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Notes

Pharmacokinetics of ciprofloxacin after intravenous administration of ciprofloxacin-TOF in rabbits

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Summary

The pharmacokinetic parameters and tissue distribution of ciprofloxacin were compared after intravenous (i.v.) administration of ciprofloxacin-HCl or ciprofloxacin-TOF salts, 30 mg kg^{-1} as free ciprofloxacin to rabbits. The pharmacokinetic parameters and tissue distribution of ciprofloxacin were not significantly different between i.v. administration of ciprofloxacin-TOF and ciprofloxacin-HCl salts, indicating that ciprofloxacin-TOF salt is pharmacokinetically equivalent to ciprofloxacin-HCl salt. Radioactivity was evenly distributed in all the tissues (or organs) studied at 48 h after i.v. administration of 1-^{14}C- or 1,2,3,4,5-^{14}C-labelled TOF, 750000 dpm kg^{-1} to rabbits and the mean percentages of i.v. dose excreted in 48 h urine as measured radioactivity were 23.6 and 26.1% for [1-^{14}C]- and [1,2,3,4,5-^{14}C]TOF, respectively.

The quinoline derivatives such as oxolinic acid and cinoxacin inhibit neither nalidixic acid-resistant microorganisms nor *Pseudomonas aeruginosa* or Gram-positive species (Brittain et al., 1985). Therefore, many fluorinated quinoline carboxylic acid derivatives have been synthesized. For example, 6,8-difluoro-1-(2-fluoroethyl)-1,4-dihydro-7-(4-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid (ciprofloxacin) has been reported to have an extremely wide in vitro spectrum of activity, including over 90% of Enterobacteriaceae at less than 1 $\mu g\ ml^{-1}$, and many *P. aeruginosa* at 1–2 $\mu g\ ml^{-1}$ (Muytjens et al., 1983; Chin and Neu, 1984). The R&D Center, Cheil Foods and Chemicals Inc. (Ichon, South Korea), has recently developed the (*s*)-tetrahydro-5-oxo-2-furancarboxylic acid (TOF) salt of ciprofloxacin in order to increase the solubility of ciprofloxacin. For example, the water solubility of ciprofloxacin is approx. 3, 7–10 and 18% (v/w) for the HCl, lactic acid and TOF salt, respectively.

The purpose of this report was to compare the pharmacokinetic parameters and tissue distribution of ciprofloxacin after intravenous (i.v.) infu-

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sion of ciprofloxacin-TOF or ciprofloxacin-HCl salt, 30 mg kg^{-1} as free ciprofloxacin to rabbits, and to determine the tissue distribution and urinary excretion of TOF after i.v. administration of [1-^{14}C]- or [1,2,3,4,5-^{14}C]TOF, 750000 dpm kg^{-1} to rabbits.

48, healthy, male unanesthetized New Zealand White rabbits (1.5–2.8 kg, Korea Laboratory Animal Development, Seoul, South Korea) were anesthetized with 50–100 mg of i.v. ketamine (kindly supplied by Yu-Han Research Center, Kunpo, South Korea) via the ear vein. The left carotid artery and the jugular vein were catheterized with polyethylene tubing (Dow Corning Inc., Midland, MI) for blood sampling and drug administration, respectively. Each cannula was exteriorized to the dorsal side of the neck where each cannula terminated with a three way stop-cock (Pharmaseal K 75, Pharmaseal Inc., Toa Alto, Puerto Rico). The exposed areas were closed using a surgical suture. Each cannula was flushed with heparinised (the heparin being kindly supplied by Choong-Wae Pharmaceutical Co., Seoul, South Korea) 0.9% NaCl solution (10 U ml^{-1}) to prevent blood from clotting. A pediatric Foley catheter (Sewoon Co., Fr. 16, Seoul, South Korea) was introduced into the urinary bladder for collection of urine samples. The animals were allowed to recover from anesthetization for 4–5 h before experiments, and fasted during the experiment.

