

adrenal insufficiency in sepsis & septic shock [created by Paul Young 10/12/07]

guidelines

- international guidelines recommend the use of low dose corticosteroids for the treatment of septic shock. However, there are some discrepancies in these recommendations.
- (i) the Surviving Sepsis Campaign recommended the use of stress dose of corticosteroids for septic shock regardless of adrenal function.
- (ii) the American College of Critical Care Medicine Task Force recommended that stress dose of corticosteroids should be used only in refractory septic shock or in adrenal insufficient patients.

mechanisms of action of corticosteroids

- genomic actions
 - Cells from most tissues are responsive to corticosteroids, which freely cross cell membranes. The glucocorticoids receptor forms an inactive intracytosolic complex with chaperone proteins like heat shock protein (HSP) 40, HSP56, HSP70, and HSP90, immunophilins, P23, and other unknown proteins
 - The receptor contains three domains: one binds corticosteroids, one binds to DNA, also involved in dimerization; and one activates the promoters within the genes.
 - Binding of corticosteroids to the glucocorticoids receptor induces the release of chaperone proteins and the dimerization of the complex, which then, enters into the nucleus and interacts with specific binding sequences, the glucocorticoid responsive element (GRE).
 - Subsequently, transcription of some genes (e.g. most cytokines, adhesion molecules, lipoxigenase, etc.) initiated by various transcriptional factors such as AP1, NF-AT and NF-kB are prevented. In addition, glucocorticoids receptor dimers induce the inhibitor of NFkB (IkB).
 - Other GRE sites upregulate the transcription of numerous other genes (e.g. lipocortin-1, thymosin-b4 sulfoxide).
- Nongenomic interactions
 - Physicochemical interactions occur in-between the cell's membrane and corticosteroids inducing very rapid (within seconds), nonspecific, nongenomic effects.
 - Some of these effects might be part of the host response to sepsis. For example, loss in the corticosteroids physicochemical interaction with hypothalamic synaptosomes, may partly explain the loss in circadian rhythm of cortisol synthesis during sepsis.
 - non genomic effects of cortisol are thought to control immediate catecholamine release from sympathetic cells. Such neural modulation by corticosteroids may explain the rapid restoration of sympathetic modulation on heart and vessels, and may account for the hydrocortisone induced rapid pressure sensitization to exogenous catecholamine in septic shock.

corticosteroid induced immune modulation

- by interacting with NF-IL6, corticosteroids enhance the synthesis of the acute phase reactants; with AP-1 and NF-kB, they inhibit the synthesis of various proinflammatory factors.
- corticosteroids prevent the migration of inflammatory cells from circulation to tissues by blocking the synthesis of various chemokines and chemotactic cytokines. They prevent the synthesis of almost all proinflammatory cytokines including several interleukins (interleukin-1, interleukin-2, interleukin-3, interleukin-6), interferon-g (IFN-g), granulocyte macrophage colony stimulating factor, and tumor necrosis factor-a (TNF-a). They also enhance the production of the macrophage migration inhibitory factor (MIF).
- by stimulating the synthesis of lipocortin-1, corticosteroids inhibit the synthesis of soluble phospholipase A2 (PLA2) and the subsequent arachidonic acid cascade, reducing the production of leukotrienes, the main inflammatory mediators in humans.
- corticosteroids also inhibit the synthesis of inducible cyclooxygenase-2 (COX2) and of inducible but not constitutive nitric oxide synthase (NOS).

corticosteroid induced cardiovascular modulation

- Chronic corticosteroid excess induces hypertension, whereas adrenal insufficiency induces hypotension.
- corticosteroids regulate vascular responses to norepinephrine and angiotensin II, but not to vasopressin. The underlying mechanisms remained unclear, and may involve multiple pathways like iNOS and COX-2 inhibitions or the stimulation of the phosphoinositide system.

