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Investigation of polypharmacy and potential drug-drug interactions in a group of hospitalized pediatric patients: a single-center study

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ABSTRACT

Aims: Polypharmacy involves the use of multiple medications to manage one or more clinical conditions. This study aimed to determine the prevalence of polypharmacy and potential drug-drug interactions during hospitalizations in childhood and to investigate the nature of common interactions.

Methods: Data for this retrospective cross-sectional observational study were obtained from the hospital database records of pediatric patients admitted to the pediatric department of a university hospital during the first six months of 2020. A total of 601 pediatric prescriptions from 877 hospitalizations involving 2620 medications were examined for drug-drug interactions using the drugs.com/interaction checker tool.

Results: Of the evaluated 601 patients, 48.1% were female and 51.9% were male children. The mean age of the hospitalized patients was 4.78±5.2 years, ranging from 0 to 18 years, with a median age of 2 years. The mean length of the hospital stay was 5.5 (min 1-max 56) days. The mean number of prescribed medications per child was 4.38±2.4 (min-max 1-16). Potential interactions were identified in 49.1% of the prescriptions. The prescription rate of antimicrobial treatment for hospitalized patients was 86%, and this group had a high occurrence of major drug-drug interactions ($p<0.05$). Patients taking multiple medications had significantly longer hospital stays ($p<0.05$). Clarithromycin and ceftriaxone are among the most commonly interacting drugs.

Conclusion: The use of multiple drugs is common among hospitalized pediatric patients. There is a high risk of interaction during multiple antimicrobial treatments, especially in tertiary care hospitals. The increased risk of interactions associated with specific drug groups should prompt clinicians to make informed decisions when prescribing drugs.

Keywords: Polypharmacy, pediatrics, hospitalized patients, drug-drug interactions

INTRODUCTION

Polypharmacy, referred to as the use of multiple medications, is a concern that needs to be consistently kept in mind in pediatric practice because of its life-threatening consequences in childhood. The most significant consequence of polypharmacy is an increased risk of drug-drug interactions (DDIs), which can result in toxicity or treatment inefficacy. Using multiple medications is known to lead to medication administration errors, an increased need for emergency interventions, and extended hospital stays.[1] Therefore, it is necessary to assess the interaction risks of medications as a routine aspect of treatments that require a combination of medications. However, uncertainties related to this subject are multifaceted. The source of information regarding potential DDIs in pediatrics largely consists of data from the adult population owing to ethical, financial, and methodological limitations that restrict studies on the consequences of polypharmacy in the pediatric population.[2] While the pediatric age group is not regarded as young adults, the neonatology, infancy, childhood, and adolescence stages are distinct from each other in terms of physiological, psychological, and pharmacological aspects. Growth and development alone significantly influence pharmacology and affect every phase of drug disposition. Absorption, distribution, metabolism, elimination, pharmacodynamic components, and expected effects were not uniform across the age groups.[3]

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In addition to the limitations of clinical drug studies in pediatric populations, the lack of standardization in definitions and guidelines for pediatric polypharmacy and drug interactions necessitates further research on this subject. Data from such studies are valuable in guiding therapeutic interventions. This study aimed to investigate the prevalence of polypharmacy and evaluate drug-drug interactions in children admitted to a university hospital to illustrate the current situation and highlight the issues related to this subject.

METHODS

Ethics

This study was initiated after the decision of the Afyonkarahisar Health Sciences University Clinical Researches Local Ethics Committee (Date: 02.10.2020, Decision No: 2020/442). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Design

This was a descriptive, cross-sectional study. The data for this study were obtained through retrospective file analysis from a single center. The study was outlined following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist, which is used for reporting observational studies in Health Sciences.

Collecting Data

The study included all pediatric patients aged 0-17 years who received inpatient treatment and follow-up within the Pediatric Health and Diseases Department of Afyonkarahisar Health Sciences University Faculty of Medicine during the first six months of 2020. The sampling period of the study was determined by considering that the frequency of polypharmacy including antibiotherapy would be higher in the first 6 months of the year. Patient data were accessed by examining the hospital's information system database. Patient names were anonymized from the hospital database. The demographic information and length of stay of 877 pediatric patients hospitalized between January 1, 2020, and June 31, 2020, were analyzed, along with all medications used during their hospitalization. The investigated prescriptions were selected from the day the patients received the highest number of medications during their hospital stay.

