ORIGINAL RESEARCH ARTICLE

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Influence of Sex on the Pharmacokinetic Interaction of Fleroxacin and Ciprofloxacin with Caffeine

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Abstract

Background: Previous pharmacokinetic studies have shown that a number of the quinolones inhibit the metabolism of caffeine.

Objective: To evaluate the effect of sex on the interaction between two quinolones and caffeine.

Design: Multiple-dose, double-blind, randomised, three-period crossover study.

Participants: Twelve male and twelve female healthy volunteers.

Methods: Subjects received by mouth either fleroxacin 400mg once daily and caffeine 100mg three times daily, ciprofloxacin 500mg twice daily and caffeine 100mg three times daily, or caffeine alone, for 3 days. Subjects received each of the other regimens after 12-day washout periods. Plasma and urine concentrations were determined by validated high-performance liquid chromatography procedures and the data were analysed by noncompartmental linear pharmacokinetic methods.

Results: Analysis of the interaction by sex revealed that females showed a significant difference in caffeine pharmacokinetics in the presence of ciprofloxacin (area under the concentration-time curve [AUC], peak plasma concentration [C_{max}], time to C_{max} [t_{max}] and apparent total body clearance [CL/F]) and fleroxacin (AUC and CL/F) when compared with males. Significant differences between sexes were also observed in the pharmacokinetics of ciprofloxacin (AUC, elimination rate constant [β] and CL/F) and fleroxacin (C_{max} and β) in the presence of caffeine. However, these significant differences disappeared when AUC and C_{max} were normalised to 70kg bodyweight and CL/F was expressed as per kg bodyweight.

Conclusion: The effect of quinolones on the pharmacokinetics of caffeine, and the reciprocal effect, are different between the sexes, due in part to different bodyweights.

Sex differences in the pharmacokinetic and pharmacodynamic profiles of numerous drugs have been reported in recent years.[1] The pharmacokinetic and pharmacodynamic parameters of drugs may be affected by sex-related factors such as body composition, hormone levels and enzyme activities.[1] Although some of the fluoroquinolones (fleroxacin and ofloxacin) have been reported to show significant differences between sexes,[2,3] other fluoroquinolones such as ciprofloxacin and gatifloxacin[4,5] did not display sex-related differences in pharmacokinetic characteristics.

In addition to accounting for sex differences, drug interactions should also be considered in prudent pharmacotherapy. Harder et al.[6] and Healy et al.[7] found that ciprofloxacin significantly decreased the total clearance of caffeine given as a single dose, although the administration of single doses of fleroxacin did not significantly affect caffeine elimination.[8] In addition, we have also reported similar findings regarding the interaction of both ciprofloxacin and fleroxacin with caffeine after multiple-dose administration.[9]

Despite a growing awareness of sex-related differences in the pharmacokinetic and pharmacodynamic profiles of certain fluoroquinolones, the effect of sex on the interaction between fluoroquinolones and caffeine has yet to be fully investigated. The purpose of this report was to evaluate the effect of sex on the interaction between two fluoroquinolones (fleroxacin and ciprofloxacin) and caffeine in a multiple-dose, double-blind, randomised, three-period crossover design.

Material and Methods

Subjects

This randomised, multiple-dose, double-blind, three-period crossover trial was approved by the Hartford Hospital institutional review board. All volunteers gave their informed consent. The study was carried out in accordance with good clinical practices as specified in the Code of Federal Regulations (CFR) and in accordance with ethical principles set forth in the Declaration of Helsinki.

Volunteers were enrolled in the study if they were healthy men or nonpregnant women, 18–55 years old and weighed within 30% of their ideal bodyweights (according to the Metropolitan Life Insurance Table). Women had to have a negative serum β-human chorionic gonadotrophin (β-HCG) pregnancy test within 30 days before study enrolment and a negative urine pregnancy test within 12 hours before the start of each regimen. Each woman used an acceptable method of birth control during the study period.

Volunteers were not enrolled in the study if they had a hypersensitivity to quinolones or caffeine, clinically significant renal disease (i.e. a measured or estimated creatinine clearance <40 mL/min, as calculated by the method of Cockroft and Gault), hepatic disease (ALT or AST greater than twice the upper limit of normal, or total bilirubin >2 mg/100mL), cardiovascular, respiratory, neurological, gastrointestinal, endocrine or haematological disease, a documented history of recurrent seizures or seizure disorder, a gastrointestinal disorder that might affect absorption, a haemoglobin concentration or haematocrit value below the normal laboratory range, had abused drugs or alcohol within a year of the study, had consumed alcohol within 72 hours of initiating the study or anticipated the need for alcohol during the course of the study, had participated in a clinical trial in the 4 weeks preceding the start of the study, received any antibacterial agents and/or prescription medications (other than oral contraceptives) within 4 weeks of the study, or had taken over-the-counter medications within 3 days of the start of the study, or anticipated the need for such medications during the course of the study, had donated or received blood or plasma within 4 weeks before the start of the study, or had other conditions that might increase the risk to the volunteer.

