ABSORPTION, DISTRIBUTION AND EXCRETION OF CEFMENOXIME (SCE-1365), A NOVEL BROAD-SPECTRUM CEPHALOSPORIN, IN MICE, RATS, RABBITS AND DOGS

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(Received for publication September 3, 1980)

The levels of cefmenoxime (SCE-1365) [7β-[2-(2-aminothiazol-4-yl)-[*Z*]-2-methoxyiminoacetamido]-3-[(1-methyl-1H-tetrazol-5-yl)thiomethyl]ceph-3-em-4-carboxylic acid] and cefotaxime [7β-[2-(2-aminothiazol-4-yl)-[*Z*]-2-methoxyiminoacetamido]-3-acetoxymethyl-ceph-3-em-4-carboxylic acid] in plasma and tissues, and the excretion in urine and bile of experimental animals were compared. A single dose of 20 mg/kg of cephalosporins was administered subcutaneously to mice and intramuscularly to rats, rabbits and dogs. The cefmenoxime and cefotaxime levels in plasma and tissues reached a peak in 15~30 minutes after administration. The cefmenoxime levels in plasma were slightly higher than that of cefotaxime in rats and slightly lower in mice, rabbits and dogs. The tissue levels of cefmenoxime, however, were much higher than those of cefotaxime. In mice and rats, cefmenoxime was distributed in high concentration to various tissues in the descending order of the kidney, plasma, liver, lung, spleen and brain; in rabbits, kidney, plasma, lung, liver, spleen and brain; and in dogs, kidney, liver, plasma, lung, spleen and brain. The plasma and tissue levels of cefmenoxime persisted much longer than those of cefotaxime. Both cephalosporins were excreted principally in the urine. A high biliary excretion of cefmenoxime was observed in rats and dogs. In the specimens from animals given cefotaxime, deacetylcefotaxime was found in various amounts.

Indole-positive *Proteus, Haemophilus influenzae, Serratia marcescens, Citrobacter freundii* and *Enterobacter cloacae* are less susceptible to commercially available cephalosporins[1,2], and recently, cephalosporin-resistant strains of *Escherichia coli* and *Klebsiella pneumoniae* are increasing[3]. Against these bacteria, cefmenoxime (SCE-1365) [7β-[2-(2-aminothiazol-4-yl)-[*Z*]-2-methoxyiminoacetamido]-3-[(1-methyl-1H-tetrazol-5-yl)thiomethyl]ceph-3-em-4-carboxylic acid] shows a more potent antibacterial activity than do cefuroxime, cefoxitin, cefmetazole, cefotiam and cefazolin, and its *in vitro* activity was comparable to cefotaxime [7β-[2-(2-aminothiazol-4-yl)-[*Z*]-2-methoxyiminoacetamido]-3-acetoxymethyl-ceph-3-em-4-carboxylic acid] against several bacterial species[2]. Similar protective activities of cefmenoxime and cefotaxime were observed in mice infected intraperitoneally with many bacterial strains. However, cefmenoxime shows a more potent activity than cefotaxime does in mice infected intraperitoneally with certain strains of *Proteus vulgaris* and *Proteus morganii* and in model infections, such as respiratory tract infection induced by *K. pneumoniae* and urinary tract infection induced by *P. mirabilis*[2].

Therefore, it is imperative to conduct a comparative study on plasma levels, tissue distribution and urinary and biliary excretion of cefmenoxime and cefotaxime.

Materials and Methods

Cephalosporins

Cefmenoxime, cefotaxime and deacetylcefotaxime [7β-[2-(2-aminothiazol-4-yl)-[*Z*]-2-methoxyimino-

acetamido]-3-hydroxymethyl-ceph-3-em-4-carboxylic acid] were prepared in Takeda Chemical Industries, Ltd. (Fig. 1). The sodium salt form of the cephalosporins was used in this study. A single dose of 20 mg/kg of cephalosporin dissolved in saline was administered subcutaneously to mice (2 mg/ml, 0.1 ml/10 g), and intramuscularly to rats (10 mg/kg, 0.2 ml/100 g), rabbits (20 mg/ml, 1 ml/kg), and dogs (100 mg/ml, 0.2 ml/kg).

Animals

Male 5-week-old Slc: ICR mice weighing 25~30 g, male 7~8-week-old JCL: Sprague-Dawley rats weighing 230~260 g, male New Zealand White (NZW-Sat, conventional) rabbits weighing 2.5~3.5 kg, male mongrel dogs weighing 6~14 kg, and female beagle dogs weighing 7~13 kg were used.