Criteria for Inclusion and Exclusion

Daycase admissions, healthy newborn follow-ups, and patients who received volume support solely for maintaining fluid and electrolyte balance without prescription (276 patients in total) were excluded from the study. The remaining 601 patients were included and evaluated in this study. The study design is illustrated in Figure 1. Nutritional support treatments, drugs administered for radiological diagnosis, blood products used for intravenous expansion, fluids, insulin, and drugs used in topical applications were excluded from the analysis. The drugs.com database, also used in various studies, was used to evaluate drug-drug interactions.[4] A total of 601 prescriptions were evaluated using the Drugs. com/Interaction Checker tool. According to this guideline, the drug interactions of the prescriptions were classified into three categories. Drug combinations with clinically significant interactions, where avoidance of co-administration is recommended because the potential interaction risk outweighs the benefits, are classified as major interactions. Drug combinations with a moderate degree of clinical significance to be used only in specific cases are categorized as moderate interactions. Drugs with minimal clinical significance in terms of interactions, where an alternative drug or monitoring plan is recommended, are classified as drugs with minor interactions.

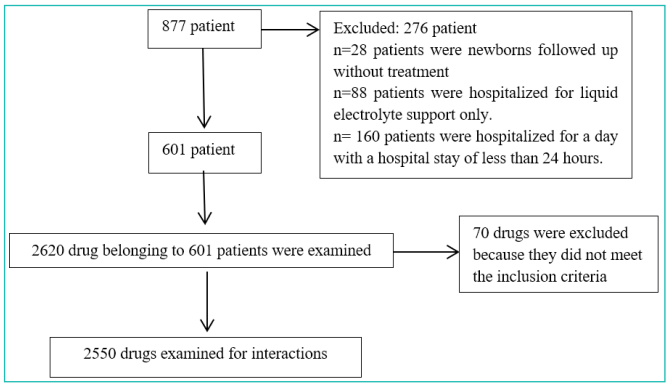

Figure 1. Inclusion and exclusion criteria for patients and prescriptions

Statistical Analysis

Statistical Package for the Social Sciences (SPSS, version 20.0; IBM Corp. 2019 IBM SPSS Armonk, NY.) was used for data analysis. The data and results of potential drug-drug interaction assessments were determined using descriptive statistics, such as mean, standard deviation, and percentage distribution. The normality distribution of the data was evaluated using the Kolmogorov-Smirnov and Shapiro-Wilk tests. The Mann-Whitney U test was used because parametric conditions could not be met for differences in the number of medications and drug-drug interactions between children receiving antibiotics and those who did not. The Chi-Square test was used to compare the percentage distributions of categorical data between the groups, while the Spearman test was used to evaluate the correlation between two continuous variables. A significance level of $p<0.05$ was adopted.

RESULTS

A total of 601 patients were evaluated, comprising 48.1% females and 51.9% males. The mean age of the hospitalized patients was 4.78±5.2 years, with an age range from 0 to 17 years and a median age of 2 years. Among the hospitalized patients, 68.9% stayed for one day, 13.8% stayed for two days, and the remaining 17.3% stayed for three or more days. As age decreased, length of hospital stay increased ($p<0.05$). No significant relationship was found between age and number of prescribed medications ($p>0.05$). A total of 2.3% of patients were admitted to the hospital seven times within six months. The mean length of the hospital stay was 5.5 days. The mean number of prescribed medications during hospitalization was 4.38±2.4 medications per child. years (Table 1). In terms of the number of medications, 97% of the patients were prescribed at least two medications. The percentage of patients who received four or more medications was 56.4%. The distribution of the number of medications used is shown in Figure 2. Of the 2,620 medications from the 601 evaluated prescriptions, 2,550 met the criteria and were evaluated for potential drug-drug interactions.

