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Original

Pharmacokinetic/pharmacodynamic serum and urine profile of cefditoren following single-dose and multiple twice- and thrice-daily regimens in healthy volunteers: A phase I study

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SUMMARY

The objectives of this randomized, double-blind study were to evaluate the pharmacokinetics, and the pharmacodynamic and gastrointestinal (GI) tolerance of cefditoren pivoxil in healthy adult male volunteers when it is administered three times a day. Twenty healthy volunteers were included in the study. On day 1, 10 subjects received a 200-mg single dose of cefditoren pivoxil and 10 received a 400-mg dose. After a washout period of 8 days, eight subjects received cefditoren pivoxil 400 mg b.i.d., eight received 400 mg t.i.d., and four received placebo for 10 days. Medication was taken 30 min after meals. Blood and urine collections were carried out on days 1, 9, 14 and 19. Volunteers were asked about any GI change, especially about bowel habits, nausea, vomiting and abdominal pain. The maximum cefditoren concentration (C_{max}) had a mean value of 3.77 ± 0.66 mg/l, and was reached between 1.5 and 3 h in the thrice-daily administration. In the twice-daily regimen, the C_{max} was 3.27 ± 0.64 mg/l. The mean time above breakpoint minumum inhibitory concentration (MIC), calculated with data from each pharmacokinetic profile, was always above 40%, in both the twice- and thrice-daily regimens. The half-life of cefditoren was 1.19 ± 0.2 h and 1.36 ± 0.2 h in the twice-daily and thrice-daily regimens, respectively. The C_{max} of cefditoren in urine was reached between 2 and 4 h postadministration, with a mean value of 154.53 mg/l in the twice-daily regimen, and 186.59 mg/l in the thrice-daily administration. There were no differences between the groups in the incidence of GI adverse events. The present data show that the administration of cefditoren pivoxil 400 mg t.i.d. is possible because it is well tolerated, and it increases the probability of success when the MIC of the causative bacteria is close to the susceptibility breakpoint. The high concentrations of active drug in the urine enable cefditoren to be considered as a useful candidate for the treatment of uncomplicated urinary tract infections (UTIs).

Key words: Cefditoren pivoxil - Pharmacokinetics - PK/PD - Tolerance - Multiple doses

Perfil farmacocinético-farmacodinámico del cefditoreno en suero y orina tras una dosis única y en pautas de dos o tres veces al día en voluntarios sanos: Estudio de fase I

RESUMEN

El objetivo del estudio fue valorar la farmacocinética, la farmacodinámica y la tolerabilidad digestiva del cefditoreno pivoxilo en 20 voluntarios varones adultos sanos tras su administración cada 8 horas. Durante el primer día la mitad de ellos recibieron una dosis única de 200 mg y la otra mitad 400 mg. Tras un periodo de lavado de ocho días, ocho voluntarios recibieron 400 mg cada 12 horas, otros ocho 400 mg ca-

da 8 horas y cuatro placebo durante 10 días, siguiendo un diseño aleatorizado y doble ciego. La medicación se tomó 30 minutos después de las comidas. Se recogieron muestras de sangre y orina en los días 1, 9, 14 y 19. Se preguntó a los voluntarios si habían notado algún trastorno digestivo, sobre todo en sus hábitos intestinales, náuseas, vómitos o dolor abdominal. El valor medio de la concentración máxima de cefditoreno (C_{max}) fue 3,77 ± 0,66 mg/l y se alcanzó tras 1,5 a 3 horas con la administración tres veces al día. En el régimen de administración cada 12 horas la C_{max} fue 3,27 ± 0,64 mg/l. El tiempo medio por encima de la CMI calculado a partir de los datos derivados de cada perfil farmacocinético superó siempre el 40%, tanto cuando se administraba el fármaco cada 12 horas como cada 8 horas. La semivida del cefditoreno fue 1,19 ± 0,2 horas y 1,36 ± 0,2 horas para la administración cada 12 y cada 8 horas, respectivamente. La máxima concentración de cefditoreno en la orina se alcanzó entre 2 y 4 horas después de la administración, con un valor medio de 154,53 mg/l cuando se administraba cada 12 horas y 186,59 mg/l cuando se hacía cada 8 horas. No se encontraron diferencias en la incidencia de efectos adversos digestivos entre los grupos. Estos datos demuestran que se puede administrar 400 mg cada 8 horas, porque esta dosis se tolera bien y aumenta la probabilidad de tener éxito cuando la CMI de la bacteria causante se encuentra cerca del punto de corte de sensibilidad. Las elevadas concentraciones de fármaco activo en la orina permiten considerar al cefditoreno como un fármaco útil en el tratamiento de las infecciones de vías urinarias no complicadas.

Palabras clave: Cefditoreno pivoxilo - Farmacocinética - FC/FD - Tolerabilidad - Dosis múltiples

INTRODUCTION

Cefditoren pivoxil is a third-generation oral cephalosporin developed by Meiji Seika Kaisha Ltd., Japan. It has a broad spectrum of activity, including both Gram-positive and -negative bacteria, and is stable to hydrolysis by many common β-lactamases. Cefditoren has demonstrated high bactericidal activity against *Haemophilus influenzae* and *Streptococcus pneumoniae* (1) and it is also highly active against *Moraxella catarrhalis* (2).

