CHROMATOGRAPHIC ANALYSIS AND PHARMACOKINETIC INVESTIGATION OF CEPHALOGLYCIN AND ITS METABOLITES IN MAN

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Metabolism and pharmacokinetics of cephaloglycin in man were investigated. High performance liquid chromatographic and gas chromatographic-mass spectrometric analyses of metabolites excreted in human urine following oral administration of cephaloglycin revealed that cephaloglycin was biotransformed in two pathways *i.e.* elimination of 3-acetyl group and hydrolysis of side chain amide linkage. The former yielded deacetylcephaloglycin, a part of which further underwent lactonization to deacetylcephaloglycin lactone, and the latter led to benzoyl formic acid *via* phenylglycine. The urinary excretion amounts of these metabolites and intact cephaloglycin were determined by a reversed phase ion pair high performance liquid chromatography. The average total excretion amounts at infinite time accounted for 0.50% of the administered dose for intact cephaloglycin, 17.09% for deacetylcephaloglycin, 0.35% for deacetylcephaloglycin lactone, and 0.86% for benzoyl formic acid. The excretion of phenylglycine was less than 0.2%, its chromatographic peak being too small to allow accurate determination. The rate constants for absorption, metabolism, and urinary excretion were estimated by the moment analysis of the excretion rate-time curves.

Cephaloglycin, introduced in 1965 as the first semisynthetic cephalosporin for oral administration, has a broad spectrum of anti-Gram-positive and anti-Gram-negative activities[1~5]. This drug, however, was rapidly superseded by cephalexin because of facile cleavage by metabolism and less absorption from intestinal tract than the latter. At the present time cephaloglycin shares a small part of antibiotic production and is used mainly for the treatment of urinary tract infections[6~9].

The *in vivo* studies of this drug have revealed that a small portion of an oral dose is excreted in human urine in the intact form, and deacetylcephaloglycin is the only metabolite found in man[10,11], while phenylglycine is the main product in the urine of rat orally dosed with D-cephaloglycin-^{14}C.[12] The analytical methods so far employed for the assays of cephaloglycin and deacetylcephaloglycin have been based on their microbiological activities against test organisms. The microbiological method, however, involves a problem in that deacetylcephaloglycin retains activity comparable to cephaloglycin itself, thus requiring selective use of test organisms for the differential assay[10,11]. It has been suggested that differential microbioassay can not yet precisely specify the amounts of cephaloglycin and deacetylcephaloglycin in biological fluids[10,11]. High performance liquid chromatography seems obviously more precise and simpler than the microbioassay.

In our studies on chromatographic determination and pharmacokinetic analysis of β-lactam antibiotics, this paper undertakes to discuss the metabolic pathways and pharmacokinetics of cephaloglycin in man on the basis of high performance liquid chromatographic determination and gas chromatographic-mass spectrometric analysis of urinary metabolites followed by moment analysis of excretion rate-time curves.

Experimental

Reagents and Materials

Cephaloglycin (1,010 μg/mg as potency) used as a standard material and cephaloglycin capsule (Kefglycin® 250 mg as potency) received by volunteers were gifts from Shionogi & Co. (Osaka, Japan). Deacetylcephaloglycin lactone was synthesized according to the established method[13] and its purity was confirmed by high performance liquid chromatography and elemental analysis. Benzoyl formic acid obtained from Sigma Co. (St. Louis, Mo. U.S.A.) was recrystallized from carbon tetrachloride before use. Sodium *n*-heptylsulfonate used as an ion-pairing agent was synthesized according to STRECKER reaction[14]. Glass distilled water and methanol were degassed and used to prepare the mobile phase. Other chemicals of analytical reagent grade were used as supplied.

High Performance Liquid Chromatography

A high performance liquid chromatograph (ALC/GPC 204, Waters Assoc., Milford, Mass. U.S.A.) equipped with a UV detector (254 nm, Model 440, Waters Assoc.) was used in a reversed phase mode with a stationary phase of LiChrosorb RP-18 (10 μm particle diameter, E. Merck & Co., West Germany) packed in a 25 cm × 4.6 mm i.d. stainless steel tubing. A short pre-column (2 cm × 4.6 mm i.d.) filled with LiChrosorb RP-2 (E. Merck) was used to guard the main column. The mobile phases were: (1) water - methanol (4: 1, v/v) containing 4 mM sodium *n*-heptylsulfonate and 10 mM $(NH_4)H_2PO_4$ whose flow rate was maintained at 1.4 ml/min for the assays of cephaloglycin, deacetylcephaloglycin, and deacetylcephaloglycin lactone; (2) water - methanol (3: 1) containing 10 mM tetrabutylammonium bromide and 1 mM $(NH_4)H_2PO_4$ at 1.0 ml/min for benzoyl formic acid; and (3) water - methanol (12: 1) containing 5 mM sodium *n*-heptylsulfonate, 5 mM $(NH_4)H_2PO_4$ and 1.5% 0.5 N HCl at 1.2 ml/min for phenylglycine.