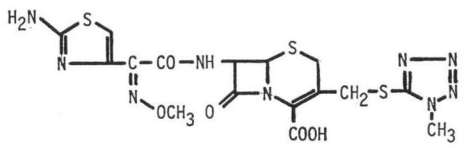
Specimens for Cephalosporin Assay

Blood specimens were collected from the axillary artery and vein of mice and rats anesthetized with ethyl ether, from the femoral artery of unanesthetized rabbits, and from the carotid artery of dogs anesthetized with sodium pentobarbital (Nembutal, Abbott Labs.). Blood specimens were also collected consecutively from the saphena and median veins in beagle dogs. Plasma was separated by centrifugation from the heparinized blood specimens. After the animals were killed by bleeding, the lung, liver, spleen, kidney and brain were removed. A small portion of each tissue was homogenized with 3~9 volumes of medium. The media used were 0.1 M phosphate buffer solution (pH 7) (PBS) for cefmenoxime and methanol for cefotaxime. The homogenates were centrifuged and the supernatants were assayed. Urine specimens were collected from mice and rats in metabolism cages, and with a urethral catheter in unanesthetized rabbits and dogs and anesthetized bile duct-cannulated rats, rabbits and dogs. Bile specimens were collected from the common bile duct-cannulated with polyethylene tubing in rats, rabbits and dogs anesthetized with sodium pentobarbital. In dogs, the cystic bile duct was also ligated. All specimens were stored at −20°C, and assayed within 7 days after collection. The cephalosporins were stable under these conditions.

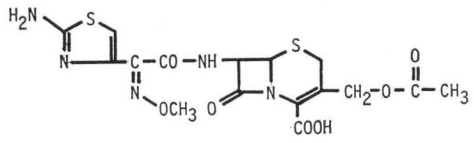
Cephalosporin Assay

The concentrations of cefmenoxime in the specimens were assayed using the cylinder plate diffusion technique with *Proteus mirabilis* ATCC 21100 as a test organism and DST agar (Oxoid). The cefotaxime concentrations in plasma, urine and bile specimens were assayed using the same method for cefmenoxime assay and the cefotaxime concentrations in the supernatants of tissue homogenates were assayed by the paper disk technique. Cephalosporin concentrations in the plasma were calculated from the standard curves of the cephalosporins dissolved in plasma. Urine and bile specimens were diluted with PBS. Cephalosporin activity in the urine and bile was not affected by diluting the specimens more than 5-fold. Cephalosporin concentrations in the diluted specimens and supernatants of the tissue homogenates were calculated from the standard curves of the cephalosporins dissolved in PBS.

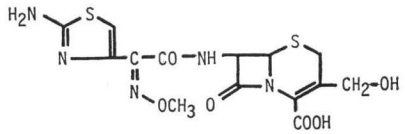
Fig. 1. Chemical structures of cefmenoxime (SCE-1365), cefotaxime and deacetylcefotaxime.



Cefmenoxime (SCE-1365)



Cefotaxime



Deacetylcefotaxime

Detection of Active Metabolite

Plasma specimens were mixed with the same volume of acetone and the supernatants were separated by centrifugation. The supernatants of the mixture of plasma and acetone, tissue homogenates, urine, bile and the standard cephalosporin solutions were spotted on a thin-layer plate (silica gel f; Spotfilm, Tokyo Chemical Industry Co., Ltd.). After development in 0.5 M NaCl, the active spots were detected by the bioautograph technique with *Proteus rettgeri*

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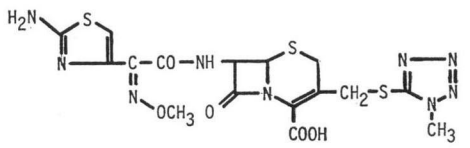
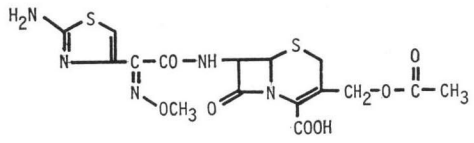
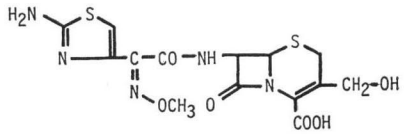


Cefmenoxime (SCE-1365)



Cefotaxime



Deacetylcefotaxime

Detection of Active Metabolite

Plasma specimens were mixed with the same volume of acetone and the supernatants were separated by centrifugation. The supernatants of the mixture of plasma and acetone, tissue homogenates, urine, bile and the standard cephalosporin solutions were spotted on a thin-layer plate (silica gel f; Spotfilm, Tokyo Chemical Industry Co., Ltd.). After development in 0.5 M NaCl, the active spots were detected by the bioautograph technique with *Proteus rettgeri*

Table 2. Urinary levels and excretion of cefmenoxime and cefotaxime after a single subcutaneous dose of 20 mg/kg in mice.

Cephalosporin	Time (hours)	Concentration in μg/ml (Mean±S.D.)	Percent excretion (Mean±S.D.)
Cefmenoxime (n=10)	0~ 8	565 ±302	62.3±9.0
	8~24	7.8± 7.5	3.9±3.4
	Total		65.8±9.1
Cefotaxime (n=10)	0~ 8 (A)*	302 ±104	39.3±4.6
	(B)	213 ± 84.1	27.0±4.6
	(C)	262 ± 83.6	34.3±9.2
	8~24 (A)	4.3± 2.4	1.2±0.9
	(B)	2.5± 1.2	0.7±0.5
	(C)	6.2± 3.0	1.8±1.2
	Total (A)		40.5±4.5
	(B)		27.8±4.7
	(C)		36.0±9.4

* (A)=as cefotaxime activity; (B)=cefotaxime; (C)=deacetylcefotaxime.

Table 3. Plasma and tissue levels of cefmenoxime and cefotaxime after a single intramuscular dose of 20 mg/kg in rats.

