Original Article

Comparison of the Incidence of Suspected Adverse Events of Commonly Prescribed Selected Drugs between Paediatric and Adult Hospitalized Patients

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Abstract

Background: *Adverse drug events (ADE) are major health problems that occur in children and adults. Some drugs are commonly prescribed in both paediatric and adult patients and safety of these drugs is a major concern. The active monitoring system is more practical for obtaining detailed data on individual adverse event reports than a passive reporting system. This study aimed at the detection of suspected adverse events (SAE) in paediatric and adult hospitalized patients by active monitoring, to find out is there any difference in the incidence of SAE between these two age group populations.* ***Materials and Methods:*** *At first through the cross-sectional study, three commonly prescribed drugs, ceftriaxone, prednisolone, and paracetamol, were identified. Based on inclusion and exclusion criteria, 219 paediatric and 234 adult patients were enrolled. Then, a prospective observational study was conducted based on a solicited adverse event list to determine the SAE of these drugs among paediatric and adult hospitalized patients.* ***Results:*** *After active monitoring of all enrolled patients by maintaining an adverse event checklist, 7.8% of paediatric patients and 5.02% of adult patients experience SAE. In the case of ceftriaxone, paediatric patients (11.26%) experience more SAE than adult patients (7.05%). In paracetamol, no adult patient experience SAE. In prednisolone, the SAE detection rate is almost similar in both adults (6.02%) and paediatric patients (4.93%). By WHO-UMC causality categories, 20% were certainly ADEs, 40% were probable/likely and 40% were possible ADEs in paediatric patients treated with ceftriaxone. On the other hand, one third of the cases were certain and the remaining had possible relationships with the drug in adult patients. In the case of prednisolone, 75% of adverse events were mild and possible event. In paracetamol, 1.4% of paediatric patients experienced ADE which was a possible reaction and mild in severity. In this study, there is no statistically significant difference in ADE detection rate in both paediatric and adult patients. However, there is an overall increase in ADE detection rate in paediatric patients.* ***Conclusion:*** *The adverse event detection rate of commonly prescribed drugs was higher in paediatric hospitalized patients compared to adult patients through the active monitoring method.*

Keywords: Suspected adverse event, Solicited adverse event, Paediatric patients, Adult patients.
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Introduction

Adverse drug events (ADE) are one of the healthcare problems that may result in temporary or permanent harm and an increase in healthcare costs[1]. The incidence of ADRs has remained relatively stable over time, with research indicating that 5% to 10% of patients may experience an ADR upon admission, during admission, or after admission despite various preventative measures[2]. In some countries, ADR is one of the top 10 leading causes of mortality[3]. About 5% of all hospital admission to children is due to ADR[4]. Several studies established that hospitalized children are at risk of suffering from ADR significantly[5, 6].

Spontaneous reporting of adverse drug reactions (ADRs) is fundamental to pharmacovigilance[7]. However, underreporting of ADRs remains a global issue, as highlighted by numerous international studies[8,9]. Data on drug efficacy and tolerability, as well as information on ADRs in children, are frequently lacking, in part because drug administration authorities and the pharmaceutical

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industry have ignored routine drug evaluation in patients of the paediatric age group[10].

According to the WHO Global Individual Case Safety Report (ICSR) database (VigiBase), 7.7% of children aged 0 to 17 years experienced ADRs[11]. VigiAccess shows that there is a difference in the ADR reporting rate of some commonly prescribed drugs in the paediatric age group compared to the worldwide adult population. However, these figures appear underestimated, as other studies stated a higher risk of ADRs in children[12,13]. It is necessary to provide beneficial techniques that can identify ADRs in the paediatric population at an early stage[14]. Active monitoring uses a continuous, pre-planned approach to fully ascertain the number of undesirable events. Suspected ADRs are generally underreported especially in reports for children with rare diseases or drugs not commonly used for these age groups[11].

