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COMMUNICATION

Pharmacokinetics and Urinary Excretion of DW116, a New Fluoroquinolone Antibacterial Agent, in Humans as a Phase I Study

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ABSTRACT

Pharmacokinetics and urinary excretion of the new fluoroquinolone antibacterial agent DW116 [1-(5-fluoro-2-pyridyl)-6-fluoro-7-(4-methyl-1-piperazynyl)-1,4-dihydro-4-oxoquinolone-3-carboxylic acid, hydrochloride] following oral administration (200, 400, 600 mg) were studied in humans as a phase I study. The plasma concentration of DW116 declined monoexponentially with a half-life range of 16–22 hr. The area under the curve (AUC) and C_{max} *increased proportionally as the dose increased. The* $T_{1/2}$ *and mean residence time (MRT) (28.3–30.9 hr) were independent of dose. The* T_{max} *appeared within 3 hr (0.9–2.7 hr) after drug administration. The* K_a *ranged from 1.3 to 4.1 (*hr^{-1}*). The plasma half-life was much longer, and* C_{max} *was higher by about two- to three-fold than conventional fluoroquinolones. Urinary recovery of DW116 was 29.6–61.6% of the dose. The maximum excretion rate appeared within 4 hr and decreased continuously after drug administration. A urinary metabolite was not detected in the urine extract obtained before and after hydrolysis by β-glucuronidase (from* Escherichia coli*); this was different from other fluoroquinolone antibacterial agents. Poor metabolism in the kidney may contribute to the good oral bioavailability, but due to the low recovery (<60%) in urine, it is possible that DW116 is metabolized in the liver or other organs.*

Key Words: *DW116; Excretion; Fluoroquinolone; Metabolism; Pharmacokinetics.*

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INTRODUCTION

Fluoroquinolones are potent broad-spectrum antibacterial agents and have excellent activity against various bacteria, a low frequency of adverse effects, and good absorption on oral administration. DW116 (Fig. 1) also showed almost 100% oral absorption in the rat (1). They have similar chemical structures, but exhibit wide differences in their pharmacokinetics and metabolic profiles. Ofloxacin is almost exclusively eliminated (70%) by the kidney (2), whereas perfloxacin is predominantly cleared by the liver. Some fluoroquinolones, such as norfloxacin, ciprofloxacin, enoxacin, fleroxacin, temafloxacin, and lomefloxacin are eliminated via both renal and hepatic routes (3). Most quinolones are metabolized to the corresponding oxo derivatives through a microsomal oxidative pathway by cytochrome P-450. Barofloxacin (4) and sparfloxacin (5) are excreted as glucuronide conjugates in urine, and the new fluoroquinolone T-3761 is excreted in both urine and bile as a glucuronide conjugate (6). DW116 was excreted as a glucuronide conjugate, but the oxidative metabolite *N*-oxide was not detected in rat urine or bile (1). In this report of a phase I study, we studied pharmacokinetics and urinary excretion profiles following oral administration of DW116 at doses of 200, 400, and 600 mg in human volunteers.

EXPERIMENTAL

Materials

DW116 was supplied by the Dong Wha Pharmaceutical Company (Anyang, Korea). All other chemicals were analytical grade or high-performance liquid chromatography (HPLC) grade and were used without further purification. β-Glucuronidase (from *Escherichia coli*) was obtained from Boeringer Mannheim (Mannheim, Germany) for enzymatic hydrolysis.

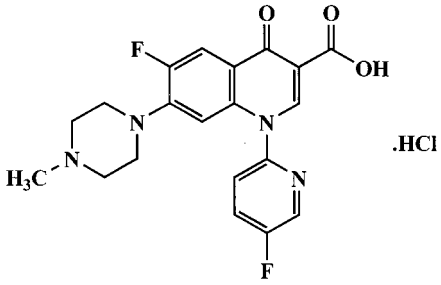

Figure 1. Chemical structure of DW116.