Potential healthy volunteers were screened by a physical examination, a medical history, blood chemistries, haematology and urinalysis to examine eligibility of subjects. All subjects were admitted and housed overnight at the Hartford Hospital clinical research centre for the study periods. Volunteers

were instructed to abstain from caffeine or caffeine-containing products for 72 hours before each dose regimen, and a xanthine-free diet was maintained throughout each of the study periods. Use of all nonprescription medications containing caffeine or that were known to interact with quinolones (i.e. cation-containing substances) was also prohibited. Volunteers were also instructed to refrain from vigorous activity during the study periods.

Study Medication and Administration

Eligible subjects (12 men and 12 nonpregnant women) were randomised to receive each of the following oral regimens in a random crossover fashion for 3 days to achieve steady state. The regimens were separated from one another by a washout period of 12 days.

Regimen A: caffeine (NoDoz®[1], lot no. 210165; Bristol-Myers Squibb Co., Princeton, NJ, USA) 100mg orally three times daily and fleroxacin (Ro 23-6240; batch no. 812022; Hoffmann-La Roche, Nutley, NJ, USA) 400mg orally once daily.

Regimen B: caffeine 100mg three times daily and ciprofloxacin (Cipro®, lot no. 2HEL; Bayer Co., West Haven, CT, USA) 500mg orally twice daily.

Regimen C: caffeine 100mg three times daily

In addition, one fleroxacin placebo tablet (C162640-011; Hoffmann-La Roche, Nutley, NJ, USA) was added to regimen A in the evening and to regimen C in the morning and evening to make regimens A and C identical in appearance. Volunteers fasted for 12 hours before the administration of the first and last morning dose of caffeine

Safety Assessment

Subjects were monitored throughout the study for adverse events. After each study regimen period, post-trial physical examination and laboratory evaluations were implemented to confirm the presence or absence of biochemical or haematological adverse events resulting from the study drug.

Blood Sample Collection

All blood samples were obtained by venipuncture. Blood samples of 10mL were collected into oxalated Vacutainer® tubes (B.D. no. 6524) before study drug administration on day 1, and 5mL samples were collected at 0 hour (before the last morning dose), then 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, and 48 hours after the administration of the last morning dose. After collection, blood samples were immediately centrifuged for 10 minutes at 2500 rpm at 10°C and were frozen at –70°C until analysis. Urine samples (30mL) were also obtained on day 1 (before the first dose) and on day 3 (0–24-hour urine collection after the administration of the last dose). Specimens were stored at –70°C within 30 minutes after the end of each collection period.

Drug Assay

Plasma and urine concentrations of caffeine were determined by reverse-phase high-performance liquid chromatography (HPLC) with UV detection following sample extraction. Caffeine was extracted from samples from volunteers and from plasma and urine containing known amounts of caffeine (22H-5951; Sigma Chemical Co., St. Louis, MO, USA) into 3.5mL of methanol and 2-propanol (4 : 1 by vol.). The extracts were evaporated, then reconstituted with mobile phase before injection onto a C_{18} column (Novapak C_{18}, 4 μm; Waters Associates, Milford, MA, USA) and elutions were monitored at 273nm. The mobile phase consisted of 0.1 mol/L phosphate buffer (pH 4.5), methanol and acetonitrile (86 : 11 : 5, by vol.). The intra- and inter-day coefficients of variation for the assay were <10% over the range of the standard curve (0.05–4 mg/L).

Plasma and urine concentrations of fleroxacin and ciprofloxacin were assayed by reverse-phase HPLC with fluorescent detection. Fleroxacin and ciprofloxacin were extracted from samples from volunteers and from plasma and urine containing known amounts of the reference compounds (flerox-

1 Use of tradenames is for product identification only and does not imply endorsement.

acin [Ro 23-6240] from Hoffmann-La Roche, Nutley, NJ, USA; ciprofloxacin [3ABW] from Miles Laboratories, West Haven, CT) into 3.5mL of chloroform or methylene chloride, respectively, after plasma protein denaturation by addition of 25% sodium sulfate, or addition of phosphate buffer (pH 7.5) to urine samples. The aqueous portion of back extractions of fleroxacin or ciprofloxacin in sodium hydroxide (plasma samples) or phosphate buffer with a pH of 12.5 (urine samples) were injected into a C_{18} column (Neucleosil, 10 μm; Alltech Associates Inc., Deerfield, IL, USA). For fleroxacin, a mobile phase consisting of phosphate buffer (pH 2.5), acetonitrile and methanol (81 : 13 : 6, by vol.) was used, and eluates were monitored at 274nm. For ciprofloxacin, a mobile phase of phosphate buffer (pH 2.5) and acetonitrile (85 : 15, by vol.) was used, and eluates were monitored at 278nm. The intra- and inter-day coefficients of variation for the assay were <10% over the range of the standard curve (0.05–5 mg/L for fleroxacin, 0.04–4 mg/L for ciprofloxacin).

Pharmacokinetic Analysis

Pharmacokinetic parameters were derived individually for each subject and each drug component from their respective plasma concentration-time data and urinary excretion data. The parameters include area under the curve (AUC), maximum plasma concentration (C_{max}), time to reach C_{max} (t_{max}), apparent total body clearance (CL/F, both in units of mL/min and mL/min/kg), renal clearance (CL_R), elimination rate constant (β) and fraction excreted unchanged in the urine during 24 hours (fe_{24}), as well as AUC normalised to 70kg bodyweight (AUC^{NL70}) and C_{max} normalised to 70kg bodyweight (C_{max}^{NL70}).

