BICYCLOMYCIN, A NEW ANTIBIOTIC
IV. ABSORPTION, EXCRETION AND TISSUE DISTRIBUTION

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Bicyclomycin, a new antibiotic active against Gram-negative bacteria and having a unique chemical structure, was investigated for its absorption, excretion and tissue distribution. Bicyclomycin was intramuscularly administered to mice, rats, rabbits and dogs at a single dose of 50 mg/kg. Although the mean peak levels in the blood and serum differed with animal species, the values were found to be fairly high. Seventy % or more of the given dose were recovered in the 24-hour urine samples.

A relatively long half-life of bicyclomycin was observed as compared with that of ampicillin, when both antibiotics were administered intravenously to rabbits at a single dose of 50 mg/kg.

The results of the study on the biliary excretion in rats showed its low excretion rate after a single intramuscular dose of 50 mg/kg. When a single intramuscular dose of 100 mg/kg was given to rats, bicyclomycin was well distributed in various tissues, and the highest concentration was observed in the kidney.

In human volunteers, mean peak serum levels were 18.0 and 31.9 mcg/ml at the first 30 minutes and 1 hour when dosed intramuscularly at 500 mg and 1 g, respectively. Urinary excretions of bicyclomycin were relatively high, *i.e.* 96.2 and 94.8 % at a dose of 500 mg and 1 g, respectively, during 24 hours. No metabolite possessing antimicrobial activity except bicyclomycin was found in the urine samples from the human volunteers. When given orally, bicyclomycin was absorbed to a certain extent in rats, but only to a limited extent in human volunteers.

In a previous paper it was reported that, bicyclomycin, a new antibiotic of a unique chemical structure,[1,2] showed *in vitro* activity against Gram-negative bacteria including *Escherichia coli*, *Klebsiella*, *Shigella*, *Salmonella*, *Citrobacter* and *Enterobacter cloacae*, but not against *Proteus* and *Pseudomonas aeruginosa*, and was also shown to be active against experimental mice infection with different strains of *E. coli* highly resistant to other commercially available antibiotic.[3] It gave good protection *in vivo*. Therefore, it is of specific interest to obtain detailed knowledge on the metabolism of this antibiotic by various routes of administrations.

This paper reports absorption, excretion, tissue distribution, and metabolism studies in animals and man.

Materials and Methods

1. Antibiotics tested

Bicyclomycin (Fujisawa Research Laboratories) and ampicillin (Beecham Research Laboratories) were used throughout this study.

2. Animals used in these experiments were as follows:

Mice; ICR male, weighing 30~31 g.
Rats; SD male, weighing 180~200 g.
Rabbits; male, weighing 2.7~3.7 kg.
Dogs; Beagle male, weighing 8~13 kg.

3. Methods for assay of drug

Levels of the aforementioned in the serum, urine, bile and tissues were assayed by the cylinder plate method using *E. coli* ATCC-27166. The test medium consisting of 0.8% (w/v) of Difco nutrient broth and 0.8% (w/v) of agar was inoculated with a 0.2% of an overnight culture of the assay organism in Trypticase soy broth. The diameters of inhibitory zones were measured after incubation at 37°C for 20 hours, and levels of the antibiotic in test samples were calculated from the results.

4. Determination of absorption, excretion and distribution after intramuscular administration of bicyclomycin in experimental animals

(1) Serum or blood levels: A total of 40 mice received intramuscular administration of bicyclomycin at a single dose of 50 mg/kg. Eight mice each were bled at 5, 10, 20, 30 and 60 minutes after administration by heart-puncture with heparin. The plasma samples thus obtained were used for the assay. A total of 25 rats were similarly administered bicyclomycin and blood samples were taken by heart-puncture from 5 rats each at 0.5, 1, 2, 3, and 5 hours after the administration. Five rabbits and 5 dogs were given bicyclomycin intramuscularly at a single dose of 50 mg/kg and blood samples were withdrawn from these animals at similar intervals. The samples were allowed to clot and sera were separated for assay by the cylinder plate method. Accompanying standards were prepared by diluting bicyclomycin in heparinized blood or sera from respective animals.