Gas Chromatography-Mass Spectrometry

A mass spectrometer (JEOL JMS-01SG-2) combined with a gas chromatograph (JGC-20K) was used to confirm the chemical structure of metabolites excreted in urine. The operating conditions were as follows; gas chromatographic stationary phase: 10% PEG/Chromosorb W (60/80 mesh) packed in a 2 m × 2 mm i.d. spiral glass tubing, carrier gas: helium (30 ml/min), column temperature: 180°C, injector temperature: 250°C, separator temperature: 270°C, ionization source temperature: 240°C, ionization voltage: 75 eV, and acceleration voltage: 8 kV.

Drug Administration and Sample Preparation

The cephaloglycin capsules (250 mg × 4) were administered with 200 ml water to each of four healthy male volunteers, 25~39 years old, weighing 62~79 kg, who had been drug-free at least one week and fasted for 12 hours before receiving the capsules. Urine samples were collected just before and 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 5.0, 6.0, 8.0, 10.0, and 12.0 hours after administration. After measuring volume, the urine was filtered through a 0.45-μ pore-size membrane filter (Fuji Photo Film Co., Tokyo, Japan). For the high performance liquid chromatographic determinations of cephaloglycin, deacetylcephaloglycin, and benzoyl formic acid, a 5~20 μl portion of the filtrate was directly applied to the instrument. For the gas chromatographic-mass spectrometric analyses of benzoyl formic acid and mandelic acid, 1 ml of the filtrate was added to 1 ml distilled water and 0.2 ml 0.5 N HCl, and the metabolites were extracted twice with 5-ml portions of ethyl ether. The combined ether layer was transferred to a flask and the solvent was removed by evaporation. The residue was dissolved in ethereal diazomethane solution and methylated for 20 minutes at room temperature. After removing excess reagent and solvent, the residue was dissolved in ethyl ether and a 5~10 μl portion was subjected to the gas chromatographic-mass spectrometric analysis.

Calibration Graph

The determination of deacetylcephaloglycin in urine was achieved according to the high performance liquid chromatographic method described in the previous paper[15], where deacetylcephaloglycin was converted to deacetylcephaloglycin lactone by acidifying the urine to pH 1.4 followed by keeping at 37°C for 2 hours. The urinary concentrations of cephaloglycin, deacetylcephaloglycin lactone, and

benzoyl formic acid were quantified by referring to their standard materials. The calibration graphs obtained by plotting peak height *vs* concentration of standard materials dissolved in control urine showed good linearity (correlation coefficient 0.999) over the ranges of $4 \sim 60$ μg/ml for cephaloglycin, $25 \sim 400$ μg/ml for deacetylcephaloglycin lactone, and $2 \sim 14$ μg/ml for benzoyl formic acid.

Results and Discussion

Metabolic Pathways

In the previous paper describing high performance liquid chromatographic determination of cephaloglycin and deacetylcephaloglycin, we found that deacetylcephaloglycin lactone is excreted in human urine as a minor metabolite of cephaloglycin following oral administration. Cephaloglycin has another possible site susceptible to biotransformation *viz.* hydrolysis of the side chain amide linkage, but this type of metabolism has not so far been found in man.

