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Therapy of Staphylococcal Infections in Monkeys

IV. Further Comparison of Triacetyloleandomycin and Erythromycins

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Intravenous inoculation of a penicillin-resistant, phage type 80/81 staphylococcus caused lethal infection in 8 of 15 untreated monkeys. Daily intragastric administration of 50 mg/kg of triacetyloleandomycin, erythromycin estolate, and erythromycin ethylsuccinate was followed by mortalities of 0 of 16, 3 of 16, and 3 of 10, respectively. At dose levels of 25 and 12.5 mg/kg, none of 7 and 4 of 7 receiving triacetyloleandomycin and erythromycin estolate, respectively, died, as compared to 3 of 4 deaths in controls. In vitro sensitivity data and serum antibacterial levels would suggest that triacetyloleandomycin would be the least effective therapeutically. However, this prediction was not fulfilled in these studies of experimental infections in monkeys wherein triacetyloleandomycin was a very effective antimicrobial agent.

Previous studies from this laboratory (5) demonstrated that intravenous inoculation of a penicillin-resistant phage type 80/81 staphylococcus caused lethal infection of all seven untreated rhesus monkeys. Daily intragastric administration of 30 to 50 mg/kg of triacetyloleandomycin and erythromycin ethylsuccinate was followed by mortalities in 2 of 8 and 7 of 8, respectively. Similar studies with intravenous streptococcal infection (6) showed that 13 of 15 untreated monkeys died, whereas only 3 of 15, 5 of 11, and 7 of 11 receiving 50 mg/kg of triacetyloleandomycin, erythromycin estolate, and erythromycin ethylsuccinate, respectively, died. It was the purpose of the present study to compare further the effect of the latter three macrolide antibiotics in experimental staphylococcal infections in monkeys.

MATERIALS AND METHODS

Seventy-five fully conditioned, young adult monkeys (*Macaca mulatta*) weighing 3.0 to 4.4 kg were used. Base line studies were conducted for 2 weeks prior to intravenous challenge with a penicillin-resistant *Staphylococcus aureus* phage type 80/81 as previously described (5, 7, 8). Minimal inhibitory concentrations (MIC) of oleandomycin and erythromycin bases for the staphylococcus were 0.31 and 0.078 μg/ml, respectively. Therapy with oral suspensions of triacetyloleandomycin, erythromycin estolate, and erythromycin ethylsuccinate, hereafter referred to as TO, EE, and ES, respectively, was initiated 16 hr postchallenge when clinical and laboratory findings consistent with well-established, acute infection were present. Daily doses of 50, 25, or 12.5 mg/kg were divided equally and given by gastric tube at 8:00 AM and 5:00 PM for 12 days; infected controls received only distilled water. The single daily feeding was withheld until 1 hr after the morning dose. Monkeys were examined at least twice daily after challenge. Laboratory studies included blood cultures, C-reactive protein (CRP) tests, serum glutamic-oxalacetic transaminase (SGOT) levels, and serum antibacterial activity (ABA) as in previous studies (5-8).

In addition, serum antibiotic levels were determined in four, three, and three normal monkeys given 50, 25, and 12.5 mg per kg per day, respectively, of TO and EE, respectively, and in five normal monkeys given 50 mg per kg per day of ES, 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. Serum ABA levels were determined as described previously (1, 2) by using the challenge staphylococcus as the test organism.

RESULTS

Experiments 1 to 3. TO and EE were compared at 50 mg per kg per day in three separate experiments and both were compared to ES, also at 50 mg per kg per day, in two of the three studies, as shown in Table 1. Challenge doses in experiments 1, 2, and 3 were 6.4×10^{10}, 5.3×10^{10}, and 5.7×10^{10} staphylococci, respectively.

