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ADVERSE DRUG REACTIONS IN PEDIATRIC PATIENTS OF BRONCHIAL ASTHMA.

Pharmacology

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ABSTRACT

Pediatric 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 variety of adverse drug reactions (ADR) and could contribute significantly to morbidity and mortality. Several studies report about the safety of asthma medications in adults but information in children is limited. Hence, we aimed to review literature to determine all the ADRs in pediatric patients of bronchial asthma. Pubmed database from Jan 2008 to Dec 2017 was searched for Randomised controlled clinical trials in children from 1-17 years of age that reported ADRs to asthma medications. Around 94 relevant articles were extracted, however, only those that could provide relevant information about ADRs in pediatric asthma were included. Most of the reported ADRs in reviewed studies are non-serious. Serious ADRs are relatively uncommon. However, the data available is very limited and extensive studies are necessary to further investigate long-term effects.

KEYWORDS

Adverse Drug Reactions, Pediatric Asthma, Anti Asthmatic Drugs

INTRODUCTION

Pediatric asthma is one of the most common chronic illnesses in childhood and affects the quality of life in children.[1] Being a heterogeneous disorder in children, it is characterized by varying degrees of airway obstruction, bronchial hyper-responsiveness, and airway inflammation.[2] Subsequently, it leads to clinical symptoms of wheezing, breathlessness, chest tightness and coughing. Asthma has been categorized as intermittent asthma & persistent asthma by National Asthma Education and Prevention Program (NAEPP). Persistent asthma is further subdivided into mild, moderate & severe asthma.[3]

The prevalence of pediatric bronchial asthma varies widely. For the age of six to seven years, it ranges from 4 to 32% and the same range is applicable for ages 13 and 14. The highest prevalence of severe bronchial asthma in the world is in UK.[4] A number of studies have been conducted to evaluate the prevalence of childhood asthma among Indian children. The median prevalence of bronchial asthma in Indian children is estimated to be about 4.75% of the pediatric population.[5]

Global Initiative for Asthma (GINA) guidelines has suggested various drugs like long and short acting β_2 agonists (salbutamol, salmetrol, formoterol), inhalational corticosteroids (beclometasone, budesonide, cyclisonide, fluticasone), systemic corticosteroids (prednisolone), long and short acting anticholinergics (tiotropium bromide and ipratropium bromide), chromones (sodium cromoglycate), leukotriene modifiers (montelukast, zafirlukast) and anti IgE (omalizumab) for the management of asthma. Either these drugs can be used alone or in conjunction with other antiasthmatic drugs.[6] However, these drugs may result in a variety of adverse drug reactions (ADR) during therapy and could contribute significantly to morbidity and mortality in pediatric population. WHO (1975) defines an ADR as "any response to a drug which is noxious, and unintended, and which occurs at doses normally used in a man for the prophylaxis, diagnosis or therapy of disease, or for modification of physiological function".[7]

There are several studies reporting about the safety of asthma medications in adults but information about safety in children is limited. Hence, we aimed to review literature to determine all the ADRs in pediatric patients of bronchial asthma.

MATERIALS AND METHODS

We searched Pubmed using the "anti asthmatic drugs, adverse drug reactions, adverse events, adverse effects, children. The search period ranged from Jan 2008 to Dec 2017. Studies were included on the basis of following criteria : (1) Randomized controlled clinical trials (RCTs) in children of age group 1-17 years that reported ADRs to anti-asthmatic drugs (2) Articles in languages other than English were excluded. (3) Studies that did not provide data on the frequency of ADRs were excluded. (4) Studies presenting aggregated pediatric and adult data, without separate pediatric subgroup analysis were excluded. We scrutinized every paper by reading 'title', and thereafter 'abstract' and assessed the full text of all potentially relevant trials. We were unable to perform a manual search of bibliographic references from retrieved papers due to funding and resource issues.

RESULTS

Around 94 relevant articles were extracted from the database by means of our search and only 10 were included in this review that could provide relevant information about ADRs in pediatric asthma (as indicated in Table-1) and frequently reported adverse drug reactions (as indicated in Table -2). Studies referred included participants of either gender between the age group of 1 - 17 years. Seven of the included studies were RCTs with double blinding and three were open label. Two studies examined inhalational corticosteroids (ICS), five combined ICS + beta 2 agonists, one combined Leukotriene Receptor Antagonists + beta 2 agonists and one ICS + anticholinergic asthma medications.

