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PREVENTION OF DEATH IN ESCHERICHIA COLI (LD100) SHOCK.(U)
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TECHNICAL REPORT NO. 134

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L. B. Hinshaw, B. K. Beller, L. T. Archer,

D. J. Flournoy, G. L. White, and R. W. Phillips

Prepared for Publication

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Surgery, Gynecology and Obstetrics

University of Oklahoma Health Sciences Center
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Studies employing exogenously administered corticosteroids as treatment for experimental septic shock in animals have yielded conflicting results. Endotoxin shock in dogs has been successfully treated with an initial bolus injection of methylprednisolone sodium succinate 15 minutes after the onset of LD_{100} endotoxin infusion, followed by maintenance infusions of the steroid. An eighty percent survival rate was achieved with this regimen, as reported by White and colleagues (27). However, the recent work of Hinshaw and others in baboons administered infusions of live Escherichia coli organisms did not demonstrate improvement in survival rate between untreated animals and those receiving methylprednisolone sodium succinate (13). Baboon studies employing methylprednisolone sodium succinate conducted by Herman and others (9) using Escherichia coli organisms and by Johnson's group using endotoxin (13) also failed to demonstrate increased survival. Schuler and others, however, observed increases in survival rate in monkeys given endotoxin followed by dexamethasone (23), and Schumer documented increased survival rates in patients with septic shock receiving dexamethasone sodium phosphate or methylprednisolone sodium succinate in conjunction with antibiotic therapy (24). Although Pitcairn and colleagues (20) obtained survival benefits with rats shocked with Escherichia coli and treated with dexamethasone alone, added improvements in survival rate were observed with the dual utilization of an antibiotic and steroid. Because of the differences in survival rates employing steroid administration in these reports and the continuing controversy regarding its use in clinical septic shock, we considered it important to test the effectiveness of a corticosteroid combined with an antibiotic in treating animals subjected to live Escherichia coli shock. Experiments were designed using dogs to evaluate survival by

employing methylprednisolone sodium succinate administration alone, gentamicin sulfate infusions alone, and the two agents in combination. Findings demonstrate that permanent recovery from Escherichia coli shock results with the utilization of combined steroid and antibiotic therapy.

METHODS

Experiments were carried out on twenty-three adult mongrel dogs of random sex screened for microfilaria (heartworms), treated for intestinal parasites, and allowed to stabilize 3 to 4 weeks. Only animals with leukocyte counts less than 21,000/mm^3 and hematocrits exceeding 36% were utilized in the study.

Animals were anesthetized intravenously with sodium pentobarbital, 25 mg/kg, and intubated. Femoral artery and veins were aseptically catheterized for sampling blood, infusing drugs, and monitoring blood pressure and heart rate.

Dogs were divided into four groups (Table I): Group A (N=7), the control group, received a one-hour intravenous infusion of Escherichia coli organisms, prepared as previously described (1,12). Animals in Group B (N=6) also received organisms but were additionally treated with methylprednisolone sodium succinate (The Upjohn Company; Kalamazoo, Michigan) and gentamicin sulfate (Schering Pharmaceutical Corporation; Kenilworth, New Jersey). Group C dogs (N=5) received Escherichia coli and gentamicin while Group D animals (N=5) received Escherichia coli and methylprednisolone. Mean numbers of organisms infused in Groups A, B, C and D, were 9.1×10^9, 11.1×10^9, 9.4×10^9, and 8.9×10^9 organisms per kilogram body weight, respectively. Each animal received a one milliliter suspension of live Escherichia coli organisms per kilogram body weight. Table II describes the treatment regimen: Group A animals received organisms only and served as the control group. Group B dogs were treated with methylprednisolone intravenously, 30 milligrams per kilogram, 15 minutes

after initiation of the Escherichia coli infusion. This was followed by infusions of methylprednisolone, 15 milligrams per kilogram, 1.5 and 5.0 hours after zero time. Gentamicin, 4.5 milligrams per kilogram, was infused intravenously following completion of organism administration. Maintenance doses of 1.0 milligram per kilogram gentamicin were infused intravenously at 3 and 5 hours, and intramuscularly, 4.0 milligrams per kilogram, at 6 hours, and once each day for three days. Methylprednisolone was omitted from the treatment regimen in Group C, while gentamicin was not included in Group D. Saline infusions were substituted for drugs when the latter were not administered. We considered the initial bolus injection of methylprednisolone at 15 minutes essential since a large number of organisms had been infused (2×10^9 organisms per kilogram body weight) by that time. We also decided that maintenance infusions of methylprednisolone would be necessary because of its short in vivo half-life (communication, The Upjohn Company). Animals were continuously monitored for a 6-hour period and returned to a recovery room for subsequent observation for 7 days or until death.

