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Pharmacokinetic Study of Cefotaxime (CTX) in Dogs

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Abstract: Cefotaxime (CTX) was injected either intravenously or intramuscularly in dogs, and its pharmacokinetics in plasma and urine were determined with the use of HPLC assay. Cephalothin (CET) was administered in a similar manner as a reference agent. While both CTX and CET rapidly disappeared from plasma after intravenous injection, the half-life of CET was approximately 2.5 times shorter than that of CTX. Both drugs were deacetylated, and desacetyl-CTX and desacetyl-CET appeared in plasma. Both drugs were rapidly excreted into urine either in unchanged or deacetylated form, the sum of which accounted for 77 % and 63 % of the CTX and CET dose, respectively. The ratio of the amount of unchanged drug over that of deacetylated drug in the urine was 1:1 for CTX and 1:2 for CET. When CTX and CET were intramuscularly injected, the plasma levels of CTX and CET reached a maximum 30 min and 15 min after injection, respectively, followed by a rapid decline. The pattern of urinary CTX excretion was similar after i.m. and i.v. injections. In contrast, the amount of desacetyl-CET in the urine was larger after i.m. than i.v. injections. CTX metabolites other than desacetyl-CTX (M_2 and M_3) that were also assayed by HPLC accounted for only 2–4 % of the dose of CTX in the urine, but were below detectable levels in this plasma.

Cefotaxime (CTX, sodium 7-[2-(2-amino-4-thiazolyl)-2-methoxy-iminoacetamide] cephalosporanate) is a semi-synthetic cephalosporin with a broad antibacterial spectrum. A pharmacokinetic study of CTX in rabbits and rats has already been reported (1, 2). In this study, the pharmacokinetic profiles were determined for CTX and cephalothin (CET) as a reference drug with the same acetyl group as CTX. Furthermore, an attempt was made to determine CTX metabolites other than desacetyl-CTX. Dogs were used as an experimental animal in the present work.

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Materials and Methods

Chemicals

CTX Sodium salt, its desacetyl metabolite (desacetyl-CTX), and the desacetyl metabolite of CET (desacetyl-CET) were supplied by Hoechst AG. The CET sample used in this study was Keflin (Shionogi and Co., Ltd.).

Animals procedures

Male beagle dogs 9 to 20 months old, weighing 8.2 to 12.2 kg (CLEA Japan, Inc.), were used. Food was withdrawn 18 hours prior to the start of the experiments. Solutions of 20 % CTX and of 20 % CET were prepared with distilled water. Desacetyl-CTX was dissolved in 0.1 M phosphate buffer (pH 7.0) (2 % solution). The drug solutions were intravenously injected in one foreleg, and venous blood samples (1.5 ml) were collected from the other foreleg with a heparin-treated syringe. Samples were immediately centrifuged at 3,000 rpm for 10 minutes to separate the plasma.

Excreted urine was collected in a metabolic cage. After each collection, the cage was washed with a small amount of water. The urine remaining in the bladder was collected with a catheter. The excreted urine, the washings from the cage, and the urine collected with the catheter were combined as a urine sample at each time point.

HPLC analysis of CTX, desacetyl-CTX, CET, and desacetyl-CET

Samples were diluted with the HPLC eluent system, and 10 μl of the sample was injected into the column. Either the TRIROTAR system (Nippon Bunko Co., Ltd.) or fully automatic (Nihon Waters Limited) HPLC equipment was used. A column 4.6 mm in internal diameter and 12.5 cm in length, and filled with SC-02 (Jasco, 10 μ), was used. The following mobile

phases were used: (1) 0.2% ammonium acetate:methanol (5:1) for CTX and desacetyl-CTX; (2) 0.1 M tetraethylammonium phosphate buffer (pH 3.5):acetonitrile (93:7) for the metabolites of CTX (M_2 and M_3) (3, 4); (3) 0.2% ammonium acetate:methanol (2:1) for CET and desacetyl-CET. The detection was performed by UV absorption at a wave-length of 254 nm. The detection limit in the plasma was 0.1 μg/ml for CTX and desacetyl-CTX and 0.2 μg/ml for CET and desacetyl-CET. The detection limit in urine was 0.2 μg/ml for CTX, desacetyl-CTX, CET, and desacetyl-CET. The detection limit of M_2 and M_3 in both plasma and urine was 5 μg/ml.

Results and Discussion

Plasma concentrations of CTX and desacetyl-CTX after intravenous injection of CTX

Figure 1 shows plasma concentrations of CTX and desacetyl-CTX after intravenous injection of 20 mg/kg CTX. The parent CTX rapidly decreased to below 0.5 μg/ml 4 hours after injection. Desacetyl-CTX was detectable 5 minutes after intravenous injection of CTX, and its plasma concentration peaked 30 minutes to 1 hour after injection. After the concentration of desacetyl-CTX peaked, the level of desacetyl-CTX exceeded that of CTX, the parent compound suggesting that CTX is deacetylated to a large extent in dogs. Therefore, the pharmacokinetics of desacetyl-CTX were also studied directly. Figure 2 shows the plasma levels of desacetyl-CTX after intravenous injection of authentic desacetyl-CTX (20 mg/kg). Desacetyl-CTX disappeared from the plasma in a fashion similar to that of CTX.