Ciprofloxacin-TOF and ciprofloxacin-HCl salts (kindly supplied by the R & D Center, Cheil Foods and Chemicals Inc., dissolved in injectable distilled water to provide a final concentration of 15 mg ml^{-1} as free ciprofloxacin), 30 mg kg^{-1} as free ciprofloxacin were injected (total injection volume, approx. 4 ml) during a period of 1 min through the cannula placed in the jugular vein of rabbits 1–14 and 15–28, respectively. To complete injection of the drug, 2 ml of the heparinised 0.9% NaCl solution were used for flushing the cannula just after infusion of the drug. A blood sample (0.5 ml) was taken from the carotid artery shortly before dosing (to serve as a control) and at 1 (the end of infusion), 5, 10, 15, 30, 45, 60, 90, 120, 180, 240, 300, 360, 480, 600, 720 and 1440 min after injection. Before each blood sampling, approx. 1 ml of blood was first withdrawn into another syringe (this blood being later returned into the catheter) in order to collect the real circulating blood. The cannula was then flushed with approx. 2 ml of the heparinised 0.9% NaCl solution to prevent blood from clotting. Blood samples were centrifuged immediately to reduce or minimize the potential 'blood storage effect' (Lee et al., 1981; Shin et al., 1992) of the plasma concentrations of ciprofloxacin, and two 0.1 ml plasma samples were stored in a freezer (−60°C) prior to HPLC analysis of ciprofloxacin. Urine samples were collected at 0–8 and 8–24 h after i.v. administration. After measuring the exact volume of urine, two 0.1 ml urine samples were stored in the freezer prior to HPLC analysis of ciprofloxacin.

Ciprofloxacin-TOF and ciprofloxacin-HCl salts, 30 mg kg^{-1} as free ciprofloxacin, were similarly infused over a 1 min period to rabbits 29–34 and 35–40, respectively. After 30 min of the injection, as much whole blood as possible was collected through the carotid artery and centrifuged immediately. The liver, kidney, spleen, heart, lung, brain, stomach, small intestine, large intestine, bile, testis, urinary bladder, mesentery, fat and muscle were excised. Each organ was either perfused or rinsed with cold 0.9% NaCl solution to eliminate blood remaining in each tissue (or organ). After blotting dry with paper tissue, exactly 1 g of each tissue (or organ) was homogenized with 4 volumes of distilled water using a tissue homogenizer (Ultra-Turrax T25, Janke & Kunkel, IKA-Labortechnik, Germany). Plasma samples were also diluted with 4 volumes of distilled water. After centrifugation, two 0.1 ml aliquots of the supernatant or plasma were stored in the freezer prior to HPLC assay of ciprofloxacin.

Two kinds of radiolabelled TOF, [1-^{14}C]- and [1,2,3,4,5-^{14}C]TOF (prepared from unlabelled (*l*)-glutamic acid, Sigma Chemical Co., St. Louis, MO), 750000 dpm kg^{-1} were injected intravenously via the ear vein of rabbits 41–44 and 45–48, respectively. Urine samples were collected at 0–24 and 24–48 h after injection. At 48 h after injection, 0.2 g of the lung, kidney, muscle, heart, brain, stomach, small intestine, large intestine

and liver were collected and total radioactivity was measured (Kim et al., 1993).

The concentrations of ciprofloxacin in plasma, urine and tissue were analyzed according to a slight modification of the reported HPLC method (Höffler et al., 1984). The HPLC system consisted of a Model 7125 injector (Rheodyne, Cotati, CA), a Model 400 solvent delivery system pump (Applied Biosystem, San Jose, CA), reversed-phase guard column (Applied Biosystem, C_{18}, 30 × 4.6 mm, 5 μm), and reversed-phase column (C_{18}, 30 cm × 3.9 mm id., 10 μm, Waters Associates, Milford, MA), a fluorescence detector (FS-980, Applied Biosystems, Foster City, CA), and a Model 1200 recorder (Linear, Reno, NV). The mobile phase, 0.027 M phosphoric acid adjusted to pH 3.0 with tetrabutylammonium hydroxide and acetonitrile (89:11, v/v), was run at a flow rate of 1.5 ml min^{-1}. The wavelength settings were at 278 and 470 nm for excitation and emission, respectively. Sample preparation was simple; 0.25 ml of acetonitrile were added to 0.1 ml of the biological sample. After vortex mixing and centrifugation, 50 μl of the supernatant were injected directly onto the HPLC column at ambient temperature. Peak height measurements were used for quantitation of ciprofloxacin.

