Getting risks right on inhaled corticosteroids and adrenal insufficiency

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Adrenal insufficiency should be considered in patients on inhaled corticosteroids presenting with suggestive symptoms http://ow.ly/kskjU

As Thomas Addison observed in his famous monograph written in 1855, the adrenal glands are ''objects of deep interest'' and so they remain [1]. In the monograph he described several patients who presented with generalised weakness and in whom abnormalities of the adrenal glands were found at *post mortem*. Addison had discovered primary hypoadrenalism, the disease that would later take his name. He observed that ''the disease is by no means of very rare occurrence, and that were we better acquainted with its symptoms and progress, we should probably succeed in detecting many cases'' [1].

With Addison's words ringing in our ears we reflect on the paper by LAPI *et al.* [2] in this issue of the *European Respiratory Journal*. LAPI *et al.* [2] describe a nested case–control study examining the association between inhaled corticosteroids and adrenal insufficiency conducted within a cohort of patients treated for respiratory conditions over a 15-year period, starting in 1990, in Quebec, Canada. They identified 392 cases of adrenal insufficiency from 368 238 prevalent users of respiratory medicines from the Régie de l'assurance médicale du Québec database. They did not find, as per their primary objective, an increased risk of adrenal insufficiency among current users of inhaled corticosteroids. However, they did report an increased risk in relation to the use of a current high dose ($\geqslant$=2000 μg beclomethasone dipropionate (BDP)–units per day, equivalent to 1000 μg fluticasone per day) of inhaled corticosteroids (OR=1.84; 95% CI: 1.16–2.90). They concluded that high doses of inhaled corticosteroids are an independent risk factor for adrenal insufficiency although the risk was much smaller than that seen with oral corticosteroids.

This study provides interesting new data, and will add fuel to the debate, about the risk of adrenal insufficiency in patients prescribed inhaled corticosteroids. In our view the conclusion that high doses of inhaled corticosteroids alone increase the risk of adrenal insufficiency is not fully supported by the data presented. Although cases were more likely than controls to be users of high doses of inhaled corticosteroids, the lack of a clear dose–response relationship across the three tertiles of cumulative inhaled corticosteroid dose in the current users and, if anything, the protective effect of recent or past use, as depicted in table 2, casts some doubt on the assertion that there is an independent dose-related impact of inhaled corticosteroids on adrenal insufficiency. A critical issue overall is the overwhelming influence of oral corticosteroid therapy; there was an order of magnitude difference in the cumulative dose of oral corticosteroids in cases *versus* controls (547.4 mg *versus* 42.5 mg). Although the authors adjusted for the effect of oral corticosteroids, it is a difficult task to completely adjust for these strong effects. Residual confounding by systemic corticosteroids is likely to be substantial and quite possibly sufficient to explain the apparent association between inhaled corticosteroids and adrenal insufficiency in this study.

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In an earlier case–control study looking at oral and inhaled corticosteroids and adrenal insufficiency, MORTIMER *et al.* [3] compared 154 cases of adrenal insufficiency and 870 controls from a UK primary care database. They found a dose-related increased risk of adrenal insufficiency in people prescribed oral (OR 2.0; 95% CI 1.6–2.5 per course of treatment per year) or inhaled corticosteroids (OR 3.4; 95% CI 1.9–5.9 for a prescription for inhaled corticosteroids during the 90 days before the diagnosis), but the inhaled corticosteroid effect was essentially lost after adjustment for oral corticosteroid exposure. Whilst an effect of inhaled corticosteroids was not excluded, the dominant effect on adrenal insufficiency was explained by oral corticosteroid use.

Nevertheless, cases of adrenal insufficiency in patients taking inhaled corticosteroids continue to be seen in clinical practice and reported [4–8]. Many have been in children taking particularly high doses of an inhaled corticosteroid, often fluticasone. For example, DENNE *et al.* [7] recently described a case of adrenal insufficiency attributed to fluticasone in an adolescent patient with cystic fibrosis and associated hepatic cirrhosis. Cases such as this emphasise the role comorbidities and interacting drugs can play in influencing the risk. This helps to illustrate that some individual patients do indeed appear to develop adrenal insufficiency from inhaled corticosteroid use.

It is now well established that inhaled corticosteroids are absorbed into the systemic circulation, that their absorption is affected by lung function and that measureable dose-related systemic biological effects can occur [9–13]. Taken together with other data including the case reports and case–control studies, there is indeed evidence that inhaled corticosteroid use is associated with adrenal insufficiency, although the absolute risk is low and the association is dominated by the effects of systemic corticosteroid therapy. Patients taking especially high doses of inhaled corticosteroids are also likely to have had high cumulative doses of oral corticosteroids and will be the group of patients at greatest risk of adrenal insufficiency.

