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MONITORING OF ADVERSE DRUG REACTIONS IN PAEDIATRIC ASTHMA PATIENTS ATTENDING A PRIVATE HOSPITAL

Pharmacology

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ABSTRACT

Background of the study: Adverse drug reactions (ADR) constitute a significant health problem in children. Pharmacotherapy of asthma includes prolonged multi drug therapy, which results in its association with different ADRs. Studies involving ADR monitoring in paediatric patients of asthma are limited. Therefore, this study was planned to observe the occurrence of the adverse drug reactions associated with pharmacotherapy of asthma in children.

Materials and Methods: After the institutional ethical approval, an observational, non-interventional and cross-sectional study was conducted in paediatric patients of bronchial asthma in outpatient as well as inpatient setting of a private hospital in Aurangabad from November 2017 to March 2019. All Asthmatic children presenting with adverse drug reactions were studied. All relevant data like patient's demographic details, type of ADR, drug suspected to cause ADR, body system affected by the ADR were extracted. The causality of ADRs was then assessed by WHO-UMC scale and Naranjo's scale. Also, modified Hartwig and Siegel's scale was utilized to assess the severity of recorded ADRs.

Results: Out of total 330 asthmatic children that attended the hospital during the study period, 41 children presented with ADRs. The incidence rate of ADRs was found to be 12.42%. The percentage of ADRs was the highest (43.9%) in patients aged between 5 to 8 years and majority of them were males. The most commonly occurring ADRs were headache (14.63%), sore throat (14.63%), tachycardia (12.19%), dryness of mouth (9.75%), cough (9.75%), drowsiness (7.31%) and oral candidiasis (7.31%). There were no severe reactions, 85.36% ADRs were mild and only 14.63% were moderate in their level of severity. Causality analysis revealed that about 41.46% ADRs were probable and 58.53% were possible. None of the reported ADR was found to be fatal, life threatening or needed hospital admission for management.

Conclusion: This study highlights the need of rigid ADR monitoring in paediatric asthma patients to ensure safe pharmacotherapy. Adherence to pharmacovigilance guidelines and practices will not only reduce the incidence of ADRs but also reduce cost. Keeping this in mind, various pharmacovigilance awareness programs should be implemented to sensitize health care professionals about spontaneous reporting of ADRs.

KEYWORDS

Adverse drug reactions, Asthma, Paediatrics, Anti-asthmatic drugs, Pharmacovigilance, causality

INTRODUCTION

Globally, adverse drug reactions (ADR) constitute a significant health problem.[1],[2] In children, ADRs are often responsible for higher rates of morbidity as well as mortality because many a times, drugs which have limited or no efficacy and safety are prescribed to them.[3-6] According to the World Health Organization (WHO), ADR is defined as "a response to a drug which is noxious, and unintended, and which occurs in doses normally used in man for prophylaxis, diagnosis or therapy of disease, or for the modification of physiological function".[7],[8]

As per Global Initiative for Asthma (GINA) guidelines, asthma is a common serious chronic disease among adults as well as children.[9] WHO estimated that 300 million people suffered from asthma resulting in death of 255,000 people in 2005.[10] By 2025, it is predicted to witness an increase of additional 100 million asthmatic individuals worldwide.[11] Across the Globe, prevalence of paediatric bronchial asthma varies considerably. Recently, there has been an increase in the prevalence of asthma among children as well as adolescents mainly belonging to Low-Middle Income Countries.[12] It ranges from 4 to 32% for 6-7 as well as 13-14 years of age.[13] However, in Indian children, the overall weighted mean prevalence has been observed to be 2.74.[14]

Pharmacotherapy of asthma includes various drugs like long acting β2 agonists (LABA), short acting β2 agonists (SABA), corticosteroids, xanthene derivatives and leukotriene receptor antagonists (LTRA). Either these drugs are used alone or in combination.[15]

Almost every drug is associated with ADRs that range from mild to serious and life threatening.[16] As compared to adults, children are more susceptible to ADRs due to various factors such as age dependent physiological changes, absence of evidence-based studies evaluating safety and efficacy of paediatric drugs and use of off-label and un-licensed drugs.[17]

About 7.7% ADR rates have been recorded in children of age group 0-17 years by the WHO Global Individual Case Safety Report (ICSR) database.[18] Since, the number of ADRs reported in paediatric population are considerably high, as such, effective methods to identify ADRs need to be implemented.[19],[20]

In 2004, the concept of Pharmacovigilance was put forth by WHO. It is defined as the science and activities related to the detection, assessment, understanding, and prevention of ADR or any other medicine related problem.[21] It mainly aims to detect new ADRs, their documentation as well as assessment of observed ADRs.[22]

