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EFFECTIVENESS OF STEROID/ANTIBIOTIC TREATMENT IN PRIMATES ADMIN--ETC(U)
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EFFECTIVENESS OF STEROID/ANTIBIOTIC TREATMENT
IN PRIMATES ADMINISTERED LD₁₀₀ ESCHERICHIA COLI

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Bruce Benjamin, Dayl J. Flournoy, Richard Passey, Michael F. Wilson

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All eight untreated animals died within 42 hours. Five of the eight baboons treated after approximately three hours of hypotension with methylprednisolone sodium succinate and gentamicin sulfate permanently survived. Treated animals had significantly higher blood glucose and insulin levels and lower blood urea nitrogen concentrations than baboons receiving E. coli alone. E. coli blood concentrations were lower in the treated than in the untreated baboon group by the sixth hour (≤ 0.02). Heart rates increased in all animals but were not as high in the treated baboons. Both groups experienced similar decreases in mean systemic arterial pressure, pCO_2 , base excess, leukocyte, lymphocyte, and platelet concentrations, and increases in creatinine and lactate concentrations. Data from the present study indicate that the probability of recovery from shock is significantly increased even when initiation of steroid/antibiotic therapy is postponed until baboons have experienced sustained systemic hypotension.

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ABSTRACT

Early aggressive therapy with maintenance infusions of methylprednisolone sodium succinate and gentamicin sulfate significantly increases the probability for survival of baboons given LD₁₀₀ E. coli. The present study was designed to determine if baboons would recover when initiation of treatment was delayed until they had sustained E. coli-induced systemic hypotension for a period of approximately three hours. Sixteen adult baboons were each administered a two-hour infusion of LD₁₀₀ E. coli. All eight untreated animals died within 42 hours. Five of the eight baboons treated after approximately three hours of hypotension with methylprednisolone sodium succinate and gentamicin sulfate permanently survived. Treated animals had significantly higher blood glucose and insulin levels and lower blood urea nitrogen concentrations than baboons receiving E. coli alone. E. coli blood concentrations were lower in the treated than in the untreated baboon group by the sixth hour (< 0.02). Heart rates increased in all animals but were not as high in the treated baboons. Both groups experienced similar decreases in mean systemic arterial pressure, pCO_2 , base excess, leukocyte, lymphocyte, and platelet concentrations, and increases in creatinine and lactate concentrations. Data from the present study indicate that the probability of recovery from shock is significantly increased even when initiation of steroid/antibiotic therapy is postponed until baboons have experienced sustained systemic hypotension.

Key Words:

Septic shock, steroid therapy, antibiotic therapy, combined steroid/antibiotic treatment, nonhuman primates, baboons, E. coli-induced shock, methylprednisolone sodium succinate, gentamicin sulfate, endotoxin shock.

INTRODUCTION

In an attempt to find a clinically relevant therapy for sepsis and/or septic shock, we have developed a regimen to treat E. coli-shocked baboons consisting of combined multiple infusions of methylprednisolone sodium succinate (MPSS) and gentamicin sulfate (GS) (1, 2). When MPSS treatment is initiated 30 minutes after the onset of a two-hour infusion of LD₁₀₀ E. coli and GS infusion begun after termination of the E. coli infusion all baboons survive (1). GS infusion alone, on the other hand, failed to prevent death (1). Delaying initiation of MPSS infusion until all E. coli are infused results in an 85% survival rate (2). Results from these and parallel studies also demonstrated that administration of either agent alone showed no improvement or reversal of physiopathologic parameters, and the mortality rate remained unchanged (1-4).

The physician is often faced with septic patients who have succumbed to severe systemic hypotension. Consequently, we designed the present study to modify our nonhuman primate septic shock model to more closely resemble that clinical situation by delaying initiation of steroid and antibiotic treatment until severe sustained systemic hypotension had occurred. We chose the baboon to study because of its phylogenetic proximity to man and because of our recent successful work using it as an experimental septic shock model.

Findings clearly support the effectiveness of the steroid/antibiotic combination treatment and indicate that its life-saving characteristics are enhanced by early administration.

