Cefpodoxime Concentrations in Human Serum and Oral Tissues Following a Single Oral Administration of Cefpodoxime Proxetil

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Abstract
Cefpodoxime proxetil, an ester prodrug of cefpodoxime, is an oral third-generation cephalosporin antibiotic that is used for the treatment of odontogenic infections such as periodontitis, pericoronitis, and osteitis of jaw. However, there are only a few studies on cephalosporin concentrations in human oral tissues. The present study therefore was undertaken to determine cefpodoxime concentrations in human oral tissues following oral administration of cefpodoxime proxetil. Cefpodoxime concentrations in human serum, gingiva, mandibular bone, and dental follicle following a single oral administration of 200-mg cefpodoxime proxetil were measured by a paper disk method. The mean peak concentrations in serum, gingiva, mandibular bone, and dental follicle occurred at the same time point, 3 hours post-dose, and were 3.07 ± 0.96 μg/mL, 1.16 ± 0.35 μg/g, 0.60 ± 0.27 μg/g, and 1.13 ± 0.34 μg/g, respectively. Mean cefpodoxime concentration ratios of gingiva/serum, mandibular bone/serum, and dental follicle/serum at the peak time were 0.40 ± 0.15, 0.20 ± 0.05, and 0.37 ± 0.03, respectively. Mean concentrations in gingiva, mandibular bone, and dental follicle at the peak time exceeded the minimum inhibitory concentration for 80% of clinically isolated strains of oral streptococci. Therefore, cefpodoxime proxetil may be a valuable antimicrobial agent for the treatment of odontogenic infection.

Introduction
Cefpodoxime proxetil, an oral third-generation cephalosporin antibiotic, is used for the treatment of odontogenic infections such as periodontitis, pericoronitis, and osteitis of jaw. The compound is a pro-drug that is cleaved by nonspecific carboxyl esterase activities in the intestinal epithelium to yield the active moiety, cefpodoxime (1). Cefpodoxime exerts antibacterial activity by binding to penicillin-binding proteins (notably PBP1 and PBP3) and inhibiting bacterial cell wall synthesis (2, 3). Cefpodoxime is highly resistant to hydrolysis by the β-lactamases produced by various species of bacteria, providing the drug with a broad spectrum of in vitro activity against many common gram-positive and gram-negative bacteria such as Staphylococcus aureus, streptococci, Escherichia coli, Klebsiella pneumoniae, Klebsiella oxytoca, Providencia rettgeri, and Haemophilus influenzae (4-8).

Cefpodoxime proxetil is well tolerated and has safety and side-effects profiles that are similar to other third-generation cephalosporins (9). The pro-drug shows a good absorption profile, with an absolute bioavailability of cefpodoxime of approximately 50% following oral administration of a 100-mg cefpodoxime proxetil tablet (10). The larger mean value for peak concentration of cefpodoxime was determined from subjects receiving any meals compared to fasted subjects, and the mean peak time of cefpodoxime from subjects receiving any meals was longer.

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than that from fasted subjects. Thus, subjects in the fasting state had lower estimate of area under the plasma cefpodoxime concentration–time curve (AUC) relative to the AUC estimate from the subjects receiving any meals. Higher plasma levels were produced when cefpodoxime proxetil was taken with food or when a low gastric pH was present (11-13).

Previous studies have reported cephalosporin concentrations in human oral tissues and discussed penetration of the drug into oral tissue (14–19). However, limited information is available regarding cefpodoxime concentrations in human oral tissues following a single oral administration of cefpodoxime proxetil (20). Therefore, the present study was undertaken to determine cefpodoxime concentrations in human serum, gingiva, mandibular bone, and dental follicle following a single oral administration of cefpodoxime proxetil for appropriate medication to odontogenic infection.

Materials and Methods

Patients

Thirty-eight patients (16 women, 22 men) who underwent the extraction of impacted mandibular third molars were studied. The mean age was 30.1 years (range, 21 to 42 years), and the mean weight was 64.4 kg (range, 46 to 94 kg). All operations were performed under block anesthesia using 2% lidocaine with 1:80,000 adrenaline (Xylocaine®, DENTSPLY International Inc., Tokyo, Japan). For all subjects, surgical sites lacked clinical signs of acute inflammation, and none of the subjects had received antimicrobial therapy for at least 3 weeks prior to the operation. The protocol was approved by the Committee on Studies Involving Human Beings of the Nihon University School of Dentistry at Matsudo (EC 04–029). Each patient gave written informed consent for the use of their specimen.

