ANTIBACTERIAL ACTIVITY OF HENEICOMYCIN

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Heneicomycin is structurally similar to efrotomycin, mocimycin (kirromycin) and X-5108 (goldinomycin). Comparisons were limited because of the small supplies available. All antibiotics show the same *in vitro* antibacterial spectrum although some test cultures were less sensitive to efrotomycin. Heneicomycin compared favorably with efrotomycin when given subcutaneously or *per os* against infections with *Moraxella bovis* and *Streptococcus pyogenes*. The rapid elimination of heneicomycin observed following oral administration may account for its poor activity against a *Bordetella bronchiseptica* infection where efrotomycin is effective. It appears more like X-5108 than efrotomycin biologically. The disaccharide on efrotomycin may account for the difference observed.

Heneicomycin[1], produced by *Streptomyces filipinensis*, is related structurally to efrotomycin[2], mocimycin (kirromycin)[3] and X-5108 (goldinomycin)[3]. Heneicomycin differs from X-5108 in lacking the hydroxyl at carbon-3 of the pyran ring. Because of the structural similarities of this group of antibiotics, we have compared their antibacterial activities in so far as supplies permitted.

In vitro antibacterial activities are shown in Table 1. None of these agents has outstanding *in vitro* activity. Comparisons show X-5108, mocimycin and heneicomycin to have similar spectra and MIC's. Some of the test bacteria which were sensitive to these three drugs were less sensitive to efrotomycin.

Supplies of X-5108, mocimycin, and heneicomycin were insufficient to permit much testing for *in vivo* efficacy. The available data are summarized in Table 2. The methods have been described previously[6]. Heneicomycin and efrotomycin are equally effective by both routes of administration against either *Moraxella bovis* or *Streptococcus pyogenes* infections. However, efrotomycin is more active than heneicomycin by gavage against the *Bordetella bronchiseptica* infection. X-5108 and mocimycin are inactive by the oral route, as well as subcutaneously, against this infection. Heneicomycin was not tested against the *B. bronchiseptica* infection by subcutaneous injection. The differences in the *in vivo* efficacy of these drugs may be due to different rates of absorption and excretion of agents in infections that progress at different rates. In the *Moraxella bovis* infection the mean day of death of untreated infected control animals was less than 0.5 day while it was 2.7 days in the *Bordetella bronchiseptica* infection. Thus a drug that was excreted fairly rapidly might still be active in the *M. bovis* infection. However, it would not be effective in the *Bordetella bronchiseptica* infection if it did not produce sufficiently high and prolonged cidal serum levels to reduce the challenge bacteria to a number which could be controlled by the host defenses. Efrotomycin does not kill rapidly *in vitro*[4]. It has the same mode of action* as mocimycin[5]. Indeed structural similarities indicate the agents in this group may act at the same site and could mimic efrotomycin in rate of kill.

Blood concentrations were investigated by dosing randomized groups of CF1 female mice by

* WANG, C. C.: Personal Communication.

Table 1. Comparative *in vitro* antibacterial activity.

Culture	Code No.	Animal source	MIC μg/ml in Brain heart +5% horse serum agar of							
			Efrotomycin[a]		Heneicomcyin		Mocimycin[a]		X-5108[a]	
			24 hr	48 hr	24 hr	48 hr	24 hr	48 hr	24 hr	48 hr
Bordetella bronchiseptica	F1728	porcine	150	150	25	100	25	100	25	50
Corynebacterium pseudotuberculosis	3165	equine	12.5	100	6.2	50	0.4~3.1	25	3.1	25
Corynebacterium pyogenes	516	?	ng[c]	6.2	ng	6.2	ng	3.1	ng	3.1
Enterococcus	198	bovine	>400	>400	>400[b]	>400[b]	>400[b]	>400[b]	200	300
Erysipelothrix rhusiopathiae	87193	porcine	150	350	250~400	>400	>400	>400	350	400
Escherichia coli	3386	bovine	350	350	150	250	25~150	25~200	250	400
Haemophilus influenzae	2261	human	12.5	12.5	1.6	1.6	≤0.4	0.4~1.6	0.4	0.8
Klebsiella pneumoniae	B3083	human	400	>400	>400[b]	>400[b]	>400[b]	>400[b]	350	350
Moraxella bovis	2884	bovine	≤0.4	≤0.4	≤0.4	≤0.4	≤0.4	≤0.4	≤0.4	≤0.4
Paracolobactrum	3335	human	>400	>400	>400[b]	>400[b]	>400	>400	350	400
Pasteurella multocida	86	avian	1.6	1.6	1.6	3.1	3.1	3.1	0.8	3.1
Providencia	2741	human	>400	>400	250~350	250~350	>400	>400	150	250
Pseudomonas aeruginosa	3210	human	400	>400	250~350	250~400	>400	>400	300	400
Salmonella typhimurium	3420	?	>400	>400	200	>400[b]	200	>400	200	350
Serratia marcescens	1543	human	250	350	>400[b]	>400[b]	>400[b]	>400[b]	>400	>400
Shigella sp.	3303	human	300	350	100	200	150	200	100	100
Staphylococcus aureus	2949	human	400	>400	>400[b]	>400[b]	300	400	200	350
Streptococcus pneumoniae	I-37	human	12.5	50	1.6	6.2	0.8~3.1	0.8~3.1	0.8	3.1
Streptococcus pyogenes	C-203	human	6.2	12.5	0.8	3.1	≤0.4	0.8~3.1	0.4	1.6
Yersinia enterocolitica	WA	?	50	100	50	150	25	25~150	50	100
Yersinia pseudotuberculosis	275	avian	12.5	25	12.5	25	12.5	25	12.5	25