Cephalosporin	Tissue	Concentration in μg/ml or g (Mean±S.D.)*						
		1/12 hr.	1/4 hr.	1/2 hr.	1 hr.	2 hrs.	4 hrs.	6 hrs.
Cefmenoxime (n=6)	Plasma	30.3± 4.5	66.7±16.4	49.1± 5.0	27.4± 3.9	6.7±1.2	0.3±0.2	0.1±0.1
	Lung	6.6± 0.9	13.4± 2.8	9.6± 1.4	5.7± 1.2	1.2±0.3	0	0
	Liver	13.0± 1.3	27.3± 3.7	19.4± 1.9	10.9± 2.0	2.3±0.5	0	0
	Spleen	1.9± 0.2	3.7± 0.3	2.8± 0.7	1.6± 0.3	0.4±0.1	0	0
	Kidney	35.8± 7.0	122 ±19.9	96.1± 6.8	42.7±11.1	11.7±2.1	0.8±0.4	0.4±0.3
	Brain	0.3± 0.1	0.5± 0.1	0.5± 0.1	0	0	0	0
Cefotaxime (n=6)	Plasma (A)**	50.9± 7.3	48.9±11.2	34.5± 7.4	17.9± 3.2	2.5±1.5	0.1±0.1	0
	(B)	41.0±17.4	36.5±10.1	29.6±11.3	13.5± 4.7	n.t.	n.t.	n.t.
	(C)	23.3±17.8	41.1± 6.9	14.1±10.4	12.5± 4.8	n.t.	n.t.	n.t.
	Lung (A)	1.9± 0.7	3.0± 0.7	2.6± 0.2	1.5± 0.3	0.3±0.3	0	0
	Liver (A)	0.6± 0.2	1.6± 0.7	1.2± 0.4	0.8± 0.4	0	0	0
	Spleen (A)	0.5± 0.1	1.0± 0.3	0.8± 0.1	0.5± 0.1	0	0	0
	Kidney (A)	4.5± 1.0	17.4± 3.5	14.1± 4.0	4.6± 0.8	1.3±1.5	0	0
	(B)	0	0	0	0	n.t.	n.t.	n.t.
	(C)	13.1± 3.0	51.1±10.2	41.4±11.6	13.5± 2.2	n.t.	n.t.	n.t.
	Brain (A)	0	0	0	0	0	0	0

* 0=Not detected; n.t.=Not tested.

** (A)=as cefotaxime activity; (B)=cefotaxime; (C)=deacetylcefotaxime.

after administration and thereafter they declined rapidly. Cefmenoxime was distributed at high concentrations to various tissues in the descending order of the kidney, plasma, liver, lung, spleen and brain. In the plasma, except at 5 minutes after administration, the cefmenoxime levels were higher than the cefotaxime levels, and in the tissues, the cefmenoxime levels were also much higher than the cefotaxime levels at all times tested. In the liver and kidney, especially, the cefmenoxime levels

Table 4. Urinary levels and excretion of cefmenoxime and cefotaxime after a single intramuscular dose of 20 mg/kg in rats.

Cephalosporin	Time (hours)	Concentration in μg/ml (Mean±S.D.)	Percent excretion (Mean±S.D.)
Cefmenoxime	0~ 8	824 ± 291	52.2±8.4
(*n*=10)	8~24	17.9± 12.1	2.6±1.8
	Total		54.8±8.0
Cefotaxime	0~ 8 (A)*	1,120 ±676	50.3±6.6
(*n*=10)	(B)	490 ±131	25.7±6.9
	(C)	1,420 ±679	69.2±4.8
	8~24 (A)	12.3± 12.1	2.1±1.8
	(B)	7.3± 6.8	1.3±1.1
	(C)	10.4± 11.1	1.8±1.7
	Total (A)		52.4±6.7
	(B)		27.1±7.8
	(C)		71.0±3.5

* (A)=as cefotaxime activity; (B)=cefotaxime; (C)=deacetylcefotaxime.

Table 5. Urinary levels and excretion of cefmenoxime and cefotaxime after a single intramuscular dose of 20 mg/kg in anesthetized bile duct-cannulated rats.

Cephalosporin	Time (hours)	Concentration in μg/ml (Mean±S.D.)	Percent excretion (Mean±S.D.)
Cefmenoxime	0~ 2	2,380 ±1,040	27.5± 8.3
(*n*=10)	2~ 4	1,200 ± 488	16.1± 8.4
	4~ 6	401 ± 223	5.1± 1.9
	6~ 8	151 ± 116	1.9± 1.6
	8~24	18.7± 10.5	1.9± 1.6
	Total		52.5±12.6
Cefotaxime	0~ 2 (A)*	2,290 ± 626	32.3± 7.8
(*n*=10)	(B)	1,180 ± 263	18.1± 2.8
	(C)	3,580 ±1,480	52.2± 7.5
	2~ 4 (A)	820 ± 268	11.8± 3.0
	(B)	370 ± 149	5.2± 1.2
	(C)	1,110 ± 489	17.8±10.7
	4~ 6 (A)	228 ± 132	2.3± 1.5
	(B)	69.3± 21.3	0.6± 0.2
	(C)	274 ± 120	2.5± 1.3
	6~ 8 (A)	101 ± 52.3	1.0± 0.4
	(B)	47.2± 27.8	0.4± 0.2
	(C)	238 ± 76.7	2.2± 0.8
	8~24 (A)	19.2± 20.8	1.4± 1.6
	(B)	10.7± 14.3	0.8± 1.1
	(C)	12.2± 1.2	0.8± 0.2
	Total (A)		48.8± 7.4
	(B)		25.2± 2.9
	(C)		75.6±19.0

* (A)=as cefotaxime activity; (B)=cefotaxime; (C)=deacetylcefotaxime.