In each of the three studies, all monkeys were acutely ill when therapy was initiated at 16 hr postchallenge; all exhibited positive blood cultures and CRP tests. Increasing lethargy, weak-

TABLE 1. *Effect of therapy with triacetyloleandomycin, erythromycin estolate, and erythromycin ethylsuccinate on response of rhesus monkeys after intravenous challenge with staphylococci*

Antibiotic[a]	Expt no.	Mortality	Total	Day of death	Duration (days) of illness in survivors			
					Acute illness	Mean	Total illness	Mean
Triacetyloleando-mycin	1	0/6[b]			2, 4, 5, 5, 6, 7		8, 12, 10, 11, 13, 13	
	2	0/5	0/16		3, 3, 6, 6, 8	4.9	7, 7, 9, 9, 12	9.9
	3	0/5			3, 3, 5, 6, 7		8, 9, 10, 11, 10	
Erythromycin esto-late	1	1/6		15	4, 5, 6, 7, 11		13, 14, 12, 10, 16	
	2	0/5	3/16		4, 7, 8, 9, 10	7.3	8, 12, 9, 12, 18	12.2
	3	2/5		2, 15	6, 8, 10		11, 11, 13	
Erythromycin ethylsuccinate	2	2/5	3/10	12, 14	13, 17, 18	14.4	19, 20, 29	21.2
	3	1/5		12	7, 11, 14, 21		13, 15, 24, 29	
Controls	1	3/5		2, 3, 5	17, 23		30, 45	
	2	3/5	8/15	4, 5, 7	19, 35	21.1	36, 50	35.6
	3	2/5		4, 5	15, 15, 24		24, 27, 37	

[a] 50 mg per kg per day, dose divided equally and given by gastric tube 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, 2, and 3 were 6.4×10^{10}, 5.3×10^{10}, and 5.7×10^{10} staphylococci, respectively.

[b] Number that died over total number.

ness, and anorexia in 8 of 15 controls was followed by prostration, coma, and death on days 2 to 7 (Table 1). Blood cultures and CRP were positive up to death in all eight monkeys. At autopsy, hemorrhage and congestion of the lungs, pericardial effusion, and splenomegaly were the principal findings, and staphylococci were isolated from heart blood and all major organs. In addition, two that died on day 5 in experiment 1 and on day 7 in experiment 2, respectively, exhibited multiple myocardial abscesses which yielded staphylococci when cultured. The remaining seven untreated controls were acutely ill for 15 to 35 days (mean, 21.1 days) and did not appear normal until after 24 to 50 days (mean, 35.6 days).

All 16 monkeys treated with TO survived. Clinical improvement was noted after 2 to 8 days (mean, 4.9 days) of therapy, and all were apparently fully recovered after 7 to 13 days (mean, 9.9 days). Three of 16 monkeys given EE died, one on day 2 after having received only two doses. Two (no. 60 and 165, Table 3) showed definite improvement during the 12-day therapy period and were only mildly ill when treatment was discontinued. Both, however, relapsed and died on day 15. Blood cultures and CRP were positive in both up to death. At autopsy, no. 60 had multiple, small abscesses in the heart, lungs, and kidneys, which yielded staphylococci when cultured. Staphylococci also were isolated from heart blood and all other major organs of both monkeys. The remaining 13 monkeys given EE began to improve after 4 to 11 days (mean, 7.3 days) of therapy and appeared normal after 8 to 18 days (mean, 12.2 days). Three of 10 monkeys treated with ES became progressively worse during the therapy period and died on days 12, 12, and 14, respectively; all three exhibited myocardial abscesses at autopsy. The remaining seven ES-treated monkeys were acutely ill for 7 to 21 days (mean, 14.4 days) and did not recover fully until after 13 to 29 days (mean, 21.2 days).

Analysis of mortality data (Table 1) by an "exact" method rather than the customary chi-square test showed that TO was significantly more effective ($P = 0.05$) in preventing death than was ES; mortalities in groups treated with TO and EE, and in those given EE and ES, were not significantly different. Data pertaining to duration of illness were analyzed by using Studentized ranges and also by using the statistic U which counts the number of times a measurement in one group exceeds measurements in another group. Both methods yielded the same results. Monkeys treated with TO and EE were not significantly different with respect to duration of acute illness or the time required for complete recovery. Monkeys in both groups were ill for a significantly shorter period ($P = < 0.01$) than were those given ES.