After oral administration, cefditoren pivoxil is rapidly and completely hydrolyzed to cefditoren by esterases on the intestinal wall. Its absolute bioavailability under fasting conditions is approximately 15-20% and increases when it is administered after a high-fat meal (2). Area under the curve (AUC) values obtained after postprandial administration of 200 mg cefditoren were 1.36 times higher than those obtained after preprandial administration of the same dose: mean values were 10.82 mg × h/l and 7.93 mg × h/l, respectively (3). The volume of distribution (V_d/F) at steady state in healthy adults is 9.3 l, and binding of cefditoren to plasma proteins averages 88%. Cefditoren is predominantly eliminated by the kidneys as unchanged drug, with a renal clearance in healthy volunteers after multiple doses of 4.1-5.6 l/h. The elimination half-life of cefditoren is 1.5 h (2). Published data show linear pharmacokinetics of a single dose of 100-300 mg cefditoren (3) and no drug accumulation following 200, 400 or 600 mg b.i.d. doses (4).

The choice of an antibiotic to treat an infectious process is based on the microorganism susceptibility, because antimicrobial dosages have been designed to maintain plasma concentrations above the bacterial minimum inhibitory concentration (MIC) throughout the dosing interval. But in clinical practice there are many variables that modify the relationship between concentrations and bacterial susceptibility in each patient. This is the reason for the development of several related pharmacokinetic-pharmacodynamic indices, such as time above MIC (T > MIC), maximum concentration (C_{max})/MIC and AUC_{0-24}/MIC. The time the antibiotic concentration exceeds the MIC of the bacteria is the principal pharmacokinetic/pharmacodynamic parameter for β-lactams (5, 6). Detailed data are available on the pharmacokinetics of single-dose and twice-daily cefditoren administration, but little data are available on the thrice-daily regimen. Published data show predose concentrations of approximately zero following two administrations (3). Therefore, in accordance with the clinical management of these infections, it is necessary to obtain more accurate data on real bacterial susceptibility.

The present study was designed to evaluate the pharmacokinetics and gastrointestinal (GI) tolerance of cefditoren pivoxil administered thrice-daily compared with a single dose and a twice-daily regimen in healthy adult male volunteers. Data of predose concentrations will allow a real T > MIC to be calculated, using the breakpoint of susceptibility.

PATIENTS AND METHODS

Patients

Twenty healthy male volunteers aged 18-30 years (mean ± SD: 23.7 ± 2.6) and weighing 73.8 ± 7.9 kg were enrolled in this 19-day study. The subjects were assessed as healthy by examination of medical history, physical examination, vital signs, 12-lead-electrocardiograph (ECG), and routine clinical laboratory tests performed 2 weeks prior to the study. Subjects were excluded if they had taken any drug during the 3-month period prior to the study, or if they were regular heavy drinkers or smokers.

The study was performed in accordance with the Declaration of Helsinki as well as ICH-Good Clinical Practice (GCP)

guidelines, and was approved by the Navarra Research Ethics Committee. Written informed consent was obtained from all subjects prior to their inclusion in the trial. The study was conducted at the Phase I Unit of Navarra University.

The study was divided into two steps (Fig. 1). The first step (day 1) corresponded to single-dose administration, in which 10 volunteers received 200 mg of cefditoren, and 10 received 400 mg. After a washout period of 8 days, the second step which was randomized and double-blind was started (days 9-19). Eight volunteers received 400 mg cefditoren b.i.d, eight received 400 mg cefditoren t.i.d. and four received placebo for 10 days plus one additional dose on the morning of day 11. Medication was taken 30 min after meals.

Blood samples were collected at baseline and after drug administration at 30, 60, 90, 120 and 150 min, and at 3, 4, 6, 8 and 12 h on days 1, 9, 14 and 19. The collection at 12 h was not carried out with the thrice-daily regimen. During the multiple-dose period, samples were collected immediately before the morning dose on days 10, 12, 15 and 17 for additional trough values. Subjects fasted for at least 10 h before each sampling day. Urine samples were collected during the following intervals: 0-2, 2-4, 4-6, 6-8, 8-12 and 12-24 hours on days 1, 9, 14 and 19.

Sample analysis

High-performance liquid chromatography (HPLC) was used to measure the plasma and urine concentrations of cefditoren; stationary phase: Nova-Pack C_{18}, 15 cm × 0.39 mm (Waters Corporation, Milford, USA); and mobile phase: 75% 0.05 M disodium hydrogen phosphate dehydrated and 25% acetonitrile, adjusted to pH 7.0 by the addition of orthophosphoric acid. The pump flow rate was 1.0 ml/min. Ultraviolet (UV) absorbance detection was used (maximum absorbance wavelength 295 nm). A Waters 700 WISP autosampler was used (Waters Corporation) and the integrator was a Maxima 820 Waters data system.

Plasma samples (0.5 ml) were prepared by mixing aliquots (25:75) of the specimen with acetonitrile; 25 µl of the working internal standard solution (aminopyrine, 0.1 mg/ml) was added to each sample. The samples were kept at room temperature and centrifuged at 2,500 rpm for 10 min. After a reduction in volume to approximately 200 µl at 30 °C under a stream of nitrogen, 25 µl of the supernatant was injected. The retention times of ceftidoren and aminopyrine were 5.5 and 11.9 min, respectively. The intra- and interday variability (SD/mean × 100) was <12.8% for plasma samples containing 0.05, 0.1, 0.5 and 1 mg/ml cefditoren (limit of quantification 0.05 mg/l).

