Reliability of the ACTH Low Dose Test in the Evaluation of Adrenal Insufficiency

Adrenal insufficiency (AI) can be the consequence of a primary impaired function of the adrenal glands, of an inadequate secretion of ACTH due to hypothalamic-pituitary diseases or of an abrupt suspension of chronic steroid treatment.

In the presence of clinical signs and laboratory findings of AI, the diagnosis is usually straightforward. However, this is not a frequent occurrence. The recognition of the sub-clinical cases is more problematic. An early diagnosis of these forms is very important because AI is a potentially life-threatening condition which needs an adequate replacement therapy.

Sub-clinical cases of AI are usually characterised by normal basal cortisol and ACTH levels and require dynamic tests for the assessment of the function of the hypothalamic-pituitary-adrenal (HPA) axis.

The insulin tolerance test (ITT) has widely been considered the "gold standard" for detecting secondary adrenal failure, but it is not devoid of side effects and contraindications.

The standard high dose ACTH test (250 µg) (HDT) has been used in the evaluation of both primary and secondary AI. The HDT is supra-physiological, because of the pharmacological ACTH concentration induced. With the aim of performing a physiological provocative test, very low doses of ACTH have been tested. The lowest ACTH dose able to maximally stimulate the adrenal cortex in normal subjects is 1 µg. A large body of evidence, collected during the last 10 years, indicates that the low dose ACTH test (1µg) (LDT) shows a high sensitivity and specificity for the assessment of central AI in patients with hypothalamic-pituitary disorders. It demonstrates a strong correlation with the ITT.

The LDT offers a very high reliability in diagnosing mild forms of primary AI or mild adrenal suppression by inhaled steroids in asthmatic children. In addition, the close correlation between cortisol, DHEA, 17OH-progesterone and aldosterone responses to the LDT in subjects with pre-clinical primary AI has also been shown. An important point is that the LDT is free of side effects, is cost effective and can easily be used for exclusion of adrenal failure in outpatients.

The definition of a standardised cut-off point of peak cortisol response to the LDT is a critical issue. The value of 18 mg/dl seems to be adequate, even though some authors have proposed significantly lower values. These differences in cut-off values may in part reflect changes in methods of preparation and storage of ACTH dilutions. The relatively small number of volunteer subjects enrolled in the different studies justifies some differences in the normal values observed. Differences in laboratory technologies add further variability in the results of different studies.

In addition, an important recommendation is that the LDT should never be used in cases of acute deprivation of ACTH (e.g. recent hypopituitarism), when the intact adrenal cortex can still respond normally to any change of plasmatic ACTH levels.

In conclusion, we think that the LDT can be considered reliable and should be used in the routine clinical practice. Its use as the first test in the evaluation of HPA axis function can be proposed. The establishment of a range of normal values for each centre is important for the interpretation of the results obtained in the patients studied. In the doubtful cases for a positive test (grey zone) a different provocative test should also be performed and interpreted taking into consideration the clinical picture. Finally, the standardisation of the preparation of ACTH dilution will reduce the variability of the LDT results. A very important help could be provided by the development of commercial preparations containing 1 µg of ACTH.

Laureti S, Falorni A

Section of Internal Medicine and Endocrine and Metabolic Sciences, Department of Internal Medicine, University of Perugia, Via E. Dal Pozzo, I-06126 Perugia, Italy.

E-mail: laureti@dimsiem.med.unipg.it

References
7. Dickstein G, Spigel D, Arad E, Schechner C. One microgram is the lowest ACTH dose to cause maximal cortisol response. There is no...