(2) Urinary excretion: Bicyclomycin was given intramuscularly to 8 mice and 5 rats at a single dose of 50 mg/kg. The urine samples were collected using metabolic cages at certain intervals during a 24-hour period after administration, *i.e.*, 0 to 6 hour and 6 to 24 hour in mice and 0 to 3 hour, 3 to 6 hour and 6 to 24 hours in rats. In the rabbits and dogs, from which blood samples were concurrently taken for serum assay, a polyethylene tube was cannulated into urethra and urine samples were collected at the same intervals as those in rats.

(3) Biliary excretion in rats: Biliary levels were determined in 5 rats. The animals were anesthetized with ether and a polyethylene tube was cannulated into bile duct by a standard laboratory procedure. Bicyclomycin was administered intramuscularly at a single dose of 50 mg/kg. Bile samples were collected at 3 intervals during the periods of 0 to 3, 3 to 6, and 6 to 24 hour after administration.

(4) Tissue distribution in rats: A total of 20 rats were divided into 2 groups of 10 each, rats in one group were given bicyclomycin intramuscularly at a single dose of 50 mg/kg and rats in another group received the antibiotic at 100 mg/kg. Thirty minutes after injection, all rats were killed by cervical dislocation. The lung, liver, kindey, spleen and heart were removed separately, washed with normal saline and homogenized with 3-fold volumes of normal saline in a Waring Blender. The homogenates were then centrifuged at 3,000 r.p.m. for 10 minutes and the supernatants were used for bioassay.

5. Determination of biological half-life of bicyclomycin in rabbits

Bicyclomycin was given intravenously to 5 rabbits at a single dose of 50 mg/kg. A half-life of bicyclomycin in serum sample was determined during the first 120 minutes of administration. As a comparison, the same experiment was conducted with ampicillin.

6. Determination of absorption and excretion and identification of active substance in healthy volunteers

(**1**) Serum levels and urinary excretion: The serum and urinary levels of bicyclomycin were determined in healthy male volunteers ranging from 56 to 75 kg of body weight. One group of 5 received intramuscular administration of bicyclomycin at a single dose of 500 mg, and another group of 4 received 1,000 mg. Blood specimens were obtained 0.5, 1, 2, 3 and 5 hours after administration. Urine samples were concurrently collected during the periods of 0 to 1, 1 to 3, 3 to 6, 6 to 8, 8 to 10 and 10 to 24 hour following administration.

(**2**) Identification of active substance excreted into human urine: Bicyclomycin was administered intramuscularly to 2 healthy volunteers at a single dose of 1,000 mg. The urine was collected over a period of 24 hours after administration, and examined by thin-layer chromatography and bioautography. The standard bicyclomycin solution and urine samples were run for chromatographic examination by the use of the Chromagram sheet (Eastman). The sheet was then dried and developed at room temperature by ascending technique.

a. Thin-layer chromatography: Solvent system; *n*-BuOH – AcOH – water (4 : 1 : 5), upper layer $CHCl_3$–MeOH (5 : 1). Adsorbent; Chromagram sheet (Eastman) No. 6061.

b. Bioautography: The dried sheet was then plated on the agar plate which had been seeded with a 0.2% of the culture broth (10^8/ml) of *E. coli* ATCC-27166. After removing the strips, the plates were incubated at 37°C for 20 hours. Areas of antibiotic activity were exhibited by inhibition of growth.