Urine samples (0.5 ml) were spiked with 50 µl of the working internal standard solution (aminopyrine, 0.1 mg/ml) and 900 µl of water. After mixing, an aliquot was transferred to HPLC microvials and 25 µl of the supernatant was injected onto HPLC. The intra- and interday variability was <9.15% for urine samples containing 10, 50 and 100 µlg/ml cefditoren (limit of quantification 10 mg/l).

Pharmacokinetic evaluation

The C_{max} and the minimum concentration (C_{min}) in plasma and the time to maximum drug concentration (t_{max}) were obtained from the experimental values.

The values of the following pharmacokinetic parameters were derived by a noncompartmental method with Winonlin Standard Edition version 1.5 (Scientific Consulting, Inc. 1984-1997): half-life ($t_{½}$); mean residence time (MRT); the AUC from time zero to the last sampling time (AUC_t); the AUC from time zero extrapolated to infinity (AUC_∞); relative total systemic clearance (Cl/F); and relative V_d/F.

A drug accumulation index was estimated from the AUC_8 or AUC_{12} (R_1) values on day 19 divided by the AUC_8 or AUC_{12} values on day 9 (first multiple dose administration). R_2 and R_3 ratios were also estimated from the C_{max} and C_{min} values on day 19 divided by the values on day 9

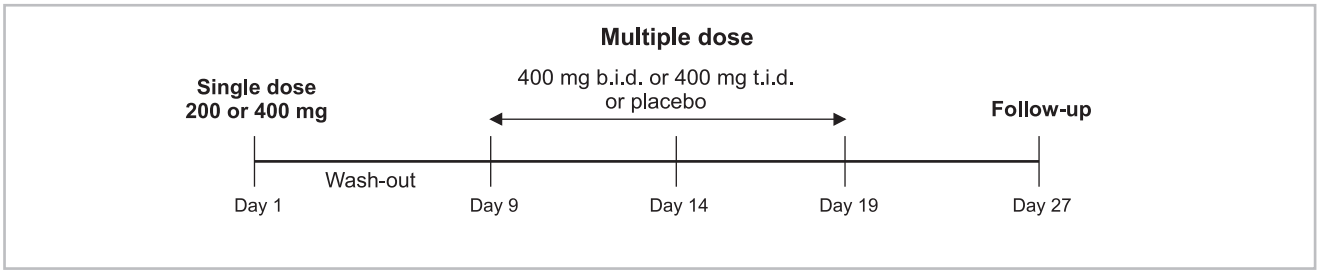

Figure 1. Study schedule.

Urinary excretion was calculated from the concentrations of cefditoren in the urine and the volumes of urine collected during each interval after drug administration.

Pharmacodynamic assessments

The time the antibiotic concentration exceeds the MIC of the bacteria was calculated for each pharmacokinetic profile (T > MIC). It was calculated between t_1 and t_2, with t_1 corresponding to the time in which the concentration reaches the MIC during the absorption phase, and t_2 to the postadministration time in which the plasma concentration equals the MIC in the elimination phase (7). Different cefditoren MIC values (0.06, 0.125, 0.25, 0.5 and 1 mg/l) observed with *S. pneumoniae* were used for estimations (2, 8). The postantibiotic effect was also considered in calculating the T > MIC (9-11).

Safety evaluation

At each visit, all adverse events, either observed by the investigator or spontaneously reported by the subject, were recorded.

One of the main study objectives was the evaluation of GI tolerance. Volunteers were asked extensively about any GI change, especially about modifications of the bowel habits, nausea, vomiting or abdominal pain. Volunteers were asked to state their normal bowel habits before their participation in the study. During the investigation, the volunteers recorded the time of all bowel movements from 24 h before the first dose until 24 h after the final dose. The following characteristics of the stool (as observed by the volunteer) were recorded as a questionnaire: consistency (watery, soft, formed or hard) and colour (black, brown, tan or other).

GI side effects were graded as shown in Table 1. Partial and total scores were recorded on each day of the study. Partial score was calculated for each symptom (nausea, vomiting, diarrhea and abdominal pain) multiplying the score by the number of the days of duration, adding three points if worsening, four in case of additional severity criteria or subtracting three points in the case of improvement. The total score for each day was the combination of the partial score for each symptom. A total score lower than four was considered normal; a score of four to eight was mild; nine to 14 was moderate; and a score >15 was severe.

The safety profile of the drug was evaluated by clinical (physical examination, including ECG) and blood and urine analytical parameters. Symptom evaluation, physical examination, hematological and blood biochemical analysis, and urinalysis were carried out prior to the single dose; prior to the first administration of the multiple dose regimen; on days 14 and 19 prior to drug administration; and 7 days after the end of the treatment.

Statistical methods

The data were analyzed using the statistical program SPSS (version 11, SPSS Inc Chicago, US. 1989-2001).

The main parameters for the assessment of the dose proportionality of cefditoren after a single-dose administration were AUC_∞ and C_{max}. The values of AUC and C_{max} were logarithmically transformed by assuming a log-normal distribution. Geometric means and 95% confidence intervals (CI) were calculated from the means and the 95% CI of the transformed values by exponentiation. A one-way analysis of variance (ANOVA) with the factor dose was performed on the logarithmically transformed and dose-normalized values of AUC and C_{max} to test the dose proportionally.