Methyl esters of standard materials of benzoyl formic acid and mandelic acid were submitted to gas chromatographic-mass spectrometric analysis, the spectra indicating the fragment ion peaks at *m/e* 77 and 105 for benzoyl formic acid methyl ester, and the molecular ion at *m/e* 166 and the fragment ions at *m/e* 107 and 77 for mandelic acid methyl ester. The molecular ion of benzoyl formic acid methyl ester was not observed at *m/e* 164. Fig. 1 shows the mass chromatograms monitored at *m/e* 77, 105, 107 and 166 for the diazomethane-treated ether extract of the urine collected 4 hours after administration. This specimen was expected to contain the metabolites at a maximum rate. It is evident from Fig. 1 that the peaks monitored at *m/e* 77 and 105 with the elapsed time (2 minutes after elution of solvent peak) corresponding to that of an authentic sample of benzoyl formic acid methyl ester indicate the presence of benzoyl formic acid in the urine specimen comming from the administered drug, because control urine gave no peaks (shown by dotted line) at the same position. The mass chromatogram monitored at *m/e* 77, 107 and 166 showed no peak at the elapsed time corresponding to that of reference mandelic acid methyl ester. The high performance liquid chromatography of the urine collected 3 hours after administration was achieved under the three different conditions; the first for the separation of unchanged cephaloglycin, deacetylcephaloglycin, and cephaloglycin lactone, the second for the separation of benzoyl formic acid, and the third for the separation of phenylglycine from endogenous urinary components. Figs. 2 and 3 show the separation profiles of these substances. The excretion of phenylglycine was observed with the concentration lower than the limit of accurate determination (10 μg/ml). These results allowed us to depict the metabolic pathways of cephaloglycin in man as given in Scheme 1.

Fig. 1. Mass chromatogram of human urine excreted after oral dose of cephaloglycin.
BFA: benzoyl formic acid, MA: mandelic acid

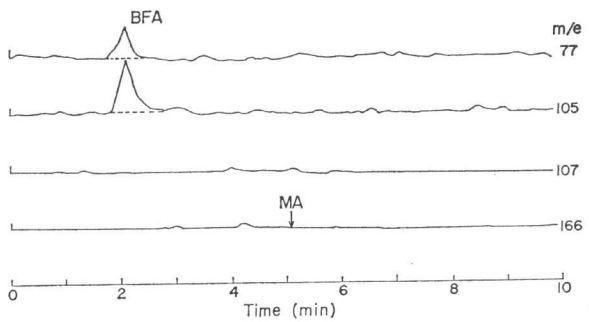


Fig. 2. HPLC separation of deacetylcephaloglycin (**1**), intact cephaloglycin (**2**), and deacetylcephaloglycin lactone (**3**) from endogenous urinary components.

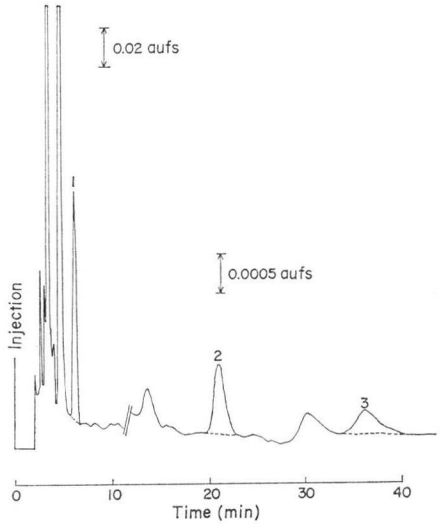
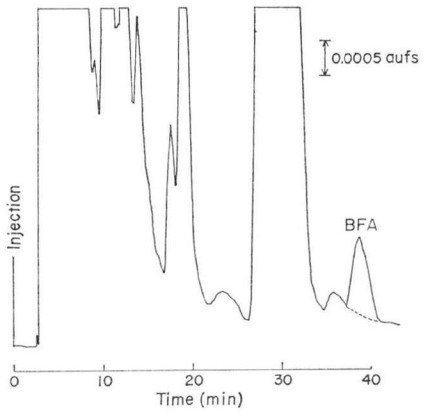
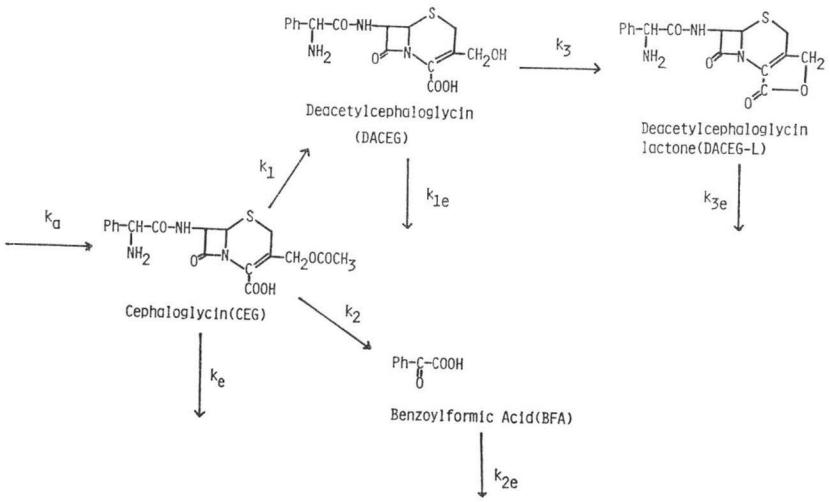


