

IDENTIFICATION AND ASSESSMENT OF ADVERSE DRUG REACTIONS IN PATIENTS WITH BRONCHIAL ASTHMA RECEIVING ANTI-ASTHMATIC MEDICATION

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Abstract:

Introduction: Bronchial Asthma is a disease of the airways characterized by increased responsiveness of the tracheobronchial tree to stimuli. More than 300 million individuals are currently suffering from asthma worldwide and about one tenth of these live in India. Treatment for asthma needs to be taken for long term and therefore, it is important to monitor the adverse drug reactions associated with the medicine use.

Methods: This was a prospective observational study conducted in a tertiary care hospital. Total 193 consecutive cases of asthma were included during one year who attended the medicine outpatient department. The enrolled patients were interviewed in OPD on weekly basis. Drug reaction history and prescription details were noted during each episode of ADR. Causality and preventability assessment was done by using Naranjo's and Modified Schumock and Thornton assessment scale.

Results: Total 23 ADRs were observed in 19 patients of age group of 21-70, out of which 11 were seen in women (52.89%) and 8 in men (42.10%). β_2 agonists (Salmeterol) showed maximum number of ADRs, 8 (34.7%). Monotherapy showed 10 ADRs (57%) in 7 patients, while 13 ADRs in 12 patients were observed with combination therapy. On causality assessment we observed 10 ADRs had probable cause, while 13 ADRs had possible cause. In the preventability assessment, 12(52%) ADRs were probably preventable.

Conclusion: The β_2 agonist drug class showed highest number of ADRs. There was no significant difference in ADRs in combination and monotherapy.

Keywords: Anti-asthmatics, Pharmacovigilence, Naranjo's, Schumock and Thornton scale

Introduction

Bronchial Asthma is a disease of the airways characterized by increased responsiveness of the tracheobronchial tree to multiple stimuli. It is manifested by narrowing of

the passages, which may be relieved either spontaneously or as a result of therapy, and clinically it is presented as paroxysms of dyspnoea, cough and wheezing.¹

The burden of asthma is immense, with

more than 300 million individuals currently suffering from asthma worldwide and about one tenth of those living in India.²

Pharmacovigilance is an integral part of clinical research. It is the science and activities relating to the detection, assessment, understanding, and prevention of ADRs, or any other medicine related problems, particularly long and short term side effects of medicines.⁸ The probability that the ADR is related to drug is confirmed by using Naranjo's scale which classifies these ADRs as definite, probable, possible or doubtful.¹⁰

Reports on monitoring of ADRs in India are scarce and prevalence and severity of these ADRs remain undetected due to lack of pharmacovigilance studies in Indian context. Hence this study was planned to observe the ADRs in patients receiving anti-asthmatic medications.

Materials And Methods

This was a prospective observational study conducted at a tertiary care hospital with the objective to observe ADRs of medications which were commonly prescribed to asthma patients. The study protocol was approved by Institutional Ethics Committee. The study was conducted by the Department of Pharmacology in collaboration with Department of Medicine from Jan 2013 to Jan 2014. Total 193 consecutive cases of asthma attending the medicine OPD of Government Medical College, Aurangabad were included. Written informed consent and detailed information were taken regarding medical history, drug history and demographic information. Study participants enrolled were having age 18 years and above, of either gender and diagnosed by the physician to be suffering from bronchial asthma. Patients excluded were those having status asthmaticus or any other complication, history of psychiatric disorders, acute coronary syndrome or any associated cardiac abnormality, patients on chemotherapy or anti-retroviral therapy or patients receiving medications from other than allopath. Patient evaluation was done weekly in OPD and later telephonically. Causality assessment was done by using Naranjo's causality assessment which classifies drug reaction into definite, probable, possible and doubtful. Preventability of ADR was assessed by using modified Schumock and Thornton scale. Data was analysed for gender and age preponderance. This assigned a weighted score of the component used to establish a

causal association between drug and ADRs. Data was analysed by using graph pad prism and association between two discrete variables was assessed using 2- sample t-test.

Result And Observation

Total 193 patients were enrolled in this study amongst whom 23 ADRs were noted in 19 patients. Maximum ADRs were observed in the age group 31-40 years (n-7) and numbers of ADRs observed in women (n-11) were more as compared to men (n-8) as shown in table 1.

Among all drug classes, β_2 agonists showed maximum ADRs as shown in Table 2 (n-10). Graph 1 shows that number of patients receiving monotherapy and combination therapy. Number of ADRs observed in combination therapy (n-13) were comparatively more than that with monotherapy (n-10) but t-test showed $P > 0.005$ indicating that the difference was not statistically significant. Causality assessment according to Naranjo's scale (Graph 2) showed that 56.52% (n=13) of ADRs were possible and 43.4% (n=10) of ADRs had probable cause. Preventability of ADRs (Graph 3) was done according to modified the Shumock Thornton scale of which 12(52%) ADRs were probable, 8(35%) ADRs were definite while only 3 (13%) ADRs were not preventable.