The parameters obtained for each dose regimen in the three kinetic days (days 9, 14 and 19) were compared using an ANOVA of one factor. Additionally, the comparison between both dose regimens was carried out day by day, using a Student's *t*-test for independent data.

The total percentage excreted in urine in each interval after cefditoren single-dose administration was analyzed using Student's *t*-test for independent data. The level of statistical significance was set at $\alpha = 0.05$. Moreover, an ANOVA of two factors was applied in each treatment, considering as sources of variation the volunteers and the kinetic days (days 9, 14 and 19).

Table 1. Grading of gastrointestinal adverse events.

Score	1	2	3	Additional severity criteria
Nausea	Mild and <60 min	Moderate and 1-4 h	Severe and >4 h	Weight loss
Vomiting	1/day	2/day	≥3/day	Weight loss
Diarrhea	Soft or watery stools ≤3/day	4-5 watery stools/day	>5 watery stools/day	Bleeding or weight loss
Abdominal pain	Mild (<60 min)	Moderate (1-4 h)	Severe (>4 h)	Neurovegetative features

Both dose regimens were compared day by day by using Student's *t*-test for independent data. The incidence of adverse events was compared between groups using the Mantel-Haenszel test.

RESULTS

All 20 subjects completed the study and were evaluated for safety. One subject from the 400 mg twice-daily dose group developed diarrhea and was excluded from the study on the seventh day of treatment. The remaining 19 subjects completed the treatment as planned.

Single dose of cefditoren 200 mg

The peak concentrations of cefditoren in plasma were reached around 2 h postdose. Mean C_{max} was 2.3±0.9 mg/l and a mean AUC_{∞} of 6.98±2.6 mg × h/l was obtained. The elimination half-life with 200 mg was 1.33±0.23 h. The MRT was 3.08±0.34 h, and relative plasma clearance and relative distribution volume was 32.91±13.46 l/h and 60.01±15.45 l, respectively.

The amount of cefditoren excreted in the urine during a 24-h period, expressed as percentage of dose, was 12.77±2.96%.

Single dose of cefditoren 400 mg

The C_{max} of cefditoren in plasma was reached 2 h postdose and was 3.7±0.7 mg/l. The value normalized by dose was the same as that observed with the 200-mg dose ($p>0.05$).

A mean AUC_{∞} of 12.5±1.6 mg × h/l was obtained, double that of the 200-mg dose. The elimination half-life was 1.54±0.20 h. Although some statistically significant differences were observed in the half-lives of the 200- and 400-mg dose ($p=0.048$), the difference in absolute values between both half-lives was small (15 min). The MRT was 3.59±0.55 h, which was statistically significantly different to the 200-mg dose ($p=0.022$). Relative plasma clearance and V_d/F reached mean values of 32.45±4.93 l/h and 72.05±14.49 l, respectively. Both parameters were similar to values observed with the 200-mg dose.

The amount of cefditoren excreted in the urine in 24 h was 18.24±5.15%, there being a statistically significant difference in the amount excreted between the 200- and 400-mg dose ($p=0.009$).

Multiple dose cefditoren 400 mg twice-daily

After the administration of cefditoren 400 mg b.i.d., the C_{max} ranged between 2.43 and 4.48 mg/l and it was reached between 1 and 3 h. The AUC_t obtained with this dose ranged from 6.79 and 15.81 mg × h/l (Table 2). The concentration values 12 h after the administration were invariable throughout the treatment, with a mean value of 0.053±0.021 mg/l in the twice-daily regimen. No statistically significant variations of the pharmacokinetic parameters were observed throughout the treatment in the plasma or urine parameters.

The amount of cefditoren excreted in the urine, expressed as a percentage of the administered dose, ranged between 4.03 and 21.35% during the study, without statistically significant differences ($p=0.74$). Maximum cefditoren concentration in urine was observed in the 2-4 h postadministration interval. Data for the concentrations are shown in Table 3 and in Figure 2.

Table 2. Pharmacokinetic parameters of cefditoren 400 mg b.i.d. on administration days 9, 14 and 19.

Multiple-dose cefditoren 400 mg t.i.d.	Day 9	Day 14	Day 19
t_{max}* (h)	2.00* (1.00-3.00)	1.75 (1.50-2.50)	2.00 (1.50-2.50)
C_{max} (mg/l)	3.34 ± 0.65 (2.56-4.26)	3.44 ± 0.58 (2.86-4.48)	3.00 ± 0.71 (2.43-4.37)
AUC_t (mg × h/l)	11.90 ± 3.28 (7.58-15.81)	10.18 ± 2.26 (7.67-14.28)	10.00 ± 2.23 (6.79-12.55)
AUC_{∞} (mg × h/l)	11.99 ± 3.30 (7.64-15.90)	10.27 ± 2.28 (7.81-14.43)	10.10 ± 2.18 (7.02-12.59)
Vd/F (l)	70.41 ± 21.37 (47.20-111.3)	80.28 ± 12.20 (60.10-98.10)	79.03 ± 20.44 (57.30-115.30)
Cl/F (l/h)	35.94 ± 10.87 (25.20-52.3)	40.56 ± 8.38 (27.70-51.20)	41.37 ± 9.66 (31.80-56.90)
$t_{1/2}$ (h)	1.37 ± 0.14 (1.11-1.51)	1.39 ± 0.17 (1.08-1.60)	1.33 ± 0.16 (1.15-1.60)
MRT (h)	3.54 ± 0.62 (2.88-4.72)	3.15 ± 0.27 (2.78-3.55)	3.06 ± 0.42 (2.65-3.90)
Ae (mg)	58.24 ± 15.49 (30.73-77.84)	52.23 ± 16.64 (16.14-68.06)	57.78 ± 17.84 (33.58-85.39)
Percentage recovered in urine (%)	14.56 ± 3.87 (7.68-19.46)	13.06 ± 4.16 (4.03-17.02)	14.44 ± 4.46 (8.40-21.35)

