BIOLOGICAL ACTIVITY OF MEGALOMICIN, A NEW *MICROMONOSPORA*-PRODUCED MACROLIDE ANTIBIOTIC COMPLEX

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In vitro studies with megalomicin A base demonstrated enhanced activity with increased pH, decreased activity with increasing serum content in the medium and serum binding in the range of 20~30 %. There is an inoculum effect with megalomicin A. *In vivo* studies in mice demonstrate that megalomicins A, B, C_1, and C_2 as well as the complex are active in conventional protection tests and have low acute LD_{50}'s. Absorption of megalomicin A and C_1 in mice like erythromycin is better after parenteral than oral administration. In rats, and dogs, megalomicin A gives higher serum levels than erythromycin after oral dosing. Megalomicin A base is not emetic in dogs. Both megalomicins A and C_1 give more prolonged serum levels in dogs than does erythromycin. Megalomicin A is absorbed along the entire intestinal tract in dogs and gives a depot effect after intramuscular dosing.

Megalomicin is a new *Micromonospora*-produced macrolide antibiotic complex described by WEINSTEIN *et al.*[1,2] These authors described the nature of the complex and reported initial biological results which indicates that megalomicin has *in vitro* and *in vivo* activity equal to or one-half that of erythromycin and is well absorbed and well tolerated orally in dogs. MARQUEZ *et al.*[3] described procedures for the isolation and purification of the individual components of the megalomicin complex. This report presents results of additional and more detailed studies with the megalomicin complex as well as several of the components. Due to its relative ease of preparation[4,5] the A component was studied most extensively.

Materials and Methods

Each of the antibiotic preparations studied was used as the base except as indicated in the text. Details concerning the isolation, purification and characterization of several of the megalomicin components are given in MARQUEZ *et al.*[5] The erythromycin used was erythromycin base USP from Internazionale Farmaceutici S. p. A. and had a potency of 980 mcg/mg. Several lots of the various megalomicin preparations were used in the studies. These ranged in potency from approximately 840~1,050 mcg/mg in terms of their own base standards. Each preparation was given in terms of its base activity as determined by bioassay procedures. Details of *in vitro* test procedures are given in the text. Protection tests were done using groups of 7~10 male CF-1 albino mice weighing 18~20 g each, with control groups of 10 mice each. Treatment was given shortly before and 4 hours after intraperitoneal injection with approximately 10^7 organisms per mouse. Control

infected mice died in 18~24 hours; survivors in treated groups were determined 48 hours after infection. PD_{50} values were calculated by probit procedures. Drug suspensions were made in 0.5 % aqueous carboxy methyl cellulose and were ultrasonicated to reduce particle size. The dogs used were beagle-type mongrels of both sexes weighing approximately 10 kg each. Cannulated dogs were prepared according to the procedure of ZEMAN[6]. Rats were males of the CF-E strain weighing approximately 150~200 g each.

Results and Discussion

In Vitro Studies

Studies reported earlier[1,2] showed the megalomicin complex to have an antibacterial spectrum similar to that of erythromycin with a potency equal to or one-half that of erythromycin depending upon the organism. Additionally, small differences were described between the several components both in potency and spectrum.

The effect of pH on the *in vitro* activity of megalomicin A base and erythromycin base in yeast beef broth is shown in Table 1. Both antibiotics are substantially more active at an alkaline pH which is characteristic for macrolide antibiotics. The pH levels at which the greatest increases in activity occurred appeared to be characteristic of the organisms rather than the antibiotic.

The effect of inoculum size on the *in vitro* activity of megalomicin A base was examined over a range of approximately 5×10^4~5×10^7 organisms in 3 ml of medium. The results obtained indicate a significant inoculum effect. The minimal inhibitory

Table 1. Effect of pH on the *in vitro* activity of megalomicin A base and erythromycin base*