The message we take from the paper by LAPI *et al.* [2] is that adrenal insufficiency remains the ''unforgiving master of nonspecificity and disguise'' [14] and should be considered in patients taking inhaled corticosteroids presenting with suggestive symptoms, irrespective of whether or not the inhaled corticosteroid was the original culprit. Since iatrogenic secondary adrenal insufficiency does not impair mineralocorticoid- or melanocyte-stimulating hormone secretion it is unlikely that electrolyte disturbance or hyperpigmentation, respectively, will be present and so the presentation may be all the more unforgiving, nonspecific and disguised [8, 15]. 150 years after Addison, adrenal suppression in asthma remains a serious but rare event; its occurrence, determinants and screening remains a subject of ongoing debate [16]. Getting the risks right is a continuous endeavour of pharmacovigilance and pharmacoepidemiology [17], with the intention to protect our patients.

References

1 Addison T. On the constitutional and local effects of the disease of the supra-renal capsules. *In:* Wilks S, Daldy TM, eds. A Collection of the Published Writings of the Late Thomas Addison MD. London, New Sydenham Society, 1868; pp. 211–239.
2 Lapi F, Kezouh A, Suissa S, *et al.* The use of inhaled corticosteroids and the risk of adrenal insufficiency. *Eur Respir J* 2013; 42: 79–86.
3 Mortimer KJ, Tata LJ, Smith CJ, *et al.* Oral and inhaled corticosteroids and adrenal insufficiency: a case–control study. *Thorax* 2006; 61: 405–408.
4 Todd GR, Acerini CL, Ross-Russell R, *et al.* Survey of adrenal crisis associated with inhaled corticosteroids in the United Kingdom. *Arch Dis Child* 2002; 87: 457–461.
5 Todd GR. Adrenal crisis due to inhaled steroids is underestimated. *Arch Dis Child* 2003; 88: 554–555.
6 Mydin HH. Case history: a case of adrenal insufficiency secondary to symbicort. *InnovAiT* 2010; 3: 182–183.
7 Denne C, Vogl-Voswinckel AE, Gruebl A, *et al.* Adrenal crisis caused by inhaled fluticasone in an adolescent with cystic fibrosis and advanced hepatopathy: a case report. *Case Rep Pulmonol* 2012; 2012: 913574.
8 Schwatz RH, Neacsu O, Ascher DP, *et al.* Moderate dose inhaled corticosteroid-induced symptomatic adrenal suppression: case report and review of the literature. *Clin Pediatr (Phila)* 2012; 51: 1184–1190.
9 Brutsche MH, Brutsche IC, Munawar M, *et al.* Comparison of pharmacokinetics and systemic effects of inhaled fluticasone propionate in patients with asthma and healthy volunteers: a randomised crossover study. *Lancet* 2000; 356: 556–561.
10 Harrison TW, Tattersfield AE. Plasma concentrations of fluticasone propionate and budesonide following inhalation from dry powder inhalers by healthy and asthmatic subjects. *Thorax* 2003; 58: 258–260.
11 Mortimer KJ, Harrison TW, Tang Y, *et al.* Plasma concentrations of inhaled corticosteroids in relation to airflow obstruction in asthma. *Br J Clin Pharmacol* 2006; 62: 412–419.
12 Donnelly R, Williams KM, Baker AB, *et al.* Effects of budesonide and fluticasone on 24-hour plasma cortisol. A dose–response study. *Am J Respir Crit Care Med* 1997; 156: 1746–1751.
13 Weiner P, Berar-Yanay N, Davidovich A, *et al.* Nocturnal cortisol secretion in asthmatic patients after inhalation of fluticasone propionate. *Chest* 1999; 116: 931–934.
14 Brosnan CM, Gowing NF. Addison's disease. *BMJ* 1996; 312: 1085–1087.

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15 Shulman DI, Palmert MR, Kemp SF, *et al.* Adrenal insufficiency: still a cause of morbidity and death in childhood. *Pediatrics* 2007; 199: e484–e494.
16 Brodlie M, McKean MC. Strategies to screen for adrenal suppression in children with asthma: there is no consensus among UK centres. *Thorax* 2008; 63: 841–842.
17 Avorn J. Powerful Medicines: The Benefits, Risks, and Costs of Prescription Drugs. New York, Alfred A. Knopf, 2004.