TITLE: METHYLPREDNISOLONE PLUS IBUPROFEN INCREASES MORTALITY IN SEPTIC RATS

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Introduction. Septic shock is an important cause of morbidity and mortality in intensive care units. While removal of the infective focus with antibiotics and/or surgery remains the primary mode of therapy, there is considerable interest in finding beneficial adjunctive treatments. Steroids or prostaglandin inhibitors[1] have been suggested to have beneficial effects in septic animals. Recently it was demonstrated that the combination of steroids and prostaglandin inhibitors had a synergistic inhibitory effect on granulocyte aggregation in vitro and it was suggested that this combination might be useful in the treatment of septic patients.[2] This study was designed to investigate the effects of steroids and prostaglandin inhibitors, used alone or in combination, in the treatment of septic shock.

Methods. Sepsis was induced in 98 Sprague-Dawley male rats (322 ± 15 gm) by the method of Chaudry et al.[3] Animals were anesthetized with sodium pentobarbital, 50 mg/kg IP. The abdomen was opened and the cecum was ligated distal to the ileocecal valve, preserving bowel continuity. The ligated cecal pouch was punctured twice with an 18 gauge needle. Saline, 3 ml/100 gm body weight, was administered subcutaneously; the wound was closed; and the animals were allowed to recover. This model has been shown to produce sepsis in rats with bacteremia evident within 2 hours after ligation and puncture.[3]

Three hours after cecal ligation the rats received one of four treatments by intraperitoneal injection: Saline (NaCl); Methylprednisone, 30 mg/kg (MP); Ibuprofen, 12.5 mg/kg (I); Methylprednisone, 30 mg/kg, plus Ibuprofen, 12.5 mg/kg (MP+I). The drugs were administered in a randomized fashion and the investigators were blinded to the therapy. The animals were returned to their cages and allowed food and water ad libitum. The rats were examined at twelve hour intervals for 14 days and cumulative survival was calculated for each group. Survival data were analyzed (χ^2) daily for 2 weeks after treatment.

Results. Survival data are summarized in the following table:

	Cumulative Survival (Percent)				
	NaCl (n=24)	MP (n=25)	I (n=24)	MP+I (n=25)	p
Day 1	96	100	100	100	.37
Day 2	71	60	67	28	.01
Day 3	62	56	54	20	.01
Day 4	58	48	50	20	.04
Day 7	58	40	38	20	.06
Day 14	50	40	33	16	.08

Analysis of the data shows no significant difference between groups treated with NaCl, MP, or I. However, animals treated with MP+I demonstrated an increase in mortality ($p<.03$) throughout.

Discussion. Both ibuprofen and methylprednisone have been shown to inhibit granulocyte aggregation in vitro, with the combination being synergistic.[2] Since granulocyte aggregation may be involved in the pathogenesis of sepsis, this study examined the effects of each of these drugs, used singly and in combination, in a cecal ligation model of septic shock. The model resembles human septic shock more closely than does an endotoxin model. Cecal ligation has been shown to produce relative hyperglycemia with a hyperdynamic cardiovascular system.[3] Using this model, we were unable to demonstrate the efficacy of steroids or ibuprofen as compared with saline treatment. More remarkably, the combination of methylprednisolone plus ibuprofen significantly increased mortality from septic shock.

While steroids have been shown to be efficacious in the treatment of endotoxin shock, their value in septic shock is not well established. Hinshaw reported that steroids alone did not decrease the mortality caused by live E. Coli infusion in baboons.[4] However, Greisman et al[5] showed that the early administration of a combination of steroids and antibiotics was more efficacious than antibiotics alone. Previous reports suggested that prostaglandin inhibitors were efficacious in endotoxic shock in baboons and septic shock in rats, but our study fails to support that conclusion.

While in vitro studies suggest potential advantages for the combination MP + I for the treatment of sepsis, the present results clearly demonstrate increased mortality with this combination in the septic model described here. It would appear that this combination should not be used in the treatment of septic shock in humans until more is known about the effects of the combination in this and other species.

References.

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