Diagnosing adrenal insufficiency using ACTH stimulation test

To the Editor:

We read with interest the real-world data of Nanzer *et al.* [1], looking at adrenal insufficiency (AI) in severe asthma patients taking oral corticosteroid-sparing anti-interleukin (IL)-5 therapy. They reported that 43% of patients apparently failed a short adrenocorticotropic hormone (ACTH) stimulation test associated with a median baseline morning serum cortisol of 86 nmol·L^{-1} and a median prednisolone dose of 5 mg. We would be interested to know the mean cortisol level after ACTH, as well as the percentage of patients who failed to achieve a post-ACTH level of 500 nmol·L^{-1} which is the accepted cut-off for impaired response [2, 3]. Pointedly they used a pharmacological 250 µg dose of ACTH instead of the more physiological 0.5–1 µg dose [3, 4]. We suggest that using the correct ACTH dose in conjunction with a 500 nmol·L^{-1} cortisol cut off would be accompanied by a higher proportion of patients designated with AI. Finally, we also note that their patients were taking high-dose inhaled corticosteroid at a fluticasone propionate equivalent dose of 1 mg·day^{-1}. In this regard, 1 mg of inhaled fluticasone propionate exhibits a cortisol suppressive potency equivalent to 8.5 mg of oral prednisolone [5]. Hence, while it might have been possible to wean the prednisolone dose to 5 mg on anti-IL-5, in reality patients were likely to have been exposed to a much higher total systemic corticosteroid burden.

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Low dose ACTH stimulation test is more likely to detect adrenal insuffiency in patients being weaned off oral corticosteroids https://bit.ly/2XsMA3i

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References

1 Nanzer AM, Chowdhury A, Raheem A, *et al.* Prevalence and recovery of adrenal insufficiency in steroid-dependent asthma patients receiving biologic therapy. *Eur Respir J* 2020; 56: 1902273.
2 Wilson AM, McFarlane LC, Lipworth BJ. Effects of low and high doses of inhaled flunisolide and triamcinolone acetonide on basal and dynamic measures of adrenocortical activity in healthy volunteers. *J Clin Endocrinol Metab* 1998; 83: 922–925.
3 Broide J, Soferman R, Kivity S, *et al.* Low-dose adrenocorticotropin test reveals impaired adrenal function in patients taking inhaled corticosteroids. *J Clin Endocrinol Metab* 1995; 80: 1243–1246.
4 Rasmuson S, Olsson T, Hagg E. A low dose ACTH test to assess the function of the hypothalamic-pituitary-adrenal axis. *Clin Endocrinol (Oxf)* 1996; 44: 151–156.
5 Wilson AM, Lipworth BJ. Short-term dose-response relationships for the relative systemic effects of oral prednisolone and inhaled fluticasone in asthmatic adults. *Br J Clin Pharmacol* 1999; 48: 579–585.

From the authors:

We acknowledge B. Lipworth's work and significant contribution in highlighting the metabolic consequences of steroid therapy in airways disease over the past decades. In their letter he and colleagues refer to a post-synthetic adrenocorticotropic hormone (ACTH, Synacthen) cortisol level of 500 nmol·L^{-1} as the accepted cut-off to diagnose impaired adrenal function. These diagnostic values were derived using older cortisol assays; however, the cortisol levels in our report relate specifically to the newer Roche Elecsys II Cortisol assay used at our centre that gives, on average, 25% lower serum cortisol values, with a cut-off of ⩾420 nmol·L^{-1} for the 250 µg intramuscular short Synacthen test (SST) at 30 or 60 min [1]. The median cortisol level after SST was 490 nmol·L^{-1} (interquartile range (IQR) 453–620 nmol·L^{-1}) in patients who passed the SST; in those who failed the SST the cortisol level after SST was 262 nmol·L^{-1} (IQR 130–310 nmol·L^{-1}).

An agreed lower reference limit for a post-SST cortisol to specifically define a normal axis or sensitively diagnose adrenal failure depends on the specific assay, timing of sampling, and on population characteristics including body size [2]. Further, values over time have tended to decrease as assay methodologies have improved, measuring cortisol more accurately.

We chose the SST, as opposed to the 1 µg Synacthen test (LD-SST), as the SST has been more widely validated against the gold standard insulin tolerance test and represents the most widely used test for diagnosing adrenal insufficiency should the morning cortisol warrant further testing [3]. The SST obviates the need to dilute the Synacthen, which comes in vials of 250 µg, reducing one potential source of error. The diagnostic levels for cortisol after LD-SST are generally lower to diagnose adrenal failure or identify normality. How important the dose is considering normal physiology is moot, that teams use a reproducible test and interpret it correctly is, we argue, more important.

B. Lipworth and colleagues point out that all of our patients were taking high-dose inhaled corticosteroids, likely resulting in systemic absorption with the potential to affect the hypothalmo-pituitary-adrenal axis; whilst the authors and others have previously shown that systemic effects are less frequently seen in severe asthma patients, compared to healthy individuals [4, 5], we attempted to reduce this possible effect further and patients were asked to withhold their inhaled steroid >12 h prior to their SST. However, we agree with B. Lipworth and colleagues on the importance of recognising that any synthetic glucocorticosteroid has the potential to lead to adrenal suppression and patients always ought to be informed of this risk, and physicians must prescribe the lowest dose required to safely manage the disease.

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References

1 Raverot V, Richet C, Morel Y, *et al*. Establishment of revised diagnostic cut-offs for adrenal laboratory investigation using the new Roche Diagnostics Elecsys((R)) Cortisol II assay. *Ann Endocrinol (Paris)* 2016; 77: 620–622.
2 Cartaya J, Misra M. The low-dose ACTH stimulation test: is 30 minutes long enough? *Endocr Pract* 2015; 21: 508–513.

3 Stewart PM, Corrie J, Seckl JR, *et al.* A rational approach for assessing the hypothalamo-pituitary-adrenal axis. *Lancet* 1988; 1: 1208–1210.
4 Harrison TW, Wisniewski A, Honour J, *et al.* Comparison of the systemic effects of fluticasone propionate and budesonide given by dry powder inhaler in healthy and asthmatic subjects. *Thorax* 2001; 56: 186–191.
5 Lee DK, Bates CE, Currie GP, *et al.* Effects of high-dose inhaled fluticasone propionate on the hypothalamic-pituitary-adrenal axis in asthmatic patients with severely impaired lung function. *Ann Allergy Asthma Immunol* 2004; 93: 253–258.