7. Determination of urinary excretion after oral adminstration of bicyclomycin in rats and healthy volunteers

The urinary levels of bicyclomycin after oral administration were determined in rats and healthy volunteers. Five rats were fasted for 24 hours

Table 1. Blood levels after intramuscular administration of bicyclomycin (50 mg/kg) in mice

Mouse	Blood level (mcg/ml)				
	5 min.	10 min.	20 min.	30 min.	60 min.
A	80.0	64.0	39.0	29.5	<12.2
B	86.0	67.0	33.0	30.5	<12.2
C	62.0	72.0	32.0	28.0	<12.2
D	74.0	80.0	38.5	26.5	<12.2
E	49.0	64.0	29.0	33.0	<12.2
F	44.0	64.0	31.0	27.5	<12.2
G	62.0	58.0	44.0	28.0	<12.2
H	69.0	58.0	36.5	27.0	<12.2
Average	65.8	65.9	35.4	28.8	<12.2

Mouse; ICR-strain, 31 g, ♂ Assay; Cylinder plate method, *E. coli* ATCC-27166.

Table 2. Serum levels after intramuscular administration of bicyclomycin in rats, rabbits and dogs (50 mg/kg)

Animal species	Body weight	Serum level (mcg/ml)				
		1/2 hr.	1 hr.	2 hr.	3 hr.	5 hr.
Rat* (SD-strain)	180～200 g ♂	42.0	20.2	8.4	< 6.0	< 6.0
		45.0	26.7	9.4	< 6.0	< 6.0
		50.0	31.0	< 6.0	< 6.0	< 6.0
		47.5	24.0	< 6.0	< 6.0	< 6.0
		59.5	24.8	< 6.0	< 6.0	< 6.0
	Average	48.8	25.3	8.9	< 6.0	< 6.0
Rabbit	3.2 kg ♂	142.0	104.0	51.5	18.2	< 4.0
	3.7 ♂	128.0	77.0	25.0	13.0	< 4.0
	2.9 ♂	131.0	72.0	23.2	10.0	< 4.0
	2.7 ♂	108.0	60.0	21.2	12.5	< 4.0
	3.3 ♂	91.0	72.0	37.5	17.5	< 4.0
	Average	120.0	77.0	31.7	14.2	< 4.0
Dog (Beagle)	13 kg ♂	79.0	74.0	35.5	22.2	< 7.0
	11 ♂	66.0	63.0	43.0	31.0	< 7.0
	11 ♂	75.5	47.0	22.3	14.6	<10.0
	8 ♂	72.5	40.5	18.3	<10.0	<10.0
	9 ♂	90.0	45.0	18.8	<10.0	<10.0
	Average	76.6	53.9	27.6	22.6	<10.0

Assay; Cylinder plate method, *E. coli* ATCC-27166
* Blood samples were taken by heart-puncture from 5 rats each at 0.5, 1, 2, 3 and 5 hours after intramuscular administration.

and each was administered orally at a single dose of 100 mg/kg of bicyclomycin. Three healthy volunteers in fasting state were given bicyclomycin orally at a single dose of 1 g each. Collection of samples and assay techniques were done as described above.

Results

1. Absorption, excretion and distribution after intramuscular administration of bicyclomycin in experimental animals

(1) Serum or blood levels

Results of serum or blood levels of bicyclomycin in mice, rats, rabbits and dogs administered intramuscularly at a single dose of 50 mg/kg are summarized in Tables 1 and 2.

(2) Urinary excretion

Results of urinary excretion of bicyclomycin in mice are summarized in Table 3. Urinary recovery averaged 82% in 24 hours.

The results with rats are shown in Table 4. Relatively high recovery rate of bicyclomycin, 93.4%, was attained from urine samples during a period of 24 hours following administration.

The results with rabbits and dogs

Table 3. Urinary excretion after intramuscular administration of bicyclomycin (50 mg/kg) in mice

Mouse	0~6 hr.		6~24 hr.		Total
	mcg/ml	%	mcg/ml	%	%
A	1,750	82.0	—	—	82.0
B	1,730	77.0	61	3.9	80.9
C	2,670	53.0	170	24.9	77.9
D	5,500	73.0	49	3.6	76.6
E	4,800	80.0	200	14.7	94.7
F	2,400	80.0	—	—	80.0
G	3,420	68.7	137	5.5	74.2
H	2,410	88.7	41	2.5	91.2
Average	3,063	75.3	82	6.9	82.2

