Effects of *Taraxacum mongolicum* on the Bioavailability and Disposition of Ciprofloxacin in Rats

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Abstract □ *Taraxacum mongolicum* (TM), also known as dandelion, is a herb widely used in the East for its antibacterial activity. The high mineral content of TM presents a potential problem for the absorption of quinolone antibiotics. This study was undertaken to discern the significance of a drug–drug interaction between TM and ciprofloxacin. Two groups of Sprague Dawley rats (220–250 g) were employed; one received a single oral dose of ciprofloxacin (20 mg/kg) with concomitant oral administration of an aqueous TM extract (2 g crude drug/kg) while the control group received oral ciprofloxacin (20 mg/kg) only. Ciprofloxacin in plasma and urine, collected over 6 and 24 h, respectively, was determined by HPLC. Noncompartment analysis was employed for pharmacokinetic parameter estimation. Results indicated that, as compared to control, maximum plasma concentration (C_{max}) of ciprofloxacin was significantly lowered by 73% in rats receiving concurrent TM dosing. Oral TM also caused a 3-fold increase in both apparent drug distribution volume ($V_{d,\lambda z}/F$: 92.0 vs 30.8 L/kg) and terminal elimination half-life ($t_{1/2,\lambda z}$; 5.71 vs 1.96 h). Partly due to the changes in drug distribution and elimination, relative bioavailability of ciprofloxacin, as assessed by $AUC_{0\rightarrow\infty}$, remained similar for both dosing groups. These findings suggest the possibility of a multifactorial drug–drug interaction between TM and ciprofloxacin. Thus, the implications of concomitant dosing of the two agents should not be overlooked.

Introduction

Ciprofloxacin is a fluoroquinolone-type antibiotic with excellent activity against Gram positive and negative bacteria as well as Mycobacteria. Its oral absorption, however, has been shown to be drastically impaired by concomitant administration of agents containing metal cations.[1,2] This phenomenon has been extensively studied for antacids, mineral supplements, and milk products.[3] Information on such an interaction is currently unavailable for herbal medicines and health foods.

The possibility of a drug−drug interaction between ciprofloxacin and a mineral rich antiinflammatory/antibacterial herbal medicine, *Taraxacum mongolicum* Hand-Mazz. (Compositae), was investigated in this study. Traditionally, the dried whole plant of *T. mongolicum* (TM) is used for the treatment of boils, sores, mastitis, lymphadenitis, inflammation of the eye, sore throat, lung and breast abscess, acute appendictis, jaundice, and urinary tract infections.[4,5] In addition, this herb has been shown to exert a bactericidal effect on numerous pathogens showing ranges of MIC from 1:10 to 1:640 with its aqueous extract.[4] In addition, in vitro antifungal, antileptospiral, and antiviral effects of the herb have also been documented.[4] Chemical investigation of TM indicates the presence of triterpenoids (e.g., taraxasterol, taraxacin, taraxarol), inulin, pectin, asparagin, and phenolic compounds.[4,6] To collect more definitive information, the content of metal cations in dried TM was independently measured. A full pharmacokinetic evaluation was conducted in the rat to elucidate the potential of a drug−drug interaction, if any, between TM and ciprofloxacin.

Experimental Section

Plant Materials—The whole dried plant of *T. mongolicum* (TM) was purchased from a local herbal shop and was authenticated by macroscopic examination and microscopic identification in the Pharmacognosy Laboratory, Department of Pharmacy, The Chinese University of Hong Kong, where the voucher specimen (TM01) was deposited. For the preparation of the aqueous TM extract used in animal studies, the powdered crude plant material (5 g) was treated with boiling deionized and distilled water (50 mL) for 1 h, and the extract was evaporated to a concentration equivalent to 0.5 g crude drug/mL.

Chemical Reagents and Apparatus—Ciprofloxacin hydrochloride was kindly provided as a gift by Bayer AG (Leverkusen, Germany). The internal standard, enoxacin, was purchased from Sigma Chemical Co. (St. Louis, MO). Acetonitrile (HPLC grade, Mallinckrodt-Baker, Inc., Phillipsburg, NJ), triethylamine (Riedel-de Haen AG, Germany), and other chemical reagents were acquired commercially.