Discussion

We observed that most of the patients with bronchial asthma received more than one drug by one or more routes of administration. Gender distribution presented with ADRs showed that 11(52.89%) were women and 8 (42.10%) were men. The higher incidence of ADRs in women can be justified on the basis of their gender specific additional sensitivity to the effect of drugs as compared to men.^{11,12} It has been reported that ADRs occur mainly in young and middle aged adults and is twice common in women.¹³

Studies have described differences in pharmacokinetics, drug response and toxicity between men and women as differences in weight and body mass index between men and women may be playing an important role.¹⁴ In our study majority of ADRs were of mild type and total ADRs (Table 5) observed were tremors, bitter taste, palpitation, oral candidiasis, oral thrush, dryness of mouth, GI distress, rash, sinus tachycardia, sore throat, cough, and nausea.

In this study maximum numbers of ADRs were observed with β_2 agonists and highest number of ADRs per prescription were found with Salmeterol (n=22, 18%) prescription, followed by Salbutamol which showed 4 ADRs in 69 (5.79%) prescriptions. This is inconsistent with other reports in which maximum ADRs (4 in 7 prescriptions, 57.1%) were reported with salbutamol followed by salmeterol (5 in 10 prescriptions, 50%).¹⁵ Our study corresponds with the observations of other workers in which tremor was associated with regular intake of short acting and long acting β_2 agonists in 2-4% of asthma patients.¹⁶

Amongst the corticosteroids, Fluticasone had total 3 (9.37%) ADRs as cough and oral thrush out of 32 prescriptions, while Budesonide showed oral candidiasis and Beclomethasone showed sore throat as associated ADRs. The results in this study were in accordance with other study in which Beclomethasone (n=1, 8.3%) showed oral candidiasis and Fluticasone (n=1, 3.2%) showed oral thrush as associated ADRs.¹⁷ Whereas, in a comparative study, a total of 19 ADRs (7.4%) were seen in 258 asthmatic patients treated with Fluticasone with varying distribution of ADRs as oral pharyngeal candidiasis (n=8, 3%), hoarseness (n=9, 3%), headache (n=4, 2%), sore throat (n=3, 1%), and insomnia (n=3, 1%).¹⁸

From Methylxanthines, Theophylline showed 2 (7.89%) ADRs i.e. GI distress and nausea. This drug is being widely prescribed as it is economical and cost alternative for poor patients especially in government hospitals despite its narrow therapeutic index. A study on Theophylline found dyspepsia (n-13,30.2%) anxiety(n-12,27.9%) and spasm of muscle (n-6,13.9%) as ADRs with it.¹⁹ Adverse drug effects of Theophylline are usually linked to plasma concentration and tend to occur when plasma concentration exceeds 25mg/l and therefore careful therapeutic drug monitoring is required to make dose individualization.

It has been reported that the maximum number of ADRs were seen with Montelukast (n=2,13.3%) which showed that headache and cough as associated ADRs.¹⁷ A similar observation was found with Montelukast in a study in 25 women patients where its 10 mg dose showed fever, rash, eosinophilia as associated ADRs.²⁰

In Anti-cholinergic group, Thiotropium as bronchodilator agent showed two (8.0%)ADRs in 24 prescriptions. The most common ADR found was dryness of mouth due to

its anticholinergic action. A similar observation was found in another study in which Thiotropium showed dryness of mouth.¹⁷ In Monotherapy (Table 7) we observed 10 (43%) ADRs in seven patients, while in combination therapy we observed 13 ADRs (57%) in 12 patients. The difference between two groups was negligible and not statistically significant (P <0.05). Similar observation was seen by others in which monotherapy showed 7(46.6%) ADRs and combination therapy showed 8(53.33%) ADRs.¹⁷ In another study there was no significant difference between monotherapy (5 ADRs in 4 patients) and combination therapy (8 ADR in 7 patients) (P <0.05).¹⁵

To strengthen the validity of the findings of our study, causality assessment was made for individual cases by using Naranjo's scale (table 8). We observed that 9 (39%) ADRs had probable cause, while 14(61%) ADRs had possible cause. Since re-challenge was not done in any patient due to ethical issues, we could not get any definite relationship. Similar observations were found by others in which Naranjo's causality scale showed 7.69% doubtful, 30.76% as possible and 53.85% as probable cause for ADRs.¹⁵ Another study observed 60% of the events were found to be possible while 40% had probable cause.¹⁷ Preventability was assessed by using modified Schumock and Thornton scale. We found that out of total ADRs, 52% were probably preventable, 35% were definitely preventable while only 13% of ADRs were not preventable. Others in Indian hospital observed that 54 (90.0%) ADRs were probably preventable and 06 (10.0%) were non preventable.²¹

Conclusion

Maximum ADRs were found in women as compared to men. The β_2 agonist drug class showed highest number of ADRs. Most of the ADRs observed were of possible causality and were probably preventable and no significant difference in ADRs was observed in combination and monotherapy. The result of this study highlights β_2 agonists or corticosteroids being the commonly prescribed anti-asthmatic medicines and therefore need careful monitoring of ADRs. It is prudent to impart proper counselling to the patients regarding the proper technique of use of inhalers which might be helpful in further prevention of ADRs. Effort should be made to replace the drugs causing ADRs with alternative drug available.