Mouse ; ICR-strain, 30 g, ♂ Assay ; Cylinder plate method, *E. coli* ATCC-27166

Table 4. Urinary excretion after intramuscular administration of bicyclomycin (50 mg/kg) in rats, rabbits and dogs

Animal species	Body weight	0~3 hr.		3~6 hr.		6~24 hr.		Total
		mcg/ml	%	mcg/ml	%	mcg/ml	%	%
Rat (SD)	200 g ♂	3,475	90.8	628	5.7	38	2.0	98.3
	200 ♂	6,750	84.5	767	6.6	40	1.7	92.8
	200 ♂	3,525	83.4	618	6.8	40	1.4	91.7
	200 ♂	4,425	88.5	243	4.2	39	2.1	94.8
	200 ♂	3,350	82.1	666	5.3	36	2.1	89.5
	Average	4,305	85.9	584	5.7	39	1.9	93.4
Rabbit	3.2 kg ♂	10,300	35.4	5,600	38.5	14	1.4	75.3
	3.7 ♂	6,000	76.2	1,090	6.1	15	1.3	83.6
	2.9 ♂	4,350	69.0	2,000	9.7	16	0.9	79.6
	2.7 ♂	7,200	58.7	1,530	9.6	9	1.5	69.8
	3.3 ♂	9,600	64.0	2,580	12.4	9	1.0	77.3
	Average	7,490	60.7	2,560	15.2	13	1.2	77.1
Dog (Beagle)	13 kg ♂	34,000	53.4	5,800	21.0	128	3.6	77.9
	11 ♂	29,000	46.4	10,000	26.0	198	3.1	75.5
	11 ♂	3,000	63.8	168	1.1	230	3.6	68.5
	8 ♂	7,000	75.3	1,450	8.0	125	3.7	86.9
	9 ♂	5,600	50.5	1,370	7.0	164	1.4	58.9
	Average	15,720	57.9	3,758	12.6	169	3.0	73.5

Assay ; Cylinder plate method, *E. coli* ATCC-27166

Table 5. Biliary excretion after intramuscular administration of bicyclomycin (50 mg/kg) in rats

Rat	0~3 hr.		3~6 hr.		6~24 hr.		Total
	mcg/ml	%	mcg/ml	%	mcg/ml	%	%
1. 280 g	16.3	0.28	—	—	—	—	0.28
2. 280	14.0	0.14	—	—	—	—	0.14
3. 280	12.8	0.22	—	—	—	—	0.22
4. 280	18.8	0.30	—	—	—	—	0.30
5. 280	13.2	0.27	—	—	—	—	0.27
Average	15.0	0.24	—	—	—	—	0.24

Assay ; Cylinder plate method, *E. coli* ATCC-27166
Rat ; SD-strain, 280 g, ♂

Table 6. Tissues levels at 30 minutes after intramuscular administration of bicyclomycin in rats

Tissue	mcg/g (mcg/ml)	
	50 mg/kg	100 mg/kg
Lung	21.6	42.0
Liver	23.4	62.4
Kidney	144.0	403.5
Spleen	< 16.0	22.8
Heart	< 16.0	26.1
Serum	41.4	93.0

Rat ; SD-strain, 180~200 g, 10/group, ♂
Dose ; 50 mg/kg, 100 mg/kg
Assay ; Cylinder plate method, *E. coli* ATCC-27166.

are also shown in Table 4. Total recoveries were 77% and 74% respectively.

