Long-acting porcine sequence ACTH in the diagnosis of adrenal insufficiency: a cost-effective alternative to the ACTH_{1–24} test

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Abstract

While the ACTH_{1–24} test has some well-documented shortcomings, it is the most widely used test to diagnose primary and secondary adrenal insufficiency. However, this synthetic ACTH preparation is not readily available in some countries. Research from India has demonstrated that using a long-acting porcine sequence ACTH has similar diagnostic performance to ACTH_{1–24} at around 25% of the cost. This may allow access to a robust test for adrenal insufficiency to developing countries and potentially allow thousands of patients to be identified and appropriately treated.

*European Journal of
Endocrinology*
(2020) **182**, C5–C7

The ACTH_{1–24} test, also known as the short Synacthen® test or the Cosyntropin test depending on your country of origin, was first used as a test of hypothalamic-pituitary-adrenal axis function in the 1960s (1). Across the ensuing decades, debate has raged about many issues such as whether it is an accurate enough measure for secondary adrenal insufficiency (2), what dose of ACTH_{1–24} should be used (2), optimal timing of blood samples (3), the effect of different cortisol assays on diagnostic cut-offs (4, 5) and thresholds for basal cortisol which might make such a test unnecessary (6). As time and further research have progressed, we now have answers to most of these questions, providing endocrinologists with a 'reasonably' clear picture of the strengths and limitations of the ACTH_{1–24} test. However one issue which I suspect most endocrinologists practising in developed countries have never needed to consider is the cost and availability of ACTH_{1–24}.

The recently published paper by Nair *et al.* from Thiruvananthapuram, India reports the results of a

comparative study between ACTH_{1–24} and long-acting porcine sequence ACTH known as Acton Prolongatum® in the diagnosis of adrenal insufficiency (7). ACTH_{1–24} is not marketed in India, and while the authors managed to access this, the cost was 14 times higher per dose of Synacthen® compared to Acton Prolongatum®. They cite several other studies, also from India, where the cortisol response to Acton Prolongatum® has been reported. For example, Gundgurutthy *et al.* examined the cortisol response in healthy volunteers and patients with adrenal insufficiency (8), while Wagmode *et al.* examined healthy volunteers but also used the ACTH_{1–24} test as a comparator (9).

Thus, there is a growing body of literature from India which attests to the safety and efficacy of Acton Prolongatum® as an alternative ACTH stimulation test – with Nair *et al.* being the first to undertake a comprehensive comparative study in adults with suspected adrenal insufficiency and publish their data in an international Endocrine journal (7). Their results demonstrate that 30 IU of Acton Prolongatum® may be a slightly more potent

stimulus to cortisol secretion than 250 µg of ACTH₁₋₂₄ at 60 min, though this failed to reach statistical significance ($P=0.072$). By receiver-operating characteristic (ROC) curve analysis, the diagnostic performance of Acton Prolongatum® was optimal using the 120-min cortisol concentration. Compared to the ACTH₁₋₂₄ test, Acton Prolongatum® showed a sensitivity of 100% in diagnosing adrenal insufficiency with specificity between 84 and 88% depending on the cortisol cut-off used. No adverse effects were noted with the administration of either Synacthen® or Acton Prolongatum®. However, the administration of a porcine protein potentially increases the likelihood of antibody formation, the clinical relevance of which remains to be determined.

The authors do not claim that the use of Acton Prolongatum® is a better or more accurate test for adrenal insufficiency than ACTH₁₋₂₄. Their results suggest that the use of a different ACTH preparation, when combined with time- and cortisol assay-specific cut-offs provides a similar degree of diagnostic performance. The main differentiating feature is the cost. As noted earlier, the cost per dose of Acton Prolongatum® 30 IU was 14 times less than Synacthen® 250 µg in India. When translated to the cost of the entire test, the authors' calculated savings were 75% – \$US44 for ACTH₁₋₂₄ versus \$US11 for Acton Prolongatum®. Given the results as presented, the 60-min cortisol sample during the Acton Prolongatum® test appears to be redundant, meaning that further savings are possible with just a baseline and 120-min cortisol. This would bring the cost down to less than \$US10 per stimulation test.

Using Acton Prolongatum® is likely to have essentially the same issues as ACTH₁₋₂₄ in terms of diagnostic accuracy and error. There will be patients with secondary adrenal insufficiency who pass the test. The dose used in the study by Nair *et al.* was different to previous Indian studies (which used 25 IU) and calculated simply because at a dose of 30 IU, ten stimulation tests were possible from a 300 IU in 5 mL vial. One could argue that using 25 IU as in the study by Gundurthi *et al.* (8) (therefore 12 tests from a 300 IU vial), could improve the financial bottom line even further. Gundurthi *et al.* reported that all participants in their validation cohort who were healthy volunteers, or had either diabetes mellitus or primary hypothyroidism, exceeded a cortisol of 20 µg/dL at 60 min (Beckman Coulter RIA) (8). Given that the cortisol would have been higher at 120 min, a dose of 25 IU probably results in a similar degree of adrenal stimulation as 30 IU. However, 30 IU is an even 0.5 mL volume, whereas 25 IU is 0.42 mL. Therefore on balance, standardising the Acton

Prolongatum® dose to 30 IU in 0.5 mL with cortisol samples at 0 and 120 min would appear to make a lot of sense in terms of ease in administration.

Any diagnostic test measuring cortisol must take into account the assay used. The newer cortisol II standard as used by Nair *et al.* has been shown to read cortisol concentrations considerably lower than other immunoassays, with cut-offs for the ACTH₁₋₂₄ test suggested between 350 and 400 nmol/L (12.7–14.5 µg/dL) rather than the traditional 500 nmol/L (18 µg/dL) (5, 10). There are an increasing number of commercial laboratories now moving to routine use of liquid chromatography-dual mass spectrometry (LC-MS/MS) to measure cortisol and other steroid hormones (5). Therefore it is imperative that laboratories establish a reference range for basal and stimulated cortisol consistent with the assay they are using.

In summary, the study by Nair *et al.* presents a diagnostic test for adrenal insufficiency in the developing world whose safety and accuracy are similar to ACTH₁₋₂₄, but at a fraction of the cost. This has the potential for thousands of people being offered a test that would have been previously unavailable, leading to the commencement of life-saving glucocorticoid replacement therapy.

Declaration of interest

The author declares that there is no conflict of interest that could be perceived as prejudicing the impartiality of this commentary.

Funding

This commentary did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

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Received 13 November 2019

Accepted 21 November 2019