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Therapy of Staphylococcal Infections in Monkeys

VI. Comparison of Clindamycin, Erythromycin, and Methicillin

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Intravenous inoculation of a penicillin-resistant, phage type 80/81 staphylococcus caused lethal infection in six of eight untreated monkeys. Daily intragastric administration of clindamycin hydrochloride and erythromycin stearate and intramuscular inoculation of clindamycin-2-phosphate and methicillin, all at a dose level of 50 mg/kg, was followed by mortalities of one of eight, one of eight, none of eight, and one of eight monkeys, respectively. Duration of obvious acute illness in surviving monkeys and time required for complete recovery were not significantly different in the four therapy groups with the exception that duration of acute illness in monkeys treated with clindamycin-2-phosphate (mean, 4.1 days) was significantly shorter than in monkeys given erythromycin stearate (mean, 7.1 days). In vitro sensitivity data and serum antibacterial levels would suggest that methicillin would be the least effective therapeutically, followed by erythromycin stearate and the two clindamycin preparations in that order. However, this prediction was not fulfilled in these studies in experimentally infected monkeys.

Clindamycin [7(S)chloro-7-deoxy-lincomycin] differs from lincomycin by the exchange of a chlorine atom for a hydroxyl group and the inversion of the involved 7 carbon (3). The antibacterial spectrum of both antibiotics is essentially identical, but studies on absorption have suggested that dose requirements are lower with clindamycin (2). The purpose of this study is to compare the efficacy of the oral preparation clindamycin hydrochloride to an injectable modification, the phosphate ester [7(S)chloro-7-deoxy-lincomycin-2-phosphate], in experimental staphylococcal infections in monkeys. In addition, concomitant studies were conducted with another oral antibiotic, erythromycin stearate, and an injectable agent, methicillin.

MATERIALS AND METHODS

Forty fully conditioned, young adult monkeys (*Macaca mulatta*) weighing 2.9 to 4.0 kg were used. Base-line physical examinations and bacteriological studies were conducted for 2 weeks prior to intravenous (saphenous) challenge with a penicillin-resistant *Staphylococcus aureus* phage type 80/81 as previously described (6, 7, 9, 10, 13, 14). Minimal inhibitory concentrations (MIC) of clindamycin base, erythromycin base, and methicillin for the staphylococcus were 0.039, 0.078, and 1.95 μg/ml, respectively. Contents of capsules containing 150 mg of clindamycin hydrochloride were suspended in distilled water to a concentration of 25 mg/ml. Similarly, erythromycin stearate tablets were ground in a mortar and pestle to a fine powder which was suspended in distilled water to a concentration of 25 mg/ml. Clindamycin hydrochloride capsules and injectable solution of clindamycin-2-phosphate were kindly provided by R. M. DeHaan. Erythromycin stearate tablets and methicillin were obtained by direct purchase from a local pharmacy. Therapy was initiated 16 hr after challenge when clinical and laboratory findings consistent with well-established infection were present. The daily dose of 50 mg/kg was divided equally and given by gastric tube (clindamycin hydrochloride and erythromycin stearate) or intramuscularly (clindamycin-2-phosphate and methicillin) at 8:00 AM and 5:00 PM for 12 days; infected controls received distilled water by gastric tube or saline intramuscularly. The single daily food offering was withheld for at least 1 hr after the morning 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, serum glutamic-pyruvic transaminase (SGPT) levels, and serum antibacterial activity (ABA) against the challenge staphylococcus. Complete autopsies were performed on all fatally infected animals.

In addition, serum antibiotic levels were determined in three groups of four normal monkeys, each given 50 mg per kg per day of clindamycin hydrochloride, clindamycin-2-phosphate, and methicillin, respectively, and in three normal monkeys given the same dose of erythromycin stearate, for 2 days. The daily dose was divided equally and given at 8:00 AM and 5:00 PM. Blood samples were obtained before and

TABLE 1. *Effect of therapy with clindamycin hydrochloride, clindamycin-2-phosphate, erythromycin stearate, and methicillin on response of rhesus monkeys after intravenous challenge with staphylococci*