MATERIALS AND METHODS

Sixteen adult baboons of the subspecies, Papio c. cynocephalus, were allowed to stabilize 1 to 2 months in the animal facility, fasted

24 hours and given water ad libitum prior to experimentation. The morning of the study they were immobilized with ketamine hydrochloride, 14 mg/kg, intramuscularly, and intravenously anesthetized with sodium pentobarbital via a percutaneous catheter positioned in the cephalic vein. The radial and cephalic vein were exposed aseptically and cannulated to measure pressures, sample blood and infuse live organisms, isotonic sodium chloride, methylprednisolone sodium succinate (MPSS) and gentamicin sulfate (GS). Each baboon was placed on its side between controlled-temperature heating pads, and a temperature probe was placed in the rectum. A tracheal cannula was orally inserted, and periodic positive pressure was applied hourly to prevent atelectasis. Each animal was allowed to equilibrate at least one hour before beginning E. coli infusion.

Baboons of either sex were divided into two groups and each infused with live E. coli for two hours: the control group (N=8; average weight, 16.8 kg) were given $2.4 (\pm 0.2) \times 10^{10}$ organisms/kg body weight prepared as previously described (1, 3, 4). The experimental group (N=8; average weight, 17.9 kg) received $2.5 (\pm 0.2) \times 10^{10}$ E. coli/kg body weight, the steroid, methylprednisolone sodium succinate (MPSS; The Upjohn Company, Kalamazoo, MI), and the antibiotic, gentamicin sulfate (GS; Schering Pharmaceutical Corporation, Kenilworth, NJ), as shown in Table 1.

MPSS and GS infusions were begun 2 hours after live organism administration was complete, that is, 4 hours after initiation of E. coli infusion. Baboons in the experimental group were administered a total of 18 mg/kg GS and 75 mg/kg MPSS from the fourth to the twelfth hour. Normal saline was infused in each baboon of both groups, 6-7 ml/kg/hr, during the 12-hour period to prevent dehydration, and control animals

received additional saline as a substitute for the drug volumes. Treated baboons were additionally injected intramuscularly with GS at 12 hours and twice daily for 3 days. Baboons were maintained in the animal facility and observed a minimum of 7 days, then arbitrarily euthanized between 7 and 15 days.

Blood pressure and heart rate were monitored with a Sanborn recorder. Arterial blood samples were taken for determinations of glucose, insulin, lactate, white blood cells and differential leukocyte concentrations, platelets, pH, pCO_2 , pO_2 , blood urea nitrogen, creatinine, serum gentamicin, and blood concentrations of viable E. coli, as previously reported (1-3).

Data were analyzed using the Student's t test for paired and unpaired data and the Fisher's Exact Test for survival statistics.

RESULTS

Untreated baboons and baboons administered MPSS and GS following sustained systemic hypotension induced by E. coli infusion were continuously monitored for 12 hours, then observed up to 15 days. A minimum of seven days was required for a baboon to be called a "permanent survivor". Table II records survival times and show that all baboons given E. coli alone, died within 42 hours (mean, 17 hours). Five of the eight baboons treated with MPSS/GS permanently survived. Using Fisher's Exact Test, the survival results are statistically significant for the treated compared with the untreated group ($p < 0.05$). During recovery, 4 of 5 permanent survivors developed dermal ulcerations of the pelvic, hind limb, or gluteal areas which were treated with septisol, hydrogen peroxide and Panolog[®] ointment (Squibb).

Table III enumerates the E. coli blood concentrations of the two groups. Each baboon's blood culture was negative at zero time. Five minutes after E. coli infusion was completed (+125 min) blood concentrations

were similar in both groups, approximately 10^7 E. coli per ml blood. By six hours after the onset of organism infusion, the concentration of E. coli in the treated group was significantly lower than that of the control group ($p < 0.02$).