Adverse event detection, management, and reporting are key to the success of the pharmacovigilance program[15]. Paediatric pharmacovigilance activities must be strengthened by encouraging spontaneous reports from paediatricians and active post-marketing surveillance[13]. To improve SAE detection, these activities need to be promoted in the hospital's paediatric services. Studies addressing ADR monitoring activities such as active monitoring are scarce in Bangladesh, especially related to hospitalized paediatric patients. The purpose of the study was to detect and evaluate the SAEs in hospitalized adult and paediatric patients in a tertiary care hospital in our country by active monitoring to improve medication safety.

Materials and Methods

The study was a prospective observational study. Ethical clearance of the study was received from the Institutional Review Board (IRB) of Bangabandhu Sheikh Mujib Medical University (BSMMU) (BSMMU/2022/785). Three drugs that are commonly prescribed to paediatric and adult hospitalized patients were selected through a questionnaire survey. The drugs were ceftriaxone, prednisolone, and paracetamol. The study was conducted in BSMMU from March 2021 to January 2023.

The study population was the indoor patients of paediatric and adult departments who were treated with Ceftriaxone, Prednisolone, and Paracetamol. Among all patients, 152 patients were treated with paracetamol, 92 patients were treated with ceftriaxone, and 87 patients were treated with prednisolone in each paediatric and adult site. A solicited adverse event list was prepared for each of the three drugs. Ten solicited adverse events are selected separately for each of the three drugs that are frequently reported to VigiAccess and easily detectable.

Informed consent was obtained in the case of adult patients, and informed assent with parental consent was taken in the case of paediatric patients. Then, inpatient data regarding the patient, disease, and treatment were documented in the data collection sheet. Each patient was monitored every day, and solicited adverse events were identified through the predesigned structured checklist. Unsolicited adverse events were identified through open questions about the onset of new signs/symptoms after admission.

According to the guide of WHO "Safety of Medicines – A guide to detecting and reporting adverse drug reactions," the following stepwise approach helps assess possible drug-related adverse events. Confirm that the prescribed medication was the one actually received and taken by the patient or administered by the nurse as instructed. Ensure that the suspected adverse event occurred after the drug was administered, not prior to its use. Determine the time interval between the beginning of the drug treatment and the onset of the event.

For each patient with a suspected adverse event, detailed information including personal information, suspected adverse event information, present and past medical history, history of previous drug allergy, and other concomitant medicine information were documented in the suspected adverse event review form which was prepared according to the 'Instructions for completing suspected Adverse Event Reporting Form' by Directorate General of Drug Administration of Bangladesh.

The relationship between the adverse events and drugs was categorized as certain, probable, possible, unlikely, conditional/unclassified, or unaccessible/ unclassifiable. All of the detected suspected adverse events were reported to the DGDA through online and offline ADR submission forms by the investigator. Statistical analysis was done with the frequency and percentage. An appropriate statistical test was used to conclude. Statistical analysis was done with Microsoft Office Excel.

Results

Demographic characteristics of the patient show that a total of 424 patients enrolled in the study. Among paediatric patients' majority (51.21%) children were from school age (6-12 years old) with the mean age of the paediatric patients being 9.79±3.98 years (Figure-1). Among adult patients above 28% were from >51-year-old age group, with the mean age of the adult patients being 41.65±14.85 years (Figure-

2). Among paediatric patients approximately 56% of study subjects were male and the rest were female. Among adult patients about 52% were male and 47% were female patients (Table-I).

Out of 424 patients, only 27 (6.36%) exhibited adverse events. More adverse events are detected in children and that is 7.80%. Out of all, 2 (0.72%), 16 (9.52%), and 9 (5.69%) were respectively from patients who got paracetamol, ceftriaxone, and prednisolone. Paediatric patients who got ceftriaxone exhibited more adverse events which were 10 (11.90%) than those adults 6 (7.14%) (Table-II).