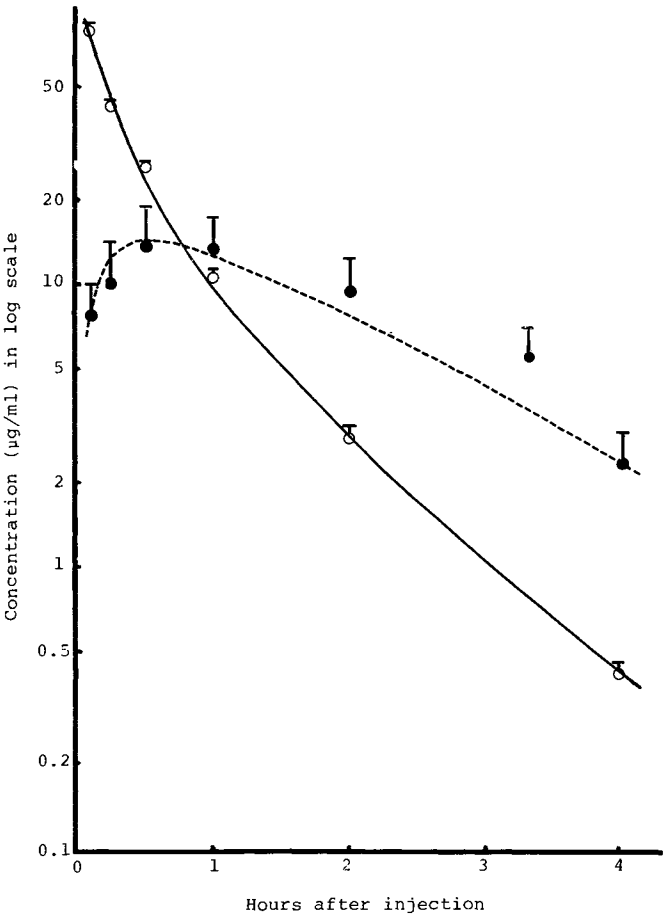


Fig. 1 Levels of CTX and desacetyl-CTX in dog plasma after a single intravenous injection of CTX (20 mg/kg, i.v.).
Key: ○, CTX; ●, Desacetyl-CTX.
Each point represents the mean of twelve dogs with the standard error.

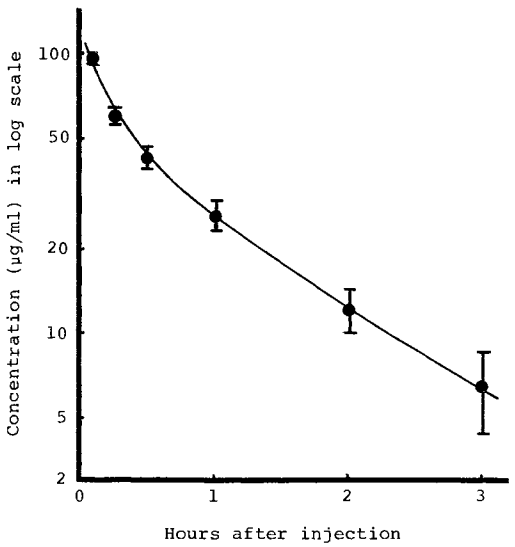


Fig. 2 Levels of desacetyl-CTX in dog plasma after a single intravenous injection of the drug (20 mg/kg, i.v.).
Each point represents the mean of three dogs with the standard error.

The results obtained after intravenous administration of CTX or desacetyl-CTX were analyzed with the use of a two-compartment model (Scheme 1). Yamaoka et al. (5) proposed a statistical evaluation of pharmacokinetic models using the Akaike's information criteria (6) (AIC) for which a minimum value is regarded as the best representation of experimental data. In the present work this two-compartment model yielded the lowest AIC among various tested models, supporting suitability of the model. The pharmacokinetic parameters of CTX and desacetyl-CTX are given in Table I. The theoretical curve of the plasma levels of CTX (Fig. 1) after injection of the drug could be described by equation (*7*) and the theoretical curve of desacetyl-CTX (Fig. 2) after injection of desacetyl-CTX by equation (*8*).

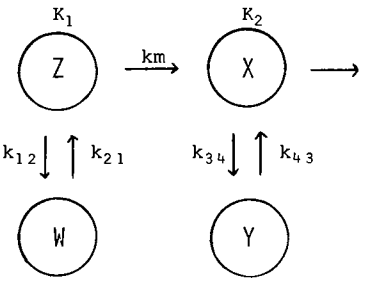
$$y = 71.9e^{-3.51t} + 19.9e^{-0.97t} \quad (7)$$

$$y = 62.3e^{-4.76t} + 53.0e^{-0.717t} \quad (8)$$

Comparison of the pharmacokinetic parameters (Table I) of CTX and desacetyl-CTX revealed that the rate constants for entering and leaving a tissue compartment (k_{12} and k_{21}) were greater for desacetyl-CTX than for CTX, suggesting that the metabolite desacetyl-CTX more readily equilibrates between tissues than the parent CTX.

