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Original Research Article

Use of Meter Dose Inhaler (MDI) Corticosteroid Therapy, May Cause Tuberculosis, in Patients with Bronchial Asthma

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Abstract
Objective: *The aim of present study was to evaluate the incidence and pattern of tuberculosis in Bronchial asthma patients receiving inhalational corticosteroid therapy by MDI.*
Materials and Method: *A total of 76 patients taking MDI steroid for bronchial asthma, and 76 patients suffering from the similar disease but not receiving MDI steroids serves as a control, were included in the study and evaluate for the incidence and pattern of tuberculosis. All the patients were followed up for 18 months.*
Results: *Out of 76 patients, 4 patients (5.26%) receiving MDI steroid developed tuberculosis as against patients not receiving MDI steroid, out of 4 patients, who developed tuberculosis, one developed sputum smear positive pulmonary disease, one had sputum smear negative disease and two had extra pulmonary tuberculosis in the form of pleural effusion and tubercular lymphadenitis one each. All patients were treated with standard anti tuberculous therapy using RNTCP guidelines and all patients recovered from the disease.*
Conclusion: *Inhalational corticosteroid in the form of MDI causes a significant increase in incidence of tuberculosis.*
Keywords: *Tuberculosis, Bronchial asthma, MDI, pleural effusion, Incidence.*

Introduction

Tuberculosis is a serious public health problem in India causing immense morbidity, mortality and distress to individual's families and community.

More than 1.7 billion people, about 25 percent of the world population are estimated to be infected with Mycobacterium tuberculosis. The global incidence of TB peaked around 2003 and appears to be declining slowly. According to the World Health Organization (WHO), in 2017, 10 million individuals became ill with TB and 1.6 million died.

In India about 40% of the population is infected with tuberculosis, 15 million suffers from Tb, of whom 3 millions are highly infectious open cases and 2.3 million peoples are affected annually. In India an estimated 0.5 million deaths occur from

tuberculosis every year, one every 3 minutes or 1000 death per day.

The predisposing factors for tuberculosis are poverty, malnutrition, overcrowding, smoking, long term corticosteroid therapy, immunosuppressive and anticancer therapy, and co-infection with HIV, alcoholic, presence of diabetes mellitus, renal transplant and gastrojejunostomy. Bronchial asthma supposed to be an allergic disease in which different allergens by a set of immunological reactions superimposed by neurological actions cause release of mediators of inflammation, causing bronchial hyper responsiveness, mucus hypersecretion and paroxysmal attacks of bronchoconstriction, manifesting as wheeze, cough and dyspnea. Anti inflammatory drugs like oral and inhalational corticosteroid in form of MDI play a major role in abutting an acute attack of asthma as well as they are useful in management of chronic asthma. Corticosteroid used in MDI are beclomethasone diapropinate (100 mcg, 200 mcg), Budesonide (100 mcg, 200 mcg), fluticasone propionate (250 mcg) and Formoterol (200 mcg, and 400 mcg) etc. have local anti-inflammatory effects and are useful in management of bronchial asthma. Corticosteroids cause systemic disease by impairing antibody production and cell mediated immunity, and there by blunting the patients response to infections. So treatment with MDI in bronchial asthma might facilitate infection with mycobacterium tuberculosis in the form of either re - infection or reactivation.

This study evaluates the possible role of corticosteroid in causing tuberculosis in patients with bronchial asthma necessitating use of MDI therapy.

Material and Methods

Present study was conducted in the Department of Pharmacology, Sri Krishna Medical College, Muzaffarpur with the help of Department of Medicine, during the period of February 2017 to October 2018.

A total of 76 patients suffering from bronchial asthma and taking MDI corticosteroid therapy were included in the study group and equal number of patients suffered from bronchial asthma not taking MDI corticosteroid therapy were serves as a control group. From all the patients detailed clinical history, use of MDI steroid, thorough clinical examinations and relevant investigations were done. After diagnosis of tuberculosis anti-tuberculosis therapy was started. Patients of both groups were followed for 18 months. Patients with preexisting tuberculosis or giving past history of intake of anti tuberculous therapy (ATT) were excluded from study. All patients in study and control groups were followed for 18 months at 3 month intervals. On each follow up visit response of MDI corticosteroids therapy and development of fresh symptoms such as fever, cough, expectoration, hemoptysis, loss of weight, loss of appetite and breathlessness were recorded. Chest X-rays were done for assessment of emergence of fresh pulmonary infections and for evaluation of previous shadows. All suspects developing fresh respiratory symptoms and infiltrates in X-rays were subjected to sputum examination for acid fast bacilli (AFB) using Ziehl-Neelson stain on two consecutive days. Additional tests such as pleural fluid analysis, pleural biopsy, fine needle aspiration cytology and/or biopsy of enlarged nodes, bronchoalveolar lavage (BAL), transbronchial lunge biopsy and HRCT scan of chest were also done for confirmation of tuberculosis whenever required. All subjects confirmed or strongly suspected to have developed tuberculosis were started on anti tuberculous chemotherapy using RNTCP regimen as per WHO guidelines, and comparison between two groups were carried out.