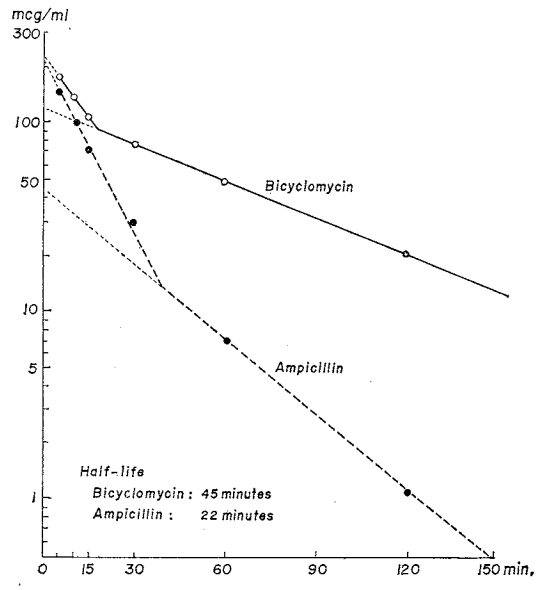
(3) Biliary excretion in rats

Table 5 summarizes the results of biliary excretion of bicyclomycin in rats. These results indicate that bicyclomycin transfers into bile at low rate when given to rats intramuscularly.

(4) Tissue distribution in rats

The results of tissue levels of bicyclomycin in rats are summarized in Table 6. Intramuscular administration of bicyclomycin at a dose of 50 mg/kg resulted in the highest concentration, 144.0 mcg/g, of the antibiotic in the kidney. The levels in the liver and the lung were 23.4 and 21.6 mcg/g, respectively, but the concentrations of the antibiotic in spleen and heart were lower than the detectable level. When bicyclomycin was given at a dose of 100 mg/kg, tissue concentrations found were highest in kidney followed by liver, lung, heart and spleen.

Fig. 1. Decline in serum levels of bicyclomycin and ampicillin in rabbits after intravenous administration.
Dose ; 50 mg/kg, I.V.
Bicyclomycin ; 5/group
Ampicillin ; 4/group



2. Biological half-life of bicyclomycin in rabbits following intravenous administration

Time course of the serum concentration of bicyclomycin after intravenous administration in rabbits are shown in Fig. 1, as compared with that of ampicillin. Half-life was 45 minutes for bicyclomycin and 22 minutes for ampicillin.

3. Absorption, excretion, and identification of active metabolites of bicyclomycin in healthy volunteers

(1) Serum levels

As shown in Table 7, when each of 5 volunteers was dosed intramuscularly with 1 g of bicyclomycin, serum concentrations (mean value) of approximately 31 mcg/ml were attained in 30 minutes to 1 hour following administration. Serum concentrations were 21.6 and 18.8 mcg/ml in 2-hour and 3-hour samples, respectively, and declined below the detectable level of 15.0 mcg/ml in 5-hour samples. Intramuscular administration at 500 mg to each of 4 volunteers resulted in mean serum concentrations of 18.0 and 17.1 mcg/ml in 30 minutes and 1 hour, respectively, after administration. All serum levels sampled 2, 3 and 5 hours after injection were lower than 15 mcg/ml.

(2) Urinary excretion

As shown in Table 8, an average of 94.8 % of bicyclomycin administered intramuscularly at a single dose of 1 g to each of 5 volunteers was recovered from the urine as active form during the first 24 hours.

Urine concentration reached its peak of 2,266 mcg/ml (ranging from 830 to 3,175 mcg/ml) during a period of 1 to 3 hour. When bicyclomycin was given intramuscularly at a single dose of 500 mg to each of 4 volunteers, mean recovery of the antibiotic from urine during the first 24 hours was 96.2 %, of which 54.3 % and 29.3 % were excreted during the periods of 0 to 3 and 3 to 8 hour, respectively. Concentrations of bicyclomycin which were effective against susceptible bacteria were con-

Table 7. Serum levels after intramuscular administration of bicyclomycin in healthy volunteers (1 g and 500 mg)

Dose	Volunteer	Serum level (mcg/ml)				
		1/2 hr.	1 hr.	2 hr.	3 hr.	5 hr.
1 g	I 60 kg	32.0	35.0	23.3	19.0	<15.0
	M 75	22.0	24.0	20.5	17.7	<15.0
	A 68	28.5	29.5	21.0	18.6	<15.0
	K 60	33.0	35.0	20.8	18.5	<15.0
	M' 56	40.0	36.0	22.5	17.5	<15.0
	Average	31.1	31.9	21.6	18.8	<15.0
500 mg	I 60 kg	17.5	17.0	<15.0	<15.0	<15.0
	M 75	16.5	16.4	<15.0	<15.0	<15.0
	A 68	20.0	17.0	<15.0	<15.0	<15.0
	N 63	18.1	17.9	15.5	<15.0	<15.0
	Average	18.0	17.1	<15.0	<15.0	<15.0

