**Society for Endocrinology Position Statement on the Use of Synthetic ACTH (Synacthen) in Patients with a History of Asthma**

Assessment of the hypothalamic-pituitary-adrenal axis (HPAA) is one of the most important tasks of the endocrinologist involved in the care of patients with pituitary disease. While the insulin tolerance test (ITT) is still considered to be the gold standard, the requirement for constant clinical oversight, plus the small but significant risks, has led to the adrenocorticotrophic hormone (ACTH) stimulation test being the most popular form of rapid HPAA assessment in most units (1). It is also frequently used in the investigation of primary adrenal failure, although measurement of basal cortisol and ACTH levels may reduce the value of its use in this situation. In its usual format, 0.25mg synthetic ACTH[1-24] (Synacthen, Cosyntropin) is injected intra-muscularly (or rarely iv) and cortisol measured basally and at 30 minutes (less commonly also at 60 minutes). Except in the early period following pituitary surgery (or soon after onset of pituitary apoplexy), 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, 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 effect (2). 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: for example, the Birmingham team reported no adverse events following some 5000 administered doses (3). We also note the apparent safety of Synacthen when used in studies of patients with asthma (2). In addition, a series of Synacthen tests (albeit at the low 1μg dose) were undertaken in more than 500 children with asthma and no serious adverse events were reported (4). 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.

We would nevertheless recommend that:

• a history of asthma or other allergic disorders be taken and noted

• 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)

• patients 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.

This position statement has been revised and updated by Prof. Jeremy Tomlinson (University of Oxford) and Prof Roland Stimson (University of Edinburgh) in March 2020 and is based upon the original position statement published by Professor Ashley Grossman (University of Oxford) in September 2011. This information is provided and endorsed by the Society for Endocrinology’s Clinical Committee.

References

1. Grossman AB. The diagnosis and management of central hypoadrenalism. J Clin Endocrinol Metab 2010; 95(11):4855-4863.

2. 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.

3. Agha A, Tomlinson JW, Clark PM, Holder G, Stewart PM. The long-term predictive accuracy of the short synacthen (corticotropin) stimulation test for assessment of the hypothalamic-pituitary-adrenal axis. J Clin Endocrinol Metab 2006; 91(1):43-47.

4. Hawcutt DB, Jorgensen AL, Wallin N et al. Adrenal responses to a low-dose short synacthen test in children with asthma. Clin Endocrinol (Oxf) 2015; 82(5):648-656.