Corticosteroids for septic shock

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Objective: To gather the data to provide a rationale for using replacement therapy with hydrocortisone in septic shock patients.

Data Sources: The Medline and the Cochrane Library databases.

Study Selection: Studies in animals and in humans were considered when significant data were available about the mechanisms of action of corticosteroids or about their use in severe sepsis.

Data Summary: Corticosteroids were the first anti-inflammatory drugs tested in septic patients. Randomized trials clearly showed that a short course of a large dose of anti-inflammatory steroids is ineffective and potentially harmful in patients with severe sepsis. Recent demonstrations of altered hypothalamic-pituitary-adrenal axis response to septic insult have led to reappraisal of the use of steroids in septic shock. Randomized trials in catecholamine-dependent septic shock patients strongly suggest that replacement therapy with hydrocortisone may alleviate the symptoms of systemic inflammatory response, reduce the duration of shock, and favorably affect survival.

Conclusions: Current evidence that the therapeutic interest of replacement therapy with corticosteroids increases suggests that low doses of hydrocortisone should be offered to patients with catecholamine-dependent septic shock. (Crit Care Med 2001; 29[Suppl.]:S117–S120)

Key Words: septic shock; adrenal insufficiency; catecholamine; corticosteroids; experimental studies; clinical controlled trials

Corticosteroids were proposed to treat patients with severe sepsis as early as 1940 (1). However, after an initial enthusiasm, several well-conducted randomized controlled trials cast serious doubts on the usefulness of steroids for the treatment of severe sepsis. A summary of all available randomized controlled trials performed between 1966 and 1993 was provided in two systematic reviews, which recommended that the use of high-dose corticosteroids to treat patients with severe infection be abandoned (2, 3). Nonetheless, a doubt still persists regarding the efficacy of a strategy of replacement therapy in catecholamine-dependent septic shock. This strategy relies mainly on the concept that septic shock may be complicated by an occult adrenal insufficiency and/or a peripheral glucocorticoid resistance syndrome.

Concepts of Occult Adrenal Insufficiency and of Peripheral Glucocorticoid Resistance Syndrome

In sepsis, the hypothalamic-pituitary-adrenal (HPA) axis is activated through systemic and neural pathways. Circulating cytokines, like tumor necrosis factor α (TNF-α), interleukin (IL) 1, and IL-6, activate the HPA axis independently and, when combined, have synergistic effects (4). In plasma, IL-6 is sought to be the major determinant of the individual variation of HPA axis responses to lipopolysaccharide (LPS), activating vagal afferents at the level of the brain stem (5). The second pathway uses the neural routes of communication between the site of inflammation and the brain. Indeed, the interruption of the vagus has been shown to blunt the HPA axis and fever responses to intravenous challenge with LPS, TNF-α, or IL-1β, albeit elevated circulating cytokine levels (6, 7).

Since the Waterhouse (8) and Fritsch (9) observations of bilateral hemorrhage of the adrenal glands, numerous experimental and clinical investigations have observed reversible dysfunction of the HPA axis during sepsis (10). In a prospective inception cohort study of 189 patients who had septic shock, thorough analyses demonstrated that the best definition of occult adrenal insufficiency should be based on a cortisol increment after a short corticotropin test of less than 9 μg/dl (11). Using this definition, the prevalence of occult adrenal insufficiency in severe sepsis was estimated at about 50%, and the 28-day mortality rate at about 75% (11). In addition, studies of mean arterial pressure responses to stepwise incremental doses of norepinephrine showed a rightward shift of the dose-response curve in septic shock patients who had occult adrenal insufficiency as compared with patients who had normal response to the short corticotropin test (12). These findings suggested that impaired adrenal function accounts, at least in part, for the vessels’ decreased sensitivity to norepinephrine in severe sepsis.

A peripheral glucocorticoid resistance syndrome may occur in patients with septic shock and may be responsible for excessive immune-mediated inflammation as in rheumatoid arthritis, corticosteroid-resistant asthma, acquired immune deficiency syndrome (AIDS), and chronic degenerative osteoarthritis (4). In septic shock, the sensitivity of peripheral blood mononuclear cells to corticosteroids is generally up-regulated (13). However, several cytokines, like IL-2 and IL-4, induce an overexpression of nuclear factor-κB (NF-κB) that alters the glucocorticoid receptor function (14, 15). Indeed, a decreased affinity of the glucocorticoid re-
Replacement Therapy with Hydrocortisone and the Systemic Inflammatory Response to Sepsis

Mechanisms of Action of Corticosteroids. Cortisol opposes virtually all of the links of the inflammatory chain. Indeed, cortisol freely penetrates the plasma membrane of inflammatory cells, and binds to the glucocorticoid receptor (GR), which, in its inactive form, is linked to heat shock proteins (17). The binding of cortisol to the GR results in the dissociation of the heat shock protein subunits and exposure of DNA binding sites. The cortisol–GR complex penetrates into the nucleus to interact with specific DNA sequences (glucocorticoid-responsive elements) within the promoter regions of various genes. So, the activated complex interacts with the nuclear factor-IL-6 (NF-IL-6) enhancing the transcription rate for acute phase reactants (18) and with the activator protein-1 (AP-1) (19, 20) and the NF-κB (21, 22), inhibiting the synthesis of various pro-inflammatory factors. The activated cortisol–GR complex also induces IkB-κ expression which, in turn, sequestrates NF-κB dimers in the cytoplasm (14, 15). Then, cortisol prevents the migration of inflammatory cells from circulation to tissues by blocking the synthesis of chemokines (23), the synthesis of almost all pro-inflammatory cytokines including several interleukins (IL-1, IL-2, IL-3, IL-6), interferon-γ, granulocyte macrophage colony-stimulating factor, and TNF-α (4), but cortisol also enhances the production of the macrophage migration inhibitory factor (24). Furthermore, by stimulating the synthesis of lipocortin-1 (25), cortisol inhibits phospholipase A2 and, subsequently, the arachidonic acid cascade. Finally, cortisol inhibits the synthesis of cyclooxygenase-2 (COX-2) (26, 27) and inducible nitric oxide synthase (iNOS) (28, 29).