Incidence of positive blood cultures during the therapy period was significantly less ($P = < 0.05$) in monkeys receiving TO than in those receiving EE or ES (Table 2). On day 11, 11 of 13 EE-treated survivors, all 7 given ES, and all 7 controls

TABLE 2. *Incidence of positive blood cultures and C-reactive protein tests in surviving monkeys treated with triacetyloleandomycin, erythromycin estolate, and erythromycin ethylsuccinate after intravenous challenge with staphylococci*

Antibiotic[a]	Expt no.[b]	Days postchallenge																
		Base line	1	3	4	5[d]	7	9	11	12[e]	14	17	21	24	28	31	35	42
Triacetyloleando-mycin	1 (6)	0/0	6/6[c]	6/6	6/6	5/-	2/6	1/5	1/5		3/2	2/1	1/0	1/0	1/0	1/0	0/0	0/0
	2 (5)	0/0	5/5	5/5	4/5	4/-	3/5	3/4	1/4		0/1	1/3	1/0	1/0	0/0	0/0	0/0	0/0
	3 (5)	0/0	5/5	5/5	5/5	4/-	2/5	2/5	2/4		1/1	2/2	0/1	0/0	0/0	0/0	0/0	0/0
Erythromycin estolate	1 (5)	0/0	5/5	5/5	5/5	5/-	5/5	5/5	5/5		4/5	3/5	2/2	1/2	1/0	1/0	0/0	0/0
	2 (5)	0/0	5/5	5/5	5/5	5/-	5/5	5/5	4/5		4/5	3/2	3/1	3/0	3/0	2/0	0/0	0/0
	3 (3)	0/0	3/3	3/3	3/3	3/-	2/3	2/3	2/3		2/1	1/1	1/2	1/1	0/0	0/0	0/0	0/0
Erythromycin ethylsuccinate	2 (3)	0/0	3/3	3/3	3/3	3/-	3/3	3/3	3/3		3/2	2/2	2/2	1/1	0/0	0/0	0/0	0/0
	3 (4)	0/0	4/4	4/4	4/4	4/-	4/4	4/4	4/4		4/3	3/2	2/1	2/0	2/0	2/0	0/0	0/0
Controls	1 (2)	0/0	2/2	2/2	2/2	2/-	2/2	2/2	2/2		2/2	2/2	2/2	1/2	0/2	0/2	0/1	0/0
	2 (2)	0/0	2/2	2/2	2/2	2/-	2/2	2/2	2/2		2/2	2/2	1/1	1/1	1/1	0/1	0/0	0/0
	3 (3)	0/0	3/3	3/3	3/3	3/-	3/3	3/3	3/3		3/3	2/1	1/0	0/0	0/0	0/0	0/0	0/0

[a] 50 mg per kg per day, divided equally and given by gastric tube 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, 2, and 3 were 6.4×10^{10}, 5.3×10^{10}, and 5.7×10^{10} staphylococci, respectively.

[b] Number in parentheses represent number of survivors.

[c] Numerator, number of monkeys showing positive blood culture; denominator, number of monkeys showing positive C-reactive protein test.

[d] C-reactive protein test not done on day 5.

[e] Therapy discontinued.

TABLE 3. *Antibacterial activity of serum from monkeys treated with triacetyloleandomycin, erythromycin estolate, and erythromycin ethylsuccinate after intravenous challenge with staphylococci*

