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A phase 1 pharmacokinetic and safety study of extended duration, high-dose cefixime for cephalosporin-resistant *Neisseria gonorrhoeae* in the pharynx

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ABSTRACT

Background: There are no fully oral recommended treatment regimens for gonorrhea. Inadequately treated pharyngeal gonococcal infections are a likely reservoir for transmission and development of antimicrobial resistance. We sought to determine an oral cefixime dosing regimen that would theoretically treat pharyngeal infections by gonococci with MICs 0.5μg/mL.

Methods: We conducted an open label, non-randomized, Phase I pharmacokinetic and safety study of cefixime in 25 healthy male and female volunteers divided into four dosing cohorts (Cohort A, 400 mg; Cohort B, 800 mg; Cohort C, 1200 mg; and Cohort D, 800 mg q8h x 3 doses [total dose 2400mg]) with a target serum concentration of ≥2.0 μg/mL for >20 hours. Cefixime concentrations from serum and pharyngeal fluid were determined with use of a validated LC/MS/MS assay. Safety measures included laboratories, physical exams and symptom diaries.

Results: None of the single-dose regimens attained the target concentration; however, 50% of subjects in cohort D attained the target concentration. Variation in absorption and protein binding contributed to differences in concentrations. Pharyngeal fluid concentrations were negligible. The single dose regimens were well-tolerated; the multi-dose regimen resulted in mild to moderate gastrointestinal symptoms in 43% of subjects.

Conclusions: None of the dosing regimens achieved the target concentration. However, the proposed theoretical target was extrapolated from penicillin data; there are no empirically derived pharmacokinetic/pharmacodynamic criteria for pharyngeal gonorrhea. Under alternative cephalosporin-specific therapeutic goals, the multi-dose regimen may be effective, although the absence of cefixime in pharyngeal fluid is concerning. A clinical trial evaluating efficacy and defining pharmacokinetic/pharmacodynamic outcomes may be warranted.

BACKGROUND

Antimicrobial resistant *Neisseria gonorrhoeae* is a major public health threat.[1] The Centers for Disease Control and Prevention (CDC) removed cefixime from the recommended treatment guidelines for gonorrhea in 2012[2] because surveillance data showed a rapid increase in isolates with reduced susceptibility to cefixime,[3] and a number of case reports documented cefixime treatment failures.[4,5,31] Although in 2016, the proportion of surveilled isolates with reduced susceptibility to cefixime remained low,[32] this change left ceftriaxone, an injectable third-generation cephalosporin, as the primary recommended treatment for gonococcal infections. There are no oral first-line treatment options.

Reliance on an injectable antibiotic presents a number of practical problems. Many physicians' offices do not stock injectable drugs, and as an injection, use of ceftriaxone often requires a second visit, a barrier to treatment and an increased cost. Additionally, expedited partner therapy (EPT) for gonorrhea among heterosexuals[6] requires a fully oral treatment regimen, and elimination of such has the potential to diminish EPT's use and effectiveness.[7]

Between 1945 and 1989, as the minimum inhibitory concentrations (MIC) of penicillin G (PenG) for *N. gonorrhoeae* gradually rose, the effectiveness of penicillin was maintained by increasing the intramuscular dose from 50,000 units in 1945 to 4.2 million units in the 1970s.[8] Based on exposure-response data[9] effective treatment was defined as a regimen that maintained total serum PenG levels more than four times the MIC for 7-10 hours. Since pharyngeal infections are more difficult to treat than anogenital infections, subsequent data recommended that treatment regimens should achieve total serum antibiotic levels >4 times the MIC_{90} for >20 hours to cure gonococcal infection at the pharynx.[10] Recommended gonorrhea treatment regimens should be effective for infections at the pharynx as these asymptomatic infections often go undiagnosed, yet contribute to community transmission[11] and may facilitate the development of antimicrobial resistance.[12] However, there are no pharyngeal pharmacokinetic data to inform this recommendation.

Given the need for an effective oral regimen in the face of rising cephalosporin resistance, we sought to define a cefixime dosing regimen that might effectively treat pharyngeal gonorrhea infections by isolates with an MIC 0.5μg/mL. We chose this MIC as it is one dilution higher than the CDC's alert value MIC and thus is likely to be both clinically significant and circulate in the near future.