Table 6. Biliary levels and excretion of cefmenoxime and cefotaxime after a single intramuscular dose of 20 mg/kg in anesthetized bile duct-cannulated rats.

Cephalosporin	Time (hours)	Concentration in μg/ml (Mean±S.D.)	Percent excretion (Mean±S.D.)
Cefmenoxime (n=10)	0~ 2	660 ±289	22.6 ±8.4
	2~ 4	223 ±138	7.0 ±3.2
	4~ 6	63.7± 44.3	2.1 ±1.5
	6~ 8	24.4± 31.9	0.5 ±0.5
	8~24	3.0± 6.4	0.4 ±0.6
	Total		32.6 ±10.1
Cefotaxime (n=10)	0~ 2 (A)*	18.1± 5.6	0.90± 0.39
	(B)	8.9± 2.1	0.50± 0.07
	(C)	32.2± 4.5	2.07± 0.24
	2~ 4 (A)	5.6± 1.9	0.27± 0.07
	(B)	2.0± 0.5	0.13± 0.06
	(C)	7.7± 2.2	0.47± 0.13
	4~ 6 (A)	1.7± 0.3	0.06± 0.01
	6~ 8 (A)	0.7± 0.2	0.02± 0.02
	8~24 (A)	0.1± 0.1	0.02± 0.01
	Total (A)		1.27± 0.44
	(B)		(0.63± 0.10)**
	(C)		(2.54± 0.12)

* (A)=as cefotaxime activity; (B)=cefotaxime; (C)=deacetylcefotaxime.
** within 4 hours.

Table 7. Plasma and tissue levels of cefmenoxime and cefotaxime after a single intramuscular dose of 20 mg/kg in rabbits.

Cephalosporin	Tissue	Concentration in μg/ml or g (Mean±S.D.)*					
		1/4 hr.	1/2 hr.	1 hr.	2 hrs.	4 hrs.	6 hrs.
Cefmenoxime (n=3)	Plasma	28.5±14.3	40.3± 5.4	17.9± 3.8	12.4± 3.1	4.8±1.3	1.6±0.5
	Lung	5.6± 3.9	7.3± 1.0	4.3± 1.3	2.0± 0.3	1.2±0.5	0.3±0.1
	Liver	3.6± 2.5	5.5± 1.2	2.7± 1.3	1.5± 0.5	0.8±0.6	0
	Spleen	1.6± 1.2	2.7± 0.3	1.3± 0.3	1.0± 0.2	0.7±0.5	0
	Kidney	63.8±43.3	90.3±13.4	65.0±35.8	29.3±10.0	12.2±4.6	4.7±2.3
	Brain	0.2± 0.1	0.3± 0.1	0	0	0	0
Cefotaxime (n=3)	Plasma (A)**	55.0±14.2	34.0± 3.2	29.0±15.2	9.7± 3.0	3.5±0.4	1.4±1.0
	(B)	54.2± 7.6	31.7± 4.4	25.3± 1.2	9.1± 0.8	n.t.	n.t.
	(C)	13.9± 5.7	14.0± 5.9	12.3± 5.7	4.1± 0.2	n.t.	n.t.
	Lung (A)	3.1± 0.4	2.3± 0.7	1.8± 0.9	0.4± 0.2	0	0
	Liver (A)	1.4± 0.8	0.7± 0.2	0	0	0	0
	Spleen (A)	0.4± 0.3	0.4± 0.1	0	0	0	0
	Kidney (A)	59.1±16.5	36.3±15.0	20.6±11.9	5.6± 2.7	2.3±0.3	0.7±0.5
	(B)	0	0	0	0	n.t.	n.t.
	(C)	174 ±48.7	107 ±44.2	60.6±35.0	16.4± 8.6	n.t.	n.t.
	Brain (A)	0	0	0	0	0	0

* 0=Not detected; n.t.=Not tested.
** (A)=as cefotaxime activity; (B)=cefotaxime; (C)=deacetylcefotaxime.

were much higher than the cefotaxime levels. No active metabolites were detected in the specimens of rats given cefmenoxime. In rats given cefotaxime, the ratio of deacetylcefotaxime to cefotaxime in the plasma increased progressively with time after cefotaxime administration. In the kidney, practically no cefotaxime activity was detected, whereas deacetylcefotaxime reached much higher levels in this organ (Table 3).

The mean values of urinary excretion of cefmenoxime were comparable with that of cefotaxime estimated as the cefotaxime activity and no difference was observed between those in the unanesthetized and anesthetized bile duct-cannulated rats. A large amount of deacetylcefotaxime was found in the urine of rats given cefotaxime and the total mean values (cefotaxime plus deacetylcefotaxime) of urinary excretion were much higher than that of cefmenoxime (Tables 4 and 5). The mean value of biliary excretion of cefmenoxime was much higher than that of the total amount of cefotaxime plus deacetylcefotaxime (Table 6).