An HPLC system (Hewelett Packard series 1050) consisting of an UV-detector, an autosampler, a reversed-phase ODS column (4.6 mm i.d. × 250 mm; particle size: 5 μm, Phenomenex), and a guard column (Novapak C_{18}, Waters) was employed for the quantitation of ciprofloxacin in plasma and urine smaples. For the assessment of the content of various cations in the TM extract, an inductive plasma emission spectrometer (Shimadzu ICPQ-1012) was used.

Assessment of Cation Content in *T. mongolicum* Extract—The TM extract was digested with an acid mixture consisting of HNO_3:$HClO_4$ (9:1). A plant-free acid control was also prepared for comparison. The content of Zn, Fe, Cu, Ca, Mn, Mg, Sr, Cr, Pb, and Ni was determined by plasma emission spectrometry.

Pharmacokinetic Studies—Male Sprague−Dawley rats (220−240 g) were housed under a controlled condition (23−25 °C, 55% relative humidity and 12 h light/dark light cycle) and were allowed free access to food and water before experiments. Under anesthetization with an ip injection of 80 mg/kg of ketamine and 10 mg/kg of xylazine, a cannula was surgically inserted into the right jugular of each animal. All study rats were fasted overnight prior to the scheduled blood sampling postdosing on the next day. In the test group, rats ($n = 5$) were dosed orally with the aqueous TM extract (2 g crude drug/kg) immediately followed by a single oral dose of ciprofloxacin (20 mg/kg). Rats ($n = 5$) that received a single oral dose of ciprofloxacin (20 mg/kg) alone were used as controls. Blood (0.6 mL) was withdrawn via the cannular just prior to ciprofloxacin dosing ($t = 0$) and at 5, 30, 60, 90, 120, 150, 180, 240, 300, and 360 min postdosing. Plasma was immediately separated by centrifugation at 10000*g* for 5 min. Urine samples were collected over 0−2, 2−4, 4−6, and 6−24 h intervals, and the total volume within each interval was recorded. Both plasma and urine samples were stored at −80 °C until assayed.

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HPLC Assay for Ciprofloxacin—The HPLC assay developed by Nix et al.[7] was utilized in the present study with minor modifications. For the quantitation of ciprofloxacin in plasma, acetonitrile (200 μL) was added to the plasma sample (0.3 mL) for protein precipitation and was followed by the addition of enoxacin (internal standard, final concentration: 1.0 ng/μL). The mixture was centrifuged at 10000*g* for 5 min, and 200 μL of the supernatant was tried using a Concentrivap Concentrator (Labconco, Kansas City, MO) at 35 °C. The residue was reconstituted in 70 μL of mobile phase, and a 50 μL aliquot of which was injected onto the HPLC. As for the urine assay, the sample was first diluted with deionized−distilled water containing 10 ng/mL internal standard. The dilution factor was 1:50 for samples collected over the 0−2, 2−4, 4−6 h intervals and 1:10 for the sample collected over the 6−24 h interval. The diluted samples were then centrifuged at 10000*g* for 5 min, and the supernatant (50 μL) was submitted to the HPLC assay.

The HPLC mobile phase consisted of 16% acetonitrile, 1% methanol, and 83% aqueous buffer (pH 3.0) which was comprised of sodium dihydrogen phosphate monohydrate (0.1 M), glacial acetic acid (1% v/v), and triethylamine (0.5% v/v). The flow rate was set at 1.1 mL/min, and detection was preformed at 278 nm. Complete separation of ciprofloxacin and enoxacin (internal standard) was achieved with retention times at 9.0 and 7.0 min, respectively. The calibration curves were linear over the range from 0 to 3 μg/mL and from 1.0 to 10 μg/mL for the respective plasma and urine assays with correlation coefficients >0.999 for both biomatrixes. The lower limit of quantitation of ciprofloxacin was 25 ng/mL for both assays. Adequacy of this analytical methodology was supported by the <9.3% coefficient of variations for the interday assay variability obtained from quality control samples.