Antibiotic	Expt 1 (50 mg per kg per day)		Expt (50 mg per kg per day)		Expt 3 (50 mg per kg per day)		Expt 4 (25 mg per kg per day)		Expt 4 (12.5 mg per kg per day)	
	Monkey no.	Day[a] 2 and 9	Monkey no.	Day, 2 and 9	Monkey no.	Day, 2 and 9	Monkey no.	Day, 2 and 9	Monkey no.	Day, 2 and 9
Triacetyloleandomycin	64	8, 8[b]	112	8, 8	147	8, 4	89	8, 8	93	4, 4
	65	2, 8	113	8, 8	148	16, 4	90	4, 8	94	2, <2
	66	4, 4	114	8, 8	153	8, 8	91	8, 4	95	2, 2
	67	4, 16	115	8, 8	154	8, 4	92	4, 4		
	68	16, 8	140	4, 8	155	8, 8				
	69	8, 8								
Erythromycin estolate	54	16, 16	121	64, 16	157	64, 32	96	16, D3[c]	106	4, 32
	55	32, 8	122	64, 32	159	32, 8	97	16, 8	107	2, D6
	56	32, 16	123	32, 16	164	128, 16	98	16, 8	108	16, 16[d]
	57	32, 8	126	8, 16	165	64, 8[d]	99	4, 8[f]		
	60	32, 32[d]	127	16, 8						
	61	32, 8								
Erythromycin ethylsuccinate			128	16, 8	166	32, 8				
			129	16, 8[e]	167	16, 16[g]				
			132	16, 2	169	32, 16				
			133	16, 16	171	32, 8				
			134	32, 32[g]	173	8, 16				

[a] Sample taken 1 hr (experiments 1 and 4) or 2 hr (experiments 2 and 3) after morning dose on therapy days 2 and 9.
[b] Reciprocal of serum dilution inhibitory for challenge staphylococcus in tube dilution (broth) test.
[c] Died on day 3. [d] Died on day 15. [e] Died on day 14. [f] Died on day 13. [g] Died on day 12.

still showed positive cultures, whereas cultures had become negative in 12 of 16 treated with TO. In experiment 1, two monkeys treated with TO which had negative cultures after day 5 exhibited positive blood cultures 2 days posttherapy (day 14), and one of two was positive on day 17, but not thereafter. In experiment 2, three TO-treated monkeys each had a single positive blood culture on days 17, 21, and 24, respectively, although cultures were negative on days 11 and 14 in all three. Similarly, in experiment 3, cultures were negative from days 5 to 14 in one monkey given TO, but a positive culture was obtained on day 17, only. Thus, 6 of 16 TO-treated survivors exhibited transient positive blood cultures after therapy was discontinued although cultures were negative at the end of the therapy period in all six. The 20 survivors treated with EE or ES showed positive cultures continuously for varying periods, as shown in Table 2. Blood cultures ultimately became negative sooner ($P = < 0.05$) in TO-treated survivors than in those given EE or ES; on day 21, 2 of 16, 6 of 13, and 4 of 7 monkeys given TO, EE, and ES, respectively, had positive cultures; all were negative by day 35 (Table 2).

CRP tests also became negative sooner ($P = <0.05$) in monkeys given TO than in those treated with EE or ES. For example, on day 21, only 1 of 16 TO-treated monkeys exhibited a positive CRP test and all subsequent tests were negative (Table 2). In contrast, 5 of 13 and 3 of 7 survivors given EE and ES, respectively, still showed positive tests on day 21. All tests were negative on day 28 and thereafter in all three therapy groups.

Serum ABA of samples obtained 1 hr (experiment 1) or 2 hr (experiments 2 and 3) after the morning dose on therapy days 2 and 9 are shown in Table 3. The MIC values of oleandomycin and erythromycin bases for the challenge staphylococcus used in measuring serum ABA were 0.31 and 0.078 μg/ml, respectively. In experiment 1, ABA titers in six monkeys receiving TO ranged from 1:2 to 1:16 on day 2 and from 1:4 to 1:16 on day 9. Six EE-treated monkeys exhibited titers of 1:16 or 1:32 on day 2, and from 1:8 to 1:32 on day 9. In experiment 2, 9 of 10 TO-treated monkeys showed titers of 1:8 on both days. Higher levels of 1:8 to 1:64 and 1:8 to 1:32 were noted on days 2 and 9, respectively, in monkeys receiving EE. Five monkeys given ES exhibited titers of 1:16 or 1:32 on day 2; on day 9 titers ranged from 1:2 to 1:32. Similarly, in experiment 3, monkeys treated with TO, EE, and ES showed titers of 1:8 or 1:16, 1:32 to 1:128, and 1:8 to