Antibiotic[a]	Expt	Mortality	Total	Day of death	Acute illness (day)	Mean	Total illness (day)	Mean
Clindamycin hydrochloride	1	1/4[b]	1/8	4	5, 6, 9	5.3	9, 15, 29	15.6
	2	0/4			3, 4, 5, 5		9, 15, 10, 22	
Clindamycin-2-phosphate	1	0/4	0/8		2, 2, 3, 6	4.1	6, 8, 7, 10	10.9
	2	0/4			3, 3, 6, 8		10, 10, 23, 13	
Erythromycin stearate	1	1/4	1/8	2	6, 6, 7	7.1	14, 13, 13	15.5
	2	0/4			5, 6, 9, 11		13, 12, 15, 29	
Methicillin	1	1/4	1/8	3	5, 6, 7	5.1	11, 28, 9	13.9
	2	0/4			3, 4, 5, 6		16, 10, 13, 10	
Controls	1	2/4	6/8	2, 4	8, 9	8.5	14, 24	19.0
	2	4/4		2, 2, 2, 3				

[a] Fifty milligrams per kg per day divided equally and given by gastric tube (clindamycin hydrochloride and erythromycin stearate) or intramuscularly (clindamycin-2-phosphate and methicillin) at 8:00 AM and 5:00 PM for 12 days beginning 16 hr after challenge with *S. aureus* 80/81. Challenge doses in experiments 1 and 2 were 5.2×10^{10} and 9.8×10^{10} staphylococci, respectively.

[b] Number that died over total number.

1, 2, 4, and 8 hr after the 8:00 AM dose on both days. Food was withheld until after the 2-hr sample.

Serum ABA was measured as previously described (1, 4). In brief, serial twofold dilutions of serum were prepared in 0.5-ml amounts of Trypticase Soy-Broth (TSB; BBL). Each tube was inoculated with 0.05 ml of a 1:1,000 dilution in TSB of a 6-hr TSB culture of the challenge staphylococcus. Tests were incubated at 37 C for 16 to 18 hr; inhibitory end points were read as the greatest serum dilution showing no growth on visual examination in a good light.

RESULTS

The four antibiotics were compared at 50 mg per kg per day in two experiments (Table 1). Challenge doses in experiments 1 and 2 were 5.2×10^{10} and 9.8×10^{10} staphylococci, respectively. In both studies, all monkeys were moderately to acutely ill when therapy was initiated at 16 hr postchallenge; the four therapy and control groups were similar in this respect. Increasing lethargy, weakness, and anorexia in six of eight untreated control monkeys was followed by prostration, coma, and death on days 2 to 4 (Table 1). Blood cultures and CRP tests were positive up to death in all six monkeys. At autopsy, the main findings were hemorrhage and congestion of the lungs, pericardial effusion, and splenomegaly; staphylococci were isolated from heart blood and all major organs of all six monkeys. In addition, the untreated control monkey that died on day 4 exhibited multiple myocardial abscesses which yielded staphylococci when cultured. The remaining two untreated controls were acutely ill for 8 and 9 days, respectively, began to recover slowly, and did not appear normal until days 15 and 25, respectively.

All eight monkeys treated with clindamycin-2-phosphate survived (Table 1). One of eight monkeys in each of the three groups given clindamycin hydrochloride, erythromycin stearate, and methicillin, respectively, did not respond to therapy and died on days 4, 2, and 3, respectively. All three monkeys exhibited gross pathology similar to that observed in untreated control monkeys, and heart blood and all major organs yielded staphylococci when cultured. Thus, from the standpoint of mortality, the response to therapy was similar in the four treatment groups.

The seven surviving monkeys treated with clindamycin hydrochloride began to improve after 3 to 9 days (mean, 5.3 days) of therapy and appeared normal after 9 to 29 days (mean, 15.6 days). One (no. 4, Tables 2 and 3) of the seven monkeys became progressively worse during the first 3 days of therapy and on day 4 was prostrate on the bottom of the cage with all reflexes markedly diminished. On day 5, however, the monkey was sitting up in the cage but was still acutely ill. It remained so through therapy day 9, and subsequent slow recovery was not complete until day 30.

The eight survivors given clindamycin-2-phosphate began to show improvement after 2 to 8 days (mean, 4.1 days) of therapy and were apparently fully recovered after 6 to 23 days (mean, 10.9 days). In contrast, the seven survivors treated with erythromycin stearate showed no change during the first 5 to 11 days (mean, 7.1 days) of therapy and did not appear normal until after 12 to 29 days (mean, 15.5 days).

