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Title: **Soft Tissue Penetration of Ceftobiprole in Healthy Volunteers Determined by In Vivo Microdialysis**

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Abstract

Ceftobiprole is a promising new broad-spectrum cephalosporin with activity against several multi-drug resistant Gram-positive and Gram-negative species including MRSA. In order to make efficacy predications against these resistant bacteria in soft tissue infections, i.e. skin and skin structure infections, ceftobiprole's ability to reach the site of action should be explored. Therefore, a microdialysis study was conducted in 12 healthy volunteers to determine the penetration of ceftobiprole into skeletal muscle and subcutaneous (s.c.) adipose tissue after a single intravenous dose, 500 mg. Plasma and tissue interstitial fluid (ISF) concentrations were measured for 24 hours from the start of the 2 hour intravenous infusion. Pharmacokinetic parameters were determined using noncompartmental analysis. The penetration of ceftobiprole into the ISF of tissues was assessed by comparing the AUC ratios between tissue and plasma. It was found that ceftobiprole distributes into the muscle, $fAUC_{muscle}/fAUC_{plasma}$ 0.69±0.13, and s.c. adipose tissue, $fAUC_{s.c.adipose}/fAUC_{plasma}$ 0.49±0.28. The concentrations in both skeletal muscle and s.c. adipose tissue met the efficacy breakpoint of $T_{>MIC}$ for at least 40% of the eight hour dosing interval for organisms with a MIC of 2 mg/L. Therefore, ceftobiprole qualifies as a potential agent with drug penetration capabilities to treat complicated skin and skin structure infections due to both Gram-negative and Gram-positive pathogens with MICs equal to or below 2 mg/L.

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Introduction

Ceftobiprole, the active compound in ceftobiprole medocaril, is a promising new cephalosporin with activity against both Gram-negative and Gram-positive bacteria. This includes good activity against methicillin-resistant *Staphyloccocus aureus* (MRSA) with reported MIC_{90} values of 2 mg/L (12) and 4 mg/L (9) and penicillin-resistant *Streptococcus pneumoniae* (PRSP) with an MIC_{90} of 2 mg/L (9). Currently, ceftobiprole is under regulatory review and is only approved in Canada and Switzerland. Two dosing regimens are recommended, 500 mg as a 2 hour i.v. infusion every 8 hours in cases with gram-positive and/or gram-negative infections including diabetic foot infections and 500 mg as a 1 hour i.v. infusion every 12 hours in cases of documented Gram-positive infections only excluding diabetic foot infections (11). This study focuses on the more general dosing regimen, i.e. the 2 hour 500 mg infusion every 8 hours, and references to the dosing interval refer to eight hours. This prolonged infusion time, 2 hours, was chosen in an attempt to prolong the time the concentration remains above the MIC.

Traditionally, plasma samples have been taken to determine the pharmacokinetic (PK) properties of a compound and make efficacy predications based on pharmacokinetic/pharmacodynamic relationships. However, these concentrations are sometimes presented as total concentrations while only the free drug is pharmacologically active (19, 26). Also, free concentrations at the site of action/infection are much more relevant to determine efficacy (15, 25) and exploring the concentration at the site of action has been recommended by regulatory agencies (1, 2, 8). One technique that has proven useful for the measurement of free drug concentrations in subcutaneous (s.c.) adipose tissue and skeletal muscle is microdialysis (6, 7, 10, 14, 16, 22).

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The aim of this study is to examine the penetration of ceftobiprole from plasma into s.c. adipose tissue and skeletal muscle using microdialysis and determine if efficacy breakpoints of relavent pathogens are met.

(This work was presented in part at the 48th Interscience Conference on Antimicrobial Agents and Chemotherapy, Washington, DC, 2008. [A. Barbour, B. Murthy, S. Schmidt, S. Sabarinath, D. Skee, H. Tian, D. Desai-Kreiger, D. Balis, M. Grant, C. Seubert, and H. Derendrof, Abstr 48th Intersci. Conf. Antimicrob. Agents Chemother].)