Rabbits

The peak levels of cefmenoxime and cefotaxime in plasma and tissues were observed 30 minutes after administration. Cefmenoxime was distributed in high concentrations to various tissues in the descending order of the kidney, plasma, lung, liver, spleen and brain. The cefmenoxime levels in

Table 8. Urinary levels and excretion of cefmenoxime and cefotaxime after a single intramuscular dose of 20 mg/kg in rabbits.

Cephalosporin	Time (hours)	Concentration in μg/ml (Mean±S.D.)	Percent excretion (Mean±S.D.)
Cefmenoxime (n=9)	0~ 2	3,270 ±1,580	38.5±17.6
	2~ 4	2,460 ±1,830	21.1± 7.8
	4~ 6	1,280 ±1,050	10.4± 5.2
	6~ 8	655 ± 615	7.1± 5.5
	8~24	86.2± 67.8	4.7± 2.8
	Total		81.8±10.6
Cefotaxime (n=6)	0~ 2 (A)*	1,270 ± 446	23.8±13.8
	(B)	743 ± 202	15.4± 8.2
	(C)	2,080 ± 629	40.3±14.9
	2~ 4 (A)	570 ± 513	12.3± 5.6
	(B)	155 ± 202	4.0± 1.3
	(C)	713 ± 863	23.3±20.4
	4~ 6 (A)	390 ± 289	4.8± 3.4
	(B)	158 ± 230	1.5± 1.4
	(C)	444 ± 456	5.6± 5.7
	6~ 8 (A)	225 ± 143	1.6± 1.1
	(B)	82.1± 73.4	0.5± 0.4
	(C)	268 ± 265	1.7± 1.5
	8~24 (A)	24.2± 19.3	1.5± 0.9
	(B)	9.0± 9.9	0.5± 0.4
	(C)	34.0± 44.7	1.6± 1.5
	Total (A)		44.0± 4.6
	(B)		21.8± 7.0
	(C)		72.5±15.4

* (A)=as cefotaxime activity; (B)=cefotaxime; (C)=deacetylcefotaxime.

plasma were lower than the cefotaxime levels but the tissue levels of cefmenoxime were much higher than those of cefotaxime. No active metabolites were detected in the specimens of rabbits given cefmenoxime. In rabbits given cefotaxime, the ratio of deacetylcefotaxime to cefotaxime in the plasma increased progressively with time after cefotaxime administration, and in the kidney, only a trace of cefotaxime was observed even 15 minutes after the administration, whereas the deacetylcefotaxime level was much higher in this organ (Table 7).

Table 9. Urinary levels and excretion of cefmenoxime and cefotaxime after a single intramuscular dose of 20 mg/kg in anesthetized bile duct-cannulated rabbits.

Cephalosporin	Time (hours)	Concentration in μg/ml (Mean±S.D.)	Percent excretion (Mean±S.D.)
Cefmenoxime	0~ 2	1,750 ±1,230	14.5±13.8
(n=10)	2~ 4	5,510 ±3,370	20.1± 9.4
	4~ 6	4,080 ±2,400	17.3± 8.1
	6~ 8	3,060 ±2,500	13.2± 6.5
	8~24	773 ± 477	16.3± 8.5
	Total		81.4± 7.9
Cefotaxime	0~ 2 (A)*	1,250 ± 981	15.7± 6.4
(n=10)	(B)	473 ± 488	5.0± 1.1
	(C)	1,830 ±1,290	24.4±14.4
	2~ 4 (A)	1,450 ±1,070	11.2± 4.4
	(B)	886 ± 686	6.0± 0.5
	(C)	3,050 ±2,500	19.8± 0.8
	4~ 6 (A)	1,080 ± 977	6.2± 1.6
	(B)	687 ± 619	3.5± 0.3
	(C)	2,900 ±2,600	15.0± 2.4
	6~ 8 (A)	566 ± 507	2.7± 1.0
	(B)	278 ± 249	1.4± 0.7
	(C)	1,400 ±1,440	5.7± 1.4
	8~24 (A)	141 ± 63.4	3.5± 1.6
	(B)	57.7± 25.6	1.6± 0.9
	(C)	267 ± 81.5	7.3± 3.3
	Total (A)		39.3± 2.0
	(B)		17.4± 1.3
	(C)		72.2± 7.8

* (A)=as cefotaxime activity; (B)=cefotaxime; (C)=deacetylcefotaxime.

The mean value of urinary excretion of cefmenoxime was much higher than that of cefotaxime estimated as the cefotaxime activity. A large amount of deacetylcefotaxime was found in the urine of rabbits given cefotaxime and the total mean value of the urinary excretion (cefotaxime plus deacetylcefotaxime) was higher than that of cefmenoxime. No difference in urinary excretion was observed between the unanesthetized and anesthetized bile duct-cannulated rabbits but the excretion rate in the former was higher than that in the latter (Tables 8 and 9). The mean values of biliary excretion of cefmenoxime and cefotaxime were similar and much lower than those in other animal species (Table 10).

Table 10. Biliary levels and excretion of cefmenoxime and cefotaxime after a single intramuscular dose of 20 mg/kg in anesthetized bile duct-cannulated rabbits.