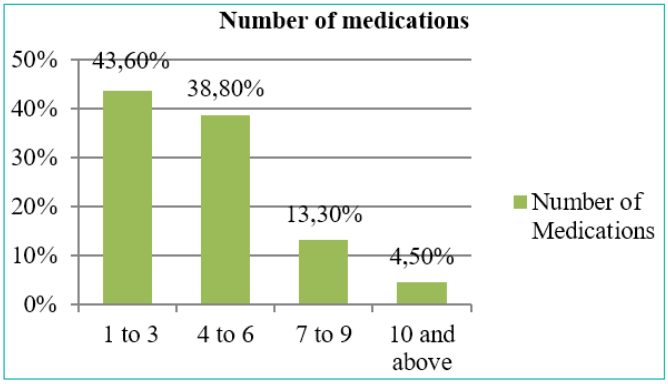

Figure 2. The distribution of the number of medications

Of all the prescriptions given to hospitalized patients, 85.5% contained at least one antibiotic. When evaluating all medications administered to hospitalized children, 34% consisted of antibiotics. Third-generation cephalosporins are the most commonly prescribed antibiotics. Specifically, cefotaxime (23.5%), ceftriaxone (23.1%), clarithromycin (16.7%), metronidazole (7.9%), amikacin (7.2%), meropenem (6.3%), vancomycin (4.1%), and other antibiotics (11.2%) were prescribed in the descending order. Within the scope of this study, the most frequently prescribed non-antibiotic drugs were paracetamol, ibuprofen, methylprednisolone, midazolam, phenobarbital, esomeprazole, levetiracetam, salbutamol, and budesonide.

A total of 49.1% of the prescriptions exhibited drug-drug interactions. Among prescriptions, 20.5% had major interactions, 43.6% had moderate interactions, and 29.8% had minor interactions. Among the 601 prescriptions, the total number of potential drug-drug interactions per patient demonstrated a significant relationship with the length of hospital stay and presence of antibiotics within the prescription ($p<0.05$). During hospitalization, the maximum interaction was found in a patient with 39 potential DDIs, and the highest number of active ingredients administered to a single patient in one day was 14 (min-max=0-39). The average number of DDIs was 2.1±3.1. A significantly higher potential interaction rate was found for prescriptions containing antibiotics ($p<0.05$). As age decreased, the number of potential drug-drug interactions increased ($p<0.05$). Strong positive ($r=0.716$) and significant ($p<0.05$) relationships were found between the number of drugs and risk of interaction (Table 2).

Table 1. Descriptive statistics and chi-square / Mann-Whitney U-test and Spearman's rho results at hospitalized children

	Variables	Drug drug interaction n(%) Yes 295(49.1) No 306(50.9)	Number of potential interactions Mean (SD) 2.1(3.7) Median (IQR) 0 (3) Min, Max 0.39
Gender	Female n(%) 289 (48.1%) Male 312 (51.9%)	p>0.05*	p>0.05**
Age (year)	Mean (SD) 4.7(5.2) Median (IQR) 2(8) Min, Max 0.17	p<0.05**	p<0.05***
Hospital stay (day)	Mean (SD) 5.07(5.2) Median (IQR) 4(4) Min, Max 1-5	p<0.05**	p<0.05***
Number of drugs	Mean (SD) 4.48(2.4) Median (IQR) 4(3) Min, Max 1.16	p<0.05**	p<0.05***
Number of prescriptions for antibiotics	Yes n(%) 514(85.5) No 87 (14.5)	p<0.05*	p<0.05**
	Total 601		

*: p: chi-square ($\chi 2$) p value; **p : MannWhitney U test p value; p***:Spearman's rho p value

Table 2. Relationship between age, number of medication and potential drug-drug interaction

		Potantial drug drug interaction
Age	Spearman's rho	-.189*
	p	0.000
	n	601
Number of medication	Spearman's rho	.716*
	p	0.000
	N	601