Experience with Low Doses of Hydrocortisone in Sepsis. Low doses of hydrocortisone were shown to reproduce most of these effects in healthy subjects challenged by endotoxin (30–32) and in septic patients (33, 34). In healthy subjects, hydrocortisone (3 μg/kg/min for 6 hrs), administered immediately before or concomitantly to endotoxin exposure, prevents LPS-induced increases in temperature, heart rate, peak plasma levels of epinephrine, C-reactive protein and TNF-α, but not of IL-6 (30). When hydrocortisone was administered 12 to 144 hrs before endotoxin exposure, circulating levels of TNF-α and IL-6 were higher than those observed with endotoxin alone, suggesting that withdrawal of hydrocortisone induced a rebound of pro-inflammatory cytokines in plasma (Table 1). Subsequent experiments in healthy volunteers challenged with endotoxin have shown that hydrocortisone enhances the release of the anti-inflammatory cytokines IL-1 receptor antagonist, soluble tumor necrosis factor receptor (31), and IL-10 (32). In septic shock patients, intravenous hydrocortisone (~300 mg for 5 days) turned down the systemic inflammatory response syndrome, i.e., decreased core temperature, heart rate, and plasma levels of phospholipase A2 and C-reactive protein (33). In addition, hydrocortisone infusion was associated with a decrease in plasma levels of pro-inflammatory cytokines, of nitrite/nitrates, and of soluble adhesion molecules (34). In septic shock, the discontinuation of hydrocortisone led to an amplified systemic inflammatory response syndrome, and to a new administration of vasopressors to maintain cardiovascular stability (33, 34).

Table 1. Summary of anti-inflammatory and cardiovascular effects of low doses of hydrocortisone in humans

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<tr>
<th>Anti-Inflammatory Effects</th>
<th>Cardiovascular Effects</th>
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<tr>
<td>In healthy volunteers challenged with endotoxin Prevents fever, tachycardia, the raise in plasma levels of epinephrine, of C-reactive protein, of TNF-α; promotes the release of IL-1ra, sTNF-R, and IL-10; withdrawal of hydrocortisone induces a rebound in inflammation</td>
<td>Prevents endotoxin induced venous insensitivity to norepinephrine, independently of the iNOS or COX-2 pathways</td>
</tr>
<tr>
<td>In septic shock patients Decreases core temperature and heart rate; decreases plasma levels of phospholipase A2, C-reactive protein, TNF-α, IL-1B, IL-6, nitrite/nitrate, and soluble adhesion molecules; withdrawal of hydrocortisone induces a rebound in inflammation</td>
<td>Increases mean arterial pressure and systemic vascular resistance; improves mean arterial pressure responses to norepinephrine and phenylephrine; decreases the time to cessation of vasopressors; decreases the duration of shock; withdrawal of hydrocortisone induces a relapse of shock</td>
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COX-2, cyclooxygenase-2; IL, interleukin; iNOS, inducible nitric oxide synthase; sTNF-R, soluble tumor necrosis factor receptor; TNF, tumor necrosis factor.
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As early as 1963, a placebo-controlled randomized trial was performed to test the efficacy of hydrocortisone in decreasing doses (from 300 mg to 50 mg) for 6 days (48). This study did not show any beneficial effects of hydrocortisone in patients with severe sepsis. However, several pitfalls must be stressed: (1) the study population consisted of children and adults, (2) a large number of patients had meningitis, (3) the two groups were unbalanced for the type of infection with more fulminating staphylococcal infections in the hydrocortisone group, and (4) the distribution of prognostic factors, the appropriateness of antibiotic therapy, and supportive care were unknown. Therefore, the results of this old study cannot be applied readily to septic patients treated at the present time. Almost 20 yrs later, in a quasi-randomized trial in 18 critically ill patients with presumed adrenal insufficiency, hydrocortisone in a dose of 100 mg twice daily was shown to dramatically improve intensive care unit survival (90% vs. 12.5% for controls) (49). In a more recent study in catecholamine-dependent septic shock, hydrocortisone administered as a 100-mg intravenous bolus three times a day for at least 5 days (and then tapered over 6 days) was associated with a 31% absolute reduction in a 28-day mortality rate (45). Finally, a recently completed multicenter, placebo-controlled, randomized, double-blind study has evaluated the efficacy and tolerance of replacement therapy with a combination of hydrocortisone (50-mg intravenous bolus four times a day) and fludrocortisone (50 μg orally once a day) administered for 7 days. This study included 300 instances of catecholamine- and ventilator-dependent septic shock patients. The results of this study will be published in the near future.

In sum, a short course with high doses of corticosteroids should not be administered in severe sepsis, except for specific entities like severe typhoid fever (50), Pneumocystis carinii pneumonia in AIDS (51), or bacterial meningitis in children (52). However, the rationale for replacement therapy with hydrocortisone in catecholamine-dependent septic shock grows stronger.

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