Results

Out of 76 patients, 4 patients (5.26%) receiving MDI steroid developed tuberculosis as against patients not receiving MDI steroid, out of 4 patients, who developed tuberculosis, one developed sputum smear positive pulmonary

disease, one had sputum smear negative disease and two had extra pulmonary tuberculosis in the form of pleural effusion and tubercular cervical lymphadenitis one each. All patients who developed tuberculosis were treated successfully with RNTCP regimen according to WHO guideline. Multiple logistic analysis were done to evaluate risk factors like age, sex, underline disease, maximum dose of inhalational corticosteroid, duration of treatment and additional supportive therapy. The incidence of tuberculosis did not show significant association with any of this variable.

Discussion

Over the years, several studies have been carried out to determine the influence of corticosteroid therapy in development of tuberculosis but none is done with inhalational corticosteroid therapy. In 1971, a joint statement of American Thoracic Society, National Tuberculosis and Respiratory Disease Association and Communicable Disease Centre, commented that there is danger of reactivation of latent tuberculosis or developing re-infection with mycobacterium tuberculosis after therapy with corticosteroid and recommended that patients with healed pulmonary tuberculosis receiving systemic corticosteroid should receive isoniazid prophylaxis. Am J Respir Crit. Care Med. 2011, also published the study of effects of inhaled corticosteroid and risk of pulmonary tuberculosis and found no positive correlation. American College of Chest Physician in October 15, 2012, published in chest journal that inhaled corticosteroid is associated with an increased risk of tuberculosis in patients with chronic obstructive pulmonary disease (COPD). Corticosteroids, through their immunosuppressive and anti-inflammatory effects on many organ systems, impair antibody formation and cell mediated immunity. They transiently sequester T-cells, decreased monocytes, lymphocyte, basophil, eosinophil count in peripheral blood, and reduce polymorphonuclear inflammatory response. They also inhibit cytokine production through the effects on lymphocyte and monocyte and additionally block the effects of cytokine on some target cells. Through these actions corticosteroid predisposes patients to a variety of secondary infections, reactivation of latent tubercular infection, and re-infection with mycobacterium tuberculosis. These effects on cells are more evident if inhaled corticosteroid doses exceed 1000 mg/day, the therapy is given continuously for longer period. The prolonged therapy has more profound immunosuppressive activity as compare with intermittent therapy. In our study, 4 cases out of 76 cases (5.26%) on MDI corticosteroid therapy developed tuberculosis. Out of 4 cases 1 were sputum smear positive (25%). The zero incidence of tuberculosis in control group (76 cases) is not surprisingly in light of estimated risk of tuberculosis of <1% per year in general population. The duration of MDI corticosteroid therapy before development of tuberculosis in the present study varied from 4 months to 18 months. This suggests that reactivation can occur either shortly after therapy is started, or several months or year later. In all 4 cases that developed pulmonary tuberculosis in this study, the appearance of fresh symptoms led to the suspicion of tuberculosis. A high index of suspicion is necessary for early detection of tuberculosis in these patients. The region for sputum negativity in one patient with pulmonary tuberculosis in this study could be antibiotics therapy (Levofloxacin and Amikacin) received by the patient before the diagnosis of tuberculosis. These drugs are second line anti tuberculosis drugs. All the patients in this study responded well to standard short course antituberculous chemotherapy under guidelines of RNTCP.

Conclusion

We conclude that there is the statistically significant increase in incidence of tuberculosis due to inhalational corticosteroid therapy, especially in areas with high prevalence of tuberculosis such as Bihar. The disease, however, response well to standard anti tuberculous

chemotherapy. Duration and dose of inhalational corticosteroid also influences the development of tuberculosis. A longer study, involving a large study population, would be desirable for further verification of these results.

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