Corelation is signifficant at the 0.01 level*

DISCUSSION

Hospitals are establishments that provide inpatient healthcare services and are characterized by the management of complex and challenging cases, often involving lengthy hospital stays. Therefore, the use of multiple medications is inevitable for many patients.[5,6] Polypharmacy was initially defined in the mid-20th century as the extensive use of several medications. While there is currently no universal consensus regarding a definitive cut-off number, the literature includes definitions such as using two or more medications, four or more medications, or five or more medications for a minimum of 240 days. Although polypharmacy is commonly encountered in the geriatric population, it is also prevalent among pediatric patients admitted to clinical settings.[7] In a study conducted in Turkiye that analyzed the active ingredients used by all hospitalized patients for a month, it was found that the average number of active ingredients per pediatric patient was 19.30±22.10.[8] There is no clear consensus regarding the definition of pediatric polypharmacy. In addition to pediatric studies that apply known polypharmacy criteria from the literature, there are also studies suggesting that the simultaneous use of two or more medications for at least one day, considering the lower burden of chronic diseases in children than in adults, could be considered as a criterion.[9] Due to variations in clinical conditions and definitions, the prevalence of polypharmacy ranges widely from 18% to 100%.[10] In this study, when the use of four or more medications was defined as a criterion, it was determined that the polypharmacy rate among hospitalized patients was approximately 56%. Numerous studies have also demonstrated that children with identified polypharmacy tend to have longer hospital stay. Polypharmacy has been explored as an independent risk factor for morbidity, mortality, and hospitalization, and its predictive value has been examined in several studies.[11,12] Determining the rates of polypharmacy among hospitalized children is significant for revealing preventable potential drug interactions and identifying the risks of side effects associated with multiple drug use.[13] While studies have suggested a higher prevalence of polypharmacy in early childhood, no such correlation was found in this study.[14]

Drug-drug interactions are defined as the occurrence of an increased or decreased effect that occurs outside the anticipated effect when at least two drugs are used concomitantly. This can complicate the clinical process and potentially lead to drug toxicity or reduced efficacy. Side effects tend to be more evident and dramatic as they present more noticeable manifestations. Studies have shown that the potential risk of side effects when using two drugs is approximately 6%, whereas this rate increases to 50% when using five drugs and nearly 100% when using eight or more drugs.[15]

This study observed that one of every two prescriptions demonstrated at least one potential risk associated with drug-drug interactions. The frequency of exposure to drugs that have a drug-drug interaction (DDI) and the frequency of related adverse effects are poorly understood. Different outcomes can also be observed in the literature.[16] This difference between studies on pediatric polypharmacy is due to many differences in sample size, age, patient groups, polypharmacy, and analysis criteria. There are also studies in the literature in which some modeling is proposed to minimize the variability related to study designs. In a methodological study, Zheng et al.[17] underlined the need for standardization to determine prevalence rates despite the existence of numerous studies investigating drug-drug interactions. Just as critical as these differences are, the potential risk of drug-drug interaction is greater than apparent due to physiological changes related to pediatric age and the potential confounding effects of the current disease and the drugs used.[18]

According to recent data, a retrospective data analysis study using the Pediatric Health Information System (PHIS) database, which included data from 498,956 hospitalized children from 43 different hospitals, found that 49% of hospitalizations in hospitalized pediatric patients were associated with ≥1 potential DDI.[19] Similar results were obtained in a study conducted by Daignault et al.[20] When we compare the results of our study, we can conclude that they are compatible with the intervals stated in the literature.

This study was based on a patient sample from a regional hospital unit with a high prevalence of infectious diseases and lower respiratory tract infections, particularly during months when complex cases are frequent, resulting in a high rate of antibiotic usage. Research conducted in Turkiye has indicated varying prevalence of antibiotic usage in pediatric hospitals, ranging from 30% to 80%.[21,22]