Fig. 3. HPLC separation of benzoyl formic acid (BFA) from endogenous urinary components.



Scheme 1. Metabolic pathways of cephaloglycin in man.



Time Courses of Urinary Excretion

In order to carry out pharmacokinetic investigation, we determined the time courses for the urinary excretion rates of respective species. Table 1 shows the results for the urinary excretion amounts of unchanged cephaloglycin and metabolites for each of four volunteers and their average values, where the values for the metabolites are given as cephaloglycin equivalent. The average maximum excretion rate is 1.88 mg/hr at 2.0 hours after administration for unchanged cephaloglycin, 46.8 mg/hr at 2.5 hours for deacetylcephaloglycin, 0.49 mg/hr at 4 hours for benzoyl formic acid, and 0.71 mg/hr at 1.5~4 hours (plateau range) for deacetylcephaloglycin lactone. The time courses of cumulative excretion amounts are illustrated in Fig. 4, where the values are again given as cephaloglycin equivalent.

Table 1. Urinary excretion amounts of cephaloglycin and its metabolites following a single oral administration of 1 g capsule.

Cephaloglycin (μg)

Subject time (hr)	J.H.	N.H.	T.N.	M.M.	Mean	S.D.
0 ~0.5	47.7	27.4	200.6	572.0	211.9	218.4
0.5~1.0	636.9	329.1	336.3	882.8	546.3	230.6
1.0~1.5	924.8	441.8	503.9	1642.6	878.3	478.8
1.5~2.0	705.9	845.1	389.5	1814.6	938.8	531.9
2.0~2.5	666.9	534.4	230.0	1278.6	679.7	380.7
2.5~3.0	679.8	357.8	205.3	998.5	560.4	305.5
3.0~4.0	1028.0	633.1	283.0	1046.3	747.6	315.0
4.0~5.0	233.2	252.8	161.7	143.0	197.7	46.3
5.0~6.0	129.2	108.5	116.1	44.1	99.5	32.8
6.0~7.0	106.6	39.9	57.0	nd	50.9	38.2
7.0~8.0	99.6	14.8	nd	nd	28.6	41.4
Total	5258.6	3593.7	2483.4	8422.5	4939.6	2240.4

Deacetylcephaloglycin (mg)

Subject time (hr)	J.H.	N.H.	T.N.	M.M.	Mean	S.D.
0 ~0.5	nd	0.20	2.97	1.91	1.27	1.23
0.5~1.0	3.33	5.02	11.64	7.08	6.77	3.11
1.0~1.5	9.02	9.70	27.17	22.32	17.05	7.88
1.5~2.0	12.25	21.95	26.32	31.61	23.03	7.10
2.0~2.5	14.82	28.03	17.66	33.08	23.40	7.44
2.5~3.0	20.08	28.68	14.56	29.59	23.22	6.23
3.0~4.0	39.37	47.20	21.45	49.33	39.34	10.97
4.0~5.0	14.64	24.65	11.14	20.36	17.70	5.19
5.0~6.0	9.68	11.80	5.69	12.34	9.88	2.61
6.0~7.0	3.04	4.03	3.57	5.86	4.13	1.06
7.0~8.0	1.47	2.05	1.64	4.07	2.31	1.04
8.0~10	nd	2.57	2.58	2.73	1.97	1.14
10 ~12	nd	1.05	0.27	0.98	0.58	0.45
Total	127.70	186.93	146.66	221.26	170.64	36.22

Benzoyl formic acid (μg)