TABLE 1- Summary of ADRs reported by studies reviewed

Author/ year	Study design	Drugs used	Sample size	Age range	Study duration	Adverse drug reactions
Noonan et al (2009) [8]	RCT OL	1.Mometasone furoate (MF) 200 µg 2. Mometasone furoate (MF) 100 µg 3.Beclomethasone dipropionate (BDP)168 µg	1. N= 78 2. N= 74 3. N= 81	4-11 yrs	52 weeks	Allergy, fever, headache, viral infection, nasal congestion, pharyngitis, rhinitis, sinusitis and URTI

Berger W et al (2010)[9]	RCT OL	1. Budesonide/ formoterol 320/9 µg 2. Budesonide 400 µg	1. N =123 2. N = 63	6-11 yrs	26 weeks	1.oral candidiasis, upper abdominal pain, diarrhea, GI upset, chest pain, Fatigue, increased heart rate, cough and ventricular extra systoles. Serious ADR- Asthma and pneumonia 2.Cough, insomnia, decreased creatinine urine and decreased cortisol free urine. Serious ADR- Sickle cell Anemia.
Arun JJ et al (2012)[10]	RCT DB	1.Budesonide/ Formoterol 200 µg /12 µg 2.Budesonide/ Salbutamol 200 µg / 200 µg)	1. N = 45 2. N = 45	5-15 yrs	11 months	Tremors
Oliver A et al (2014)[11]	RCT DB 2-way CO	1.Fluticasone furoate/ Vilanterol (FF/VI) 100/25 µg 2.Fluticasone furoate 100 µg	N = 26	5-11 yrs	≤ 11 weeks	1.Headache, conjunctivitis, bronchitis, streptococcal pharyngitis 2.Headache and Upper respiratory tract infection (URTI)
Vogelberg C et al (2014)[12]	RCT DB In CO	1.Tiotropium Bromide 5 µg/ Budesonide 2.Tiotropium Bromide 2.5 µg/ Budesonide 3.Tiotropium Bromide 12.5 µg/ Budesonide	1. N =80 2. N=75 3. N=75	12-17 yrs	12 weeks	Nasopharyngitis, asthma, bronchitis and pharyngitis, rhinitis, sinusitis, gastroenteritis, viral infection. Four serious ADR- pre-syncope, asthma exacerbations, H1N1 influenza and mycoplasma pneumonia.
Meltzer E O et al (2015)[13]	RCT DB	Budesonide 160 µg	N=152	6 to < 12 yrs	6 weeks	Nasopharyngitis, pharyngitis, asthma, viral URTI, influenza, cough, oropharyngeal pain, epistaxis and sinusitis.
Emeryk A et al (2016)[14]	RCT DB	1.Fluticasone propionate/ Formoterol (FP/FORM) 100/10 µg 2.Fluticasone propionate/ Salmeterol (FP/SAL)100/50µg	1.N =106 2.N =105	4–12 years	12 weeks treatment phase 24 weeks extension phase	Nasopharyngitis, pharyngitis, bronchitis in both groups. One case of mild dizziness in FP/ FORM group.
Stampel DA et al (2016)[15]	RCT DB	1.Fluticasone propionate/ Salmeterol 100/50 µg and 250/50 µg 2.Fluticasone propionate100 µg and 250 µg	1.N =3107 2.N =3101	4-11 yrs	26 weeks	Asthma exacerbations, pneumonia, bronchitis, pneumonia viral, pharyngotonsillitis, URTI, arrhythmia, hypersensitivity, Henoch-Schonlein purpura Serious ADR reported were hospitalizations.
Hamelmann E et al (2016)[16]	RCT DB	1.Tiotropium bromide5 µg / Budesonide 2.Tiotropium bromide2.5 mg / Budesonide	1.N =134 2.N =125	12-17 yrs	48 weeks	Asthma exacerbations, nasopharyngitis, viral respiratory tract infections, headache and viral infection.
Nagao M et al (2017)[17]	RCT OL	1.Montelukast 4 mg 2.Beta 2 agonist	1.N= 47 2.N= 46	1-5 yrs	48 weeks	URTI, gastroenteritis, hand-foot-and-mouth disease, urticaria, acute sinusitis, mycoplasma pneumonia, croup, Influenza type A, Influenza type B, Streptococcus haemolyticus Infection, Mycoplasma infection, Pneumonia, Chicken pox, Rotavirus infection and Asthma exacerbations

Randomized- RCT; open label – OL; Double-blind- DB; 2-way Cross-over- 2-way CO; Incomplete cross-over- In CO;

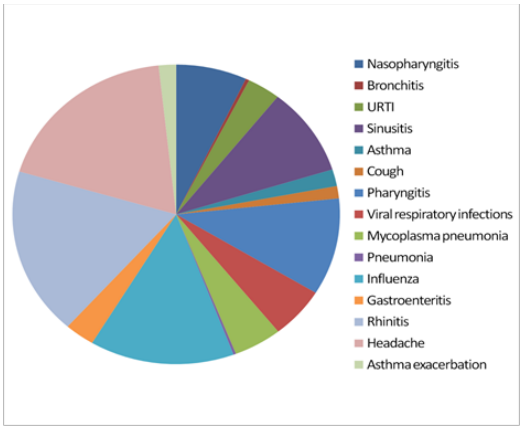
TABLE 2: Frequently reported ADRs by RCTs