The seven methicillin-treated monkeys that survived remained acutely ill for 3 to 7 days (mean, 5.1 days) and appeared well after 9 to 28

TABLE 2. *Incidence of positive blood cultures in surviving monkeys treated with clindamycin hydrochloride, clindamycin-2-phosphate, erythromycin stearate, and methicillin after intravenous challenge with staphylococci*

Antibiotic[a]	Expt[b]	Monkey	Blood culture at postchallenge day[c]											
			3	5	7	9	11	12[d]	14	17	21	28	35	42, 49, 56
Clindamycin hydrochloride	1 (3)	1	+	+	−	−	—[e]		−	−	−	−	−	−
		3	+	+	−	−			−	−	−	−	−	−
		4	+	+	+	−			−	−	−	−	−	−
	2 (4)	21	+	+	+	+	+		+	−	−	−	−	−
		22	+	+	+	+	+		−	−	−	−	−	−
		23	+	−	−	−	−		−	−	−	−	−	−
		24	+	+	−	−	−		−	−	−	−	−	−
Clindamycin-2-phosphate	1 (4)	5	+	−	−	−			−	−	−	−	−	−
		6	+	+	+	−			−	−	−	−	−	−
		7	+	+	−	−			−	−	−	−	−	−
		8	+	−	−	−			+	−	−	−	−	−
	2 (4)	25	+	+	−	−	−		−	+	−	−	−	−
		26	+	+	−	−	−		+	+	+	+	+	−
		27	+	+	−	−	−		−	−	−	−	−	−
		28	+	+	−	−	−		−	−	−	−	−	−
Erythromycin stearate	1 (3)	9	+	+	+	+			+	+	+	−	−	−
		10	+	+	+	+			+	+	−	−	−	−
		12	+	+	−	−			+	+	+	−	−	−
	2 (4)	29	+	+	+	+	+		−	−	−	−	−	−
		30	+	+	+	+	+		+	+	−	−	−	−
		31	+	+	+	+	+		+	+	+	+	+	−
		32	+	+	−	−	−		−	+	+	−	−	−
Methicillin	1 (3)	13	+	−	−	−			−	−	−	−	−	−
		15	+	+	−	−			+	+	+	−	−	−
		16	+	+	+	+			+	−	−	−	−	−
	2 (4)	33	+	+	−	−	−		−	−	−	−	−	−
		34	+	+	+	+	+		−	−	+	−	−	−
		35	+	+	+	+	+		+	+	+	+	−	−
		36	+	+	+	+	+		−	+	+	−	−	−
Controls	1 (2)	17	+	+	+	+			+	+	+	+	−	−
		18	+	+	+	+			+	+	+	−	−	−
	2 (0)													

[a] Dose of 50 mg per kg per day.
[b] Number in parentheses represents number of survivors.
[c] All blood cultures negative before challenge.
[d] Therapy discontinued on the 12th day.
[e] Blood cultures not obtained on 11th day in experiment 1 due to campus disruptions.

days (mean, 13.9 days). One (no. 15, Tables 2 and 3) of the seven monkeys began to improve after 6 days of therapy and was apparently normal by day 13. However, it appeared lethargic, weak, and anorectic on day 17 and became progressively worse during days 18 to 25. Subsequent recovery was rapid and complete by day 29. Blood cultures (Table 2) were positive on days 3 and 5, negative during the remainder of the 12-day therapy period, positive again from days 14 to 21, and negative on day 28 and subsequently. Similar clinical relapse after therapy was discontinued was not observed in any of the other 28 treated monkeys that survived.

Thus, in summary, treatment failures were observed in one of eight, none of eight, one of eight, and one of eight monkeys given clindamycin hydrochloride, clindamycin-2-phosphate, erythromycin stearate, and methicillin, respectively. Analysis of data pertaining to duration of acute illness and time required for complete recovery showed that none of the observed differences was significant at the 5% level with the single exception that duration of acute illness in monkeys treated with clindamycin-2-phosphate was significantly shorter ($P = 0.05$) than in those given erythromycin stearate.

