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Comparison of Cephalexin, Penicillin V, and Ampicillin in Streptococcal Infections in Monkeys

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Intravenous inoculation of a group A hemolytic streptococcus caused lethal infections in all of 11 untreated monkeys. Daily intragastric administration of either 25 or 50 mg per kg per day, given in two equal morning and afternoon doses, yielded similar results in monkeys treated with cephalexin, penicillin V, and ampicillin; all eight monkeys in each therapy group survived. At dose levels of 12.5 mg per kg per day, six of eight, four of eight, and one of eight receiving cephalexin, penicillin V, and ampicillin, respectively, died. The differences observed at the lower dose level between cephalexin and ampicillin could be attributed, in part, to differences in the minimal inhibitory concentrations (MIC) of cephalexin (MIC = 0.24 μg/ml) and ampicillin (MIC = 0.01 μg/ml). The differences in results between penicillin V, which had the same MIC as ampicillin, could perhaps be attributed, in part, to shorter duration of antibacterial activity and higher protein binding of penicillin V. These studies support previous observations that cephalexin at 25 to 50 mg/kg doses is effective in severe streptococcal sepsis in monkeys.

Cephalexin monohydrate, a new semisynthetic derivative of cephalosporin C, is acid-stable and almost completely absorbed after oral administration (3, 10). Previous studies from this laboratory have demonstrated its efficacy in experimental staphylococcal (6, 9) and streptococcal infections in monkeys (7; S. Saslaw and H. N Carlisle, Am. J. Med. Sci., *in press*). It is the purpose of this report to compare cephalexin to penicillin V and ampicillin in streptococcal infections in monkeys.

MATERIALS AND METHODS

Fifty-nine fully conditioned, young adult monkeys (*Macaca mulatta*) weighing 3.1 to 4.5 kg were used. Base-line observations included physical examinations and serological and bacteriological studies for 2 weeks prior to intravenous (saphenous) challenge with the Stollerman T14 strain of *Streptococcus hemolyticus* group A as previously described (5, 7, 8). Tube dilution sensitivity tests (1) showed that minimal inhibitory concentrations (MIC) of cephalexin, penicillin V, and ampicillin for the streptococcus were 0.24, 0.01, and 0.01 μg/ml, respectively. Oral preparations of the three antibiotics were given by gastric tube, beginning 8 hr postchallenge when monkeys were lethargic, weak, and anorectic but not acutely ill. Daily doses of 50, 25, or 12.5 mg/kg were divided equally and given at 8:00 AM and 5:00 PM for 10 days; infected controls were given only distilled water. The single daily food offering was withheld for at least 1 hr after the 8:00 AM dose. Monkeys were examined at least twice daily for 3 weeks after challenge and daily thereafter for at least 3 months. Laboratory studies included blood cultures, C-reactive protein (CRP) tests, blood urea nitrogen (BUN) levels, and serum antibacterial activity (ABA) (5, 7, 8) against the challenge streptococcus. Complete autopsies were performed on all fatally infected monkeys.

In addition, serum ABA was determined in six pairs of normal monkeys, each given 50 or 25 mg per kg per day of cephalexin, penicillin V, or ampicillin, respectively, for 2 days. The daily dose was divided equally and administered intragastrically at 8:30 AM and 4:30 PM. Blood samples were obtained before and 1, 2, 4, and 8 hr after the morning dose on both days. Food was withheld until after the 2-hr sample.

Binding of the three antibiotics by normal human and monkey serum proteins was compared by the tube dilution method of Kirby et al. (2). Diluents for the antibiotics were Trypticase Soy Broth (BBL) and 50% human and monkey serum prepared by diluting normal serum pools with an equal volume of the same broth. The Stollerman T14 strain of *S. hemolyticus* group A was employed as the test organism. In addition, binding of the three antibiotics by normal human and monkey serum was studied by the ultrafiltration technique of Rolinson and Sutherland (4).