METHODS

We conducted a pharmacokinetic (PK) and safety study of high- and multi-dose cefixime. We aimed to identify a dosing regimen that would result in total serum cefixime concentrations ≥2.0μg/ml for >20 hours, which theoretically would be effective in treating pharyngeal infections by isolates with MICs 0.5μg/mL. Secondary objectives included 1) establishing the PK of each dosing regimen, 2) determining protein binding (i.e. free serum cefixime concentrations) in individual subjects, 3) quantifying the concentration of cefixime in pharyngeal fluid (Cohorts C and D), and 4) assessing the safety and tolerability of each treatment regimen.

Twenty-five adults who met criteria of the NIH Healthy Volunteer policy[13] were enrolled in four cohorts of a Phase 1, open label, non-randomized, dose–and frequency escalation study. Successive cohorts of six subjects each received oral doses of 400mg (cohort A), 800mg (cohort B), 1200mg (cohort C) or 800mg given every 8 hours for three doses (cohort D; total dose 2400 mg).

Subjects

Volunteers were healthy men and women between ages 18-45 with a body mass index <35 kg/m^2. Exclusion criteria included histories of gastrointestinal diseases or surgeries that might alter drug absorption and allergic reactions to cephalosporins and/or penicillin, and renal impairment which might prolong half-life. Female subjects were screened for pregnancy and required to use two forms of contraception during the study period and for 30 days thereafter.

Inclusion criteria included normal electrocardiogram (ECG); hematology, chemistry, liver function, coagulation values, urinalysis and negative urine toxicology. Subjects were asked to refrain from using any prescription or over-the-counter medications for at least 7 days (5 half-lives) prior to dosing, with the exception of oral contraceptives.

Study Design

The study (clinicaltrials.gov NCT01949363) was conducted at the Johns Hopkins Bayview Clinical Trials (JHBMC) Unit between December 17, 2013 and December 1, 2014. It was reviewed and approved by the Institutional Review Board of Johns Hopkins University. Cefixime was manufactured by Lupin Pharmaceuticals, Inc., Mumbai, India, and was supplied in 400 mg tablets. Study drug was maintained in the Research Pharmacy at JHBMC and dispensed by the research pharmacist.

Subjects were screened within four weeks of enrollment, during study intervention were admitted to an inpatient unit for dosing, blood and pharyngeal fluid collection and safety monitoring. Dosing followed a six-hour fast; subjects were permitted to eat three hours after dosing and to drink water *ad libitum*. A pre-dose blood sample was obtained from all subjects in all cohorts. Blood samples were obtained at 1, 2, 4, 8, 12, 16, 20, 24, 48 and 168 hours after dosing in cohorts A and B; 0.5, 1, 1.5, 2, 4, 9, 13, 18, 24, 48 and 168 hours after dosing in cohort C; and 4, 8, 12, 16, 24, 48, and 168 hours for Cohort D. Pharyngeal fluid was collected using pre-weighted Dacron swabs [BBL Culture Swabs™ (Becton Dickinson, Franklin Lakes, NJ)] held in the tonsillar fossa for 30 seconds. For cohort C, pharyngeal fluid was collected at 0, 4, 9, 13, and 18 hours, and for cohort D, at 0, 4, 8, 12, 16 and 24 hours.

Cefixime Concentration Measurement

The Pediatric Pharmacology Research Center at the University of Toledo processed the samples which were received on dry ice from the JHBMC and stored at -70◦ C until analyzed.

Pharyngeal swabs were thawed and reweighed. The difference between the two weights was the amount of pharyngeal fluid collected. Serum and pharyngeal fluid cefixime concentrations were measured with validated LC/MS/MS techniques that used cephalexin as the internal standard.[14] (Detailed methods available in Supplemental Data.)

Pharmacokinetic Analysis

We generated serum cefixime time-concentration plots for individual subjects and cohort means using SAS (Cary, NC). The following serum PK parameters were estimated using non-compartmental techniques with Phoenix™ WinNonlin®, version 6.3 (Pharsight Corp, Mountain View, CA): Cmax (maximum plasma concentration), Tmax (time to maximum concentration), $t_{1/2}$ (elimination half-life), $AUC_{0-\tau}$ (area under the plasma drug concentration versus time curve, to last measurable concentration), AUC_{0-inf} (area under the plasma drug concentration versus time curve, to infinity), Ke (elimination rate constant), CL/F (apparent clearance), V/F (apparent volume of distribution).

