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A prospective study on the pharmacotherapy of bronchial asthma in pediatric patients at a tertiary care hospital; emphasis on adverse drug reactions

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Background: Paediatric asthma is one of the most common chronic illnesses in childhood and affects the quality of life in children. Anti-asthmatic drugs used in children may result in a beneficial and adverse drug reaction (ADR) and could contribute significantly to morbidity and mortality. Several studies report about the safety and efficacy of asthma medications in adults but the information in children is limited. **Material and Methods:** A prospective, observational, non-interventional study of children who presented between January 2018 and December 2019 to the Department of Paediatric of Noor Hospital. Pediatric patients of bronchial asthma (both acute and chronic cases) of either gender within the age limit of 1-13 years who attended the outpatient department (OPD) as well as the inpatient department (IPD) were included in the study. **Results:** Out of 120 patients, most of the pediatric patients suffering from asthma 42% were found in the age group of 5-8 years followed by (39%) 1-4 years and the last one is 9-13 years (19%). Demographic analysis of data revealed that there were 61.6% male and 38.4% female in the study. Out of 120 Paediatric asthma patients, 34.1% were suffering from mild persistent and the remaining 59.1% were patients of moderate persistent and 6.6% are least one of severe asthma. The percentages of the patients who were 58.4 % treated with a single anti-asthmatic drug (monotherapy) excluding other concomitant medications used together. **Conclusion:** It has been concluded that a study may be more meaningful to further improve the prescribing as well as dispensing practices of the pharmacist through the successful implementation of interventional programs in health centers.

Keywords: Bronchial asthma, Children, Anti-asthmatics, Adverse drug reactions

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Introduction

Bronchial asthma is a chronic inflammatory condition of the respiratory tract associated with bronchial hyper-reactivity and airflow restriction due to airway smooth muscle contraction often leading to difficulty in breathing and hypoxia [1]. The pathogenesis of asthma involves mast cell activation, eosinophil, and T helper 2 (TH 2) lymphocytes infiltration, IgE formation by B lymphocytes, and release of other inflammatory mediators, chemokines, and growth factors by airway epithelium [2]. On allergen exposure, the asthmatic patients show an early phase characterized by sudden onset of bronchoconstriction, and then a late phase occurring 8–24 hours post-exposure. The late phase is characterized by the influx of inflammatory cells into the airways and airway hyper-responsiveness to nonspecific stimuli [3].

Asthma is a principal cause of illness in childhood and can lead to psychological disturbances in the family. Statistics say 10-15% of boys and 7-10% of girls may have asthma at some time during childhood. Before puberty boys are affected more than girl's incidence becomes equal thereafter [4]. Asthma affects an estimated 300 million individuals worldwide the prevalence of asthma is increasing especially in children's. The WHO has estimated that 15 million disability-adjusted life years are lost and 2, 50,000 asthma deaths are reported worldwide [5]. Approximately 5,00,000 annual hospitalization (34.6% in individuals aged 18 years or younger) are due to asthma [6]. The cost of illness related to asthma is around $6.2 billion. Each year; an estimated 1.81 million people (47.8% individuals aged 18 years or younger) require treatment in the emergency department [7]. Proper drug therapy is one that controls both phases. Asthma produces a substantial economic and social burden on families and generally requires long-term treatment and patient cooperation to achieve clinical control [8]. According to Global Initiative for Asthma (GINA) guidelines, various drugs are suggested for the management of asthma that includes long and short-acting β2 agonists (salbutamol, salmeterol, formoterol), corticosteroids (fluticasone, prednisolone, budesonide), xanthine derivatives (theophylline) and leukotriene receptor antagonists (Montelukast), mast cell stabilizers, antihistamines, and mucolytic. These drugs can be used alone or in conjunction with other antiasthmatic drugs [9].

Moreover, among children and adolescents aged 5-17 years asthma accounts for a loss of 10 million school days and cost caretaker $726.1 million because of work absence [10]. There are only a few studies from India on the epidemiology of asthma. In a study conducted more than 30 years ago, the prevalence of asthma was reported to be 2.78% in an urban population aged 30-49 years [11]. Asthma is responsible for significant medical resource utilization and given that it is a chronic condition, cost-effectiveness is a major consideration in the evaluation of treatment options. With this point of view, the study has been designed. The objective of this study was to pool the data on drug utilization patterns and adverse drug effect analysis used for pediatric asthma patients. In addition, the anti-asthmatic drug usage pattern, correlation between environmental factors and asthma and patient's knowledge of the drug used was also determined.

