Treatment of Allergic Bronchopulmonary Aspergillosis with Fluconazole and Itraconazole

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Abstract

Treatment of allergic bronchopulmonary aspergillosis (ABPA) has remained both problematic as well as controversial. Although the sheet anchor in treatment of ABPA still remains steroids, various workers have tried oral antifungals (fluconazole and itraconazole) with encouraging results. This study evaluates the effect of fluconazole or itraconazole in the treatment of ABPA patients and compares them with the patients who had received palliative therapy other than antifungals. Case records of 44 proven cases of ABPA treated at our referral service hospital during February 1998 to April 2001 were analyzed. In addition to oral and inhaled bronchodilators, 16 patients received fluconazole 150 mg OD and 13 patients itraconazole 200 mg OD for six months. Response to therapy was assessed clinically, radiologically and by spirometry every 3 months. Patients who did not receive antifungals had chronic course characterized by airway obstruction, recurrent pulmonary consolidation and obstructive defect on pulmonary function test (PFT). Patients treated with itraconazole had better control of asthma symptoms, less requirement of reliever inhalers, steroids and lesser exacerbations of asthma during follow-up even after stopping antifungal. Fluconazole group had better control of symptoms but improvement in other parameters was not statistically significant. From this study it was evident that itraconazole improved the symptoms of airway obstruction, pulmonary functions, pulmonary opacities and decreased exacerbations during follow up.

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Key Words : Allergic bronchopulmonary aspergillosis; Fluconazole; Itraconazole

Introduction

ABPA is an interesting form of hypersensitivity, which affects the tracheobronchial tree and can provoke asthma [1]. Hinson et al first described it in 1952 [2]. The initial British criteria of asthma, peripheral eosinophilia, pulmonary opacity and hypersensitivity to aspergillus antigen was further elaborated by American workers with addition of features like positive serum precipitin test to aspergillus antigen and central bronchiectasis [3-5]. Asthma predisposes to the development of ABPA and about 1-2% of all asthmatic patients present with ABPA [4]. ABPA is known to be present in more than 1/5th of all asthmatics who require hospitalization [4] and cases of severe persistent asthma are the potential candidates for ABPA. This condition was thought to be a rare disease in India [6] but with the availability of better diagnostic facilities like HRCT, aspergillus IgE, precipitin test and spirometry, increasing number of patients are being diagnosed.

Therapy can be long and protracted. While prednisone remains the mainstay of therapy for control and stability of ABPA [1,7-9] appropriate therapy of underlying asthma with anti-inflammatory and bronchodilator agents is essential. Attempts to prevent the growth of fungal mycelia within the bronchial tree with antifungals (ketoconazole, fluconazole and

itraconazole) have been tried with encouraging results [10-13]. We have thus carried out this study to evaluate the effects of treating ABPA patients with oral antifungal (fluconazole or itraconazole) and contrast the patients with a group who received only anti-inflammatory and bronchodilator agents and no antifungal drug.

Material and Methods

Case records of 44 cases of ABPA treated by us from February 1998 to April 2001 were analyzed. The patient population included serving and retired personnel and their family members. A detailed history and meticulous clinical evaluation was carried out. Investigations included chest X-ray, total and differential blood count, sputum for fungal stain, culture and eosinophilia, spirometry (pre and post bronchodilator), skin testing for aspergillus and IgE and IgM precipitin test in all patients. We could do HRCT chest in 40 patients and IgE against aspergillus by RAST in 36 patients. Pulse oxymetry and arterial blood gas was done only in severe cases. Fiberoptic bronchoscopy was done when required.

The diagnosis of ABPA was established as per the criteria in Table 1. The patients were grouped into control group and study group II and I. Group I comprised patients who received fluconazole 150 mg OD for 6 months (n=16). Patients in group II received itraconazole 200 mg OD for 6 months (n=13). Control group comprised 15 patients of ABPA who did not receive antifungals. The patients in all groups also received

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Table 1**Criteria used for diagnosing ABPA**

Criteria	Patients fulfilling criteria (N=44)
History of asthma	33
Peripheral eosinophilia	25
Recurrent pulmonary opacity	35
Skin reactivity to <i>A. fumigatus</i>	35
Fungal hyphae in sputum	15
Serum precipitin against aspergillus	11
Raised IgE against aspergillus	32/36
Central bronchiectasis	38/40