Drug Administration and Sample Collection

The 12 healthy volunteers were divided into three groups to participate in this study. They were all men, 20–25 years of age, and 60–80 kg of body weight. After overnight abstinence from food, DW116 was administered orally at doses of 200, 400, and 600 mg to each group at 08:00.

Venous blood samples were collected at 0 (predose), 0.5, 1, 2, 4, 8, 12, 24, 36, and 48 hr, and all urine samples were collected at 0 (predose) and from 0 to 4, 4 to 8, 8 to 12, 12 to 24, 24 to 36, 36 to 48, and 48 to 72 hr. Blood was centrifuged, and plasma was selected and stored at −20°C. Urine samples were also stored at −20°C until sample analysis.

Sample Preparation and High-Performance Liquid Chromatography Analysis

The concentrations of DW116 in plasma and urine were determined by the HPLC method (1). The HPLC systems consisted of a Hewlett Packard (HP) 1090 liquid chromatograph and a HP 3392 integrator. A Lichrosorb RP-18 column (particle size 5 μm; length 20 cm; id 4.6 mm; Hewlett Packard) was used for all analyses.

The mobile phase was a mixture of acetonitrile (A) and 0.1 M potassium dihydrogen phosphate containing 0.01% tetrabutylammoniumchloride and 1% 1-heptanesulfonic acid, which was adjusted to pH 2.5 with phosphoric acid (B). An isocratic system (A:B = 15:85, v/v) was used for the detection of metabolites, and a gradient system was used for quantification of DW116 (10% A to 25% A in 7 min and to hold 25% A and 75% B for 3 min). The flow rate was 1.0 ml/min, and the column eluent was monitored by an ultraviolet (UV) detector at 280 nm.

For quantification, plasma was prepared after simple protein precipitation. One and a half volumes of acetonitrile were added to plasma, and the mixture was vortexed for 1 min at 12,000 rpm and centrifuged. Urine was prepared after centrifugation (12,000 rpm for 2 min) only. To detect the urinary metabolite, 10 ml of urine collected for 24 hr after administration of the 600-mg dose were prepared by the same method used in the rat urine treatment of Park et al. (1). The urinary extracts and supernatant obtained from sample treatment were analyzed with HPLC.

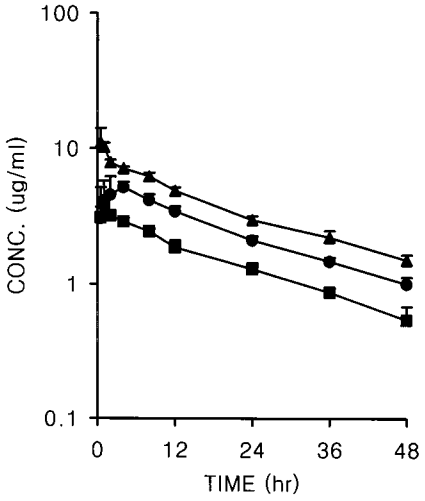

Figure 2. Temporal plasma profiles of DW116 following oral administration at the doses of ■, 200 mg; ●, 400 mg; and, ▲, 600 mg.

Linear regression was obtained ($r > .99$) and the CV (coefficient of variation; %) was below 10% at the concentration range of 1–50 μg/ml in the urine and 0.5–15 μg/ml in plasma.

Pharmacokinetic Analysis

The elimination rate constant was obtained by the monoexponential decay model using the PCNONLIN program (SCI Software, USA). The area under the curve (AUC) of the plasma concentration versus time from 0 to infinity and the area under the first moment curve (AUMC) were calculated by the trapezoidal method with extrapolation to infinity. MRT was calculated using AUC divided by AUMC. Renal clearance was calculated as the mean amount of drug in the urine X_u divided by the corresponding AUC value. All pharmacokinetic parameters were calculated for each individual rat.

RESULTS AND DISCUSSION

Temporal plasma profiles are shown in Fig. 2, and the pharmacokinetic parameters are shown in Table 1.

