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LETTERS

Deteriorating diabetic control associated with high-dose inhaled budesonide

To the Editor:

Inhaled corticosteroids are considered an important therapy for asthma. They have potent local effects and few adverse systemic effects [1, 2]. Oral corticosteroid administration frequently leads to deteriorating diabetes, but few data exist on clinically significant changes in glucose homeostasis in diabetic subjects associated with the use of inhaled corticosteroids. In a recent report, a deterioration in glucose control in a diabetic subject who took high-dose inhaled fluticasone propionate (FP) for asthma has been described [3]. The authors now report a further deterioration in glucose control in the same subject with the use of high-dose inhaled budesonide.

A 67-yr-old male, with a 10-yr history of asthma and a 40-yr history of noninsulin dependent diabetes mellitus, was referred for assessment of moderately severe asthma (forced expiratory volume in one second 45% of predicted). The patient took glibenclamide 5 mg and metformin 1,700 mg daily and was meticulous in recording twice daily urinary glucose measurements (Ames Keto-Diastix; Bayer Diagnostics, Puteaux, France). His percentage of glycosylated haemoglobin (HbA_{1c}) in whole blood was measured approximately every 6 weeks using the Corning Drew "Glycomat" low pressure chromatography system (Corning Drew, Emeryville, CA, USA). He was prescribed inhaled FP (2,000 $\mu g \cdot day^{-1}$) and inhaled salmeterol (200 $\mu g \cdot day^{-1}$) by metered dose inhaler (*via* a "Volumatic" spacer device (Allen & Hanburys, Stockley Park, UK)), and for a 40-week follow-up period, he took no oral or systemic corticosteroid, with the salmeterol dose remaining constant. Diabetic medication as well as the strict diet and exercise regimens remained unchanged. His weight remained stable. The mean peak expiratory flow rate increased and there was no deterioration in asthma control. However, therapy with high-dose inhaled FP was associated with persistent glycosuria and a rise in HbA_{1c}, both of which matched the changes in FP. Full details of these challenges with inhaled FP are presented in full elsewhere [3].

In order to determine whether this hyperglycaemic effect of inhaled FP was a class effect of corticosteroids, the subject later agreed to be challenged with high-dose budesonide (single blind fashion). Inhaled FP was discontinued, and immediately replaced with high-dose inhaled budesonide (2 $mg \cdot day^{-1}$, administered by metered dose inhaler *via* a "Nebuhaler" spacer (Astra Pharmaceuticals Ltd., Hertfordshire, UK)). He developed increased glycosuria during weeks 1–6 of therapy with high-dose budesonide (of a total 70 readings, 29 were positive for glucose). The dose of budesonide was reduced in a step-wise manner to 800 $\mu g \cdot day^{-1}$ on week 10. The severity of glycosuria decreased, and by week 11 all urinary readings for glucose were negative. This deterioration in diabetic control was mirrored by a rise in HbA_{1c} to 8.2% at the end of week 5 followed by a fall to 7.4% by the end of week 15. There was no deterioration in asthma control with this reduction in inhaled budesonide intake.

Table 1. – The effect of inhaled budesonide on glycaemic control in a diabetic subject with asthma

Budesonide dose $\mu g \cdot day^{-1}$	Week of treatment	Glycosylated haemoglobin% (end week)	Positive urinary glucose*
2000	1–2	-	6
1600	3–5	7.8 (3)	5.66
		8.2 (5)	
1200	6–9	7.8 (8)	0.75
800	10–20	7.4 (15)	0
		7.2 (20)	0

*: mean number of measurements per week.

In diabetes mellitus, the severity of hyperglycaemia correlates with microvascular complications [4]. As a general rule, HbA_{1c} (normal individuals have an HbA_{1c} <6%) correlates well with mean blood glucose levels measured over the previous 4–12 weeks. Since an HbA_{1c} level of 7%±2SD extends from 6.62% to 7.38%, the changes seen in this case were both clinically significant and outside of laboratory error. Throughout the period of monitoring, the administration of high-dose inhaled steroids was matched exactly by both a rise in the level of HbA_{1c} and by worsening glycosuria (table 1).

Corticosteroids cause hyperglycaemia in three ways: 1) by decreased insulin binding and hence glucose uptake in adipose tissue and hepatocytes; 2) by increased gluconeogenesis in the liver and kidney; and 3) by hyperglucagonism (leading to increased gluconeogenesis) [5]. This case did not demonstrate tolerance to the effects of inhaled steroids on diabetic control. Tolerance to glucocorticoid-induced hyperglycaemia, at least in animals, is tissue-specific and does not occur in hepatocytes [6]. Moreover, since FP and budesonide are extensively removed by first pass metabolism in the liver after absorption *via* the lung and gut [7], the metabolic effects seen in this case are most likely to be due to glucocorticoid actions on hepatocytes.