Plasma glucose concentrations were determined with a Beckman glucose analyzer, leukocyte counts with a Coulter automatic particle counter, rectal temperature with a Tele-Thermometer probe, serum insulin by radioimmunoassay, blood lactate with perchloric acid, glycine-hydrazine buffer, NAD^+ and lactic dehydrogenase, and pH, pCO_2 and pO_2 with an Instrumentation Laboratories blood gas analyzer. Escherichia coli blood concentrations were determined by standard colony count procedures, and serum concentrations of gentamicin were monitored by bioassay using Staphylococcus epidermidis (ATCC 27626) as the assay organism and Antimicrobial Medium #5 (Difco; Detroit, Michigan).

Statistics were carried out utilizing a Student t test for paired or unpaired data.

RESULTS

Effects of methylprednisolone and gentamicin on the survival of dogs challenged with LD_{100} Escherichia coli organism infusions. Table III summarizes individual animal survival times in the control and three treatment groups. Seven dogs were administered Escherichia coli alone and served as controls. All died within 24 hours following Escherichia coli infusion. However, all six animals receiving steroid and antibiotic survived the LD_{100} Escherichia coli challenge and appeared to be in excellent condition when sacrificed 6 to 7 days later. Animals receiving steroid or antibiotic separately, but not in combination, died within 30 hours following Escherichia coli infusion, except one given the antibiotic, which became a permanent survivor. Typical adverse intestinal responses occurring early in animals given *Escherichia coli alone*, without the combined treatment, were bloody diarrhea and sloughing of the intestinal intimal lining.

Effects of methylprednisolone and gentamicin on factors related to survival in dogs subjected to lethal infusions of Escherichia coli. Figure 1 presents alterations in mean systemic arterial pressure and hematocrit in treated and untreated animals. No differences in mean pressure changes were seen between the four groups of animals. Pressures significantly declined within one hour following the onset of Escherichia coli infusion in both treated and untreated dogs, and mean values remained depressed until termination of pressure recordings at 6 hours. Significant increases in hematocrits are seen in all of the groups when each group is compared to its own zero time value ($p<0.05$). On the average, the smallest increases were observed in Group B animals receiving both steroid and antibiotic. However, because of the wide range of values, there is no statistically significant difference in hematocrit changes between Groups A and B.

Figure 2 illustrates mean changes in blood glucose and insulin concentrations in treated and untreated animals. Dogs receiving Escherichia coli alone (Group A) demonstrated notable decreases in glucose concentration from 3 to 6 hours ($p<0.05$). In contrast, administration of methylprednisolone and gentamicin after Escherichia coli (Group B) and methylprednisolone alone (Group D) resulted in significantly elevated blood glucose concentrations compared to Group A dogs challenged with Escherichia coli only ($p<0.05$). Group C animals, administered gentamicin alone after Escherichia coli, responded similarly to those untreated dogs in Group A ($p>0.05$). Serum insulin concentrations during shock were insignificantly altered from zero time values in each of the four groups although mean values in both steroid-treated groups were elevated at 2 hours. Hypoinsulinemia was not observed in any of the groups, although the mean insulin concentration of the treated animals (Group B) was significantly below its own control at 6 hours ($p<0.05$).

Changes in leukocyte and neutrophil concentrations are depicted in Figure 3, and results show a marked early development of leukopenia and neutropenia to a similar degree in all of the groups ($p<0.05$). Very large increases in leukocyte and neutrophil concentrations, exceeding 45,000 cells/mm^3, are seen at 24 hours in Group B, the fully-treated animals (p, 0.005).

Alterations in heart rate and rectal temperature are shown in Figure 4. Heart rates were relatively constant during the 6-hour observation period, while increases in rectal temperature of 1 to 2 degrees centigrade were noted in all groups. Mean temperature had recovered in Group B animals by 24 hours.

Table IV presents changes in pH, pCO_2, pO_2 and blood lactate in treated and untreated animals administered Escherichia coli. Of special note is the

improved pH of Group B dogs at 6 hours ($p<0.05$) and the significantly sustained reductions in pCO_2 in all groups. Slight but statistically significant decreases in pO_2 were observed in Groups A, B, and C at 4 to 6 hours following the onset of Escherichia coli infusion. Mean increases in arterial blood lactate are seen in all groups at some time during the course of shock. The highest values range between two and three times the control, zero time concentrations of each group. Treatment with methylprednisolone and gentamicin (Group B) did not lower the concentrations of lactate below those of the untreated animals (Group A).