Table I. Study population

Demographics	Female	Male
Age (y)	32.6 ± 9.71	24.1 ± 3.92[a]
Height (cm)	166 ± 5.29	181 ± 7.57[a]
Weight (kg)	64.9 ± 6.80	81.3 ± 13.6[a]
Serum creatinine (mg/dL)	0.953 ± 0.128	1.21 ± 0.103[a]
Caucasian race	10 (83%)	10 (83%)
Other race	2 (17%)	2 (17%)

a Statistically significantly different ($p < 0.05$) versus females.

Table II. Number of volunteers with adverse events by regimen

Adverse event	Number of adverse events (female/male)		
	Regimen A[a]	Regimen B[b]	Regimen C[c]
Gastrointestinal system			
Diarrhoea	0/0	0/0	1/0
Dyspepsia	0/0	1/0	0/0
Nausea	2/0	1/1	1/0
Retching	1/0	0/0	0/0
Stomach discomfort	0/1	0/0	1/1
Stomach pain	1/0	0/0	0/0
Vomiting	0/0	0/0	1/0
Total	4/1	2/1	4/1
Central/peripheral nervous system			
Dizziness	0/0	0/2	1/0
Flushing	1/0	0/0	0/0
Headache	0/0	1/1	1/1
Insomnia	3/3	1/1	1/1
Nervousness	0/1	0/1	0/1
Tremor	0/0	0/1	0/0
Total	4/4	2/6	3/3
Body as a whole			
Asthenia	0/0	0/0	0/1
Total	0/0	0/0	0/1
Grand total of events reported	8/5	4/7	7/5

a Caffeine 100mg three times daily and fleroxacin 400mg once daily.

b Caffeine 100mg three times daily and ciprofloxacin 500mg twice daily.

c Caffeine 100mg three times daily.

Individual AUC values were determined by the linear trapezoidal rule. C_{max} and t_{max} values were directly obtained from the observed plasma data. β was estimated by linear least-squares regression analysis of the terminal phase of the log-linear plot of concentration-time data. CL/F was calculated as dose (D)/AUC. fe_{24} (%) was calculated as total amount of drug excreted unchanged in the urine in 24 hours $(Ae_{24}) \times 100/(D \times F)$ when $F = 1$. CL_R was calculated as Ae_{24}/AUC_{24}. In addition, AUC^{NL70} was calculated as AUC × bodyweight (BW)/70. Similarly, C_{max}^{NL70} was calculated as $C_{max} \times BW/70$.

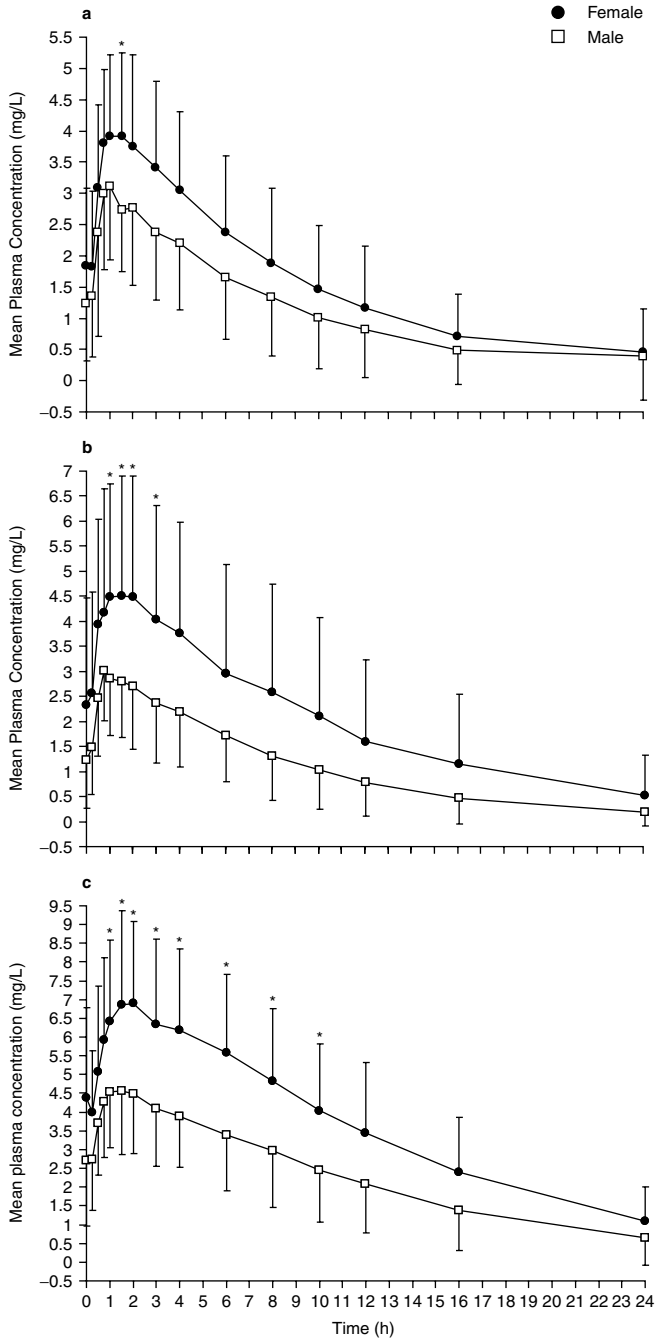

Fig. 1. Mean (± SD) plasma concentrations of caffeine around the administration of the last dose of caffeine. Plasma concentrations of caffeine was determined after 12 male and 12 female healthy volunteers were administered multiple-dose regimens of (**a**) regimen C (caffeine 100mg three times daily), (**b**) regimen A (caffeine 100mg three times daily and fleroxacin 400mg once daily) and (**c**) regimen B (caffeine 100mg three times daily and ciprofloxacin 500mg twice daily). * indicates a statistically significantly different ($p < 0.05$) plasma concentration between females and males.