Upon examining frequently observed interactions in this study, certain antibiotics associated with major side effects were found to be responsible for this rate, especially clarithromycin, which strongly inhibits the CYP450 3A4 microsomal enzyme. This

inhibition can lead to increased blood concentrations of the co-administered drugs, resulting in toxicity.[23] During winter, when there is an increased incidence of lower respiratory tract infections, careful monitoring is recommended for signs and symptoms of hypercortisolism due to enhanced systemic absorption when using the inhaler budesonide with clarithromycin. Adrenal and immunosuppressive effects in children and adolescents, along with ocular manifestations, such as glaucoma and cataracts, as well as growth and developmental issues, should be closely observed. The literature reports cases of secondary Cushing's syndrome associated with this combination. In cases where combined use is unavoidable, dose intervals should be widened, and an alternative with lower lipophilicity and shorter half-life, such as beclomethasone, should be considered.[24,25]

The frequency of combinations involving clarithromycin with drugs such as methylprednisolone, digoxin, midazolam, and colchicine is noteworthy, considering the potential for specific toxic manifestations of the affected drug to emerge.[26]

Another major risk factor was an increase in nephrotoxicity risk during the concomitant or sequential use of cephalosporins, one of the most commonly used antibiotic therapies, with a second nephrotoxic agent. Monitoring renal function is important for the combined use of amikacin, vancomycin, acyclovir, and furosemide with cefotaxime and ceftriaxone.[27]

The co-administration of ceftriaxone and furosemide has a hypokalemic effect, and prolonged use of proton pump inhibitors with furosemide can lead to hypomagnesemia-related fluid and electrolyte imbalances, which should not be overlooked.[28]

A point-prevalence study conducted in a Turkish pediatric clinic to investigate the prevalence of inappropriate drug use reported that clarithromycin and ceftriaxone were the most commonly used antibiotics.[21] Although not examined in this study, considering the rates of potential interaction risks, further studies on the necessity of using these two drugs could be the subject of another research endeavor.

In cases of co-administration of aminoglycoside derivatives and nonsteroidal anti-inflammatory drugs (NSAIDs), especially during the treatment of patent ductus arteriosus using ibuprofen or indomethacin along with amikacin, renal damage and electrolyte balance should be monitored. A study examining the hospitalization data of 107 neonatal infants revealed that infants were exposed to a nephrotoxic agent every six days on average.[29] Another study that identified polypharmacy and potential interactions between antiepileptics and cardiovascular drugs emphasized the importance of avoiding therapeutic duplications.[30]

Limitations

The limitation of this study lies in the fact that knowledge about evidence-based pediatric drug interactions is largely derived from studies conducted on adults, and the effects of drugs in specific age groups of children are yet to be established through well-documented research. Therefore, there is a need for more pediatric pharmacokinetic studies, and more research is required to determine the clinical significance of theoretically identified interactions.[31,32]

Drugs with a narrow therapeutic index should be administered similar to those that result in harmful consequences. Small amount of dosage beyond this range. However, this may occasionally result in toxic effects. It is essential to recognize the increased chances of drug interactions when taking various medications. Renal function and serum drug concentrations should be monitored if patients being treated in hospitals are simultaneously taking medications, such as vancomycin, aminoglycosides, and phenytoin.[33]

Research conducted on clinicians' awareness of polypharmacy and potential interactions, as shown in Zapata et al.'s[34] extensive review of 34 studies covering a wide geographical area, indicated that alerts and reminders regarding drug interactions are often overlooked by clinicians, ranging from 58% to 98%.

It is necessary for potential interactions to have a level of evidence that prompts clinicians to take action, and for physicians managing polypharmacy to be well-versed in alternative preventive solutions before interactions occur. Increasing the visibility of drug-drug interaction pharmacovigilance data and developing programmes based on artificial intelligence technology in the clinic can be recommended to reduce risks. The use of technologies that support clinical decision-making and the determination of their contribution to the solution may be the subject of another study.[35]

CONCLUSION

Polypharmacy is common among hospitalized pediatric patients, particularly in tertiary care hospitals where the use of multiple antibiotics increases the risk of potential interactions. Elevated interaction risks within specific drug groups should prompt clinicians to make informed decisions when prescribing these drugs. Pediatric hospitalized patients should have their complete therapeutic regimen optimized by considering potential drug-drug interactions and using antibiotics more effectively.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Afyonkarahisar Health Sciences University Clinical Researches Local Ethics Committee (Date: 02.10.2020, Decision No: 2020/442).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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