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Canine Endotoxin Shock: Reversal with Aldosterone and Angiotensin II (Hypertensin) (27255)

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Previous studies from this laboratory have shown that a combination of hydrocortisone and metaraminol will reverse the lethal progress of canine endotoxin shock(1). Such steroid-pressor therapy has been employed in the management of patients with shock associated with bacteremia due to Gram-negative bacteria. A combination of aldosterone and metaraminol has also been found to be effective in reversing experimental endotoxin shock(2). The present report is concerned with the marked pressor activity of angiotensin II when used in combination with synthetic d-aldosterone to reverse endotoxin shock.

Methods. Forty-three mongrel dogs anesthetized with Na pentobarbital were used. A lipopolysaccharide suspension of *E. coli* endotoxin injected in a dose of 0.55 mg/kg into the femoral vein, initiated a state of shock that could be studied for 8 hours or until death of the animal. Systemic arterial pressure was measured continuously by a catheter placed in the femoral artery and recorded on a Sanborn twin-viso. Arterial blood pH and hematocrit were measured hourly. Urine outputs were determined at hourly intervals by means of an indwelling catheter in the urinary bladder. Sera from aldosterone-treated dogs were analyzed serially for sodium and potassium with the Baird flame photometer. D-aldosterone was given in a single intravenous dose of 0.2 mg.* One mg of angiotensin II in 100 ml of 5% dextrose and distilled water was administered as a slow intravenous infusion in amounts necessary to maintain blood pressure at approximately 100 mm Hg.* Permanent survivors were those animals alive 48 hours post-endotoxin.

Results. The combined results with 43 dogs given a lethal dose of endotoxin are shown in Table I. The average survival time for 13 control animals given endotoxin was 12.8 hours. These dogs showed marked hemoconcentration, acidosis, hypotension, and renal failure characteristic of this type of shock(3).

A second group of 10 animals given endotoxin were treated with angiotensin II at that point when the foregoing characteristics of otherwise irreversible shock appeared. Five of the 10 animals treated in this manner survived. An average dose of 650 γ of angiotensin II was required to maintain the blood pressure at approximately normal values. Some degree of acidosis was noted in these animals at about 2 hours post-endotoxin, but this had subsided at 4 hours post-endotoxin. An increase in hematocrit, from a control value of 42 to a maximum of 55, was seen 9 hours post-endotoxin. Oliguria and anuria were not observed; actually, diuresis occurred following therapy.

Two of the 10 dogs treated with aldoster-

* Supplied by Research Dept. of Ciba Pharmaceutical Products, Inc., Summit, N. J.

TABLE I. Results in 43 Dogs Given a Lethal Dose of *E. coli* Endotoxin.

	A	B	C	D
	Control	Angiotensin II	Aldosterone	Aldosterone-Angiotensin II
No. of animals	13	10	10	10
Avg dose in mg	0	.650	.20	Ald. .20 Ang. .09
Range	0	(.075-2.0)		(.05-.15)
Avg hematocrit				
Initial	39	42	41	41
2-hr post-endotoxin	51	50	55	51
8-" " "	69	55	54	49
Avg arterial pH				
Initial	7.40	7.38	7.39	7.38
2-hr post-endotoxin	7.24	7.33	7.34	7.36
8-" " "	7.15	7.45	7.45	7.42
Survivors (permanent)*	0/13	5/10	2/10	8/10

* The P value of Groups A and B, and of A and C is >0.05, whereas the value of A and D is <0.05.

one survived. There were no significant changes in serum Na or K during the 8-hour post-endotoxin observation period. Although hemoconcentration and acidosis did occur, the changes were less pronounced than in control endotoxin animals.

In view of the few survivors that occurred following therapy with either aldosterone or angiotensin II, a fourth group of 10 animals were treated with a combination of aldosterone and angiotensin II. Eight of the 10 animals in this group survived, and displayed minimum hemoconcentration and acidosis. The most remarkable feature of this experiment, however, was the apparent potentiation of the pressor effect of angiotensin II by aldosterone. The average total amount of angiotensin II required to maintain systemic pressure was 0.09 mg, the dose varying between 0.05 and 0.15 mg. This is in contrast to an average dose of 0.65 mg required to maintain blood pressure when angiotensin II was used alone.

Discussion and summary. Aldosterone, alone, was first shown to protect animals against endotoxin when Halberg, Spink and Bittner(4) used preparations of the steroid in adrenalectomized mice. Bein and Jaques (5) corroborated and extended these observations with more satisfactory preparations of aldosterone in mice, rats and cats. Studies in our laboratory indicate that aldosterone is the most potent corticosteroid available for potentiating the pressor effect of pressor agents in experimental endotoxin shock. The results with the aldosterone-angiotensin II combination are especially impressive.

The action of exogenous aldosterone in endotoxin shock is not known. With the doses of aldosterone used, no alterations in serum sodium and potassium concentrations were detected. Although endotoxin shock results in a reduced output of urine, neither aldosterone nor angiotensin II augmented this effect. In fact, urine flow was improved following steroid-pressor therapy.

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