Pharmacodynamic Analysis

To evaluate the haemodynamic effects of caffeine in the absence or presence of study drugs, haemodynamic parameters including sitting systolic and diastolic blood pressure and pulse rate were measured at the following times: just before administration of the morning dose on day 1 (baseline), 90 minutes after the morning dose on day 1, immediately before and 60–90 minutes after the evening dose on day 2, immediately before and 90 minutes after the morning dose on day 3, and 24 hours (day 4) and 48 hours (day 5) after the last dose of test medication during each study period. For each parameter at each timepoint, changes from baseline were calculated, and the results compared between sexes to assess any sex difference on the pharmacological properties of caffeine in the presence or absence of fleroxacin or ciprofloxacin.

Statistical Analysis

The results were expressed as the mean ± SD. The analysis of variance (ANOVA) for a three-period crossover design was used to compare the pharmacokinetic parameters of all three regimens. A two-tailed independent t-test was used to compare the estimated pharmacokinetic parameters for each drug between sexes when the data fitted the normal distribution. Otherwise, the Wilcoxon rank sum test was performed for skewed data. Similarly, the t-test was used to compare the changes of vital signs between two sexes in each study regimen.

Results

Subjects and Safety Assessments

Twelve males and twelve females completed all three study regimens and were evaluated. Demographic data for the study population are listed in table I.

The incidence of adverse events from each regimen was compared between sexes and is listed in table II. Females tended to have a higher incidence of gastrointestinal adverse events with regimens A and C. In contrast, males appeared to have higher incidence of central nervous system adverse events with regimen B.

Pharmacokinetic Analysis

Figure 1 shows the mean plasma concentration-versus-time profiles of caffeine around the administration of the last dose of caffeine after multiple doses of regimen A, B, and C. When caffeine was administered alone in regimen C, as shown in figure 1(a), the caffeine concentrations observed in females did not significantly differ from those of males at most timepoints, with the exception of the time at 1.5 hours. However, this difference between sexes was further amplified when caffeine was administered with fleroxacin or ciprofloxacin. As shown in figure 1(b), caffeine concentrations of females were significantly higher than those of males at 1, 1.5, 2 and 3 hours when caffeine was administered with fleroxacin in regimen A. Furthermore, when caffeine was administered with ciprofloxacin in regimen B, as shown in figure 1(C), caffeine concentrations of females were significantly higher than those of males at 1, 1.5, 2, 3, 4, 6, 8 and 10 hours.

Figure 2 demonstrates the mean plasma concentrations of fleroxacin or ciprofloxacin in the presence of caffeine around the administration of the last dose of caffeine after multiple doses of regimen A and B. As shown in figure 2(a), fleroxacin concentrations of females were significantly higher than those of males at 2, 3, 4, 6, 8 and 10 hours. Furthermore, ciprofloxacin concentrations of females were also significantly higher than those of males at 1.5, 2, 3, 4, 6, 8, 10 and 12 hours, as shown in figure 2(b).

The pharmacokinetic parameters (mean ± SD) of caffeine with or without fleroxacin or ciprofloxacin in both males (n = 12) and females (n = 12) are listed in table III. Analysis of the interaction by sex revealed that ciprofloxacin significantly ($p \leq 0.05$) affected AUC, C_{max}, CL/F, fe_{24} and β of caffeine in both males and females, whereas fleroxacin did not significantly alter the pharmacokinetics of caffeine for either sex. Comparison of caffeine pharmacokinetics in males versus females for each regimen showed no differences for caffeine alone. In con-