Cephalosporin	Time (hours)	Concentration in μg/ml (Mean±S.D.)	Percent excretion (Mean±S.D.)
Cefmenoxime	0~ 2	5.9±3.5	0.11±0.06
(*n*=10)	2~ 4	4.4±2.5	0.06±0.04
	4~ 6	4.5±3.4	0.04±0.02
	6~ 8	2.7±2.6	0.02±0.01
	8~24	1.1±0.8	0.04±0.02
	Total		0.27±0.13
Cefotaxime	0~ 2 (A)*	3.8±1.0	0.07±0.02
(*n*=10)	(B)	1.6±1.3	0.02±0.02
	(C)	7.7±1.2	0.12±0.04
	2~ 4 (A)	2.4±0.8	0.04±0.01
	4~ 6 (A)	1.8±0.6	0.02±0.01
	6~ 8 (A)	1.9±1.1	0.02±0.01
	8~24 (A)	0.9±0.2	0.06±0.02
	Total (A)		0.21±0.05

* (A)=as cefotaxime activity; (B)=cefotaxime; (C)=deacetylcefotaxime.

Table 11. Plasma and tissue levels of cefmenoxime and cefotaxime after a single intramuscular dose of 20 mg/kg in mongrel dogs.

Cephalosporin	Tissue	Concentration in μg/ml or g (Mean±S.D.)*				
		1/2 hr.	1 hr.	2 hrs.	4 hrs.	6 hrs.
Cefmenoxime	Plasma	22.7± 3.8	13.3± 4.1	4.5± 1.9	0.5± 0.4	0
(*n*=3)	Lung	7.9± 1.7	5.5± 1.3	2.2± 0.7	0.2± 0.2	0
	Liver	63.6± 16.8	55.7± 8.8	28.4±11.3	0.4± 0.3	0
	Spleen	2.5± 0.2	1.7± 1.1	0.5± 0.2	0	0
	Kidney	281 ±117	180 ±113	61.0±29.7	9.6±12.9	1.9±0.9
	Brain	0.2± 0.1	0	0	0	0
Cefotaxime	Plasma (A)**	34.0± 11.5	25.3± 7.1	6.3± 0.6	2.1±2.4	0
(*n*=3)	(B)	30.5± 13.4	22.8± 8.3	4.7± 0.4	n.t.	n.t.
	(C)	10.2± 8.2	7.2± 3.6	4.6± 0.7	n.t.	n.t.
	Lung (A)	8.4± 2.9	6.1± 1.8	1.3± 0.5	0	0
	(B)	6.8± 2.5	n.t.	n.t.	n.t.	n.t.
	(C)	4.6± 1.7	n.t.	n.t.	n.t.	n.t.
	Liver (A)	4.6± 1.2	3.0± 2.5	0.8± 0.1	0	0
	(B)	0.3± 0.2	n.t.	n.t.	n.t.	n.t.
	(C)	12.5± 4.1	n.t.	n.t.	n.t.	n.t.
	Spleen (A)	2.7± 1.1	1.1± 0.2	0	0	0
	Kidney (A)	76.8± 18.1	95.3± 30.2	10.9± 2.4	6.7±9.5	0.2
	(B)	53.9± 26.6	57.6± 15.7	5.3± 1.8	n.t.	n.t.
	(C)	67.1± 47.1	111 ± 42.7	16.2± 8.4	n.t.	n.t.
	Brain (A)	0	0	0	0	0

* 0=Not detected; n.t.=Not tested.

** (A)=as cefotaxime activity; (B)=cefotaxime; (C)=deacetylcefotaxime.

Dogs

The peak levels of cefmenoxime and cefotaxime in plasma and tissues were observed 30 minutes after administration. Cefmenoxime was distributed at high concentrations to various tissues in the descending order of the kidney, liver, plasma, lung, spleen and brain. Although the plasma level of cefmenoxime was lower than that of cefotaxime, the tissue level of the former was higher than that of the latter. No active metabolites were detected in the specimens from dogs given cefmenoxime. In dogs given cefotaxime, the deacetylcefotaxime levels in the liver and kidney were higher than the cefotaxime levels but in the plasma and lung, the cefotaxime levels were higher than the deacetylcefotaxime levels (Table 11). In anesthetized bile duct-cannulated dogs, the cefmenoxime and cefotaxime levels in plasma were higher than those in unanesthetized dogs (Table 12).

The mean value of urinary excretion of cefmenoxime was higher than that of cefotaxime, estimated as the cefotaxime activity, and the excretion in anesthetized bile duct-cannulated dogs was slightly delayed compared to that in normal dogs. The mean value of biliary excretion of cefmenoxime, however, was much higher than that of cefotaxime. Compared to other animal species, a relatively small amount of deacetylcefotaxime was recovered in dogs (Tables 13 and 14).

Table 12. Plasma levels of cefmenoxime and cefotaxime after a single intramuscular dose of 20 mg/kg in dogs.

