

Original research article

A prospective study on adverse drug reactions associated with antihistamines among children

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Abstract

Background: ADRs are one of the leading causes of morbidity and mortality in healthcare. Due to increased industrialization, there is an increase in the incidence of asthma, especially in children. As a result of this, pediatric patients on anti-asthmatics are more prone to develop adverse drug effects. A sound knowledge of ADR's is always better to avoid further morbidity.

Material and Methods: This prospective, single-center study was done on children who presented to the Department of Pediatrics, Gayatri Vidya Parishad Institute of Health Care and Medical Technology over 1 year. Pediatric patients of bronchial asthma (both acute and chronic cases) of either gender within the age limit of 1-13 years who attended outpatient department (OPD) as well as in-patient department (IPD) were included in the study.

Results: During the study period, a total of 17 ADRs were reported among 75 patients. The incidence rate of ADRs was found to be 22.67%. Our study revealed that out of 17 reported cases of ADR, boys were affected more than girls. The most commonly reported ADRs were anorexia, palpitation, and dryness of the mouth. No severe ADRs were recorded during the study period.

Conclusion: As compared to adults, ADRs in children can have a relatively more severe effect. Adverse drug reactions associated with anti-asthmatic drugs are quite common. This study highlights the incidence and pattern of ADRs associated with pharmacotherapy of pediatric bronchial asthma.

Keywords: Adverse drug reactions, pediatrics, bronchial asthma, anti-asthmatics

Introduction

World Health Organization defined adverse drug reactions (ADRs) as "a response to a drug that is noxious and unintended and occurs at doses normally used in human or the prophylaxis, the pharmacodynamic and pharmacokinetic aspects of drugs is crucial in the management of any disease so as to minimize and even avoid the potential adverse effects associated with the drug. It is obvious that adverse reactions to drugs can occur with any class of drug. Adverse drug effects not only accounts for significant morbidity and mortality but can also lead to increase in the length of hospital stay and health-care cost.

Asthma is a common childhood problem, affecting children before their third birthday. As a result, asthma medications are frequently prescribed to children ^[1]. Considering their frequent labeled and off-labeled use, an understanding of adverse drug events associated with asthma medications is crucial to safe medical practice ^[2,3].

This study was undertaken to evaluate the adverse drug reactions with anti-asthmatic in children.

Material and Methods

This prospective study was conducted in the Department of Pediatrics at Gayatri Vidya Parishad Institute of Health Care and Medical Technology over 1 year. 75 pediatric patients of bronchial asthma (both acute and chronic cases) of either gender within the age limit of 1-13 years were included in the study. Patients who were <1 and >13 years old or with other co-morbid conditions or other systemic disorders were excluded.

A standardized questionnaire was administered to identify any ADR. Patients along with their guardians were enquired regarding the reason for initiating asthma drugs and reason for drug cessation, whether or not the child had experienced an ADR to any asthma medication and finally, a list of ADRs was read out to parents to determine if any of them had ever occurred with any asthma drug. If an ADR was reported in any of these three questions, parents were asked to describe the type and onset of symptoms, circumstances related to the event, dose adjustments or drug discontinuation resulting from the ADR, and, when applicable, the evolution of the ADR after discontinuation of the drug (de-challenge) and after restarting the medication (re-challenge) ^[4].

ADR report was assessed using the Naranjo algorithm, which evaluates the drug causality for an adverse drug reaction based on 10 questions. The Naranjo's probability scale assigns a weighted score to the components used to establish a causal association between drug and adverse events (temporal sequence, pattern of response, withdrawal, re-exposure, alternative, placebo response, drug levels in body fluids or tissues, dose-response relationship, previous patient experience with the drug, and confirmation by objective evidence). These factors were analyzed and scored using the ADR probability scale. Each question could be answered positive (yes), negative (no), or unknown or not applicable (do not know). The ADR was assigned to a probability category from the total score as follows: definite ≥ 9 , probable 5-8, possible 1-4 and doubtful ≤ 0 [5, 6]. The severity of the reactions was analyzed using a modified Hartwig and Siegel scale.

Statistical analysis

Statistical Analysis was performed using the Statistical Software SPSS 25th Version. The data was presented using frequencies, and percentages along with appropriate graphs and charts.

Results

Most of the pediatric patients suffering from asthma were found in the age group of 5-10 years (52%) followed by 1-5 years (26.67%) and lastly 10-13 years (21.33%).

Table 1: Age-wise Distribution of Pediatric Patients

Age (in years)	No. of patients (n=75)	Percentage
1-5yrs	20	26.67%
5-10 yrs	39	52%
10-13 yrs	16	21.33%
Total	75	100

Males (66.67%) were the predominant population in this study than females (33.3%).

Table 2: Drugs used in asthma

Drug class	No. of patients	Percentage
Short-acting $\beta 2$ -agonists	28	37.3%
Steroids + Beta-agonists	24	32%
Steroids alone	10	13.3%
Anticholinergic+ Beta-agonists	6	8%
Long-acting $\beta 2$ -agonists	5	6.7%
Leukotriene Modifiers	2	2.7%

The overall utilization of Anti-asthmatic drugs among pediatric patients was found to be – short-acting $\beta 2$ Agonists (37.3%) followed by Steroids + Beta-agonists (32%), followed by steroids alone (13.3%). Other classes of anti-asthmatic drugs used were – anti-cholinergics + beta-agonists (8%), long-acting beta-agonists (6.7%), and leukotriene modifiers (2.7%).