The half-life during the α-phase was 12 minutes for CTX and 9 minutes for desacetyl-CTX. Among the pharmacokinetic parameters of CTX and desacetyl-CTX shown in Table I, greater differences were observed with total body clearance and distribution volume. The smaller distribution volume of desacetyl-CTX accounts for its higher plasma levels than those of unchanged CTX after 1 hour or more following intravenous injection of CTX (Fig. 1).

Desacetyl-CTX was excreted mainly into the urine; that is, approximately 86% of the dose of desacetyl-CTX was



$$Z = FA_0\left\{\frac{(\gamma + k_{21})}{(\gamma - \delta)}e^{\gamma t} + \frac{(\delta + k_{21})}{(\delta - \gamma)}e^{\delta t}\right\} \text{-------(1)}$$

$$X = kmFA_0\left\{\frac{(\alpha + k_{43})(\alpha + k_{21})}{(\alpha - \beta)(\alpha - \gamma)(\alpha - \delta)}e^{\alpha t} + \frac{(\beta + k_{43})(\beta + k_{21})}{(\beta - \alpha)(\beta - \gamma)(\beta - \delta)}e^{\beta t} + \frac{(\gamma + k_{43})(\gamma + k_{21})}{(\gamma - \alpha)(\gamma - \beta)(\gamma - \delta)}e^{\gamma t} + \frac{(\delta + k_{43})(\delta + k_{21})}{(\delta - \alpha)(\delta - \beta)(\delta - \gamma)}e^{\delta t}\right\} \text{-------(2)}$$

$$\alpha = \frac{1}{2}\left\{-(k_{34} + k_{43} + K_2) + \sqrt{(k_{34} + k_{43} + K_2)^2 - 4k_{43}K_2}\right\} \text{-------(3)}$$

$$\beta = \frac{1}{2}\left\{-(k_{34} + k_{43} + K_2) - \sqrt{(k_{34} + k_{43} + K_2)^2 - 4k_{43}K_2}\right\} \text{-------(4)}$$

$$\gamma = \frac{1}{2}\left\{-(k_{12} + k_{21} + K_1) + \sqrt{(k_{12} + k_{21} + K_1)^2 - 4k_{21}K_1}\right\} \text{-------(5)}$$

$$\delta = \frac{1}{2}\left\{-(k_{12} + k_{21} + K_1) - \sqrt{(k_{12} + k_{21} + K_1)^2 - 4k_{21}K_1}\right\} \text{-------(6)}$$

Scheme 1. Model and equations for CTX and desacetyl-CTS after intravenosuly injection.

Where,
- Z: Concentration of CTX in a central compartment
- X: Concentration of desacetyl-CTX in a central compartment
- W: Concentration of CTX in a tissue compartment
- Y: Concentration of desacetyl-CTX in a tissue compartment
- K_1: Elimination rate constant of CTX
- K_2: Elimination rate constant of desacetyl-CTX
- km: Metabolic rate constant of CTX
- k_{12}: Rate constant of CTX for entering a tissue compartment
- k_{21}: Rate constant of CTX for leaving a tissue compartment
- k_{34}: Rate constant of desacetyl-CTX for entering a tissue
- k_{43}: Rate constant of desacetyl-CTX for leaving a tissue compartment
- A_0: Dose administered
- F: Fraction of drug absorbed.

Table I. Pharmacokinetic parameters of CTX, desacetyl-CTX and CET calculated from plasma data in dogs after a single injection of the drugs.

Parameters	CTX	Desacetyl-CTX	CET
$T_{1/2}$ (α) (h)	0.197	0.146	
$T_{1/2}$ (β) (h)	0.715	0.973	
$T_{1/2}$ (h)			0.277
K (h^{-1})	2.24	1.31	2.50
k_{12} (h^{-1})	0.72	1.59	
k_{21} (h^{-1})	1.52	2.58	
km (h^{-1})	0.91		
V_1 ($ml.kg^{-1}$)	218	174	349
Vss (l)	5.32	2.42	
TC ($ml.min^{-1}\ kg^{-1}$)	8.13	3.80	14.6
AUC ($\mu g.ml^{-1}.h$)	41.0	87.5	22.9