Cephalosporin	Dog		Concentration in μg/ml (Mean±S.D.)*				
			1/2 hr.	1 hr.	2 hrs.	4 hrs.	6 hrs.
Cefmenoxime	Beagle (unanesthetize)		18.6±6.1	13.2±1.6	6.5±2.3	1.2±0.6	0.2±0.1
(n=3)	Beagle (anesthetize)**		23.8±8.6	15.4±9.9	7.0±4.0	1.5±0.3	0.6±0.4
	Mongrel (anesthetize)		15.3±3.5	11.8±1.8	7.4±2.2	2.9±1.0	1.3±0.8
Cefotaxime	Beagle (unanesthetize)	(A)***	25.2±6.9	18.6±6.4	10.4±3.2	2.5±1.0	0.6±0.5
(n=3)		(B)	25.2±6.9	17.8±7.1	8.6±3.8	1.8±1.2	n.t.
		(C)	0	2.1±2.2	5.2±3.1	1.7±1.0	n.t.
	Beagle (anesthetize)	(A)	25.2±6.0	22.8±5.0	12.4±5.1	5.2±4.1	2.4±1.9
		(B)	24.3±5.2	21.0±4.1	11.4±4.8	4.5±3.9	n.t.
		(C)	2.5±2.3	5.1±4.0	2.8±1.4	1.7±0.7	n.t.
	Mongrel (anesthetize)	(A)	32.7±8.5	21.5±8.9	8.0±2.4	3.4±1.4	2.2±1.3
		(B)	28.5±6.4	17.7±8.4	6.2±1.9	2.4±1.2	n.t.
		(C)	12.0±6.3	10.8±4.2	5.0±1.5	2.7±2.1	n.t.

* 0=Not detected; n.t.=Not tested.

** Dogs were anesthetized with sodium pentobarbital and the common bile duct was cannulated for collection of bile.

*** (A)=as cefotaxime activity; (B)=cefotaxime; (C)=deacetylcefotaxime.

Discussion

The therapeutic activity of antibiotics is affected by several factors such as the antibacterial activity, resistance to enzymes, and pharmacokinetic profiles. In general, the cephalosporins with an acetoxymethyl group at the 3-position of a cephem-ring is metabolized to the 3-hydroxymethyl form and the 3-hydroxymethyl compounds are less active than the parent compounds[4~10]. Cefmenoxime, like cefotaxime, has a potent antibacterial activity against Gram-positive and Gram-negative bacteria. The side chains of the 3-position of cefmenoxime and cefotaxime are a methyltetrazolthio group and an acetoxymethyl group, respectively. Like other cephalosporins, cefotaxime is metabolized in the

Table 13. Urinary levels and excretion of cefmenoxime and cefotaxime after a single intramuscular dose of 20 mg/kg in dogs.

Cephalosporin	Unanesthetize (Beagle)			Anesthetized bile duct-cannulation (Beagle)			Anesthetized bile duct-cannulation (Mongrel)		
	Time (hours)	Concentration in μg/ml (Mean±S.D.)	Percent excretion (Mean±S.D.)	Time (hours)	Concentration in μg/ml (Mean±S.D.)	Percent excretion (Mean±S.D.)	Time (hours)	Concentration in μg/ml (Mean±S.D.)	Percent excretion (Mean±S.D.)
Cefmenoxime (n=3)				0~1	2,250±1,850	9.7± 2.4	0~1	3,310±2,060	9.3±5.9
	0~2	12,400±6,110	55.3± 4.9	1~2	7,850±7,090	27.1±10.0	1~2	9,550± 520	20.8±5.1
	2~4	5,890±1,530	18.1± 4.2	2~4	4,090±2,370	21.5± 6.1	2~4	7,340±5,870	30.0±7.8
	4~6	1,330± 106	3.6± 0.6	4~6	910± 260	6.2± 1.8	4~6	3,060±1,850	12.0±4.3
	Total		77.0± 8.0	Total		64.5±11.4	Total		72.1±5.1
Cefotaxime (n=3)				0~1 (A)*	5,230±5,240	11.2± 7.7	0~1 (A)	3,870±2,050	20.2±7.3
				(B)	4,940±4,880	10.7± 7.2	(B)	2,760±1,930	19.6±6.9
				(C)	881±1,060	1.8± 1.6	(C)	312± 338	1.9±1.9
	0~2 (A)	6,600±3,610	42.9± 9.4	1~2 (A)	3,950±1,770	16.9± 8.7	1~2 (A)	5,540±3,910	18.1±5.4
	(B)	6,080±3,540	38.9±10.0	(B)	3,620±1,540	15.1± 7.3	(B)	5,250±3,760	16.9±4.7
	(C)	1,690± 219	13.3± 2.2	(C)	1,010± 831	5.4± 5.0	(C)	860± 757	4.0±3.0
	2~4 (A)	3,190± 755	12.0± 1.0	2~4 (A)	3,390±1,510	17.8± 1.9	2~4 (A)	1,930± 277	15.4±5.2
	(B)	2,670± 770	9.9± 0.5	(B)	3,210±1,460	16.7± 2.0	(B)	1,690± 254	13.4±4.5
	(C)	1,540± 422	6.8± 2.6	(C)	555± 358	3.6± 2.3	(C)	679± 123	6.4±2.7
	4~6 (A)	796± 234	3.3± 0.1	4~6 (A)	1,840±1,300	9.6± 7.2	4~6 (A)	684± 268	3.7±2.9
	(B)	573± 135	2.3± 0.2	(B)	1,750±1,330	9.1± 7.4	(B)	469± 203	2.4±1.7
	(C)	647± 299	2.9± 0.6	(C)	265± 96	1.6± 0.9	(C)	643± 222	4.2±3.8
	Total (A)		58.2± 9.3	Total (A)		55.5±10.5	Total (A)		57.4±9.9
	(B)		51.2±10.3	(B)		51.5± 8.6	(B)		52.3±9.6
	(C)		23.1± 4.0	(C)		12.6± 9.6	(C)		16.7±4.4

* (A)=as cefotaxime activity; (B)=cefotaxime; (C)=deacetylcefotaxime.