Table 3: Gender of patients with adverse drug reaction (n = 75)

Gender	No. of patients		Total
	With ADR (%)	Without ADR (%)	
Male	9 (12%)	41 (54.6%)	50 (66.6%)
Female	8 (10.67%)	17 (22.6%)	25 (33.3%)
Total	17 (22.67%)	68 (90.67%)	75 (100%)

During the study period, a total of 17 ADRs were reported among 75 patients. The incidence rate of ADRs was found to be 22.67%. Our study revealed that out of 19 reported cases of ADR, 8 (10.67%) occurred in males and 9 (12%) in females.

Table 4: Percentage of various reported adverse drug reactions

ADS	No. of patients
Palpitation	5
Dryness of mouth	4
Anorexia	4
Sore throat	1
Oral candidiasis	1
Nausea/vomiting	1
Headache	1
Total	17

The most commonly reported ADRs were palpitation, anorexia and dryness of the mouth. Other uncommon ADRs were sore throat, oral candidiasis, nausea/vomiting and headache.

Table 5: Causality assessment of ADRs according to the WHO-UMC scale

Type of reaction	No. of patients	Percentage
Certain	2	2.7%
Probable	5	6.7%
Possible	10	13.3%

On causality assessment by the WHO-UMC method, it was observed that 2 (2.7%) were certain, 5 (6.7%) were probable and 10 (13.3%) were possible ADR.

Table 6: Severity of reported ADRs by modified by Hartwig and Siegel scale

Type of reaction	No. of patients	Percentage
Mild	11	14.7%
Moderate	6	8%
Severe	0	0

Assessment of severity of ADRs was done using the Hartwig and Siegel scale, according to which, 11 (14.7%) had mild reactions and 6 (8%) had moderate reactions. No severe ADRs were recorded during the study period.

Discussion

The pathophysiology of asthma involves infiltration of inflammatory cells into airways, activation of mast cells, and damage to the epithelial cells. These inflammatory responses lead to the classical features i.e., airway swelling, increased mucus production and bronchial muscle dysfunction, which produce airway flow limitation and asthma symptoms^[7].

The increasing incidence of asthma in children is due to the industrialization of small towns, leading to the production of dust and other air pollutants. 75 children with asthma presented to the Department of Pediatrics with complaints of ADRs to anti-asthmatics drugs.

In the present study, the majority of patients belong to the 5-10 yrs of age group. This is further reinforced by a systematic review study done by Aagard *et al.*^[8], who observed that the majority of the affected children belonged to the 6-10 yrs age group. Our study found that boys (66.6%) suffered from asthma more than girls (33.3%). The most commonly used anti-asthmatic drugs among pediatric patients were found to be short-acting β_2 Agonists (37.3%) followed by Steroids + Beta-agonists (32%), followed by steroids alone (13.3%). Salmeterol among children was the most commonly used LABA, while Budesonide and fluticasone were the more widely used Inhalational Corticosteroids. Luyu Xie *et al.*^[9] also found that β_2 Agonists were the most commonly prescribed anti-asthmatics.

In the present study, we observed that 17 patients were affected by ADRs. Males were affected more than females. During pharmacotherapy administered to the patient, a short-acting β_2 agonist (salbutamol) was found to be responsible for causing the highest number of ADRs, followed by corticosteroids (budesonide) and anti-cholinergics (ipratropium bromide) and the least was leukotriene receptor antagonist (montelukast)^[10].

In our study, it was observed that administration of salbutamol by inhalational route in children resulted in palpitations, nausea/vomiting, and rhinorrhoea out of which palpitations were the most frequently accounted ADRs. The dose was decreased in one case of palpitations, while in another case, metered dose inhaler (MDI) salbutamol was discontinued and a combination of salbutamol and ipratropium bromide was administered via nebulization.

With the use of montelukast, headache was the most common ADR for which symptomatic treatment was given. These findings are consistent with a review article by Gupta *et al.*, (2016)^[11], which stated that headaches were most frequently reported to the Dutch database for both the whole population and children^[12]. Other ADRs encountered due to the administration of montelukast include cough, nausea/vomiting, upper respiratory tract infections, rhinorrhoea and anorexia.

Administration of inhalational budesonide in children majorly resulted in sore throat and oral candidiasis. Antifungal therapy was given to manage oral candidiasis whereas, for sore throat, patients and their parents were counseled to ensure oral hygiene after every inhalation.

The most common ADR encountered with the use of ipratropium bromide was dryness of the mouth (3.3%). However, the milder reaction was only symptomatically managed by rehydration.

All drug-related ADRs were evaluated for causality by Naranjo's scale as well as the WHO-UMC scale. On causality, assessment by the WHO-UMC method, 2 (2.7%) were certain ADRs, 5 (6.7%) were probable ADRs and 10 (13.3%) were possible ADRs.

None of the reported ADRs were found to be fatal, life-threatening, or needed hospital admission for

management. The absence of direct observation of ADR by a healthcare professional, the inability to obtain blood levels to prove toxicity and the fixed dosage preventing the assessment of a potential variation in ADR severity with dosage change, resulted in the automatic loss of three out of 12 points on the Naranjo scale, making it difficult to conclude to a “definite” immutability.

Conclusion

An increase in the incidence of asthma in children also is associated with an increase in the usage of anti-asthmatic medications. The risk of ADRs also is on the rise. Hence, adverse drug reaction monitoring is imperative to ensure long-term adherence.

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