Administration of cefpodoxime proxetil, sampling procedure, and preparation of analytical samples

One to 2 hours after meals, each patient was given a single preoperative oral dose of cefpodoxime proxetil 200 mg (two 100-mg tablets of BANAN®, Daichí Sankyo Co Ltd, Tokyo, Japan) with 200 mL of water. Surgery to remove the indicated teeth and to obtain the surgical specimens was done at 1, 1.5, 2, 2.5, 3, 3.5, or 4 hours following administration of cefpodoxime proxetil. A sample of blood (approximately 3 mL) was taken from the antecubital vein of each patient at the time of surgery. Since the tissue specimens and blood sample could not be collected at the same time, there was generally a lag of about 5 minutes. At collection, the specimens of gingiva, mandibular bone, and dental follicle were agitation for approximately 3 seconds in sterile physiological saline to wash away blood, and then weighed. Three to 4 parts of 1% phosphate buffer (pH 6.0) were added and the mixture was homogenized using a glass micro-homogenizer in an ice bath. The resulting homogenate was stored at 4°C for 18 hours to extract the cefpodoxime. The mixture then was centrifuged at 1,500 g for 15 minutes at 4°C. The resulting supernatant and serum obtained by centrifugation were further diluted with 1% phosphate buffer (pH 6.0) in an appropriate manner for assay purposes.

Statistical analysis

All data were expressed as the mean ± SD. Statistical analysis was made by using One-Way ANOVA with the Bonferroni post-hoc test to determine the significance level of the difference between mean values. P values of <0.05 were considered statistically significant.

Results

Serum

The distribution of cefpodoxime concentrations in serum is shown in Fig. 1. Cefpodoxime concentrations in serum (n=38), sampled 1 to 4 hours after administration of cefpodoxime proxetil, ranged from below the lower limit of detection (not detectable, N.D. (1 hour, n=1)) to 4.76 μg/mL. The mean peak serum concentration of cefpodoxime, which occurred at 3 hours, was 3.07 ± 0.96 μg/mL. The mean cefpodoxime
concentrations in serum and in the corresponding oral tissues are summarized in Fig. 5. Cefpodoxime concentrations in serum at 1.5 to 4 hours post-dose were significantly higher than those in oral tissues at the respective time points ($P < 0.001$).

**Gingiva**

The distribution of cefpodoxime concentrations in gingiva is shown in Fig. 2. Cefpodoxime concentrations in gingiva ($n = 38$) ranged from N.D. (1 hour, $n = 1$) to 1.89 $\mu$g/g. The mean cefpodoxime concentrations in gingiva and in the corresponding serum are summarized in Fig. 5. The mean peak concentrations in gingiva and serum occurred at the same time point, 3 hours after administration, and were $1.16 \pm 0.35 \mu$g/g and $3.07 \pm 0.96 \mu$g/mL, respectively. The mean ratio of the gingival cefpodoxime concentration to the corresponding serum cefpodoxime concentration at the peak time was $0.40 \pm 0.15$ and ranged (excepting the N.D. value) from 0.16 to 0.86.

**Mandibular bone**

The distribution of cefpodoxime concentrations in mandibular bone is shown in Fig. 3. Cefpodoxime concentrations in mandibular bone ($n = 38$) ranged from N.D. (1 hour, $n = 1$) to 1.13 $\mu$g/g. The mean cefpodoxime concentrations in mandibular bone and in the corresponding serum are summarized in Fig. 5. The mean peak concentrations in mandibular bone and serum occurred at the same time points, 3 hours after administration, and were $0.60 \pm 0.27 \mu$g/g and $3.07 \pm 0.96 \mu$g/mL, respectively. The mean ratio of the mandibular bone cefpodoxime concentration to the corresponding serum cefpodoxime concentration at the peak time was $0.20 \pm 0.05$ and ranged (excepting the N.D. value) from 0.08 to 0.62.
Dental follicle

The distribution of cefpodoxime concentrations in dental follicle is shown in Fig. 4. Cefpodoxime concentrations in dental follicle (n=38) ranged from N.D. (1 hour, n=1) to 1.74 μg/g. The mean cefpodoxime concentrations in dental follicle and in the corresponding serum are summarized in Fig. 5. The mean peak concentrations in dental follicle and serum occurred at the same time points, 3 hours after administration, and were 1.13 ± 0.34 μg/g and 3.07 ± 0.96 μg/mL, respectively. The mean ratio of the dental follicle cefpodoxime concentration to the corresponding serum cefpodoxime concentration at the peak time was 0.37 ± 0.03 and ranged (excepting the N.D. value) from 0.14 to 0.89.