Subject time (hr)	J.H.	N.H.	T.N.	M.M.	Mean	S.D.
0 ~0.5	nd	nd	nd	nd		
0.5~1.0	68.0	53.9	113.9	84.6	80.1	22.3
1.0~1.5	185.6	104.0	221.9	114.9	156.6	49.0
1.5~2.0	231.3	197.3	128.9	184.5	185.5	36.9
2.0~2.5	293.1	187.7	133.1	154.7	192.2	61.4
2.5~3.0	358.2	211.7	159.2	157.4	221.6	81.8
3.0~4.0	678.7	435.3	418.4	433.8	491.6	108.3
4.0~5.0	538.7	444.3	575.9	309.7	467.2	102.8
5.0~6.0	482.0	448.0	275.2	215.5	355.2	112.5
6.0~7.0	479.7	326.0	274.1	192.4	318.1	104.8
7.0~8.0	447.2	252.7	218.6	228.3	286.7	93.5
8.0~10	859.1	495.1	466.0	392.4	553.2	180.6
10 ~12	nd	513.9	195.7	311.9	255.4	186.3
Total	4621.6	3669.6	3182.7	2780.1	3563.6	687.3

Deacetylcephaloglycin lactone (μg)

Subject time (hr)	J.H.	N.H.	T.N.	M.M.	Mean	S.D.
0 ~0.5	nd	nd	nd	nd		
0.5~1.0	nd	nd	377.9	nd	94.5	163.6
1.0~1.5	nd	157.9	416.0	327.6	225.4	159.8
1.5~2.0	197.9	314.7	414.2	563.3	372.5	134.1
2.0~2.5	240.7	387.4	280.7	425.6	333.6	75.5
2.5~3.0	363.5	389.7	277.3	411.4	360.5	50.9
3.0~4.0	553.0	564.2	410.6	154.0	420.5	165.3
4.0~5.0	103.9	422.2	nd	nd	131.5	173.1
Total	1459.0	2236.1	2176.7	1881.9	1938.4	307.6

It is found that the excretion of deacetylcephaloglycin is almost completed at 7 hours after dosing (which is about 2 hours later than that of unchanged cephaloglycin), while a very slight increase in the excretion of benzoyl formic acid still continues.

Pharmacokinetic Considerations

The evaluation of pharmacokinetic parameters was achieved by moment analysis of the time course data. The statistical moments for a urinary excretion rate-time curve (dX_u/dt) have been defined as[16]

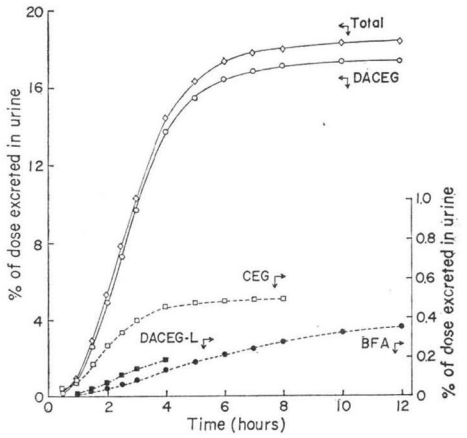
$$X_u^\infty = \int_0^\infty (dX_u/dt)\,dt \quad (1)$$

$$MRT_u = \int_0^\infty t(dX_u/dt)\,dt / X_u^\infty \quad (2)$$

$$VRT_u = \int_0^\infty (t - MRT_u)^2 (dX_u/dt)\,dt / X_u^\infty \quad (3)$$

where the area under the urinary excretion rate-time curve (X_u^∞) and the mean and variance of residence time of the urinary excretion rate-time curve (MRT_u and VRT_u) are the zero, first normal and second central moments, respectively. The significance and calculation of these moments have been described in the previous paper[16]. Provided that cephaloglycin is biotransformed according to the metabolic pathways given in Scheme 1, where all the steps inclusive of absorption and excretion can be regarded as linear processes, the rate constants can be related to the statistical moments by

Fig. 4. Time course curves for cumulative urinary excretion (%) of intact cephaloglycine (CEG), deacetylcephaloglycin (DACEG), deacetylcephalo glycin lactone (DACEG-L), and benzoyl formic acid (BFA) after oral dose of 1 g cephaloglycin.