Figure 1 illustrates the changes in mean systemic arterial pressures (MSAP) and heart rates (HR) for both groups. The MSAP means of the treated baboons were lower compared with the zero time value at 1 through 6 hours ($p < 0.05$) and the MSAP means of the untreated group were significantly less than their zero time value from 2 through 4 hours. However, the MSAP of the two groups did not differ significantly from each other during the 12-hour observation period. Consequently, each baboon experienced marked sustained systemic hypotension (approximately 2-3 hours) before treatment was initiated at 4 hours. Mean heart rates of both groups were significantly higher than zero time values from 1 through 12 hours, but heart rates of the treated baboons were less than those of the untreated animals from 3 through 12 hours ($p < 0.05$).

Figure 2 pictures changes in blood glucose and serum insulin concentrations of treated and untreated baboons. All baboons became hypoglycemic and hypoinsulinemic by 4 hours. Blood glucose and serum insulin levels in treated animals returned to normal levels by 12 hours, while those of the untreated baboons remained low.

Total leukocyte concentrations were significantly decreased from zero time levels in both groups at 2 and 4 hours after initiation of E. coli infusion; however, leukocyte concentrations of treated animals were returning toward normal at 8 and 12 hours. Decreased concentrations of mature and immature neutrophils appear to be recovering in the treated baboons from 8-12 hours (Figure 3). Lymphocyte concentrations decreased similarly in both groups of animals. Platelet concentrations decreased

progressively throughout the 12 hours of monitoring ($p < 0.05$) in both groups with no statistical differences between treated and untreated baboons (Figure 3).

Figure 4 shows pH, pCO_2 , HCO_3^- , base excess, and lactate concentrations for the treated and untreated baboons. PCO_2 , HCO_3^- , and base excess decreased and lactate increased in both groups from 4 through 12 hours ($p < 0.05$). Both groups maintained relatively constant pH and pO_2 levels during the monitoring period. No statistically significant differences between the two groups were found in any of these parameters during 12 hours.

Blood urea nitrogen (BUN) concentrations moderately increased in both groups (Figure 5), but the values of the treated group were lower at 8 and 12 hours than those of the untreated group ($p < 0.05$). Creatinine concentrations increased similarly in all baboons. Mean serum gentamicin sulfate concentrations in the eight treated animals were 27.7 (± 3.3), 20.4 (± 2.6), and 26.6 (± 4.8) $\mu g/ml$ at 5.5, 10.5 and 12 hours, respectively. Urine flow was observed in the treated baboons, but the untreated animals were anuric.

Saline administration was similar in both groups with an average of 6 and 7 ml/kg/hr infused in untreated and treated baboons, respectively. Hematocrits of the two groups did not significantly differ; values ranged from 43 to 47% in untreated baboons and from 45 to 50% in treated animals.

DISCUSSION

We recently reported that combined glucocorticoid and antibiotic therapy effectively reverses or prevents the lethal pathophysiology of E. coli-induced shock in both dogs (5) and nonhuman primates (1, 2). We documented that baboons administered LD_{100} E. coli are effectively treated with infusions of methylprednisolone sodium succinate (MPSS)

administered after one-fourth of the organisms are given, followed by subsequent infusions of MPSS and gentamicin sulfate (GS) during a 12-hour period (1). All animals treated thusly were healthy permanent survivors. Although a massive number of organisms had been administered (7×10^9 organisms/kg body weight) prior to MPSS treatment in that study (1), aortic pressure had not yet fallen to the lowest point it would have had treatment not been initiated. A second study (2) was designed to extend this work by delaying steroid/antibiotic treatment until all organisms were given (2.5×10^{10} organisms/kg body weight) to allow the early maximal drop in blood pressure to occur prior to beginning steroid treatment (2). Although 85% of the baboons thus treated were permanent survivors, they returned to normal eating and physical activities slowly and some developed body surface ulcers.

The present study was designed to further delay steroid/antibiotic treatment of the baboons until two hours after all organisms were given (4 hours after E. coli infusion was initiated) and sustained systemic hypotension had occurred making the shock model more clinically relevant to those situations in which the physician is faced with patients with severe hypotension. Results demonstrate the notable effectiveness of MPSS and GS even when they are administered during sustained systemic hypotension: 65% of the baboons survived permanently (7 days or more). However, this survival rate was lower than that obtained when treatment was initiated earlier (1,2). Surviving animals of the present study developed body surface ulcerations, refused to eat for several days, and lost weight.