Globally, several pharmacovigilance studies for monitoring ADRs related to anti-asthmatic drugs have been performed. But in India, such ADR reporting is scarce.[23] Moreover, studies involving ADR monitoring in paediatric asthma patients are also limited. Hence, this study was planned to observe the occurrence of the adverse drug reactions associated with pharmacotherapy of pediatric bronchial asthma

MATERIALS AND METHODS

It was an observational, non-interventional and cross-sectional study that was conducted in Department of Pediatrics, Niramay Hospital at Aurangabad. The study commenced following the approval of the Institutional Ethics Committee. A written informed consent form (ICF) and Assent form (if applicable) were obtained from paediatric patients participating in the study. Pediatric patients of bronchial asthma (both acute and chronic cases) of either sex and age between 1-17 years who attended outpatient department (OPD) or inpatient department (IPD) from November 2017 to March were included in the

study. Following patients were excluded: immunocompromised, with other co-morbid conditions like TB, Diabetes/renal failure, with other systemic disorders and those taking more than ten prescription drugs.

All information pertaining to the patient such as their age, gender, demographic details, relevant history, past history and drug therapy was recorded. Details of the anti-asthmatic drugs, and all other drugs used in the patient during treatment were also recorded. The ADRs experienced by the patients were documented. Further, all the information required for the assessment of reported ADR such as the type of reaction, its onset, duration, suspected drug, system affected and treatment for the drug reaction was also recorded.

The causality of the reported ADRs was assessed by using the WHO-UMC and Naranjo's scale and the severity of the reactions were analyzed using modified Hartwig and Siegel's scale in accordance with the recommendation by the WHO Uppsala Monitoring Center.[24]

RESULTS

During the study period, 330 asthmatic children attended paediatric OPD and IPD. A total of 41 ADRs were reported in 330 patients. Analysis of the gender distribution among the patients who experienced ADRs revealed that 24 (58.53%) were males and 17 (41.46%) were females.

The incidence rate of ADRs was found to be 12.42%. The frequency of ADRs was maximum (43.9%) in patients of age group of 5-8 years followed by patients of age group of 9 to 12 years with 31.7% of ADRs. However, minimum (7.31%) ADRs were observed in the age group of 1-4 years. (Table-1) Among the reported ADRs, 40 (97.56%) cases were of type A reactions which are predictable. Only 1 (2.43%) suffered from Type B reaction. None of the ADRs were of type B, C, D, E and F. The number of ADRs were more with patients who were treated with polypharmacy (92.68%) as compared to monotherapy (7.32%).

Table-1: Age and Gender wise distribution of ADRs

Age group in years	Number of patients with ADRs		Number of patients with ADRs (%)
	Male	Female	
1-4	1	2	2 (7.31)
5-8	10	8	18 (43.9)
9-12	10	3	13 (31.7)
13-17	3	4	7 (17.07)
Total	24	17	41

Figures in parentheses show percentage

Adverse drug reactions affecting the central nervous system predominated with 26.82% followed by gastro-intestinal system (19.51%) and ENT (19.51%). Other affected systems were cardiovascular system (12.19%), respiratory system (9.75%), skin and mucus membranes (9.75%) and musculoskeletal system (2.43%). The above details are shown in Table-2.

Table-2 Adverse drug reaction and organ system involved

Organ System Involved	No. of ADRs (%)
CNS	11 (26.82)
GIT	8 (19.51)
ENT	8 (19.51)
CVS	5 (12.19)
Respiratory	4 (9.75)
Skin and Mucus membranes	4 (9.75)
Musculoskeletal	1 (2.43)
Total	41 (100)

Figures in parentheses show percentage

On distribution of ADRs across therapeutic classes, it was observed that corticosteroids (budesonide and fluticasone) were responsible for causing highest number of ADRs i.e. 11 (26.82%). These were succeeded by SABA (salbutamol and levosalbutamol) responsible for 21.95% of ADRs and LTRA (montelukast) with 17.07% of ADRs. Use of anticholinergics (ipratropium bromide) caused 14.63% of ADRs. Administration of antibiotics (amoxicillin, azithromycin) as well as antihistamines (phenylephrine and levocetirizine) resulted in 7.31% of ADRs as shown in Table-3.

