

Adverse drug reactions associated with Antiasthmatics among children: A Prospective study

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Abstract

Background: Childhood asthma can cause bothersome daily symptoms that interfere with play, sports, school and sleep. In some children, unmanaged asthma can cause dangerous asthma attacks. The condition is a leading cause of emergency department visits, hospitalizations and missed school days. Anti-asthmatic drugs used in children may result in a beneficial and adverse drug reactions (ADR) and could contribute significantly to morbidity and mortality. **Material and Methods:** This is a Prospective and single centre study of children who presented to the Department of Paediatrics, Gayatri Vidya Parishad Institute of Health Care and Medical Technology over a period of 1 year. Paediatric 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 19 ADRs were reported among 90 patients. The incidence rate of ADRs was found to be 21.1%. Our study revealed that out of 19 reported cases of ADR, 12 (13.3 %) occurred in males and 7 (7.7%) in females. The most commonly reported ADRs were 5.5% of Anorexia followed by 4.4% of palpitation, 3.3% of dryness of mouth and Headache, and least were 1.1% of oral candidiasis and nausea/vomiting. On causality assessment by WHO-UMC method, it was observed that 1 (1.1%) were certain, 7 (7.7%) were probable and maximum 11 (12.2%) was possible ADR. Assessment of severity of recorded adverse drug reactions with the help of Hartwig and Siegel scale showed that 12 (13.3%) accounted for mild reactions and 7 (7.7 %) were moderate reactions. No severe ADR 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, Paediatrics, Bronchial asthma, Anti-asthmatics.

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Introduction

Respiratory drugs are frequently prescribed to paediatric patients for a wide range of airway diseases but most of these drugs are only approved for asthma and COPD from a particular age onwards [1]. In young children, diagnosing asthma is difficult due to general limitations (e.g. ability to follow instructions for lung function measurements) which might contribute to a low fraction of patients with lung function testing and an underdiagnosis of asthma [2].

In addition, respiratory drugs are frequently used for symptomatic improvement of airway diseases (e.g. acute respiratory infections) or are prescribed as a diagnostic instrument to confirm a diagnosis of asthma [3]. All these reasons contribute to a high fraction of children receiving respiratory medication as off-label treatment, a factor which has been reported as a risk for adverse drug reactions [4].

Bronchial biopsy specimen shows that the inflammatory substrate of atopic asthma is increased activation of "Th2" lymphocytes. These cells release cytokines that promote the terminal differentiation of committed eosinophil precursors, activate mature eosinophils to

release histotoxic mediators, and enhance the recruitment of circulating eosinophils into the lung. [5] A hallmark of atopic asthma is therefore increased numbers of eosinophils in the airway and bronchial mucosa. Increased numbers of eosinophils have also been found in the lower airways of school age children with asthma, and it is reasonable to assume that the inflammatory substrate (and therefore phenotype) of asthma in the majority of school age children, and teenagers is similar. [6] In childhood asthma, the lungs and airways become easily inflamed when exposed to certain triggers, such as inhaling pollen or catching a cold or other respiratory infection. Childhood asthma can cause bothersome daily symptoms that interfere with play, sports, school and sleep. In some children, unmanaged asthma can cause dangerous asthma attacks. [8] Childhood asthma isn't a different disease from asthma in adults, but children face unique challenges. The condition is a leading cause of emergency department visits, hospitalizations and missed school days. Unfortunately, childhood asthma can't be cured, and symptoms can continue into adulthood. But with the right treatment, you and your child can keep symptoms under control and prevent damage to growing lungs.