Table 2**Results in ABPA patients after one year**

Results	Control (N=15)	Group I (N=16) (p value)	Group II (N=13) (p value)
Symptomatic improvement	2	9 (p < 0.05)	11 (p < 0.01)
Required hospitalization	3	1 (NS)	0 (NS)
Required bronchodilators			
Regularly > once/day	12	8 (NS)	5 (p < 0.05)
Intermittent	3	6 (NS)	6 (NS)
Required rescue steroids	12	9 (NS)	5 (p < 0.05)
Maintenance steroids	11	8 (NS)	4 (p < 0.05)

NS - not significant

anti-inflammatory and oral or inhaled bronchodilator depending on their requirement. Patients were followed-up monthly in OPD and assessment of response was done once in 3 months.

Statistical test of significance between two proportions was calculated and p value obtained using EPIINFO-2000 software. In Table 2, we have compared control with group I and group II. Pulmonary function tests done initially and at 6 months treatment were compared in each group.

Results

During the study period a total of 44 patients were diagnosed as ABPA. There were 13 males and 31 females, their ages ranging from 20 to 78 years. Average age of the cohort was 45.6 years. History of bronchial asthma was present in 33 patients and bronchiectasis in 8 patients. History of antitubercular treatment was present in 27 patients (62%). Aspergillus was isolated in sputum on stain and culture in only 15 patients (34%). Skin test for aspergillus was positive

Table 3**PFT in ABPA patients**

PFT	Control (N=15)		Group I (N=16)		Group II (N=13)	
	Initial	At 6 months	Initial	At 6 months	Initial	At 6 months
Normal	0	0	0	1	1	2
Mild obstruction	1	3	3	5	4	5
Mod obstruction	5	4	5	4	4	3
Severe obstruction	7	6	7	6	3	2
Restriction	2	2	2	2	1	1

p value > 0.05 (not significant) in all groups

Fig.1: CT scan of chest showing bilateral central cystic bronchiectasis

Fig.2: CT scan of chest showing bilateral patchy pulmonary infiltrate with central bronchiectasis

in 35 patients (80%). IgE against aspergillus (by RAST technique) was raised in 32 out of 36 patients. Proximal

bronchiectasis was noted in 38 out of 40 patients in whom CT chest was done. Radiologic evidence of infiltrates was noted in decreased frequency in patients treated with itraconazole. No drug toxicity was noted in any patient.

Statistically significant symptomatic improvement was noted in group II patients receiving itraconazole. They required less dosage of reliever bronchodilators, rescue steroids and maintenance steroids for control of symptoms and prevention of exacerbations. The difference was statistically significant (Table 2). Group I patients receiving fluconazole also showed improvement in symptoms but improvements in other parameters were statistically not significant. The difference in pulmonary function test done initially and after 6 months in all the groups was statistically insignificant ($p > .05$).

Discussion

ABPA is a potentially destructive lung disease. Therefore, early diagnosis is essential to prevent the development of end stage lung fibrosis. Imaging and immunological techniques have been crucial in the early diagnosis of the disease and also help to monitor the progress of the disease. The evaluation of short-term therapy for ABPA is very difficult because of intermittent nature of the disease and its tendency to resolve spontaneously. Treatment is decided, for most part by the severity of symptoms and pulmonary function derangement. Prednisone remains the mainstay of therapy for ABPA [8, 9]. High dose of inhaled steroids may be useful in some patients and may allow reduction in the dose of oral corticosteroids [14].

Antifungal agents have been used to eradicate aspergillus from the bronchial tree, hopefully reducing the need for corticosteroids and thus stabilizing the patient. The administration of amphotericin-B by aerosol, along with corticosteroids, has been shown to be useful in small number of cases [10]. After a one year study with ketoconazole in patients with ABPA, asthma improved [11]. The newer imidazoles such as itraconazole and fluconazole have fewer side effects than ketoconazole. These drugs may be effective in eliminating aspergillus from the tracheobronchial tree and help in reduction in the dose of corticosteroids needed for control [12,13]. Long term safety and the effect of these oral antifungal drugs on progression of ABPA have not yet been studied.

The present study concludes that newer imidazoles, especially itraconazole has got definite adjunctive role in the management of ABPA and is relatively safe. It led to better control of asthma, improvement in lung function, reduction in steroid dose and mean total serum IgE levels.

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