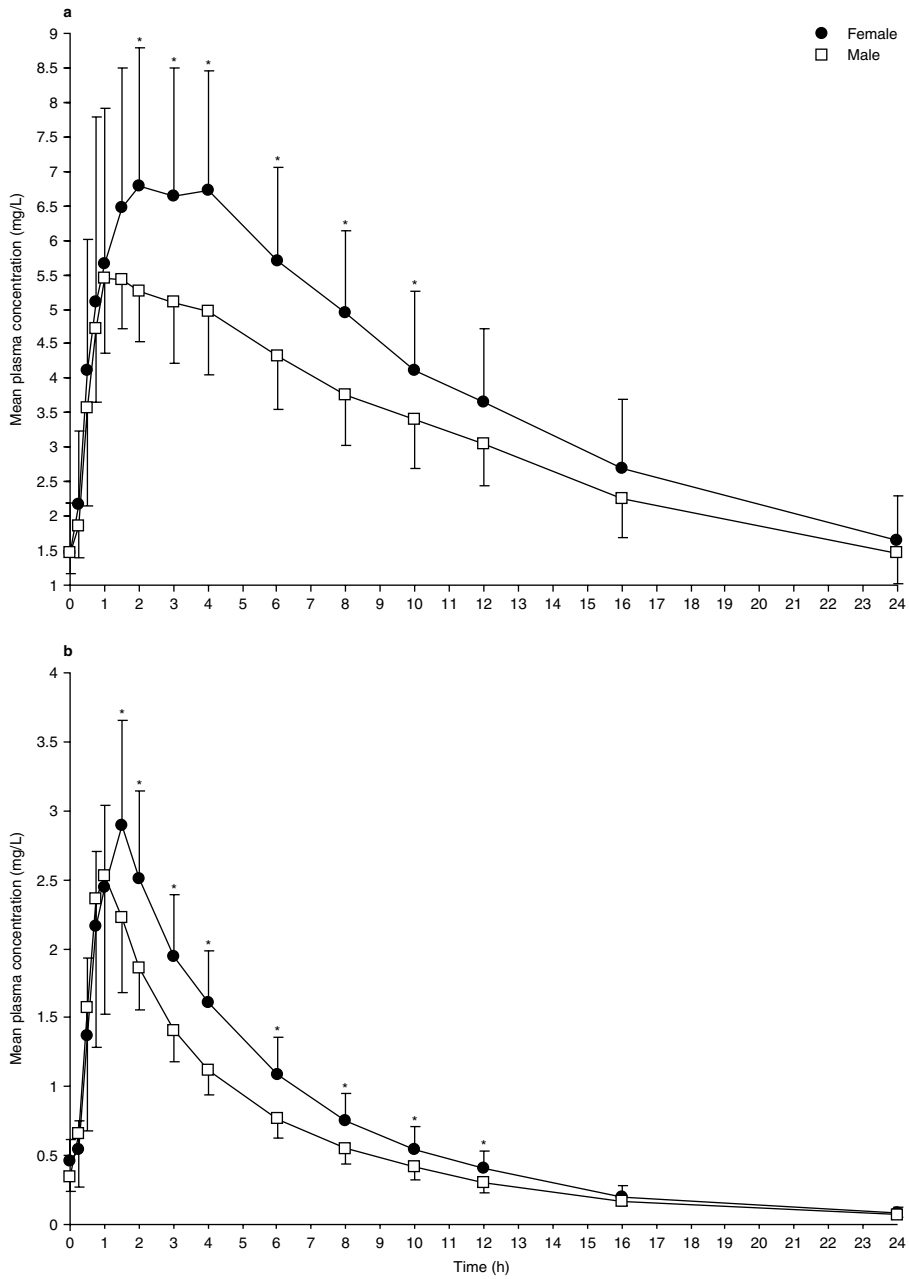

Fig. 2. Mean (± SD) plasma concentrations of (**a**) fleroxacin or (**b**) ciprofloxacin around the administration of the last dose of caffeine. Plasma concentrations of fleroxacin or ciprofloxacin was determined after 12 male and 12 female healthy volunteers were administered multiple-dose regimens of (**a**) caffeine 100mg three times daily with fleroxacin 400mg once daily and (**b**) caffeine 100mg three times daily with ciprofloxacin 500mg twice daily. * indicates a statistically significantly different ($p < 0.05$) plasma concentration between females and males.

Table III. Pharmacokinetic parameters (mean ± SD) of fleroxacin 400mg or ciprofloxacin 500mg in the presence of caffeine in 12 males and 12 females

Parameter and unit	Fleroxacin + caffeine		Ciprofloxacin + caffeine	
	female	male	female	male
AUC_{12} (mg • h/L)	ND	ND	14.9 ± 3.45	11.5 ± 1.84[a]
AUC_{12}^{NL70} (mg • h/L)	ND	ND	13.7 ± 2.98	13.1 ± 1.46
AUC_{24} (mg • h/L)	93.3 ± 27.6	75.5 ± 13.9	17.2 ± 4.26	13.4 ± 2.08[a]
AUC_{24}^{NL70} (mg • h/L)	85.1 ± 20.7	86.1 ± 11.4	15.8 ± 3.61	15.3 ± 1.75
C_{max} (mg/L)	7.48 ± 2.00	6.07 ± 0.653[a]	2.95 ± 0.770	2.78 ± 0.843
C_{max}^{NL70} (mg/L)	6.84 ± 1.57	6.98 ± 0.934	2.71 ± 0.674	3.13 ± 0.737
t_{max} (h)	2.83 ± 1.54	1.83 ± 1.13	1.35 ± 0.271	1.19 ± 0.454
CL/F (mL/min)	77.1 ± 21.6	90.9 ± 15.9	597 ± 180	744 ± 122[a]
CL/F (mL/min/kg)	1.18 ± 0.281	1.13 ± 0.167	9.20 ± 2.65	9.20 ± 1.10
CL_R (mL/min/kg)	0.706 ± 0.234	0.756 ± 0.220	5.31 ± 1.12	4.80 ± 1.19
β (h^{-1})	0.0708 ± 0.010	0.060 ± 0.00850[a]	0.148 ± 0.0159	0.131 ± 0.0138[a]
fe_{24} (%)	59.6 ± 12.8	66.3 ± 12.4	68.4 ± 13.2	60.7 ± 13.6

a Statistically significant different ($p < 0.05$) versus females.

