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Clinical Study

Pediatric hospital admission due to adverse drug reactions: Report from a tertiary center

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ABSTRACT

Objective: Adverse drug reactions (ADRs) are known as a cause of hospital admission. We have carried out a prospective study to characterize and assess the frequency, probability, preventability, and severity of ADRs, which lead to hospital admission in children.

Methods: In a prospective observational study, a cohort of children admitted to a tertiary pediatric hospital was randomly screened to assess ADR as the cause of admission from June 2014 to January 2015. ADRs causing admissions were detected based on patients' records, interviewing their parents, and confirmation by medical team. The probability of the ADRs was assessed based on WHO criteria and Naranjo tool. The preventability assessment was performed using Schumock and Thornton questionnaire.

Findings: Of the 658 evaluated emergency admissions, 27 were caused by an ADR giving an incidence of 4.1%. Among ADRs, 37.1% were estimated to be preventable. Antibiotics were the most common medication class which caused hospital admission.

Conclusion: Pediatric pharmacotherapy still needs evidence-based strategies to improve child care including education, monitoring, planning for medications after ADR occurrence, and implementing preventive measures when applicable.

Keywords: Adverse drug reaction; children; hospitalization; incidence

INTRODUCTION

Adverse drug reactions (ADRs) are reported to be a cause of hospital admission in adult as well as pediatric population,[1-7] thus, far incurring an important public health problem. The studies in children have reported the various incidences of ADR-related hospitalizations. Moreover, various drug classes, different organ systems, and clinical presentations are frequently reported.[5-7] In light of ADR-related hospitalization incidence, a systematic review performed in 2001 elucidated weighted average of 2.09%.[8] Likewise, a systematic review in 2012 demonstrated a pooled estimate incidence of 2.9%.[9] A prospective observational study conducted in the Czech Republic illustrated an incidence of 2.2% of pediatric hospital admissions.[6] However, to the authors' knowledge, there is no study evaluating ADRs causing admission in the pediatric population in Iran. Thus, in a prospective manner, we sought to determine the frequency, preventability, severity, and causality of these reactions. The secondary outcome was to characterize the pattern of ADRs.

METHODS

This prospective observational study was conducted in the emergency ward of a referral tertiary level

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hospital, the Children's Medical Center, Tehran University of Medical Sciences between June 2014 and January 2015. A cohort of pediatric patients (≤18 years) admitted was randomly screened in order to assess ADR as the cause of admission. ADR was defined according to Edwards and Aronson.[10]

Exclusion criteria were as following: Hospitalization period <6 h, drug overdoses, and drug consumption due to suicide and hospitalization due to medication error. We excluded ADRs that resulted in patient hospitalization of <6 h according to Gallagher *et al*. study methodology[7,11] in order to identify more severe reactions. Gallagher *et al*. illustrated incidence of admissions leading to early discharge are lower and less severe than the main ward admissions.[7,11]

ADRs were identified by reviewing patients' records, interviewing their parents, and confirmation by treating pediatrician and the research pharmacist. Whenever an ADR was detected, the pharmacist recorded demographic data, patient diagnosis, age, gender, concurrent medications, allergies, medication history, medical history, laboratory tests, and filled the national yellow form for ADRs. Medication history comprised any medication taken within the 4 weeks prior to admission. The pharmacist also followed up the patients during hospitalization to monitor the outcome.

The severity of ADR was defined as those causing death, life-threatening, or causing hospital admission.[12] Causality assessment was performed by using Naranjo score[13] and WHO criteria for causality assessment.[12] Preventability was determined by Schumock and Thornton questionnaire.[14]

RESULTS

In total, 7909 children were admitted during 6 months study period. A total of 752 nonsuccessive admissions were evaluated, of which 658 fulfilled the eligibility criteria to be screened for ADRs as the reason of admission. Overall, 48 ADRs were seen in 27 patients including 11 females and 16 males. Two of 27 patient admissions were exposed to cancer chemotherapy (7.4%). Mean ± standard deviation age of participants was 40.6 ± 36 months.

The incidence of hospital admission due to ADRs was 4.1% (27/658). Most adverse reactions were detected in the children < 1-year old. Based on study definition, all ADRs considered to be severe because of hospital attendance; however, all patients recovered without a sequel. According to Schumock and Thornton questionnaire, 37.1% of ADRs were preventable.

The WHO causality assessment of ADRs revealed that 33.3% of ADRs were detected as certain, followed by 48.2% as probable, and 18.5% as possible. Causality assessed by Naranjo algorithm illuminated 3.7% as definite, 85.2% as probable, and 11.1% as possible.

Table 1: Drug classes implicated in causing ADRs in the study population

Drug classes	Number (%) of ADRs
Anti-infective agents	10 (37)
Central nervous system agents	6 (22.2)
Serums, toxoids, and vaccines	5 (18.5)
Antineoplastic agents	3 (11.2)
Miscellaneous therapeutic agents*	2 (7.4)
Antihistamine drugs	1 (3.7)
Total	27 (100)

*Miscellaneous therapeutic agents included citicolin. ADRs=Adverse drug reactions

Table 2: System-organ classes implicated in causing ADRs in the study population

Organ of reaction	Number (%) of ADRs
Skin and appendages disorders	19 (39.6)
Gastro-intestinal system disorders	13 (27.1)
Body as a whole/general disorders	5 (10.4)
Central and peripheral nervous system disorders	4 (8.4)
Respiratory system disorders	3 (6.2)
Psychiatric disorders	2 (4.2)
White cell and RES disorders	1 (2)
Platelet, bleeding and clotting disorders	1 (2)
Total	48 (100)

ADRs=Adverse drug reactions, RES=Reticuloendothelial system

The most frequent and the highest number of ADRs occurred with cefixime (5 patients), 9 (18.8%) of ADRs, followed by phenobarbital (4 patients), 4 (8.3%) of ADRs. Drug classes implicated in ADRs are shown in Table 1.