RESULTS

In experiments 1 and 2 (Table 1), the three antibiotics were compared at 50 and 25 mg per kg per day, respectively, in monkeys challenged with 1.4×10^9 and 2.1×10^9 streptococci, respectively. All monkeys in both studies were

TABLE 1. *Effect of dose of cephalexin, penicillin V, and ampicillin on response of rhesus monkeys after intravenous challenge with streptococci*

Antibiotic	Expt	Dose[a]	Mortality	Total	Day of death	Duration (days) of illness in survivors			
						Acute illness	Mean	Total illness	Mean
Cephalexin	1	50.0	0/4[b]	6/16		2, 3, 4, 6	5.0	6, 5, 7, 9	7.6
	2	25.0	0/4			5, 6, 7, 8		6, 7, 12, 10	
	3	12.5	3/4		1, 1, 2	3		6	
	4	12.5	3/4		1, 1, 1	6		8	
Penicillin V	1	50.0	0/4	4/16		4, 5, 6, 7	6.8	7, 8, 10, 8	10.0
	2	25.0	0/4			6, 8, 9, 9		7, 12, 11, 13	
	3	12.5	3/4		1, 4, 7	9		11	
	4	12.5	1/4		1	3, 6, 9		9, 7, 17	
Ampicillin	1	50.0	0/4	1/16		3, 3, 6, 7	5.9	6, 7, 8, 9	8.3
	2	25.0	0/4			5, 5, 6, 9		6, 8, 8, 11	
	3	12.5	1/4		2	5, 6, 8		7, 7, 12	
	4	12.5	0/4			4, 4, 7, 10		6, 8, 10, 12	
Controls	1	None	4/4	11/11	1, 1, 2, 5				
	2	None	3/3		1, 1, 2				
	3	None	2/2		1, 1				
	4	None	2/2		1, 1				

[a] Milligrams per kilogram per day, dose divided equally and given by gastric tube at 8:00 AM and 5:00 PM for 10 days beginning 8 hr after challenge with the Stollerman T14 strain of *S. hemolyticus* group A. Challenge doses in experiments 1, 2, 3, and 4 were 1.4×10^9, 2.1×10^9, 2.4×10^9, and 1.6×10^9 streptococci, respectively.

[b] Number that died over total number.

weak, lethargic, and anorectic when therapy was started 8 hr after challenge. All seven untreated controls became progressively worse and died by day 5. At autopsy, splenomegaly, pericardial effusion, and hemorrhage and congestion of the lungs were the main findings; group A streptococci were isolated from heart blood and all major organs of all monkeys.

All 24 treated monkeys in experiments 1 and 2 survived. Four monkeys in each of three groups receiving daily doses of 50 mg/kg of cephalexin penicillin V, and ampicillin, respectively, in experiment 1 began to show clinical improvement after only 2 to 6, 4 to 7, and 3 to 7 days, respectively, of therapy; all appeared well after days 9, 10, and 9, respectively. Of those given the lower dose, 25 mg per kg per day, in experiment 2, improvement was noted after 5 to 8, 6 to 9, and 5 to 9 days of therapy with cephalexin, penicillin V, and ampicillin, respectively; all were apparently fully recovered after days 12, 13, and 11, respectively. Thus, at the 50 and 25 mg per kg per day dose levels, the clinical response to therapy was similar in the three treatment groups.

In experiments 3 and 4 (Table 1), the daily dose was reduced to 12.5 mg/kg; challenge doses were 2.4×10^9 and 1.6×10^9 streptococci, respectively. In each experiment, groups of four monkeys were treated with each of the three antibiotics, and two monkeys received only distilled water. All four untreated controls were dead by the afternoon of the first day after challenge. Gross pathology was similar to that in controls in experiments 1 and 2, and heart blood and all major organs of all four monkeys yielded group A streptococci when cultured.

Five of eight monkeys treated with cephalexin died on day 1 after receiving only one or two doses. A sixth monkey which had received three doses died on day 2. Clinical, laboratory, and autopsy findings in all six monkeys were similar to those in untreated controls. One of two surviving cephalexin-treated monkeys began to improve after 3 days of therapy and appeared normal on day 7 and thereafter. The other was acutely ill for 6 days, but then recovered rapidly and was active and alert after day 8.