Blood cultures were not obtainable in experi-

TABLE 3. *Serum antibacterial activity in monkeys treated with clindamycin hydrochloride, clindamycin-2-phosphate, erythromycin stearate, and methicillin after intravenous challenge with straphylococci*

Antibiotic[a]	Antibacterial activity: expt 1				Antibacterial activity: expt 2			
	Monkey no.	Day 2[b]	Day 4	Day 9	Monkey no.	Day 2	Day 4	Day 9
Clindamycin hydrochloride	1	128[c]	128	32	21	128	128	32
	2	128	D4[d]		22	128	512	32
	3	64	128	64	23	256	128	64
	4	64	128	32	24	128	64	64
Clindamycin-2-phosphate	5	128	128	128	25	512	256	256
	6	128	128	128	26	512	256	128
	7	512	512	256	27	256	512	128
	8	256	512	256	28	512	512	256
Erythromycin stearate	9	16	64	32	29	128	64	8
	10	128	32	4	30	64	128	64
	11	D2			31	128	256	128
	12	128	128	2	32	128	128	32
Methicillin	13	<2	<2	<2	33	<2	<2	2
	14	2	D3		34	<2	2	<2
	15	<2	2	<2	35	<2	2	<2
	16	2	2	2	36	2	2	<2

[a] Dose of 50 mg per kg per day.
[b] Sample taken 2 hr after morning dose on therapy days 2, 4, and 9.
[c] Antibacterial activity expressed as reciprocal of serum dilution inhibitory for the challenge staphylococcus in tube dilution (broth) test. Minimal inhibitory concentration values of clindamycin base, erythromycin base, and methicillin for the staphylococcus were 0.039, 0.078, and 1.95 μg/ml, respectively.
[d] Died on day 4.

ment 1 on day 11 (Table 2), the day before therapy was discontinued. On day 9, however, cultures were negative in all eight monkeys treated with clindamycin-2-phosphate, whereas two of seven, five of seven, and four of seven monkeys given clindamycin hydrochloride, erythromycin stearate, and methicillin, respectively, still showed positive cultures at this time. Similarly, none of the four monkeys treated with clindamycin-2-phosphate in experiment 2 exhibited positive blood cultures on day 11, whereas positive cultures were obtained on this day from two of four, three of four, and three of four monkeys given clindamycin hydrochloride, erythromycin stearate, and methicillin, respectively. Blood cultures became positive after therapy was discontinued in three of the eight monkeys treated with clindamycin-2- phosphate. For example, cultures from one monkey (no. 26, Table 2) were positive on therapy days 3 and 5, negative on days 7, 9, and 11, positive again on days 14 through 35, and negative on day 42 and thereafter. Similar bacteriological relapse was observed in two monkeys in each of the two groups of seven monkeys treated with erythromycin stearate and methicillin, respectively, but not in any of the seven monkeys given clindamycin hydrochloride. None of these eight monkeys in which blood cultures returned to positive after therapy was discontinued exhibited any signs of clinical relapse. One additional monkey (no. 15, Table 2) in the methicillin-treated group did show clinical relapse with associated positive blood cultures, as discussed previously. In the two surviving untreated controls, blood cultures were positive for at least 21 and 28 days, respectively.

Both untreated control monkeys that survived exhibited positive CRP tests continuously for 28 days. In the treated groups, CRP tests became negative by therapy day 9 in three of seven, four of eight, one of seven, and none of seven monkeys given clindamycin hydrochloride, clindamycin-2-phosphate, erythromycin stearate, and methicillin, respectively; in experiment 2, in which an 11-day sample was obtained, tests were negative in three of four, four of four, three of four, and two of four monkeys respectively, on this day. None of the monkeys with negative CRP tests on days 9 or 11 exhibited positive tests after therapy was discontinued with the exception that the methicillin-treated monkey that relapsed clinically showed positive tests on days 17 and 21. Tests became negative by days 17 or 21 in all monkeys that were positive on days 9 or 11; the four therapy

TABLE 4. *Antibacterial activity of serum from normal monkeys given clindamycin hydrochloride, clindamycin-2-phosphate, erythromycin stearate, and methicillin*