*t_{max}: median (range); C_{max}: highest drug concentration, AUC_t area under the plasma drug concentration-time curve from time zero to the last sampling time; AUC_{∞}: AUC from time zero extrapolated to infinity; V_d/F: relative volume of distribution; CL/F: relative total systemic clearance; $t_{1/2}$ half-life; MRT: mean residence time; Ae: cumulative amount of drug excreted unchanged in the urine.

Table 3. Mean (SD) urine concentrations of cefditoren in single- and multiple-dose regimens (mg/l).

Interval (h)	200 mg	400 mg	400 mg/12 h	400 mg/8 h
0-2	67.31 ± 46.13 (15.5-144.4)	105.21 ± 53.64 (49.9-165.8)	109.25 ± 53.49 (5.1-191.8)	162.05 ± 66.65 (38.2-296.3)
2-4	109.56 ± 67.47 (34.22-278.3)	186.47 ± 79.94 (62.5-338.2)	154.53 ± 92.98 (23.9-321.8)	186.59 ± 106.95 (34.8-393.6)
4-6	45.04 ± 41.36 (1.8-148.5)	96.67 ± 46.18 (11.5-172.5)	77.87 ± 59.50 (5.6-227.3)	100.08 ± 40.10 (53.1-236.6)
6-8	16.67 ± 13.08 (4.44-51.1)	37.18 ± 16.71 (2.8-63.1)	46.20 ± 25.94 (9.6-125.3)	32.80 ± 11.38 (11.2-52.2)
8-12	2.23 ± 2.35 (0-8.2)	12.69 ± 16.88 (0.5-56.0)	14.11 ± 22.61 (1.2-109.3)	6.15 ± 2.69* (3.1-10.6)
12-24	0.27 ± 0.38 (0-1)	5.05 ± 11.14 (0-36.2)	1.6 ± 2.2* (0-4.7)	1.44 ± 3.16* (0-4.1)

*Only data for last dose on day 19.

T > MIC values for the twice-daily administration are shown in Table 4.

Multiple dose cefditoren 400 mg three times daily

Mean plasma levels of cefditoren in healthy male volunteers after the multiple-dose administration of the 400-mg dose in two or three administration regimens are shown in Figure 3. The pharmacokinetic parameters after the administration of the thrice-daily 400-mg dose of cefditoren are presented in Table 5. The mean value of C_{max} of cefditoren did not change significantly throughout the treatment, and was reached at the same time each day. The maximum concentration ranged between 2.53 and 5.96 mg/l, and was reached between 1.5 and 3 h. Nineteen volunteers showed plasma concentrations of cefditoren higher than 0.125 mg/l 30 min after the first administration. Mean trough value was 0.297±0.20 mg/l, with no statistical differences between days (p=0.072). The mean value of the AUC_t on the

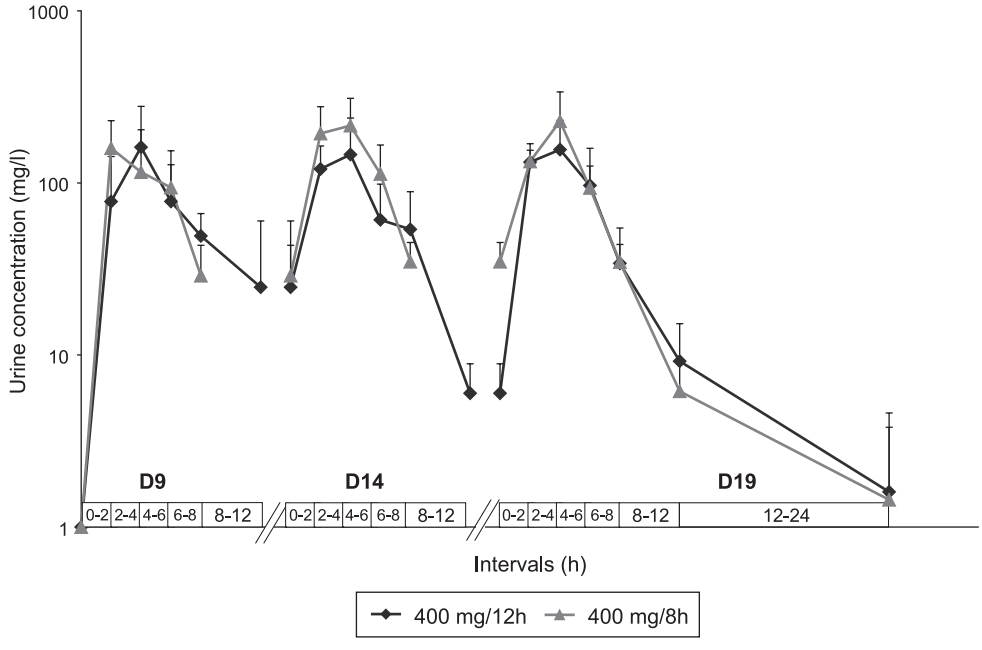

Figure 2. Mean cefditoren urine concentrations in multiple doses on administration day 9, 14 and 19.

