consequence of our relatively small sample size.

Tecen-Yucel et al. [18] evaluated Lexicomp, Micromedex® and Medscape databases in adult renal transplant recipients and compared the 3 databases in terms of compatibility of the severity of the interactions detected and found that minor and moderate interactions showed poor agreement, while major interactions showed mild and severe interactions showed moderate agreement. In our study, it was found that the interactions of minor severity showed poor agreement, the interactions of moderate severity showed substantial agreement, the interactions of major severity showed moderate and contraindicated interactions showed substantial agreement between Micromedex® and Lexicomp databases.

Reis et al. [6] have analyzed the accuracy of the Micromedex® and Lexi-Interact (Lexicomp) databases by assuming Stockley's Drug Interactions 8th edition as the standard for identifying drug interactions. They found sensitivity, specificity, positive predictive value and negative predictive value for Drug-reax system as 88%, 91%, 88%, 91% and for Lexi-Interact as 87%, 88%, 88%, 87%; respectively. We used the UpToDate® (Lexicomp) database as the reference standard in our study, and we discovered that the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of the Micromedex® database in terms of determining pDDIs were 79.41%, 94.12%, 96.43 %, 69.56%, and 84.51%, respectively.

Our research has some limitations. Because the study is only interested in pDDIs, more research is needed to illuminate these interactions from a clinical aspect. The study was limited to one center and a small patient population; a larger sample size is required to draw more generalizable conclusions about pDDIs.

There are numerous studies in the literature regarding assessment of pediatric pDDIs. Although patient population remains the same across these literatures, the treatment protocols may be different from each other. Hence, the pDDIs encountered are differed as well. As a result, the ability of drug

interaction databases to detect pDDIs may vary. Here in this study, we aimed to put an emphasis on this diversity seen among various drug interaction databases through a university experience. We expect that when more studies similar to the current study is published, awareness of pDDIs in vulnerable patient populations such as pediatrics will grow.

In conclusion, the active participation of clinical pharmacists in the healthcare team could aid in the determination of pDDIs. In addition, the utilization of multiple drug interaction databases may be effective in preventing the omission of a pDDI.

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AUTHOR CONTRIBUTIONS

Concept: Z.Ü.G.; Design: N.Ö.; Control: N.Ö., Z.Ü.G.; Sources: - ; Materials: - ; Data Collection and/or Processing: H.M., A.Ç.; Analysis and/or Interpretation: H.M., A.Ç.; Literature Review: H.M., A.Ç.; Manuscript Writing: H.M., A.Ç., N.Ö.; Critical Review: N.Ö., Z.Ü.G.; Other: -

CONFLICT OF INTEREST

The authors declare that there is no real, potential, or perceived conflict of interest for this article.

ETHICS COMMITTEE APPROVAL

This cross-sectional study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the ethics committee of Inonu University (25th January 2022 - No: 2022/3055).

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