Because Cohort D concentrations for the first 24 hours resulted from multiple doses, as opposed to the single doses in Cohorts A-C, comparable PK parameters could not be estimated using the same methods. In order to produce parameters that could be compared to those of Cohort B, half- life, terminal slope and concentration at 24 hours (assuming no additional doses) were calculated using standard formulas. $AUC_{0-\tau}$ could then be estimated using WinNonlin:

$$half\ life = \frac{t \ln(2) \ln}{(0) - \ln(N\ t)}$$

$$slope = \frac{\ln(2)}{half\ life}$$

$$Concentration\ at\ 24\ h = N(0)\left(\frac{1}{2}\right)^{\frac{t}{t1/2}}$$

Where

N(t) is the unknown concentration at time t

N(0) is the starting concentration

t is the elapsed time

$t_{1/2}$ is the half life

ln is the natural log

Cl/F, V_d/F, $AUC_{0-\infty}$ were not able to be estimated using these methods.

Free cefixime concentrations were measured at three time points for each subject. The mean and range of values, as well as the percent free drug, were calculated for each time point.

Safety Analyses

Routine laboratory studies, including hematology, chemistry, liver function tests, coagulation panel, urinalysis; ECG; vital signs and targeted physical exams were performed at 24, 48 and 168 hours. Subjects recorded symptoms on a symptom diary card throughout the study period. These were reviewed with a study physician at 24, 48 and 168 hours. All adverse events (AEs) were evaluated by a study physician to grade severity and relationship to study drug. Severity was graded with use of standard National Institute of Allergy and Infectious Diseases, Division of Microbiology and Infectious Diseases criteria. An independent safety monitoring committee reviewed all adverse event data following cohort C and again after cohort D.

RESULTS

Study Participants

Six subjects each were enrolled in cohorts A–C, and seven in cohort D. One subject in cohort D was withdrawn after completing dosing due to a positive urine toxicology (mislabeled on the laboratory report). He was included in safety analyses but not in PK analyses. No subject discontinued the study. Overall, the study population was young, predominately male (n=17, 71%) and African-American (n=15, 62.5%).

Pharmacokinetics

Figure 1 depicts the mean and standard deviation (SD) total serum cefixime concentration versus time curves for each of the four cohorts; corresponding PK parameters are listed in Table 1. At each dose there was wide variability. The concentration versus time curves for the 400mg and 800mg dose regimens are similar to those reported previously.[15] Cohorts A, B and C demonstrate that the Cmax, Cl/F and $t_{1/2}$ are independent of dose; however, drug exposure is not dose-proportional. Cmax and AUC begin to plateau at single doses of 800mg resulting in little impact of increasing dose on the time above the target. Cohorts A-C achieved approximately 8, 10 and 11 hours above the target concentration, respectively (Figure1).

The multi-dose cohort demonstrated a similar PK pattern. Cmax was analogous to the value seen with a single 800mg dose without any apparent drug accumulation upon subsequent dosing and the calculated $AUC_{0-\tau}$ was indistinguishable from that calculated for cohort B. The elimination half-life showed greater interindividual variability, but, with the exception of one outlier, the mean was comparable to that seen in the single-dose cohorts.

Serum Free Cefixime Concentrations

Serum free cefixime concentrations (Figure 2), showed a similar protein-binding pattern in the single dose cohorts. Approximately 1 hour after dosing, the concentration of free cefixime

was lowest, peaking about four hours after dosing, followed by a gradual decline to the one hour level by 12 to 13 hours. Cohort D showed a time-dependent decrease in serum free cefixime concentrations. Free drug concentrations appeared to decline with increasing dose (Figure 3), and overall ranged from just over 20% of total serum concentrations for some subjects in cohort D to greater than 95% for some subjects in cohorts A-C.

Pharyngeal Fluid Concentrations

Seven pharyngeal fluid samples from cohort C had insufficient fluid for analysis and only two (9%) of the remaining 23 had measurable cefixime concentrations above the lower limit of quantitation (LLOQ) of the assay (10 ng/ml). Both concentrations were <50ng/ml. One cohort D sample had insufficient fluid for analysis and all other 29 samples were below the LLOQ.

Therapeutic Target

None of the single dose regimens resulted in total serum cefixime concentrations >2.0µg/ml for >20 hours in all subjects. Visual inspection of the summary serum concentration versus time curve for the multi-dose regimen (cohort D, Figure 1d) shows that the mean value achieved this target, albeit with wide inter-individual variation. The cohort D average consecutive time >2.0µg/mL was 22.3 hours while the average total time >2.0µg/mL was slightly higher at 25.2 (SD 10.3; range 11 – 35 hours). The time > 2.0µg/mL varied by individual from 8.5 to 35 hours. Only 3 of 6 (50%) subjects had total serum cefixime concentrations >2.0µg/mL for >20 hours consecutively, and 4 of 6 (66.7%) subjects' total serum cefixime concentration exceeded >2.0µg/mL for a total time >20 hours.

