The role of high- and low-dose corticotropin tests in the diagnosis of secondary adrenal insufficiency

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Introduction
Secondary adrenal insufficiency (SAI) results from hypothalamic or hypophyseal damage or from prolonged administration of supraphysiological doses of glucocorticoids. SAI may be mild, potentially leading to decompensation in stressful situations, or it may be severe per se with symptoms similar to an Addisonian crisis (without hyperpigmentation and hyperkalemia, however). Severe SAI is easy to diagnose. The patients are pale (adrenocorticotropin (ACTH) deficiency), weak, hypotensive and often suffer from gastrointestinal symptoms. Amenorrhea, loss of libido, small testicles, scanty pubic hair and secondary hypothyreosis or visual field defects may be accompanying signs and symptoms pointing to the diseased pituitary. In those patients, basal plasma cortisol is often low (<100 nmol/l). If plasma ACTH is also low or low-normal, the diagnosis of SAI is confirmed, no further dynamic testing of the hypothalamo–pituitary–adrenal (HPA) axis is necessary, and the patient needs regular substitution with hydrocortisone.

The diagnosis is much more difficult if the HPA axis is only mildly impaired, other endocrine deficits of the pituitary are missing or also mild, and neurological symptoms hinting at a hypothalamic lesion like visual field defects are missing. With such non-specific complaints as tiredness, reduced appetite and occasional dizziness, it is important that the patient is lucky enough to find a physician whose threshold of suspicion is low enough to consider the possibility of SAI at all. What test is to be done in such a patient, and likewise in another who presents with an ‘incidentally’ detected pituitary tumor (on CCT or MRT ordered for other than pituitary reasons) without the clinical symptoms and signs of hypocortisolism or SAI?

The standard tests for diagnosing or excluding SAI are the insulin hypoglycemia test (IHT) and the metyrapone test (MT). In order to give a normal result (IHT: increase of plasma cortisol to >500 or >550 or >580 nmol/l in different reports; MT: increase of plasma 11-deoxy-cortisol to >200 nmol/l at 0800 h after taking metyrapone at midnight), the entire HPA axis needs to be intact (1–6). With very few exceptions (7), patients with a normal IHT or MT do not need hydrocortisone substitution, although they may need hydrocortisone later on, if the underlying pituitary disorder is progressive.

The standard (high-dose) corticotropin test
Since the 1960s, an increasing number of endocrinological centers have used the short corticotropin injection test (SCT) as a screening procedure in patients suspected of having adrenal insufficiency. While the sensitivity of this test in symptomatic primary adrenal insufficiency is almost 100% (8), it is a problematic procedure as a screening test for SAI for the following reasons. The IHT and the MT provoke a rise in endogenous ACTH that acts on the adrenal and stimulates the secretion of cortisol or 11-deoxy-cortisol respectively. A normal test, therefore, indicates that ACTH can increase in response to the stressor, and that the adrenal cortex has not yet undergone atrophy as a consequence of ‘chronic’ ACTH deficiency. Adrenal atrophy or functional impairment of the adrenal following partial or total withdrawal of the ACTH stimulus needs some weeks to occur and can be found in all grades of severity in patients with pituitary disorders or following pharmacological glucocorticoid treatment.

In contrast to these tests, the SCT only tests adrenal reactivity to exogenous corticotropin 1–24 (endogenous human corticotropin has 39 amino acids but is equipotent with synthetic corticotropin 1–24), but patients with a normal increase of plasma cortisol (to >500 or >550 nmol/l) in this test may have undiscovered hyporesponsiveness of endogenous corticotropin in stressful situations. It was therefore not surprising that beginning in the 1980s many publications appeared reporting patients in whom the IHT or the MT was subnormal, while the SCT seemed to indicate an intact ‘adrenal function’ (reviews 1–3). In response to this insight, three different strategies were followed by endocrinologists:
(i) Not to use the SCT any more in patients with possible SAI.
(ii) To raise the ‘cutoff’ level of the plasma cortisol response in the SCT quite pragmatically to 600 nmol/l.
or even higher, since it was found that the higher the cortisol response in the SCT the smaller was the likelihood that the same patient had a subnormal response in the IHT or the MT.

(iii) The development of a new SCT with much smaller doses of corticotropin 1–24 than in the conventional SCT (250 μg), in the hope that avoiding ‘overstimulation’ of the adrenal cortex might improve the sensitivity of the test in patients with mild SAI.