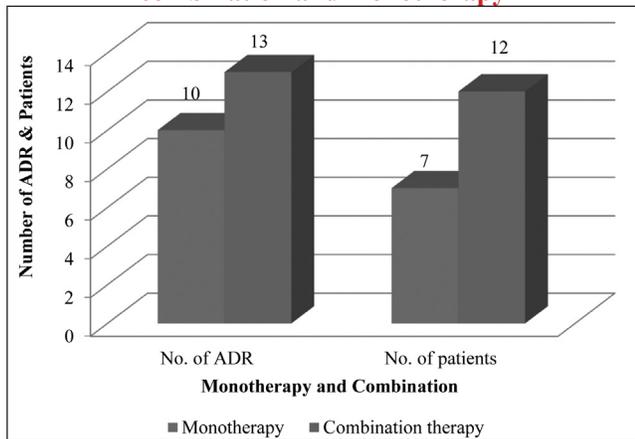
Table 1: Demographic characteristics of Asthma patients

| Age group (Years) | Adverse drug reactions | | | |
|-------------------|------------------------|-----|-------|----------------|
| | Women | Men | Total | Percentage (%) |
| 21-30 | 2 | 1 | 3 | 15.78 |
| 31-40 | 5 | 2 | 7 | 36.84 |
| 41-50 | 2 | 3 | 5 | 26.34 |
| 51-60 | 1 | 1 | 2 | 10.52 |
| 61-70 | 1 | 1 | 2 | 10.52 |
| Total | 11 | 8 | 19 | 100 |

Table 2: Anti-asthmatics Drug class and Incidence of ADRs

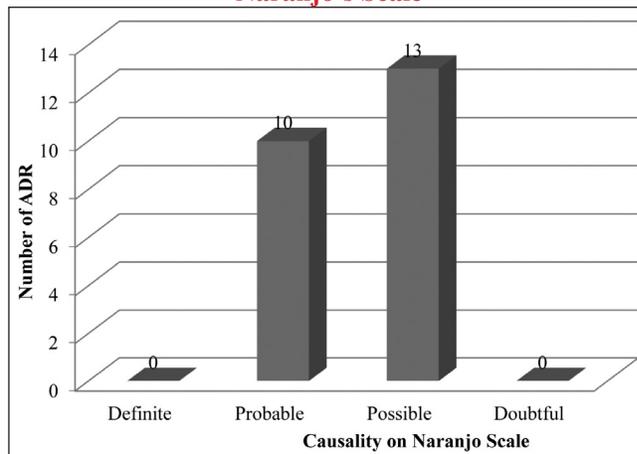
| Drug classes | Number of ADR's | Percentage (%) |
|------------------------|-----------------|----------------|
| β 2 agonist | 10 | 43.47 |
| Salbutamol | 4 | |
| Salmeterol | 4 | |
| Formeterol | 2 | |
| Corticosteroids | 6 | 26.0 |
| Budesonide | 2 | |
| Fluticasone | 3 | |
| Beclomethasone | 1 | |
| Methylxanthines | 3 | 13.10 |
| Anticholinergic | 2 | 8.69 |
| Leukotriene antagonist | 2 | 8.69 |
| TOTAL | 23 | 100 |

Graph 1: Incidence of ADRs in patients receiving combination and monotherapy

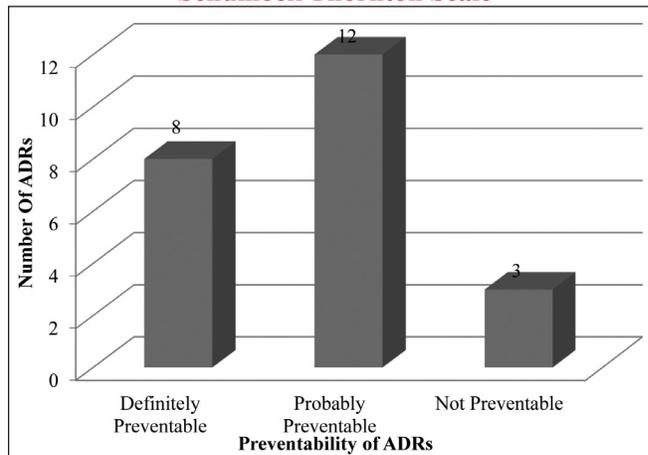


Causality assessment

Graph 2: Causality Assessment of ADRs according to Naranjo's Scale



3: Preventability of ADRs According to Modified Schumock Thornton Scale



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