Using the high-dose corticotropin test to diagnose relative adrenal insufficiency in vasopressor-dependent septic shock

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The Clinical Consultation column provides brief recommendations on handling specific pharmacotherapeutic problems in clinical practice. The problems addressed may be general or specialized but of wide interest. The column provides readers with relevant insights into optimum drug-therapy management by pharmacists. Recommendations are made on the basis of scientific literature and the author’s clinical judgment and personal experience. Pharmacists in various settings, including drug information centers, are encouraged to submit manuscripts, ideas, and comments to AJHP (ajhp@ashp.org).

Septic shock is associated with high mortality, with approximately 50% of patients failing to survive intensive-care-unit (ICU) admission. Clinicians began using corticosteroids over 40 years ago to treat patients with sepsis based on animal data that revealed the potent effects of these medications on hemodynamics. In states of severe illness and stress, the hypothalamic–pituitary–adrenal axis is stimulated to release corticotropin, which in turn stimulates the release of cortisol from the adrenal cortex. Patients with septic shock have prolonged inflammatory responses and an increase in circulating suppressive factors. This appears to be the cause of relative adrenal insufficiency in this population. Relative adrenal insufficiency is characterized by cortisol concentrations that would appear normal or near normal (3–10 μg/dL) if measured in a healthy individual. In the setting of severe stress, much higher cortisol concentrations are necessary to preserve hemodynamic stability.

Through the regulation of gene transcription, cortisol exerts a wide range of physiological actions, including metabolic, cardiovascular, anti-inflammatory, and immunosuppressive effects. Glucocorticoids increase blood glucose levels and stimulate lipid and protein metabolism to supply energy and substrate to the cell. Additionally, they are essential for cardiovascular reactivity to circulating catecholamines. This effect is mediated by increased α- and β-adrenergic receptors and increased synthesis of catecholamines. The action of glucocorticoids on specific receptor mechanisms of most cells that are involved in immune and inflammatory action is what leads to their anti-inflammatory and immunosuppressive actions.

Administration of exogenous glucocorticoids presents a valuable treatment strategy in septic patients who are likely to have relative adrenal insufficiency by replacing physiological doses of the hormone. Up-regulation of α- and β-receptors and improved cardiovascular response to catecholamines are important therapeutic effects of glucocorticoids in patients who are hemodynamically compromised.

Although early studies in humans supported the notion that corticosteroid use could improve clinical outcomes in patients with sepsis, subsequent randomized clinical trials showed no benefit in the treatment of severe sepsis with respect to prevention of shock, reversal of shock, or mortality. In addition, clinical-trial meta-analyses published as re-
Vasopressor-dependent septic shock

The purpose of this article is to evaluate the usefulness of the high-dose corticotropin test for relative adrenal insufficiency in trials in which stress-dose steroids were beneficial in patients with vasopressor-dependent septic shock. Our focus is on the high-dose corticotropin test due to the paucity of data on the other diagnostic methods for relative adrenal insufficiency in this patient population. We conducted a computerized search of MEDLINE using the following search terms: adrenocorticotropic hormone (ACTH), co-syntropin, adrenal insufficiency, corticosteroids, septic shock, and vasopressors. We included randomized controlled trials, reviews, and abstracts. References of articles were also reviewed for relevant articles not identified by the initial search.

Assessing relative adrenal insufficiency in sepsis. Because there are no standardized diagnostic criteria for relative adrenal insufficiency, the biggest challenge in treatment is identifying the septic shock patient who is most likely to benefit from corticosteroid therapy. While there are nonspecific signs of relative adrenal insufficiency, including hyponatremia, hyperkalemia, and eosinophilia, these may be present in a variety of other disease states. Methods of diagnosing relative adrenal insufficiency include the high-dose corticotropin test, the low-dose corticotropin test, and the random cortisol level.

The high-dose corticotropin test includes the intravenous administration of corticotropin 250 μg and serial serum cortisol measurements at baseline, 30 minutes, and 60 minutes after administration. The test involves stimulation of the adrenal glands with a dose of corticotropin that exceeds the endogenous amount. During stress, the serum concentration of corticotropin may rise to 40–200 pg/mL. The high-dose corticotropin test will produce a much larger serum corticotropin concentration, up to 60,000 pg/mL. This excessive stimulation can override adrenal resistance and produce a normal response, therefore representing adrenal reserve. This is not a true representation of adrenal function and potentially misidentifies patients as responders of the test, although they may actually have relative adrenal insufficiency.