Analysis of Pharmacokinetic Parameters of Ciprofloxacin—The plasma concentration−time data of ciprofloxacin were assessed by noncompartmental analysis. The maximum plasma concentration (C_{max}) and the time achieving C_{max} (T_{max}) were directly observed from the individual concentration vs time profiles. Least-squares regression analysis was employed on the terminal elimination phase for estimation of elimination rate constant (λ_z). Elimination half-life ($t_{1/2,\lambda z}$) was computed as 0.693/λ_z, and the area under curve from time zero to infinity ($AUC_{0\to\infty}$) was estimated by trapezoidal integration as:

$$AUC_{0\to\infty} = AUC_{0\to t} + C_t/\lambda_z$$

where $AUC_{0\to t}$ is the AUC from time zero to time t and C_t is the plasma ciprofloxacin concentration at time t. Other parameter estimates including oral clearance (CL/F), renal clearance (CL_r), and apparent volume of distribution ($V_{d,\lambda z}/F$) were estimated by standard procedures.[8] The relative bioavailability (F') of ciprofloxacin was estimated as the ratio of the mean $AUC_{0\to\infty}$ values for the animals receiving both ciprofloxacin and TM to that of ciprofloxacin alone. Statistical significant differences in the derived pharmacokinetic parameter estimates between the groups were assessed by Student-t-test with the level of statistical significance (α) set at 0.05.

Results

Assessment of Cation Content in *T. mongolicum*—Concentrations of the 10 metal cations contained in the aqueous TM extract were determined to be 5760, 4941, 2311, 111.3, 62.4, 31.4, 16.1, 15.3, 6.0, and 1.5 μg/g for Mg, Ca, Fe, Mn, Zn, Sr, Cr, Cu, Ni, and Pb, respectively.

Pharmacokinetics of Ciprofloxacin in Rats—Data obtained from the control group revealed that ciprofloxacin, administered as a single oral dose (20 mg/kg), was rapidly absorbed with C_{max} (1.31 ± 0.49 μg/mL) achieved at 0.42 ± 0.17 h. Distribution of the drug was extensive with $V_{d,\lambda z}/F$ estimated to be 30.8 ± 11.1 L/kg and is approximately 50-fold of total body water. Though affected by F, this large distribution volume suggests a significant degree of tissue penetration and uptake. Oral clearance (CL/F) of the antibiotic was estimated to be 10.8 ± 2.7 L/h/kg and a mean ± SD $t_{1/2,\lambda z}$ of 1.96 ± 0.43 h was observed. Urinary recovery (X_u) of the antibiotic represented approximately 20% of the oral dose administered. All pertinent paramacokinetic parameter estimates are listed in Table 1.

Table 1—Mean (±SD) Pharmacokinetic Parameter Estimates[a] (n = 5) of Ciprofloxacin after a Single Oral Dosing (20 mg/kg) with or without Aqueous Preparation of *T. Mongolicum* (TM, 2 g crude drug/kg) Coadministration

PK parameter estimates	ciprofloxacin	ciprofloxacin + TM
C_{max} (mg L^{-1})	1.31 ± 0.49	0.35 ± 0.04***
T_{max} (h)	0.42 ± 0.17	0.50 ± 0
$t_{1/2,\lambda z}$ (h)	1.96 ± 0.43	5.71 ± 0.91***
λ_z (h^{-1})	0.37 ± 0.07	0.12 ± 0.02***
$AUC_{0\to\infty}$ (mg L^{-1} h)	1.97 ± 0.51	1.90 ± 0.55
$V_{d,\lambda z}/F$ (L kg^{-1})	30.8 ± 11.1	92.0 ± 20.8**
CL/F (L h^{-1} kg^{-1})	10.8 ± 2.7	11.1 ± 2.6
CL_r (L h^{-1} kg^{-1})	2.36 ± 0.45	1.93 ± 0.32
X_u (% dose)	22.9 ± 5.3	18.3 ± 4.4

[a] Significance levels: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.005$.