Table 14. Biliary levels and excretion of cefmenoxime and cefotaxime after a single intramuscular dose of 20 mg/kg in anesthetized bile duct-cannulated dogs.

Cephalosporin	Beagle			Mongrel		
	Time (hours)	Concentration in μg/ml (Mean±S.D.)	Percent excretion (Mean±S.D.)	Time (hours)	Concentration in μg/ml (Mean±S.D.)	Percent excretion (Mean±S.D.)
Cefmenoxime (n=3)	0~1	880 ±380	1.8 ±0.7	0~1	130 ±140	0.2 ±0.2
	1~2	2,120 ±480	4.1 ±0.9	1~2	767 ±340	1.3 ±0.8
	2~4	1,110 ±120	3.1 ±0.7	2~4	583 ±596	1.7 ±0.9
	4~6	307 ± 97	0.9 ±0.1	4~6	233 ±257	0.8 ±0.6
	Total		9.9 ±1.8	Total		4.0 ±1.5
Cefotaxime (n=3)	0~1 (A)*	38.1± 20.2	0.06±0.04	0~1 (A)	37.0± 29.0	0.03±0.03
	(B)	15.5± 9.1	0.02±0.01	(B)	35	0.01±0.02
	(C)	66.2± 40.5	0.11±0.08	(C)	56	0.03±0.04
	1~2 (A)	136 ± 48.5	0.17±0.08	1~2 (A)	204 ± 98	0.06±0.02
	(B)	59.4± 35.4	0.06±0.03	(B)	124 ± 69	0.03±0.01
	(C)	224 ± 96.3	0.31±0.19	(C)	234 ±113	0.07±0.04
	2~4 (A)	94.5± 44.2	0.21±0.02	2~4 (A)	225 ±158	0.08±0.01
	(B)	40.9± 36.2	0.08±0.05	(B)	109 ± 69	0.04±0.02
	(C)	157 ± 23.7	0.40±0.12	(C)	340 ±305	0.11±0.04
	4~6 (A)	46.0± 31.7	0.10±0.03	4~6 (A)	137 ±112	0.06±0.03
	(B)	26.0± 25.5	0.05±0.03	(B)	86 ± 67	0.03±0.01
	(C)	60.3± 24.8	0.15±0.06	(C)	148 ±156	0.05±0.05
	Total (A)		0.54±0.10	Total (A)		0.22±0.03
	(B)		0.22±0.09	(B)		0.12±0.03
	(C)		0.97±0.40	(C)		0.26±0.08

* (A)=as cefotaxime activity; (B)=cefotaxime; (C)=deacetylcefotaxime.

body to deacetylcefotaxime, a less active metabolite[11]. Absorption of cefmenoxime and cefotaxime from the injection site was rapid and the plasma and tissue levels reached the peak at 15~30 minutes after administration, as is known for various parenteral cephalosporins[12~14]. The plasma level of cefmenoxime was lower than that of cefotaxime plus deacetylcefotaxime, but the tissue level of cefmenoxime was much higher than that of cefotaxime plus deacetylcefotaxime. This finding does coincide with the fact that the plasma and tissue levels of cephalothin (3-acetoxymethyl; 7-thienylacetamido) were lower than those of cephaloridine (3-pyridylmethyl; 7-thienylacetamido)[12,13]. The urinary excretion of cefmenoxime was similar to or higher than that of cefotaxime, when estimated as cefotaxime activity, but the latter was much higher than the former when estimated as the total amount of cefotaxime plus deacetylcefotaxime. The biliary excretion of cefmenoxime was much higher than that of cefotaxime. These findings suggest that the substituent at the 3-position of cephalosporins may not only increase the enzymatic resistance, but also play an important role in increasing the tissue permeability. BRAUER[15] reported that organic carboxylic acids having a molecular weight of the order of 300 or more, were excreted into bile after storage in the hepatic cells from the blood. It is also reported that compounds with molecular weight of 300~500 show a species difference in the biliary excretion and compounds showing high biliary excretion are concentrated in the hepatic cells and biliary excretion occurs against a concentration gradient from liver to bile[15~18]. Recently, WRIGHT and LINE[19] reported that above a threshold molecular weight of about 450, biliary excretion of cephalosporin increased in a generally progressive way. The hepatic levels of cefmenoxime reached a peak at 15~30 minutes after administration and the highest cefmenoxime levels in the bile were observed in 1~2 hours. These results indicate that cefmenoxime was excreted in the bile according to the general rule of biliary ex-

cretion of anionic polar compounds. The biliary excretion of cefmenoxime was much higher in rats, moderate in dogs and much lower in rabbits, but the hepatic levels of cefmenoxime were higher in dogs and decreased in the order of rats and rabbits. The relationship between the physicochemical properties and the tissue distribution and excretion of cephalosporins should receive further studies.

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