Table 4. Time above minimum inhibitory concentration (MIC) (%) of both cefditoren doses in relation to different MICs of *S. pneumoniae*.

	MIC (mg/l)				
Cefditoren regimen	≤0.06 (%)	0.125 (%)	0.25 (%)	0.5 (%)	1 (%)
400 mg t.i.d.	100	99.7	91.6	75.4	58.7
400 mg b.i.d.	94.4	81.2	67.6	55.6	44.1
Accumulated susceptible strains related to MIC (%) ARISE study (8)					
	71.1	75.2	82.7	94	99.8
If postantibiotic effect is considered (9-12)					
400 mg t.i.d.	100	100	99.3	92.1	77.2
400 mg b.i.d.	98.2	91.8	79.6	67.6	56.2

first day of the study was 11.72±1.68 mg x h/l, with no significant variations during the treatment. Values of AUC_t ranged between 8.98 and 16.95 mg × h/l. Accumulation was not observed throughout the treatment, with mean rates of R_1: 0.97±0.16; R_2: 1±0.2; and R_3: 0.76±0.22. The relative plasma clearance and the V_d/F were invariable during the treatment, showing no interindividual differences. Minimal variations in the MRT were observed throughout the treatment. However, some differences were observed regarding the elimination half-life and the elimination rate, with some significant statistical variations throughout the treatment. Considering the absolute values and taking into account the behavior of the drug, this difference does not seem to be relevant (15 min).

The amount of cefditoren excreted in the urine, expressed as a percentage of the administered dose, ranged between 9.09 and 21.15% during the study, with statistically significant differences (p=0.42) between days 9 and 14. Maximum cefditoren concentration in the urine was observed in the 2-4 h postadministration interval. Data of concentrations is shown in Table 3 and in Figure 2.

T>MIC values for thrice-daily administration are shown in Table 3.

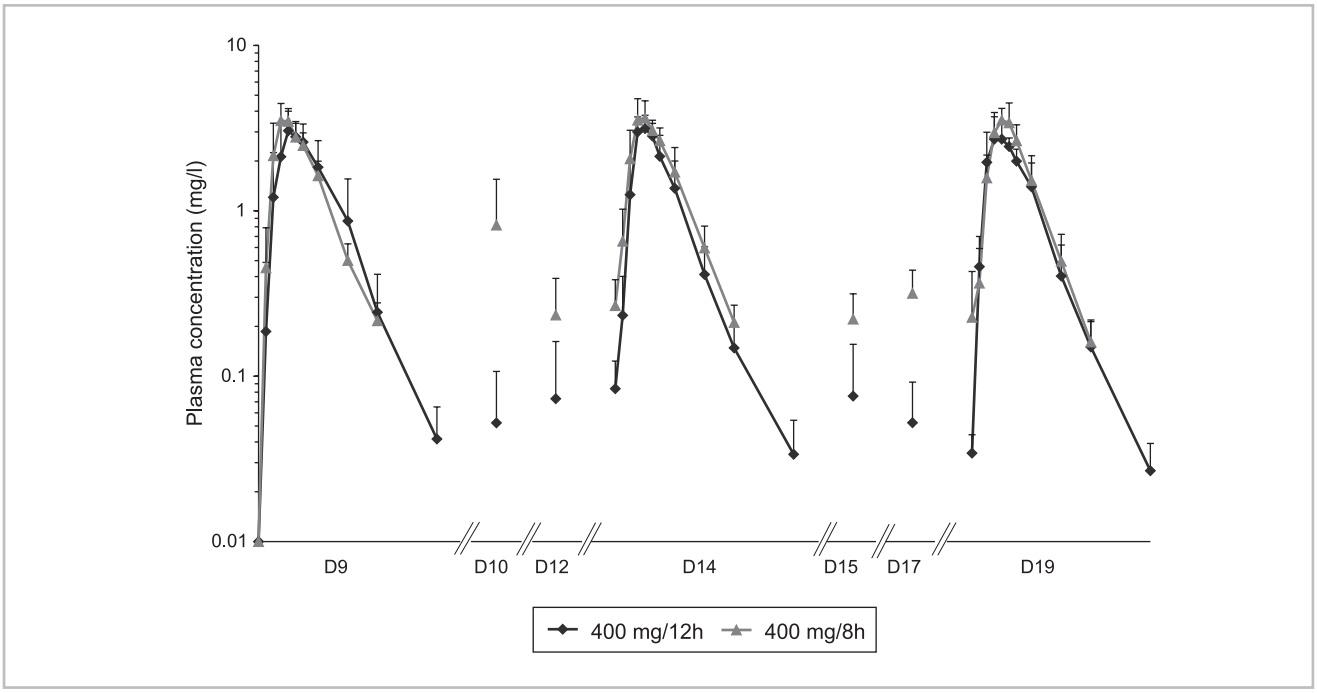

Figure 3. Mean cefditoren plasma concentrations in multiple dose on administration day 9, 14 and 19, and predose values on second treatment day 10, 12, 15 and 17.