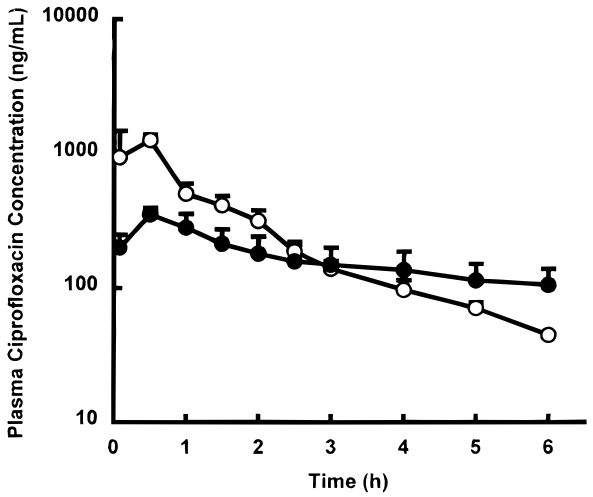

Figure 1—The plasma versus concentration time profiles of ciprofloaxcin. concentration (mean ± SD) measured for oral ciprofloxacin only (20 mg/kg) and oral ciprofloxacin (20 mg/kg) plus TM (2 g crude drug/kg) are depicted by ○ and ●, respectively.

Pharmacokinetics of Ciprofloxacin: Impact of *T. mongolicum* Coadministration—The mean plasma concentration−time profiles of ciprofloxacin for the control group and that with concomitant oral administration of TM are shown in Figure 1. The derived pharmacokinetic estimates for this study group are also available in Table 1. In comparison to the control group, significant alterations in certain pharmacokinetic estimates of ciprofloxacin were observed with concurrent TM administration. In particular, C_{max} of ciprofloxacin was lowered by 73% ($p < 0.005$) with T_{max} slightly prolonged by 16% ($p > 0.05$) (Table 1). Despite the reduction in C_{max}, the $AUC_{0\to\infty}$ estimate for ciprofloxacin remained similar (Figure 1). Although not statistically significant ($p = 0.2$), mean urinary ciprofloaxcin recovery in the TM group showed a 20% decrease. The mean $V_{d,\lambda z}/F$ estimate significantly increased (3-fold) with TM dosing (92.0 vs 30.8 L/kg, $p < 0.01$). In line with this, the average $t_{1/2,\lambda z}$ value was 3 times longer than that observed in the control group (5.71 vs 1.96 h, $p < 0.005$). However, the CL/F estimates were not significantly different between the two groups (Table 1). As a result, the relative bioavailability (F') of ciprofloxacin in the TM group as compared to control was estimated to be 0.96.

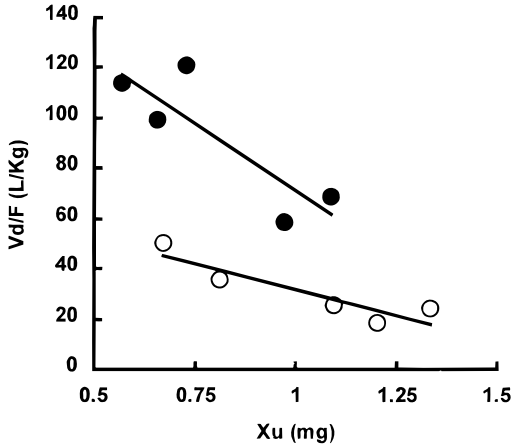

Figure 2—The relationship between apparent tissue distribution ($V_{d,\lambda z}/F$) and urinary drug recovery; equations describing the regression are $y = -40.9x + 72.6$, $p < 0.05$ for oral ciprofloxacin only (20 mg/kg) (○), and $y = -106.7x + 177.7$, $0.05 < p < 0.1$ for oral ciprofloxacin (20 mg/kg) plus TM (2 g crude drug/kg) (●).