AUC_{12} = area under the concentration-time curve from zero to 8 hours; **AUC_{12}^{NL70}** = AUC_8 normalised to 70kg bodyweight; β = elimination rate constant; **C_{max}** = peak plasma concentration; **C_{max}^{NL70}** = C_{max} normalised to 70kg bodyweight; **CL/F** = apparent total body clearance; **CL_R** = renal clearance; **fe_{24}** = fraction excreted unchanged during 24 hours; **ND** = not determined; **t_{max}** = time to reach C_{max}.

trast, females showed a significant difference ($p \leq 0.05$) in caffeine pharmacokinetics in the presence of fleroxacin (AUC, CL/F [mL/min]) and ciprofloxacin (AUC, C_{max}, t_{max} and CL/F [mL/min]) when compared with males. However, statistically significant differences disappeared when parameters were corrected for bodyweight (AUC^{NL70}, C_{max}^{NL70}, CL/F [mL/min/kg]).

The pharmacokinetic parameters (mean ± SD) of fleroxacin and ciprofloxacin in both females and males are listed in table IV. Significant differences ($p \leq 0.05$) between sexes were also observed in the pharmacokinetics of fleroxacin (C_{max}, β) and ciprofloxacin (AUC, β, CL/F [mL/min]) in the presence of caffeine. Similarly, significant differences disappeared when parameters were corrected for bodyweight (AUC^{NL70}, C_{max}^{NL70}, CL/F [mL/min/kg]).

Pharmacodynamic Analysis

Following administration of regimens A, B, and C in both males and females, changes from baseline haemodynamic parameters are listed in table V. In general, no clear plasma concentration-drug effect relationship was observed with the administration of each regimen. Within each regimen, changes from baseline in sitting blood pressure and pulse rate were not statistically significant. Similarly, changes in sitting blood pressure and pulse rate between regimens were not statistically significant. In addition, there was no significant difference in the changes from baseline between sexes ($p > 0.05$), except that the elevation of pulse from baseline in males was significantly higher than in females at 1 day pre- and post-dose of regimen A, and 1 day post-dose of regimen B. These results suggest that the effect of elevated caffeine concentrations in females was of insufficient magnitude to induce haemodynamic changes.

Discussion

Fleroxacin (Ro 23-6240) is a fluoroquinolone that acts by inhibition of an essential bacterial enzyme, DNA gyrase.[10] It exhibits potent *in vitro* activity against Gram-positive and Gram-negative bacteria.[10-12] The pharmacokinetics of fleroxacin are characterised by an excellent absolute bioavailability (>95%), high concentrations in plasma and body fluids, good tissue penetration, long elimination half-life (10–12 hours), low protein binding (23%), high renal excretion (50–60%), and low metabolism (10–15% in urine).[13] The pharmacokinetic

Table IV. Pharmacokinetic parameters (mean ± SD) of caffeine 100mg with or without fleroxacin or ciprofloxacin in 12 males and 12 females

Parameter and unit	Female			Male		
	alone	+ fleroxacin	+ ciprofloxacin	alone	+ fleroxacin	+ ciprofloxacin
AUC_8 (mg • h/L)	23.2 ± 10.4	28.4 ± 18.5	47.0 ± 18.0[a]	16.7 ± 8.77	16.8 ± 8.56[b]	30.0 ± 12.3[ab]
AUC_8^{NL70} (mg • h/L)	21.3 ± 9.03	25.5 ± 14.3	42.9 ± 14.4[a]	18.7 ± 7.88	18.7 ± 7.56	33.7 ± 10.7[a]
C_{max} (mg/L)	4.17 ± 1.39	4.81 ± 2.50	7.09 ± 2.55[a]	3.36 ± 1.36	3.33 ± 1.15	4.87 ± 1.67[ab]
C_{max}^{NL70} (mg/L)	3.84 ± 1.25	4.34 ± 1.91	6.47 ± 2.00[a]	3.78 ± 1.17	3.76 ± 0.995	5.48 ± 1.40[a]
t_{max} (h)	1.23 ± 0.458	1.38 ± 0.758	1.88 ± 0.483[a]	1.00 ± 0.413	0.917 ± 0.444	1.29 ± 0.531[b]
CL/F (mL/min)	87.3 ± 43.0	79.8 ± 41.8	41.2 ± 18.2[a]	118 ± 40.7	116 ± 39.1[b]	62.7 ± 20.0[ab]
CL/F (mL/min/kg)	1.35 ± 0.666	1.22 ± 0.635	0.633 ± 0.273[a]	1.45 ± 0.507	1.43 ± 0.455	0.769 ± 0.228[a]
CL_R (µL/min/kg)	14.8 ± 3.20	15.0 ± 5.13	15.8 ± 8.90	16.5 ± 11.4	16.9 ± 6.93	13.6 ± 3.90
β (h^{-1})	0.151 ± 0.0504	0.143 ± 0.0486	0.104 ± 0.0368[a]	0.158 ± 0.0518	0.158 ± 0.0481	0.100 ± 0.0422[a]
fe_{24} (%)	2.07 ± 1.31	2.39 ± 1.27	4.52 ± 1.45[a]	2.09 ± 2.10	2.21 ± 1.81	3.73 ± 2.54[a]

a Statistically significantly different ($p < 0.05$) versus caffeine alone.

b Statistically significantly different ($p < 0.05$) versus females.