Effects of gentamicin on the in vivo survival of Escherichia coli (LD_{100}). Bioassays demonstrated the achievement of gentamicin levels ranging from 10 to 17 micrograms per milliliter blood in Groups B and C up to 6 hours after the onset of Escherichia coli infusion (Table V). Although levels at 24 hours are lower, it is assumed that optimal concentrations were achieved prior to that time. Data from Table V indicate that the introduction of gentamicin into the blood does not significantly alter the concentration of circulating Escherichia coli. Results from the four groups reveal similar decreases in concentrations during the study.

DISCUSSION

The present study was undertaken to evaluate the effects of steroid and antibiotic treatment on dogs subjected to live Escherichia coli-induced shock (LD_{100}). All control dogs receiving Escherichia coli alone died within 24 hours, while all animals treated with initial and sustaining doses of methylprednisolone and gentamicin survived. Methylprednisolone- and gentamicin-treated animals appeared healthy and demonstrated normal behavior and eating

habits when sacrificed 6 to 7 days after Escherichia coli administration. On the other hand, shocked dogs treated with either steroid alone or antibiotic alone were not protected against the adverse effects of the Escherichia coli; all but one of those animals died within 30 hours.

These results are consistent with recent work by Herman's group and by Hinshaw and colleagues on baboons challenged with Escherichia coli, in which steroid administration alone failed to improve hemodynamic and metabolic parameters or to increase survival (9,13). The present observations are in partial contrast to those of Pitcairn and others who reported increased survival with corticosteroids alone in Escherichia coli-challenged rats (20). The present results differ from White and colleagues' recent study using LD_{100} endotoxin rather than Escherichia coli organisms in which methylprednisolone alone significantly increased survival of dogs. These recent findings together with those of the present study suggest that the mechanisms of Escherichia coli organism- versus endotoxin-induced shock may significantly differ.

There is a wide disparity of findings concerning the effectiveness of steroid administration in experimental septic shock. We believe that this may be due in part with failure to treat early before the appearance of bloody diarrhea and sloughing of the intestinal intimal lining which invariably signals the onset of irreversible shock; failure to continue maintenance doses of the steroid in view of its short half-life, as evidenced by the development of hypoglycemia when steroid is not utilized; failure to combine antibiotic with steroid therapy during Escherichia coli shock; and finally, failure to utilize maintenance doses of antibiotic in order to sustain optimal plasma concentrations.

Hypoglycemia is a consistent finding in dogs, rats, monkeys and baboons following Escherichia coli or endotoxin administration as reported by Filkins (6), Griffiths (7), Hinshaw (12-14), Schuler (23), White (27) and their colleagues, and Archer (1). Inhibition of hepatic gluconeogenesis (6,8) and the development of hepatic lesions (1-3,14) demonstrated in these animals significantly contribute to the elicitation of hypoglycemia.

Data from the present study indicate that methylprednisolone administration elicits hyperglycemia and prevents the destructive onset of progressive hypoglycemia and subsequent death. Berry (4) and Holtzman and colleagues (16) reported that corticosteroid administration stimulated hepatic gluconeogenesis, while Schuler and associates (23) observed that it supported carbohydrate metabolism in shocked nonhuman primates. Schuler's group utilized dexamethasone sodium phosphate in endotoxin shock and reported that it prevented the endotoxin-induced inhibition of gluconeogenesis, the subsequent metabolic derangements, and the depletion of high-energy adenine nucleotides (23). Balis and colleagues found that treatment of endotoxin-shocked monkeys with methylprednisolone inhibited the development of disseminated intravascular coagulation, fibrin deposition in hepatic sinusoids and lesions of the liver (3). Latour and co-workers (18) also found that glucocorticoids prevented generalized intravascular clotting. Although Balis and others (2,3) reported that the steroid also inhibited blood-vascular reactions and lesions of the lung in the monkey, Pingleton and colleagues' observations are not in agreement with this finding (19).

Hypoinsulinemia as reported in baboons administered Escherichia coli (12,13) was not seen in the present study, although at 6 hours the mean insulin concentration in the fully-treated group was below the zero time value ($p<0.05$). The maintenance of adequate insulin levels in the presence of normal glucose concentrations should promote normal glucose transport into the cell.

Balis' group (3) showed that methylprednisolone protected leukocytes in endotoxin shock by inhibiting their degranulation and fragmentation, an observation also not in agreement with Pingleton's work (19). Hinshaw and others found no detrimental effects of methylprednisolone on neutrophils in vitro, in the presence or absence of live Escherichia coli (11). The methylprednisolone conceivably may be protecting the leukocytes, which may in turn aid in protecting the liver by removing Escherichia coli from the peripheral circulation.