$T^{1/2}$ (α): Half-life in α-phase
$T^{1/2}$ (β): Half-life in β-phase
$T^{1/2}$: Half-life
K: Elimination rate constant
k_{12}: Rate constant for entering a peripheral compartment
k_{21}: Rate constant for leaving a peripheral compartment
km: Metabolic rate constant
V_1: Apparent volume of a central compartment
Vss: Distribution volume
TC: Total clearance
AUC: Area under the drug plasma concentration versus time curve from zero to infinity

excreted in the form of unchanged desacetyl-CTX (Fig. 3). The case of CTX is different because it was metabolized to a larger extent (Fig. 4). Therefore, attention was given to the metabolic rate constant (km) of deacetylation of CTX. The km of CTX was calculated with equation (*2*) and by inserting the observed plasma levels of desacetyl-CTX, which gave 0.91 h^{-1} on the average. There was no significant difference in the km values obtained at any time point. On the basis of the mean km value, the theoretical curve of the plasma level of desacetyl-CTX after intravenous injection of CTX (Fig. 1) can be expressed by equation (*9*).

$$y = 53.6e^{-0.71t} - 38.9e^{-4.77t} - 37.8e^{-0.97t} + 22.1e^{-3.51t} \quad (9)$$

Plasma Concentration of CET after intravenous injection

Because CET is a chemical analogue of CTX with the carboxymethyl group is linked at the position 3, the pharmacokinetics of CET at the same dose level were also studied. CET disappeared from plasma in accordance with a one-compartment model (Fig. 5). The resulting pharmacokinetic parameters are given in Table I. The disappearance rate of CET was faster than that of CTX. Desacetyl-CET was detected at a high concentration in the plasma (Fig. 5).

The theoretical curve of the CET plasma concentration time curve (Fig. 5) is given by equation (*10*). The rapid disappearance of CET from plasma can be explained by a markedly larger total body clearance than that of CTX.

$$y = 57.3e^{-2.5t} \quad (10)$$

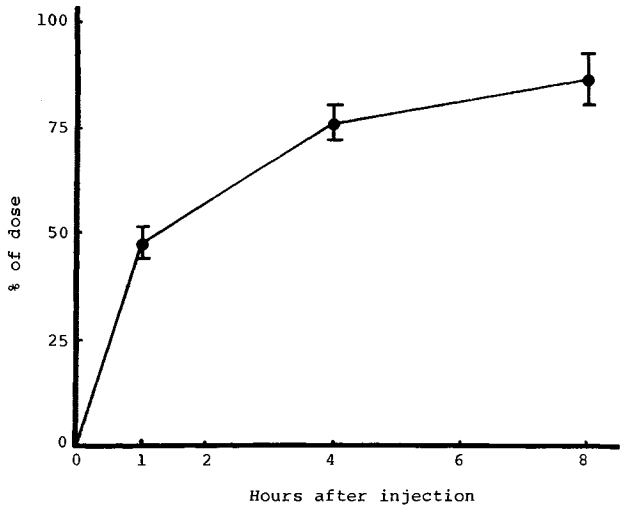


Fig. 3 Cumulative urinary excretion of desacetyl-CTX in dogs after a single intravenous injection of the drug (20 mg/kg, i. v.).
Each point represents the mean of four dogs with the standard error.

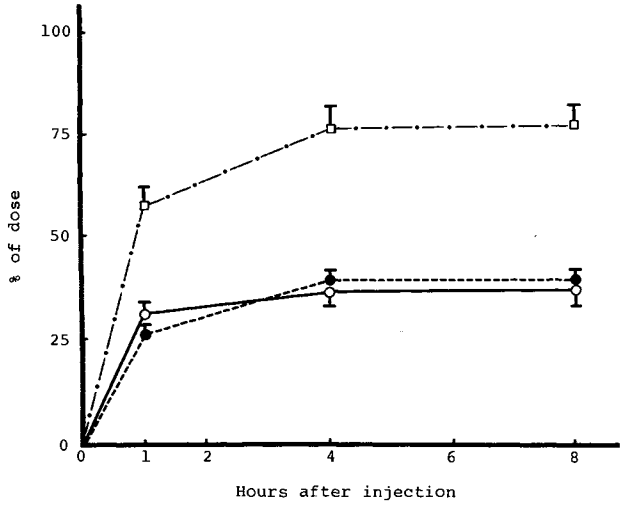


Fig. 4 Cumulative urinary excretion of CTX and desacetyl-CTX in dogs after a single intravenous injection of CTX (20 mg/kg, i. v.).
Key: ○, CTX; ●, Desacetyl-CTX; □, Sum of CTX and desacetyl-CTX.
Each point represents the mean of eleven dogs with the standard error.

Urinary excretion of CTX and CET after intravenous injection

Figure 4 shows the cumulative urinary excretion of both unchanged CTX and desacetyl-CTX after intravenous injection of 20 mg/kg CTX. CTX and desacetyl-CTX were excreted in almost equal quantities into the urine. The total amount of urinary excretion of unchanged CTX and desacetyl-CTX within 8 hours after the injection of CTX was 76.6 % of the dose.

Within 8 hours after CET was intravenously injected, 22.4 % of the dose was excreted into the urine as unchanged CET while 40.9 % was excreted as desacetyl-CET, revealing that deacetylation of CET occurred to a greater extent than deacetylation of CTX (Fig. 6).