Three of four monkeys given penicillin V in experiment 3 died on days 1, 4, and 7, respectively. The single survivor showed no improvement during the first 9 days of therapy. Subsequent recovery was rapid, however, and complete by day 12. One of four monkeys given penicillin V in experiment 4 received only two doses and died on

day 1. Two of the other three began to improve after 3 and 6 days, respectively, of therapy, and appeared well after days 9 and 7, respectively. The fourth penicillin-treated monkey remained in very poor condition for 9 days and did not recover fully until day 18.

Only one of eight monkeys treated with ampicillin died. Seven survivors were acutely ill for 4 to 10 days, and all were active and alert after day 12.

All 11 treated monkeys that died in experiments 3 and 4 exhibited gross pathology similar to that observed in untreated control monkeys. In addition, group A streptococci were isolated from heart blood and all major organs of all 11 monkeys.

Thus, in experiments 1 to 4 combined, treatment failures were observed in 6 of 16, 4 of 16, and 1 of 16 monkeys given cephalexin, penicillin V, and ampicillin, respectively. Duration of acute illness in survivors treated with cephalexin, penicillin V, and ampicillin ranged from 2 to 8 days (mean, 5.0 days), 3 to 9 days (mean, 6.8 days), and 3 to 10 days (mean, 5.9 days), respectively, whereas time required for complete recovery varied from 5 to 12 days (mean, 7.6 days), 7 to 17 days (mean, 10.0 days), and 6 to 12 days (mean, 8.3 days), respectively. Analysis of mortality data showed that none of the differences was significant at the 5% level. However, duration of acute illness and time to complete recovery both were significantly shorter ($P = 0.05$) in monkeys treated with cephalexin than in those given penicillin V.

Blood cultures (Table 2) and CRP tests became negative at approximately the same time in groups treated with cephalexin, penicillin V, and ampicillin. With few exceptions, blood cultures and CRP tests were negative by therapy days 7 and 9, respectively, in all three study groups. A monkey (no. 17, Table 2) treated with 25 mg of cephalexin per kg per day in experiment 2 exhibited positive blood cultures continuously for 42 days and positive CRP tests intermittently for 35 days. It had recovered fully by therapy day 7, however, and remained normal thereafter. Similarly, a second monkey (no. 19) given 25 mg of cephalexin per kg per day appeared well after therapy day 10, but blood cultures and CRP tests were positive for 14 and 21 days, respectively. The single survivor (no. 34) treated with 12.5 mg of cephalexin per kg per day in experiment 3 had a single positive blood culture on day 14, whereas cultures had been negative on days 4 through 11. CRP tests became positive on days 14 and 17 after having been negative since therapy day 7. No evidence of clinical relapse was noted; the monkey appeared well after therapy day 6 and was active and alert throughout the post-therapy period. Similar bacteriological relapse was observed after therapy was discontinued in two penicillin-treated monkeys (no. 6 and 38) and in one monkey (no. 26) given ampicillin (Table 2). None of the three monkeys showed any signs of clinical relapse, and all CRP tests were negative after treatment was stopped.

Significant increases in BUN (Table 3) were noted on therapy day 2 in 4 of 10, 8 of 12, and 13 of 15 survivors treated with cephalexin, penicillin V, and ampicillin, respectively; values ranged from 31 to 60 mg/100 ml, 30 to 95 mg/100 ml, and 30 to 192 mg/100 ml, respectively. BUN values were normal in 33 of 37 treated survivors on day 4; four given 25 or 12.5 mg of ampicillin per kg per day still showed increased levels (30 to 46 mg/100 ml). All 37 survivors were normal in this respect on days 9, 11, and 14. Two monkeys (no. 36 and 37, Table 3) treated with 12.5 mg of penicillin V per kg per day exhibited BUN values of 184 and 206 mg/100 ml on days 4 and 2, respectively, and died on days 7 and 4, respectively. In the single untreated control that survived long enough to study this aspect, BUN values on days 2 and 4 were 44 and 40 mg/100 ml, respectively, as compared to 17 mg/100 ml prior to challenge; it died on day 5.