	Organism	MIC (mcg/ml)					
		pH 7.0	pH 7.2	pH 7.4	pH 7.6	pH 7.8	pH 8.0
Megalomicin A base	*Sarcina lutea* ATCC 9341	0.75	0.75	0.75	0.75	0.03	0.008
	Staphylococcus aureus ATCC 6538P	3.0	3.0	0.75	0.75	0.03	0.3
	Staphylococcus aureus var. W	>10.0	7.5	7.5	3.0	0.75	0.3
	Streptococcus pyogenes var. C 203	>10.0	>10.0	7.5	3.0	3.0	0.75
Erythromycin base	*Staphylococcus aureus* var. W	3.0	3.0	0.75	0.75	0.3	0.3
	Streptococcus pyogenes C 203	0.3	0.3	0.3	0.3	0.08	0.08

* The medium used was yeast beef broth. Tubes containing 3 ml were inoculated with 0.05 ml of a 10^3 dilution of an 18-hour broth culture. End points were determined after 18 hours at 37°C.

Table 2. Effect of serum on the *in vitro* activity of megalomicin A base and erythromycin base

	Organism	Percent horse serum and MIC (mcg/ml)		
		0 %	10 %	25 %
Megalomicin A base	*Staphylococcus aureus* ATCC 6538P	0.03	0.3	0.3
	Staphylococcus aureus var. W	0.3	0.75	3.0
	Streptococcus pyogenes var. C	0.75	0.75	3.0
	Streptococcus pyogenes var. C 203	0.75	3.0	3.0
Erythromycin base	*Staphylococcus aureus* ATCC 6538P	0.3	0.3	0.3
	Streptococcus pyogenes var. C	0.08	0.08	0.08

Yeast beef broth, pH 7.8. Inoculum and conditions as in Table 1.

concentration (MIC) of megalomicin A against *Staphylococcus* and *Streptococcus* strains was usually 10 times higher with the larger inoculum than with lower ones.

The presence of serum in the medium (Table 2) usually resulted in an increase in the MIC values for megalomicin A base. This prompted evaluation of the degree of serum binding of megalomicin A and C_1 as well as erythromycin base. Dialysis sacks containing horse serum plus varying amounts of antibiotic were placed in buffer solution. Periodic assay of buffer solution indicated binding of approximately 25 % for megalomicin A, 32 % for megalomicin C_1 and 29 % for erythromycin base.

In Vivo Studies

The protective activity of several megalomicin preparations as well as erythromycin was determined against infections with a variety of clinically important bacteria (Table 3). As indicated in earlier reports[1,2], the A component is the preferred one and thus the greatest amount of data have been obtained with it. As shown in Table 3, the *in vivo* activity of megalomicin A base appears to be equal to or one-half that of erythromycin. Megalomicin C_1 base has activity similar to that of megalomicin A against gram-positive infections but appears to be less active against gram-negative infections. Only limited material was available for study with the B, C_2 and C complex (a mixture primarily containing C_1 and C_2) fractions. They were however active *in vivo* against the infections studied.

Table 3. Protective activity of megalomicin preparations and erythromycin in mice

Organism	PD_{50} mg/kg											
	Complex base		A base		B base	C complex base		C_1 base		C_2 HCl		Erythromycin base	
	Oral	S.C.	Oral	S.C.	S.C.	Oral	S.C.	Oral	S.C.	Oral	S.C.	Oral	S.C.
Staphylococcus aureus Smith	—	—	250	75	—	310	86	180	117	—	—	167	40
Staphylococcus aureus Gray	>500	90	300	20	—	270	85	>250	130	125	30	106	30
Staphylococcus aureus W	—	—	117	20	—	—	—	150	25	—	—	53	20
Staphylococcus aureus 41	—	—	150	20	—	—	—	170	25	—	—	75	20
Streptococcus pyogenes C 203	—	—	300	220	—	—	—	207	118	—	—	147	134
Streptococcus pyogenes C	500	51	300	134	150	300	95	225	150	200	25	180	90
Streptococcus pyogenes 22	—	—	180	180	—	—	—	>250	200	—	—	100	50
Streptococcus pyogenes 9	—	—	250	167	—	—	—	>250	250	—	—	120	140
Diplococcus pneumoniae eye	—	35	300	90	—	—	—	300	167	—	—	134	90
Diplococcus pneumoniae 2	—	—	250	70	—	—	—	200	170	—	—	134	75
Enterococcus sp. 802	—	—	300	160	—	—	—	>250	180	—	—	300	180
Enterococcus sp. 804	—	—	250	180	—	—	—	250	250	—	—	250	250
Escherichia coli 10536	—	>500	200	100	—	>500	>500	250	250	—	>500	>250	160
Klebsiella pneumoniae 10031	>500	>500	250	150	250	—	—	>250	>250	—	>500	>250	>250
Pseudomonas aeruginosa 8689	>500	>500	>250	161	250	—	—	>250	>250	—	>500	>250	130