[a] Data were reported previously in reference 4.

[b] Marked reductions of growth at lower concentrations.

[c] No growth on nonmedicated agar after 24 hours; growth occurred after 48 hours incubation.

[d] Test organisms were grown for 16 hours in brain heart broth (including 5% horse serum when necessary) diluted to 10^3 in fresh medium and spot inoculated onto the surface of antibiotic supplemental agar. The number of viable cells inoculated in each spot varied from 3×10^2 to 7×10^3. Plates were scored visually after 24 and 48 hour incubation at 37°C. Concentrations tested=400, 350, 300, 250, 200, 150, 100, 50, 25, 12.5, 6.2, 3.1, 1.6, 0.8 and 0.4 μg/ml.

Table 2. Comparative *in vivo* activities.

Test organism	Code No.	ED_{50} mg/dose × 2 doses							
		Heneicomycin		Efrotomycin		X-5108		Mocimycin	
		s.c.	p.o.	s.c.	p.o.	s.c.	p.o.	s.c.	p.o.
Bordetella bronchiseptica	F1728		>4.0[a]	0.94	1.93	>6.0[a,b]	>6.0[a,b]	>6.0[b]	>6.0[b]
Moraxella bovis	526	0.49	1.82	0.52	1.03				
Streptococcus pyogenes	C203	0.22	0.86	0.5	0.67				

[a] At this dose there was a prolongation of mean survival time.
[b] Data were reported previously in reference 4.

Fig. 1. Plasma concentrations of heneicomycin and efrotomycin in mice after a single oral dose of 200 mg/kg.

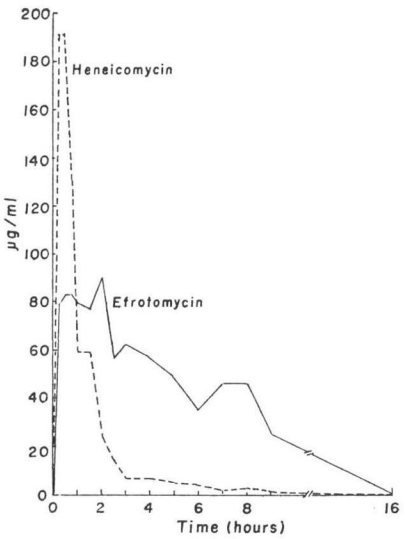
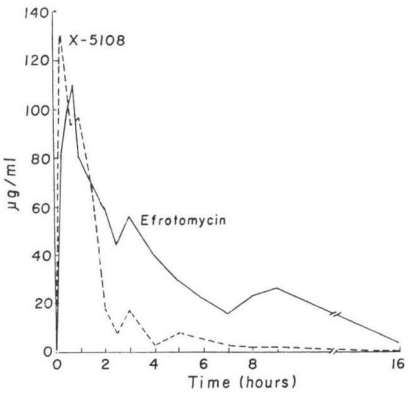


Fig. 2. Plasma concentrations of X-5108 and efrotomycin in mice following single oral dose of 200 mg/kg.



gavage with 4 mg per 20 g animal. Blood was taken from the hearts with heparinized syringes and plasmas from each group were pooled and assayed by a cylinder plate agar diffusion method using *M. bovis* as the test organism. The data are in Figs. 1 and 2.

The rapid oral absorption and prolonged blood levels of efrotomycin are in agreement with previous data[4]. Equally evident is the rapid absorption and rapid elimination of both heneicomycin and X-5108. Failure to maintain a sufficiently high blood level of heneicomycin and X-5108 is one reason for failure of these drugs to protect against the *B. bronchiseptica* infection.

Heneicomycin appears to be similar biologically as well as chemically to X-5108. The presence of the disaccharide on efrotomycin may account for the differences observed.

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