CGP 9000: A NEW ORALLY ACTIVE, BROAD-SPECTRUM CEPHALOSPORIN

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CGP 9000, (7-[D-2-amino-2-(1,4-cyclohexadienyl)-acetamido]-3-methoxy-3-cephem-4-carboxylic acid), is a new broad-spectrum cephalosporin antibiotic. Its antibacterial activity *in vitro* (MIC) is similar, but its bactericidal efficacy superior to that of cephalexin and cephradine. Upon oral administration to mice infected with various bacteria, CGP 9000 is, in general, 2 to 7 times more effective than either cephalexin or cephradine.

Although there are several cephalosporins available that are active when given parenterally, orally active cephalosporins are rare. The only ones that have become established in clinical use are cephalexin and cephradine. CGP 9000, 7-[D-2-amino-2-(1,4-cyclohexadienyl)-acetamido]-3-methoxy-3-cephem-4-carboxylic acid, is an orally active compound belonging to a new group of cephalosporins, which are N-acyl-derivatives of 3-alkoxy-7-amino-3-cephem-4-carboxylic acid (Chemical Abstracts 80: 83019, 1974).

The minimum inhibitory concentrations (MIC) of CGP 9000, cephalexin and cephradine against various bacteria were determined by the gradient plate method[1] in brain-heart infusion (BHI) agar; for *Neisseria* only, the dilution method[2] with MUELLER-HINTON agar and 10% blood was used. Table 1 shows that the three cephalosporins are almost equally effective in this respect.

The relative potency of the bactericidal effects of CGP 9000, cephalexin and cephradine against proliferating bacterial cells, was compared on the basis of the recoveries of viable organisms. Figs. 1

Fig. 1. Bactericidal effect of 100 mcg/ml of CGP 9000, cephalexin and cephradine (added at arrow) on proliferating cells of *Escherichia coli* 2018.

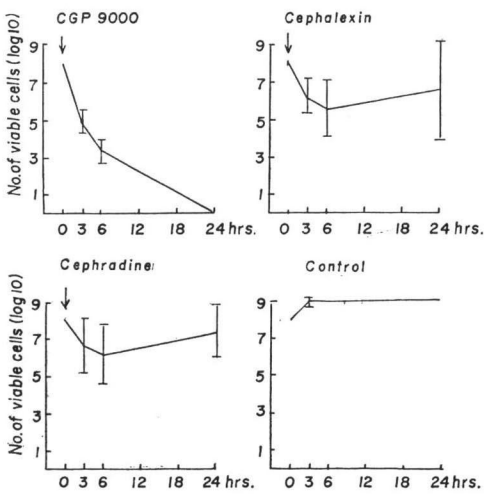
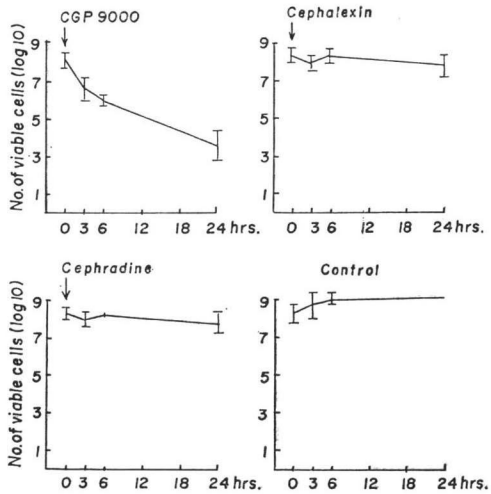


Fig. 2 Bactericidal effect of 100 mcg/ml of CGP 9000, cephalexin and cephradine (added at arrow) on proliferating cells of *Klebsiella pneumoniae* K 1081.



and 2 indicate that CGP 9000 has a more rapid and more intensive bactericidal action on *Klebsiella pneumoniae* and *Escherichia coli* than both cephalexin and cephradine.

The bactericidal effect of CGP 9000 was also compared with that of cephalexin in an experimental

Table 1. Minimum inhibitory concentrations of CGP 9000, cephalexin and cephradine against strains of various genera

Organism	MIC (mcg/ml)		
	CGP 9000	Cephalexin	Cephradine
Staphylococcus aureus K 1098	0.6	0.6	0.5
Streptococcus pyogenes Aronson	1.5	2.0	2.0
Diplococcus pneumoniae III/84	0.6	2.0	2.0
Neisseria meningitidis K 1318	0.6	1.25	0.6
N. gonorrhoeae K 1317/2	0.2	0.8	0.8
Escherichia coli 205	2.5	4.0	7.0
* *E. coli* 205 (R^{+}_{TEM})	35.0	20.0	25.0
* *E. coli* 2018	2.5	3.0	5.0
* *E. coli* K 1109	>100	>100	>100
Salmonella typhimurium 277	2.0	2.5	3.5
* *Enterobacter cloacae* P 99 WT	>100	>100	>100
* *Klebsiella pneumoniae* K 1081	3.0	2.5	5.0
* *Proteus rettgeri* K 856	60.0	>100	>100
* *P. morganii* K 1078	>100	>100	>100
P. mirabilis K 1108	15.0	15.0	25.0
* *Pseudomonas aeruginosa* K 799	>100	>100	>100