Table 4. Acute toxicity of megalomicin preparations and erythromycin in mice

Preparation	LD_{50} (mg/kg)			
	Oral	S.C.	I. P.	I. V.
Megalomicin complex base	>1,160	>1,160	350	—
Megalomicin A base	7,500	7,000	350	—
Megalomicin B base	—	—	>500	—
Megalomicin C_1 base	>1,000	>1,000	500	—
Megalomicin C_2 HCl	>500	>500	>500	275
Erythromycin base	7,500	8,000	500	—

The acute toxicity of the megalomicin preparations was determined in mice as indicated

Table 5. Absorption of megalomicin preparations in mice*

Preparation	mg/kg	Route	No. tests	Average serum levels (mcg/ml) at time after dosing (hours)							
				0	1/4	1/2	1	2	4	6	24
Megalomicin A base	250	Oral	3	0	0.3	0.4	2.9	0.9	0.4	0.3	0
	125	//	1	0	0	0.6	A**	A	A	A	0
	50	//	2	0	0	0.3	A	0	0	0	0
	250	S.C.	1	0	—	13.5	14.5	33.0	17.5	8.8	0.4
	125	//	1	0	—	8.0	22.0	9.0	3.5	3.0	0.5
Megalomicin C_1 base	250	Oral	1	0	—	1.6	3.0	3.7	—	2.4	0.4
	125	//	1	0	—	0.5	1.6	0.9	0.5	0.6	0.3
	250	S.C.	1	0	—	4.3	4.9	5.6	2.4	3.1	0.8
	125	//	1	0	—	1.8	1.8	1.6	1.6	1.2	1.4
Erythromycin base	250	Oral	3	0	0.1	1.5	1.6	2.2	0.2	0.3	0
	125	//	1	0	—	0.3	0.6	0.3	0.2	0	0
	50	//	2	0	0.06	0.05	0.3	0.1	0.04	0	0
	250	S.C.	1	0	—	6.1	6.8	6.7	4.1	1.0	0.04
	125	//	1	0	—	—	9.0	1.4	0.8	0.3	0

* Each determination represents serum from the pooled blood of 5 mice.
** A—Active but below the lower limit of the assay procedure (0.3 mcg/ml).

Table 6. Abosorption of megalomicin preparations in rats after a single oral dose

Preparation	mg/kg	No. rats/ time	Serum levels (mcg/ml) at times after dosing (hours)							
			0	1/4	1/2	1	2	4	6	24
Megalomicin complex base	50	7	0	—	0.5	0.2	1.0	1.2	0.8	A*
Megalomicin A base	200	2	0	0	4.1	0.2	0.3	0.3	A	0
	50	4	0	—	0.2	0.3	0.3	0.3	0.5	0.5
Erythromycin base	200	2	0	0.9	0.9	0.6	0.8	0.3	0.3	0
	50	3	0	—	0.2	0.2	0.1	0.05	0	0

* Active but below the lower limit of the assay procedure (0.3 mcg/ml).

in Table 4. All preparations had low toxicity in mice and thus end points were not obtained except for megalomicin A which has an acute toxicity in mice very similar to erythromycin base.

Studies of the absorption of megalomicin A base, C_1 base and erythromycin base in mice are shown in Table 5. All of the preparations gave substantially better serum levels after parenteral administration than after oral administration which was suggested by *in vivo* protection studies. Over the dose range studied, megalomicin A base gave the highest serum levels parenterally but gave the lowest levels of the three antibiotics orally. Megalomicin C_1 base gave slightly higher levels than erythromycin base after oral administration.

In contrast to what was seen in mice, oral administration of megalomicin A to rats (Table 6) resulted in somewhat higher serum levels than did similar oral doses of erythromycin. The megalomicin complex gave later peak levels than did either megalomicin A or erythromycin.