Assay ; Cylinder plate method, *E. coli* ATCC-27166

Table 8. Urinary excretion after intramuscular administration of bicyclomycin in healthy volunteers (1 g and 500 mg)

		0~1 hr.		1~3 hr.		3~6 hr.		6~8 hr.		8~10 hr.		10~24 hr.		Total
		mcg/ml	%	mcg/ml	%	mcg/ml	%	mcg/ml	%	mcg/ml	%	mcg/ml	%	%
1 g	I	1,400	18.2	2,125	38.3	745	21.6	935	15.0	555	2.4	52	4.7	100.0
	M	605	11.6	2,750	27.0	2,125	25.9	1,060	12.2	415	5.9	92	7.0	89.6
	A	825	16.5	2,450	38.7	650	29.3	228	6.0	278	2.2	24	3.9	96.6
	K	625	20.9	830	41.5	2,500	15.0	400	10.4	210	6.0	88	3.8	97.6
	M'	4,050	16.2	3,175	44.5	260	10.1	1,005	12.6	505	3.8	108	3.2	90.4
	Ave.	1,501	16.7	2,266	38.0	1,256	20.4	726	11.3	393	4.1	73	4.5	94.8
500 mg	I	640	20.5	980	41.2	215	17.6	145	11.0	48	4.1	43	3.7	98.1
	M	380	17.6	1,800	43.2	580	22.0	390	6.2	65	2.9	37	3.9	96.0
	A	980	28.4	1,200	43.2	275	20.4	92	5.7	44	1.8	22	3.5	99.5
	N	915	16.8	1,150	28.5	905	25.3	230	10.6	94	5.1	31	4.7	91.0
	Ave.	729	15.3	1,283	39.0	494	21.3	214	8.4	63	3.5	33	4.0	96.2

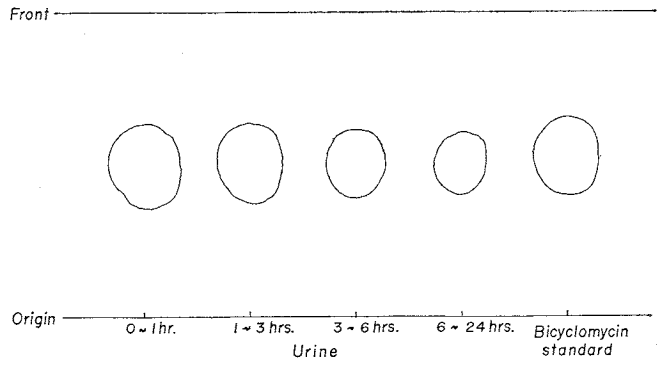
Assay ; Cylinder plate method, *E. coli* ATCC-27166

tinuously excreted in urine for at least 8 hours after administration.

(3) Identification of active substance excreted into human urine

As shown in Fig. 2, the position of the inhibition zone originated from urine sample was identical with that of bicyclomycin control and there was no other substance possessing antibacterial activity. Regardless of differences in solvent systems and absorbents, only bicyclomycin could be identified on the bioautogram.

Fig. 2. Bioautograms of urine after intramuscular injection of bicyclomycin in healthy volunteers
Urine ; Healthy volunteer (adult), single dose 1 g
TLC ; Adsorbent, Eastman chromagram sheet 6061
Solvent system ; $CHCl_3$: MeOH (5 : 1)



4. Excretion after oral admistration of bicyclomycin in rats and healthy volunteers

Rats receiving oral dose of bicyclomycin at 100 mg/kg excreted 24.1 % (ranging from 10.7 to 38.0 %) of the antibiotic during a 24-hour period (Table 9).