Significant increases in antistreptolysin O (ASO) titer were noted in 31 of 37 treated survivors 1 or 2 weeks after challenge. One monkey (no. 27) given 25 mg of ampicillin per kg per day in experiment 2 and two monkeys (no. 43, 55) given 12.5 mg of ampicillin per kg per day in experiments 3 and 4 showed no change in ASO titer until the third week. In one monkey (no. 6) treated with 50 mg of penicillin V per kg per day in experiment 1, the ASO response was delayed for 4 weeks. No increase in ASO titer was observed in two monkeys (no. 54, 56) given 12.5 mg of ampicillin per kg per day in experiment 4. The six monkeys in which the ASO response was delayed or not detected were not unique with respect to duration of illness, positive blood cultures and CRP tests, or to ABA titer. Six of the seven, however, were in ampicillin-treated groups.

Serum ABA of samples obtained 2 hr after the morning dose on therapy days 2, 4, and 9 is shown in Table 3. MIC values of cephalexin, penicillin V, and ampicillin for the challenge streptococcus used in measuring serum ABA were 0.24, 0.01, and 0.01 μg/ml, respectively. In experiments 1 and 2, monkeys treated with 50 and 25 mg of cephalexin per kg per day exhibited ABA titers of 1:8 to 1:32 and 1:2 to 1:16, respectively. Higher titers of 1:16 to 1:256 and 1:8 to 1:128 were observed in monkeys given the same two doses of penicillin V, respectively. Titers in ampicillin-treated monkeys were similar

TABLE 2. *Incidence of positive blood cultures in surviving monkeys treated with cephalexin, penicillin V, and ampicillin after intravenous challenge with streptococci*

Antibiotic	Expt[a]	Dose[b]	Monkey	Days postchallenge[c]													
				3	4	5	7	9	11	14	17	21	24	28	35	42	49, 56
Cephalexin	1 (4)	50.0	1	−	−	−	−	−	−	−	−	−	−	−	−	−	−
			2	−	−	−	−	−	−	−	−	−	−	−	−	−	−
			3	+	−	−	−	−	−	−	−	−	−	−	−	−	−
			4	+	+	−	−	−	−	−	−	−	−	−	−	−	−
	2 (4)	25.0	17	+	+	+	+	+	+	+	+	+	+	+	+	+	−
			18	+	+	+	−	−	−	−	−	−	−	−	−	−	−
			19	+	+	+	+	+	+	+	−	−	−	−	−	−	−
			20	+	+	−	−	−	−	−	−	−	−	−	−	−	−
	3 (1)	12.5	34	+	−	−	−	−	−	+	−	−	−	−	−	−	−
	4 (1)	12.5	48	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Penicillin V	1 (4)	50.0	5	−	−	−	−	−	−	−	−	−	−	−	−	−	−
			6	+	+	−	−	−	+	−	−	−	−	−	−	−	−
			7	+	+	+	−	−	−	−	−	−	−	−	−	−	−
			8	+	−	−	−	−	−	−	−	−	−	−	−	−	−
	2 (4)	25.0	21	+	+	−	−	−	−	−	−	−	−	−	−	−	−
			22	+	+	−	−	−	−	−	−	−	−	−	−	−	−
			23	+	−	−	−	−	−	−	−	−	−	−	−	−	−
			24	+	+	+	−	−	−	−	−	−	−	−	−	−	−
	3 (1)	12.5	38	+	+	−	−	−	−	+	−	−	−	−	−	−	−
	4 (3)	12.5	50	+	+	−	−	−	−	−	−	−	−	−	−	−	−
			51	+	+	−	−	−	−	−	−	−	−	−	−	−	−
			52	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Ampicillin	1 (4)	50.0	9	+	+	−	−	−	−	−	−	−	−	−	−	−	−
			10	+	+	+	−	−	−	−	−	−	−	−	−	−	−
			11	−	−	−	−	−	−	−	−	−	−	−	−	−	−
			12	−	−	−	−	−	−	−	−	−	−	−	−	−	−
	2 (4)	25.0	25	+	−	−	−	−	−	−	−	−	−	−	−	−	−
			26	+	+	−	−	−	+	+	+	+	+	+	+	−	−
			27	+	+	+	+	−	−	−	−	−	−	−	−	−	−
			28	+	−	−	−	−	−	−	−	−	−	−	−	−	−
	3 (3)	12.5	41	+	+	−	−	−	−	−	−	−	−	−	−	−	−
			42	+	−	−	−	−	−	−	−	−	−	−	−	−	−
			43	+	+	−	−	−	−	−	−	−	−	−	−	−	−
	4 (4)	12.5	54	+	−	−	−	−	−	−	−	−	−	−	−	−	−
			55	+	−	−	−	−	−	−	−	−	−	−	−	−	−
			56	+	−	−	−	−	−	−	−	−	−	−	−	−	−
			57	−	−	−	−	−	−	−	−	−	−	−	−	−	−