Material and Methods

Study Design: A prospective, observational, non-interventional study of children who presented between January 2018 and December 2019

Study center and patients consent: Department of Paediatric of Noor Hospital and parents provided written consent to enroll in the Paediatric Asthma study.

Inclusion criteria

- Pediatric patients of bronchial asthma (both acute and chronic cases)
- Patients of either gender within the age limit of 1-13 years
- Who attended the outpatient department (OPD) as well as the inpatient department (IPD),
- Willing to enroll in a study with informed consent forms were included in the study.

Exclusion criteria

- Patients who are <1 and >13 years,
- Patients with other co-morbid conditions like TB, Diabetes/renal failure
- Patients with other systemic disorders
- Patients who were immunocompromised were also excluded.

Sample size: The study included 100 patients who confirmed the following predetermined inclusion and exclusion criteria.

Method

Once their consultation with the pediatrician was over, the prescriptions were collected and necessary details were noted on the questionnaire. The patient's parents were also interviewed on the predesigned questionnaire. The details of the drugs prescribed were noted down. After noting down the required parameters, prescriptions were returned to the patients. After the completion of the study, the questionnaires were analyzed to obtain the drug utilization pattern and from the Current Index of Medical Specialties (CIMS) and Indian Pharmaceutical Guide. It also included the OPD number, demographical details, and patients name, age, sex. A brief questionnaire was designed specifically for the study is attached to the case report form which chief complaints, and history of asthma, severity and the current status of asthma. The details of the drugs prescribed (dose, route, frequency, duration), the cost of therapy.

Evaluation Parameters

1) Prescription Indicators
01. A number of drugs/per prescription

02. Encounters with the brand name (%)

Iii. Most commonly prescribed β2 agonist
01. Most commonly prescribed Inhaled corticosteroid

02. Encounter with antibiotics

Parents of eligible patients were contacted by phone or in-person a pediatrician. Using a non-leading interview script, a standardized questionnaire was administered to identify any ADR-related drug cessation, reported spontaneously or after prompting, using three approaches. First, it was enquired about the occurrence and reason for any asthma drug cessation. Second, it was 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) [20].

ADR report to assess event severity, evolution and immutability using the Naranjo score [20], 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 analyzed using modified Hartwig and Siegel's scale.

Statistical analysis: Statistical Analysis was performed using Statistical Software SPSS 17.0. The Data was entered into the SPSS sheet and analyzed. The data was presented using frequencies, percentages along with appropriate graphs and charts. The quantitative variables were presented using descriptive statistics such as mean, and Standard deviation. The Association between variables was tested using the chi-square test. The level of significance was set at 0.05. All p values less than 0.05 are considered significant.

Results

During the study, 120 pediatric asthma patients' prescriptions were included for data analysis as per the inclusion and exclusion criteria. The study was conducted between January 2018 to December 2019 at Noor Hospital and IIMSR Medical college.

The various parameter analyzed are as follows

Table-1: Age-wise Distribution of Paediatric Patients

Age (in a year)	No. of patients (n=120)	Percentage
1-4	47	39
5-8	51	42
9-13	22	19
Total	120	100

The pediatric group patients were divided into three classes as per the age-group. Most of the pediatric patients suffering from asthma 42% were found in the age group of 5-8 years followed by (39%) 1-4 years and the last one is 9-13 years (19%).

Table-2: Gender wise Distribution of Paediatric Patients

Gender	No. of patients	Percentage
Male	74	61.6
Female	46	38.4
Total	120	100

Demographic analysis of data revealed that there were 61.6% male and 38.4% female in the study.

Table-3: Grading of asthma severity (% of patients).

Grading	No. of patients	Percentage
Mild	41	34.1
Moderate	71	59.1
Severe	8	6.6
Total	120	100

Out of 120 Paediatric asthma patients, 34.1% were suffering from mild persistent and the remaining 59.1% were patients of moderate persistent and 6.6% are least one of severe asthma.

Table-4: Anti-asthmatic drug combinations

Drug therapy	No. of patients	Percentage
Monotherapy	70	58.4
Combination therapy	50	41.6
Total	120	100

The percentages of the patients who received either monotherapy or combination therapy, i.e., two, three, or four-drug regimens, showed that 58.4 %, of all the patients, were treated with a single anti-asthmatic drug (monotherapy) excluding other concomitant medications used together. 41.6 % of children were treated with anti-asthmatic drug combinations. The results of this study showed that most of the patients received multiple drug therapy as compared to single-drug therapy. All the drugs were prescribed by their brand names.