After the experiments, we found that two of the treated animals, which died, numbers 4 and 6, had elevated zero time LDH isoenzyme concentrations indicating preexisting lesions of liver or lung. Post mortem examinations confirmed this suspicion. These prior pathophysiological

conditions may have compromised the two animals' ability to recover from shock.

Possible explanations for the success of the steroid/antibiotic combination therapy are suggested by changes in several of the measured parameters of the present study. Treated baboons appeared to have better liver and pancreatic function in that blood glucose and serum insulin concentrations were maintained at higher levels. Renal function was supported as evidenced by urine flow in treated baboons in contrast to the anuria observed in the untreated baboons and significantly smaller elevations of BUN in the treated group. The circulating phagocytic defense system was augmented in the treated baboons as suggested by the appearances of increased mature and immature neutrophil concentrations, and the significantly enhanced killing rates of E. coli. The cardioacceleratory response was depressed in the treated baboons compared with the untreated animals, which is consistent with the alleviation by the steroid of the stress caused by E. coli shock.

Parameters which appeared to be unaltered by steroid/antibiotic treatment were systemic arterial blood pressure, pO_2 , pCO_2 , pH, base excess, and blood lactate concentrations. Systemic pressure, pCO_2 , and base excess were similarly depressed in all animals; pO_2 and pH values remained relatively constant while lactate concentrations were equally elevated in both groups. These parameters were therefore not helpful in predicting probability of survival.

Fluid administration averaged 6 and 7 ml/kg/hr for the 12-hour observation period in untreated and treated baboons, respectively, and hematocrit values remained relatively constant. Results from the present study and our earlier reports in dogs and baboons (1, 2, 5) suggested that fluid administration, neither prevents nor influences survival of animals in E. coli-induced shock.

The explanation for this may be that the volume of blood in the animal's circulation is inappropriately distributed in septic shock as has been suggested in human septic shock patients (7), with blood translocated to the venous segments of the vasculature and other sites (8). So the problem may be more one of inappropriate distribution of blood, rather than a lowered total blood volume. We postulate that this "distributive" defect (7), occurring specifically in septic shock (7), may be prevented or reversed with steroid administration by effecting intravascular shifts of blood from sequestered regions to the active circulation (5, 9).

Our findings have consistently shown that steroid administration or antibiotic treatment are separately ineffective in the treatment of E. coli shock in both dogs (5) and primates (1, 3, 4). It appears essential that steroid and antibiotic be given concomitantly. Proposed mechanisms of protection with MPSS and GS infusions against the pathophysiologic effects of E. coli in the baboon have been suggested in a previous report (1) and include improvement of hemodynamic, metabolic, endocrinologic and phagocytic functions resulting in the maintenance of normal morphologic-status of tissues including brain, liver, heart, kidneys, and adrenals (1). Our research has been pursued using the baboon because of the animal's phylogenetic proximity to man as evidenced by increasingly similar findings between the two species (10-13).

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TABLE I

TREATMENT PROTOCOL OF BABOONS FOLLOWING SUSTAINED HYPOTENSION INDUCED BY ESCHERICHIA COLI INFUSION

GROUP	(N)	AGENT ADMINISTERED	DOSAGE	TIME AFTER ON- SET OF <u>E. COLI</u> INFUSION	DURATION AND ROUTE OF ADMINISTRATION
<u>E. coli</u> only	8	<u>E. coli</u> organisms	$2.4(\pm 0.2) \times 10^{10}/\text{kg}$		0-120 min, iv
<u>E. coli</u> + MPSS + GS	8	<u>E. coli</u> organisms	$2.5(\pm 0.2) \times 10^{10}/\text{kg}$		0-120 min, iv
		Methylprednisolone*	30 mg/kg	+ 4 hrs	15 min, iv
		Gentamicin†	9 mg/kg	+ 4 hrs 5 min	60 min, iv
		Methylprednisolone	15 mg/kg	+ 6 hrs	120 min, iv
		Gentamicin	4.5 mg/kg	+ 8 hrs	30 min, iv
		Methylprednisolone	15 mg/kg	+ 9.5 hrs	90 min, iv
		Gentamicin	4.5 mg/kg	+ 11 hrs	30 min, iv
		Methylprednisolone	15 mg/kg	+ 11 hrs	60 min, iv
		Gentamicin	4.5 mg/kg	+ 12 hrs	im
		Gentamicin	4.5 mg/kg	TWICE DAILY, 3 DAYS	im