Given the high prevalence of asthma, many patients are potential candidates for inhaled corticosteroids because of their proven efficacy. In the present subject, high-dose inhaled fluticasone proprionate [3] and budesonide were associated with persistent heavy glycosuria and significant rises in glycosylated haemoglobin. Lower doses minimized this adverse systemic effect without loss of asthma control. The current data, albeit in one subject with diabetes mellitus, suggest a class effect of high-dose inhaled steroids that may be important in the management of diabetic patients with asthma.

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Ulcerative colitis following introduction of zafirlukast and corticosteroid withdrawal in severe atopic asthma

To the Editor:

The leukotriene (LT) receptor antagonist accolate (zafirlukast) has recently been approved for use in the US and most European countries as an oral preventative, as well as a chronic treatment, for asthma in both adults and children aged ≥12 yrs [1, 2]. The drug specifically blocks the docking of LT molecules to the cysteinyl leukotriene ($CysLT_1$) receptor subtype on airway smooth muscle cells and represents the first really new class of anti-asthmatic drugs to be introduced in 20 yrs [3]. Although LT receptor antagonists are generally well tolerated and side-effects associated with these drugs are rare, several cases of an eosinophilic disorder reminiscent of the Churg-Strauss syndrome have been reported in patients taking zafirlukast [4, 5] and montelukast (post-marketing informational letter). Characteristically, these patients were on a high-dose of inhaled or oral corticosteroid therapy, and were able to reduce the dose as a beneficial consequence of the effects of the LT antagonists. However, it is unclear whether the Churg-Strauss syndrome is a result of the reduction of corticosteroid dose or an idiosyncratic effect of LT agonists.

This article reports the case of a 65 yr old male Caucasian patient with severe atopic asthma, who experienced an exacerbation of ulcerative colitis after initiation of zafirlukast treatment. The patient presented with a 25-yr history of ulcerative colitis, that was in remission for >10 yrs. In addition, in 1972, he was diagnosed with severe atopic asthma, for which he had been receiving a daily dose of 5–15 mg prednisolone during the past 6 yrs. He also used inhaled beclomethasone diproprionate (BDP; 500 μg *b.i.d.*), oral theophylline (375 mg *b.i.d.*) and ketotifen (1 mg at night), as well as inhaled fenoterol on demand. The patient was seeking medical advice since he was concerned about the potential side effects of long-term oral steroid therapy.

On examination, the patient was comfortable at rest but a reduced breath sound and prolonged expiratory wheeze were heard over both lungs. He had a normal erythrocyte sedimentation rate (10 $mm \cdot h^{-1}$) and total leukocyte count ($cells \cdot \mu L^{-1}$), and peripheral eosinophilia (8% of leukocytes). Sputum cultures were negative. Total serum immunoglobulin (Ig)E levels were elevated to 1,640 $IU \cdot L^{-1}$ (<100 $IU \cdot L^{-1}$), and specific IgE directed against common allergens, including grass pollen, birch pollen, and house dust mite, were detected. His chest radiograph revealed moderate hyperinflation, while a high-resolution computed tomographic scan of the lung was normal. Lung function testing revealed an obstructive defect, with an increased residual volume of 152% of predicted, reduced forced expiratory volume in one second (FEV_1) (44.6% pred), and a mean forced mid-expiratory flow ($FEF_{25–75\%}$) <10% pred, consistent with obstruction of the small airways. Diffusion capacity for carbon monoxide ($D_{L,CO}$) was normal.

A treatment with zafirlukast (20 mg), in combination with inhaled formeterol (24 μg) and fluticasone (500 μg) twice daily, resulted in an alleviation of the asthma symptoms. Mean peak expiratory flow improved from 300 to 440 $L \cdot min^{-1}$. The stable clinical condition allowed a gradual reduction of oral prednisolone, which could be discontinued 8 weeks after the initiation of zafirlukast. Thirteen days following discontinuation of corticosteroid treatment, the patient began experiencing lower abdominal cramps accompanied by up to 10 attacks of bloody diarrhoea per day. A colonoscopy confirmed the clinically-suspected diagnosis, and revealed an exacerbation of the ulcerative colitis. Consequently, while zafirlukast therapy was continued, resumption of the oral prednisolone therapy (5–7.5 mg) led to a gradual resolution of his bowel symptoms.

To the authors knowledge, this is the first report of an inflammatory bowel disease deteriorating under treatment with zafirlukast. A small number of cases of the Churg-Strauss syndrome have recently been reported among patients with severe asthma, in whom corticosteroids were either reduced or discontinued [4, 5]. The case reported herein parallels these reports, in as much as the discontinuation of chronic steroid therapy in a patient with severe atopic asthma res-ulted in the recurrence of a co-existing immunologic disorder, which previously may have been controlled by the anti-inflammatory asthma treatment. While the underlying pathomechanism of zafirlukast-associated exacerbation of ulcerative colitis remains to be elucidated, this observation has important clinical implications for physicians prescribing zafirlukast, and possibly other leukotriene receptor antagonists, to paients with corticosteroid-dependent asthma.

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