In this issue of European Journal of Endocrinology we find two papers (9, 10) dealing with this problem. The one by Bangar & Clayton (9) follows the second of the above strategies. They reviewed the data of 69 patients with confirmed pituitary disease in whom both the IHT and the conventional SCT (250 μg) had been performed within 4 weeks. For both tests, they regarded an increase of plasma cortisol to >500 nmol/l (‘cutoff point’) as a ‘pass’, i.e. a normal response. They report that with this cutoff point ‘7 out of 69 patients (10%) who passed the SCT (cortisol measured 30 min after injection) failed the IHT’. However, only 20 out of the 69 patients had a subnormal IHT, so that the failure rate of the SCT was 7/20 = 35%. If they pragmatically took 600 nmol/l as the cutoff point of the SCT, its failure rate decreased to 3 out of 69, in reality to 3/20 = 15%. The authors conclude that the SCT with a cutoff level of 600 nmol/l is a sufficiently sensitive screening test for SAI. We will discuss later whether 500 nmol/l is a realistic cutoff point for the IHT.

The approach of pragmatically raising the cutoff level of the SCT to 600 nmol/l (i.e. to a level higher than the lower limit of responses measured in most studies on healthy subjects) is not new. It was previously proposed by Lindholm (11) and by Hurel et al. (12). In the latter paper, 6 out of 60 patients (10%) with pituitary disease who failed the IHT (out of a total number of 166 patients) passed a cutoff level of 600 nmol/l in the SCT at 30 min. Even if the cutoff level of the SCT was raised to 700 nmol/l, 4 out of 60 patients with a subnormal IHT passed the SCT (6.6%). In a paper by Mukherjee et al. (5) from London, in which the approach of pragmatically raising the cutoff level of the SCT was scrutinized, the authors finally suggested that ‘the IHT should remain the preferred test for assessing ACTH secretory capacity compared with the standard short ACTH stimulation test’.

The low-dose corticotropin test

The second paper in this issue dealing with corticotropin testing in patients with pituitary disease is by Ambrosi et al. (10). These authors compared the results of the IHT (cortisol cutoff point 500 nmol/l) with a low-dose SCT (i.v. injection of 1 μg corticotropin 1–24) in 57 patients with pituitary or hypothalamic disorders, and they established a normal range in 18 healthy volunteers (for the 1 μg SCT only). They did not compare the low-dose with the conventional SCT. With post-injection blood sampling at 30 and 40 min after low-dose ACTH injection, the maximum cortisol response in the normals was between 541 and 1215 nmol/l. With an assumed cutoff point of 500 nmol/l for both the IHT and the SCT, 4 out of 14 patients with a pathological IHT (28%) had a normal low-dose SCT, while 3 out of 43 patients with a normal IHT (7%) had a subnormal low-dose SCT. In the end, the authors followed the same strategy as Bangar & Clayton (9). Since among their patients with a cortisol response in the low-dose SCT of >750 nmol/l (!) none had a subnormal cortisol response in the IHT, they recommend the 1 μg SCT with a cutoff point of 750 nmol/l as a safe screening test for SAI, without saying why it should be any better than the conventional SCT. A similar approach, recommending a high cutoff point for the low-dose corticotropin test was recently also used by Arafah et al. (13).

Where are we at this point? It is necessary to briefly comment on the history of the low-dose SCT. It has been known for many years that 250 μg corticotropin is a dose at least 50-fold higher than is necessary for the acute maximal stimulation of cortisol secretion (14).

Ten years ago, our group showed (15) that the adrenal cortex is almost maximally stimulated by plasma corticotropin 1–39 levels of about 100 pg/ml (normal levels in the morning are about 5–50 pg/ml), while after i.v. injection of 250 μg corticotropin 1–24, the peak plasma corticotropin level is about 60 000 pg/ml!! Dickstein et al. (16), Broide et al. (17) and Tordjman et al. (18) recently published data on low-dose SCT tests (1 μg in adults or 0.5 μg/1.73 m² in children) that seemed to show that these low-dose SCTs are as sensitive as the IHT in detecting mild SAI in asthmatics who use topically applied corticosteroids or in patients with pituitary disease, although even a low-dose test can only measure adrenal reactivity but not endogenous ACTH reserve. Dickstein et al. (16) maintained that with the low-dose test, the cortisol response at 30 min after i.v. injection of corticotropin 1–24 is indistinguishable from that after 250 μg, since 1 μg was said to be ‘the lowest ACTH dose to cause a maximal cortisol response’ (19). Tordjman et al. (18), however, found 1 μg stimulated cortisol less than 250 μg corticotropin 1–24. In spite of this finding, they used the same cutoff point for the low-dose and the high-dose test (500 nmol/l) in comparison with the IHT (assumed cutoff also 500 nmol/l) in their patients and concluded that the low-dose test is more sensitive than the high-dose test and as sensitive as the IHT in disclosing mild SAI. We recently established normal ranges for cortisol responses in the low-dose (0.5 μg/m² corticotropin 1–24) and high-dose tests in 35 endocrinologically healthy subjects (20). Mean responses minus 2 standard deviations were used as the cutoff point. The results were as follows: low-dose test at 30 min after injection, 535 nmol/l; high-dose test at 30 min after injection, 621 nmol/l; high-dose test at 60 min after injection, 726 nmol/l.
Thus, it is very important to use different cutoff points in the low- and high-dose tests. In our experience, derived from studies in 44 patients with pituitary disease, the sensitivities of both variants of the test in comparison with the IHT and MT were almost identical, and inferior to the IHT or MT, in detecting milder degrees of SAI (20). In that paper, we used 550 nmol/l as the cutoff point for the plasma cortisol response in the IHT, as suggested by Pavord et al. (4). More recently we tried to establish a new normal range for the cortisol response in the IHT in 25 healthy subjects. Using the same plasma cortisol kit that was applied in the studies of Mayenknecht et al. (20), we found the maximum cortisol values in the IHT to range between 600 and 1266 nmol/l, and the mean minus 2 standard deviations was 568 nmol/l. Thus, since the low-dose corticotropin test does not seem to fulfill the expectations put on it, in respect to its increased sensitivity for detecting mild SAI, it is understandable that Ambrosi et al. in the paper published in this issue (10) had to take the same step as Bangar & Clayton (9), namely to pragmatically raise the cutoff point of the low-dose test in order to avoid underdiagnosis of SAI in patients with pituitary disease.