*methylprednisolone sodium succinate

†gentamicin sulfate

TABLE II

SURVIVAL DATA OF BABOONS ADMINISTERED ESCHERICHIA COLI AND TREATED AFTER
SUSTAINED HYPOTENSION WITH METHYLPREDNISOLONE SODIUM SUCCINATE AND GENTAMICIN SULFATE

Group	Baboon Number	Weight (kg)	<u>E. coli</u> /kg	Sex	Survival Time
<u>E. coli only</u>	1	15.8	2.1×10^{10}	F	11 hrs
	2	16.2	2.1×10^{10}	F	3 hrs
	3	19.9	1.7×10^{10}	M	5 hrs
	4	19.0	2.5×10^{10}	M	32 hrs
	5	18.2	2.3×10^{10}	M	42 hrs
	6	16.0	3.6×10^{10}	M	13 hrs
	7	15.5	2.2×10^{10}	M	16 hrs
	8	14.0	2.7×10^{10}	M	11 hrs
	Mean	16.8	2.4×10^{10}		17 hrs
		$\pm$	(0.2×10^{10})		
<u>E. coli plus</u> methylprednisolone sodium succinate and gentamicin sul- fate	1	26.6	2.7×10^{10}	M	8 days*
	2	15.0	2.1×10^{10}	F	41 hrs
	3	14.4	2.4×10^{10}	F	9 days*
	4	22.7	2.5×10^{10}	M	49 hrs
	5	13.3	3.5×10^{10}	F	15 days*
	6	21.0	2.1×10^{10}	M	10 hrs
	7	14.9	2.4×10^{10}	M	14 days*
	8	15.7	2.5×10^{10}	M	7 days*
	Mean	17.9	2.5×10^{10}		
		$\pm$	(0.2×10^{10})		

*euthanized

TABLE III

ESCHERICHIA COLI COLONY FORMING UNITS PER ML BLOOD IN RABOONS ADMINISTERED LD₁₀₀ ESCHERICHIA COLI
AND TREATED AFTER SUSTAINED HYPOTENSION WITH METHYLPREDNISOLONE SODIUM SUCCINATE AND GENTAMICIN SULFATE

<u>Group</u>	<u>No. E. coli infused per kg body weight</u>	<u>Zero time</u>	<u>+125 min</u>			
			<u>+4 hr</u>	<u>+6 hr</u>	<u>+12 hr</u>	
<u>E. coli only</u>	Mean	Negative	1.5x10 ⁷	2.5x10 ³	1.1x10 ³	1.2x10 ³
	SE (±)		0.8x10 ⁷	0.9x10 ³	0.4x10 ³	0.5x10 ³
	N	8	8	7	6	4
<u>E. coli plus *MPSS and *GS</u>	Mean	Negative	1.0x10 ⁷	1.5x10 ⁴	1.1x10 ²	1.6x10 ²
	SE (±)		0.3x10 ⁷	0.8x10 ⁴	0.3x10 ²	0.8x10 ²
	N	8	8	8	8	7
	P				< 0.02	< 0.02

*MPSS = methylprednisolone sodium succinate

*GS = gentamicin sulfate

LEGENDS FOR ILLUSTRATIONS

Figure 1. Changes in mean systemic arterial pressure and heart rate ($M \pm SE$) in baboons receiving E. coli alone, and those with E. coli followed by intermittent infusions of methylprednisolone sodium succinate (MPSS) and gentamicin sulfate (GS). MPSS and GS infusions were begun 4 hours after the onset of a two-hour infusion of LD_{100} E. coli ($N=8$, each group).

