CASE REPORT

Profound adrenal suppression secondary to treatment with low dose inhaled steroids and itraconazole in allergic bronchopulmonary aspergillosis in cystic fibrosis

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The case history is presented of a patient with cystic fibrosis in whom the treatment of allergic bronchopulmonary aspergillosis with itraconazole produced an initial response but was complicated by profound adrenal shutdown and impairment of inhaled steroid clearance resulting in paradoxical Cushing's syndrome. The authors conclude that, while it is laudable to attempt to reduce the steroid burden in any patient, it is imperative that due vigilance is exercised when using a combination of agents which interact. If such a combination therapy is embarked upon, regular assessment of the pituitary adrenal axis is advisable.

Aspergillus is a widespread mould with a worldwide distribution whose spores have a diameter of 3 µm which allows them easy access to the small airway. While *Aspergillus* itself is relatively innocuous, except in severely immunocompromised individuals, the immunogenic response it excites produces the clinical syndrome of allergic bronchopulmonary aspergillosis (ABPA) and also provides markers of the disease.

Allergic bronchopulmonary aspergillosis in cystic fibrosis (CF) was first recognised by Mearns *et al*[1] in 1965 and since then has been estimated to occur in 2–15% of patients.[2 3] This broad range reflects the lack of consensus on diagnostic criteria. In patients with CF this is further compounded by the many diagnostic features of ABPA which overlap with CF, so separation of the two clinical syndromes may be difficult.

It is thought that a reduction in the quantity of *Aspergillus* and hence the antigenic burden will improve symptoms and also decrease the reliance on oral and inhaled corticosteroids. During the last year there have been a number of reports and a single randomised crossover trial of the use of itraconazole in patients with ABPA.[4] In this randomised trial 13 of 28 patients on itraconazole achieved a 50% reduction in the dose of steroids, a significant improvement in immunological markers and in exercise tolerance, but no significant differences in lung function.[5] Here we report a case in which the treatment of ABPA with itraconazole produced an initial response but was complicated by profound adrenal shutdown and impairment of inhaled steroid clearance resulting in paradoxical Cushing's syndrome.

CASE REPORT

Clinical history

A 28 year old man was under the care of the Adult Cystic Fibrosis Centre for a number of years during which time he had been relatively stable (FEV_1 2.1 l, FVC 3.2 l). He was pancreatic insufficient and a non-insulin dependent diabetic but had no evidence of liver disease. Genetic testing showed him to be a heterozygote for Δ508 and S5491. Over the preceding 6 years his enzyme requirement had been relatively stable but his diabetic control had become increasingly difficult and had progressively declined, especially over the previous 8 months, necessitating an increase in oral hypoglycaemic treatment which resulted in improved control. A DEXA scan confirmed a mild degree of osteoporosis with a spinal T score of –3.97. The sputum was chronically colonised with *Pseudomonas aeruginosa* but he had had infrequent exacerbations over the previous 2–3 years. At a previous annual review a single sputum culture had identified an atypical *Mycobacterium chelonae* but this was not identified on subsequent occasions despite careful examination.

At annual review it was noted that he had progressively declining lung function which had accelerated over the preceding months. There had been a single episode of asthma-like symptoms which had responded well to a short course of oral steroids (30 mg for 7 days) and subsequent inhaled fluticasone dipropionate. This was initially given at a high dose of 1000 µg/day but was reduced to an unconventional dose of 250 µg/day as a single puff after problems with mouth soreness. The sputum at annual review once again grew *P aeruginosa* but, on this occasion, also grew *Aspergillus fumigatus* with a density of 4000 colony forming units. Further investigation at this time showed that he had positive precipitins but negative RAST, a normal IgE, no eosinophilia, and no evidence of new shadowing on the chest radiograph; no skin prick tests were performed.

It was decided at this stage to watch carefully and to treat empirically any further deterioration with intravenous antipseudomonal agents. Two subsequent exacerbations were treated in this way and produced some initial success with moderate improvement in the respiratory symptoms and function. However, the improvement was short lived and the sputum continued to grow large quantities of *Aspergillus* without evidence of a new pathogenic organism. In view of the potential hazards of oral corticosteroids in a fragile diabetic with osteoporosis, itraconazole was prescribed in a dose of 200 mg twice a day. Initially there was improvement in lung function and respiratory symptoms over the first 2 months. At routine follow up 2 months later it was observed that liver function tests were deteriorating and, in view of this, itraconazole was stopped. One month later he remained well with no further *Aspergillus* grown but was noted to be grossly cushingoid without any other clinical features of Cushing's syndrome. Careful questioning and discussion with the GP revealed that he had had no further courses of oral steroids and was maintained purely on a single 250 µg puff of inhaled fluticasone via a metered dose inhaler.

Endocrine investigations

Endocrine investigations gave the following results:

- 09.00 hours cortisol level <36 nmol/l;

- short synacthen test (250 µg) performed 6 weeks after stopping itraconazole: 20 nmol/l cortisol at baseline, 35 nmol/l at 30 minutes, 46 nmol/l at 60 minutes;
- ACTH <6 ng/l;
- FSH/LH/TSH normal;
- GH slightly high;
- anti-adrenal antibodies negative;
- CT scan of abdomen showed normal adrenal glands;
- liver function tests normal.