The pharmacokinetic parameters, such as the area under the plasma concentration-time curve from time zero to time infinity (AUC; Chiou, 1978), area under the first moment of the plasma concentration-time curve (AUMC), mean residence time (MRT), apparent volume of distribution at steady state (V_{ss}), and time averaged total body (CL), renal (CL_R) and nonrenal (CL_{NR}) clearances were estimated by the standard method (Gibaldi and Perrier, 1982). The harmonic mean was employed for the calculation of the mean values of half-life, each clearance and V_{ss} (Chiou, 1979a). Statistical analysis was assessed using *t*-test between means for unpaired data. Significant differences were judged as $p < 0.05$. All results are expressed as mean ± standard deviation.

The mean arterial plasma concentration-time profiles of ciprofloxacin after 1 min i.v. infusion of ciprofloxacin-TOF and ciprofloxacin-HCl salts to rabbits 1–14 and 15–28, respectively, are shown in Fig. 1, and the relevant pharmacokinetic parameters are listed in Table 1. After i.v. infusion, plasma concentrations of ciprofloxacin declined polyexponentially in all the rabbits studied with mean terminal half-lives of 109 and 116 min for ciprofloxacin-TOF and ciprofloxacin-HCl salts, respectively. The values were not significantly different. It should be noted that the plasma concentrations of ciprofloxacin at 5, 10, 15, 30 and 45 min after i.v. infusion of ciprofloxacin-TOF salt were significantly higher than those in the case of the ciprofloxacin-HCl salt (Fig. 1). However, the plasma concentrations of ciprofloxacin at other blood collection times were not significantly different between ciprofloxacin-TOF and ciprofloxacin-HCl salts (Fig. 1). It is of interest to note that the plasma concentration of cipro-

TABLE 1

Mean (±standard deviation) pharmacokinetic parameters of ciprofloxacin after 1 min i.v. infusion of ciprofloxacin-TOF salt and ciprofloxacin-HCl salt, 30 mg kg^{-1} as free ciprofloxacin to rabbits 1–14 and 15–28, respectively

Parameter	Ciprofloxacin-TOF salt	Ciprofloxacin-HCl salt
Body weight (kg)	2.09 ± 0.235	1.96 ± 0.221
$t_{1/2}$ (min)	109 ± 20.3	116 ± 56.1
AUC (μg min ml^{-1})	1350 ± 312	1230 ± 575
AUMC (μg min^2 ml^{-1})	136000 ± 50700	186000 ± 235000
MRT (min)	98.6 ± 22.0	126 ± 64.4
CL (ml min^{-1} kg^{-1})	22.3 ± 6.65	22.4 ± 9.77
CL_R (ml min^{-1} kg^{-1})	2.68 ± 2.01	2.05 ± 5.65
CL_{NR} (ml min^{-1} kg^{-1})	18.3 ± 7.41	20.0 ± 7.37
V_{ss} (ml kg^{-1})	2150 ± 548	2930 ± 768
Xu_∞ (μg)	9320 ± 6110	12800 ± 7090

TOF, (*s*)-tetrahydro-5-oxo-2-furancarboxylic acid. Each parameter was not significantly different ($p < 0.05$).

floxacin at 1 min was lower than that at 5 min in all the rabbits studied except rabbit 8. This could be due to the problem caused by the low solubility of ciprofloxacin, and the second peak phenomenon after i.v. administration of some drugs could also be attributed to low solubility in blood (Chiou, 1979b).