Table 5. Pharmacokinetic parameters of cefditoren 400 mg t.i.d. on administration days 9, 14 and 19.

Multiple-dose cefditoren 400 mg t.i.d.	Day 9	Day 14	Day 19
t_{max} (h)*	1.52 (1.48-2)	2 (1.50-3)	2.01 (1.50-2.5)
C_{max} (mg/l)	3.87 ± 0.84 (2.53-4.83)	3.98 ± 0.57 (3.27-5.12)	3.80 ± 0.97 (2.95-5.96)
AUC_t (mg×h/l)	11.72 ± 1.68 (9.05-13.63)	12.69 ± 1.90 (10.95-16.42)	11.40 ± 2.59 (8.98-16.95)
AUC_∞ (mg×h/l)	12.18 ± 1.76 (9.26-14.14)	13.10 ± 1.93 (11.26-16.7)	11.69 ± 2.69 (9.13-17.48)
V_d/F (l)	70.15 ± 12.62 (57.20-88.8)	59.81 ± 8.65 (40.90-67.2)	62.08 ± 12.03 (44.00-77.2)
Cl/F (l/h)	33.50 ± 5.24 (28.30-43.2)	31.08 ± 4.15 (24.00-35.5)	35.54 ± 6.83 (22.90-43.8)
$t_{1/2}$ (h)	1.46 ± 0.2 (1.23-1.87)	1.34 ± 0.14 (1.18-1.62)	1.22 ± 0.13 (1.06-1.41)
MRT (h)	3.17 ± 0.34 (2.79-3.70)	3.11 ± 0.40 (2.75-3.96)	3.08 ± 0.24 (2.86-3.55)
Ae (mg)	55.75 ± 7.49 (45.58-64.85)	67.47 ± 8.15 (57.14-84.59)	57.64 ± 11.58 (36.38-72.05)
Percentage recovered in urine (%)	13.94 ± 1.87 (11.39-16.21)	16.87 ± 2.04 (14.28-21.15)	14.41 ± 2.89 (9.09-18.01)

t_{max}: time to maximum concentration; C_{max}: highest drug concentration, AUC_t area under the plasma drug concentration-time curve from time zero to the last sampling time; AUC_∞: AUC from time zero extrapolated to infinity; V_d/F: relative volume of distribution; Cl/F: relative total systemic clearance; $t_{1/2}$ half-life; MRT: mean residence time; Ae: cumulative amount of drug excreted unchanged in the urine.
*Median (range).

Comparison of both multiple-dose regimens

The pharmacokinetic parameters were compared day by day for both dose regimens and no statistically significant differences were observed between them except for the C_{max} that was higher when cefditoren was administered three times a day. Similarly, the C_{min} was higher when cefditoren was administered three times a day, with a mean of 0.243 mg/l higher (CI 95%: 0.164-0.322 mg/l).

There were no statistically significant differences in the accumulation rates between either regimen doses.

Statistical differences among the cumulative percentage of the excreted drug in urine between each day of both dosage regimens were observed only on day 14 (p=0.035).

T > MIC calculated with data from each pharmacokinetic profile was higher in the thrice-daily regimen. T > MIC values of both cefditoren pivoxil regimens are shown in Table 4. If the postantibiotic effect is considered, higher values of efficacy can be established with both dose regimens (Table 4).

Safety

Twelve volunteers reported twelve adverse events: two headache and 10 GI events. Following the criteria previously established, the GI adverse events were classified as mild, with the exception of two cases of a combination of diarrhea and abdominal pain that were considered moderate, and one case classified as severe diarrhea. This volunteer recovered 3 days after discontinuation. In the remaining subjects, the symptoms resolved spontaneously and the treatment continued without any remedial action.

The evaluation of the intensity of GI effects showed the following results: one of the 20 volunteers scored over 15 points; two volunteers reached 10 points; four scored 5-8 points; nine scored 1-4 points; and four had 0 points.

There were no adverse events during the single-dose step, and only one case of dyspepsia was observed during the placebo treatment.

There were no differences between groups in the incidence of GI events.

Comparison of the analytical parameters between the different dosage regimens did not show significant differences, with the exception of a reduction in the hemoglobin count, serum creatinine, glucose, uric acid or alkaline phosphatase. Most values obtained were normal and did not seem to be clinically significant. Physical examination and ECG showed no abnormality in the volunteers and no apparent changes before and after treatment were observed.

DISCUSSION

From a pharmacokinetic point of view, cefditoren is a drug with linear behavior, showing a good linear relationship between the AUC_∞ and C_{max} after the administration of a single dose of cefditoren 200 mg and 400 mg. Other authors have observed linearity between 100 and 300 mg (3).

The AUC_∞ and C_{max} following both dosage regimens (400 mg b.i.d. and 400 mg t.i.d.) were similar during the different days, although the dose interval was different, since the dose was the same and there was no drug accumulation.

The pharmacokinetic parameters obtained (C_{max}, t_{max}, $t_{½}$ and AUC) correspond to those described in the literature (3, 12-15). However, the estimated V_d/F and renal clearance values appear to be falsely increased when compared with the rest of the β-lactams and with published data (16), and it should be taken into account that they are estimated

parameters that depend on the real bioavailability. Further study is required to determine the bioavailability of cefditoren pivoxil through a pharmacokinetic study of its intravenous administration, or to determine whether the value of these parameters is related, since they depend on the real value of relative bioavailability.