AUC_8 = area under the concentration-time curve from zero to 8 hours; **AUC_8^{NL70}** = AUC_8 normalised to 70kg bodyweight; β = elimination rate constant; **C_{max}** = peak plasma concentration; **C_{max}^{NL70}** = C_{max} normalised to 70kg bodyweight; **CL/F** = apparent total body clearance; **CL_R** = renal clearance; **fe_{24}** = fraction excreted unchanged during 24 hours; **t_{max}** = time to reach C_{max}.

profile of fleroxacin in conjunction with its minimum inhibitory concentrations for susceptible pathogens supports the proposed once-a-day administration of the drug for therapy. However, fleroxacin development has been discontinued worldwide because of phototoxicity; the structural configuration (fluorine atom on position 8) that ablates the metabolic interaction is responsible for this effect.

The results of the present study showed that fleroxacin 400mg administered once daily for 3 days does not significantly affect the clearance or any other pharmacokinetic parameters of caffeine 100mg given three times daily for 3 days in either sex. This lack of significant effect on the elimination of caffeine was previously reported after the administration of both single and multiple dose regimens of fleroxacin and caffeine.[8,9]

In contrast, ciprofloxacin significantly affects the pharmacokinetics of caffeine in both males and females. Ciprofloxacin administered at a dosage of 500mg twice daily for 3 days resulted in a marked decrease (47% in females and 53% in males) in caffeine clearance, as reflected by significant increases in AUC and C_{max} and prolongation of t_{max} and half-life. This interaction has been attributed to alterations in metabolism via competitive inhibition of the cytochrome P450 enzyme system.[6] The absence of a significant decrease in CL_R of caffeine in this study confirms that the effect of ciprofloxacin on caffeine disposition is the result of interference with one or more of the metabolic pathways of caffeine.

The interaction between ciprofloxacin and caffeine was previously described by Harder et al.[6] and Healy et al.[7] In the study conducted by Harder et al,[6] the authors reported a 33% decrease in the total clearance of single doses of caffeine when ciprofloxacin was coadministered at a dosage of 250mg every 12 hours. In the study by Healy et al,[7] of similar design, ciprofloxacin administered at a dosage of 750mg every 12 hours resulted in a 38% decrease in total caffeine clearance. Our previous report revealed a more pronounced effect of ciprofloxacin on the clearance of caffeine.[9] This could have been attributed to a cumulative effect of five

Table V. Pharmacodynamic parameters (mean ± SD) of caffeine with or without a quinolone in 12 males and 12 females

Day	Time	Female			Male		
		pulse (beats/min)	SBP (mmHg)	DBP (mmHg)	pulse (beats/min)	SBP (mmHg)	DBP (mmHg)
Regimen A (caffeine 100mg three times daily and fleroxacin 400mg once daily)							
0	Baseline[a]	70.1 ± 12.2	106 ± 12.3	68.3 ± 8.06	66.5 ± 7.00	116 ± 8.06	73.4 ± 8.52
	Postdose[b]	2.83 ± 10.4	3.58 ± 5.47	0.92 ± 3.66	0.17 ± 5.21	3.92 ± 4.37	−2.00 ± 5.94
1	Predose[b]	0.33 ± 12.1	3.42 ± 10.4	−1.67 ± 7.41	14.9 ± 10.1[c]	8.58 ± 9.35	−1.50 ± 9.41
	Postdose[b]	2.58 ± 9.30	2.67 ± 6.26	−0.92 ± 7.43	11.4 ± 7.47[c]	4.17 ± 6.85	−3.67 ± 6.02
2	Predose[b]	−0.08 ± 10.52	0.92 ± 6.06	−0.67 ± 8.34	1.67 ± 9.17	1.17 ± 10.9	−1.08 ± 9.30
	Postdose[b]	3.25 ± 15.0	−2.42 ± 13.8	2.58 ± 9.60	3.50 ± 9.18	−2.08 ± 11.4	−3.67 ± 9.37
3	24h postdose[b]	1.58 ± 12.2	−3.42 ± 9.48	−3.83 ± 9.60	4.42 ± 8.05	−0.08 ± 9.04	−4.25 ± 6.94
4	48h postdose[b]	6.17 ± 11.9	−1.50 ± 7.54	−6.67 ± 7.72	7.33 ± 12.7	2.58 ± 11.9	−3.83 ± 8.35
Regimen B (caffeine 100mg three times daily and ciprofloxacin 500mg twice daily)							
0	Baseline[a]	68.8 ± 8.87	106 ± 9.90	65.9 ± 8.26	66.3 ± 6.13	119 ± 7.60	68.5 ± 9.18
	Postdose[b]	1.67 ± 12.5	2.33 ± 7.74	4.17 ± 5.54	−1.08 ± 8.36	1.50 ± 4.11	6.08 ± 6.05
1	Predose[b]	4.25 ± 9.54	1.33 ± 8.46	2.25 ± 7.58	6.58 ± 9.37	3.42 ± 10.7	1.83 ± 11.0
	Postdose[b]	1.83 ± 7.51	1.33 ± 10.1	2.25 ± 6.44	11.1 ± 7.50[c]	1.42 ± 8.86	3.17 ± 8.23
2	Predose[b]	2.42 ± 11.2	6.33 ± 10.5	5.25 ± 7.66	−0.92 ± 10.9	2.67 ± 8.11	6.25 ± 9.44
	Postdose[b]	−3.08 ± 8.73	4.50 ± 10.2	3.67 ± 7.49	1.08 ± 8.06	3.00 ± 11.6	7.17 ± 10.6
3	24h postdose[b]	4.42 ± 8.50	−2.25 ± 9.19	0.33 ± 12.1	−0.17 ± 15.4	−2.42 ± 8.13	2.67 ± 10.6
4	48h postdose[b]	3.08 ± 13.0	−1.33 ± 8.13	−1.92 ± 7.60	−0.42 ± 10.3	−3.33 ± 6.38	0.00 ± 7.54
Regimen C (caffeine 100mg three times daily)							
0	Baseline[a]	71.8 ± 7.10	108 ± 11.7	67.8 ± 9.33	69.3 ± 8.30	119 ± 5.95	71.2 ± 7.00
	Postdose[b]	−1.25 ± 9.27	2.00 ± 8.25	2.25 ± 7.51	−5.00 ± 7.59	−0.75 ± 7.56	0.67 ± 5.45
1	Predose[b]	−0.92 ± 5.54	0.33 ± 9.36	−2.42 ± 7.29	−0.08 ± 10.8	1.42 ± 10.9	1.25 ± 7.69
	Postdose[b]	0.00 ± 7.51	1.42 ± 10.3	−1.17 ± 9.42	3.50 ± 6.64	−0.17 ± 5.73	−1.42 ± 7.45
2	Predose[b]	−2.58 ± 8.38	−4.67 ± 12.0	−1.08 ± 11.9	−1.83 ± 11.1	−3.17 ± 9.81	2.33 ± 7.1
	Postdose[b]	−6.75 ±9.05	−6.42 ± 10.5	−2.83 ± 6.95	−7.33 ± 9.41	0.42 ± 10.7	2.50 ± 8.19
3	24h postdose[b]	0.50 ± 9.03	−7.50 ± 9.23	−4.58 ± 8.68	−1.08 ± 10.6	−3.00 ± 10.5	0.58 ± 10.8
4	48h postdose[b]	−0.08 ± 7.99	−3.75 ± 11.7	−3.25 ± 9.18	−0.17 ± 11.7	−4.00 ± 10.2	−4.58 ± 8.26