The majority of system-organ classes are shown in Table 2, depicting skin and appendages disorders (39.6%) and gastrointestinal systems (27.1%) being the two most frequently involved organs. Maculopapular rashes (12.5%), diarrhea (12.5%), and vomiting (10.4%) were the most frequent clinical complications.

DISCUSSION

To the authors' knowledge, this is the first study reporting pediatric ADR-related admissions in Iran. In the present study, we determined to have an incidence of 4% ADR-related admissions.

A systematic review and meta-analysis of 17 prospective studies elucidated the rate of pediatric admissions due to ADRs ranges from 0.59% to 4.1% with the weighted average of 2.09%.[8] Easton *et al*.[15] evaluated a broader set of 8 categories of drug-related

problems (DRPs), one of which included ADR. The authors reported 4.3% hospital admissions due to DRPs in children with <25% of them being ADRs.

Gallagher *et al*.[7] conducted a study in the UK to ascertain the occurrence of ADRs causing hospital attendance in children and illustrated an incidence of 2.9% over the 1-year period. The other study conducted earlier by Gallagher *et al*.[11] reported the estimated incidence of 4% hospital admissions. However, the primary outcome of the study was to develop a methodology of such trials. Langerova *et al*. illuminated that 2.2% of pediatric hospital admissions were caused by an ADR.[6] A systematic review in 2012 by Smyth *et al*. demonstrated a range of 0.4% to 10.3% incidence rate for ADRs causing hospital attendance, with a pooled estimate of 2.9%.[9] However, after excluding an outlier, Smyth *et al*. reported a reduction in hospital admission incidence rate to 0.4% to 4%.[9] Another trial performed by Posthumus *et al*.[5] reported 6.9% ADR-related acute admissions in children. Of note, the majority of the participants comprised pediatric undergoing cancer chemotherapy.[5]

Of note, exposure to cancer chemotherapy agents has been demonstrated to be a risk factor for ADR occurrence. The studies with a high proportion of oncology participants have a higher ADR incidence rate.[5,7]

We observed an incidence of 4% ADR-related admissions. Putting together, by considering that children exposed to cancer chemotherapy agents compromised a limited number in the present study, it seems ADRs-related acute hospital admissions are in the upper limit. This high incidence calls for the need for implementation of pediatric pharmacovigilance.

The results of our study depicted that ADRs were more detected in the children <1-year old, which is in line with the previous trials showing a higher incidence during the 1st year of life.[16]

In the present study, we detected 37.1% of ADRs as preventable. In studies on children population, preventability of ADRs has noted to be between 33% and 51.3%.[5]

To relate an ADR to a medication, it has been stated to encompass certain (definite), probable and possible probabilities into the total number of ADRs.[6] In the present study, the most of the ADRs were determined to be in the definite and probable category and all of the ADRs were in the certain (definite), probable, and possible probabilities by WHO and Naranjo algorithm as well.

In this study, anti-infective agents were the most class of drugs caused ADRs (proportion of 37%). In a systematic review by Smyth *et al*. in children,[9] anti-infectives determined to be the most prevalent drug class involved in the three settings: ADRs causing admission, ADRs occurring during hospital stay, and ADRs within the community. Smyth *et al*. reported anti-infectives were responsible for 3.5–66.6% of ADRs causing admission.[9] Anti-cancers, immunosuppressants, vaccines, anti-epileptics, and nonsteroidal anti-inflammatory drugs (NSAIDs) are also frequently reported drug classes in causing admissions, reflecting prescribing practices in various settings.[7,9,11] Likewise, studies in which oncology patients constituted the majority of participants,[6,7] anti-cancer medications reported to be the most common drug class contributing to ADR-related admissions.

In the adult population, however, cardiovascular drugs and NSAIDs are commonly implicated in causing hospital admissions.[1,2] In accordance with these results, it has been demonstrated that ADRs are different in children to those in adults in terms of drugs implicated and reactions noticed.[17]

It has been demonstrated that probiotics diminish the incidence of antibiotic-associated diarrhea in pediatrics.[18] When started with the initiation of antibiotic therapy, probiotics can prevent 1 in 7 cases of antibiotic-associated diarrhea in children.[18] Thus, based on the results of this study illuminating a major cause of hospital admission in children being a prevalent gastrointestinal adverse effect, including diarrhea associated with antibiotics use, it is worth considering use of probiotics for prevention of antibiotic-associated diarrheas.

Pediatric pharmacotherapy still needs evidence-based strategies to improve child care including education, monitoring, planning for medications after ADR occurrence, and implementing prophylactic measures when applicable. Pharmacist and clinical pharmacists should have a definite role.

AUTHORS' CONTRIBUTION

Kheirollah Gholami has proposed the concept, designed the study, defined the intellectual content, edited and reviewed the manuscript. Fatemeh Babaie was responsible for literature review and data collection. Gloria Shalviri has designed the study, defined the intellectual content, edited and reviewed the manuscript and controlled study progress. Mohammad Reza Javadi has designed the study, edited and reviewed the manuscript. Toktam Faghihi has designed the study, defined the intellectual content, done literature research, prepared, edited and reviewed the manuscript.

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Conflicts of interest

There are no conflicts of interest.

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