The low-dose corticotropin test differs from the high-dose test in that the dose of corticotropin is 1 μg rather than 250 μg. Clinical trials evaluating the efficacy of the low-dose test are few, but it has been hypothesized that the low-dose test would result in fewer false-positive cortisol responses. The random cortisol level may also be used to assess relative adrenal insufficiency. Because the critically ill, stressed patient loses the normal diurnal excretion of cortisol, a random cortisol concentration can be drawn at any time throughout the day. Table 1 lists six studies reviewing the use of these three diagnostic tests in patients with sepsis.

Marik and Zaloga compared the sensitivity and specificity of the low-dose corticotropin test, the high-dose corticotropin test, and random cortisol concentrations in 59 ICU patients requiring vasopressors for septic shock. All patients met the Society of Critical Care Medicine–American College of Chest Physicians criteria for septic shock. Within 48 hours of admission, a baseline cortisol was drawn. Patients received a 1-μg corticotropin test and 60 minutes later a 249-μg corticotropin test to evaluate the diagnostic criteria for relative adrenal insufficiency. Cortisol concentrations were measured 30 and 60 minutes after the corticotropin tests. Immediately after the high-dose test, all patients empirically received 100 mg of hydrocortisone sodium succinate i.v. every 8 hours for at least 24 hours. The authors defined steroid-responsive patients as those who were able to discontinue vasopressors within 24 hours of steroid administration. They stratified the attainment of this endpoint according to the results of three adrenal insufficiency tests. For the random cortisol test, relative adrenal insufficiency was defined as a cortisol concentration of <25 μg/dL. Both the low-dose and high-dose corticotropin tests defined adrenal insufficiency as a post-stimulation cortisol concentration of <18 μg/dL.

Twenty-two of 59 patients (37%) were able to discontinue vasopressors within 24 hours and were thus classified as steroid responsive. The ability of the random cortisol test, the low-dose corticotropin test, and the high-dose corticotropin test to identify steroid-responsive patients was 96%, 54%, and 22%, respectively (sensitivity). The ability to correctly identify patients who would not respond to steroids was 57%, 97%, and 100% for the three tests, respectively (specificity).

Based on the results of this trial, the high-dose test grossly underdiagnosed relative adrenal insufficiency...
Table 1. Diagnostic Tests and Definitions Used for Determining Relative Adrenal Insufficiency

<table>
<thead>
<tr>
<th>Variable</th>
<th>18</th>
<th>23</th>
<th>30</th>
<th>31</th>
<th>17</th>
<th>32</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. patients</td>
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<td>59</td>
<td>189</td>
<td>300</td>
<td>40</td>
<td>100</td>
</tr>
<tr>
<td>Study design</td>
<td>Double-blind RCT</td>
<td>Open label</td>
<td>Prospective cohort study</td>
<td>Double-blind RCT</td>
<td>RCT</td>
<td>Prospective clinical trial</td>
</tr>
<tr>
<td>Definition of sepsis</td>
<td>ACCP–SCCM</td>
<td>SCCM</td>
<td>ACCP–SCCM</td>
<td>…</td>
<td>ACCP–SCCM</td>
<td>Bacteremia, severe sepsis, septic shock</td>
</tr>
<tr>
<td>Adrenal-function test</td>
<td>HD test</td>
<td>Baseline plasma cortisol, LD test, HD test</td>
<td>HD test</td>
<td>HD test</td>
<td>HD test</td>
<td></td>
</tr>
<tr>
<td>Relative adrenal insufficiency diagnosis</td>
<td>Peak posttest cortisol conc., &lt;6 μg/dL</td>
<td>Baseline conc., &lt;25 μg/dL</td>
<td>…</td>
<td>Peak posttest cortisol conc., ≤9 μg/dL</td>
<td>Peak posttest cortisol conc., &lt;20 μg/dL</td>
<td>Peak posttest cortisol conc., &lt;20 μg/dL</td>
</tr>
<tr>
<td>Treatment</td>
<td>Hydrocortisone 100 mg i.v. every 8 hr or placebo</td>
<td>Hydrocortisone 100 mg i.v. every 8 hr</td>
<td>…</td>
<td>Hydrocortisone 50 mg i.v. every 6 hr plus fludrocortisone 50 μg p.o. daily</td>
<td>Prednisolone 5 and 10 mg i.v. or placebo</td>
<td>…</td>
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<td>Treatment duration</td>
<td>≥5 days</td>
<td>…</td>
<td>…</td>
<td>7 days</td>
<td>10 days</td>
<td>…</td>
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<td>Primary endpoint</td>
<td>Shock reversal</td>
<td>Steroid responsiveness</td>
<td>28-day mortality</td>
<td>28-day survival in nonresponders</td>
<td>28-day all-cause mortality</td>
<td>Severity of injury, hospital mortality rate, APACHE III score</td>
</tr>
<tr>
<td>Secondary endpoint</td>
<td>28-day all-cause mortality, hemodynamic changes during therapy</td>
<td>None</td>
<td>Cortisol levels and response to corticotropin</td>
<td>Time to vasopressor withdrawal during 28 days</td>
<td>Adverse occurrences</td>
<td>Laboratory characteristics</td>
</tr>
</tbody>
</table>