Studies with several preparations in dogs are shown in Tables 7~11. Erythromycin base which was used as a reference, was emetic in approximately one-half of the dogs given a single oral dose of 500 mg (approximately 50 mg/kg) therefore only

Table 7. Absorption of megalomicin preparations and erythromycin in dogs after a single oral dose of 500 mg

Preparation	Dog	mg/kg	Serum levels (mcg/ml) at time after dosing (hours)						
			1	2	4	6	24	48	72
Megalomicin C_1 base	19	56	4.9	5.4	3.0	2.8	1.0	0.8	0.7
	6	46	4.5	4.8	2.9	4.8	1.7	1.1	0.8
	90	47	4.1	2.7	2.0	1.8	0.8	0.4	0.2
	85	48	9.6	5.0	4.8	2.5	0.8	1.0	0.5
	90	47	4.6	6.0	5.7	3.0	1.5	1.1	—
	290	56	1.2	4.8	7.4	2.9	1.8	0.8	—
	Mean		4.8	4.7	4.3	2.9	1.2	0.8	0.5
Megalomycin C complex base	86	40	4.9	4.2	2.6	2.2	2.1	0.6	—
	8	40	5.0	4.5	1.4	1.1	0.6	0.4	—
	85	43	4.8	2.8	2.4	2.5	1.3	0.7	—
	19	59	0	2.1	2.4	1.7	1.0	0.4	—
	Mean		3.6	3.4	2.2	1.8	1.3	0.5	—
Erythromycin base	17	51	1.4	3.7	2.0	1.5	0	0	—
	85	48	1.1	2.1	1.4	1.7	0	0	—
	8	64	6.2	2.5	0.8	0.2	0	0	—
	49	53	3.4	2.5	1.1	0.6	0	0	—
	50	56	5.9	3.8	2.1	1.0	0	0	—
	86	48	6.5	5.0	2.9	1.4	0	0	—
	19	59	10.0	5.6	2.8	1.5	0	0	—
	Mean		4.9	3.6	1.8	1.1	0	0	—

Table 8. Urine and feces levels of megalomicin and erythromycin in dogs after a single oral dose of 500 mg

Preparation	Dog	mg/kg	Urine levels				Fecal levels			
			mg excreted		percent of dose		mg recovered		percent of dose	
			0~24 hrs.	25~48 hrs.	0~24 hrs.	25~48 hrs.	0~24 hrs.	25~48 hrs.	0~24 hrs.	25~48 hrs.
Megalomicin C_1 base	19	56	55.2	23.0	11.0	4.6	1.4	—	0.3	—
	6	46	65.3	29.8	13.1	5.9	3.0	—	0.6	—
	90	47	230.0	19.7	40.6	3.9	5.0	4.1	1.0	0.8
	85	48	65.0	25.9	13.0	5.2	0.6	2.4	0.1	0.5
	90	47	60.6	28.0	12.1	5.6	—	—	—	—
	290	56	56.1	23.0	11.2	4.6	—	—	—	—
	Mean		88.7	24.9	16.8	4.9	2.5	3.2	0.5	0.6
Megalomycin C complex base	86	40	46.3	13.3	11.8	3.4	—	—	—	—
	8	40	36.8	12.6	7.9	3.2	—	—	—	—
	85	43	51.3	31.5	10.2	6.3	—	—	—	—
	19	59	41.3	17.2	8.3	3.4	—	—	—	—
	Mean		43.9	18.6	9.5	4.1	—	—	—	—
Erythromycin base	17	51	45.6	0.7	9.1	0.1	62.4	—	12.5	—
	85	48	48.0	0.4	9.6	0.1	6.0	—	1.2	—
	8	64	86.5	—	17.3	—	—	—	—	—
	49	53	34.8	0	6.9	0	7.0	0.1	1.4	<0.1
	50	56	44.7	1.7	8.9	0.3	9.1	7.8	1.8	1.5
	86	48	119.6	0.4	23.9	0.1	—	—	—	—
	19	59	38.8	<0.1	7.8	0	—	—	—	—
	Mean		59.7	<0.5	11.9	0.1	21.1	3.9	4.2	<0.8