TABLE 4. *Effect of dose of triacetyloleandomycin and erythromycin estolate on response of rhesus monkeys after intravenous challenge with staphylococci*

Antibiotic	Dose[a]	Mortality	Day of death	Duration (days) of illness in survivors:	
				Acute illness	Total illness
Triacetyloleandomycin	25.0	0/4[b]		3, 4, 6, 6	14, 13, 13, 15
	12.5	0/3		18, 20, 24	24, 27, 37
Erythromycin estolate	25.0	2/4	3, 13	8, 15	23, 27
	12.5	2/3	6, 15	21	28
Controls	None	3/4	2, 2, 7	27	47

[a] Milligrams per kilogram per day, dose divided equally and given by gastric tube at 8:00 AM and 5:00 PM for 12 days beginning 16 hr after challenge with 6.6×10^{10} *S. aureus* 80/81.

[b] Number that died over total number treated.

1:32, respectively, on day 2; on day 9, titers of 1:4 or 1:8, 1:8 to 1:32, and 1:8 or 1:16, respectively, were observed. In experiments 1, 2, and 3 combined, 18 of 25 monkeys receiving EE or ES showed lower serum ABA titers on therapy day 9 than on therapy day 2, whereas titers were lower on day 9 than on day 2 in only 4 of 16 given TO.

Experiment 4. In experiments 1 to 3, all treated monkeys received 50 mg/kg of TO, EE, or ES per day. In experiment 4, TO and EE were compared at 25 and 12.5 mg per kg per day. Two groups of four monkeys each were treated with 25 mg per kg per day of TO and EE, respectively, and two groups of three monkeys each were given 12.5 mg per kg per day of the two preparations, respectively, after challenge with 6.6×10^{10} staphylococci. Four monkeys served as infected, untreated controls.

Three of 4 controls died on days 2, 2, and 7, respectively (Table 4). The fourth remained in very poor condition for 27 days and did not appear normal until day 48; blood cultures and CRP were positive for 31 days. Four monkeys treated with 25 mg per kg per day of TO began to improve after 3, 4, 6, and 6 days, respectively, of therapy and appeared fully recovered by days 14 to 16. Two of 4 monkeys given the same dose of EE died on days 3 and 13, respectively. The latter (no. 99, Table 3) showed definite improvement on days 11 and 12, but suddenly became worse on the day after therapy was discontinued and died later the same day. Positive blood cultures and CRP were observed up to death. At autopsy, staphylococci were isolated from all major organs. The other two monkeys given 25 mg per kg per day of EE were acutely ill for 8 and 15 days, respectively, and did not appear normal until days 24 and 28, respectively.

Although all three monkeys treated with 12.5 mg per kg per day of TO survived, none showed any clinical improvement during the 12-day therapy period; they remained acutely ill through days 18, 20, and 24, respectively, and did not recover fully until days 25, 28, and 38, respectively. Two of three monkeys given 12.5 mg of EE did not respond to therapy and died on days 6 and 15, respectively. Clinical, laboratory, and autopsy findings were similar to those in untreated controls. The third remained in very poor condition for 21 days, and did not recover fully until day 29.

Blood cultures were positive continuously throughout the 12-day therapy period and also on days 14 and 17 in all 11 surviving monkeys. Cultures subsequently became negative in all after 28 to 35 days. Similarly, CRP tests were positive continuously during the therapy period in all 11 monkeys and all became negative after 24 to 31 days.