The hepatic circulation is presumed to be augmented by steroid administration (15). Delpin and others prevented liver ischemia with steroid (5). The cardiovascular actions of methylprednisolone which may indirectly aid the liver include increased cardiac output reported by Sambhi and colleagues (22), positive inotropic support of the heart observed by Rao and Cavanagh (21), elevated coronary blood flow described by Hinshaw and associates (10), and enhanced regional blood flow noted by Vaughn (26) and Hinshaw and others (15). The fact that fluid administration was not required to enhance survival in the present study and that pH values were normalized in spite of increases in lactic acid are consistent with the above findings.

Bacteria are extensively distributed in many organ systems as observed by Schloerb and others in canine septic shock (23). In order to kill or inhibit these bacteria, it appears necessary to transport adequate amounts of antibiotic to these sites. Since methylprednisolone improves both systemic and regional blood flows, it should aid in the distribution of the antibiotic.

By improving blood flow, methylprednisolone should aid hepatic gluconeogenesis, acid base balance, and antibiotic distribution, which may explain the advantages of combined steroid and antibiotic treatment in experimental septic shock.

SUMMARY

This study was designed to determine the efficacy of maintenance infusions of methylprednisolone sodium succinate and gentamicin sulfate in live Escherichia coli organism shock. Twenty-three conditioned dogs were anesthetized, instrumented aseptically, infused for one hour with approximately 9.5×10^9 organisms per kilogram, studied for 6 hours and observed for 7 days or until death. All seven untreated dogs died within 24 hours following variable periods of hypoglycemia, hemoconcentration, intestinal hemorrhage, diarrhea, and acidemia. Six dogs were treated with a total of 60 milligrams per kilogram methylprednisolone sodium succinate slowly infused at 15, 90 and 300 minutes following onset of Escherichia coli administration. A total of 6.5 milligrams per kilogram gentamicin sulfate was additionally infused at 65, 180 and 300 minutes, with 4.0 milligrams per kilogram gentamicin sulfate given intramuscularly at 360 minutes and daily for three days. The six treated dogs maintained normal blood glucose and pH values during the initial 6-hour period, and adverse intestinal findings were absent. These treated animals were sacrificed 6 to 7 days later in a healthy state. Ten additional animals received the same regimen of either steroid or antibiotic and nine died within 36 hours. Findings stress the importance of maintenance infusions of both steroid and antibiotic agents following lethal Escherichia coli administration.

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TABLE I.--DOSAGES OF ESCHERICHIA COLI ADMINISTERED TO ANESTHETIZED DOGS

Group	*Description of experimental group*	*Animal number*	*Number of organisms per milliliter**
A	Escherichia coli alone (control)	1	8.4×10^9
		2	8.7×10^9
		3	9.2×10^9
		4	8.6×10^9
		5	9.0×10^9
		6	10.0×10^9
		7	9.5×10^9
		Mean	9.1×10^9
B	Escherichia coli, methylprednisolone†, gentamicin§	8	17.0×10^9
		9	8.6×10^9
		10	8.1×10^9
		11	11.0×10^9
		12	13.0×10^9
		13	8.7×10^9
		Mean	11.1×10^9
C	Escherichia coli, gentamicin	14	9.0×10^9
		15	10.0×10^9
		16	9.6×10^9
		17	9.7×10^9
		18	8.7×10^9
		Mean	9.4×10^9
D	Escherichia coli, methylprednisolone	19	8.5×10^9
		20	9.0×10^9
		21	10.0×10^9
		22	8.7×10^9
		23	8.4×10^9
		Mean	8.9×10^9

*One milliliter infused per kilogram body weight

†methylprednisolone sodium succinate

§gentamicin sulfate

TABLE II.--TREATMENT REGIMEN IN DOGS SUBJECTED TO LIVE ESCHERICHIA COLI ORGANISM-INDUCED SHOCK (LD_{100})

Group	*Agent administered*	*Dosage*	*Time after onset of Escherichia coli infusion*	*Duration and route of administration*
A	Escherichia coli organisms	1.0 ml/kg*	Zero time (0)	0-60 min, IV
B	Escherichia coli organisms	1.0 ml/kg	Zero time (0)	0-60 min, IV
	Methylprednisolone†	30 mg/kg	+15 min	15 min, IV
	Gentamicin§	4.5 mg/kg	+65 min	75 min, IV
	Methylprednisolone	15 mg/kg	+95 min	120 min, IV
	Gentamicin	1.0 mg/kg	+185 min	30 min, IV
	Gentamicin	1.0 mg/kg	+305 min	30 min, IV
	Methylprednisolone	15 mg/kg	+310 min	50 min, IV
	Gentamicin	4.0 mg/kg	+365 min	IM
	Gentamicin	4.0 mg/kg	Daily, 3 days	IM
C	Same procedure as Group B, no methylprednisolone given			
D	Same procedure as Group B, no gentamicin given			

Saline infusions are substituted for drugs, when the latter are not administered.