Discussion

Ciprofloxacin is one of the newer fluoroquinolones that shows good oral absorption; however, the presence of cation-containing agents can impair oral absorption of this antibiotic.[1,9] In this study, coadministration of TM significantly decreased the C_{max} of ciprofloxacin by 73% with T_{max} essentially unaltered (Table 1). These observations suggest a reduction in oral ciprofloxacin absorption when TM was given concurrently. Independently, the TM extract was shown to contain a large amount of magnesium (5.8 mg/g,) calcium (4.9 mg/g), iron (2.3 mg/g), manganese (0.1 mg/g), zinc (0.06 mg/g), and copper (0.02 mg/g). Since the cation content of the TM extract, i.e., 5−6 mg of total cations received by the study rats, was high relative to the 4−5 mg of oral ciprofloaxcin, the lower ciprofloxacin absorption observed is not unexpected. It has been shown that chelation of quinolones generally requires ligands possessing positive charges and suitable molecular sizes.[1] Therefore, triterpenoids and inulin, the major components of TM reported,[4] should induce a minimal effect on the absorption of this antibiotic because they do not meet the structural requirements for chelation.

A 3-fold increase in the mean $V_{d,\lambda z}/F$ estimate for ciprofloxacin was observed in the rats concomitantly dosed with TM. Such alteration can be a result of an increase in tissue distribution ($V_{d,\lambda z}$) and/or a reduction in F. To further delineate the contribution of these two factors, plots of $V_{d,\lambda z}/F$ vs urinary recovery were constructed with individual data collected for the two animal groups (Figure 2). As anticipated for the control animals, $V_{d,\lambda z}/F$ decreased as the amount of ciprofloxacin excreted into the urine was larger. Interestingly, the regression line derived from the data of the TM group shifted higher and leftward with a steeper slope indicating that, in addition to the decrease in F, an increase in $V_{d,\lambda z}$ is also evident.

The magnitude of the change observed for $V_{d,\lambda z}$ appears to correspond to that of drug elimination (Table 1). The exact reason of this association is unclear but it may be a result of chelate formation in the systemic circulation when both ciprofloxacin and cations existed simultaneously following their independent absorption. Although not statistically significant ($p > 0.05$), the presence of TM caused a lowering of CL_r (Table 1). Interestingly, the pharmacokinetic perturbations observed for ciprofloaxcin in this study were also evident in a number of recent studies with another herb, *Sanquisorba officinalis*,[10] and also with ferrous sulfate when the antibiotic was given intravenously.[11] Although the data were not as vigorously scrutinized, prolongation of elimination half-life for a number of oral quinolones was also noticed in a human study as a result of iron supplementation.[2] All the pharmacokinetic perturbations observed for ciprofloxacin, i.e., lower C_{max}, wider tissue distribution, and slower elimination induced by TM, might be a direct result of an increase in molecular size and thus lipophilicity of metal-ciprofloxacin chelates. Therefore, the factor affecting drug absorption, in this case, may also play a role in the changes observed for drug distribution and elimination.

The relative bioavailability of ciprofloxacin, assessed using $AUC_{0\to\infty}$ estimates obtained for the concomitant TM dosing group relative to control, was 0.96. The similar $AUC_{0\to\infty}$ estimate observed in the TM group is a mixed result of lower drug absorption, wider distribution, and slower elimination. From a pharmacokinetic prospective, comparison of relative bioavailability of a drug under different testing conditions is based on the assumption of a stationary pharmacokinetic system. The secondary effects on drug distribution and elimination induced by TM may have complicated the use of $AUC_{0\to\infty}$ as an estimator for bioavailability. Because CL/F was derived from $AUC_{0\to\infty}$, this estimate should also be interpreted with caution.

The *Taraxacum* species, commonly known as dandelion, can be found in most parts of the globe. In addition to its claimed therapeutic activities, dandelion is also consumed as food and even as beverages in the form of a coffee substitute.[6] Regardless of its intended use, the high mineral content of this herb greatly increases the chance of drug−drug interactions with the conventional medicines that are sensitive to cations. Findings in the present study suggest that coadministration of TM may have clinical implications on the dosing of ciprofloxacin or other quinolone antibiotics.

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