Materials and Methods

This study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Prior to study initiation approval was received from the local ethics committee, the Institutional Review Board (IRB) at UF/Shands. All volunteers were consented verbally and in writing prior to participation in the study and written consent was obtained.

Healthy Volunteers

This study included 15 healthy volunteers (9 males and 6 females) between the ages of 20 and 34. Health was determined based on physical examination, medical history, vital signs, 12-lead ECG, clinical laboratory tests (serum chemistry, hematology, and urinalysis), BMI, negative hepatitis B surface antigen, negative hepatitis C antibodies, negative human immunodeficiency antibodies, and normal renal function based on serum creatinine and the Cockcroft-Gault equation. Subjects also had a negative urine drug test and alcohol breath test at screening and admission and were nonsmokers. Females in the study had a negative pregnancy test at screening and admission and were postmenopausal, sterile, abstinent, or practicing an effective measure of birth control. Additionally, subjects did not use any other medication one week prior

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to the study drug administration until after the last blood draw with the exceptions of acetaminophen for pain, hormonal contraceptive medications, or hormonal replacement drugs.

Microdialysis

Microdialysis is a sampling technique which is based on simple diffusion of free analyte through the semipermeable membrane at the tip of a microdialysis probe. This technique has been explained in detail previously (23). Once in the ISF of the tissue of interest the flexible probe is continuously perfused with a physiological solution at a low flow rate by use of a syringe pump. The equilibrium between the probe and the tissue is incomplete and therefore the probes must be calibrated once in place, typically by retrodialysis (24). In this technique, a low concentration of the analyte is perfused through the microdialysis probe and the disappearance into the tissue is measured from the dialysate. This recovery value is later used to calculate the true tissue ISF concentration. The recovery value is calculated as recovery%=100-($C_{dialysate}/C_{perfusate}$ *100); where $C_{perfusate}$ is the analyte concentration following into the probe and $C_{dialysate}$ is the concentration of the analyte leaving the probe.

Study Design

Pilot Study

Pilot study subjects were admitted to the General Clinical Research Center (GCRC) at Shands Hospital the morning of the study and underwent only the calibration procedures. After the site of probe insertion was cleaned and disinfected, two microdialysis probes (CMA 60, CMA Microdialysis AB, Solna, Sweden) were implanted without anesthesia into the same thigh by a study physician, one into the skeletal muscle and one into the s.c. adipose tissue. The probes were perfused with lactated Ringer's solution for 30 minutes at a flow rate of 1.5 µL/min. The pilot study subjects then received ceftobiprole via the microdialysis probes at a

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concentration of 200 mg/L and a flow rate of 1.5 µL/min for 60 min. A sample was collected during the last 30 min to determine the individual recovery% values. The probes were then flushed with blank lactated Ringer's solution for three hours and samples were collected every 30 min.

Main Study

Subjects in the main study (6 male, 6 female) were admitted to the GCRC the evening before dosing. On the morning of dosing, two microdialysis probes were implanted and each was calibrated via retrodialysis as described above. After a four hour washout period, subjects received a single 666.7mg dose of ceftobiprole medocaril (Johnson & Johnson Pharmaceutical Research and Development, Raritan, NJ, USA), corresponding to 500 mg ceftobiprole, as a two hour i.v. infusion. The microdialysis probes were perfused with lactated Ringer's solution at a flow rate of 1.5 µl/min by a syringe pump from the start of the washout phase until after the 24 h sample was collected. Dialysate samples were collected in 20 min intervals from pre-dose through 12 hours after the start of the infusion and at 16 and 24 hours. Blood samples for PK determinations were collected at pre-dose, 40 min, 1 h, 1 h 40 min, 2 h, 2 h 20 min, 3 h, 4 h, 6 h, 8 h, 12 h, 16 h, and 24 h. Blood samples for protein binding determination were collected at 2 h and 12 h. Blood sampling occurred from the opposite arm that the drug was administered and K_2EDTA tubes were used for collection.