In the case of paediatric patients, according to the WHO-UMC Causality Categories 2 (20%) of adverse events cases were certain events, 4 (40%) probable and 4 (40%) possible events. On the other hand, in the case of adult patients, 2 (33.33%) of adverse events were certain events and 4 (66.66%) were possible events. In the case of prednisolone, 75% are possible adverse events in the case of paediatrics, and among children, 60% are possible reactions (Table-III).

Table-IV shows the treatment of detected cases of adverse events of ceftriaxone and its outcome. In the case of paediatric patients, all the ten adverse events were treated. In 4 (40%) cases, ceftriaxone stopped, and the reaction subsided after stopping the drug. Out of these 4 in 1 (10%) cases, ceftriaxone was reintroduced, and the reaction reappeared after reintroduction. All the cases were recovered. In the case of adult patients, all the cases were treated. In 2 (33%) cases ceftriaxone stopped and the reaction subsided after stopping the drug. Then again ceftriaxone was reintroduced in these 2 cases, and the reaction reappeared.

Table-V shows the association of ADE detection with paediatric and adult age groups. There is no significant association of ADE detection rate between paediatric and adult age group patients.

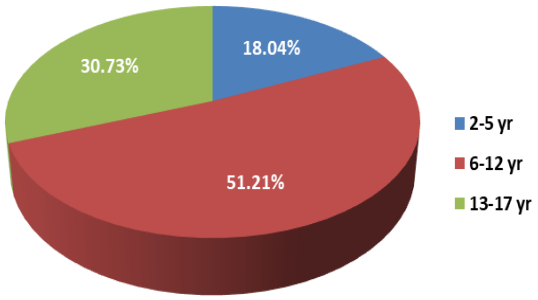

Figure-1: Pie diagram shows the distribution of paediatric patients according to age in the study cases

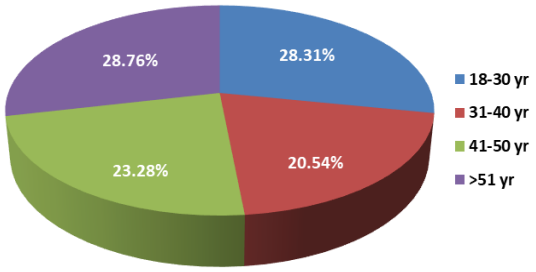

Figure-2: Pie diagram shows the distribution of adult patients according to age in the study cases

Table-I: Distribution of patients by their gender (n=424)

Characteristics	Gender	Frequency (%)
Paediatric patient (n=205)	Male Female	115 (56.09) 90 (43.90)
Adult patient (n=219)	Male Female	116 (52.96) 103 (47.03)

Table-II: Distribution of patients by their suspected adverse events

Characteristics	Number of Cases	Frequency of adverse events	Percentage (%)
Total participant's	424	27	6.36
Paediatric patient	205	16	7.80
Adult patient	219	11	5.02
Adverse event of specific drug			
Paracetamol	284	2	0.70
Paediatric patient	142	2	1.4
Adult patient	142	0	0.00
Ceftriaxone	173	16	9.24
Paediatric patient	88	10	11.36
Adult patient	85	6	7.05
Prednisolone	164	9	5.48
Paediatric patient	81	4	4.93
Adult patient	83	5	6.02

Table-III: Causality assessment of the detected adverse events

Name of the Drug	Age group of patients	WHO-UMC Causality categories					
		Certain	Probable	Possible	Unlikely	Unclassifiable	Unclassified
Ceftriaxone	Paediatric (n=10)	2	4	4	0	0	0
	Adult (n=06)	2	0	4	0	0	0
Prednisolone	Paediatric (n=04)	0	1	3	0	0	0
	Adult (n=05)	0	2	3	0	0	0
Paracetamol	Paediatric (n=02)	0	0	2	0	0	0
	Adult (n=00)	0	0	0	0	0	0

Table-IV: Treatment of detected cases of adverse events of selected drugs and its outcome