Table-5: Drugs used in asthma

Drug class	No. of patients	Percentage
Short acting β2 -agonists	39	32.5
Long-acting β2 -agonists	11	9.1
Steroids alone	17	14.1
Leukotriene Modifiers	3	2.5
Steroids + Beta-agonists	39	32.5
Anticholinergic+ Beta-agonists	11	9.1

The overall utilization of Anti-asthmatic drugs among pediatric asthma patients was found to be – short-acting β2 Agonists (32.5%) long-acting β2agonist (LABA) (9.1%), steroids (14.1%) and leukotriene modifiers (2.5%). The pattern of drug prescription in asthmatics showed the highest prevalence of β2 Agonists followed by corticosteroids and finally, the leukotriene modifiers. One additional antiasthmatic drugs: anticholinergics was also used among patients.

Table-6: Distribution According to Class of Drugs Prescribed (Asthmatic Medication)

Drug	No. of patients	Percentage
Salbutamol	39	32.5
Salmeterol	11	9.1
Deflazacort	2	1.6
Budesonide	9	7.5
Prednisolone	6	5
Montelukast	3	2.5
Salmeterol+Fluticasone	39	32.5
Salbutamol+Ipratropium Bromide	11	9.1

Salbutamol is the most commonly used short-acting β2 Agonists, Salmeterol was the most commonly used long-acting β2 Agonists. Budesonide, Deflazacort, and Fluticasone are the most commonly used corticosteroids among children.

Table-7: Route of administration of Drugs

Route	No. of patients	Percentage
Inhalational	74	61.6
oral	46	38.3
Total	120	100

Different dosage forms used by the asthmatic patient: 61.6% of patients were given by inhalational route and remaining were given by oral route 38.3%.

Table-8: Gender of patients and adverse drug reaction (n = 120)

Gender	No. of patients		Total
	With ADR (%)	Without ADR (%)	
Male	8 (6.6%)	66 (55%)	74 (61.6%)
Female	5 (4.1%)	41 (34.1%)	46 (38.4%)
Total	13 (10.8%)	107 (89.1%)	120 (100%)

During the study period, a total of 35 ADRs were reported among 330 patients. The incidence rate of ADRs was found to be 10.6%. The current study revealed that out of 35 reported cases of ADR, 19 (54.28 %) occurred in males and 16 (45.71%) in females as shown in Table 8.

Table-9: Percentage of various reported adverse drug reactions

ADR	No. of patients	Percentage
Palpitation	2	1.6
Dryness of mouth	2	1.6
Headache	3	2.5
Sore throat	2	1.6
Oral candidiasis	1	0.8
Nausea/vomiting	1	0.8
Anorexia	2	1.6
Total	13	10.8

The most commonly reported ADRs were 2.5% of headache, 1.6% of palpitation, dryness of mouth, sore throat, anorexia, and 0.8% of oral candidiasis nausea/vomiting.

Table-10: Causality assessment of ADRs according to WHO-UMC scale

Type of reaction	No. of patients	Percentage
Certain	1	0.83
Probable	5	4.1
Possible	7	5.8

On causality assessment by WHO-UMC method, it was observed that 1 (0.83%) were certain, 5 (4.1%) were probable and a maximum of 7 (5.8%) was possible ADR.

Table-11: Severity of reported ADRs by modified by Hartwig and Siegel scale

Type of reaction	No. of patients	Percentage
Mild	8	6.6
Moderate	5	4.2
Severe	0	0

Assessment of severity of recorded adverse drug reactions with the help of the Hartwig and Siegel scale showed that 8 (6.6%) accounted for mild reactions and 5 (4.2 %) were moderate reactions. No severe ADR was recorded during the study period.

Discussion

The prescription-based study evaluates the rationality of the prescription. Guidelines for rational prescribing practices are put forth to improve the standards of prescribing [12]. An international body on asthma has enhanced the prescribing practice of the physicians through various recommendations. The present study was conducted in Noor hospital which caters to a population of Jalna. The demographic characteristics show the number of pediatric patients in the study. This is anticipated as Jalna 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. [13] Whereas, demographic characteristics, of the present study found that more males (61.6%) suffered from asthma than females (38.4%).

