Can 1 microg of cosyntropin be used to evaluate adrenal insufficiency in critically ill patients?

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CRD summary
This poorly reported review concluded that all patients diagnosed as having adrenal insufficiency (AI) by the 250-microg cosyntropin test should be detected using the 1-microg test. The poor reporting of review methodology, lack of a quality assessment, and lack of a comparison with the currently accepted 'gold' standard for AI, severely undermine the reliability of the authors' conclusions.

Authors' objectives
To assess the usefulness of 1 microg cosyntropin in assessing adrenal insufficiency (AI) in critically ill patients.

Searching
MEDLINE, EMBASE, International Pharmaceutical Abstracts and the Cochrane Library were searched from 1966 to August 2004; the search terms were reported. The reference lists of retrieved studies were checked.

Study selection
Study designs of evaluations included in the review
Inclusion criteria relating to the study design were not stated.

Specific interventions included in the review
Studies of cosyntropin 1 microg were eligible for inclusion. The included studies compared low-dose adrenocorticotropic-releasing hormone (ACTH; 1 and 5 microg) with high-dose ACTH (259 and 250 microg).

Reference standard test against which the new test was compared
Inclusion criteria relating to the reference standard were not stated. The authors identified the insulin tolerance test (ITT) as the 'gold' standard, but stated that ACTH is often used because of contraindications and safety concerns of ITT. The reference standards used included ITTs and 250 microg ACTH.

Participants included in the review
Studies of critically ill patients were eligible for inclusion. The included studies were undertaken in non-critically ill patients (e.g. healthy volunteers, patients with suspected or proven pituitary disease or hypothalamic-pituitary disorders, and patients on long-term glucocorticoids) and critically ill patients (e.g. intensive care unit patients with the human immunodeficiency virus, septic shock, clinically suspected AI, and patients requiring vasopressor support for at least 24 hours).

Outcomes assessed in the review
Studies reporting measures of AI were eligible for inclusion. The included studies reported changes in serum cortisol levels.

How were decisions on the relevance of primary studies made?
The authors did not state how the studies were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction.

Methods of synthesis
How were the studies combined?
The studies were grouped according to patient characteristics (critically ill or not) and combined in a narrative.

How were differences between studies investigated?
Some differences between the studies were described in the text and presented in tabular format.

Results of the review
Details of 5 studies in non-critically ill patients (n=128) and 3 studies in critically ill patients (n=137) were tabulated. The text of the review also referred to an additional 2 studies in non-critically ill patients.

Non-critically ill patients (7 studies).
Five studies showed that 1 microg ACTH was comparable to 250 microg when compared with ITT; two of these studies showed 1 microg was more sensitive than 250 microg. The other 2 studies did not find 1 microg to be more sensitive and/or specific than 250 microg.

Critically ill patients (3 studies).
In all 3 studies, the 1-microg ACTH test was performed 1 or 5 hours before the 250-microg ACTH test. All 3 studies found the 1-microg test to be more sensitive than the 250-microg test in diagnosing AI.

Authors' conclusions
All patients diagnosed as having AI using 250 microg cosyntropin should be detected using 1 microg cosyntropin.

CRD commentary
The review question was clear but the inclusion criteria were poorly defined, and those stated were not adhered to. Several relevant sources were searched, but no attempt was made to locate unpublished studies and it was unclear whether any language limitations had been applied; there is therefore the potential for both publication and language bias. Methods used to select studies and extract the data were not described, so it is not known whether any efforts were made to reduce errors and bias. Validity was not assessed though some limitations of the data were briefly mentioned.

Some studies discussed in the text were not presented in the tables; it is unclear why details of all studies were not presented in a similar fashion. The narrative synthesis of studies was appropriate given the differences between the studies. Appropriate outcomes (sensitivity, specificity etc.) for assessing diagnostic accuracy were rarely reported for the included studies, making interpretation of the results difficult. None of the 3 included studies in critically ill patients compared the diagnostic accuracy of 1 microg ACTH with the currently accepted 'gold' standard ITT, and the carry-over effect of consecutive dosing with ACTH was not examined. These limitations make it difficult to assess the usefulness of 1 microg ACTH in diagnosing AI. This, along with the poor reporting of review methodology, severely undermines the reliability of the authors' conclusions.

Implications of the review for practice and research
Practice: The authors stated that clinicians should be reassured that 1 microg ACTH is adequately sensitive to identify all patients who would be labelled with AI using the 250 microg dose.

Research: The authors stated that large studies are required to directly compare 1- and 250-microg ACTH stimulation tests for the detection of AI in multiple intensive care unit populations and a variety of subgroups of critically ill patients.
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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.