The mean pharmacokinetic parameters of ciprofloxacin, such as AUC (1350 vs 1230 μg min ml^{-1}), AUMC (136 000 vs 186 000 μg min^2 ml^{-1}), MRT (98.6 vs 126 min), $t_{1/2}$ (109 vs 116 min), CL (22.3 vs 22.4 ml min^{-1} kg^{-1}), CL_R (2.68 vs 2.05 ml min^{-1} kg^{-1}), CL_{NR} (18.3 vs 20.0 ml min^{-1} kg^{-1}), V_{ss} (2150 vs 2930 ml kg^{-1}) and the amount of ciprofloxacin excreted in 24 h urine (Xu_∞, 9320 vs 12 800 μg) were not significantly different between i.v. infusion of ciprofloxacin-TOF and ciprofloxacin-HCl salts (Table 1). These data strongly suggest that ciprofloxacin-TOF and ciprofloxacin-HCl salts are equivalent in terms of the pharmacokinetics of ciprofloxacin. The mean percentages of i.v. dose excreted in 24 h urine as unchanged ciprofloxacin were 14.9 and 21.8% for ciprofloxacin-TOF and ciprofloxacin-HCl salts, respectively, a comparable value, 11.7% (ranging from 0.6 to 36.1%) also being reported in six rabbits (Kusajima et al., 1986). However, the values were somewhat lower than those reported after i.v. administration to humans (Wingender et al., 1984; Wise et al., 1984; Höffken et al., 1985).

The mean amount (μg per g tissue) of ciprofloxacin remaining per g tissue (or organ), and the tissue-to-plasma (T/P) ratio at 30 min after i.v. infusion of ciprofloxacin-TOF and ciprofloxacin-HCl salts to rabbits 29–34 and 35–40, respectively are listed in Table 2. It should be noted that the amount of ciprofloxacin remaining per g tissue (or organ) and the T/P ratio were not significantly different in all the tissues (or organs) studied between ciprofloxacin-TOF and ciprofloxacin-HCl salts. Again, the foregoing observations strongly suggest that ciprofloxacin-TOF and ciprofloxacin-HCl salts are equivalent in terms of tissue distribution. Ciprofloxacin has a strong affinity to all the tissues (or organs) studied except fat and brain as shown by the T/P ratio above unity for both ciprofloxacin-TOF and ciprofloxacin-HCl salts. Similar results have also been obtained from rats after the i.v. administration of radioactive ciprofloxacin (Siefert et al.,

TABLE 2

Mean (±standard deviation) amount (μg per g tissue) of ciprofloxacin remaining per g tissue (or organ) at 30 min after 1 min i.v. infusion of ciprofloxacin-TOF salt and ciprofloxacin-HCl salt, 30 mg kg^{-1} as free ciprofloxacin to rabbits 29–34 and 35–40, respectively

Tissue	Ciprofloxacin-TOF salt	Ciprofloxacin · HCl salt
Plasma	2.57 ± 0.889	2.58 ± 0.791
Muscle	14.0 ± 2.63 (5.78 ± 1.60)	11.0 ± 1.44 (4.61 ± 1.53)
Bile	68.6 ± 58.4 (32.6 ± 36.7)	33.7 ± 15.6 (13.3 ± 5.41)
Fat	1.30 ± 0.389 (0.534 ± 0.172)	2.39 ± 1.56 (0.891 ± 0.402)
Testis	7.88 ± 1.91 (3.17 ± 0.602)	6.81 ± 0.646 (2.83 ± 0.759)
Urinary bladder	47.9 ± 50.4 (19.0 ± 21.9)	12.8 ± 8.04 (4.99 ± 2.75)
Lung	7.26 ± 3.18 (2.77 ± 0.210)	6.28 ± 2.35 (2.49 ± 0.699)
Heart	6.47 ± 5.44 (2.64 ± 2.40)	3.19 ± 0.885 (1.26 ± 0.183)
Spleen	11.2 ± 5.86 (4.32 ± 1.53)	10.7 ± 4.49 (4.15 ± 1.09)
Kidney	161 ± 167 (61.6 ± 65.7)	211 ± 152 (74.7 ± 40.0)
Liver	9.03 ± 5.45 (3.58 ± 2.13)	9.07 ± 2.57 (3.62 ± 0.801)
Mesentery	2.97 ± 1.14 (1.24 ± 0.606)	5.02 ± 4.28 (1.88 ± 1.23)
Stomach	6.79 ± 2.97 (2.59 ± 0.586)	4.80 ± 1.86 (1.89 ± 0.651)
Small intestine	4.97 ± 1.41 (1.97 ± 0.346)	3.68 ± 2.30 (1.40 ± 0.598)
Large intestine	10.0 ± 6.10 (4.32 ± 3.12)	4.88 ± 2.11 (1.97 ± 0.657)
Brain	1.26 ± 0.238 (0.526 ± 0.169)	1.23 ± 0.594 (0.521 ± 0.307)