aRCT = randomized clinical trial; ACCP = American College of Chest Physicians, SCCM = Society of Critical Care Medicine, HD test = high-dose corticotropin-stimulation test (tetracosactrin acetate 250 μg), LD test = low-dose corticotropin-stimulation test (tetracosactrin acetate 1 μg), APACHE III = Acute Physiology and Chronic Health Evaluation.

bDocumented site of infection and the following: temperature, >38.3 °C or <35.6 °C; heart rate, >90 beats/min; systolic arterial pressure, <90 mm Hg for more than one hour despite fluid replacement and more than 5 μg/kg of dopamine or current treatment with epinephrine or norepinephrine; urine output, <0.5 mL/kg for more than one hour or ratio of oxygen tension to fraction of inspired oxygen of <280 mm Hg; arterial lactate concentration, >2 mmol/L; and need for mechanical ventilation.

cBacteremia = positive blood culture, severe sepsis = more than two criteria for systemic inflammatory response syndrome (SIRS), suspected site of infection, and organ dysfunction or hypoperfusion, septic shock = more than two criteria for SIRS, suspected site of infection, and hypotension after 500-mL bolus of 0.9% sodium chloride injection. SIRS criteria = temperature, >38 °C or <36 °C, heart rate, >90 beats/min; systolic arterial pressure, <90 mm Hg for more than one hour despite fluid replacement and more than 5 μg/kg of dopamine or current treatment with epinephrine or norepinephrine; urine output, <0.5 mL/kg for more than one hour or ratio of oxygen tension to fraction of inspired oxygen of <280 mm Hg; arterial lactate concentration, >2 mmol/L; and need for mechanical ventilation.

dLow = baseline, ≤34 μg/dL and peak posttest cortisol, >9 μg/dL; medium = baseline, ≤34 μg/dL and peak posttest cortisol, ≤9 μg/dL; high = baseline cortisol, >34 μg/dL, and peak posttest cortisol, ≤9 μg/dL.

eRestation of norepinephrine to maintain mean arterial blood pressure of >65 mm Hg within 24 hours of first dose of hydrocortisone.
by capturing only 22% of those patients who were clinically responsive to steroids per study definition. Because of a high ability to identify steroid-responsive patients (high sensitivity), the authors concluded that a random cortisol level is a reasonable diagnostic indicator of relative adrenal insufficiency. These results should be interpreted with caution. The authors defined time to vasopressor withdrawal as steroid response. Although this is an important effect of steroids, this endpoint is not a universally accepted definition. Additionally, it is difficult to compare these patient groups with those of other studies, since the cutoff values used to determine relative adrenal insufficiency have not been reproduced among all trials.