Type of ADR reported	Number of studies reporting ADR	Total number of patients	Number of patients with ADR	Incidence (%)
Nasopharyngitis	4	1060	78	7.35%
Bronchitis	4	6883	26	0.37%
Upper Respiratory Tract infection (URTI)	4	3413	118	3.45%
Sinusitis	3	512	53	10%
Asthma	2	307	6	1.9%
Cough	2	338	5	1.4%
Pharyngitis	5	985	108	11%
Pharyngotonsillitis	1	3107	1	---
Viral respiratory infections	2	411	24	5.8%
Mycoplasma pneumonia	2	122	6	5%
Pneumonia	3	6377	17	0.26%
Influenza	2	198	31	15%
H1N1 influenza	1	75	1	---
Croup	1	47	13	---
Oropharyngeal pain	1	152	3	---
Oral candidiasis	1	123	2	---
Diarrhea	1	123	1	---
GI upset	1	123	1	---
Upper abdominal pain	1	123	1	---

Gastroenteritis	2	127	4	3.1%
Rhinitis	2	388	74	19%
Urticaria	1	47	2	---
Allergy	1	233	53	---
Hypersensitivity	1	3101	1	---
Henoch-Schonlein purpura	1	3107	1	---
Headache	3	518	102	19.6%
Dizziness	1	106	1	---
Tremors	1	90	3	---
Epistaxis	1	152	1	---
Chest pain	1	123	1	---
Pre-syncope	1	80	1	---
Ventricular extra-systoles	1	123	1	---
Increased heart rate	1	123	1	---
Arrhythmia	1	3101	1	---
Hand-foot-and-mouth disease	1	47	2	---
Conjunctivitis	1	26	1	---
Decreased creatinine urine	1	63	1	---
Decreased cortisol free urine	1	63	1	---
Asthma exacerbation	3	6635	119	1.8%
Insomnia	1	63	1	---
Chicken pox	1	46	15	---
Rotavirus infection	1	46	15	---
Sickle cell anemia	1	63	1	---

Incidence of ADRs was calculated from the RCTs when more than one study reported ADR

FIGURE 1: Incidence of frequently reported ADRs in RCTs



In the study by Noonan et al, most of the reported ADRs were considered unrelated to the study drug. 47% to 51% of patients reported URTI as ADR. The most frequently reported ADRs which were found related to the study drug were headache and oral candidiasis. No deaths were reported. Only few treatment interruptions or discontinuations due to ADRs were reported.[8] Berger W et al study observed similar ADR profile across both the treatment groups. In both the groups, the incidence of asthma related adverse events (AE) was low and similar. However, the incidence of cough was found to be slightly higher in Budesonide/Formoterol group (12.2%).[9] In another study by Arun JJ et al, only three children experienced tremors, two from Budesonide/ Salbutamol group and one from Budesonide/Formoterol group. Also, no deterioration in health or hospitalization was observed during study period.[10] Similarly, in Oliver A et al study, there were no serious AEs leading to death or withdrawal. None of the ADRs were considered related to the study and were of mid intensity except bronchitis and streptococcal pharyngitis which were moderate.[11] In another study by Vogelberg c et al, commonly reported ADRs were nasopharyngitis, asthma, bronchitis and pharyngitis and most of them were mild to moderate in intensity.[12] Meltzer E O et al reported no serious ADRs in a phase II multicentric study. Most of them were related to respiratory infections and their frequency was similar between the two treatment groups[13]. In Emeryk et al study, nasopharyngitis, pharyngitis and bronchitis were the commonly observed ADRs and their intensity was mild to moderate[14]. Similarly, in two other studies, most ADRs were mild or moderate in intensity.[16,17] In another multicentric trial conducted in 32 countries, 48 patients reported serious asthma related events which were asthma related hospitalizations only.[15]

The most frequently reported ADRs were nasopharyngitis (7.35%), upper respiratory tract infection (3.4%), pharyngitis (11%), sinusitis (10%), headache (19.6%), asthma (1.9%), cough (1.4%), rhinitis (19%), influenza (15%), viral respiratory infections (5.8%), mycoplasma pneumonia (5%), gastroenteritis (3.1%), asthma exacerbation (1.8%), pneumonia (0.26%), bronchitis (0.37%). Serious asthma-related events (all were hospitalizations) were observed only in few studies (as indicated in figure-1).

DISCUSSION AND 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. They not only result in hospital admissions but also may lead to permanent disability or even death. We searched 10 RCTs to investigate the relationship between use of anti-asthma medications in pediatrics and occurrence of ADRs. The duration of the included studies ranged from 6 weeks to 52 weeks. 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 in reviewed studies are non-serious. However, the data available is very limited and extensive studies are necessary to further investigate long-term effects. Moreover, the major limitation of our review is that majority of the studies used combination of anti-asthmatic drugs. As such, causality assessment of non-serious ADRs was missing. Hence, new and innovative methods may be required to better evaluate ADRs of antiasthmatic drugs in children.

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