Endotoxin Shock in the Primate: Treatment with Phenoxybenzamine *

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There is a growing interest in the treatment of endotoxin shock with vasodilating agents. Reports vary as to the relative success of employing drugs such as Apresoline (1-hydrazinophthalazine) (1, 2) and Dibenzyline (phenoxybenzamine) (3, 4) in the treatment of this form of shock. Although most of the work indicates that in the experimental animal increased survival is effected (1–6), others (7) have shown that large doses of phenoxybenzamine actually decrease survival time. The peripheral pooling, stagnation of blood flow, tissue anoxia, and decreased renal function so commonly observed during shock (5, 8, 9) appear to be somewhat improved with vasodilator therapy (4, 5, 10, 11). Limited observations in the human also suggest beneficial effects of such treatment (12, 13), yet definitive studies are lacking and data obtained in the dog may not be transposed to the human. The present study was carried out to assess the effectiveness of phenoxybenzamine in the treatment of endotoxin shock in the monkey and to bridge the gap which naturally exists between data obtained in the dog and that which is applicable to man.

Methods

Seventeen adult male and female monkeys of the Cynapithecoid group, *Cercocebus torquatus Atys* (sooty mangabey), were used in the present study. Animals were anesthetized with ether followed by Surital sodium (thiamylal sodium), given intravenously, in amounts to maintain a surgical stage of anesthesia between planes I and II. Mean systemic blood pressures were obtained by electrical integration and recorded by means of a Statham strain gauge and a Sanborn direct writer.

In the six animals comprising group I, blood pressure, respiratory rate, urine output, hematocrit, and arterial blood pH were determined at hourly intervals before and for 9 hours after a lethal injection of purified *Escherichia coli* endotoxin [1] (7.5 mg per kg). Each

experiment was separately controlled. Paired monkeys of the same sex and comparable age and weight were used. Both monkeys were treated in an identical manner, except one received the therapeutic agent under study, the other an equal volume of saline. Control monkeys received an infusion of 50 ml of sterile saline while the treated were given phenoxybenzamine (0.5 mg per kg) diluted in the same volume of saline and infused between 3 to 6 hours after endotoxin. Survivors were those animals alive 72 hours after endotoxin.

Group II comprised the remaining eleven monkeys, six controls and five treated with phenoxybenzamine. Blood pressure, renal plasma flow (RPF), glomerular filtration rate (GFR), urine output (UO), and the extraction ratio of para-aminohippurate (E_{PAH}) were determined at hourly intervals before and for 6 hours after the injection of 7.5 mg per kg *E. coli* endotoxin. Treated animals were given phenoxybenzamine (0.5 mg per kg) in 50 ml of sterile saline infused between 3 to 6 hours after endotoxin. Control monkeys received only the infusion of saline. Renal functions were calculated by standard clearance techniques previously reported by Hinshaw, Bradley, and Carlson (14). Arterial and venous blood samples for creatinine and para-aminohippurate (PAH) determinations were obtained from catheters placed in the right femoral artery and left renal vein. Urine samples were collected from a plastic catheter inserted and advanced into the left ureter to the level of the renal pelvis. The E_{PAH} was calculated by the formula $E_{PAH} = (A - V)/A$.

Results

Group I. Individual data obtained from the six monkeys comprising this group are shown in Tables I and II. Average values for blood pressure, respiratory rate, urine output, hematocrit, and blood pH observed at hourly intervals in the control and the treated groups of monkeys are shown in Figure 1. The three untreated animals showed progressive hypotension, hyperpnea, oliguria, and anuria after endotoxin. Slight increases in hematocrit and a slow progressive fall in blood pH were also noted. All untreated animals died within 24 hours at an average survival time of 14.2 hours. In contrast, the three monkeys receiving therapy showed recovery