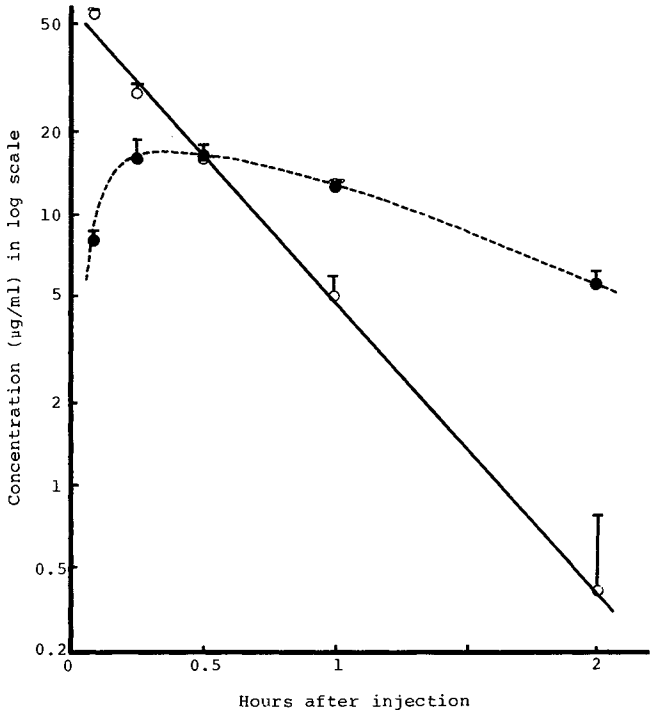


Fig. 5 Levels of CET and desacetyl-CET in dog plasma after a single intravenous injection of CET (20 mg/kg, i. v.).
Key: ○, CET; ●, Desacetyl-CET.
Each point represents the mean of five dogs with the standard error.

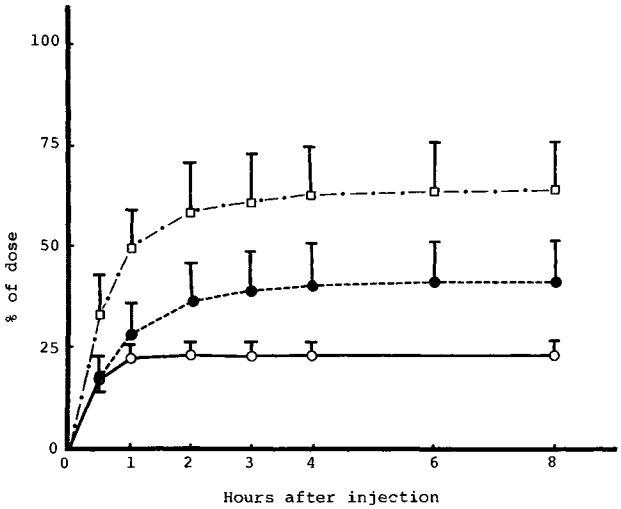


Fig. 6 Cumulative urinary excretion of CET and desacetyl-CET in dogs after a single intravenous injection of CET (20 mg/kg, i. v.).
Key: ○, CET; ●, Desacetyl-CET; □, Sum of CET and desacetyl-CET.
Each point represents the mean of five dogs with the standard error.

Plasma concentrations of CTX and CET after intramuscular injection

CTX (20 mg/kg) and CET (20 mg/kg) were injected intramuscularly in dogs to compare the results with those obtained by intravenous injection. The plasma levels of unchanged CTX

and desacetyl-CTX are shown in Fig. 7. CTX diffused rapidly from the injection site into the plasma. The maximum level of CTX in the plasma was attained 30 minutes after the drug was intramuscularly injected, but CTX could no longer be detected in the plasma 4 hours after injection. Desacetyl-CTX was detected at high concentration 15 minutes after CTX was injected and reached a peak 30 minutes after CTX was injected.

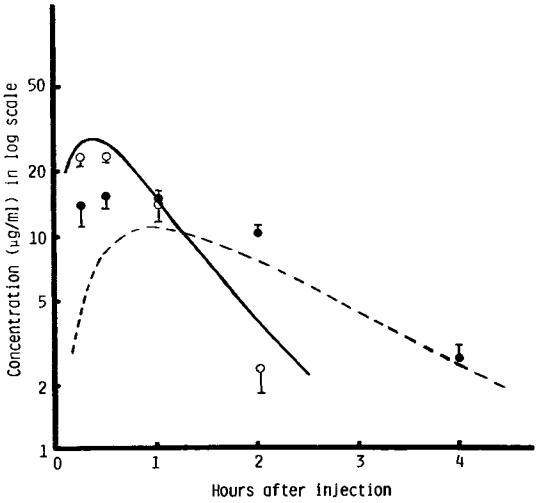


Fig. 7 Levels of CTX and desacetyl-CTX in dog plasma after a single intramuscular injection of CTX (20 mg/kg, i.m.).
Key: ○, CTX; ●, Desacetyl-CTX.
Each point represents the mean of six dogs with the standard error.

