

## Short communication

# Pulmonary tuberculosis in patients treated with inhaled beclomethasone

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W. A. Shaikh

Allergy Clinic, Bombay Hospital Institute of  
Medical Sciences, India

Inhaled beclomethasone dipropionate (BDP) has been used with few side-effects in the treatment of bronchial asthma for 2 decades. Until now the manifestation of tuberculosis (TB) in patients on inhaled BDP has not been reported. Eight patients with allergic asthma, of a total of 548 asthmatics (1.46%) seen over a 2-year period, developed active TB following the use of inhaled BDP. All were sputum-positive for acid-fast bacilli (AFB) on smear and/or culture, all responded well to a combination of anti-TB drugs, and none showed evidence of immunological or pituitary-adrenal suppression. Two patients agreed to a repeat administration of BDP; both developed TB again within 2 weeks and are again on anti-TB treatment.

Key words: allergy; asthma; beclomethasone dipropionate; tuberculosis.

Dr. Wiqar A. Shaikh  
Akash Apartments  
6th Floor, Flat no. 6  
Sane Guruji Road  
Bombay - 400011, India

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It is widely held that treatment with systemic corticosteroids may reactivate quiescent TB or increase the risk of new infection (7, 11, 17, 18). Inhaled BDP has been used in the treatment of bronchial asthma since 1972 (15) with a few side-effects such as local irritation, oropharyngeal candidiasis and hoarseness (12, 14). However, until now there have been no reports of manifestation of TB following inhaled BDP (2, 4, 5, 6, 8, 9, 12-17, 20).

Eight patients with allergic asthma of a total of 548 asthmatics (1.46%), seen over a 2-year period, developed active TB following the use of inhaled BDP. All eight patients were sputum-positive for acid-fast bacilli (AFB) on smear and/or culture; all responded well to a combination of isoniazid, rifampicin, and ethambutol; and none showed evidence of immunological or pituitary-adrenal suppression.

Two patients agreed to a readministration of BDP; both again developed TB within 2 weeks and are at present on treatment with isoniazid, rifampicin and pyrazinamide.

The Z-test was applied to compare the control (general) population with our sample TB population, and the test suggested that BDP had a statistically significant causal effect.

## Material and methods

A total of 548 allergic asthmatics were seen in the Allergy Clinic over a 2-year period; 218 had asthma and 330 had asthma with rhinitis. Each patient un-

derwent clinical evaluation, complete blood count, fasting erythrocyte sedimentation rate (ESR), serum IgE levels (radioimmunoassay), chest radiograph, allergy skin prick test with 90 common allergens, and spirometry and peak nasal inspiratory flow (by Youtlen's nasal inspiratory flow meter).

Each patient was started the same day on a BDP metered dose inhaler, 400 µg/day in four equally divided doses of 100 µg BDP. Patients were followed up regularly and the dose was increased up to 800 µg/day if symptoms were not alleviated.

Three of the above patients, each on 400 µg BDP for 3 weeks or more, coincidentally attended the clinic simultaneously for productive cough, fever, loss of appetite and malaise. Pulmonary TB was suspected and each patient was subjected to a chest radiograph, fasting ESR, and sputum for AFB smear (ZN stain) and culture (modified LJ medium). Since three patients with similar symptoms presented together, BDP was suspected as the possible causative factor and they were further subjected to evaluation of plasma cortisol levels (8 a.m. and 4 p.m.) (19), estimation of serum IgG levels (radial immunodiffusion) (19), Mantoux test (MT) (using PPD 1:1000 conc.), and ELISA test for human immunodeficiency virus (HIV). BDP was discontinued and salbutamol inhalations, 100 µg 3 times daily, were started in each patient.

Pulmonary TB being confirmed in the first three patients they were treated with isoniazid 300 mg, rifampicin 450 mg and ethambutol 800 mg/day.

Table 1.