Safety and Tolerability

Overall, 23 subjects (92.2%) reported or were found to have an AE, but only 20 (80%) subjects' AEs were deemed to either be related to study drug or the study drug could not be

excluded.(Table 2) There were no severe or life-threatening AEs. The most commonly reported symptoms were gastrointestinal with 24% (n=6) of the study population complaining of flatulence and nausea, and 20% (n=5) reporting diarrhea. These complaints were reported more frequently by the cohort D subjects. Most events were mild in severity. Five subjects reported moderate AEs: two in Cohort B experienced headaches; one in Cohort D had increased liver transaminases; and one in Cohort A reported hematuria. Seven subjects experienced moderate laboratory abnormalities across the four cohorts. All were considered not clinically significant except for elevated transaminases in a Cohort D subject on day 7, which resolved without intervention.

DISCUSSION

There is an urgent need for effective oral antibiotic treatment of *N. gonorrhoeae.* We aimed to determine whether an alternative dosing strategy of cefixime could treat potentially cephalosporin-resistant pharyngeal gonococcal infections. The study was designed under the assumption that, similar to PenG, clinical cure of anogenital gonococcal infections required total serum concentrations 4x above the organism's MIC for 7-10 hours,[9] and treatment of pharyngeal infections would require concentrations at least 4x the MIC for at least 20 hours.[10] Thus, in order to treat infections caused by *N. gonorrhoeae* with cefixime MIC 0.5μg/ml, the target was defined as a total cefixime concentration ≥2.0μg/ml for 20 hours. None of the single dose regimens resulted in cefixime plasma levels that met our pre-specified target concentration (Figure 1), and only half of the subjects in the multi-dose regimen achieved our target.

Cefixime pharmacokinetics of 400 mg and 800 mg doses were indistinguishable from those reported previously.[16,17] Pharmacokinetics in subjects who received the 1200 mg single dose showed preservation of the parameter estimates for drug elimination (e.g. $t_{1/2}$ and Cl/F) (Table 1). The multi-dose regimen resulted in target attainment in half of the subjects (Figure 1d).

While the pharmacokinetics of this regimen were more complex, those parameter estimates related to drug elimination were preserved.

Cefixime exposure was not dose-proportional. This was not unexpected, as studies done during the drug's development noted that it had several distinctive characteristics. The Cmax plateau at higher doses is a function of the absorption kinetics.[15,18] Bioavailability of 200 mg and 400 mg doses is reported to be 40 to 50% and variable. When cefixime absorption kinetics at standard doses were examined in detail the observed data best fit a rather complex Michaelis-Menten model with an "absorption window" (M-M Δt).[18] Clinically this is reflected in an apparent saturation of drug absorption with increasing doses. This phenomenon is seen with other orally-administered beta-lactam agents, such as amoxicillin, that have decreasing bioavailability with increasing doses.[19] The phenomenon is confounded further with multi-dose cefixime. Its poor absorption would leave drug from the previous dose(s) in the intestinal lumen at the time of the subsequent dose, which would result in further decreased bioavailability, as compared to the expected values.

Although both beta-lactams, PenG and cefixime are chemically distinct and have quantitative differences in absorption, distribution and elimination. Cefixime is moderately protein bound in serum,[16,17] whereas protein binding of PenG is virtually nonexistent. In our study the time-dependent protein binding of cefixime was assessed in individual subjects, and whereas the average serum protein binding was 62%, consistent with previous reports;[16] individual subjects had time-dependent and dose-dependent differences in free drug concentrations. These differences amplified the inter-individual differences between total and active (unbound) drug concentrations. The observations that most reported cefixime failures have occurred in patients infected with highly susceptible organisms[20] may reflect the inter-individual impact of some of the pharmacokinetic idiosyncrasies of the drug.

Our target, >2.0µg/mL for 20 hours, was extrapolated from exposure-response data for PenG and urethral gonorrhea. However, the differences in protein binding between PenG and cefixime are substantial. The evidence supporting PK criteria for defining clinical efficacy for either drug class are very limited, and no single criteria are universally accepted. Chisholm et al estimated the potential value of different gonorrhea treatments assuming that therapy would be effective if *free* cephalosporin levels exceeded the MIC for 24 hours.[21] Using Chisholm's criteria, it appears that 800mg every 8 hours for three doses would meet that goal. Other investigators have assumed a treatment would be bactericidal, and likely effective, if free drug exceeds the MIC for ~65% of the dosing interval,[22] a threshold which our multi-dose cefixime regimen would also achieve.