*See Table I for exact number of organisms per milliliter.

†Methylprednisolone sodium succinate.

§Gentamicin sulfate.

TABLE III.--SURVIVAL DATA IN DOGS RECEIVING ESCHERICHIA COLI ORGANISMS AND TREATED WITH METHYLPREDNISOLONE* AND GENTAMICIN†

Group number	*Description and treatment of experimental group*	*Animal number*	*Survival time*§
A	Escherichia coli alone (control)	1	<24 hrs
		2	<24 hrs
		3	<24 hrs
		4	<24 hrs
		5	5 hrs
		6	<24 hrs
		7	<12 hrs
B[Ω]	Escherichia coli, methylprednisolone*, gentamicin†	8	7 days
		9	7 days
		10	6 days
		11	7 days
		12	7 days
		13	7 days
C	Escherichia coli, gentamicin	14	7 days
		15	6 hrs
		16	30 hrs
		17	12 hrs
		18	<24 hrs
D	Escherichia coli, methylprednisolone	19	24 hrs
		20	23 hrs
		21	23 hrs
		22	19 hrs
		23	21 hrs

*Methylprednisolone sodium succinate.

†Gentamicin sulfate.

§Six-day survival in good condition represents permanent recovery.

ΩAll animals sacrificed at 6 or 7 days.

TABLE IV.--CHANGES IN pH, pCO_2, pO_2 AND LACTATE IN TREATED AND UNTREATED DOGS ADMINISTERED ESCHERICHIA COLI ORGANISMS

Parameter	*Group*	*Zero time*	*+15 min*	*+60 min*	*+120 min*	*+240 min*	*+360 min*	*+24 hr*
pH	A	7.36(0.01)	7.37(0.01)	7.32(0.03)	7.33(0.02)	7.31(0.03)	*7.29(0.02)	
	B	7.38(0.01)	7.39(0.20)	7.35(0.01)	7.36(0.02)	7.42(0.04)	†7.41(0.03)	7.29(0.02)
	C	7.35(0.01)	7.36(0.03)	*†7.27(0.03)	7.20(0.04)	7.27(0.05)	7.24(0.07)	
	D	7.37(0.01)	7.39(0.01)	7.34(0.03)	7.35(0.02)	7.35(0.06)	7.37(0.06)	
pCO_2	A	32(2)	30(1)	*24(2)	*23(1)	*23(1)	*23(1)	
	B	32(1)	*28(2)	*26(2)	*24(1)	*19(2)	*21(1)	
	C	34(1)	*31(1)	*22(2)	*24(2)	*21(2)	*20(2)	
	D	36(2)	*31(2)	*26(3)	*24(2)	*21(2)	*20(1)	
pO_2	A	78(3)	82(2)	80(4)	77(4)	*71(3)	*66(5)	
	B	82(4)	85(5)	77(7)	*73(5)	*68(5)	68(4)	
	C	81(3)	82(4)	74(5)	76(6)	*73(5)	*72(5)	
	D	78(3)	75(3)	71(5)	69(6)	73(5)	72(4)	
Lactate	A	15.1(4.1)	16.3(3.8)	*44.4(5.3)	*40.2(3.2)	*34.0(3.8)	*37.5(3.5)	
	B	14.5(2.1)	*23.3(4.3)	*46.3(5.2)	*47.6(5.1)	*†43.4(1.9)	*36.7(2.9)	17.2(2.5)
	C	19.1(6.0)	*27.3(5.7)	*54.4(4.1)	50.0(5.3)	36.2(2.6)	48.7(11.7)	25.3(12.8)
	D	17.6(5.7)	33.2(9.1)	*45.3(5.0)	53.6(8.6)	*†50.6(6.7)	*50.2(7.7)	

*Significantly different from zero time values, $p<0.05$.

†Significantly different from Group A (Escherichia coli alone, control group) values, $p<0.05$.

TABLE V.--ESCHERICHIA COLI ORGANISM AND GENTAMICIN BLOOD CONCENTRATIONS IN DOGS SUBJECTED TO LD_{100} ESCHERICHIA COLI SHOCK AND TREATED WITH STEROID AND ANTIBIOTIC

ESCHERICHIA COLI ORGANISM CONCENTRATION (number/ml blood)