TABLE I

Control endotoxin group*

Time	Monkey 1 wt, 4.9 kg					Monkey 2 wt, 5.0 kg					Monkey 3 wt, 4.7 kg				
	BP	Resp.	UO	Hct	Blood pH	BP	Resp.	UO	Hct	Blood pH	BP	Resp.	UO	Hct	Blood pH
hr	*mm Hg*	*/min*	*ml/hr*			*mm Hg*	*/min*	*ml/hr*			*mm Hg*	*/min*	*ml/hr*		
Control															
1	115	21	4.8	38	7.49	118	25	5.0	40	7.51	121	29	5.2	42	7.53
2	114	22	5.5	40	7.45	118	25	5.9	40	7.50	122	28	6.3	40	7.55
3	115	23	5.9	39	7.46	120	24	6.1	41	7.50	125	25	6.3	43	7.54
4	120	22	6.1	36	7.46	122	24	6.2	41	7.49	124	26	6.4	46	7.52
After endotoxin, *7.5 mg/kg*															
1	42	43	0.9	45	7.49	51	48	1.2	45	7.51	60	53	1.5	45	7.53
2	51	48	0.9	41	7.49	62	52	1.3	44	7.50	73	56	1.7	47	7.51
3	68	53	1.4	41	7.46	72	54	1.5	43	7.48	76	55	1.6	45	7.50
4	63	52	0.7	39	7.44	68	54	0.8	43	7.45	73	56	0.9	47	7.46
5	55	51	0.3	41	7.42	58	53	0.5	42	7.44	61	55	0.7	43	7.46
6	55	50	0.0	41	7.43	60	55	0.2	42	7.43	65	60	0.4	43	7.43
7	54	59	0.2	39	7.41	55	60	0.1	41	7.41	56	61	0.0	43	7.41
8	45	60	0.0	39	7.39	50	62	0.0	40	7.40	55	74	0.0	41	7.41
9	41	58	0.0	40	7.37	45	62	0.0	40	7.38	49	66	0.0	40	7.39
	Survival time, 11.1 hrs					Survival time, 13.6 hrs					Survival time, 18.0 hrs				

* BP = blood pressure, resp. = respiratory rate, UO = urine output, hct. = hematocrit.

of blood pressure and urine output to near control levels, as well as a more alkaline blood pH and a decrease in respiratory rate. All treated animals survived permanently.

Group II. Results of renal function studies carried out in six control and five treated monkeys are shown in Tables III and IV. Included are mean values and ranges. Figure 2 compares average values for blood pressure, RPF, GFR, UO, and E_{PAH} recorded at hourly intervals in the control and treated groups. The six control animals all showed a marked progressive fall in blood pressure and renal function after endotoxin, with the exception of an increase in UO at 3 hours. This increase was due largely to the outpouring of urine in one monkey that subse-

TABLE II

Treated endotoxin group*

Time	Monkey 1 wt, 4.6 kg					Monkey 2 wt, 5.1 kg					Monkey 3 wt, 4.5 kg				
	BP	Resp.	UO	Hct	Blood pH	BP	Resp.	UO	Hct	Blood pH	BP	Resp.	UO	Hct	Blood pH
hr	*mm Hg*	*/min*	*ml/hr*			*mm Hg*	*/min*	*ml/hr*			*mm Hg*	*/min*	*ml/hr*		
1	110	30	4.6	40	7.45	115	32	4.8	42	7.47	120	34	5.0	44	7.49
2	112	30	4.9	42	7.50	116	31	4.9	43	7.51	120	32	4.9	44	7.52
3	111	28	4.9	41	7.50	115	30	5.1	42	7.50	119	32	5.3	43	7.50
4	115	29	5.0	41	7.49	118	29	5.0	41	7.49	121	29	5.0	41	7.49
After endotoxin, *7.5 mg/kg*															
1	50	50	1.8	45	7.47	52	52	2.0	46	7.48	54	53	2.2	47	7.49
2	59	58	0.5	44	7.43	60	60	1.1	48	7.45	61	62	1.7	52	7.47
3†	62	57	0.4	44	7.38	65	59	0.9	45	7.39	68	61	1.4	46	7.40
4	65	43	5.9	43	7.50	70	44	6.1	44	7.53	75	45	6.3	45	7.56
5	70	40	6.3	43	7.50	75	42	6.5	44	7.51	80	44	6.7	45	7.52
6	100	40	6.0	42	7.55	105	40	6.2	43	7.58	110	40	6.4	44	7.61
7	107	41	10.1	41	7.56	112	45	12.4	43	7.60	117	50	14.8	45	7.64
8	100	41	8.8	41	7.61	104	42	10.1	43	7.64	110	43	11.4	45	7.67
9	98	36	9.0	42	7.64	104	38	10.6	42	7.66	106	40	12.2	42	7.68
	Permanent survivor					Permanent survivor					Permanent survivor				