Table-3: Therapeutic classes of drugs involved in causing adverse drug reactions

Therapeutic Class	Number of ADRs (%)
SABA	9 (21.95)
LABA	2 (4.87)
Corticosteroids	11 (26.82)
Anticholinergics	6 (14.63)
LTRA	7 (17.07)
Antibiotics	3 (7.31)
Antihistamines	3 (7.31)

Figures in parentheses show percentage; SABA- Short acting beta 2 agonist, LABA- Long acting beta 2 agonist, LTRA- Leukotriene receptor antagonist

Percentage of various kinds of ADRs for suspected drugs were also calculated individually as shown in Table-4. The most commonly occurring ADRs were headache (14.63%), sore throat (14.63%), tachycardia (12.19%), dryness of mouth (9.75%), cough (9.75%), drowsiness (7.31%) and oral candidiasis (7.31%). Other ADRs were comparatively less.

Table-4: Number and types of adverse drug reactions and their suspected drugs

Type of ADR	Suspected Drugs	No. of ADRs (%)
Headache	Montelukast, Salmeterol	6 (14.63)
Sore throat	Budesonide, Fluticasone	6 (14.63)
Tachycardia	Salbutamol, Levosalbutamol, Salmeterol	5 (12.19)
Dryness of mouth	Ipratropium bromide	4 (9.75)
Cough	Levosalbutamol, Montelukast, Ipratropium bromide	4 (9.75)
Drowsiness	Phenylephrine, Levocetirizine	3 (7.31)
Oral candidiasis	Budesonide, Fluticasone	3 (7.31)
Tremors	Salbutamol	2 (4.87)
Nausea/ Vomiting	Levosalbutamol, Azithromycin	2 (4.87)
Diarrhoea	Azithromycin, Amoxicillin	2 (4.87)
Rhinitis	Levosalbutamol	1 (2.43)
Rash	Montelukast	1 (2.43)
Hoarseness	Fluticasone	1 (2.43)
Myalgia	Fluticasone	1 (2.43)

Figures in parentheses show percentage

According to the WHO causality assessment scale, 17 (41.46 %) ADRs were probable and 24 (58.53 %) were possible as shown in Figure-1. Similarly, causality assessment of ADRs by Naranjo's scale revealed that 17 (41.46%) ADRs were probable and 24 (58.53%) were possible as shown in Figure-2. All the recorded ADRs were also assessed for their severity with the help of Hartwig's scale and it was observed that 35 (85.36 %) ADRs were mild and only 6 (14.63 %) were moderate in their level of severity as indicated in Figure-3. However, no severe ADR was recorded during the study period.

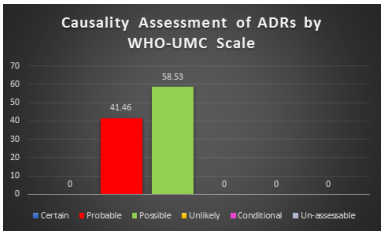

Figure-1: Causality assessment of ADRs according to WHO-UMC Scale

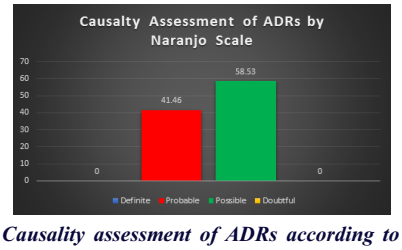

Figure-2: Causality assessment of ADRs according to Naranjo's Scale

Out of 41 cases of the Adverse drug reactions, the suspected drug was continued despite the occurrence of ADR with or without utilizing medical treatment to overcome the reactions in 31 (85.42 %) patients. 1 (2.43%) case experienced decrease in the dose of the suspected drug the suspected drug was discontinued from use and medical treatment was given to manage ADR in 1 (2.43 %) case. In 6 (14.63%) patients, the suspected drug was discontinued without involving any medical treatment for ADR management. In the remaining 2 (4.87%) cases, the suspected drug was discontinued and replaced by another suitable drug.

DISCUSSION

Adverse drug reactions constitute an important clinical problem in children. Studies have confirmed that every year minimum one in 500 children will suffer from ADRs.[25]

In the present observational study, total 41 ADRs were reported in 330 asthmatic children. It has been observed that females are more susceptible to the adverse drug reactions as compared to males.[26] This is because females exhibit gender specific additional sensitivity to the effect of drugs.[27],[28]

In studies by Bhosale et al (2013) and Gawali UP et al (2017), ADRs were majorly observed in females.[16],[29] However, the incidence of ADRs in our study was more in males (58.53%) as compared to females (41.46%).

Maximum number of ADRs (43.9%) were observed in asthmatic children of age group of 5-8 years. All the reported ADRs were of mild to moderate category. None of the ADR was severe.