*Experimental group**	*Number of organisms infused per kilogram body weight*	*Zero time*	*+65 min*	*+240 min*	*+360 min*	*+24 hr*
A	9.1×10^9		6.5×10^5	3.1×10^3	3.2×10^3	6.8×10^2 1†
	(0.2×10^9) 7†	Negative 5†	(4.7×10^5) 5†	(1.3×10^3) 5†	(8.4×10^2) 5†	
B	11.0×10^9		2.8×10^6	3.3×10^3	3.4×10^3	7.1×10^2
	(1.0×10^9) 6	Negative 6	(1.9×10^6) 6	(8.9×10^2) 6	(1.3×10^3) 6	(3.8×10^2) 5
C	9.4×10^9		1.1×10^6	4.9×10^3	1.4×10^4	7.0×10^2
	(0.2×10^9) 5	Negative 5	(0.8×10^6) 5	(1.9×10^3) 5	(1.2×10^4) 5	(7.0×10^2) 2
D	8.9×10^9		1.2×10^6	3.5×10^6	1.4×10^4	
	(0.3×10^9) 5	Negative 2	(0.6×10^6) 2	(3.5×10^6) 2	(0.6×10^4) 2	

GENTAMICIN CONCENTRATION, µg/ml blood

Experimental group	*Zero time*	*+120 min*	*+180 min*	*+360 min*	*24 hr*
A§					
B	0 4	12.3 (3.4) 4	10.3 (1.8) 4	13.1 (1.6) 4	4.7 (2.2) 4
C	0 5	17.1 (2.6) 5	15.7 (3.4) 4	13.8 (3.2) 5	<1.5 2
D§					

Figures are mean, ±SE.

*Group designations: A, Escherichia coli alone; B, Escherichia coli + methylprednisolone sodium succinate + gentamicin sulfate; C, Escherichia coli + gentamicin sulfate; D, Escherichia coli + methylprednisolone sodium succinate.

† No. of dogs.

§ No gentamicin administered.