[a] Number in parentheses represents number of survivors.
[b] Values expressed as milligrams per kilogram per day.
[c] All blood cultures negative before challenge. Therapy discontinued on the 10th day.

to those in monkeys given penicillin, and ranged from 1:16 to 1:128 and 1:8 to 1:64 in the 50 and 25 mg per kg per day groups, respectively. In experiments 1 and 2 combined, ABA titers were lower on day 9 than on day 2 in six of eight, seven of eight, and eight of eight monkeys treated with cephalexin, penicillin V, and ampicillin, respectively.

In experiments 3 and 4, monkeys receiving only 12.5 mg of cephalexin per kg per day showed ABA titers of 1:2 to 1:8 as compared to 1:8 to 1:32 and 1:2 to 1:16 in those given 50 and 25 mg per kg per day, respectively, in experiments 1 and 2. Titers in monkeys treated with 12.5 mg of penicillin V or ampicillin per kg per day were variable, and, in general, monkeys with higher ABA titers were those that showed marked increases in BUN (Table 3). For example, three monkeys given penicillin V in experiment 4 exhibited ABA titers of 1:8, 1:64, and 1:2 on day 2; correspond-

TABLE 3. *Serum antibacterial activity and blood urea nitrogen levels in monkeys treated with cephalexin, penicillin V, and ampicillin after intravenous challenge with streptococci*

Expt[a]	Antibiotic	Monkey no.	Day 0	Day 2[b]		Day 4		Day 9	
			BUN[c]	ABA[d]	BUN	ABA	BUN	ABA	BUN
1	Cephalexin	1	12	16	21	16	15	8	12
		2	13	8	60	16	23	8	9
		3	20	8	27	8	11	8	12
		4	11	32	40	16	15	8	12
	Penicillin V	5	13	32	24	16	15	16	9
		6	11	256	44	32	13	64	9
		7	15	64	41	64	13	256	9
		8	17	64	42	32	19	32	17
	Ampicillin	9	17	64	36	16	14	32	12
		10	19	128	36	32	21	16	19
		11	21	64	31	32	19	32	12
		12	23	128	39	32	19	64	8
	Control	14	17		44		40		D5[e]
2	Cephalexin	17	17	16	31	16	20	8	14
		18	19	16	45	4	21	4	15
		19	17	8	14	2	25	2	12
		20	21	16	21	8	18	4	13
	Penicillin V	21	13	128	13	64	15	16	11
		22	17	32	30	16	15	16	21
		23	24	64	23	32	11	8	12
		24	19	64	47	32	26	16	14
	Ampicillin	25	15	32	38	32	19	8	9
		26	16	16	55	16	27	8	15
		27	23	64	125	64	46	16	21
		28	18	64	30	64	30	16	12
3	Cephalexin	34	12	8	26	2	13	2	13
	Penicillin V	36	24	32	101	64	184	D7	
		37	19	32	206	D4			
		38	25	8	39	4	23	8	12
	Ampicillin	41	18	32	94	32	15	32	12
		42	23	64	192	64	43	64	12
		43	17	64	44	32	17	32	13
4	Cephalexin	48	23	4	28	4	20	4	16
	Penicillin V	50	20	8	39	8	20	2	17
		51	22	64	95	32	29	4	14
		52	16	2	22	4	21	2	22
	Ampicillin	54	17	8	31	64	14	4	17
		55	21	128	91	16	44	8	33
		56	17	4	20	32	13	16	18
		57	18	16	15	32	9	32	14

[a] In experiment 1, dose levels were 50 mg per kg per day. In experiment 2, dose levels were 25 mg per kg per day. In experiments 3 and 4, dose levels were 12.5 mg per kg per day.