| Criteria/Investigations                                          | Patients                    |                                                                                                                           |                                |                                 |                                                                                                                           |                                |                                       |                                |
|------------------------------------------------------------------|-----------------------------|---------------------------------------------------------------------------------------------------------------------------|--------------------------------|---------------------------------|---------------------------------------------------------------------------------------------------------------------------|--------------------------------|---------------------------------------|--------------------------------|
|                                                                  | 1                           | 2                                                                                                                         | 3                              | 4                               | 5                                                                                                                         | 6                              | 7                                     | 8                              |
| 1. Sex                                                           | Female                      | Male                                                                                                                      | Female                         | Male                            | Male                                                                                                                      | Female                         | Female                                | Male                           |
| 2. Age (in yr)                                                   | 18                          | 28                                                                                                                        | 29                             | 26                              | 38                                                                                                                        | 21                             | 22                                    | 22                             |
| 3. Diagnosis                                                     | Asthma + rhinitis           | Asthma + rhinitis                                                                                                         | Asthma + rhinitis              | Asthma + rhinitis               | Asthma                                                                                                                    | Asthma                         | Asthma + rhinitis                     | Asthma + rhinitis              |
| 4. Serum IgE levels (kU/l) normal: <50 kU/l                      | 620                         | 1500                                                                                                                      | 750                            | 450                             | 250                                                                                                                       | 1280                           | 310                                   | 1200                           |
| 5. Allergy skin test (No. positives)                             | 16                          | 24                                                                                                                        | 12                             | 11                              | 11                                                                                                                        | 11                             | 28                                    | 12                             |
| 6. Pulmonary functions                                           | Normal                      | Mild obstruction                                                                                                          | Mild obstruction               | Normal                          | Combined moderately severe obstruction and restriction                                                                    | Mild obstruction               | Severe obstruction                    | Normal                         |
| 7. Pre-treatment chest radiograph (taken on day BDP was started) | Normal                      | Normal                                                                                                                    | Normal                         | Normal                          | Normal                                                                                                                    | Normal                         | Normal                                | Normal                         |
| 8. Fasting ESR levels in mm (pretreatment)                       | 12                          | 4                                                                                                                         | 10                             | 8                               | 8                                                                                                                         | 10                             | 11                                    | 7                              |
| Normal: (Westgreen)                                              |                             |                                                                                                                           |                                |                                 |                                                                                                                           |                                |                                       |                                |
| Males: 0 to 10 mm in 1 h                                         |                             |                                                                                                                           |                                |                                 |                                                                                                                           |                                |                                       |                                |
| Females: 0 to 15 mm in 1 h                                       |                             |                                                                                                                           |                                |                                 |                                                                                                                           |                                |                                       |                                |
| 9. Past H/O TB or anti-TB treatment                              | No                          | No                                                                                                                        | Anti-TB treatment in childhood | No                              | No                                                                                                                        | Anti-TB treatment in childhood | No                                    | Anti-TB treatment in childhood |
| 10. Time lag between starting BDP and discovery of active TB     | 26 days                     | 21 days                                                                                                                   | 30 days                        | 20 days                         | 25 days                                                                                                                   | 35 days                        | 31 days                               | 30 days                        |
| 11. Fasting ESR levels in mm (after onset of symptoms)           | 32                          | 26                                                                                                                        | 52                             | 30                              | 21                                                                                                                        | 56                             | 19                                    | 24                             |
| 12. Sputum for AFB (smear)                                       | Negative                    | Positive                                                                                                                  | Positive                       | Positive                        | Negative                                                                                                                  | Positive                       | Negative                              | Positive                       |
| 13. Sputum for AFB (culture)                                     | Positive                    | Positive                                                                                                                  | Positive                       | Positive                        | Positive                                                                                                                  | Positive                       | Positive                              | Positive                       |
| 14. Chest radiograph (after onset of symptoms)                   | Rt. upper lobe infiltration | Bilateral upper lobe infiltration                                                                                         | Rt. Upper lobe infiltration    | Extensive rt. lung infiltration | Bilateral upper lobe infiltration                                                                                         | Lt. upper lobe infiltration    | Lt. upper and lower lobe infiltration | Bil. upper lobe infiltration   |
| 15. Mantoux test (positive reaction in mm)                       | 18 mm                       | 28 mm                                                                                                                     | 21 mm                          | 27 mm                           | 32 mm                                                                                                                     | 19 mm                          | 21 mm                                 | 33 mm                          |
| 16. Plasma cortisol levels                                       | 8 am<br>147                 | 152                                                                                                                       | 136                            | 175                             | 164                                                                                                                       | 166                            | 153                                   | 146                            |
| Normal values –                                                  |                             |                                                                                                                           |                                |                                 |                                                                                                                           |                                |                                       |                                |
| 8 am = 110-200 mg/ml                                             |                             |                                                                                                                           |                                |                                 |                                                                                                                           |                                |                                       |                                |
| 4 pm = 60-100 mg/ml                                              |                             |                                                                                                                           |                                |                                 |                                                                                                                           |                                |                                       |                                |
| 17. Serum IgG levels. Normal-800-1800 mg/dl                      | 66                          | 72                                                                                                                        | 70                             | 90                              | 74                                                                                                                        | 62                             | 66                                    | 70                             |
| 18. Reintroduction of BDP                                        | 1162                        | 1400                                                                                                                      | 1286                           | 1364                            | 1640                                                                                                                      | 1566                           | 1188                                  | 1392                           |
|                                                                  | Refused                     | a) Cough, fever on 13th day<br>b) Sputum for AFB smear-positive<br>c) Chest radiograph: bilateral upper lobe infiltration | Refused                        | Refused                         | a) Cough, fever on 15th day<br>b) Sputum for AFB smear-positive<br>c) Chest radiograph: bilateral upper lobe infiltration | Refused                        | Refused                               | Refused                        |

