



Position statement on the use of synthetic ACTH (Synacthen) in patients with a history of asthma

Assessment of the hypothalamo-pituitary-adrenal axis (HPAA) is one of the most important tasks of the endocrinologist involved in the care of patients with pituitary disease. While for most the insulin tolerance test (ITT) remains the gold standard, the requirement for constant clinical oversight, plus the small but significant risks, has led to the ACTH stimulation test being the most popular form of rapid HPAA assessment in most units¹. It is also frequently used in the investigation of primary adrenal failure, although measurement of basal cortisol and ACTH levels often render its use in this situation of little value. In its usual format, 0.25mg synthetic ACTH[1-24] (*Synacthen*, *Cosyntropin*) is injected im (or rarely iv) and cortisol measured basally and at 30 minutes, and possibly also at 60 minutes. Except in the early period following pituitary surgery, the peak 30 minute serum cortisol is closely correlated with the results of the ITT, although normative values are assay-dependent. The test is also used, and is useful, in investigating the endogenous cortisol reserve in patients on current or previous corticosteroid therapy, such as those with chronic respiratory or rheumatological disease, and is also frequently used (less usefully) in intensive care units.

While the Synacthen test appears to be safe and well-tolerated in the vast majority of patients, there were early reports of severe allergic reactions, including one death, following the use of synthetic ACTH in patients with allergic tendencies. This has led to the data sheet for Synacthen in the UK to advise that "patients who are also susceptible to allergies (especially asthma) should not be treated with Synacthen unless other therapeutic measures have failed to elicit the desired response and the condition is severe enough to warrant such medication". In spite of this, we became aware that in the UK the awareness of such adverse events is highly variable. Some endocrinologists always enquire for a history of asthma and avoid the use of Synacthen in any patient with any such history, others avoid its use only when the asthma is severe and on-going, while yet others use Synacthen regardless of any history of asthma; indeed, the Synacthen test has been extensively used in patients with asthma on inhaled corticosteroids to assess HPAA suppression – apparently without ill effect². This clearly chaotic situation is unsatisfactory, and we believe it is appropriate to provide advice on the use of Synacthen.

To our knowledge, there are no published deaths attributable to synthetic ACTH that have been published since 1972. Synacthen consists of synthetic ACTH[1-24] plus diluents. It is difficult to attribute any adverse effect following administration of a truncated form of an endogenous peptide to that peptide, as it is improbable that ACTH[1-24] is immunogenic. It is possible that the early deaths attributable to ACTH administration were related to the diluents used at that time. It is remarkable that no severe adverse events have been reported over the subsequent 40 years, when many thousands of doses of Synacthen have been administered: the Birmingham team have reported no adverse events following some 5000 administered doses³. We also note the apparent safety of Synacthen when used in many studies of patients with asthma². Under such circumstances, we believe it is unreasonable and unnecessary to automatically avoid the use of Synacthen in patients with a history of asthma or related disorders.

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However, we would nevertheless recommend that:

- (1) A history of asthma or other allergic disorders be taken and noted, and that;**
- (2) Resuscitation equipment relevant to the treatment of anaphylaxis be available for patients where this history is present. Synacthen tests should not be performed where such equipment is unavailable for these patients, and where clinical staff are inexperienced in the treatment of anaphylaxis. Finally, we recommend that;**
- (3) Patients also be questioned as to whether they have had a previous untoward reaction to Synacthen, and that its use be avoided where such reactions have occurred.**

We appreciate that such recommendations have a poor evidence base, but are offered so as to allow the widespread use of this helpful investigative tool while minimising the risk of potential rare complications.

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**... for and on behalf of the Society for Endocrinology
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References

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2. Wlodarczyk JH, Gibson PG, Caeser M (2008). Impact of inhaled corticosteroids on cortisol suppression in adults with asthma: a quantitative review. *Ann Allergy Asthma Immunol.* **100**, 23-30
3. Agha A, Tomlinson JW, Clark PM, Holder G, Stewart PM (2006). The long-term predictive accuracy of the short synacthen (corticotropin) stimulation test for assessment of the hypothalamic-pituitary-adrenal axis. *J Clin Endocrinol Metab.* **91**, 43-7.