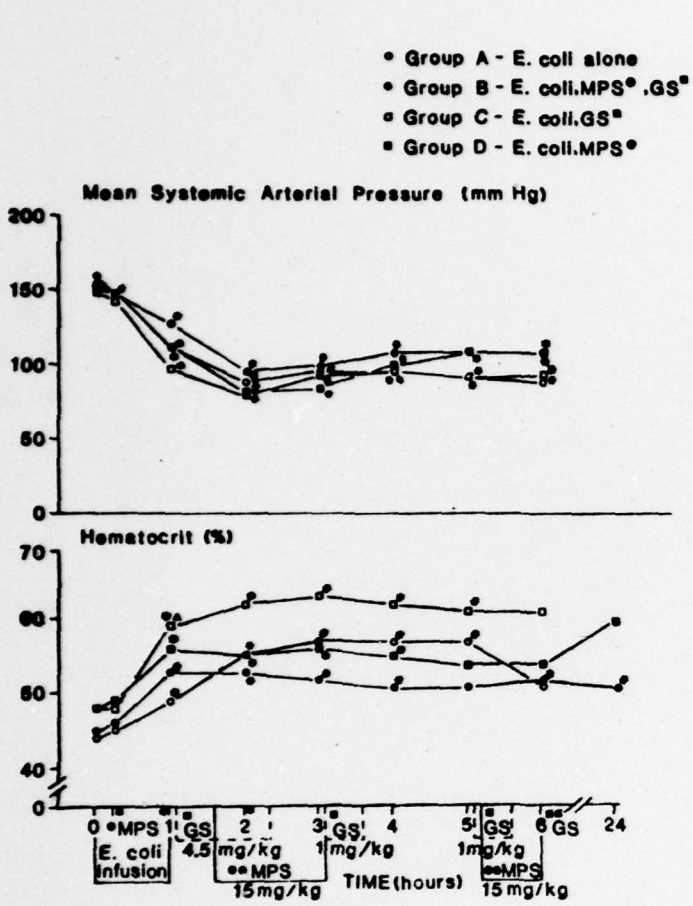
FIGURE LEGENDS

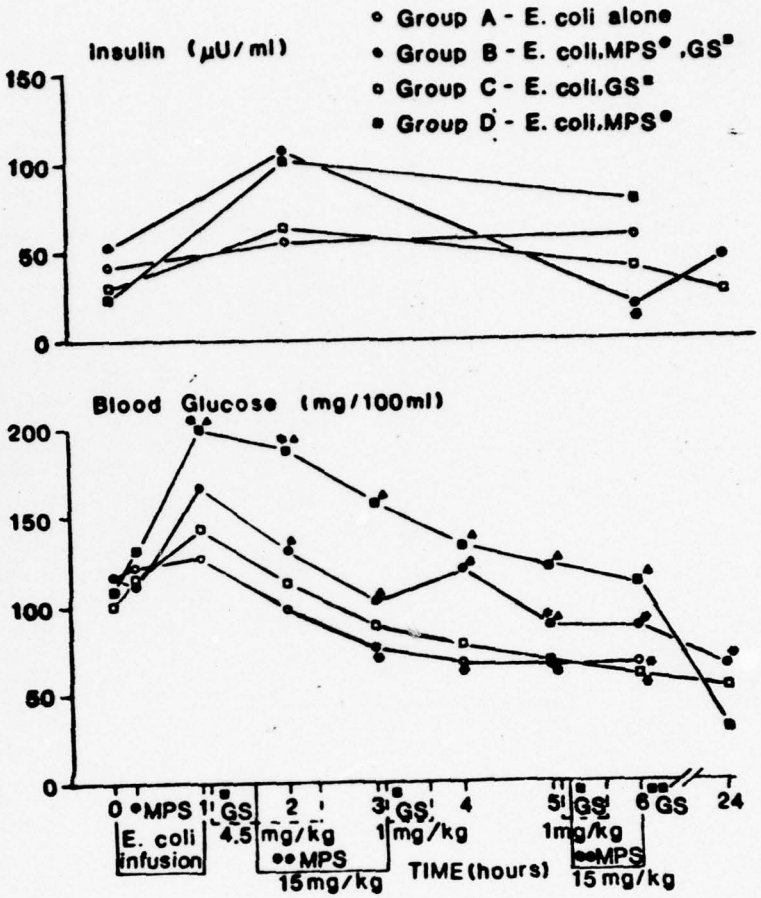
Figure 1. Effects of methylprednisolone sodium succinate and gentamicin sulfate on blood pressure and hematocrit in canine Escherichia coli shock. (Mean values with paired and unpaired statistical analyses.)

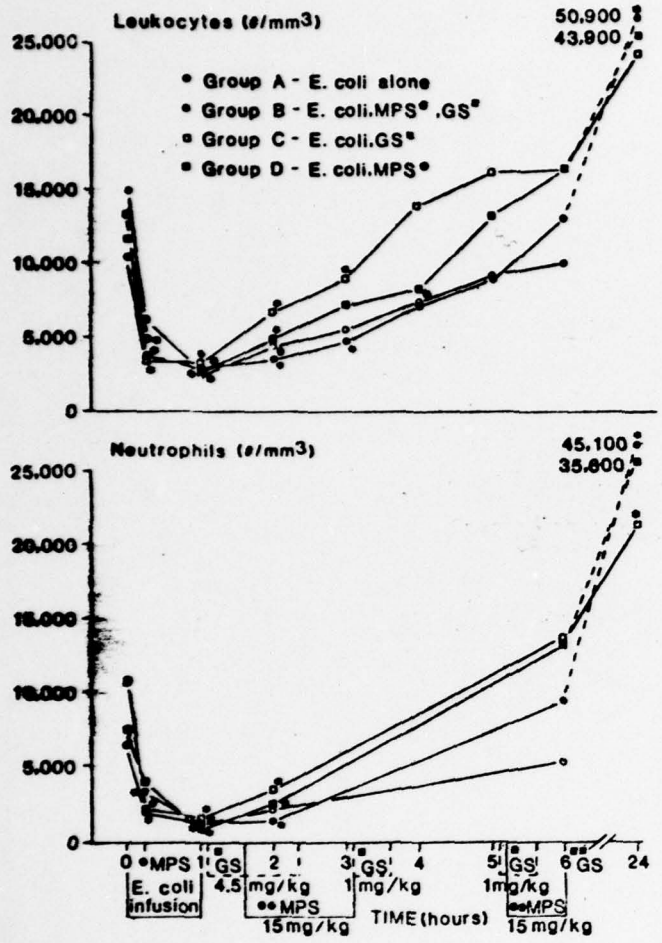
Figure 2. Effects of methylprednisolone sodium succinate and gentamicin sulfate on blood glucose and insulin concentrations in canine Escherichia coli shock. (Mean values with paired and unpaired statistical analyses.)

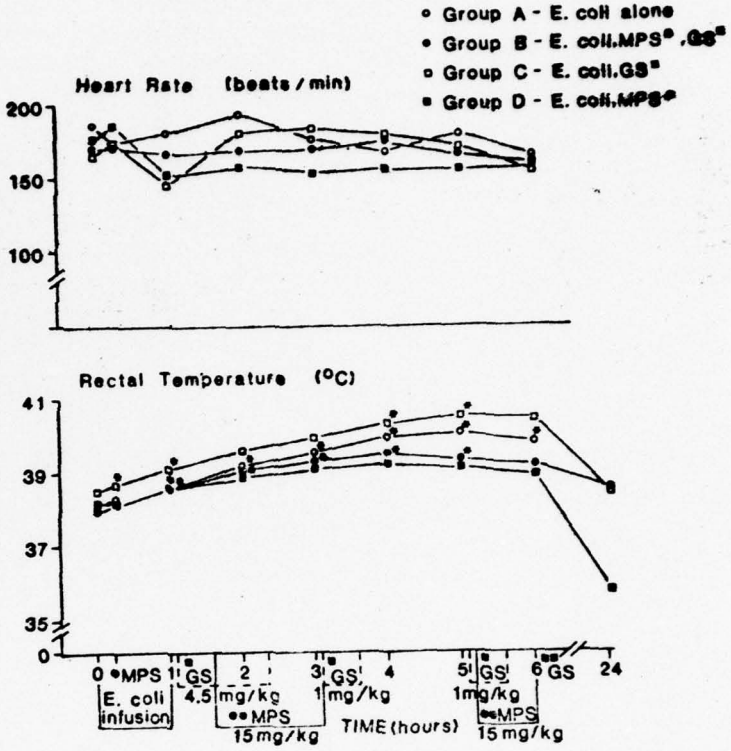
Figure 3. Effects of methylprednisolone sodium succinate and gentamicin sulfate on leukocyte and neutrophil concentrations in canine Escherichia coli shock. (Mean values with paired and unpaired statistical analyses.)