In the multiple-dosage regimens, the elimination half-life was the same as that observed after the single dose, with a mean value of 1 h (1.06-1.23 h); this was in accordance with other studies (12-15).

The urinary elimination of unaltered cefditoren was approximately 30% of the administered dose (range: 4.03-26.34%). According to the sponsor's data, the bioavailability of cefditoren is 15-20% in fasting conditions (17). Therefore, it is possible that the entire absorbed drug was later eliminated in the urine and that the percentage of dose excreted (approximately 20%) corresponds to its bioavailability.

In order to compare the appropriate dosage regimen based on pharmacokinetic parameters, several factors have been proposed to explain the pharmacodynamic interaction between the antibiotic and the microorganism at the infection site. This has enabled several relationships between pharmacokinetic parameters and measures of antimicrobial activity to be evaluated. For β-lactams the principal pharmacokinetic/pharmacodynamic parameter is the T>MIC. Different studies have proposed the need to maintain plasma concentrations of β-lactams above the bacterial MIC throughout almost half of the dosing interval (18), because the postantibiotic effect plays an important role in antibacterial activity. For cefditoren, a postantibiotic effect of 1-2 h has been described against penicillin-susceptible and -resistant strains of *S. pneumoniae*, *Staphylococcus pyogenes* and β-lactamase-negative *M. catarrhalis* strains (19). The administration of cefditoren twice a day is sufficient to reach plasma concentrations above MIC for almost 81% and 44% of the administration interval, if the MIC value is ≤0.125 mg/l or 1 mg/l, respectively. Wellington and Curran estimated a T>MIC above 2 or 1 mg/l of 5.3-6.7 hours with the same dose (2). If the postantibiotic effect is considered, the T>MIC will exceed 1 mg/l for almost half of the dosing interval, as Cars proposes (18). Although nowadays there are no established breakpoints by the Clinical and Laboratory Standards Institute (CLSI) or the European Committee on Antimicrobial Susceptibility Testing (EUCAST), the above results endorse the susceptibility breakpoints approved by the Spanish Agency during the registration procedure in Europe (S ≤0.5 mg/l, R >1), which are more realistic than the ones proposed previously by the Food and Drug Administration (FDA) (S 0.125, R >0.25). Other authors consider it necessary to maintain plasma concentrations above MIC for the whole dosing interval (20-23). The administration of cefditoren three times a day increases the T>MIC in an appreciable manner, and could be of interest when a microorganism has an MIC in the upper limit of susceptibility. It is then possible to increase the time in which plasma concentration exceeds the MIC during the dosing interval using a thrice-daily administration of cefditoren.

Cefditoren shows excellent activity against *Escherichia coli,* the main causative pathogen of uncomplicated urinary tract infections (UTIs). A recent study that evaluated the *in vitro* activity of cefditoren against 199 *E. coli* strains showed MIC_{50} and MIC_{90} values of cefditoren against this pathogen of 0.25 and 0.5 mg/l, respectively (24). In another recent survey of *E. coli* isolates with different resistance phenotypes (25), cefditoren showed MIC values much lower than urine concentrations even against quinolone-resistant strains.

Mean urinary elimination of cefditoren as unchanged drug after single oral doses of 200 mg and 400 mg were 13% and 18%, respectively. The administration of these doses resulted in concentrations of cefditoren in urine higher than the susceptibility breakpoint of *E. coli* (MIC_{90}: 0.5 mg/l) during the following 12 or 24 h after administration, respectively, which means a T>MIC of 100%. Therefore cefditoren could be considered a useful candidate in the treatment of UTIs produced by susceptible microorganisms.

From a clinical point of view, the administration of cefditoren pivoxil to healthy male volunteers, either single oral dose (200 or 400 mg) or multiple oral dose (400 mg b.i.d. and 400 mg t.i.d.), did not produce any relevant alteration in the physical examination, blood pressure, heart rate or ECG. Although some statistically significant differences were found in some analytical parameters, they were not considered to be clinically relevant.

One volunteer was excluded from the study due to GI adverse events. None of the volunteers that completed the study reported nausea and vomiting. However, a majority of volunteers manifested diarrhea of different intensity, according to the criteria established beforehand. In seven volunteers, it was moderate and disappeared spontaneously. It is important to emphasize that the study methodology was favorably established to highlight subjective GI symptoms, but in only one case was treatment discontinuation deemed necessary. The GI discomfort was similar to that observed in previous studies and commonly described with the use of antibiotics (26).

In any case the incidence of adverse events between treatments (placebo, cefditoren pivoxil 400 mg b.i.d. and cefditoren pivoxil 400 mg t.i.d.) was similar.

CONCLUSION

The recommended regimen of cefditoren pivoxil is 200 mg or 400 mg b.i.d., depending on the indication. The present data show that the administration of 400 mg t.i.d. is also possible because this regimen is well tolerated and could increase the probability of success when the MIC of the causative bacteria is close to the susceptibility breakpoint. The high concentrations of active drug in urine allow consideration of cefditoren as a useful candidate in the treatment of UTIs.

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CONFLICT OF INTEREST (AUTHORS)

M. Gimeno and P. Coronel work for Tedec-Meiji Farma, S.A. The other authors have nothing to declare.

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