* Abbreviations as in Table I.
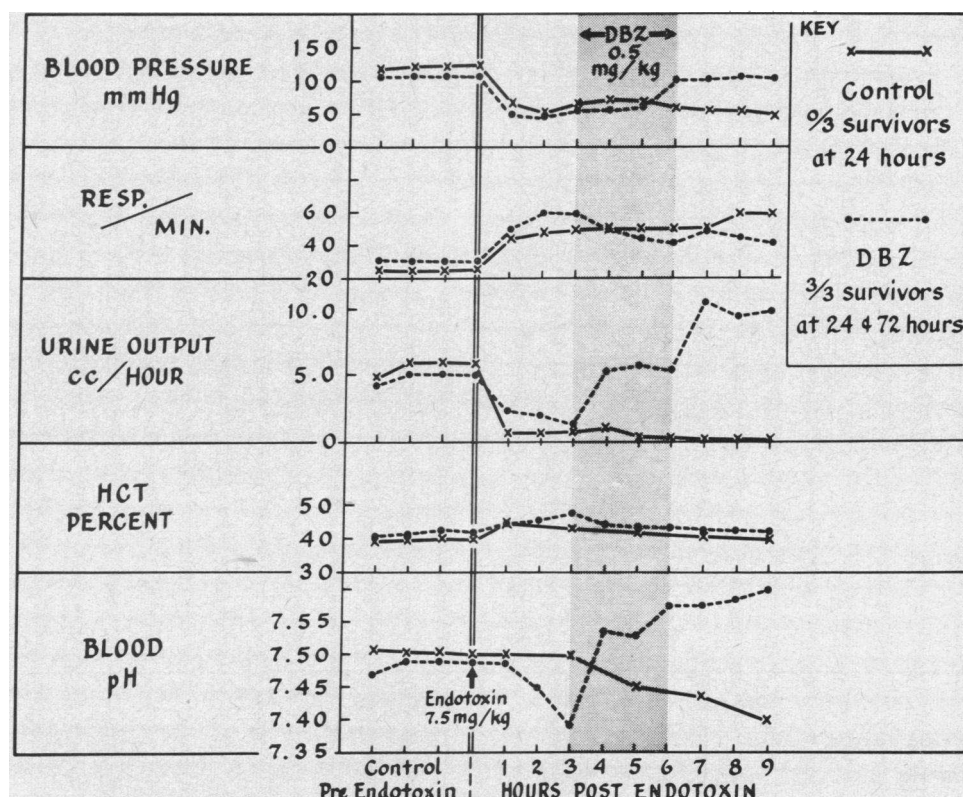† Therapy begun—phenoxybenzamine, 0.5 mg per kg.

FIG. 1. ENDOTOXIN SHOCK IN THE MONKEY. A comparison of mean changes in arterial blood pressure, respiratory rate, urine output, hematocrit, and arterial blood pH observed in three control and three phenoxybenzamine (DBZ)-treated monkeys after a lethal injection of endotoxin.

TABLE III

*Control endotoxin group**

Time	BP	RPF	GFR	UO	E_PAH
hr	mm Hg	ml/kg/min	ml/kg/min	ml/min	
Control					
1	115 (105–120)	16.9 (11.5 –17.8)	3.35 (2.41–4.62)	0.25 (0.19 –0.29)	0.84 (0.69–0.91)
2	120 (110–125)	18.2 (13.6 –20.0)	3.20 (2.22–4.28)	0.19 (0.10 –0.21)	0.76 (0.68–0.84)
3	115 (100–125)	17.1 (12.8 –21.2)	3.25 (2.62–4.91)	0.21 (0.15 –0.26)	0.79 (0.62–0.85)
4	112 (105–125)	17.0 (11.6 –20.8)	3.22 (2.12–5.01)	0.22 (0.11 –0.25)	0.80 (0.70–0.91)
After endotoxin, 7.5 mg/g					
1	90 (60–100)	5.9 (1.8 – 7.5)	1.85 (0.62–2.10)	0.08 (0.01 –0.12)	0.56 (0.28–0.68)
2	60 (40– 85)	3.9 (0.8 – 6.6)	1.15 (0.50–2.05)	0.09 (0.04 –0.11)	0.52 (0.26–0.64)
3	65 (45– 80)	4.8 (0.6 – 6.1)	1.10 (0.40–2.20)	0.18 (0.04 –0.22)	0.16 (0.08–0.51)
4	75 (40– 85)	0.3 (0.1 – 2.5)	0.08 (0.02–0.95)	0.10 (0.08 –0.14)	0.16 (0.06–0.48)
5	50 (30– 65)	0.25 (0.1 – 1.8)	0.09 (0.01–0.65)	0.03 (0.01 –0.08)	0.14 (0.09–0.46)
6	45 (20– 60)	0.20 (0.05– 1.1)	0.01 (0.00–0.85)	0.01 (0.005–0.04)	0.12 (0.05–0.34)

Average survival time, 10.8 hrs

* Six animals. Mean values and ranges (in parentheses) given. BP = blood pressure, RPF = renal plasma flow, GFR = glomerular filtration rate, UO = urine output, E_{PAH} = extraction ratio of para-aminohippurate.