**High-dose corticotropin-stimulation test.** Patients who do not respond to the high-dose corticotropin test will benefit from stress-dose steroid treatment. Annane and colleagues measured 28-day mortality in 300 ICU patients with septic shock who were treated with hydrocortisone and fludrocortisone. Study participants were mechanically ventilated and had infection and evidence of metabolic dysfunction, as well as either renal dysfunction or acute lung injury. Based on their response to the high-dose corticotropin test, patients were randomized within three hours of shock onset to receive either 50 mg of hydrocortisone hemisuccinate i.v. every six hours and 50 μg of a 9α-fludrocortisone tablet orally daily or placebo for seven days. Response to the high-dose corticotropin test was defined as an increase in cortisol of >9 μg/dL measured 30 and 60 minutes after the test dose. Those patients with a change of 9 μg/dL or less were determined to have relative adrenal insufficiency. There were 229 patients (76%) in the nonresponder group and 70 patients (23%) in the responder group. No differences in baseline characteristics were noted between the groups.

Nonresponders who received steroid treatment had a significant reduction in 28-day mortality compared with nonresponders who received placebo (53% versus 63%, p = 0.04), as well as in ICU mortality rate (58% versus 70%, p = 0.02) and hospital mortality rate (61% versus 72%, p = 0.04). There were no differences in adverse events in the treatment group versus the placebo group.

Annane et al. demonstrated that steroid treatment is beneficial in patients who do not respond to the high-dose test; however, there are some important considerations regarding this trial. All patients had severe sepsis, as evidenced by the requirement of mechanical ventilation and at least one organ dysfunction, and were randomized to receive steroid treatment within three hours of the onset of shock. This was a very specific patient population, and it could be argued that the population to which the mortality benefit may apply in clinical practice is narrow. Additionally, as with most trials that use diagnostic criteria in assessing relative adrenal insufficiency, the cutoff values were different from those in many other trials, restricting the ability to compare outcomes across patient groups.

Because of a low ability to diagnose patients with relative adrenal insufficiency, the use of the high-dose corticotropin test as the sole indicator of adrenal reserve may not capture a significant number of patients who will respond to steroids. Published trials have used varying cutoffs of the high-dose corticotropin test to stratify their patient populations. Annane et al. used a cutoff value of 9 μg/dL to identify nonresponders, while Marik and Zaloga defined nonresponders as patients with posttest cortisol concentrations of <25 μg/dL. Bollaert et al. conducted a placebo-controlled trial to determine the efficacy of hydrocortisone hemisuccinate 100 mg daily in achieving shock reversal in 41 patients with late septic shock. All patients were mechanically ventilated, had evidence of at least one organ dysfunction, and had been on vasopressors for more than 48 hours. The primary endpoint of shock reversal was defined as a stable systolic arterial pressure of >90 mm Hg for ≥24 hours without volume expansion or catecholamine use or both and a blood lactate concentration of <2 mmol/L. Treatment was randomized regardless of response to the high-dose corticotropin test, but a subgroup analysis compared the rates of shock reversal in patients who had failed to increase their cortisol concentration by 6 μg/dL or greater. Four patients in the treatment group (18%) and 8 patients in the placebo group (42%) did not increase their posttest cortisol concentration by 6 μg/dL and were defined as nonresponders.

Seven-day shock reversal was achieved in significantly more patients in the treatment group than in the placebo group (15 [68%] versus 4 [21%], p = 0.007). While only 18% of patients treated with corticosteroids had relative adrenal insufficiency per study definition, the primary endpoint was achieved by 68% of all these patients. It is also important to note that, in a subgroup analysis, 67% of patients without relative adrenal insufficiency who were treated with steroids experienced shock reversal. Eighteen percent of patients without relative adrenal insufficiency who were not treated experienced shock reversal (p = 0.03).

If response to the high-dose corticotropin test had been used as a cutoff for treatment, the majority of patients in this study would not have
received steroids. There are important limitations of this trial. First, assessing the significance of these results should be done with caution, since the subgroup analysis was done in a small trial of 41 patients. Second, as previously mentioned, the primary endpoint of shock reversal is not a universal definition for response to steroid treatment. The definition of shock reversal used in this trial differed from that used in the Marik and Zaloga trial, which considered shock reversal as withdrawal of vasopressors within 24 hours. Additionally, these patients had been on vasopressors for two days before steroids were administered, indicating prolonged septic shock compared with patients in the Annane et al. trial, who were randomized to treatment within three hours of shock onset.