Samples for serum ABA were obtained 1 hr after the morning dose on therapy days 2 and 9. On both days, four monkeys treated with 25 mg per kg per day of TO exhibited ABA titers of 1:4 or 1:8, and, after 12.5 mg, lower titers of <1:2 to 1:4 were observed (Table 3). ABA titers were higher in monkeys receiving EE. After 25 mg, four monkeys had titers of 1:4, 1:16, 1:16, and 1:16, respectively, on day 2, and 1:8 on day 9 in the three survivors. After 12.5 mg per kg per day of EE, titers of 1:2, 1:4, and 1:16 were observed on day 2 in three monkeys, and, at 9 days, titers of 1:16 and 1:32, respectively, were found in the latter two survivors.

In experiments 1 to 4 combined, SGOT was significantly elevated during the therapy period in 17 of 23 (73.9%), 15 of 23 (65.2%), and 7 of 10 (70.0%) monkeys treated with TO, EE, and ES, respectively. Similar elevations were noted in 13

TABLE 5. *Antibacterial activity of serum from normal monkeys given triacetyloleandomycin, erythromycin estolate, and erythromycin ethylsuccinate*

Antibiotic	Dose[a]	Monkey no.	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]
Triacetyloleando-mycin	50.0	83	<2	2[c]	8	4	4	<2	4	8	4	2	<2
	50.0	84	<2	2	4	8	8	<2	2	8	8	4	<2
	50.0	85	<2	16	16	16	8	<2	8	16	16	2	<2
	50.0	100	<2	4	4	4	4	<2	2	4	4	4	<2
	25.0	7	<2	4	4	4	2	<2	2	8	4	2	<2
	25.0	9	<2	8	8	4	2	<2	4	4	4	2	<2
	25.0	13	<2	4	4	4	2	<2	4	8	8	2	<2
	12.5	16	<2	<2	2	2	<2	<2	<2	<2	<2	<2	<2
	12.5	74	<2	<2	<2	2	<2	<2	<2	2	4	<2	<2
	12.5	75	<2	<2	<2	2	<2	<2	<2	4	2	<2	<2
Erythromycin esto-late	50.0	86	<2	<2	2	8	4	<2	4	8	8	2	<2
	50.0	87	<2	2	4	4	<2	<2	8	16	16	8	<2
	50.0	88	<2	8	16	16	4	<2	8	16	16	4	2
	50.0	101	<2	8	16	16	8	<2	16	16	16	8	<2
	25.0	76	<2	2	4	2	<2	<2	<2	4	8	2	<2
	25.0	77	<2	2	8	4	<2	<2	2	4	4	2	<2
	25.0	78	<2	<2	2	2	<2	<2	2	2	4	2	<2
	12.5	79	<2	<2	<2	<2	<2	<2	<2	<2	<2	<2	<2
	12.5	80	<2	4	2	<2	<2	<2	<2	2	<2	<2	<2
	12.5	81	<2	<2	<2	<2	<2	<2	<2	<2	2	<2	<2
Erythromycin ethylsuccinate	50.0	E1	<2	2	2	<2	<2	<2	16	4	2	2	2
	50.0	E2	<2	16	16	4	2	2	16	8	2	2	2
	50.0	E3	<2	8	4	2	<2	<2	16	4	2	<2	<2
	50.0	E4	<2	4	4	<2	<2	<2	8	4	2	<2	<2
	50.0	E5	<2	4	4	2	<2	<2	8	8	4	<2	<2

[a] Values expressed as milligrams per kilogram per day.
[b] Sixteen hours after 4:30 PM dose on day 2.
[c] Reciprocal of serum dilution inhibitory for *S. aureus* 80/81 in tube dilution (broth) test.

of 19 (68.4%) untreated controls. At the last determination made on day 14 (2 days posttherapy), SGOT was still modestly increased in 5 of 23 (21.7%), 5 of 19 (26.3%), and 2 of 7 (28.6%) given TO, EE, and ES, respectively, whereas all 8 surviving controls had normal SGOT.