$$X^\infty = k_e FD/(k_1+k_2+k_e) \quad (4)$$

$$MRT = 1/k_a + 1/(k_1+k_2+k_e) \quad (5)$$

$$VRT = 1/k_a^2 + 1/(k_1+k_2+k_e)^2 \quad (6)$$

$$X_1^\infty = k_1 k_{1e} X^\infty / k_e (k_3+k_{1e}) \quad (7)$$

$$MRT_1 = 1/(k_3+k_{1e}) + MRT \quad (8)$$

$$X_2^\infty = k_2 X^\infty / k_e \quad (9)$$

$$MRT_2 = 1/k_{2e} + MRT \quad (10)$$

$$X_3^\infty = k_3 X_1^\infty / k_{1e} \quad (11)$$

$$MRT_3 = 1/k_{3e} + MRT_1 \quad (12)$$

where D is dose, F is the fraction of the dose absorbed, X^∞, X_1^∞, X_2^∞, and X_3^∞ are the excreted amounts of cephaloglycin, deacetylcephaloglycin, benzoyl formic acid, and deacetylcephaloglycin lactone at infinite time, respectively, and k's are the rate constants specified in Scheme 1. In using Eqs. 1, 2, and 3, the moments were calculated by rectangular integration with extrapolation of time course curve to infinite time using a monoexponential equation. The equation was determined by the least squares method using the last three to seven points on the urinary excretion rate-time curve. The selection of the number of the points depends on individual time course data which were weighted by unity. The calculation of the moments according to Eqs. 1~3 and the estimation of pharmacokinetic parameters from the moments according to Eqs. 4~12 were carried out on a microcomputer with programming in BASIC.

The results thus obtained are given in Table 2, indicating that the average total excretion amounts at infinite time account for 0.50% of the dose for unchanged cephaloglycin, 17.09% for deacetylcephaloglycin, 0.35% for deacetylcephaloglycin lactone, and 0.86% for benzoyl formic acid (total 18.8%). These results contrast to those of the rat[12]; the urinary recovery in 24 hours after a single oral dose of D-cephaloglycin-^{14}C to the rats was 8.5% of the dose for phenylglycine, 5.0% for benzoyl formic acid 2.0% for deacetylcephaloglycin, and 1.5% for mandelic acid. Although such difference in the metabolic behavior of cephaloglycin are likely due to species difference, it is interesting to note that the enzymatic hydrolysis of the side chain amide linkage did occur to some extent in man yielding benzoyl

Table 2. Pharmacokinetic parameters for cephaloglycin (1 g) administered orally.

Subject parameter	J.H.	N.H.	T.N.	M.M.	Mean	S.D.
k_a (hr^{-1})	2.692	1.264	2.045	1.460	1.865	0.5571
k_1 (hr^{-1})	0.3377	0.7361	0.4936	1.220	0.7037	0.3348
k_2 (hr^{-1})	0.0354	0.0244	0.0131	0.0242	0.0243	0.0079
k_3 (hr^{-1})	0.0549	0.0211	0.0880	0.0160	0.0450	0.0290
k_e (hr^{-1})	0.0143	0.0139	0.0085	0.0456	0.0206	0.0146
k_{1e} (hr^{-1})	2.957	1.154	3.421	0.8402	2.093	1.114
k_{2e} (hr^{-1})	0.0544	0.1064	0.0647	0.0941	0.0799	0.0211
k_{3e} (hr^{-1})	1.004	1.140	0.7348	0.9634	0.9516	0.1353
F	0.1510	0.2010	0.1607	0.2394	0.1880	0.0351
f_{CFG}	0.0370	0.0180	0.0162	0.0353	0.0266	0.0096
f_{DACEG}	0.8573	0.9344	0.9169	0.9271	0.9089	0.0304
f_{BFA}	0.0898	0.0305	0.0433	0.0199	0.0459	0.0267
$f_{DACEG\text{-}L}$	0.0159	0.0171	0.0236	0.0177	0.0186	0.0030

f: fraction of total excretion amount

formic acid and a trace of phenylglycine.

A variety of data have appeared in the literatures about the excretion of cephaloglycin in human urine; the reported values for average excretion % of dose are 25~30% of 500 mg[1], 19% of 250 mg[2], 8.6% of 500 mg[2], 6.2% of 1 g[2], 35% of 500 mg[4], 25.7% of 500 mg[10], and 8~10% of 500 mg[11]. The variability of these results depends not only on individual difference in subjects and in experimental conditions, but also on the assay method. Microbioassay, by which all the above data were obtained, distinguishes poorly between unchanged cephaloglycin from deacetylcephaloglycin (active metabolite). The present method offers reliable results which allows for the first time to discuss pharmacokinetic behavior of cephaloglycin in man.

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