$\square, \star = p < 0.05$, paired comparisons within each group with zero time value.

$\Delta = p < 0.05$, unpaired comparison between groups.

Figure 2. Alterations in blood glucose and serum insulin concentrations in treated and untreated baboons receiving LD_{100} infusions of E. coli ($M \pm SE$) ($N=8$, each group). Methylprednisolone sodium succinate (MPSS) and gentamicin sulfate (GS) infusions were begun 4 hours after the onset of a two-hour infusion of E. coli.

$\square, \star = p < 0.05$, paired comparisons within each group with zero time values.

$\Delta = p < 0.05$, unpaired comparison between groups.

Figure 3. Changes in concentrations of mature and immature neutrophils, lymphocytes and platelets in baboons receiving E. coli alone versus those receiving E. coli and subsequently treated with methylprednisolone sodium succinate (MPSS) and gentamicin sulfate (GS). ($N=8$, each group, $M \pm SE$).

$\square, \star = p < 0.05$, paired comparisons within each group with zero time values.

$\Delta = p < 0.05$, unpaired comparison between groups.

Figure 4. Alterations in respiratory, acid-base parameters and lactate concentrations in baboons receiving E. coli alone and E. coli plus subsequent infusions of methylprednisolone sodium succinate (MPSS) and gentamicin sulfate (GS). ($N=8$, each group, $M \pm SE$).

$\square, \star = p < 0.05$, paired comparisons within each group with zero time values.

Figure 5. Changes in blood urea nitrogen and creatinine concentrations in treated and untreated baboons (N=8, each group, $M \pm SE$).

Lower portion of figure = serum gentamicin sulfate concentrations in treated group.

□, ☆ = $p < 0.05$, paired comparisons within each group with zero time values.

Δ = $p < 0.05$, unpaired comparison between groups.

FIGURE 1

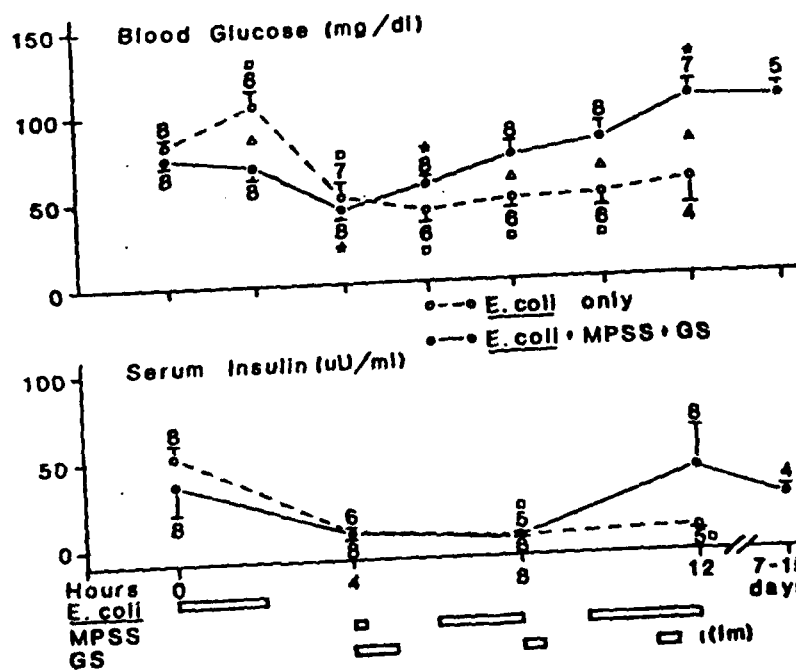
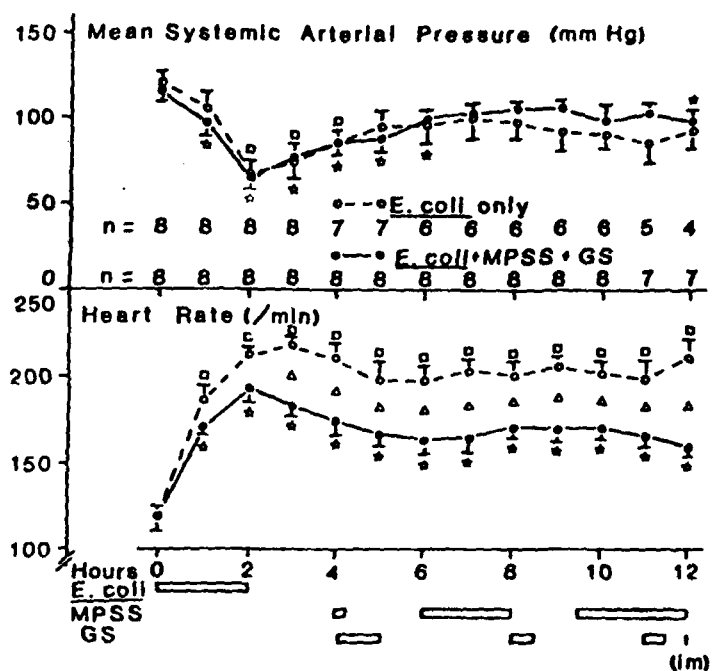