a Baseline value.

b Change from baseline.

c Statistically significantly different ($p < 0.05$) versus females.

DBP = diastolic blood pressure; **SBP** = systolic blood pressure.

doses of ciprofloxacin compared with three doses given in previous trials.

The pharmacokinetics of caffeine alone were not different when analysed by sex. In contrast, females had significantly greater caffeine AUC in the presence of both ciprofloxacin and fleroxacin when compared with males. However, this difference disappeared when the AUC was corrected for bodyweight. Thus, the increased AUCs in females may be due to their significantly lower bodyweights compared with those of males.

Examining the reciprocal interaction, our pharmacokinetic parameters of fleroxacin and ciprofloxacin were not noticeably different from previously reported pharmacokinetic parameters of fleroxacin and ciprofloxacin in the absence of caffeine.[13,14]

As listed in table IV, significant differences ($p \leq 0.05$) between sexes in the pharmacokinetics (C_{max}, β) of fleroxacin in the presence of caffeine were observed. This is consistent with the results of a previous study,[2] which demonstrated sex differences in the pharmacokinetics of fleroxacin in the absence of caffeine. Of note, an earlier study demonstrated a lack of sex effect on ciprofloxacin pharmacokinetics in the absence of caffeine.[4] In contrast, in our study, the AUC and β of ciprofloxacin in the presence of caffeine were significantly elevated in females compared with males. However, as seen with the case of caffeine pharmacokinetic parameters, the statistically significant differences in the C_{max} of fleroxacin and the AUC of ciprofloxacin disappeared when they were normalised by bodyweights. Again, the lower bodyweights of females may account for the increased C_{max} of fleroxacin and AUC of ciprofloxacin.

From a pharmacodynamic perspective, detection of meaningful changes in the haemodynamic effects of caffeine in the presence or absence of a quinolone antibiotic was not achieved. Although the elevation of pulse from baseline in males was significantly higher than in females at 1 day pre- and post-dose of regimen A, and 1 day post-dose of regimen B, this finding was a temporary phenomenon with minimal clinical significance, considering overall trends. The lack of significant difference in pharmacodynamics between the sexes may have been reflected by the fact that no significant difference in the normalised AUC of caffeine between the two groups was observed.

Conclusion

This study demonstrated that females showed a significant difference in caffeine pharmacokinetics in the presence of ciprofloxacin (AUC, C_{max}, t_{max}, CL/F [mL/min]) and fleroxacin (AUC, CL/F [mL/min]) when compared with males. Significant differences between sexes were also observed in the pharmacokinetics of ciprofloxacin (AUC, β, CL/F [mL/min]) and fleroxacin (C_{max}, β) in the presence of caffeine. However, these significant differences disappeared when parameters were corrected for bodyweight (AUC^{NL70}, $C_{max}{}^{NL70}$, CL/F [mL/min/kg]). Therefore, this study suggested that the quinolone effect on the pharmacokinetics of caffeine and the reciprocal effect are different between sexes, due in part to the different bodyweights of the sexes.

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