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Effects of oral and inhaled corticosteroids on the hypothalamic-pituitary-adrenal axis

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To the Editor:

We read with interest the recent article of Li et al (Li JTC, Goldstein MF, Gross GN, Noonan MJ, Weisberg S, Edwards L, et al. Effects of fluticasone propionate, triamcinolone acetonide, prednisone, and placebo on the hypothalamic-pituitary-adrenal axis. J Allergy Clin Immunol 1999;103:622-8) showing an apparent lack of effect of 220 µg twice daily of fluticasone propionate metered-dose aerosol on the hypothalamic-pituitary-adrenal (HPA) axis as assessed by the 250-µg cosyntropin 6-hour infusion test. The authors also reported significant suppression of mean values for 8 hours area under the curve (AUC) for plasma cortisol in response to cosyntropin, after treatment with triamcinolone acetonide 400 µg twice daily, amounting to a 13.0% change from baseline. The suppressive effect of 10 mg of prednisone once daily (32.5% change) on the 8-hour AUC response was in turn significantly greater than that of either triamcinolone acetonide 400 µg twice daily or fluticasone propionate 220 µg twice daily. It seems rather curious that the authors chose to use the 8-hour AUC response as the primary end point for power calculations when they went to the trouble of performing cortisol measurements for up to 12 hours after the start of the cosyntropin infusion. Indeed, the authors report that prednisone but not triamcinolone acetonide 400 µg twice daily or fluticasone 200 µg twice daily produced significant

suppression of the mean 12-hour response.

It is also important to point out that interpretation of the 250 µg cosyntropin response is somewhat limited because this represents a 500-fold higher dose of cosyntropin than is required to produce a stimulated cortisol response and as such represents a

supraphysiologic dose.¹ The low-dose cosyntropin test is more sensitive at detecting more subtle degrees of adrenal insufficiency in patients receiving exogenous corticosteroids, as might conceivably occur with inhaled fluticasone 220 µg twice daily.²

There are other data using more sensitive parameters to suggest that low doses of inhaled fluticasone propionate are associated with a significant degree of detectable systemic bioactivity, including HPA axis suppression. For example, in a study of asthmatic patients, steady-state dosing for 4 days with fluticasone propionate aerosol 220 µg twice daily was associated with a 40% mean suppression of overnight cortisol-creatinine excretion.³

Boorsma et al⁴ reported 21% suppression of 24-hour plasma cortisol with fluticasone metered-dose aerosol 176 µg twice daily for 4 days. Andersson et al⁵ reported that 4 weeks of treatment with fluticasone propionate 250 µg twice daily with use of the dry-powder Diskhaler (Glaxo-Wellcome, Stockley Park, UK) metered-dose inhaler produced 33% mean suppression of 24-hour urinary cortisol excretion. In the same study there was also a 71% mean reduction in peripheral blood lymphocyte messenger RNA expression, which would be in keeping with a significant degree of systemic effect of fluticasone.

The greater degree of systemic potency with inhaled fluticasone compared with other inhaled corticosteroids is supported by data from a recent meta-analysis of 22 dose-response studies,⁶ where the slope for dose-related adrenal suppression was significantly steeper with fluticasone propionate in comparison with either beclomethasone dipropionate (2.1-fold, $P < .01$, budesonide (2.5-fold, $P < .001$), or triamcinolone acetonide (3.6-fold, $P < .01$). In another meta-analysis of 13 studies evaluating dose-related adrenal suppression, oral prednisolone and inhaled fluticasone propionate were systemically equivalent on a 10:1 milligram basis.⁷

The results of Li et al showing significant suppression of the 250-µg cosyntropin response with triamcinolone acetonide 400 µg twice daily are also not consistent with previously published data. For example, Altman et al⁸ found in asthmatic patients no effect on the 250-µg cosyntropin response after treatment for 6 months with triamcinolone acetonide 400 µg twice daily. Wilson et al^{9 10} have also reported no significant effect of triamcinolone acetonide 400 µg twice daily on overnight urinary cortisol-creatinine excretion or on the cortisol response to 0.5-µg cosyntropin stimulation.^{9 10} It is also difficult to explain why in the study of Li et al there appeared to be significant suppression of the 8-hour AUC response with 800 µg per day of triamcinolone acetonide administered in 2 divided daily doses but not when given as 4 divided daily doses. Given the short elimination half-life of triamcinolone

acetonide at 3.6 hours, ¹¹ drug levels at steady state would, if anything, be expected to be higher with the 4 times twice daily dosing regimen, in terms of the propensity for accumulation.

We therefore are of the opinion that the data of Li et al should be interpreted with extreme caution in terms of assessing the effects of therapeutic low doses of fluticasone propionate on the HPA axis in patients with asthma.

*B. J. Lipworth, MD, FRCPE
C. M. Jackson, MBCHB, MRCP
Asthma and Allergy Research Group
Department of Clinical Pharmacology and Therapeutics
Ninewells Hospital and Medical School
University of Dundee DD1 9SY
Scotland, United Kingdom*

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