[b] Sample taken 2 hr after morning dose on therapy days 2, 4, and 9.

[c] Blood urea nitrogen (mg/100 ml of serum). Normal values in humans, 5 to 25 mg/100 ml.

[d] Antibacterial activity expressed as reciprocal of serum dilution inhibitory for challenge streptococcus in tube dilution (broth) test. MIC values of cephalexin, penicillin V, and ampicillin for the streptococcus were 0.24, 0.01, and 0.01 μg/ml, respectively.

[e] Died on day 5.

TABLE 4. *Antibacterial activity of serum from normal monkeys given cephalexin, penicillin V, and ampicillin*

Antibiotic	Dose[a]	Monkey	Day 1 (hr after 8:30 AM dose)					Day 2 (hr after 8:30 AM dose)					
			0	1	2	4	8	0	1	2	4	8	16[b]
Cephalexin	50	60	—	64[c]	32	2	—	—	64	64	8	—	—
	50	61	—	32	16	16	—	—	64	64	16	—	—
	25	62	—	32	32	2	—	—	64	32	2	—	—
	25	63	—	32	16	8	—	—	64	32	2	—	—
Penicillin V	50	64	—	128	256	4	—	—	512	64	—	—	—
	50	65	—	128	256	—	—	—	512	64	4	—	—
	25	66	—	256	128	4	—	—	256	64	—	—	—
	25	67	—	512	128	4	—	—	512	128	2	—	—
Ampicillin	50	68	—	128	512	64	4	—	256	256	16	8	—
	50	69	—	512	512	32	8	—	512	256	16	8	—
	25	70	—	256	512	4	—	—	256	256	4	—	—
	25	71	—	256	64	8	8	—	256	64	4	—	—

[a] Values expressed as milligrams per kilogram per day.
[b] Sixteen hr after 4:30 PM dose on day 2.
[c] Reciprocal of serum dilution inhibitory for Stollerman T14 strain of *S. hemolyticus* group A in tube dilution (broth) test. Dash (—) indicates no inhibition at 1:2, the lowest dilution tested. MIC values of cephalexin, penicillin V, and ampicillin for the streptococcus were 0.24, 0.01, and 0.01 μg/ml, respectively.

ing BUN values were 39, 95, and 22 mg/100 ml. Similarly, in the group of four monkeys receiving ampicillin in experiment 4, the one (no. 55) with the highest ABA titer, 1:128, also had the highest BUN, 91 mg/100 ml.

Antistreptococcal activity in serum of *normal* monkeys receiving daily doses of 50 or 25 mg/kg of cephalexin, penicillin V, and ampicillin for 2 days was compared (Table 4). With all three antibiotics, ABA titers at 1 and 2 hr on both days were not dose-dependent and varied from 1:16 to 1:64, 1:64 to 1:512, and 1:64 to 1:512 in monkeys given cephalexin, penicillin V, and ampicillin, respectively. Four monkeys receiving cephalexin exhibited titers of 1:2 to 1:16 at 4 hr on both days, but no ABA (< 1:2) was detected at 8 hr on either day. Three of four moneys given penicillin V showed titers of 1:4 at 4 hr on day 1, but no activity was observed at this time in serum from the fourth monkey. Similar results were obtained at 4 hr on day 2. Thus, ABA titers declined more rapidly between 2 and 4 hr in monkeys receiving penicillin V than in those given cephalexin. As with cephalexin, no activity was detected at 8 hr on either day in sera from monkeys given penicillin V. In contrast, sera from three of four and two of four monkeys receiving ampicillin still showed significant activity at 8 hr on days 1 and 2, respectively, and titers at 4 hr were higher on both days than in monkeys given penicillin V (Table 3). Thus, antibiotic activity persisted longest in normal monkeys given ampicillin, followed by cephalexin and penicillin in that order.