Analysis Methods

Sample Analysis-Microdialysis Samples

The dialysate samples were stored at -80ºC until analysis at the University of Florida, Department of Pharmaceutics (Gainesville, FL) using a validated HPLC-UV method. The limit of quantification (LOQ) for this method was 0.1 µg/mL. An Agilent 1100 series HPLC with an

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UV detector was used with a reverse phase column (Supelco C18 Discovery). The mobile phase consisted of water and acetonitrile (95:5). The flow rate was 1 mL/min. The injection volume was 20 μL and the detection wavelength was 300 nm. The true tissue ISF concentrations were calculated from the dialysate concentrations and adjusted with the recovery value. The calculation was as follows: $C_{ISFtissue}=100*C_{dialysate}*recovery\%^{-1}$.

Sample Analysis-Plasma Samples

Plasma samples were stored at -80ºC until shipment with dry ice to SFBC Analytical Laboratories, North Wales, PA. They were analyzed there using a validated LC/MS/MS method for ceftobiprole with K_2EDTA and citric acid. The LOQ was 0.050 μg/mL. A Perkin-Elmer 200 HPLC autosampler (4ºC) and pump were used. A gradient elution with two mobile phases (A-1:5:95 formic acid/methanol/water and B-1:50:50 formic acid/methanol/water) on a reverse phase column (Synergi 4μ Polar-RP, 50 x 2 mm) was used. The tandem mass spectrometer (PE Sciex API 4000 Series) with a turbo ionspray interface was set to monitor ceftobiprole at m/z 535-308 and m/z 539-312 for the internal standard (ceftobiprole-d4). Plasma samples were prepared by adding 50μL of sample to 50 μL of internal standard, mixing, then adding 200μL of 0.1% formic acid in acetonitrile and 300μL of 10% perchloric acid. The samples were then vortexed for one minute and centrifuged at 3000rpm for 15 minutes. Protein binding was determined by ultrafiltration.

Data Analysis

Total plasma concentrations were adjusted based on individual protein binding prior to PK analysis to determine the free plasma concentrations. PK analysis was performed using commercially available software (WinNonlin 5.2, Pharsight Corporation, Mountain View, CA, USA) by noncompartmental analysis. The $AUC_{0\text{-}last}$ was calculated using the linear trapezoidal

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rule. The $AUC_{0-\infty}$ was calculated as $AUC_{0-last} + C_{last}/\lambda_z$. The elimination rate constant, λ_z, was calculated using linear regression of the concentration-time data. The points chosen for calculation of λ_z were based on the best fit of the terminal phase and visual inspection. The AUCs were compared using Wilcoxon's matched paired tests. A two-sided $P<0.05$ was considered significant.

Results

The aim of this study was to assess the tissue penetration of ceftobiprole into skeletal muscle and subcutaneous adipose tissue. A pilot study was first conducted to test the feasibility of using microdialysis with ceftobiprole and to determine the washout period needed to ensure that no drug was remaining in the tissues and the microdialysis system at the time of dosing. The mean recovery values (±SD) in the pilot study were 64.1%±12.6 and 47.5%±3.3 for s.c. adipose and muscle tissue respectively. In the pilot study one probe malfunctioned after insertion and therefore the mean recovery value for the muscle is calculated from two samples. From the pilot study it was determined that the recovery was high enough to continue to the main study and a four-hour washout period should be allotted after calibration, prior to dosing.

The mean protein binding between all subjects was 21.7%±6.6. The mean recovery values in muscle and s.c. adipose tissue for the main study were 58.3%±5.1 and 59.4%±5.4, respectively, and the measured concentrations were adjusted accordingly. The mean concentration-time profiles for plasma, free plasma, muscle, and s.c. adipose tissue are presented in figure 1. The pharmacokinetic parameters are summarized in table 1. The mean $fAUC_{0-\infty}$ (±SD) ratios of tissue ISF compared to plasma were 0.69±0.13 and 0.49±0.28 for skeletal muscle and s.c. adipose tissue, respectively. The results show that there is a significant difference

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between the *f*AUC in plasma and the AUCs of both soft tissues. Additionally, the AUC of skeletal muscle is significantly higher than the AUC of s.c. adipose tissue.