The response to synacthen confirmed primary adrenal failure and the low normal ACTH level in the context of such low cortisol levels indicated suppression of the normal pituitary response. These findings were in keeping with primary adrenal failure with secondary Cushing's syndrome. However, it is unusual for such a low dose of inhaled steroids to produce this effect.

To examine this issue further we measured plasma fluticasone levels to assess its metabolism after a single puff and achieved levels of 112 pg/ml, 203 pg/ml, and 129 pg/ml at baseline, 1 hour and 6 hours, respectively. The predose level of 112 pg/ml is very high, with a larger than expected subsequent rise for a single puff of 250 µg. The calculated area under the curve is approximately twice that expected for a healthy subject and approximately six times that seen in asthmatic patients. There are no comparable data for patients with CF and changes in pulmonary blood flow may produce a different normal range.

DISCUSSION

This case indicates the potential hazards of combining inhaled steroids with itraconazole in patients with ABPA. Fluticasone is a potent medication which has many of the attributes desirable in an inhaled steroid. It is well absorbed in the lungs and, if swallowed, is poorly absorbed via the gastrointestinal tract. The small amount which is absorbed is rapidly cleared by first pass metabolism.[6] These qualities limit side effects and improve the therapeutic index. However, there is some systemic bioavailability from absorption within the lung vasculature and it is this which is responsible for the adrenal suppression. In our patient this clearance was clearly inhibited. On a weight equivalence it is estimated that fluticasone exhibits twice the potency for adrenal suppression seen with budesonide.

In this case it is difficult to ascertain exactly the primary cause as itraconazole has been implicated in suppression of adrenal steroid production via the inhibition of hydroxylases critical to steroid synthesis. Indeed, this side effect has been used for therapeutic gain in the treatment of Cushing's disease.[7] However, the dose usually required to produce this effect is much higher than that used in our case. Equally, the profound inhibition of fluticasone metabolism could result in adrenal suppression. The mechanism by which itraconazole causes adrenal suppression has not been established. However, its capacity to inhibit liver enzymes has been carefully examined. The major enzyme system which is inhibited is the cytochrome P450 and the CYP 34A isoform both in the liver and, to a much lesser extent, in the gastrointestinal tract.[8] Interactions with a number of therapeutic agents have been described including cyclosporin, erythromycin, phenytoin, and warfarin. In fact, this interaction has been exploited in transplant medicine to produce higher levels of cyclosporin where difficulty has occurred in attaining sufficiently high levels. These interactions are only evident at doses of >200 mg/day. The evidence of an interaction with steroids comes from a randomised double blind study of intravenous methylprednisolone with itraconazole or placebo in healthy volunteers. In the itraconazole group the clearance of methylprednisolone was reduced to 40% of that of the placebo group. More strikingly, the mean morning cortisol level of those receiving methylprednisolone and itraconazole was reduced to 9% of that in the placebo treated group.[9] In our patient the high initial level of fluticasone indicates severe impairment. While this may have contributed to the level of adrenal suppression, this is improbable as measurable cortisol suppression has only been described with high dose inhaled corticosteroids and no significant effect on the area under the curve for cortisol secretion was seen over 20 hours for fluticasone given in a dose of 200 µg twice daily.[10] However, the marked inhibition seen in our case could explain the usual effect observed with such a low dose of inhaled steroids.

While it is laudable to attempt to reduce the steroid burden in any patient, this report highlights that it is imperative that due vigilance is exercised when using a combination of agents which interact. If such a combination therapy is embarked upon, regular assessment of the pituitary adrenal axis is advisable. When and how frequently this should be performed has yet to be established.

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REFERENCES

1 **Mearns M**, Young W, Batten JC. Transient pulmonary infiltrates in CF due to allergic aspergillosis. *Thorax* 1965;**20**:385–92.
2 **Geller D**, Light MJ, Colin AA. ABPA in CF. *Chest* 1999;**116**:639–44.
3 **Marchant JR**, Warner JO, Bush A. A rise in IgE as an indicator of ABPA in CF. *Thorax* 1994;**49**:1002–5.
4 **Salez F**, Brichet A, Tonnel AB. Effects of itraconazole therapy in ABPA. *Chest* 1999;**116**:1665–8.
5 **Stevens DA**, Schwarz HJ, Lee JY, *et al*. A randomised trial of itraconazole in allergic bronchopulmonary aspergillosis. *N Engl J Med* 2000;**342**:756–63.
6 **Sastre J**. Pharmacology of fluticasone propionate. *J Invest Allergy Clin Immunol* 1997;**7**:382–4.
7 **Farwell AP**, Devlin JT, Stewart JA. Total suppression of cortisol excretion by ketaconazole in the therapy of ectopic ACTH syndrome. *Am J Med* 1988;**84**:1063–6.
8 **Venkatkrishnan K**, Von Molkte LL, Greenblatt DJ. Effects of antifungal agents on oxidative metabolism. *Clin Pharmacol* 2000;**38**:111–80.
9 **Varis T**, Kivisto KT, Neuvonen PJ. Itraconazole decreases the clearance and enhances the effects of intravenously administered methylprednisolone in healthy volunteers. *Pharmacol Toxicol* 1999;**85**:29–32.
10 **Derom E**, Van Schoor J, Verhaeghe W, *et al*. Systemic effects of inhaled fluticasone propionate and budesonide in adult patients with asthma. *Am J Respir Crit Care Med* 1999;**160**:157–61.