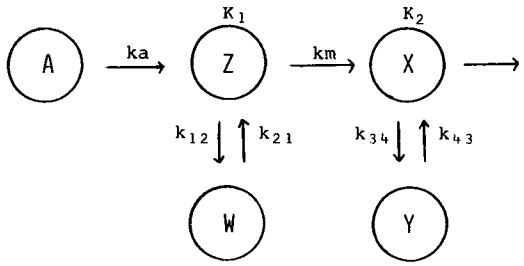
Theoretical curves for plasma levels of CTX and desacetyl-CTX after intramuscular injection of CTX were attained with the use of equations (*11*) and (*12*) shown in Scheme 2 and the values of pharmacokinetic parameters obtained after intravenous injection of CTX, except for Ka and F values. Ka values were calculated by the non-linear least squares method (Gauss-Newton's method) taking F value as 1. However, any Ka values thus obtained did not provide theoretical curves favorably fitting with actual plasma levels of CTX and desacetyl-CTX. The use of the Ka value of 3 gave theoretical values relatively similar to actual ones; theoretical CTX concentrations exceeded actual values at all plotted data points. Therefore, the theoretical curves were again obtained using the Ka value of 3 and the minimum permissible F value of 0.85 which was calculated from the ratio of the total amount of CTX and desacetyl-CTX excreted into urine after intravenous administration of CTX (76.6 %) to that after intramuscular injection (65.4 %) As illustrated in Fig. 7, this approach yielded an approximate fit of the actual CTX levels, but a rather poor fit of the desacetyl-CTX levels. These results suggest that intramuscular CTX, unlike intravenous CTX, does not obey simple first order kinetics.

Fig. 8 shows the plasma levels of unchanged CET and desacetyl-CET after intramuscular injection of CET. The plasma level of CET peaked 15 minutes after administration of the drug and then decreased. On the other hand, the maximum concentration of desacetyl-CET in the plasma was higher than that of CET 30 minutes to 1 hour after CET administration. After that, the level gradually decreased.

On the basis of the plasma levels of CTX after intramuscular injection, the AUC's of unchanged CTX and of desacetyl-CTX were obtained. The ratio of the AUC of desacetyl-CTX over that of unchanged CTX was 1.46, which is higher than the ratio after intravenous injection of CTX (0.85). On the basis of the data in Figs. 5 and 8, the AUC's of unchanged CET and desacetyl-CET were obtained. The AUC ratio of desacetyl-CET over that of unchanged CET was much higher after intramuscular injection of CET (3.56) than that after intravenous injection (1.12).

Urinary excretion of CTX and CET after intramuscular injection

Figure 9 shows that urinary excretion of unchanged CTX and desacetyl-CTX was 61.1 % of the dose within 6 hours after injection (32.9 % for unchanged CTX and 28.2 % for desacetyl-CTX). There was not significant difference in urinary



$$Z = kaFA_0\left\{\frac{(\gamma + k_{21})e^{\gamma t}}{(\gamma - \delta)(\gamma + ka)} + \frac{(\delta + k_{21})e^{\delta t}}{(\delta - \gamma)(\delta + ka)} + \frac{(k_{21} - ka)e^{-kat}}{(ka + \gamma)(ka + \delta)}\right\} \quad -----(11)$$

$$X = kakmFA_0\left\{\frac{(\alpha + k_{43})(\alpha + k_{21})e^{\alpha t}}{(\alpha - \beta)(\alpha - \gamma)(\alpha - \delta)(\alpha + ka)}\right.$$
$$+ \frac{(\beta + k_{43})(\beta + k_{21})e^{\beta t}}{(\beta - \alpha)(\beta - \gamma)(\beta - \delta)(\beta + ka)} + \frac{(\gamma + k_{43})(\gamma + k_{21})e^{\gamma t}}{(\gamma - \alpha)(\gamma - \beta)(\gamma - \delta)(\gamma + ka)}$$
$$\left. + \frac{(\delta + k_{43})(\delta + k_{21})e^{\delta t}}{(\delta - \alpha)(\delta - \beta)(\delta - \gamma)(\delta + ka)} + \frac{(k_{43} - ka)(k_{21} - ka)e^{-kat}}{(ka + \alpha)(ka + \beta)(ka + \gamma)(ka + \delta)}\right\}$$
$$-----(12)$$

Scheme 2. Model and equations for CTX after intramuscular injection.

Where,
Ka: Absorption rate constant
For other symbols, see Scheme 1.