Discussion

This study shows that ceftobiprole distributes into the interstitial space fluid (ISF) of s.c. adipose tissue, $AUC_{s.c.adipose}/fAUC_{plasma}$ 0.49±0.28, and skeletal muscle, $AUC_{muscle}/fAUC_{plasma}$ 0.69±0.13. The degree of tissue penetration with ceftobiprole correlates well other cephalosporins such as cepodoxime (14), cefixime (14), cefpirome (10, 22), and cefaclor (6) (table 2). There was a significant difference between the *f*AUC of plasma and the AUC of both tissues and between the AUC of muscle and the AUC of s.c. adipose tissue. The differences in penetration ratios can be due to several factors including the perfusion of the particular tissue, local capillary density (6), the degree of tissue binding, the possibility of active transporters (7), loss of drug from the peripheral compartments (13), and physiochemical properties of the compound (7), such as lipophilicity. Therefore, it is important to measure the free, active drug in each tissue and not make the assumption that free plasma levels equal free tissue levels, even in well perfused tissues.

The pharmacokinetics determined in this study are in good agreement with previously summarized results (17). The half-life, clearance, C_{max}, and AUC of 2.61 hr, 5.15 L/hr, 25.8 mg/L, and 98.0 mg/L*hr, respectively, were all within one standard deviation of the previously reported parameters with the same dosing regimen (17, 18). The V_{ss} of 14.6 L is lower in this study than the reported value of 21.7 L for a single dose. However, it is in agreement with the multiple dose V_{ss} of 15.5 L. The volume of distribution suggests that this compound distributes to the ISF which is common with this antibiotic class. This property is advantageous because the ISF is often the location of infectious pathogens.

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The major advantage to the microdialysis technique is the ability to measure the free drug at the site of action, usually the ISF of soft tissues in regards to skin and skin structure infections. It is this concentration that should be used to measure if efficacy breakpoints are met. For β-lactams the time the free concentration remains above the minimum inhibitory concentration ($fT_{>MIC}$) is thought to predict efficacy. It has been shown in neutropenic animals that efficacy is established if the concentration remains above the MIC for at least 40-50% of the dosing interval (3-5), i.e. 3.2-4 h of an 8 h dosing interval. The MIC_{90} for ceftobiprole to MRSA (12) and PRSP (9) has been reported as 2 mg/L. The concentrations in the ISF of both skeletal muscle and s.c. adipose tissue remained above 2 mg/L for at least 50% of the dosing interval and, therefore, this dosing regimen should be efficacious with these subcutaneous soft tissue pathogens. Also, sufficient concentrations are achieved to meet the efficacy breakpoint in organisms with an MIC_{90} of 4 mg/L in skeletal muscle, 53.6%±9.62 $\%fT_{>MIC}$. In s.c. adipose tissue the time the concentration remains above the MIC is close to 40% of an 8 h dosing interval, 35.1%±22.2 $\%fT_{>MIC}$, and it has been suggested that the time free concentration needs to remain above the MIC is less than 40% for *Staphylococcus aureus* and *Streptococcus pneumoniae* (5). It is important to remember that further studies should be conducted in patients to see the relationship between the host response, free ceftobiprole concentration at the site of action, and clinical outcome. Additionally, ceftobiprole has demonstrated similar clinical cure rates compared to vancomycin in Gram-positive complicated skin and skin structure infections and vancomycin plus ceftazidime in both Gram-positive and Gram-negative complicated skin and skin structure infections in large-scale pivotal studies (20, 21). This study demonstrates that ceftobiprole distributes into the ISF of soft tissues in healthy volunteers. This finding and ceftobprole's wide-range of activity make it a promising new single agent for the treatment of complicated skin and

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skin structure infections.