ABA titers in normal monkeys. As shown in Table 5, ABA titers were similar at all time intervals in normal monkeys receiving 50, 25, or 12.5 mg per kg per day of TO and EE. For example, four monkeys given 50 mg/kg of TO exhibited titers of 1:4, 1:4, 1:8, and 1:16, respectively, at 2 hr on day 1, and titers of 1:2, 1:4, 1:16, and 1:16 were observed at this time in 4, respectively, receiving the same dose of EE. These results are in contrast to those in infected monkeys in the above therapy studies in which serum ABA titers were higher in EE-treated than in TO-treated monkeys. Five normal monkeys given 50 mg per kg per day of ES showed peak ABA titers similar

TABLE 6. *Summary of effect of therapy with 50 mg per kg per day of triacetyloleandomycin, erythromycin estolate, and erythromycin ethylsuccinate in staphylococcal infections of monkeys*

Antibiotic	No. of monkeys treated[a]	Mortality	Duration (days) of illness in survivors:	
			Acute illness (mean)	Total illness (mean)
Triacetyloleandomycin	22	1/22	5.0	13.0
Erythromycin estolate	16	3/16	7.3	12.2
Erythromycin ethylsuccinate	16	8/16	15.1	28.3
Controls	22	15/22	21.1	35.6

[a] Data in this and previous studies from Saslaw and Carlisle (5).

to those in normal monkeys given the same dose of TO or EE. However, titers declined more rapidly after ES. For example, on day 2, monkeys receiving 50 mg/kg of TO and EE showed titers of 1:2 to 1:4 and 1:2 to 1:8, respectively, at 8 hr, whereas sera from 3 of 5 given ES showed no activity at a dilution of 1:2 and the other two were inhibiting at dilutions of 1:2 only. As with TO and EE, infected monkeys treated with ES had higher ABA titers than did normal monkeys given the same dose (Tables 3 and 5).

DISCUSSION

Under the conditions of this and our previous study (5), experimental staphylococcal infections in monkeys responded more readily to therapy with 50 mg per kg per day of TO than to the same dose of ES. As shown in Table 6, only 1 of 22 TO-treated monkeys died as compared to 8 of 16 receiving ES, and recovery was much more rapid in surviving monkeys in the former group. These differences in mortality and duration of illness were highly significant ($P = <0.01$). Further comparison of the combined results (Table 6) showed that monkeys treated with TO and EE were not significantly different with respect to number of deaths or rate of recovery of survivors. Although mortalities in the two groups treated with EE and ES, 3 of 16 and 8 of 16, respectively, were not significantly different at the 5% level ($P = 0.10$), the observed number of deaths, together with the highly significant difference ($P = <0.01$) in duration of illness would suggest superiority of EE over ES in these studies in monkeys.

Studies in humans have demonstrated that an ester of erythromycin such as EE in the capsule form gave antibacterial levels that were 10 times as high as those observed with TO (3). Unpublished data in this laboratory have shown a similar relationship in humans given the liquid preparations used in this study. In these studies in infected monkeys, serum ABA titers were also usually higher with the erythromycin preparations, but the difference was not as marked as in humans. However, in normal monkeys, as shown in Table 5, erythromycin levels were not as high in relationship to TO as noted in humans. This could suggest differences in absorption or metabolism, or both, of erythromycin esters in monkey as compared to man. The additional fact that the staphylococcus was more sensitive in vitro to erythromycin would tend to support the premise that greater efficacy could be expected with the erythromycins than with TO. In recent years there has been considerable discussion concerning the significance of serum levels of antibiotics in relation to therapeutic effect, as recently reviewed (4). Since the comparative in vitro effect in this study employed antibacterial activity of serum rather than concentration of antibiotic, one could expect a more precise correlation between in vitro and in vivo observations. It would seem that this prediction can not be completely fulfilled. This was also demonstrated when comparison was made at lower dosage levels of 25 and 12.5 mg/kg with mortalities of 4 of 7 and 0 of 7 in monkeys receiving EE and TO, respectively.

A comparison of these macrolide antibiotics in controlled studies in man for severe staphylococcal infections is not possible. With the monkey model, however, it is suggested that further insight may be gained in the total assessment of in vitro and in vivo data when comparing relative efficacy of antimicrobial agents.

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