In the present study, 58.4% of asthmatic patients were on single-drug therapy (monotherapy) and 41.6% Multiple drug therapy (combination). A similar study conducted at Dehradun, India, reported that 84% of asthmatic patients were on multiple drug therapy and only 16% of patients were on single-drug therapy [14]. The result of this study demonstrates that different prescribing patterns in comparison to published studies.

On the other hand, a study conducted by Pinal et al. showed that 84% of patients and 76% of patients in Shimpi et al. were given combination therapy over monotherapy [15,16].

The overall utilization of Anti-asthmatic drugs among pediatric asthma patients was found to be - β2 Agonists (32.5%), Corticosteroids (14.1 %) and leukotriene modifiers (2.5%). 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. In the present study found that 61.6% of patients among children were prescribed with oral medicaments and 38.4 % with inhalers. A similar study conducted by Shimpi et al. found that 54%, 34% and 12% of anti-asthmatic drugs were prescribed orally, via inhalation and by injection respectively [16].

Prescription of inhalational dosage forms for anti-asthmatic drugs was approximate similar in both the studies. The inhalation route causes a high local concentration in the lungs with a low systemic delivery, significantly improves the therapeutic effectiveness and minimizes systemic side effects. It was also found that 75 % of the parents of pediatric patients were aware of the drug schedule. Satisfactory knowledge about spacer and meter dose inhalers was also found. However, most patients were unaware of the asthma control action plan. Thus, the present study highlights that certain steps towards patient education need to be taken in order to improve the awareness among the pediatrics patients regarding medication and management of asthma for a better prognosis. In the future, informative leaflets may be prepared and distributed among the patients based upon their awareness.

In the present study majority of the prescriptions used nebulization as a preferred route of drug delivery to manage acute exacerbations of asthmatic episodes. Nebulizer produces an aerosol by blowing air or oxygen through a solution to produce droplets requiring little coordination from the patient as a drug is inhaled through a facemask or a mouthpiece using normal tidal breathing. Thus, it is useful for patients who are unable to use conventional inhaler. The disadvantages of using a nebulizer include the long-time commitment maintenance treatments and lack of portability [17].

However, the inhalation therapy through metered dose inhalers was given to all patients who had treatment for acute exacerbation of bronchial asthma at the time of discharge. The inhalational route delivers more drugs locally and the dose used is also less with fewer side effects. This is in accordance with treatment guidelines, i.e. Inhalational therapy for asthma to be the first choice [18]. The effectiveness of inhaler therapy also depends on the inhaler technique.

Patients may not be adequately instructed in the inhaler technique, thereby reducing the amount of drug delivered to the lungs. Cochrane, in a study, stated it is important to reinforce the simple concept that failure to instruct patients on how to use inhalers and to reinforce these instructions will decrease compliance, whatever the drug or inhalation device [19].

The most commonly prescribed inhaled bronchodilator was salbutamol with ipratropium bromide (32.5%) followed by formoterol with budesonide (31.5%) which was in coherence with the study done in Malaysia in which salbutamol was the most commonly prescribed and also study done in Bareilly, which showed inhaled salbutamol was received by 100% of the patients irrespective of the severity [20,21]. The reason for using short-acting β2 agonist i.e salbutamol is due to its rapid onset and its low cost. In the current study, injection hydrocortisone was also used in managing an acute asthma attack.

It prevents the side effect of inhaled medication which causes irritation on the respiratory tract. National Asthma Education and Prevention Program (NAEPP) guidelines recommend corticosteroids by oral route even for severe exacerbation and it is reported to be as effective as intravenous route [22].

Anticholinergics were not prescribed as monotherapy but were given in combination with, as they are preferred medication for treating asthma. Doxophylline is preferred over theophylline for it has less cardio-toxic effects than the former with preserved much-regulatory and anti-inflammatory properties. Hence, doxophylline may constitute a safe and effective alternative treatment to aminophylline/theophylline in the treatment of acute exacerbation of bronchial asthma [23].

However, Akram et al. conclude that there is no significant difference in spirometric variables between doxophylline and theophylline [24].

The conclusions of Akram et al. are further reinforced by the study of Margay et al [25], but he concludes that doxophylline has a better safety profile over theophylline.