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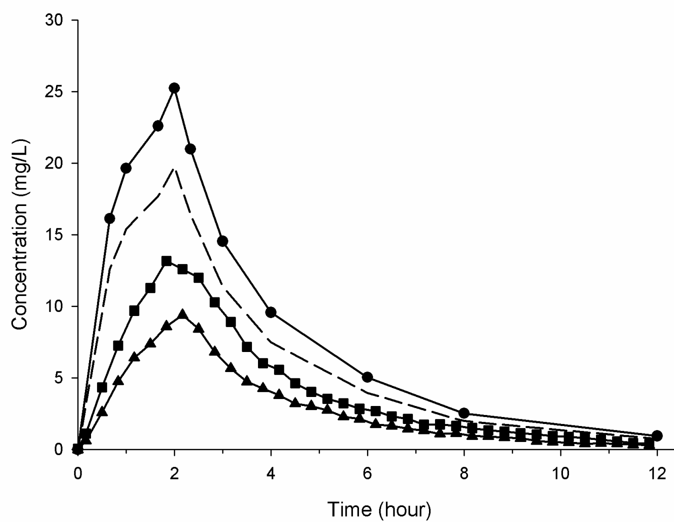

Figure 1: Mean ceftobiprole concentration in plasma (circles), skeletal muscle (squares), and s.c. adipose tissue (triangles) over twelve hours. Free plasma concentration (dashed line) was calculated based on the plasma protein binding of each individual patient.

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Table 1: Noncompartmental Pharmacokinetic Analysis. Values are mean±standard deviation.				
PK parameter	Plasma (total)	Plasma (free)	S.C. Adipose	Muscle
C_{max} (mg/L)	25.8±2.96	20.2±2.63	9.61±4.74	14.0±3.22
T_{max} (mg/L)	1.92±0.15	ND	2.25±0.21	2.25±0.14
$t_{1/2}$ (hr)	2.61±0.33	ND	2.56±0.39	2.61±0.52
$AUC_{0\text{-last}}$ (hr*mg/L)	97.1±10.3	76.0±8.81	34.3±19.0	50.6±10.9
$AUC_{0\text{-}\infty}$ (hr*mg/L)	98.0±10.5	76.9±8.94	36.5±19.4	53.2±11.5
CL (L/hr)	5.15±0.53	ND	ND	ND
V_z (L)	19.4±3.61	ND	ND	ND
V_{ss} (L)	14.6±2.17	ND	ND	ND
$AUC_{ISF}/fAUC_{plasma}$	-	-	0.49±0.28	0.69±0.13

ND: Not Determined

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Table 2: Soft tissue penetration of four cephalosporins determined by microdialysis

	Cefpodoxime[a]	Cefixime[a]	Cefpirome[b]	Cefpirome[c]	Cefpirome[d]	Cefaclor[e]	Cefaclor[f]	Cefaclor[g]
AUC_{plasma}	22.4	25.6	-	-	-	17.6	13.7	22.1
$fAUC_{plasma}$	17.7	9.0	275.0	230.7	175.0	13.2	10.3	16.6
$fAUC_{muscle}$	15.4	7.3	-	130.0	80.0	9.49	7.02	11.53
$fAUC_{s.c.adipose}$	-	-	218.5	117.0	87.2	-	-	-
$fAUC_{muscle}$/ $fAUC_{plasma}$	0.89	0.84	-	0.56	0.46	0.73	0.67	0.70
$fAUC_{s.c.adipose}$/ $fAUC_{plasma}$	-	-	0.79	0.51	0.50	-	-	-

All AUCs are in mg/L*hr. Data presented as mean values from each study.
a. Dosed orally 400 mg. $AUC_{0-\infty}$ presented. fAUC calculated based on protein binding.(14)
b. Dosed i.v. over 15 minutes 2 g. AUC_{0-4} presented. Data from healthy volunteers only.(22)
c. Dosed i.v. over 10 minutes 2g. AUC_{0-8} presented.(10)
d. Dosed i.v. over 12 hours 2g (only 10 hours observed). AUC_{0-8} presented.(10)
e. Dosed orally 500mg IR. $AUC_{0-\infty}$ presented. fAUC calculated based on protein binding.(6)
f. Dosed orally 500mg MR. $AUC_{0-\infty}$ presented. fAUC calculated based on protein binding.(6)
g. Dosed orally 750mg MR. $AUC_{0-\infty}$ presented. fAUC calculated based on protein binding.(6)

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