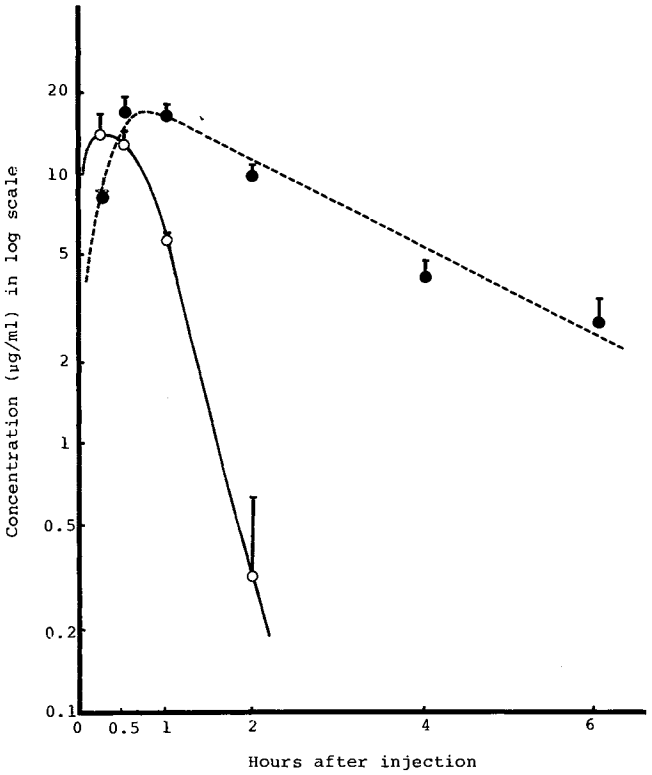


Fig. 8 Levels of CET and desacetyl-CET in dog plasma after a single intramuscular injection of CET (20 mg/kg, i. m.).
Key: ○, CET; ●, Desacetyl-CET.
Each point represents the mean of three dogs with the standard error.

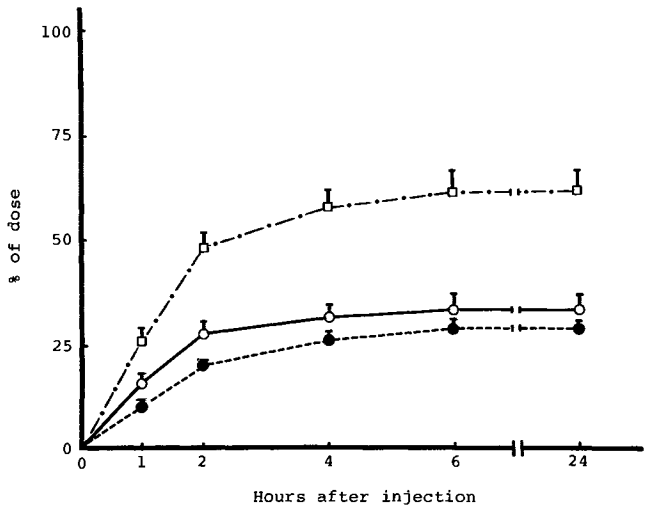


Fig. 9 Cumulative urinary excretion of CTX and desacetyl-CTX in dogs after a single intramuscular injection of CTX (20 mg/kg, i. m.).
Key: ○, CTX; ●, Desacetyl-CTX; □, Sum of CTX and desacetyl-CTX.
Each point represents the mean of six dogs with the standard error.

excretion ratio of desacetyl-CTX over unchanged CTX (1.16) after the intramuscular injection, as compared with the ratio after intravenous injection of CTX (1.06).

Figure 10 shows urinary excretion of unchanged CET and desacetyl-CET when CET was injected intramuscularly. Within 8 hours after injection, 12.9 % of the dose was excreted in the urine in unchanged form, while 47.3 % was excreted in the deacetylated form. The ratio of desacetyl-CET to unchanged CET in urine after the intramuscular injection was 3.7, which was much larger than the ratio (1.8) obtained after the intravenous injection of CET. Hence, desacetyl-CET was excreted in much larger quantities when CET was injected intramuscularly than when it was injected intravenously.

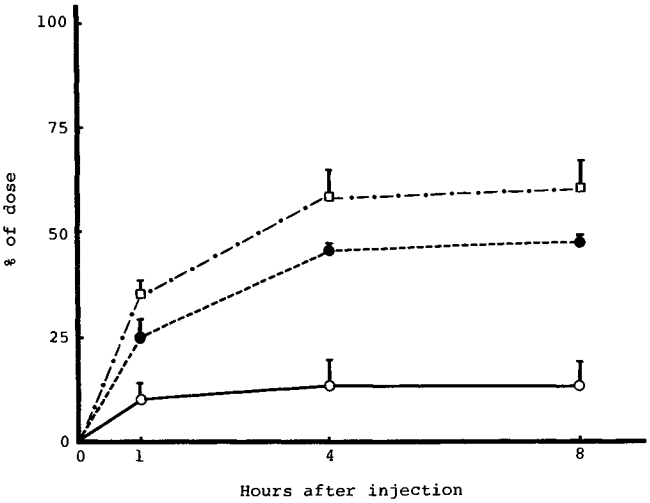


Fig. 10 Cumulative urinary excretion of CET and desacetyl-CET in dogs after a single intramuscular injection of CET (20 mg/kg, i. m.).
Key: ○, CET; ●, Desacetyl-CET; □, Sum of CET and desacetyl-CET.
Each point represents the mean of five dogs with the standard error.