Newer PK theory posits that to be effective an antibiotic must reach the site of infection in unbound concentrations that are antimicrobially important. We hoped to identify a regimen that would reliably eradicate *N. gonorrhoeae* with cefixime MIC 0.5 µg/ml from the oropharynx, but we detected negligible cefixime concentrations in oropharyngeal fluid, and only among subject receiving 1200mg. The absence of cefixime in oropharyngeal fluid after the 400mg, 800mg and 800mg q8h doses was not expected, as this drug has long been used to treat pharyngeal gonococcal infections, and appears to be at least partially effective.[20,23,24] Mroczkowski, *et al.* reported that 400mg of cefixime cured 11 of 16 persons with pharyngeal gonorrhea with tests of cure (TOC) 5-10 days after treatment.[25] Others have estimated the efficacy of a single 400 mg dose at 70-80%. Gratrix, *et al.*, who reported an efficacy of 70% (38/54; TOC 7-34 d) among persons treated between 2008-2011, reported that treatment failures were not related to cefixime MICs, and that an 800mg dose was not superior to 400mg.[20] While these studies suggest cefixime is at least somewhat effective in the treatment of pharyngeal gonorrhea caused by susceptible gonococci, none of these studies included an untreated control

group, and it is possible that at least some persons cured with antibiotics spontaneously cleared their infections. Relatively small previous studies have found that oropharyngeal gonococcal infections are self-limited[26-28] and spontaneously clear without therapy by 60 days after detection.[26,27] Chow et al reported that 19/33 infections cleared 3-14 days after no treatment.[28] In the context of an undefined duration of untreated pharyngeal gonococcal, and at least some apparent efficacy for pharyngeal gonococcal infection, it is difficult to interpret the lack of cefixime in pharyngeal fluid in this study.

Taken together, our findings highlight the many uncertainties surrounding the natural history, pathophysiology and treatment of pharyngeal gonococcal infections. These infections are clearly more difficult to treat than genital tract infections,[10] likely due to some combination of relatively low drug levels as the site of infection and the poor bioavailability of commonly used drugs, like cephalosporins, a problem which also affects the treatment of pharyngeal carriage of *Neisseria meningitides.*[29] Multi-dose intramuscular PenG failed to eradicate pharyngeal carriage of *Neisseria meningitidis* and was abandoned for chemoprophylaxis of high risk populations,[29] and high protein-binding of ceftriaxone in tonsillar tissue was found to explain the poor efficacy of a single 500 mg dose of this cephalosporin in curing group A streptococcal tonsillopharyngitis.[30]

In conclusion, single dose cefixime was well tolerated, including the 1200mg dose. Although the 800mg q8h dose met our target in half of the subjects, it occasioned mild gastrointestinal complaints in 43% of subjects. Although this dosing regimen did not achieve our target, the observed drug levels met some other widely used PK targets for drug efficacy.[21,22] Considering cefixime in this context, it is likely that the 800 mg single dose regimen would effectively treat anogenital infections caused by most organisms, and that 800mg every 8 hours for three doses may cure pharyngeal infection with gonococcal isolates with MIC $\leq$0.5μg/mL. However, only a clinical trial of persons infected with *N. gonorrhoeae* with elevated MICs can truly answer that question.

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FIGURE LEGENDS.

Figure 1: Total Serum Cefixime Concentration versus Time. Cohort A 400 mg dose; Cohort B 800 mg dose, Cohort C 1200 mg dose, and Cohort D 3 doses of 800 mg at 8 hour intervals. Each value is the mean for all subjects in the cohort. Error bars are standard deviation (SD). The red line indicates the target concentration of 2.0 µg/ml. Note the very wide SD for concentrations among subjects in cohort D.

Figure 2. Free Cefixime Concentrations in Serum versus Time. Cohort A 400 mg dose; Cohort B 800 mg dose, Cohort C 1200 mg dose, and Cohort D 3 doses of 800 mg at 8 hour intervals. Each value is the mean for all subjects in the cohort. Error bars are standard deviation (SD).

Figure 3. Dose-Dependence of Free Drug Concentration. Percentage of plasma cefixime that was unbound after each of the single doses (**A**, 400 mg; **B**, 800 mg; **C,** 1200 mg) one hour (black), four hours (red) and 12 hours (blue) after each dose. Each dot represents the proportion of free drug for an individual subject at the given time and dose. Note that the percentage of absorbed drug that was free diminished as the dose increased, and that the percentage of cefixime that was free did not appear to be affected by time after dosing.