dogs which did not have emesis were included (Tables 7 and 8). In these erythromycin dosed dogs, peak levels were generally seen 1 hour after dosing with an average peak serum level of 4.9 mcg/ml after a 50 mg/kg dose. Serum levels declined rapidly to approximately 1.1 mcg/ml 6 hours after dosing and all dogs had negative serum levels 24 hours after dosing. An average of approximately 12 % of the erythromycin dose was recovered in the urine collected 24 hours after dosing; little more was found in the 25~48 hour samples. Fecal levels were low and variable though recovery studies suggest that only 50 % of added erythromycin is recovered from normal feces. Megalomicin C_1 base and a C complex base (approximately 80 % C_1 and 20 % C_2) gave peak serum levels (Table 7) with the same magnitude as those obtained with a comparable dose of erythromycin but these were not emetic. The decline in serum levels with these preparations was considerably less than with erythromycin however, and measurable serum levels were present 48 hours and in some instances 72 hours after a single oral dose of 50 mg/kg. This was also reflected in the amount excreted in the urine during the 25~48 hour period (Table 8). As with erythromycin, fecal levels of megalomicin C_1 were low and variable; only about half of added megalomicin C_1 was recovered from normal feces.

Oral administration of megalomicin A to dogs at a level of 50 mg/kg (Table 9) did not induce emesis and resulted in peak serum levels 1~2 hours after dosing. The magnitude of the peak levels was greater than that obtained with erythromycin and these levels persisted longer than with erythromycin. Measurable levels were seen in

Table 9. Absorption of megalomicin A base in dogs after a single dose

Preparation	Dog	mg/kg	Serum levels (mcg/ml) at times after dosing (hours)						
			1	2	4	6	24	48	72
500 mg oral gelatin capsule	85	47	8.8	4.8	2.9	1.8	0.6	0.3	A*
	90	47	16.5	7.3	2.1	2.2	0.7	0.3	A
	290	56	18.0	8.6	3.3	3.2	1.2	0.4	A
	90	47	9.0	5.4	2.5	2.4	0.6	0.3	A
	11	42	11.0	14.0	4.5	3.3	0.5	A	A
	K-86	40	11.0	3.4	2.8	3.3	0.8	A	A
	33	39	3.7	11.5	5.0	3.5	1.2	0.4	A
	290	53	5.6	6.6	4.6	4.6	0.7	0.4	A
	85	48	0.3	8.6	4.2	2.9	0.6	0.3	A
	17	51	8.1	9.6	1.1	0.5	—	—	—
	85	46	11.0	13.0	4.1	3.3	1.6	—	—
	90	45	6.8	7.4	1.2	1.9	0.3	—	—
	290	45	6.3	9.4	3.1	2.1	1.0	—	—
	6	41	3.9	5.8	4.0	1.6	0.3	—	—
	Mean		8.5	8.2	3.5	2.6	0.8	<0.3	A
50 mg oral enteric coated capsule	19	55	A	A	0.7	0.7	0.6	A	0
	6	45	2.5	1.8	1.6	2.4	0.9	A	0
Suspension intramuscular	90	48	1.2	2.0	1.4	2.3	2.0	1.2	0.7
	17	51	0.8	1.2	0.7	2.5	2.1	1.4	0.6
	89	9	0.6	2.0	1.3	0.7	0.4	A	0
	63	9	2.0	2.3	1.7	1.1	A	A	0
	6	9	0.3	0.5	0.3	0.4	0.3	A	—
	6	9	1.5	1.1	0.7	0.4	0.4	0	—

* Active but below the lower limit of the assay (0.3 mcg/ml).