Corticosteroids constituted the second most commonly used medication for the inhalational and oral route, and was prescribed in 14.1% of the prescriptions, in contrast, to study done by Sayadeda et al., corticosteroid was given by IV route in 100% cases of severe exacerbation and some cases of severe exacerbation were also given MgSO4 (28.57%) for additional bronchodilation [26]. In addition to the reduction of severity and exacerbation, they reduce airway hyperresponsiveness.

They also help in reducing inflammation by inhibiting the activation and recruitment of T cells, macrophages, and dendritic cells, by decreasing mast cell survival, and by inhibiting the release of inflammatory mediators [27]. In addition, they reduce hospitalization, improve quality of life, and reduce overall mortality and morbidity. A recent systematic review established the myriad benefits of systemic steroids in the management of asthma [28]. Montelukast, a leukotriene receptor antagonist (2.5%) was seen in the prescription. According to Rajathilagam et al. it was prescribed as a fixed-dose combination with levocetirizine (36.8%) [29].

In the present study, it was observed that in a period of 2 years, a total of 13 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 [30].

During the course of pharmacotherapy administered to the patient, short-acting β2 agonist (salbutamol), as well as leukotriene receptor antagonist (montelukast), were found to be responsible for causing the highest number of ADRs i.e. 10 (28.57%). It also stated that followed by corticosteroids (budesonide) causing 17.14% and anticholinergics (ipratropium bromide) causing 14.28% of ADRs [31].

Furthermore, in the current study, it was observed that the 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 whereas in the 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, pediatric patients reported headaches as the most common ADR for which symptomatic 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 [32]. 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 the 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.

Similarly, the most common ADR encountered with the use of ipratropium bromide was dryness of the mouth (11.42%). Out of these 13 cases, 8 were mild reactions whereas 5 was of moderate and was managed by discontinuation of ipratropium bromide. 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 the WHO-UMC scale. Whereas, type of reaction such as 0.83 was certainly followed by 4.1 % were found to be probable ADRs and 5.8 % as the possible ADRs. None of the reported ADRs were found to be fatal, life-threatening or needed hospital admission for management.

Limitation of the study

- As for all observational studies, there are few limitations worth to be mentioned. First, as the inclusion of the clinical data (e.g. lung function parameter) was not done and thus focus on drug prescription was more instead of analyzing patients in detail comparing on- and off-label users (as already done.
- Second, there are some uncertainties in matching specific ICD-codes needed for analyzing databases and indications stated in the (summary of product characteristics) SPC in particular when general terms have been used in the SPC. This might have influenced the number of calculated off-label prescriptions. Nevertheless, most of the terms used for defining off-label usage are comparable to other publications [1].
- Third, the current study was lack of follow up and cost-effectiveness which should have been done. For higher authenticity, more number of prescriptions should have been included in the current study.
- Lastly, only a few serious ADRs were reported, but patients' withdrawal from clinical studies due to ADRs should be investigated more clearly.

Conclusion

Asthma symptoms aggravated during the daytime and winter season. β2 agonists and Combinations with corticosteroids are the most commonly prescribed combination drugs for asthma followed by corticosteroids alone. Nebulization was the preferred route to tackle the acute exacerbation of asthmatic symptoms. In addition, 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. As such, increased awareness regarding the occurrence of the adverse drug reactions among parents and the Health care professional may result in early detection of ADRs, their early reporting and minimize the risk of ADR related harms. 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. Further studies may help to improve the prescribing and dispensing practices of pharmacists through the successful implementation of interventional programs in health care centers.

What does the study add to the existing knowledge?

The current study found that pediatrics patients especially males age between 5-8 showed a greater incidence of asthma but were unaware of anti-asthmatic drugs. It was also noticed that pharmacists usually distributed medicines without giving any written or detailed oral instructions. Thus, the current study highlights the lacunae in the prescription trends which prevent proper, rational utilization of drugs by patients.

This study also highlights some very important issues about the information on ADRs of asthma medication in clinical studies. Firstly, the patients included are mostly male at the age of 5–8 years. Information on ADRs in younger children, who are more vulnerable, is scarce.

Although in practice salbutamol and steroids are used most frequently, most information on ADRs was on leukotriene receptor antagonists. It was believed that giving correct and reliable information on ADRs in asthma medication in clinical studies is the responsibility of researchers, authors, editors of journals, pharmaceutical companies, and regulatory agencies.

Author's Contributions

Dr. Sharad Bansal: Concept and Manuscript preparation, **Dr. Lalit Une**: Study design and data analysis.

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