DW116 declined monoexponentially, and the half-life was relatively long, 16–21 hr. It is much longer—about fivefold—than ciprofloxacin, enoxacin, and norfloxacin, and twice as long as fleroxacin and perfloxacin. This is very useful for reducing the number of drug administrations in a day. The T_{max} was similar to other conventional fluoroquinolones, ciprofloxacin (7), and fleroxacin (8), and the C_{max} was higher than that of any other fluoroquinolones (7).

Dose dependency was not apparent. AUC and C_{max} increased proportionally as the dose increased, and half-life and MRT were independent of dose. In urine, 27.61%, 51.67%, and 61.55% of DW116 dose were recovered with 200-, 400-, and 600-mg doses, respectively. Urinary recovery of the 400- and 600-mg doses was not significantly different, but there was some difference with the 200-mg dose. The urinary excretion rate reached a maximum within 4 hr after dosing and declined continuously (Fig. 3). Because DW 116 showed perfect absorption following oral administration in the rat, it was extrapolated to humans; the renal clearance (*CLr*) was calculated by dividing oral AUC by X_u(0–72 hr). *CLr* was not different between doses; it is a much smaller value than for ciprofloxacin, enoxacin, fleroxacin, norfloxacin, and ofloxacin (7). It may contribute to the long half-life and large C_{max}, but unmetabolized DW116 was recovered below 60% of the dose in the urine, indicating that other

Table 1

Pharmacokinetic Parameters of DW116 Afer Oral Administration in Human

	Dose		
Parameter	200 mg	400 mg	600 mg
K_a (hr^{-1})	3.36 ± 0.97	1.30 ± 1.32	4.08 ± 1.36
$T_{1/2}$ (hr)	21.6 ± 1.83	16.4 ± 1.73	16.4 ± 5.16
AUC (μg · hr/ml)	94.1 ± 10.9	147.7 ± 8.65	224.1 ± 34.5
MRT (hr)	30.9 ± 2.46	28.8 ± 4.52	28.3 ± 3.18
CLr (L/hr)	1.78 ± 0.73	1.41 ± 0.44	1.65 ± 0.08
C_{max} (μg/ml)	3.74 ± 0.39	7.18 ± 2.02	9.76 ± 2.27
T_{max} (hr)	1.26 ± 0.40	2.73 ± 2.12	0.91 ± 0.40

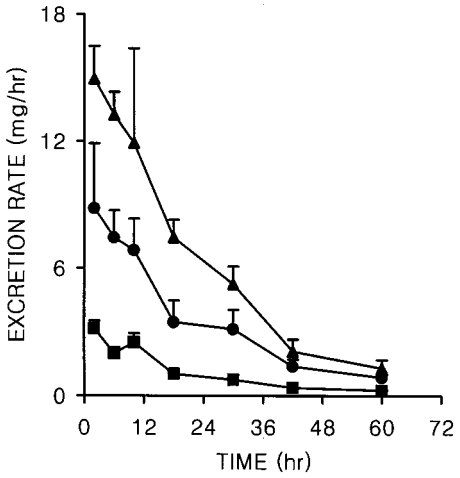

Figure 3. Urinary excretion rates of DW116 following oral administration at the doses of ■, 200 mg; ●, 400 mg; and ▲, 600 mg.

metabolic pathways may exist in DW116 metabolism. However, there was no glucuronide conjugate in the unhydrolyzed urine fraction, and any difference in DW116 amount was not detected after the hydrolysis by β-glucuronidase from *E. coli* in urine. In the rat, minor amounts of glucuronide exist in urine, and a large amount exists in bile. Further study of metabolism may show that the glucuronide conjugate may be detected in human bile.

CONCLUSION

DW116 declined monoexponentially and has a long half-life (16–21 hr). It also has a large C_{max} and small *CLr*; this seems to contribute to the ability of patients to reduce the number of administrations of drug in a day. There was no dose dependency in the dose range 200–600 mg. No metabolite was detected in unhydrolyzed and hydrolyzed fractions of urine, so it is necessary that a further metabolism study with human bile must be performed.

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