Figure 1: Total Serum Cefixime Concentration versus Time – Cohorts A to Cohort D

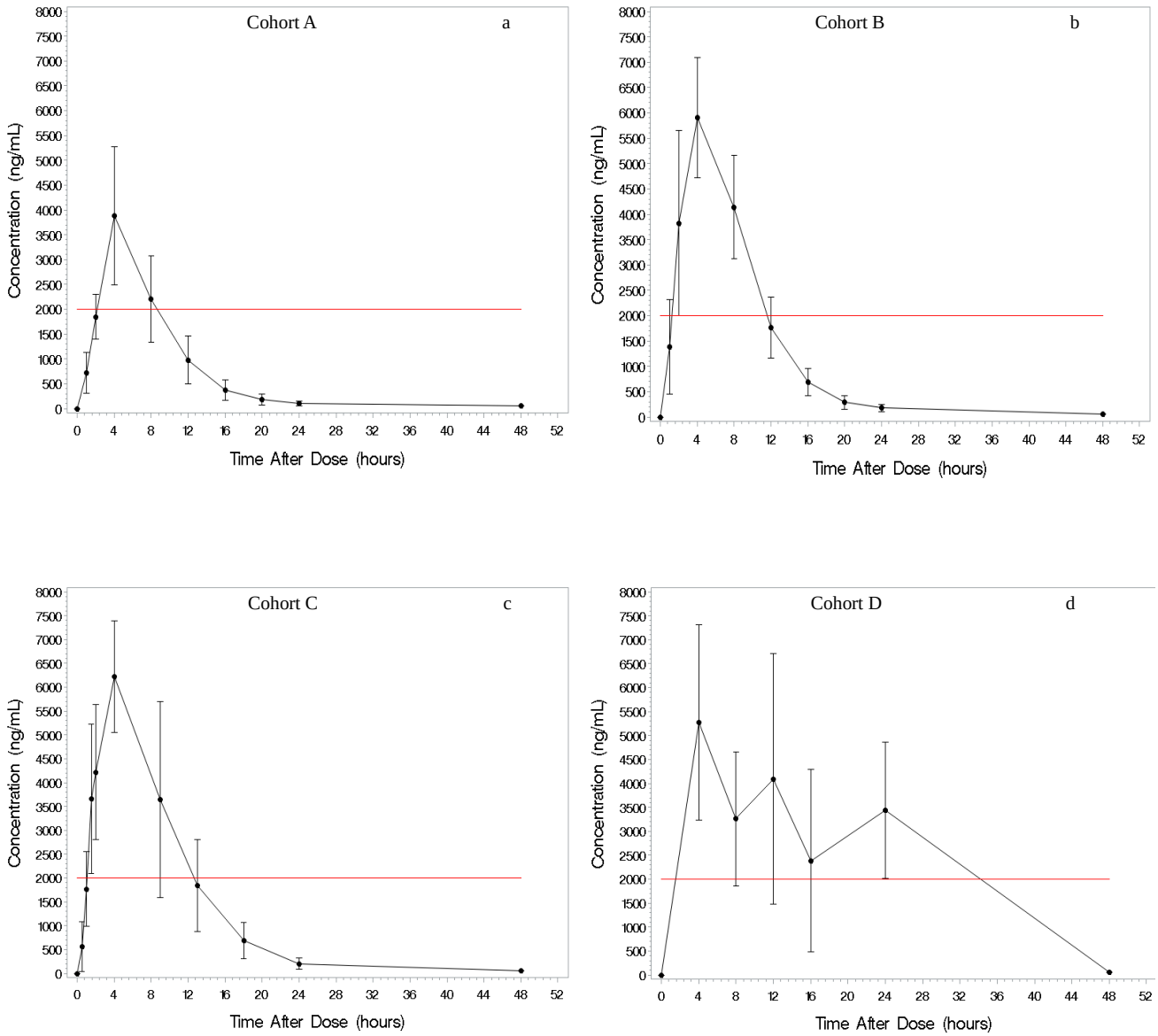

Figure 2: Serum Free Cefixime Concentration versus Time – Cohorts A to Cohort D

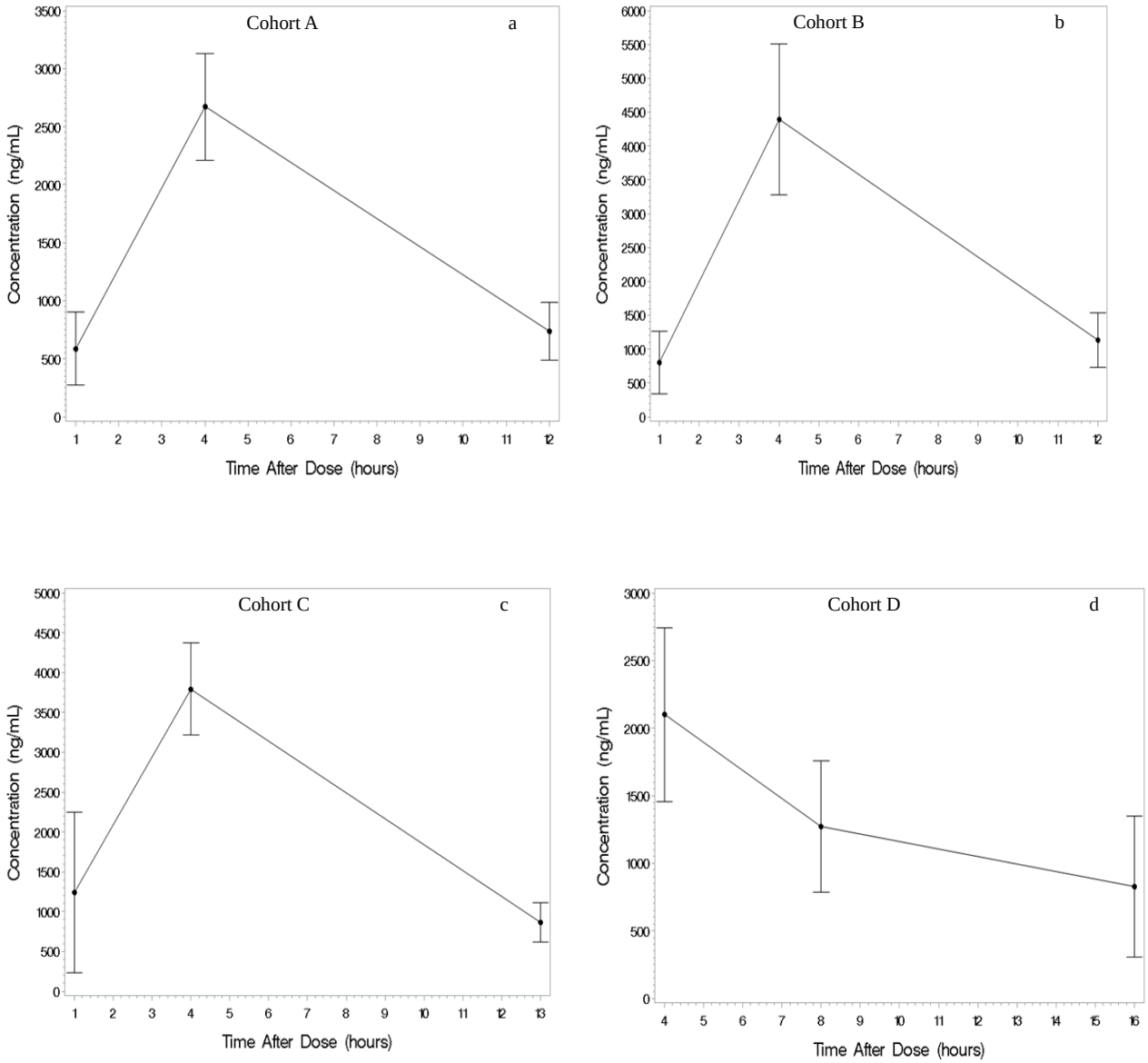

Figure 3: Dose-Dependence of Free Drug Concentration

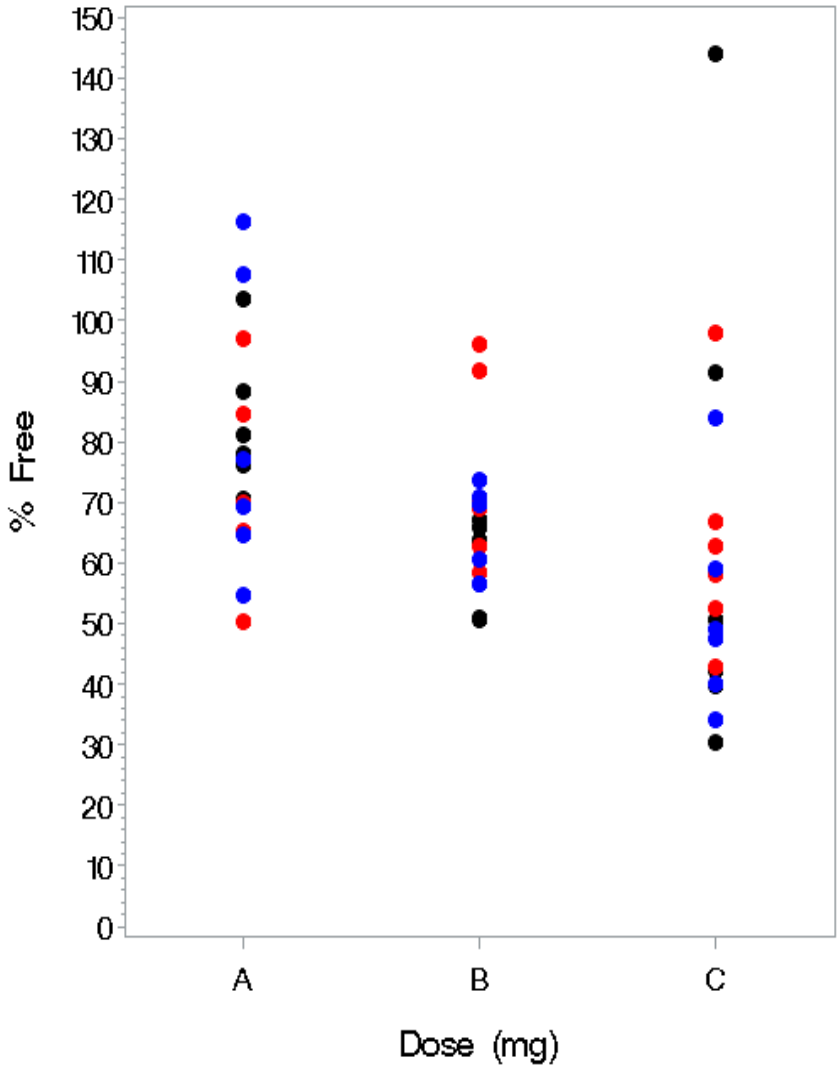

Table 1: Pharmacokinetic parameters in serum of various cefixime doses, means and SD

PARAMETER	Cohort A 400mg	Cohort B 800mg	Cohort C 1200mg	Cohort D 800mg q8 x 3
C_{max} (mcg/ml)	3.88 (1.40)	6.10 (1.16)	6.32 (9.55)	5.28 (2.04)