TABLE IV

*Treated endotoxin group**

Time	BP	RPF	GFR	UO	E$_{PAH}$
hr	*mm Hg*	*ml/kg/min*	*ml/kg/min*	*ml/min*	
Control					
1	110 (95–125)	15.4 (9.8–17.4)	3.14 (2.01–4.14)	0.18 (0.11–0.22)	0.74 (0.64–0.86)
2	105 (90–120)	14.9 (11.1–16.8)	2.95 (1.96–3.84)	0.20 (0.09–0.23)	0.76 (0.68–0.91)
3	115 (100–130)	16.1 (12.4–19.8)	3.11 (2.08–4.24)	0.17 (0.12–0.21)	0.77 (0.66–0.89)
4	110 (95–125)	16.2 (12.8–21.2)	3.01 (2.11–4.08)	0.18 (0.11–0.26)	0.77 (0.69–0.90)
After endotoxin, *7.5 mg/g*					
1	80 (45– 95)	4.3 (2.1– 8.1)	0.99 (0.35–2.02)	0.10 (0.05–0.20)	0.48 (0.25–0.68)
2	80 (40– 90)	2.0 (1.1– 4.5)	1.12 (0.28–1.96)	0.09 (0.04–0.18)	0.41 (0.22–0.65)
3†	60 (35– 75)	1.1 (0.5– 2.1)	0.20 (0.06–0.94)	0.03 (0.01–0.05)	0.33 (0.18–0.41)
4	50 (40– 60)	6.8 (2.4–12.8)	0.98 (0.38–3.01)	0.08 (0.02–0.14)	0.29 (0.18–0.44)
5	65 (50– 75)	8.9 (4.1–14.4)	2.24 (0.91–3.58)	0.21 (0.09–0.36)	0.51 (0.24–0.60)
6	95 (55–105)	12.3 (10.1–18.8)	3.44 (2.11–4.85)	0.28 (0.11–0.49)	0.68 (0.48–0.76)

Average survival time, 72.0 hrs

* Five animals. Mean values and ranges (in parentheses) given. Abbreviations as in Table III.
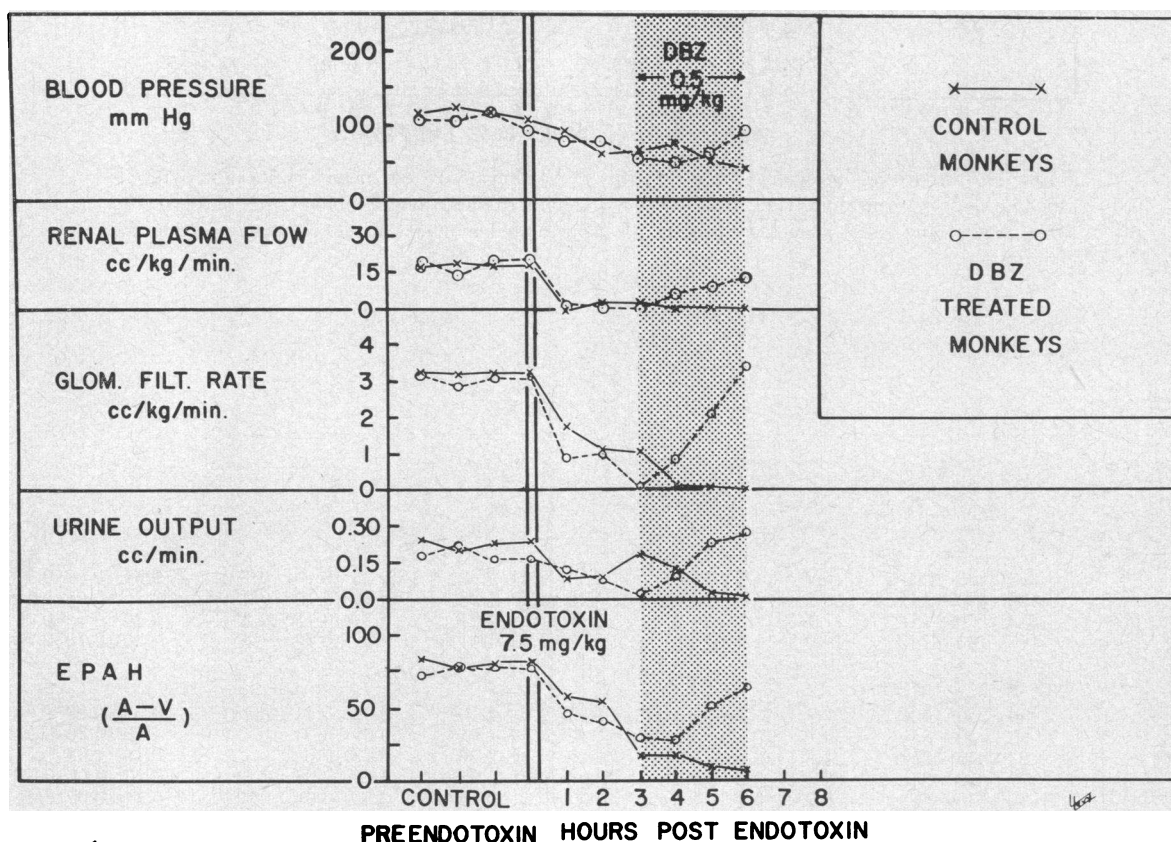† Therapy begun—phenoxybenzamine, 0.5 mg per g.