Of the different group of Anti-asthmatic drugs that were administered to the patients, corticosteroids (budesonide and fluticasone) were responsible for causing maximum ADRs (26.82%) followed by short acting beta 2 agonists and leukotriene antagonists. Similar findings were reported in a study by Bajaj et al (1999) that observed highest incidence of ADRs with corticosteroids usage followed by the use of beta 2 agonists.[30]

As per the summary of product characteristics (SmPC), use of montelukast in children results in headaches, abdominal pain, rash, thirst, hyperkinesia, asthma and eczema.[31] In our study, use of montelukast was found to be associated with ADRs like headache, cough and rash. Montelukast was discontinued in patient that developed rash and symptoms were treated with antihistamines.

The administration of salbutamol, levosalbutamol and salmeterol through inhalational route caused Tachycardia in 5 children for which the suspected drugs were discontinued. Only in case of salbutamol induced tachycardia, salbutamol was replaced by levosalbutamol.

Budesonide and fluticasone administered via inhalational route caused sore throat and oral candidiasis in 14.63% and 7.61% children respectively. Maintaining oral hygiene after using the steroid inhaler may reduce the risk of oral candidiasis.[32] As such, counselling was provided to maintain oral hygiene after every inhalation of corticosteroids.

Tremors caused due to salbutamol necessitated discontinuation of suspected drug. Use of ipratropium bromide commonly caused dryness of mouth and its dose was reduced in one patient. Similar trend was observed in a study by Bhosale et al (2013).[16] Cough was seen in patients receiving levosalbutamol, montelukast and ipratropium bromide, out of which, only ipratropium bromide induced cough was managed with antitussives.

Antibiotic associated diarrhea can be treated by discontinuation or change of implicated antibiotic and give supportive management with fluid and electrolytes, if required.[33] In present study, use of antibiotics caused diarrhea in only 2 patients which was managed only by rehydration. One patient reporting nausea/vomiting due to levosalbutamol administration was treated with an antiemetic. Remaining ADRs were well tolerated.

Evaluation of ADRs according to WHO-UMC and Naranjo's scale showed that majority of the ADRs were in possible category. A similar study was conducted by Jamali et al (2010) which showed that most of the ADRs had a possible causality score (60%), followed by probable causality score (40%).[23]

CONCLUSION

Adverse drug reactions associated with anti-asthmatic drugs are quite common. This study highlights the need of rigid ADR monitoring in paediatric asthma patients to ensure safe pharmacotherapy. Adherence to pharmacovigilance guidelines and practices will not only reduce the incidence of ADRs but also reduce cost. As such, various pharmacovigilance awareness programs should be implemented to sensitize health care professionals about spontaneous reporting of ADRs. This will help in preventing morbidity as well as mortality in this vulnerable population.