**Recommendations for using dynamic tests**

What can be done in the present situation if one tries to avoid performing an IHT (that needs experience by the investigator, is time consuming and often disagreeable for the patient, and is sometimes contraindicated) or an MT (metyrapone and a method for measuring plasma 11-deoxy-cortisol are not everywhere available) in every patient in whom SAI has to be excluded?

Based on published reports, the following recommendations can be made. Measure plasma cortisol on two different days in the morning between 0800 and 0900 h. If the mean level is <100 nmol/l, adrenal insufficiency is confirmed (provided the patient has not taken dexamethasone or prednisolone recently), no further testing is necessary, and regular hydrocortisone substitution is indicated. If there is any doubt whether the patient has secondary or primary adrenal insufficiency, a basal plasma ACTH level will decide. If the mean cortisol level is >500 nmol/l, adrenal insufficiency is extremely unlikely, and dynamic testing is, likewise, unnecessary (1, 2, 4, 21, 22).

In all other patients dynamic testing is indicated. An IHT or an MT is the best choice. If you cannot do it yourself, refer the patient to an experienced endocrinologist, as you refer a patient with angina pectoris to a cardiologist. Adrenal insufficiency is a potentially life-threatening disorder, and appropriate tests, not necessarily the easiest and cheapest, should be used to diagnose or exclude it.

If you decide to use the SCT, use a high cutoff point (600 or 700 nmol/l) in order to minimize underdiagnosis of SAI. If the cortisol response in a thoroughly performed SCT is <400 nmol/l, adrenal insufficiency is very likely. If the patient has a cortisol response in the SCT between 400 and 700 nmol/l, an IHT or MT should be performed in addition. Never use an SCT in the first 3 weeks after pituitary surgery, since in cases of impaired ACTH secretion the adrenal cortex needs some time to become hyporesponsive to corticotropin. By using basal morning plasma cortisol levels as a screening test and the SCT (low or high dose) with a pragmatically high cutoff level, it should be possible to avoid IHTs of MTs in at least 50% of patients, depending on the composition of the population screened.

A last word on the low-dose SCT. In this test, plasma corticotropin 1–24 still rises to levels >1000 pg/ml 1 min after injection. However, due to the rapid clearance of ACTH, plasma ACTH levels are higher than 100 pg/ml (the lowest concentration that stimulates the adrenal maximally in man) for about 12 min only (20). At 30 min post-injection, cortisol levels start falling in the low-dose test, since the adrenal is no longer maximally stimulated. Exact timing of blood sampling is, therefore, very important with this test, and dilution errors of the 250 µg corticotropin 1–24 ampoule can also occur. I assume that in the three patients in the paper of Ambrosi et al. (10) in whom the IHT was normal but the response to 1 µg corticotropin was subnormal, blood sampling time or dilution of the ampoule was not quite exact, because a test that stimulates the adrenal maximally (19) theoretically cannot result in a smaller cortisol response than the IHT that stimulates plasma ACTH to between 100 and 300 pg/ml in normal subjects.

Whether the SCT (high or low dose) is a recommendable screening test for SAI is still a matter of debate. The expectation that the low-dose test would be more sensitive than the 250 µg test does not seem to have stood up to several criticisms. If one wants to avoid the large overdose of corticotropin 1–24 in the SCT, one could inject 5 or 10 µg of the peptide i.v. and use the same cutoff points between normal and subnormal for the 30 min post-injection plasma cortisol that have been elaborated for the high-dose test (16, 18). I would not recommend the use of these cutoff points after i.m. injection of low doses of corticotropin 1–24 without establishing a normal range in control subjects.

**References**


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