FIGURE 2

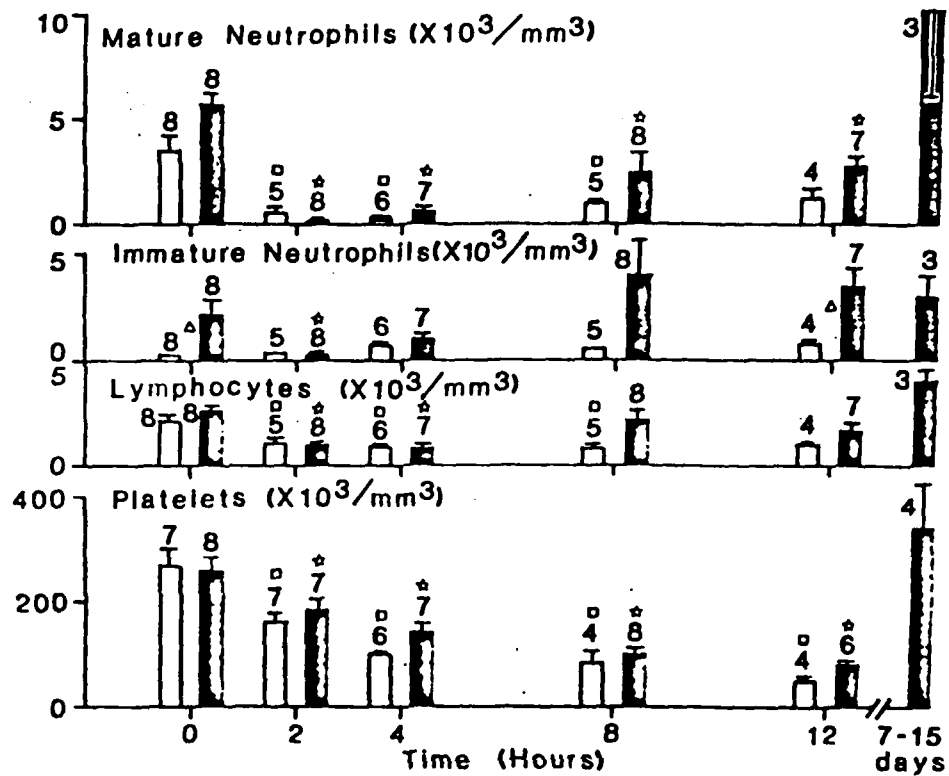


FIGURE 3

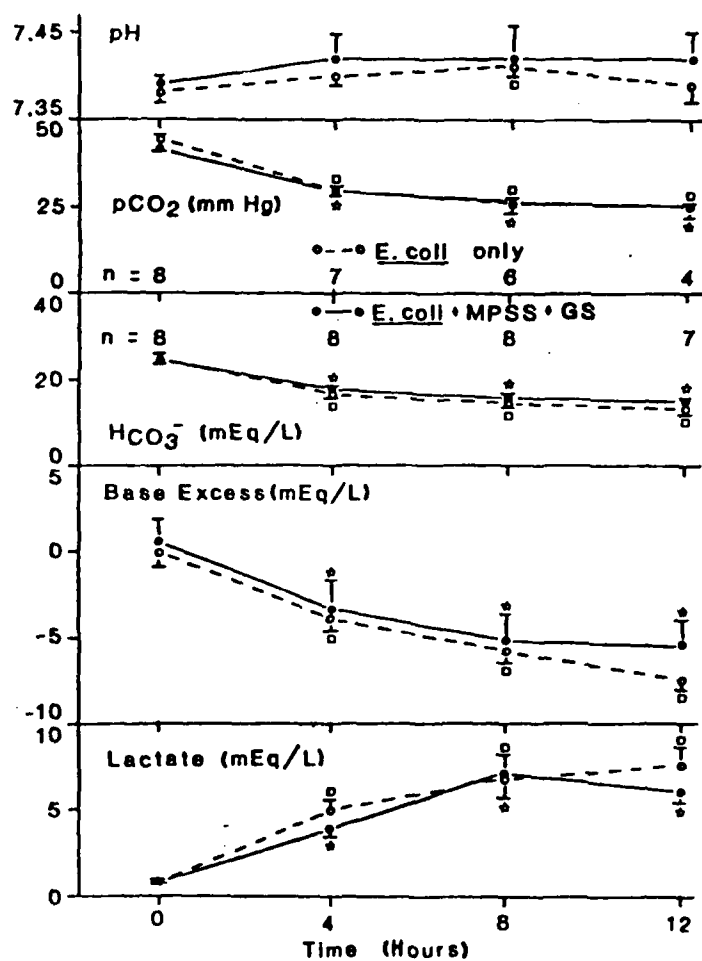