Discussion. Although corticosteroids have shown a morbidity benefit and a potential mortality benefit in patients with relative adrenal insufficiency and vasopressor-dependent septic shock, several important questions remain to be answered, including the optimal corticosteroid dose, the duration of therapy, and the diagnostic criteria for relative adrenal insufficiency. Briel, and Chawla et al., demonstrated that hydrocortisone significantly decreased time to vasopressor withdrawal in vasopressor-dependent septic shock. However, neither of these studies provided data regarding the patient’s adrenal status. Selecting the appropriate patients who would benefit from corticosteroids remains a challenge.

In a recent trial, Hamrahian et al. recommended the use of free serum cortisol concentrations, as opposed to serum total cortisol concentrations, to assess adrenal function in critically ill patients with low albumin. Because cortisol is more than 90% protein bound in the serum, lower circulating protein leads to higher free cortisol. This may not be accurately reflected by the total cortisol concentration. Fewer than 10% of the patients in this trial had sepsis; therefore, the results may not be applicable to the patient population in this review. Furthermore, in the trials that demonstrated a mortality benefit of corticosteroids in patients with vasopressor-dependent shock, all cortisol concentrations were total cortisol concentrations. The concept of free serum cortisol concentrations is promising for the future; however, total serum cortisol concentrations should be used pending evidence-based diagnostic protocols.

Because of its low sensitivity, the high-dose corticotropin-stimulation test alone may be an inefficient diagnostic tool for relative adrenal insufficiency in patients with septic shock. Trials have shown that, in patients with relatively low baseline cortisol concentrations (<25 μg/dL) and without an adequate response to the high-dose test (a change in cortisol concentration of <9 μg/dL), the diagnosis of relative adrenal insufficiency is highly likely. Annane et al. supported the specificity of the high-dose corticotropin test by showing a mortality benefit of corticosteroid use in the nonresponder group. However, the sensitivity of the high-dose corticotropin test was not adequately evaluated in this trial due to the small number of patients in the responder group.

Controversy continues to surround the significance of a relative change in serum cortisol concentration exceeding 9 μg/dL. Based on the results of Marik and Zaloga, up to 74% of patients may be misdiagnosed by the high-dose corticotropin test as having adequate adrenal function. The poor sensitivity of the high-dose test may be attributed to the testing of adrenal reserve rather than adrenal insufficiency, because excessively high doses of the hormone are likely to stimulate a cortisol response even in patients with relative adrenal insufficiency. Since there is a potential mortality benefit from corticosteroids in patients with vasopressor-dependent septic shock, reliance on the high-dose test as the sole measure of adrenal function may cause the withholding of a potentially lifesaving medication in a number of patients.

A more appropriate use of the high-dose corticotropin test may be in combination with the random cortisol serum concentration test. Based on the trial by Marik and Zaloga, a random cortisol concentration threshold value of 25 μg/dL yields a higher sensitivity than the high-dose corticotropin test, diagnosing a greater number of patients with relative adrenal insufficiency. Because of its high sensitivity, the random cortisol concentration test may overdiagnose rather than underdiagnose patients with relative adrenal insufficiency. Currently, the sepsis guidelines recommend the high-dose corticotropin test as a diagnostic option but make no recommendations for assessing a random cortisol concentration.

Although only a small number of clinical trials have been published to date, a low rate of adverse drug events has been reported with short-term stress-dose corticosteroids in patients with septic shock. Hyperglycemia is the only adverse event that was significantly greater in corticosteroid-treated patients compared with placebo in the aforementioned trials. Inadequate glycemic control in critically ill patients has been associated with morbidity and mortality. Intensive insulin infusion protocols have been studied in clinical trials with positive outcomes on morbidity and mortality; however, it is important to note that a direct effect on steroid-induced hyperglycemia has not been studied. Other adverse effects seen with steroids in this patient population were observed in earlier trials that used higher doses. Since we have relatively few data on physiological-dose steroids, it is important to keep these important adverse effects in mind.
Conclusion. With the low incidence of adverse drug reactions observed in recent clinical trials and the potential survival benefit from corticosteroids, undertreatment of relative adrenal insufficiency may be more detrimental than overtreatment. Questions still remain regarding the specifics of corticosteroid therapy, yet these trials do demonstrate that the high dose corticosterin pin test is likely to underdiagnose relative adrenal insufficiency.

References