Fig. 2. Renal function in the shock monkey. Blood pressure and renal function in six control and five phenoxybenzamine (DBZ)-treated monkeys before and after the injection of a lethal dose of endotoxin. EPAH = extraction ratio of para-aminohippurate.

quently developed oliguria and expired 7 hours after endotoxin. The average survival time of this group was 10.8 hours. The five treated animals showed marked recovery in renal parameters within 1 hour after having received the phenoxybenzamine. UO, RPF, and GFR returned to normal or near normal values even after periods of reduced function. The E_{PAH} was also somewhat improved with treatment. All animals in this group survived for 72 hours after having received endotoxin and were sacrificed because of experimental design.

Discussion

Renal failure and decreased peripheral vascular flow are two of the factors contributing to the irreversibility of endotoxin shock (5, 8, 9). The mechanism by which renal shutdown and tissue anoxia occur remains vague in spite of the intense efforts of certain investigators (14, 15). The present study emphasizes the importance of maintaining adequate kidney perfusion and flow to vital tissue during shock. This is impossible in untreated endotoxin shock where the liberation of large amounts of endogenous catecholamines and histamine results in a reduction of flow to vital tissues of the body (16, 17). This decrease in flow is thought to be the combined result of a catecholamine-induced arteriolar vasoconstriction and a histamine-induced venospasm (18). Although the effect of phenoxybenzamine in increasing flow may occur at the expense of pressure, survival data indicate that this is consistent with adequate perfusion of vital tissues and decreased mortality. Renal parameters are also improved with this therapy, and the kidneys appear adequately perfused. The exact mechanism by which phenoxybenzamine favorably influences renal hemodynamics and survival in endotoxin shock is not known, but is most probably due to inhibition of catecholamine and histamine action on peripheral vessels (19). These studies were carried out in the primate and the parameters followed might be of clinical importance in the evaluation and treatment of endotoxin shock in the human.

The apparent conflict between the concept of treatment suggested in this study and that previously reported in which adrenal steroids and vasoconstrictor agents were employed as shock therapy is as yet unresolved (20, 21). This dilemma, however, appears prevalent among many investigators (22, 23).

Summary

The growing interest in the use of vasodilator agents in the treatment of endotoxin shock has prompted the present investigation. Seventeen monkeys were used to study the effects of a lethal injection of endotoxin and subsequent treatment with phenoxybenzamine on renal function and survival in the primate. Progressive hypotension, decreased renal function, and hyperpnea were consistently noted after endotoxin. Results indicate the effectiveness of vasodilator therapy in this form of shock. Renal parameters, such as renal plasma flow, glomerular filtration rate, and the extraction ratio of para-aminohippurate, recover to near normal levels as do the urine output, blood pH, and respiratory rate. Although blood pressure may be maintained at a somewhat lower level with this therapy, results indicate that this is consistent with adequate kidney perfusion and increased survival. The current dilemma of vasoconstrictor versus vasodilator therapy in the treatment of endotoxin shock is noted.

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