FIGURE 4

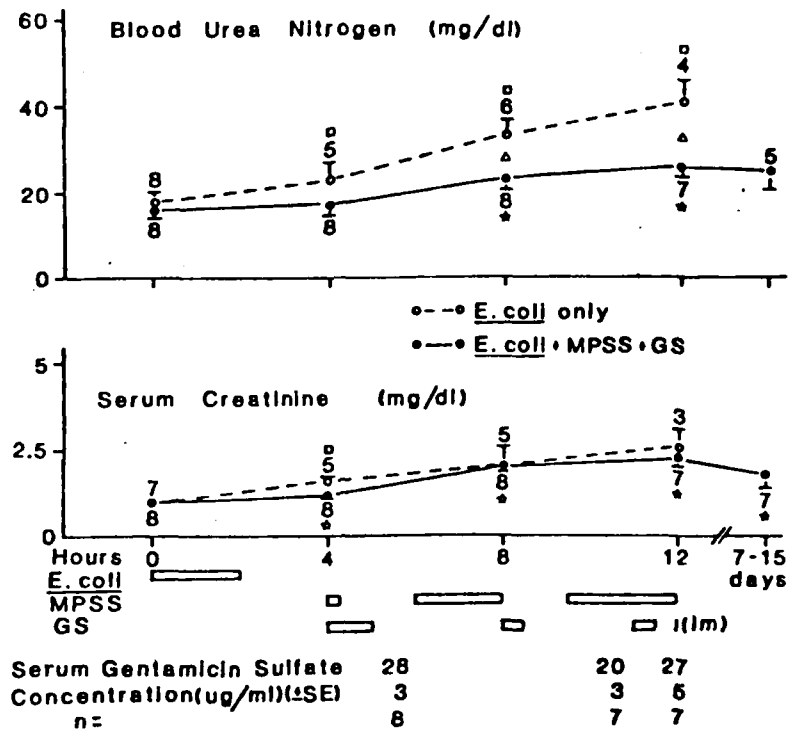


FIGURE 5

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