human studies

- in healthy volunteers, a 6-hour infusion of 3 mg/kg/min hydrocortisone, either immediately before or concomitantly to endotoxin exposure, prevented LPS-induced fever, tachycardia, increase in plasma levels of epinephrine, CRP, and TNF-a, but not interleukin-6.
- In septic shock, intravenous hydrocortisone (about 300 mg for 5 days) decreases core temperature, heart rate, and plasma levels of PLA2 and C-reactive protein.
 - In a French multicenter trial on low dose corticosteroids in septic shock, it was shown that the systemic inflammatory response to sepsis, assessed by interleukin-6 levels, was significantly altered by corticosteroids only in adrenal insufficient patients
 - nonresponders (increment in cortisol of 9 mg/dl or less) to 250 mg of corticotropin. In that study, the adrenal insufficient septic shock had higher TNFa, interleukin-6 and interleukin-8 levels than the remainders.
- In another placebo-controlled, randomized trial, 41 patients with septic shock received 50mg bolus followed by a continuous infusion of 0.18 mg/kg/h of hydrocortisone until shock reversal. In that study, as compared with the placebo, interleukin-6 levels were also significantly decreased by hydrocortisone infusion, whereas interleukin-10 levels remained unaltered.
- low dose of hydrocortisone has been shown to downregulate sepsis-associated overexpression of the 'late' inflammatory mediator, MIF by peripheral blood monocytes
- In a recent randomized study, the acute vascular effects of hydrocortisone (200 mg intra-arterial over 3 hours) were investigated in healthy adult male volunteers. This study elegantly demonstrated that hydrocortisone did not affect biochemical or physiologic markers of nitric oxide activity. Thus, one can conclude that any early (within 3 h) vascular effect of hydrocortisone is not mediated through the NO pathway.
- In septic shock, several placebo-controlled randomized studies have reported the cardiovascular effects of low dose of corticosteroids (about 200-300 mg/day) given for a prolonged period. These studies consistently showed that corticosteroids increased systemic vascular resistance with little effects on the cardiac index and pulmonary hemodynamics.
 - trials consistently show that corticosteroids reduce the duration of shock. The probability of being weaned from vasopressor at one week was greater in corticosteroid-treated septic shock than in placebo-treated septic shock and the relative risk was 1.60
- Only three trials have subgroup analyses based on adrenal insufficiency. However, only two studies used the same definition for adrenal insufficiency. In both of them, the favorable effects of corticosteroids on shock reversal were observed only in the adrenal insufficient patients (nonresponders to corticotropin).
- In the first study of 300 patients with septic shock, the median time to weaning from vasopressors was reduced by 3 days in the corticosteroid-treated adrenal insufficient patients compared with the placebo group (P = 0.001), while there were no difference between corticosteroids and placebo in the responders to corticotropin. In the second study, hydrocortisone significantly shortened the duration of shock (P = 0.02). This effect was seen only in the adrenal insufficient septic shock (n=26; P=0.06), and not in the responders to corticotropin (n = 15; P = 0.90).
- Confalonieri et al. have investigated the efficacy and safety of a 7-day treatment with intravenous hydrocortisone (240 mg/day) in community-acquired pneumonia associated sepsis. In their study, treatment with hydrocortisone significantly prevented onset of shock (P = 0.001), reduced multiple organ dysfunction score (P = 0.003), hospital length of stay (P = 0.03), and in-hospital mortality (P = 0.009).
- In septic shock, evidence from five randomized trials suggested that prolonged treatment with low dose corticosteroids reduced 28-day mortality (relative risk = 0.80, 95% confidence interval 0.67-0.95), in-hospital mortality (relative risk = 0.83, 95% confidence interval 0.71-0.97), and ICU mortality (relative risk = 0.83, 95% confidence interval 0.70-0.97). It is important, however, to note that one study accounted for 70% of patients included in that meta-analysis. In this study, corticosteroids improved survival only in adrenal insufficient septic shock.
- In a meta-analysis of all published randomized trials that evaluated the effects of high or low doses of corticosteroids for short or long periods of time, there was no evidence for significant increases of super-infection, gastroduodenal bleeding, or hyperglycemia.

conclusion

- Corticosteroids could be a valuable treatment for septic shock, depending upon the way they are used.
- There is no evidence to support the use of short courses of high doses of corticosteroids in patients with severe sepsis.
- Current evidence suggests that, in septic shock, one-week treatment with 200-300 mg of hydrocortisone alleviates the symptoms of systemic inflammatory response, reduces the duration of shock, and increases survival. Corticosteroids favorable effects on inflammation, hemodynamics, and survival are more marked in patients with an increment in cortisol of 9 mg/dl or less after 250 mg of corticotropin (nonresponders or adrenal insufficient).