Antibiotic[a]	Monkey no.	Antibacterial activity on day 1 (hr after 8:00 AM dose)					Antibacterial activity on day 2 (hr after 8:00 AM dose)					
		0	1	2	4	8	0	1	2	4	8	16[b]
Clindamycin hydrochloride	41	—	64[c]	32	16	8	2	64	32	4	4	2
	42	—	32	16	8	4	4	64	64	32	8	8
	43	—	128	64	4	4	2	128	32	4	2	2
	44	—	64	64	16	4	2	64	32	8	4	2
Clindamycin-2-phosphate	45	—	128	128	4	2	—	256	128	8	2	—
	46	—	256	64	8	2	—	128	64	16	8	—
	47	—	256	128	8	2	—	256	256	64	4	2
Erythromycin stearate	48	—	1024	256	8	—	—	512	128	32	2	—
	49	—	32	16	4	—	—	8	8	2	—	—
	50	—	64	32	8	—	—	8	4	2	—	—
	51	—	8	4	2	—	—	2	2	—	—	—
Methicillin	52	—	2	—	—	—	—	2	—	—	—	—
	53	—	4	2	—	—	—	4	2	—	—	—
	54	—	2	—	—	—	—	2	—	—	—	—
	55	—	4	—	—	—	—	2	—	—	—	—

[a] Dose of 50 mg per kg per day.

[b] Sixteen hours after 5:00 PM dose on day 2.

[c] Reciprocal of serum dilution inhibitory for *S. aureus* 80/81 in tube dilution (broth) test. Dash (—) indicates no inhibition at 1:2, the lowest dilution tested. Minimal inhibitory concentration values of clindamycin base, erythromycin base, and methicillin for the staphylococcus were 0.039, 0.078, and 1.95 μg/ml, respectively.

groups were not significantly different in this respect.

SGPT levels were determined prior to, and at 7, 14, and 28 days after, staphylococcal challenge. Base-line values in the 40 monkeys in experiments 1 and 2 ranged from 9 to 37 units (mean, 20 units) as compared to 15 to 45 units in normal humans. Four treated monkeys that survived exhibited changes in SGPT levels. One monkey given clindamycin hydrochloride showed levels of 14 units on the day of challenge and on day 7, and 105 and 88 units on days 14 and 28, respectively. One erythromycin-treated monkey with SGPT levels of 26 and 28 units on days 0 and 7, respectively, showed 49 units on day 14 and 22 units on day 28. One monkey given clindamycin-2-phosphate intramuscularly had a base-line SGPT level of 32 units, 23 units at 7 days, 55 units at 14 days, and 29 units on day 28. One monkey treated with methicillin which had a base-line SGPT level of 16 units showed 44 and 75 units on days 7 and 14, respectively; no specimen was obtained on day 28. In addition, one of the two untreated control monkeys that survived exhibited an increase in SGPT from 37 units on day 0 to 50 units on day 7 and then a decrease to 16 units on day 14. The above five monkeys were not unique with respect to duration of illness or positive blood cultures and CRP tests. Only two fatally infected monkeys survived long enough for SGPT studies. One monkey treated with clindamycin hydrochloride exhibited a marked increase in SGPT from 12 to 168 units on day 3 and died on day 4. The untreated control monkey that died on day 4 showed 61 units on the day before death as compared to 26 units at the time of challenge.

None of the 16 monkeys given clindamycin-2-phosphate or methicillin exhibited any evidence of local reactoin at the site of intramuscular inoculation during therapy or subsequently. Mild diarrhea beginning on therapy day 5 and ending 2 days after therapy was discontinued was observed in one monkey given clindamycin hydrocloride intragastrically. The remaining 15 monkeys treated with the oral preparation of clindamycin or erythromycin were normal in this respect throughout the observation period.

Serum ABA of samples obtained 2 hr after the 8:00 AM dose on therapy days 2, 4, and 9 is shown in Table 3. MIC values of clindamycin base, erythromycin base, and methicillin for the challenge staphylococcus used in measuring serum ABA were 0.039, 0.078, and 1.95 μg/ml, respectively. Monkeys given clindamycin hydrochloride intragastrically showed ABA titers of 1:64 to 1:512 on therapy days 2 and 4 and less serum ABA (1:32 to 1:64) was noted on day 9. All eight monkeys receiving clindamycin-2-

phosphate showed titers of either 1:128, 1:256, or 1:512 on days 2, 4, and 9. Serum ABA titers in monkeys given erythromycin stearate intragastrically in experiment 1 were generally lower and more variable than in monkeys treated with either of the two clindamycin preparations (Table 3). On days 2, 4, and 9, titers were 1:16 to 1:128, 1:32 to 1:256, and 1:2 to 1:128, respectively. Monkeys treated with methicillin, intramuscularly, exhibited very low levels of serum ABA. Titers of only 1:2 or <1:2 were observed in all monkeys on days 2, 4, and 9 in both experiments.