Drugs	Age group of patients	Adverse event treated	Action taken after the reaction		
			Drug dose stopped/ reduced	Reaction subsided after stopping the drug	Reaction reappears after reintroduction of the drug
Ceftriaxone	Paediatric (n=10)	10	4	4	1
	Adult (n=6)	5	2	2	2
Prednisolone	Paediatric (n=4)	4	1	1	0
	Adult (n=5)	5	2	2	0
Paracetamol	Paediatric (n=2)	2	0	0	0
	Adult (n=0)	0	0	0	0

Table-V: Association of detection of adverse events of specific drug with paediatric and adult patient

Drug name	Age group of patients	Detection of ADE		p-value
		Yes	No	
Ceftriaxone	Paediatric (n=88)	10	78	0.131
	Adult (n=85)	6	79	
Prednisolone	Paediatric (n= 81)	4	77	0.760
	Adult (n=83)	5	78	
Paracetamol	Paediatric (n=142)	2	140	0.155
	Adult (n=142)	0	142	

p-value obtained from $\chi 2$-test

Discussion

In this prospective observational study suspected adverse events of ceftriaxone, paracetamol, and prednisolone were detected through active monitoring. After active monitoring, it was found that the most common drug causing an adverse reaction in the index study was ceftriaxone, with similar findings found in other studies[16,17]. The incidence of the suspected adverse event of ceftriaxone in paediatric patients (11.36%), was higher than that found in the case of an adult patient (7.05%). Similar findings were found in the study conducted in Romania[18], where enrolled patients were also monitored by active monitoring. The higher detection rate in the index study may be due to the methodology applied as active monitoring of patients done by maintaining a solicited checklist. That study also emphasizes the importance of closely monitoring antibiotic-associated adverse drug reactions in the paediatric population[18].

This study reveals 9 (5.69%) adverse events of prednisolone among paediatric and adult patients. Among the enrolled patients, the incidence of the adverse event of prednisolone in paediatric patients (5.06%) is less than that detected in an adult patient (6.32%). In our study, the ADE detection rate in adult and paediatric patients is almost similar. Though the long-term complications of chronic corticosteroid use are well known, clinical data on the potential short-term adverse effects of corticosteroid use are lacking[19]. Among these, a fourth of the adverse events in the child have a possible causal relationship with the drug and are mild in severity.

Paracetamol is one of the most widely used medicines in both children and adults as over the counter and also as prescribed medicine. The safety issue of paracetamol is mostly associated with long-term usage and overdose of paracetamol[20]. In this study, 1.4% of adverse events detected among paediatric patients, all of them are possible reactions and are mild in severity. Adverse events of paracetamol are less detected in this study. It may be due to the adverse events that cannot be differentiated from the clinical manifestation of the disease. When taken in the recommended doses, paracetamol has a well-known safety profile. Overdose, on the other hand, may result in liver

damage[21]. Paediatricians could play a key role in recognizing, evaluating, monitoring, communicating, and documenting ADRs[22]. Active monitoring after starting treatment and remembering the solicited adverse events can be a good method for the detection of adverse events in paediatric patients.

Limitations

The study does not include patients of less than 2 years of age, and patients admitted to the emergency department, NICU, or ICU. In this study, adverse events of only three drugs were detected, which did not show the generalized scenario of adverse events in the hospitalized patient. The study was conducted by the investigator only, teamwork of internists, paediatricians, and pharmacologists could play a better role in this type of study. Adverse events might be underdiagnosed in the paediatric population due to difficulties in differentiating clinical manifestations of disease from adverse events.

Conclusion

The adverse event detection rate of commonly prescribed drugs was higher in paediatric hospitalized patients compared to adult patients through the active monitoring method underscoring the importance of age-specific pharmacovigilance strategies.

Recommendations

A further larger scale, longer-duration study on ADE detection is recommended to determine whether the occurrence of ADE is higher in paediatric patients than adult hospitalized patients.

Consequently, measures should be taken to ensure active monitoring of all hospitalized patients, especially in the case of paediatric patients to recognize, evaluate, monitor, and document ADRs.

Conflict of interest

The authors declared that they have no conflicts of interest.

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