Table 10. Urine and feces levels of megalomicin A in dogs after a single dose

Preparation	Dog	Urine levels				Fecal levels			
		mg excreted		percent of dose		mg recovered		percent of dose	
		0~24 hrs.	25~48 hrs.	0~24 hrs.	25~48 hrs.	0~24 hrs.	25~48 hrs.	0~24 hrs.	25~48 hrs.
500 mg oral gelatin capsule	85	61.0	10.7	12.2	2.1	—	—	—	—
	90	52.0	10.4	10.4	2.1	—	—	—	—
	290	69.3	16.2	13.9	3.2	14.8	—	2.9	—
	90	50.6	10.5	10.1	2.1	132.0	—	26.4	—
	11	82.5	18.1	16.5	3.6	99.2	—	19.8	—
	K-86	74.0	18.6	14.8	3.7	99.4	9.8	19.8	2.0
	33	80.1	24.0	16.0	4.8	30.5	8.3	6.1	1.7
	290	82.4	19.8	16.5	3.9	65.0	12.4	13.0	2.5
	85	34.8	10.0	6.9	2.0	7.4	13.9	1.5	2.8
	17	83.0	31.2	16.6	6.2	—	—	—	—
	85	125.0	—	25.0	—	—	—	—	—
	90	48.0	—	9.8	—	—	—	—	—
	290	99.0	—	22.0	—	—	—	—	—
	6	109.0	—	24.0	—	—	—	—	—
	Mean	68.0	16.9	15.3	3.4	64.0	11.1	12.7	2.2
500 mg oral enteric coated capsule	19	20.2	8.6	4.0	1.7	68.3	7.0	13.7	1.4
	6	39.8	8.6	7.9	1.7	9.5	26.7	2.0	5.3
Suspension intramuscular	90	58.9	64.7	11.8	12.9	5.2	8.7	1.0	1.8
	17	57.0	77.7	11.4	15.5	2.6	5.1	0.5	1.0
	89	19.5	7.6	19.5	7.6	1.9	3.1	1.9	3.1
	63	24.5	6.0	24.5	6.0	1.2	3.4	1.2	3.4
	6	25.0	8.3	35.0	8.3	1.2	4.2	1.2	4.2
	6	29.0	10.5	29.0	10.5	—	—	—	—

all dogs 24 hours after oral dosing. In all dogs, activity below the limit of the assay (0.3 mcg/ml) was detected 72 hours after dosing. As with the other megalomicin preparations, urinary excretion of significant quantities of megalomicin A continued through the 25~48 hour period (Table 10) reflecting the prolonged serum levels. Fecal recovery was variable and only an average of 32% of the administered dose was accounted for in the urine and feces up to 48 hours after dosing.

Table 11. Absorption of megalomicin A base in cannulated dogs after a single dose of 500 mg

Dog	Route	Serum levels (mcg/ml) at time in hours						
		0	1	2	4	6	24	48
31	Oral	0	0.4	11.0	6.8	3.4	0.8	A**
67	//	0	0.3	6.4	1.4	1.1	0.3	0
31	Duodenal*	0	2.7	4.0	1.8	1.3	0.6	A
67	//	0	9.2	5.8	2.6	2.0	0.6	0
31	Jejunal*	0	11.0	9.8	4.2	2.5	0.9	A
67	//	0	10.0	6.6	2.3	1.6	1.4	A
31	Rectal*	0	1.1	0.74	0.5	0.4	A	
67	//	0	2.8	1.9	0.9	0.7	A	

* Oral administration was done in gelatin capsules. Duodenal, jejunal and rectal administration was done using a suspension in 0.5% carboxymethyl cellulose.

** Active but below the lower limit of the assay (0.3 mcg/ml).

Administration of megalomicin A in capsules coated with cellulose acetate phthalate, to resist action of gastric fluids, resulted in substantially decreased serum and urine levels suggesting that significant absorption occurs in the stomach and/or the first part of the small intestine. Peak serum levels of 1~2.5 mcg/ml were obtained after dosing with enteric-coated capsules in contrast to an average of 8.5 mcg/ml

after dosing with normal capsules.

A "depot" effect was noted after intramuscular administration of megalomicin A to dogs (Table 9). Increasing the dose from 10 mg/kg to 50 mg/kg resulted in similar peak levels with longer duration. This was confirmed by the pattern of urinary excretion. Recovery of approximately 1.5~5 % of the antibiotic in the feces during the 48 hours after intramuscular dosing suggests significant biliary excretion of drug with the possibility of entero-hepatic cycling participating in the prolonged serum levels.

A study in two dogs prepared with double cannulae in the duodenum and in the jejunum (Table 11) indicates that megalomicin A base is absorbed throughout the entire intestinal tract since substantial serum levels were obtained after oral, duodenal, jejunal and rectal administration.

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