Metabolites of CTX

Although only desacetyl-CTX has been established as a metabolite of CTX, Chamberlain et al. (3) and Reeves et al. (4) have described the presence of the two metabolites (M_2 and M_3) that were formed from a deacetylated metabolite of CTX through lactone formation. Therefore, in the present study, an attempt was made to determine M_2 and M_3 in urine and plasma samples when CTX was injected intravenously or intramuscularly. However, neither M_2 nor M_3 were detectable in plasma; however, they were detectable in the urine (detection limit, 5 μg/ml) (Table II). Within 24 hours after intravenous or intramuscular injection, approximately 4 % of the CTX dose was excreted as M_2 or M_3.

The following conclusions can be drawn from the aforementioned results.

(1) The present results on urinary excretion revealed that the ratio of the parent drug to the deacetylated drug after intravenous injection was approximately 1:1 in the case of CTX and approximately 1:2 in the case of CET. This suggests that CET is deacetylated more readily than CTX. The increased velocity of deacetylation of CET is also considered to be responsible for the rapid disappearance of CET from plasma.

(2) In the present study, when CTX was injected intravenously, no change in km dependent upon time was observed.

Table II. Urinary excretion of M_2 and M_3 in dogs after intravenous or intramuscular injection of CTX (20 mg/kg)

Time after injection (h)	Intravenous injection		Intramuscular injection	
	M_2(%)	M_3 (%)	M_2 (%)	M_3 (%)
0–1	0.57±0.03	0.61±0.15	0.16±0.04	0.29±0.04
1–2	1.47±0.09	1.65±0.08	0.81±0.07	1.25±0.17
2–4	1.59±0.30	1.55±0.58	0.85±0.11	0.94±0.04
4–6	0.43±0.10	0.58±0.13	0.38±0.08	0.50±0.11
6–24	n.d.	n.d.	n.d.	n.d.
Total	4.00±0.34	4.63±0.40	2.35±0.33	4.38±0.57

Each value represents the mean of six dogs with standard error.
n.d.: not detectable.

Therefore, CTX disposition appears to obey linear pharmacokinetics. On the other hand, theoretical curves for plasma levels of CTX and desacetyl-CTX after intramuscular injection of CTX, obtained with the use of the pharmacokinetic parameters after intravenous administration, did not fit well with actual values, suggesting that intramuscular CTX, unlike intravenous CTX, does not show a simple first order kinetic pattern. The kinetic difference between the two routes of administration seems unrelated to the production of desacetyl-CTX, M_2, and M_3, because there was no significant difference between the urinary excretion of the three metabolites after intramuscular and intravenous administration of CTX.

(3) When CTX and CET were injected intramuscularly, they were detected in high concentrations in the blood, revealing that both drugs rapidly diffused from the injection site into the blood.

(4) When CET was injected intramuscularly, a large quantitity of desacetyl-CET was detected in the urine. Desacetyl-CET was produced to a much greater extent when CET was injected intramuscularly than when injected intravenously. These results were consistent with the higher AUC ratio of desacetyl-CET over unchanged CET after intramuscular than after the intravenous injection of CET. On the other hand, the urinary pharmacokinetics of CTX were almost the same when the drug was injected intramuscularly or intravenously.

(5) CTX metabolites other than desacetyl-CTX (M_2 and M_3) after intravenous and intramuscular injection were detected in trace amounts in the urine but were not detectable in the plasma. There was no significant difference for M_2 and M_3 between the two injection routes.

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Salutary Effects of Two Verapamil Analogs in Traumatic Shock[5]

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Abstract: We studied the effects of two verapamil analogs, anipamil and ronipamil, in traumatic shock. Noble-Collip drum trauma produced a shock state characterized by an eight-fold increase in plasma cathepsin D activity, a 13-fold increase in the rate of plasma myocardial depressant factor (MDF) accumulation, and a survival time of 1.9 ± 0.1 hours. Neither verapamil analog had any significant effect on attenuating the shock-induced rise in plasma cathepsin D activity. However, both anipamil and ronipamil ($p < 0.01$) significantly blunted the rate of MDF accumulation in the plasma. In addition, these agents significantly inhibited proteolysis *in vitro*. Both analogs significantly prolonged survival time to 3.1 ± 0.6 h at 0.25 mg/kg ($p < 0.05$) and to 4.4 ± 0.3 h at 1.0 mg/kg ($p < 0.001$). Anipamil appears to provide a more potent protection in this shock model; however, both verapamil derivatives possess promising anti-shock potential.

Agents that inhibit calcium influx are beneficial in protecting hypoxic and ischemic cells (1, 2, 3) and are useful in the treatment of hypertension (4, 5) as well as the hypodynamic

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