Material and Methods

This is a Prospective and single centre study of children who presented to the Department of Paediatrics at Gayatri Vidya Parishad Institute of Health Care and Medical Technology over a period of 1 year. Paediatric patients of bronchial asthma (both acute and chronic cases) of either gender within the age limit of 1-13 years. Patients

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who are <1 and >13 years with other co-morbid conditions or other systemic disorders were also excluded. A standardised questionnaire was administered to identify any ADR-related drug cessation, reported spontaneously or after prompting, using three approaches. First, we enquired about the occurrence and reason for any asthma drug cessation. Second, we asked if the child had experienced an ADR to any asthma medication. Finally, a list of ADRs was read 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 (dechallenge) and after restarting the medication (rechallenge) [9]. ADR report to assess event severity, evolution and immutability using the Naranjo score [10], briefly, the Naranjo algorithm evaluates the drug causality

for an adverse drug reaction based on 10 questions. Each answer is assigned a value (-1 to +2) for a maximum score of 12, with causality considered definite if the total score is ≥ 9 , probable if 5-8, possible if 1-4 and doubtful if ≤ 0 . Moreover, the severity of the reactions was analysed using modified Hartwig and Siegel's scale.

Statistical analysis

The Data was entered into SPSS sheet and analysed. Statistical Analysis was performed using Statistical Software SPSS 25th Version. The data was presented using frequencies, percentages along with appropriate graphs and charts.

Results

In our study, the paediatric group patients were divided into three classes as per the age-group. Most of the paediatric patients suffering from asthma 32.2% were found in the age group of 7-9 years followed by (27.7%) 4-6 years and least one is 10-13 years (18.8%) in table 1.

Table 1: Age wise Distribution of Paediatric Patients

Age (in year)	No. of patients (n=90)	Percentage
1-3	19	21.2
4-6	25	27.7
7-9	29	32.2
10-13	17	18.8
Total	90	100

Table 2: Gender wise Distribution of Paediatric Patients

Gender	No. of patients	Percentage
Male	53	58.8
Female	37	41.2
Total	90	100

Demographic analysis of data revealed that there were 58.8% male and 41.2% female in the study in table 2.

Table 3: Drugs used in asthma

Drug class	No. of patients	Percentage
Short acting β_2 -agonists	31	34.4
Steroids + Beta-agonists	28	31.1
Steroids alone	13	14.4
Anticholinergic+ Beta-agonists	9	10
Long acting β_2 -agonists	7	7.7
Leukotriene Modifiers	2	2.2

The overall utilization of Anti-asthmatic drugs among paediatric asthma patients were found to be -short acting β_2 Agonists (34.4%) followed by Steroids with Beta-agonists (31.1%). Pattern of drug prescription in asthmatics showed the highest prevalence of β_2

Agonists followed by corticosteroids with Beta-agonists and finally, the leukotriene modifiers. One additional antiasthmatic drugs: anticholinergics was also used among patients in table 3.

Table 4: Gender of patients with adverse drug reaction (n = 90)

Gender	No. of patients		Total
	With ADR (%)	Without ADR (%)	
Male	12 (13.3%)	41 (45.5%)	53 (58.8%)
Female	7 (7.7%)	30 (33.3%)	37 (41.2%)
Total	19 (21.1%)	71 (78.8%)	90 (100%)

During the study period, a total of 19 ADRs were reported among 90 patients. The incidence rate of ADRs was found to be 21.1%. Our

study revealed that out of 19 reported cases of ADR, 12 (13.3 %) occurred in males and 7 (7.7%) in females as shown in Table 4.

Table 5: Percentage of various reported adverse drug reactions

ADR	No. of patients	Percentage
Palpitation	4	4.4
Dryness of mouth	3	3.3
Headache	3	3.3
Sore throat	2	2.2
Oral candidiasis	1	1.1
Nausea/vomiting	1	1.1
Anorexia	5	5.5
Total	19	21.1

The most commonly reported ADRs were 5.5% of Anorexia followed by 4.4% of palpitation, 3.3% of dryness of mouth and

Headache, and least were 1.1% of oral candidiasis and nausea/vomiting in table 5.

Table 6: Causality assessment of ADRs according to WHO-UMC scale

Type of reaction	No. of patients	Percentage
Certain	1	1.1
Probable	7	7.7
Possible	11	12.2

On causality assessment by WHO-UMC method, it was observed that 1 (1.1%) were certain, 7 (7.7%) were probable and maximum 11 (12.2%) was possible ADR.