Antistaphylococcal activity in serum of *normal* monkeys receiving a daily dose of 50 mg/kg of the four antibiotics, respectively, for 2 days was compared (Table 4). In monkeys given clindamycin hydrochloride, serum ABA titers at 1, 2, 4, and 8 hr after the morning dose on day 1 ranged from 1:32 to 1:128, 1:16 to 1:64, 1:4 to 1:16, and 1:4 to 1:8, respectively. Samples obtained before the morning dose on day 2, i.e., about 16 hr after the afternoon dose on day 1, still showed antistaphylococcal activity at dilutions of 1:2 to 1:4. ABA titers at 1, 2, 4, and 8 hr after the morning dose and 16 hr after the afternoon dose on day 2 were similar to those observed on day 1. Monkeys given clindamycin-2-phosphate exhibited ABA titers of 1:128 to 1:1,024 and 1:64 to 1:256 at 1 and 2 hr, respectively, on day 1. At 4 hr, however, titers had declined to only 1:4 to 1:8, and at 8 hr all four monkeys showed titers of only 1:2. No antistaphylococcal activity was detected 16 hr after the 5:00 PM dose on day 1. Results were similar on day 2 except that ABA titers were higher at 4 and 8 hr than on day 1. In addition, serum obtained from one of the four monkeys at 16 hr after the afternoon dose was inhibitory at a dilution of 1:2.

Serum ABA titers in normal monkeys receiving erythromycin stearate were lower than in monkeys given either of the two clindamycin preparations. On day 1, titers of 1:8 to 1:64, 1:4 to 1:32, and 1:2 to 1:8 were observed at 1, 2, and 4 hr, respectively. Lower titers of 1:2 to 1:8,1:2 to 1:8, and <1:2 or 1:2 were noted at 1, 2, and 4 hr on day 2. No ABA was detected in any of the sera obtained after 4 hr on both days.

All four normal monkeys given methicillin exhibited antistaphylococcal titers of 1:2 or 1:4 1 hr after the morning dose on both days. No ABA was observed at any of the subsequent intervals with the exception that one monkey showed titers of 1:2 at 2 hr on both days.

DISCUSSION

Under the conditions of this study, comparable results in reference to mortality were obtained in staphylococcal sepsis in monkeys treated with 50 mg per kg per day of erythromycin stearate and clindamycin hydrochloride intragastrically and methicillin and clindamycin-2-phosphate intramuscularly. All of eight monkeys receiving clindamycin-2-phosphate survived, whereas one of eight monkeys died in each of the other three therapy groups. Duration of obvious acute illness was similar in the four therapy groups except that in those receiving clindamycin-2-phosphate the duration of illness (mean, 4.1 days) was significantly shorter than in those receiving erythromycin stearate (mean, 7.1 days). Blood cultures taken after discontinuation of 12 days of therapy were positive in one of seven, three of eight, six of seven, and five of seven monkeys receiving clindamycin hydrochloride, clindamycin-2-phosphate, erythromycin stearate, and methicillin, respectively. These latter differences could be attributed, in part, to the differences in MIC values of 0.039, 0.078, and 1.95 μg/ml of clindamycin base, erythromycin base, and methicillin, respectively. This, in turn, was reflected by the higher serum ABA in both normal and infected monkeys receiving the clindamycin and erythromycin preparations as compared to the low ABA in methicillin-treated monkeys. Another factor could have been related to duration of activity since significant measureable serum ABA was observed as late as 16 hr after clindamycin hydrochloride administration, 8 hr after clindamycin-2-phosphate injection, and 4 hr after erythromycin ingestion, whereas only one of four normal monkeys showed an ABA titer of 1:2 at 2 hr after injection of methicillin. However, despite the higher MIC of methicillin against the staphylococcus, the lower ABA in sera and its shorter duration, the final outcome in reference to mortality was the same as with the other agents. Discussions concerning the significance of serum levels of antibiotics to relative therapeutic effect have become more frequent in recent years (5). Studies, to date, in this laboratory involved with therapy of experimental staphylococcal (7, 9, 10, 13, 14) and streptococcal (8, 11, 12) sepsis in monkeys have supported the generally held thesis that organisms sensitive in vitro will usually be successfully controlled in sepsis by appropriately selected antibiotics. However, the previous and present studies raise some question concerning the predictability of comparative in vivo efficacy of antimicrobials in relation to the usually employed in vitro data.

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