Corticosteroids in the Sepsis Syndrome

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The mechanisms for many of the changes that occur in the sepsis syndrome have eluded investigators for years. Despite the fact that we have made great progress in evaluating the role of the coagulation, complement, arachidonic acid and other systems in the sepsis syndrome, we have not been able to clearly differentiate the initiating event causing the alterations from the "innocent bystanders". Without a clearer understanding of the epidemiology and the pathophysiologic mechanisms causing the changes in the sepsis syndrome, it may be unrealistic to expect major improvement in survival with our current therapeutic modalities. The present chapter will summarize some of the animal and human data concerning the use of corticosteroids in the sepsis syndrome. We have defined the sepsis syndrome as a spectrum of disease from early sepsis - a systemic response to invading microorganisms to septic shock. A more detailed review of the subject can be found elsewhere [1, 2].

The use of corticosteroids in the sepsis syndrome remains controversial. Investigations have included in vivo and in vitro studies of corticosteroid actions, several animal models of septic shock, such as the infusion of live bacteria or endotoxin, and a variety of studies in critically ill patients.

Potentially Beneficial and Detrimental Actions of Corticosteroids in the Sepsis Syndrome

There are many potential mechanisms for the beneficial actions of corticosteroids in the sepsis syndrome, but most are controversial and remain unproven. The most physiologic benefit of corticosteroids in the sepsis syndrome would be for the treatment of hypoadrenalism. Unfortunately, it has not been demonstrated that cortisol levels are uniformly depressed with sepsis [3]. In fact, many patients have extremely elevated cortisol levels in septic shock. Hypoadrenalism would also not explain the fact that large doses of corticosteroids are typically required for reversal of most shock models.

Another potential benefit of corticosteroids is an improvement in the cardiovascular system which is depressed in septic shock. Various studies have shown no effect of corticosteroids on cardiac output, whereas others have shown improved cardiac output [2]. Corticosteroids may also act as vasodilators and improve cardiac function.
The metabolic effects of corticosteroids include increased secretion of glucagon, liver protein synthesis and gluconeogenesis. Corticosteroids may also be helpful by causing a rightward shift in the oxyhemoglobin dissociation curve.

One of the major reasons clinicians have used corticosteroids is their ability to stabilize cell membranes and in particular lysosomal membranes [4].

Recently, complement-induced activation of polymorphonuclear leukocytes and the subsequent action of these cells on the microvasculature and various organ systems have gained a prominent role in the sepsis syndrome [5]. The presence of endotoxin from gram-negative organisms or teichoic acid from gram-positive organisms stimulates the intravascular production of various complement components. These components activate polymorphonuclear leukocytes to produce arachidonic acid metabolites and to release lysosomal enzymes which contribute to microcirculatory vasodilation, endothelial cell destruction, and increased capillary permeability. These events contribute to the sepsis-induced hypovolemia and the interstitial edema seen in septic shock. In vitro studies have shown that pharmacologic doses of corticosteroids (equivalent to 30 mg/kg of methylprednisolone) inhibit complement-induced granulocyte aggregation, cause disaggregation of granulocytes, and ameliorate endothelial cell damage by preventing oxygen radical generation [2, 5]. Corticosteroids have been shown to decrease the increased permeability in patients with septic adult respiratory distress syndrome when they are given early in the course of the disease [6].

Even more recently, the interaction of corticosteroids with the endorphin system has provoked interest because corticosteroids inhibit the release of ACTH and because ACTH and beta-endorphin are derived from a common precursor. The release of beta-endorphins may also be inhibited by corticosteroids.

In contrast to the beneficial actions of corticosteroids, one must always be concerned about the potential detrimental effects of corticosteroids. These include superinfection (probably the most important complication), electrolyte disturbances, hyperglycemia, gastrointestinal bleeding, psychosis and arrhythmias [7].

**Effects of Corticosteroids on the Sepsis Syndrome in Animals**

Whereas animal models of sepsis may not truly mirror the human sepsis syndrome, they do provide an important foundation for the use of corticosteroids. Important differences between studies that are worth noting include the model of sepsis (endotoxin or live bacteria), the time of administration of corticosteroids with respect to the onset of sepsis or shock, dosage of medication, similarity of end-organ damage to that found in man, and the phylogenetic relation of the experimental animal tested to man.

Optimal dosage and time of administration were considered in a rat model injected with live *E.coli* [8]. Dexamethasone and methylprednisolone significantly increased the survival time when given prophylactically, but this effect was reduced if the drug was given later. Survival was prolonged with doses of dexamethasone (1–32 mg/kg) and methylprednisolone (6.25–75 mg/kg) with no advantage to the higher dose ranges. So pharmacological doses of corticoste-