TOF, (*s*)-tetrahydro-5-oxo-2-furancarboxylic acid. Numbers in parentheses represent tissue-to-plasma (T/P) ratio. Each value was not significantly different ($p < 0.05$).

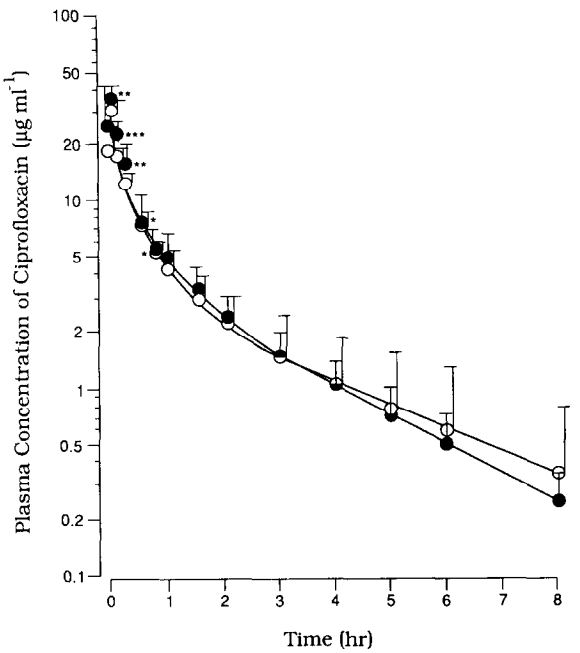

Fig. 1. Mean arterial plasma concentration-time profiles of ciprofloxacin after 1 min intravenous infusion of ciprofloxacin-TOF salt (●) and ciprofloxacin-HCl salt (○), 30 mg kg^{-1} as free ciprofloxacin to rabbits 1–14 and 15–28, respectively. Bars represent standard deviation. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

1986). Ciprofloxacin was highly concentrated in the bile, urinary bladder and kidney as shown by the extremely high value of the T/P ratio for both ciprofloxacin-TOF and ciprofloxacin-HCl salts.

The amount (dpm) of total radioactivity remaining per g tissue (or organ) at 48 h after i.v. administration of [1-^{14}C]- and [1,2,3,4,5-^{14}C]TOF, 750000 dpm kg^{-1} to rabbits 41–44 and 45–48, respectively is listed in Table 3. In the present TOF study, the total radioactivity was measured which therefore does not represent unchanged TOF only, but rather corresponds to the sum of the total radioactivity of TOF and its possible metabolites. Generally, the total radioactivity was evenly distributed in each tissue (or organ); the mean amount (dpm per g tissue) of total radioactivity remaining was determined as 212, 396, 190, 201, 196, 218, 251, 217 and 316 dpm per g tissue for the lung, kidney, muscle, heart, brain, stomach, small intestine, large intestine and liver, respectively, after i.v. administration of 1-^{14}C-labelled TOF to rabbits 41–44. The corresponding values after i.v. administration of 1,2,3,4,5-^{14}C-labelled TOF to rabbits 45–48 were 360, 806, 243, 289, 308, 323, 456, 347 and 560 dpm per g tissue. TOF exists in aqueous solution as TOF itself and α-hydroxyglutaric acid. α-Hydroxyglutaric acid is converted to α-ketoglutaric acid in animals (Well-Malherbe, 1937). The metabolism of α-ketoglutaric acid is then involved in the tricarboxylic acid cycle. Therefore, the even distribution of radiolabelled TOF in tissues could be expected.