REFERENCES

1. Elzagallaai AA, Greff M, Rieder MJ. Adverse drug reactions in children: the double-edged sword of therapeutics. Clin Pharmacol Ther. 2017;101(6):725–35.
2. Wester K, Jonsson AK, Spigset O, Druid H, Hagg S. Incidence of fatal adverse drug reactions: a population-based study. Br J Clin Pharmacol. 2008; 65: 573–579.
3. Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. JAMA. 1998; 279:1200–5.
4. Impicciatore P, Choonara I, Clarkson A, Provasi D, Pandolfini C, Bonati M. Incidence of adverse drug reactions in paediatric in/out-patients: a systematic review and meta-analysis of prospective studies. Br J Clin Pharmacol. 2001; 52:77–83.
5. Temple ME, Robinson RF, Miller JC, Hayes JR, Nahata MC. Frequency and preventability of adverse drug reactions in paediatric patients. Drug Saf. 2004; 27:819–29.
6. Kongkaew C, Noyce PR, Ashcroft DM. Hospital admissions associated with adverse drug reactions: A systematic review of prospective observational studies. Ann Pharmacother 2008; 42:1017-25.
7. Smyth RM, Gargon E, Kirkham J, et al. Adverse drug reactions in children--a systematic review. PLoS One. 2012;7(3): e24061. doi:10.1371/ journal. pone. 0024061
8. Kohli SK, Sattigeri BM. Adverse drug reactions in pediatric asthma patients attending a tertiary care teaching hospital. 2018; 8 (7): 44-46.
9. GINA report. Global Strategy for Asthma Management and Prevention, 2011, http://www.ginasthma.org/
10. Braman SS. The global burden of asthma. Chest. 2006;130 1 Suppl:4S-12.
11. Whealth reports 2001. Fifty facts from the world health report 1998: Global Health Situation and Trends 1955-2025. WHO. 2001
12. Ferrante G, La Grutta S. The Burden of Pediatric Asthma. Front Pediatr. 2018; 6:186.
13. International study of Bronchial Asthma and allergies in childhood (ISAAC) Worldwide variations in the prevalence of Bronchial Asthma symptoms. Euro Respir J. 1998; 12: 315–35.
14. Pal R, Dahal S, Pal S. Prevalence of bronchial asthma in Indian children. Indian J Community Med. 2009;34(4):310–316.
15. Sun HL, Kao YH, Chou MC, Lu TH, Lue KH. Differences in the prescription patterns of anti-asthmatic medications for children by paediatricians, family physicians and physicians of other specialties. J Formos Med Assoc. 2006 Apr; 105(4):277-83.
16. Bhosale U, Jaiswal S, Yegnanarayan R, Godbole G. A pharmacovigilance study of anti-asthmatic agents in patients of bronchial asthma at a tertiary care hospital. J Clin Exp Res 2013; 1: 26-30.
17. Black C, Tagiyeva-Milne N, Helms P, Moir D. Pharmacovigilance in children: detecting adverse drug reactions in routine electronic healthcare records. A systematic review. Br J Clin Pharmacol. 2015;80(4):844–854.
18. Star K, Noren GN, Nordin K, Edwards IR. Suspected adverse drug reactions reported for children worldwide: an exploratory study using VigiBase. Drug Safety. 2011; 34(5): 415-428.
19. Al Tajir GK, Kelly WN. Epidemiology, comparative methods of detection, and preventability of adverse drug events. Ann Pharmacother. 2005; 39:1169–74.
20. Kunac DL, Kennedy J, Austin N, Reith D. Incidence, preventability, and impact of adverse drug events (ADEs) and potential ADEs in hospitalized children in New Zealand: A prospective observational cohort study. Pediatric Drugs. 2009; 11: 153–60.
21. WHO policy perspective of medicines, Pharmacovigilance: Ensuring the safe use of medicines. Geneva: WHO; 2004. p. 1222-39.
22. Malcolm G, Kavita D, Akanksha S, Preeti G. Pattern of adverse drug reactions to antibiotics commonly prescribed in department of medicine and pediatrics in a tertiary care teaching hospital, Ghaziabad. JAPS. 2015; 5(4):78–82.
23. Jamali AN, Aqil M, Alam MS, Pillai KK, Kapur P. A pharmacovigilance study on patients of bronchial asthma in a teaching hospital. J Pharm Bioallied Sci. 2010;2(4):333–336.
24. Smith CC, Bennett PM, Pearce HM, Harrison PI, Reynolds DJ, Aronson JK, et al. Adverse drug reactions in a hospital general medicine unit meriting notification to the Committee on Safety of Medicines. Br J Cln Pharmacol. 1996; 42: 423–9.
25. Sindhu AR, Sebastian M, Panicker PR, Muthusamy S, Nallasamy V5, Ramanathan R, Perumal S. A study on adverse drug reactions in hospitalized pediatric patients in a Tertiary Care Hospital. J Appl Pharm Sci, 2019; 9(09):072–076.
26. Choi IS. Gender-specific asthma treatment. Allergy Asthma Immunol Res. 2011;3(2):74–80.
27. Barranco P, Lopez-Serrano MC. General and epidemiological aspects of allergic drug reactions. Clin Exp Allergy 1998; 28:61-2.
28. Riedl MA, Casillas AM. Adverse drug reactions: Types and treatment options. Am Fam Physician 2003; 68:1781-91.
29. Gawali UP, Deshkar A. Pharmacovigilance study of anti-asthmatic agents in patients of bronchial asthma at a tertiary care centre. Int. J. Adv. Res.2017; 5(3), 1867-71.
30. Bajaj A, Balakrishna S, Sawarkar S. Assessment of therapeutic performances of inhalation aerosols and clinical pharmacist's services in PFT lab. Indian J Hosp Pham. 1999; 36:138–142.
31. Dutch Children's Formulary . (2016). Avaliable at: https://www.kinderformularium.nl
32. Al-Moamary MS, Alhaider SA, Alangari AA, Al Ghobain MO, Zeitouni MO, Idrees MM, Alanazi AF, Al-Harbi AS, Yousef AA, Alorainy HS, Al-Hajjaj MS. The Saudi Initiative for Asthma - 2019 Update: Guidelines for the diagnosis and management of asthma in adults and children. Ann Thorac Med 2019; 14: 3-48
33. Alam S, Mushtaq M. Antibiotic associated diarrhea in children. Indian Pediatr 2009; 46: 491– 6.