T_{max} (hr)	3.88 (0.06)	3.54 (0.84)	3.17 (1.10)	3.87 (0.04)
$t_{½}$ (hr)	4.23 (1.42)	3.37 (0.57)	3.67 (0.61)	7.03 (4.99)
$AUC_{0-\tau}$ (mcg/ml*hr)	30.28 (10.77)	52.75 (11.02)	58.90 (16.1)	56.71 (24.54)
$AUC_{0-\infty}$ (mcg/ml*hr)	30.89 (10.98)	53.57 (11.32)	60.00 (16.56)	--
V_Z/F (L)	86.38 (35.73)	75.13 (18.06)	116.06 (52.69)	--
Cl/F (L/hr)	14.25 (4.63)	15.70 (4.44)	21.42 (6.45)	--

Table 2: Treatment-Related Adverse Events Experienced by ≥5% of Total Study Population*

Treatment-Related Adverse Event	Cohort A 400mg N=6	Cohort B 800 mg N=6	Cohort C 1200 mg N=6	Cohort D 800 mg x 3 N=7
Any Adverse Event	5 (83.3%)	4 (66.7%)	5 (83.3%)	6 (85.7%)
Gastrointestinal System				
Diarrhea	1 (16.7%)	1 (16.7%)	0	3 (42.9%)
Nausea	1 (16.7%)	1 (16.7%)	2 (33.3%)	2 (28.6%)
Flatulence	1 (16.7%)	0	1 (16.7%)	4 (57.1%)
Abdominal Pain	0	0	0	2 (28.6%)
Headache	0	2 (33.3%	0	0
Abnormal Laboratory Tests				
Hyponatremia	0	0	1 (16.7%)	1 (14.3%)
Decreased Neutrophil Count	1 (16.7%)	1 (16.7%)	0	0
Urine Leukocyte esterase	0	0	1 (16.7%)	2 (28.6%)
aPTT	1 (16.7%)	0	1 (16.7%)	0
Hypertension	0	0	0	2 (28.6%)

*Subjects could have more than one adverse event.