Table 7: Severity of reported ADRs by modified by Hartwig and Siegel scale

Type of reaction	No. of patients	Percentage
Mild	12	13.3
Moderate	7	7.7
Severe	0	0

Assessment of severity of recorded adverse drug reactions with the help of Hartwig and Siegel scale showed that 12 (13.3%) accounted for mild reactions and 7 (7.7 %) were moderate reactions. No severe ADR were recorded during the study period.

Discussion

Paediatric asthma best practice not only includes prescribing the correct therapeutic mix based on consensus guidelines, but also reducing therapy once control has been achieved. [11] The pathophysiology of asthma involves the infiltration of inflammatory cells, including neutrophils, eosinophils, and lymphocytes into the airway, activation of mast cells, and damage to the epithelial cells. These inflammatory responses lead to the classic features of airway swelling, increased mucus production, and bronchial muscle dysfunction, which produce airway flow limitation and asthma symptoms. [12] Remodelling, a term used to describe persistent changes in the airway structure, can occur, ultimately leading to fibrosis, mucus hypersecretion, epithelial cell injury, smooth muscle hypertrophy, and angiogenesis. [13] The demographic characteristics shows number of paediatric patients in the study. This is anticipated as our area is becoming a heavy industrial city and pollution producing units are gradually coming closer to the Hospital. These facts are further reinforced by a similar study in Taburet AM. [14] Whereas, demographic characteristics, of our study found that more male (58.8%) suffered from asthma than females (41.2%). The overall utilization of Anti-asthmatic drugs among paediatric asthma patients were found to be - β_2 Agonists (34.4%), Corticosteroids (14.4 %) and leukotriene modifiers (2.2%). Salmeterol among children was the most commonly used LABA, while Budesonide, Fluticasone were the more widely used Inhalational Corticosteroids. The results demonstrate that mast cell stabilizers are not used much clinically. They have been overshadowed by the other antiasthmatic medications. A similar study conducted by Shimpi et al., found that β_2 Agonists most commonly prescribed. [15] In the present study, we observed that in a period of 1 year, total 19 ADRs occurred affecting patients of either gender but the number was higher in males as compared to females. This does not comply with the statement that females are more sensitive to the effect of drugs as in comparison to males. [16] During the course of pharmacotherapy administered to the patient, short acting β_2 agonist (salbutamol) was found to be responsible for causing highest number of ADRs and least was leukotriene receptor antagonist (montelukast). Also stated that followed by corticosteroids (budesonide) and anticholinergics (ipratropium bromide) causing ADRs. [17] Furthermore, 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. Dose was decreased in one case of palpitations whereas in case of rhinitis, metered dose inhaler (MDI) salbutamol was discontinued and a combination of salbutamol and ipratropium,

bromide was administered via nebulization. With the use of montelukast, paediatric patients reported headache as the most common ADR for which symptomatically treatment was given. These findings are consistent with a review article by Gupta et al (2016), which stated that headaches were most frequently reported to the Dutch database for both the whole population and children. [18] Other ADRs encountered due to administration of montelukast include cough, nausea/vomiting, upper respiratory tract infections, rhinorrhoea and anorexia. In addition, it was also observed that 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 counselled to ensure oral hygiene after every inhalation. Similarly, the most common ADR encountered with the use of ipratropium bromide was dryness of mouth (3.3%). However, the milder reaction was only symptomatically managed by rehydration. All drug related ADRs were evaluated for causality in accordance with Naranjo's scale as well as WHO-UMC scale. Whereas, type of reaction such as 1.1 were certain followed by 7.7 % were found to be probable ADRs and 12.2 % as the 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

Adverse Drug Reactions are an unfortunate burden on the society, both financially as well as in terms of human suffering. They are associated with almost every drug and may range from mild to serious and even life threatening. As compared to adults, ADRs in children can have a relatively more severe effect. Most of the patients with bronchial asthma received more than one drug. The class of drug primarily studied was corticosteroids either alone or in combination with other anti-asthmatic drugs. Serious ADRs were relatively uncommon. Most of the reported ADRs are non-serious. Physicians seem to be aware of recent guidelines in the management of asthma. This may be partially attributed to mandatory CMEs, protocol based treatment, and impact of extensive asthma education campaign.

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