



## **Position statement of the Society for Endocrinology on the endocrine effects of inhaled corticosteroids in respiratory disease**

The use of corticosteroids (“steroids”) to treat bronchoconstriction and other disorders in lung disease was revolutionised by the introduction of inhaled steroids, as by this means high concentrations of anti-inflammatory agents could be delivered to the lung with minimal impact on other organs. Only very small amounts of these agents are able to reach the gastro-intestinal tract, and thus orally-absorbed doses are usually considered to be trivial. Such selective absorption was enhanced by the change to ‘ozone-friendly’ propellants. Whilst there is no doubting the clinical benefit that inhaled corticosteroids can have upon some chronic lung diseases, with the development of newer, highly potent steroids such as fluticasone (*Seretide*), the absorption of these agents through the lung parenchyma to the circulating blood can become physiologically significant (1). In response to such absorbed steroids, the patient’s endogenous hypothalamo-pituitary-adrenal axis (HPAA) will down-regulate, such that the overall steroid burden remains within the physiological range. At higher doses, the total steroid burden may become pathological, and the patient will manifest the clinical stigmata of Cushing’s syndrome (2,3). However, even sub-pathological absorption may lead to suppression of the HPAA (4) such that sudden cessation of long-term treatment can lead to adrenal crisis, as can severe trauma, sepsis and surgery (5). Whilst it is likely that those on higher doses of inhaled corticosteroids are more likely to have HPAA suppression, studies have shown that there is linear relationship between inhaled steroid dose and suppression of the HPAA, passing through ‘zero’, so no dose is completely without effect (6). Furthermore, HPAA suppression due to inhaled corticosteroids (ICS) may be far more prevalent than is currently appreciated - up to 50% of patients using ICS in some series (4,5). In addition, co-administration of common drugs may prolong the availability and augment the systemic effects of ICS (3,7), notably itraconazole and HIV protease inhibitors including ritonavir (e.g. *Kaletra*). Despite the potential severity of the clinical problem, it is all too easily overlooked (8), and it is therefore imperative that the community of endocrinologists and respiratory physicians are aware of such possible events. Patients with partial or full suppression of their HPAA will show very low or even undetectable levels of serum and urinary cortisol, but without evidence of Cushing’s syndrome (4). With higher absorbed doses, Cushing’s syndrome becomes obvious, with the apparent paradox of a Cushingoid habitus but suppressed cortisol levels (2,3). Even in the absence of clear clinical features, the absorbed steroids may induce osteoporosis or, at least in theory, clinical signs of the metabolic syndrome. Such problems may also occur with other forms of corticosteroid administration, such as intra-articular or topical steroids. Awareness of these possibilities should avoid the potential catastrophe of an unsuspected adrenal crisis, and should alert the clinician to the possible presence of iatrogenic Cushing’s syndrome.

**Ashley Grossman FMedSci, University of Oxford  
Jeremy W Tomlinson MRCP PhD, University of Birmingham**

**... for and on behalf of the Society for Endocrinology  
July 2011**

*...continued*



## References

1. Niitsuma T, Okita M, Sakurai K, et al. Adrenal function as assessed by low-dose adrenocorticotropin hormone test before and after switching from inhaled beclomethasone dipropionate to inhaled fluticasone propionate. *J Asthma* 2003; 40: 515–522
2. Matos AC, Srirangalingam U, Barry T and Grossman AB. Cushing's syndrome with low levels of serum cortisol: the role of inhaled steroids. *Clinical Science* 2011 (in press)
3. Woods DR, Arun CS, Corris PA, Perros P . Cushing's syndrome without excess cortisol. *BMJ*. 2006;332(7539):469-70
4. Holme J, Tomlinson JW, Stockley RA, Stewart PM, Barlow N, Sullivan AL . Adrenal suppression in bronchiectasis and the impact of inhaled corticosteroids. *Eur Respir J*. 2008;32(4):1047-52
5. Todd GR, Acerini CL, Buck JJ, Murphy NP, Ross-Russell R, Warner JT, McCance DR. Acute adrenal crisis in asthmatics treated with high-dose fluticasone propionate. *Eur Respir J*. 2002 Jun;19(6):1207-9
6. Wlodarczyk JH, Gibson PG, Caeser M. Impact of inhaled corticosteroids on cortisol suppression in adults with asthma: a quantitative review. *Ann Allergy Asthma Immunol*. 2008;100(1):23-30
7. Daveluy A, Raignoux C, Miremont-Salamé G, Girodet PO, Moore N, Haramburu F, Molimard M. Drug interactions between inhaled corticosteroids and enzymatic inhibitors.. *Eur J Clin Pharmacol*. 2009;65(7):743-5
8. Irwin RS, Richardson ND Side effects with inhaled corticosteroids: the physician's perception. *Chest*. 2006;130(1 Suppl):41S-53S