PostScript

LETTERS TO THE EDITOR

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GM-CSF therapy in pulmonary alveolar proteinosis

Treatment with granulocyte-macrophage colony stimulating factor (GM-CSF) has been shown to benefit a subset of patients with adult pulmonary alveolar proteinosis (PAP). A 47 year old woman with PAP, confirmed by lung biopsy, and severe physiological and symptomatic disturbances was not improved by repeated unilateral whole lung lavages. Six months after the last lavage we started treatment with daily subcutaneous GM-CSF in increasing doses beginning at 3 μg/kg. When a daily dose of 6 μg/kg was reached a haematological response was detected and dose escalation ceased. After 4 weeks at this dose the patient began to improve. By week 11 at a dose of 6 μg/kg/day the treatment was stopped and after a further 3 weeks without treatment she attained maximal clinical, radiological, and physiological improvement (from arterial oxygen tension (Pa_{O_2}) 6.1 kPa, alveolar–arterial oxygen gradient ($(A–a)_{O_2}$) 8.2 kPa, total lung capacity (TLC) 63.3%, and carbon monoxide transfer factor (T_{LCO}) 58.7% at diagnosis to 10.9 kPa, 2.6 kPa, 99%, and 101.1%, respectively). At that point, as the haematological parameters were normal, we decided empirically to restart treatment at a maintenance dose of 3 μg/kg/day twice a week to avoid relapse. Five months later, with no evidence of clinical deterioration or haematological response, treatment was stopped and after a further 18 months the patient remains symptom free.

The successful remission of our patient, the seven published cases of GM-CSF in the treatment of PAP,[1–3] and the low incidence of side effects compared with the whole lung lavage technique prompt us to recommend GM-CSF as a first line treatment option in these patients.

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Conventional RIA underestimates cortisol suppression in the presence of prednisolone

The recent letter from Meijer *et al*[1] concludes that measuring serum cortisol by RIA severely underestimates serum cortisol suppression in the presence of oral prednisolone. This is rather a sweeping statement as the underestimation will, of course, depend on the degree of the cross reactivity with the particular assay. For example, in another study where inhaled fluticasone and oral prednisolone were compared in asthmatic patients and the cross reactivity of the RIA was quoted at 11%, it was found that 1 μg inhaled fluticasone (pMDI plus spacer) was equivalent to 8.5 mg (95% CI 5.7 to 11.2) oral prednisolone for suppression of 08.00 hour plasma cortisol.[2]

From the data from Meijer *et al* for HPLC morning serum cortisol levels, prednisolone 30 mg per day produced 72% suppression compared with 38% suppression for fluticasone 2 mg per day (by DPI). Extrapolating between these two values, it seems that 1 mg per day inhaled fluticasone produces equivalent serum cortisol suppression to 7.9 mg per day oral prednisolone. This is similar to our own estimated ratio of 8.5 μg:1 using RIA. Furthermore, in another dose ranging study by Casale *et al*[3] in asthmatics which compared the effects of inhaled fluticasone and prednisone on 22.00 hour serum cortisol levels (area under the curve) using HPLC, the relative degree of suppression was 15% for fluticasone MDI 440 μg daily compared with 55% for prednisone 7.5 mg daily, which extrapolates to 1 mg fluticasone MDI being systemically equivalent to 4.6 mg prednisone for adrenal suppression. As the addition of a large volume spacer doubles the adrenal suppression with fluticasone via MDI,[4] the ratio reported by Casale *et al* in asthmatic patients equates to 1 mg fluticasone via MDI plus spacer producing equivalent suppression to 9.2 mg prednisone, which is similar to our own ratio of 8.5 μg:1.[2]

Taking all these data together clearly suggests that inhaled fluticasone is highly systemically bioavailable and produces systemic adverse effects at high doses which are equivalent to those produced by low doses of oral prednisolone.

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Authors' reply

We thank Dr Lipworth for his comments. The ratio of systemic effects of fluticasone to prednisolone cannot be deduced reliably from our data, but we agree that the suppression we found is probably not markedly different from the one found by his group or from that of others in the literature.

However, this was not the content of—or the reason for—our note in *Thorax*. Our attention was drawn at a rather late stage to the fact that assessing prednisolone induced cortisol suppression by conventional radioimmunoassay (RIA) could lead to underestimation of suppression due to cross reactivity in the assay.[1 2] We therefore subsequently compared cortisol results measured by conventional RIA with values measured by HPLC and, indeed, a significant underestimation in the presence of prednisolone was detected. Other researchers and clinicians might not be aware of this problem when assessing cortisol suppression by systemic corticosteroids.

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Inhaled corticosteroid dosage in asthma

We would like to congratulate Ward and colleagues[1] on their very important study which showed that significant changes in airway basement membrane thickness in asthma were not observed until after 3