TABLE 5. *Comparison of normal human and monkey serum protein binding of cephalexin, penicillin V, and ampicillin*

Antibiotic	Ultrafiltration method (95% serum)		Tube dilution method[a] (50% serum)	
	Human	Monkey	Human	Monkey
Cephalexin	9[b]	11	—[c]	—
Penicillin V	68	60	50	56
Ampicillin	20	14	17	13

[a] Test organism: *S. hemolyticus* group A, Stollerman T14 strain.
[b] Per cent of antibiotic bound.
[c] Method not applicable since degree of binding varies with cephalexin concentration. For example, protein binding of 6, 9, 13, 20 and 41% was observed with concentrations of 3.2, 1.6, 0.8, 0.4, and 0.2 μg/ml, respectively (R. S. Griffith, *personal communication*). Test results depend on sensitivity of test organism used.

Measurement of the degree of serum-protein binding of cephalexin by the ultrafiltration technique, using 10 μg/ml in 95% serum, showed that only 9 and 11% of the antibiotic was bound by human and monkey serum, respectively (Table 5). Penicillin V and ampicillin, also studied at a

concentration of 10 μg/ml, showed 68 and 20% binding, respectively, by human serum, as compared to 60 and 14%, respectively, by monkey serum. Use of the tube dilution method showed 50 and 17% binding of penicillin V and ampicillin, respectively, by 50% human serum and 56 and 13%, respectively, by 50% monkey serum.

DISCUSSION

Under the conditions of these studies, comparable results were obtained in streptococcal sepsis in monkeys after oral administration of 25 or 50 mg per kg per day of cephalexin, penicillin V, and ampicillin; all monkeys so treated survived while all controls died. In studies employing doses of 12.5 mg per kg per day, however, six of eight cephalexin-treated monkeys and four of eight penicillin-treated monkeys died, as compared to only one of eight deaths in those receiving ampicillin. The differences in results between the cephalexin and ampicillin therapy groups at this low dose could be due, in part, to the greater sensitivity of the streptococcus to ampicillin (MIC = 0.01 μg/ml) as compared to cephalexin (MIC = 0.24 μg/ml). This reasoning, however, could not be carried over to explain the higher mortality in the penicillin-treated monkeys, since the MIC for the streptococcus was the same with penicillin V and ampicillin. It is conceivable that the longer duration of ABA noted after ampicillin, as well as the lower protein-binding of this agent, could account in part for the observed differences in response. Administration of the antibiotics more frequently than twice daily, as done in this study, could clarify the former point. Such studies are in progress.

These studies also confirm previous observations (6, 7, 9; S. Saslaw and H. N. Carlisle, Amer. J. Med. Sci., *in press*) that the BUN is frequently increased early in the course of infection, and the rapid return to normal levels during therapy suggests lack of renal toxicity of the new antibiotic, cephalexin, at the dose levels studied. In this respect, all three antbiotics were similar.

The comparable serum-protein binding by human and monkey sera of the three antibiotics studied adds further support to previous observations (9; S. Saslaw and H. Carlisle, Am. J. Med. Sci., *in press*) that man and monkey are similar in this respect.

The present studies afford additional confidence in the ultimate clinical application of cephalexin. Previous studies comparing cephalexin to semisynthetic penicillins demonstrated the efficacy of this drug in staphylococcal sepsis (6, 9) at a dose of 50 mg per kg per day, and in streptococcal sepsis at doses of 25 to 50 mg per kg per day (7, 8). The present study shows that, with the administration of 25 to 50 mg per kg per day, results comparable to those observed with penicillin V and ampicillin were obtained in streptococcal infections. Preliminary studies in humans have also indicated the effectiveness of cephalexin in streptococcal and staphylococcal infections (R. J. Fass, R. L. Perkins, and S. Saslaw, Amer. J. Med. Sci., *in press*).

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