An average of 2.9 % of bicyclomycin administered orally to healthy volunteers was recovered from the urine as active antibiotic during the first 24 hours (Table 10).

Table 9. Urinary excretion after oral administration of bicyclomycin (100 mg/kg) in rats

Rat	0~3 hr.		3~6 hr.		6~24 hr.		Total
	mcg/ml	%	mcg/ml	%	mcg/ml	%	%
1. 195 g	2,478	11.4	2,170	5.9	630	20.7	38.0
2. 200	1,320	9.9	2,533	9.5	680	11.9	31.3
3. 195	406	6.7	524	4.6	140	2.8	14.0
4. 190	695	8.1	1,067	6.7	660	11.5	26.3
5. 205	386	6.6	980	2.3	100	1.7	10.7
Average	1,057	8.5	1,455	5.8	442	9.7	24.1

Assay ; Cylinder plate method, *E. coli* ATCC-27166
Rat ; SD-strain, 190~205 g, ♂

Table 10. Urinary excretion after oral administration of bicyclomycin (1 g) in healthy volunteers

	0~2 hr.		2~4 hr.		4~6 hr.		6~8 hr.		8~10 hr.		10~24 hr.		Total
	mcg/ml	%	mcg/ml	%	mcg/ml	%	mcg/ml	%	mcg/ml	%	mcg/ml	%	%
I 60 kg	31	0.5	37	0.7	44	0.4	19	0.2	—	—	—	—	1.8
M 75	39	0.7	84	0.7	—	—	80	0.4	31	0.3	8	0.3	2.4
A 68	—	—	53	1.0	69	1.9	51	0.8	16	0.5	11	0.3	4.4
Average	35	0.6	58	0.8	57	1.1	50	0.5	24	0.4	10	0.3	2.9

Assay ; Cylinder plate method, *E. coli* ATCC-27166

Discussion

The present investigations revealed that bicyclomycin, when given intramuscularly, was quite rapidly absorbed not only in mice, but also in rats, rabbits and dogs as well as in man, and that this substance was distributed at high levels in various visceral organs as unchanged active substance. This fact may account for the considerably high *in vivo* activity in spite of its relatively low *in vitro* action. Bicyclomycin was stable in rats and volunteers, and most of the antibiotic dosed was recovered from urine as unchanged active form. In mice bicyclomycin excreted in urine as active form was believed to be much greater than the results obtained, 82.2 % recovery, considering the fact that difficulty was encountered in obtaining urine sample and that rate of increase of blood level of bicyclomycin was found to be very rapid.

In rabbits serum levels of bicyclomycin were prominent very high and long-lasting as compared with rats, but urinary level was lower than that in rats. In dogs serum levels were lower than in rabbits but greater than in rats. Prolonged serum levels in dogs was somewhat similar to that of rabbits, but fluctuation in levels of the 3-hour sample was greater than in rabbits. Total urinary excretion in dogs, 73.5 %, was nearly equal to that of rabbits, although in both animals similar fluctuation in recovery values was noted during the first 6 hours after administration.

Serum concentrations of bicyclomycin in man administered intramuscularly were not low as compared with experimental animals, because of the fact that recovery rates in urine samples were similar to those in rats and greater than those in rabbits and dogs, but excretion into urine persisted longer than in rats. There were fluctuations in the lowest detectable level in serum or urine samples from man. These were believed to be due partly to the use of less sensitive bacteria for bioassay. MICs of bicyclomycin for most of sensitive bacteria ranged from 25 to 50 mcg/ml, therefore it is considered to be of less value in measuring serum concentration lower than 10 mcg/ml.

When bicyclomycin was given orally, approximately 24 % of the antibiotic was excreted in urine samples from rats, whereas only 2.9 % of bicyclomycin was recovered from urine specimens of human volunteers. This low absorption and excretion rate in man as compared with that in rats suggest that satisfactory efficacy would not be expected with systemic bacterial infections in man when bicyclomycin is administered orally.

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