Discussion

Several studies have assessed cefpodoxime concentrations in serum following a single oral dose of 200mg of cefpodoxime proxetil in fasted subjects, with reported values ranging from 2.24 to 2.62 μg/mL at the peak concentration time (2.25 to 2.75 hours) (9-12). Additionally, the pharmacokinetic parameters of cefpodoxime have been shown to be influenced by the contents of the gastrointestinal tract following a single oral administration of cefpodoxime proxetil (11-13). Cefpodoxime concentrations in serum following a single oral dose of 200mg of cefpodoxime proxetil ranged from 2.57 to 3.11 μg/mL at the peak concentration time (3.25 to 3.32 hours) in the non–fasting state (11, 12). In the present study, the mean peak serum concentration of cefpodoxime was 3.07 ± 0.96 μg/mL and occurred at 3 hours after dosing with cefpodoxime proxetil.

Thus, our results yielded values similar to those previously reported for non–fasting subjects. Our study examined non–fasted outpatients, treated in general practice dentistry, who were administered cefpodoxime proxetil in combination with 200 ml of water at 1–2 hours after meals. It is difficult to control accurately the conditions under which patients take medicine. However, under conditions of administration in the present study, serum cefpodoxime levels were sufficient for exerting antibacterial activity. Although these were the only conditions that we were able to control, the results were applicable to clinical practice.

Ratios of mean peak concentrations in oral tissue / serum are summarized for seven cephalosporins in Table 1 (14-19). For a given tissue, the ratios were highly similar among the various compounds, yielding values of 0.39 to 0.54 for gingiva / serum, 0.16 to 0.21 for mandibular bone / serum, and 0.32 to 0.41 for dental follicle / serum. Mean cefpodoxime concentration ratios in gingiva / serum at the peak time were slightly lower than those of other cephalosporins. However, mean cefpodoxime concentration ratios in mandibular bone / serum and dental follicle / serum were similar to those of other cephalosporins in the respective tissues.
Our study revealed that cefpodoxime concentrations in serum at 1.5 to 4 hours were significantly higher than those in gingiva, mandibular bone, and dental follicle. However, cefpodoxime concentrations did not differ significantly among gingiva, mandibular bone, and dental follicle. These results suggest that cefpodoxime shows a similar distribution to gingiva, mandibular bone, and dental follicle. The minimum inhibitory concentration of cefpodoxime for 80% (MIC₈₀) of clinically isolated strains of oral streptococci is 0.39 μg/mL (8). Thus, in our study, the mean peak concentrations of cefpodoxime in gingiva, mandibular bone, and dental follicles following a single oral administration of 200-mg cefpodoxime proxetil exceeded this MIC₈₀. These results suggest that cefpodoxime proxetil may be a valuable antimicrobial agent for the treatment of odontogenic infection. However, in several subjects the cefpodoxime concentrations in gingiva (4 out of 38 cases) at 1 hour, in dental follicles (3 out of 38 cases) at 1 hour, and in mandibular bone (9 out of 38 cases) at 1 to 2 hours after administration did not exceed the MIC₈₀. Therefore, prophylactic single oral administration of cefpodoxime proxetil should be performed more than two hours before surgery.

In conclusion, we assessed cefpodoxime concentrations in human serum, gingiva, mandibular bone, and dental follicle following a single oral administration of cefpodoxime proxetil. Notably, a single oral administration of 200-mg cefpodoxime proxetil yielded cefpodoxime concentrations in gingiva, mandibular bone, and dental follicles that exceeded the MIC₈₀ of clinically isolated strains of oral streptococci. These results suggest that cefpodoxime proxetil may be a valuable antimicrobial agent for the treatment of odontogenic infection.

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