Chest radiographs and sputum smear and culture were repeated every 3 months and each patient was closely supervised during the period of anti-TB treatment to prevent default. Five more patients (of the 548 patients seen) developed pulmonary TB within 3 to 5 weeks of using a BDP inhaler during the next 2 years, making 8 in all. None of these patients had contact with TB in the family, neighbourhood, or place of work/study. The clinic staff (doctors, nurses, clerical staff, technicians) were screened and all were TB excluded. The contents of the BDP canisters used by the patients, were cultured for presence of AFB, and all cultures were negative. Three months after having completed the course of anti-TB drugs, each patient was requested to restart BDP inhalation to find whether the TB had returned. The nature and possible consequences of such an experiment were explained to the patients and only two out of eight agreed to participate. Their consent was obtained in writing and their parents/guardians were likewise informed. Both patients were restarted on 400 µg BDP daily and both developed cough and fever on days 13 and 15 of BDP usage, respectively. They were subjected to a chest radiograph and sputum for AFB (smear), and, reactivation of TB having been confirmed, were treated with isoniazid 300 µg, rifampicin 450 mg and pyrazinamide 1500 mg/day.

## Results

The results obtained are shown in Table 1. All eight patients were given anti-TB drugs for a period ranging from 9 to 12 months, all complied with the prescribed drugs and all had clinical, sputum, and radiological resolution. The ELISA test for HIV was negative in all eight patients.

The sputum cultures in each patient showed *M. tuberculosis* and there was no evidence of atypical mycobacteria in any of them.

The two patients (Nos. 2 and 5 in the table) who redeveloped TB following reintroduction of BDP are still on treatment with isoniazid, rifampicin and pyrazinamide. The remaining six patients are receiving salbutamol inhalations and have no evidence of TB. The incidence of TB in this country is estimated at between 51 and 75 cases per 100 000 population (13). The Z-test was applied to compare the incidence of TB in the general population with our sample population. The present study suggests that BDP had a statistically significant effect in causing TB.

## Discussion

It is widely accepted that corticosteroid (CS) therapy may reactivate a latent TB infection or increase

the risk of new infection by suppressing cell-mediated immune responses and thus causing a reduction in resistance to infections (7, 20). It is also known that large doses of CS suppress antibody formation (1). Several studies have shown an emergence/reactivation of TB in patients treated with systemic CS; the percentage varies from 0% to 3% (7, 17, 10, 18, 11). An extensive review of literature to date revealed no reports of TB manifesting in patients on inhaled CS. In the present study, each patient had a normal chest radiograph immediately before treatment. All eight patients had a similar clinical profile and each was prescribed a BDP inhaler only (and no other medications), and since there was no evidence of TB contact during or before the period of BDP usage, it would be reasonable to assume that the TB was due to BDP alone. The diagnosis of TB was adequately confirmed by radiological findings and sputum smear/culture. The reemergence of TB in the two patients who repeated the BDP inhalations provides added evidence that BDP was the causative factor. The results of the Z-test suggest that BDP had a significant effect in causing TB in the sample population studied. Since there is no convincing evidence to date that asthma predisposes to TB (2), the figures for the incidence of TB in the general population together with the results of the Z-test could also be applied to the asthmatic population.

It is difficult to propose a mechanism for the emergence of TB. None of the eight patients showed any signs of primary or acquired immunodeficiency, as is borne out by normal IgG levels, negative ELISA tests for HIV, and a positive response to the MT. It could be speculated that the high topical activity of BDP may have more potential in causing TB than systemic CS. Also, all eight patients had normal plasma cortisol levels and a normal cortisol diurnal variation, thus excluding the possibility of BDP-induced pituitary-adrenal suppression (which is known to occur at doses > 1000 µg/day) (15). It must be conceded that this is not a controlled, prospective study. Until such studies are performed, asthmatics (especially in countries with a higher incidence of TB) with a positive MT who are using BDP should be carefully monitored for TB manifestation/reactivation.

Despite the results of this study, it must be emphasized that a fear of TB should not affect our decisions about using systemic or inhaled CS in treating asthma, especially since the chances of manifestation are low (1.46% in the present study and between 0% and 3% in others) (3).

Finally, it must be noted that the eight patients in this study belonged to the younger age group and all were atopic. It would be interesting to study the possibility of TB presenting in older patients on BDP therapy, as also in non-atopics.

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