TABLE 3

Amount (dpm per g tissue) of total radioactivity remaining in each tissue at 48 h after i.v. administration of 1-^{14}C- and 1,2,3,4,5-^{14}C-labelled TOF, 750000 dpm kg^{-1} to rabbits 41–44 and 45–48, respectively

Rabbits	Lung	Kidney	Muscle	Heart	Brain	Stomach	Small intestine	Large intestine	Liver
41 (2.1 kg)	222	434	183	222	213	242	252	218	336
42 (2.25 kg)	190	447	205	201	204	211	262	224	312
43 (2.2 kg)	213	339	200	178	157	221	254	197	272
44 (2.25 kg)	222	365	172	204	209	198	237	230	345
Mean (S.D.)	212 (14.9)	396 (52.3)	190 (15.1)	201 (18.0)	196 (26.2)	218 (18.8)	251 (10.4)	217 (14.3)	316 (32.6)
45 (2.3 kg)	333	752	255	310	307	312	399	314	549
46 (2.55 kg)	343	849	222	288	293	349	466	380	556
47 (2.75 kg)	405	900	235	300	380	329	530	374	606
48 (2.8 kg)	358	721	260	259	254	300	428	318	531
Mean (S.D.)	360 (32.2)	806 (83.2)	243 (17.6)	289 (22.0)	308 (52.7)	323 (21.4)	456 (57.0)	347 (35.4)	560 (32.3)

S.D., standard deviation.

TABLE 4

Cumulative amount (dpm) of total radioactivity excreted in urine for up to 48 h after i.v. administration of 1-^{14}C- and 1,2,3,4,5-^{14}C-labelled TOF, 750000 dpm kg^{-1} to rabbits 41–44 and 45–48, respectively

Rabbits	0–24 h	24–48 h	0–48 h
41 (2.1 kg)	135000 (8.58) [a]	112000 (7.10)	247000 (15.7)
42 (2.25 kg)	250000 (15.2)	75000 (4.55)	325000 (19.8)
43 (2.2 kg)	364000 (22.0)	604000 (3.66)	425000 (25.7)
44 (2.25 kg)	528000 (31.3)	328000 (1.94)	561000 (33.2)
Mean ± S.D.	319000 ± 168000 (19.3 ± 9.72)	70000 ± 33000 (4.31 ± 2.15)	389000 ± 135000 (23.6 ± 7.64)
45 (2.35 kg)	676000 (39.2) [a]	135000 (7.83)	811000 (47.0)
46 (2.55 kg)	331000 (17.3)	188000 (9.82)	519000 (27.1)
47 (2.75 kg)	247000 (12.0)	94200 (4.57)	341000 (16.5)
48 (2.8 kg)	165000 (7.86)	130000 (6.3)	296000 (14.1)
Mean ± S.D.	355000 ± 225000 (19.1 ± 14.0)	137000 ± 39000 (7.11 ± 2.25)	492000 ± 234000 (26.1 ± 15.0)

[a] Percent of i.v. dose excreted in urine. S.D., standard deviation.

The cumulative amount (dpm) of total radioactivity excreted in 48 h urine after i.v. injection of [1-^{14}C]- and [1,2,3,4,5-^{14}C]TOF, 750000 dpm kg^{-1} to rabbits 41–44 and 45–48, respectively, is listed in Table 4. The mean percentages of total radioactivity excreted in 48 h urine were not considerable; approx. 23.6% (ranging from 15.7 to 33.2%) and 26.1% (ranging from 14.1 to 47.0%) of the administered total radioactivity were excreted in 48 h urine after i.v. injection of [1-^{14}C]- and [1,2,3,4,5-^{14}C]TOF, respectively. In preliminary studies, the LD_{50} values of TOF and lactic acid were determined to be 1638 and 1140 mg kg^{-1}, respectively, when the compounds were injected intravenously to male ICR mice.

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