Figure 4. Effects of methylprednisolone sodium succinate and gentamicin sulfate on heart rate and rectal temperature in canine Escherichia coli shock. (Mean values with paired and unpaired statistical analyses.)


Group A - E. coli alone
Group B - E. coli.MPS●,GS■
Group C - E. coli.GS■
Group D - E. coli.MPS●
Mean Systemic Arterial Pressure (mm Hg)
200
150
100
50
0
Hematocrit (%)
70
60
50
40
0
0 ●MPS
1 GS
4.5 mg/kg
●●MPS
15 mg/kg
2
3 GS
1 mg/kg
4
5 GS
1 mg/kg
●●MPS
15 mg/kg
6 GS
24
E. coli infusion
TIME (hours)


Group A - E. coli alone
Group B - E. coli.MPS●,GS■
Group C - E. coli.GS■
Group D - E. coli.MPS●
Insulin (μU/ml)
150
100
50
0
Blood Glucose (mg/100ml)
200
150
100
50
0
0 ●MPS
1 GS
4.5 mg/kg
●●MPS
15 mg/kg
2
3 GS
1 mg/kg
4
5 GS
1 mg/kg
●●MPS
15 mg/kg
6 GS
24
E. coli infusion
TIME (hours)


Leukocytes (ø/mm3)
50,900
43,900
25.000
20.000
15.000
10.000
5.000
0
• Group A - E. coli alone
• Group B - E. coli.MPS• ,GS•
▫ Group C - E. coli.GS▪
▪ Group D - E. coli.MPS•
Neutrophils (ø/mm3)
45,100
35,600
25.000
20.000
15.000
10.000
5.000
0
0 •MPS 1 GS 4.5
E. coli infusion
2 mg/kg
••MPS
15 mg/kg
3 GS 1 mg/kg
4
5 GS 1mg/kg
••MPS
15 mg/kg
6 GS
24
TIME (hours)


◦ Group A - E. coli alone
• Group B - E. coli.MPS• ,GS▪
▫ Group C - E. coli.GS▪
▪ Group D - E. coli.MPS•
Heart Rate (beats / min)
200
150
100
Rectal Temperature (°C)
41
39
37
35
0
0 •MPS 1 GS 4.5
E. coli infusion
2 mg/kg
••MPS
15 mg/kg
3 GS 1 mg/kg
4
5 GS 1mg/kg
••MPS
15 mg/kg
6 GS
24
TIME (hours)

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20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

This study was designed to determine the efficacy of maintenance infusions of methylprednisolone sodium succinate and gentamicin sulfate in live Escherichia coli organism shock. Twenty-three conditioned dogs were anesthetized, instrumented aseptically, infused for one hour with approximately 9.5×10^9 organisms per kilogram, studied for 6 hours and observed for 7 days or until death. All seven untreated dogs died within 24 hours following variable periods of hypoglycemia, hemoconcentration, intestinal hemorrhage,

10 to the 9th power

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diarrhea, and acidemia. Six dogs were treated with a total of 60 milligrams per kilogram methylprednisolone sodium succinate slowly infused at 15, 90 and 300 minutes following onset of Escherichia coli administration. A total of 6.5 milligrams per kilogram gentamicin sulfate was additionally infused at 65, 180 and 300 minutes, with 4.0 milligrams per kilogram gentamicin sulfate given intramuscularly at 360 minutes and daily for 3 days. The six treated dogs maintained normal blood glucose and pH values during the initial 6-hour period, and adverse intestinal findings were absent. These treated animals were sacrificed 6 to 7 days later in a healthy state. Ten additional animals received the same regimen of either steroid or antibiotic and nine died within 36 hours. Findings stress the importance of maintenance infusions of both steroid and antibiotic agents following lethal Escherichia coli administration.

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