* Ampicillin-resistant strains

Table 2. Chemotherapeutic activity of CGP 9000, cephalexin and cephradine against systemic infections in female MF2 mice

Infecting organism	No. of oral doses	ED_{50} (mg/kg)		
		CGP 9000	Cephalexin	Cephradine
Staphylococcus aureus K 1098	1	3.0†	6.6	6.0
* *S. aureus* K 1072	1	25 †	85	32
Streptococcus pyogenes Aronson	2	1.0†+	6.3	5.5
Diplococcus pneumoniae III/84	2	8.5†+	30	40
Escherichia coli 205	2	9.5†+	42	52
* *E. coli* 205 (R^{+}_{TEM})	2	6.5†+	33	16
* *E. coli* K 1109	2	>300	>300	>300
Salmonella typhimurium 277	2	30 †+	100	110
* *Klebsiella pneumoniae* K 1132	2	17 †+	47	120
* *Enterobacter cloacae* P 99 WT	2	>300	>1,000	1,000
Proteus mirabilis K 1108	2	16 †	80	ND
* *P. rettgeri* K 856	2	6.5†+	20	30
* *P. morganii* K 1078	2	>300	>1,000	>1,000
* *Pseudomonas aeruginosa* K 799	2	>1,000	>1,000	>1,000

* Ampicillin-resistant strains

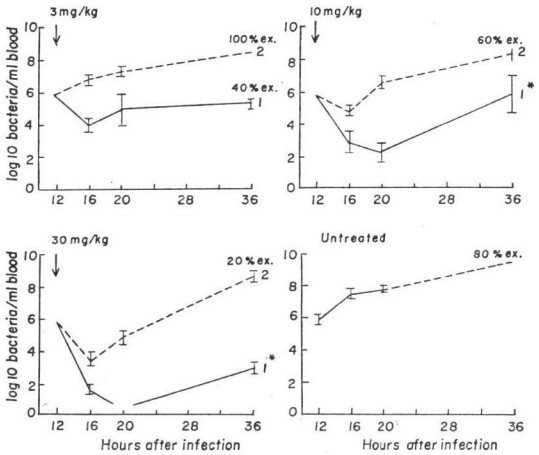
ND not done

†+ ED_{50} of CGP 9000 significantly ($p<0.05$) different[8] from that of cephalexin (†) or cephradine (+)

Table 3. Acute toxicity of CGP 9000 and cephalexin in mice

Mode of application	LD_{50} (mg/kg)	
	CGP 9000	Cephalexin
1 × p.o.	>6,000	5,330
1 × i. p.	7,090	560

Fig. 3 Effect of a single oral dose (administered at arrow) of CGP 9000 (*1*) and cephalexin (*2*) on blood-borne *Streptococcus pyogenes* in female MF2 mice.
n=5; mean ± S. D.; % ex = mortality; * = no deaths; i.p. challenge with 100 bacteria/mouse; the bacterial counts were only made in the surviving mice. Limit of detectability was 1.3 $\log_{10}$ bacteria per ml blood.



infection in the mouse. The counts of viable micro-organisms in the blood of the animals were determined at various times after the oral administration of the antibiotics. Fig. 3 shows that under these experimental conditions CGP 9000 was more effective against *Streptococcus pyogenes* than cephalexin.

The chemotherapeutic efficacy of CGP 9000 was tested in MF2 mice (BALB/c × Charles River hybrids) infected with 4 different gram-positive and 10 gram-negative bacteria and compared with that of cephalexin and cephradine. The mice were challenged by intraperitoneal injection of 3 ~ 40 times the LD_{100} of the test organisms, suspended in BHI-broth, with or without 2% hog gastric mucin depending on the strain. Groups of ten mice at each dose level were then treated orally once only, immediately after infection (*Staphylococcus aureus* infection) or twice, immediately after infection and three hours later, with the cephalosporin derivatives dissolved or suspended in water. All experiments were repeated 3 ~ 6 times. The ED_{50} values (mg/kg) are shown in Table 2. CGP 9000 was two to seven times more effective than cephalexin and cephradine against *Staphylococcus aureus, Streptococcus pyogenes, Diplococcus pneumoniae, Escherichia coli, Salmonella typhimurium, Klebsiella pneumoniae, Proteus mirabilis* and *Proteus rettgeri.* All three cephalosporin derivatives were equally ineffective against *Enterobacter cloacae, Proteus morganii,* and *Pseudomonas aeruginosa* and against strains of *E. coli* producing large quantities of β-lactamase.

The acute toxicity of CGP 9000 in the mouse was compared with that of cephalexin. CGP 9000 was better tolerated after oral and intraperitoneal administration (Table 3).

References

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