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CASE REPORT

Relationship between the clinical efficacy and AUC/MIC of intravenous ciprofloxacin in Japanese patients with intraabdominal infections

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Abstract The efficacy of fluoroquinolones (FQs) correlates with the pharmacokinetic/pharmacodynamic (PK–PD) parameter, AUC/MIC. To our knowledge, however, no prospective studies have reported the relationship between FQ efficacy and PK–PD parameters in intraabdominal infection; therefore, we prospectively investigated the relationship between the efficacy of intravenous ciprofloxacin (CPFX IV) and PK–PD parameters. The study included 16 patients diagnosed with peritonitis between 2006 and 2008: 14 patients infected with a single organism and 2 patients infected with more than one organism. Each patient was treated with CPFX IV (300 mg twice daily). The response rate was 56 % (9 responders and 7 non-responders). Non-responders were infected with *Escherichia coli*, *Pseudomonas aeruginosa*, and *Bacteroides fragilis* (6 patients were infected with a single organism and 1 with more than one organism). Plasma drug concentrations were measured 1 h and 2 or 4 h after administration of CPFX IV. AUC for 24 h (AUC_{0-24})/MIC values was calculated. The range of AUC_{0-24}/MIC values in responders [95.3–3628.4 (geometric mean, 521.6)] was significantly different from that in non-responders [7.0–45.2 (geometric mean, 16.5)] ($p = 0.001$). The target AUC/MIC value of CPFX IV would be considered to be 45–95 in patients with peritonitis.

Keywords Ciprofloxacin · Intraabdominal infection · Pharmacokinetic/pharmacodynamic parameter

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Introduction

Many antimicrobial agents are presently used to treat a variety of bacterial infections. Bacteriological and clinical analyses based on pharmacokinetic/pharmacodynamic (PK–PD) parameters are used to determine the drug dose needed to optimize clinical efficacy. Fluoroquinolones (FQs) are antimicrobial agents with plasma concentration-dependent clinical effects. A number of studies have reported that the area under the plasma concentration-versus-time curve/minimum inhibitory concentration (AUC/MIC) ratio was predictive of the fluoroquinolone outcome [1–3]. Forrest et al. [1] investigated the clinical effect of intravenous ciprofloxacin (CPFX IV) in seriously ill patients, such as lower respiratory tract infections, and reported that a CPFX IV AUC/MIC ratio of 125 or more was effective in at least 80 % of patients. For this reason, this value was considered to be the target value required to achieve the maximum efficacy of FQs; however, subsequent studies have revealed that the target value varied among FQs and depended on the causative organisms. Some studies have reported that the target AUC/MIC ratio was lower in the treatment of gram-positive infections such as *Streptococcus pneumoniae* than in gram-negative infections [2, 4]. Craig [5] reported that the AUC/MIC ratio was 25–35 for pneumococci and 100–125 for gram-negative bacteria and staphylococci; however, the approved dose of CPFX IV in Japan differs from that in other countries. This difference may be an obstacle to the achievement of target values such as those reported in other countries. There have been a few reports on investigations of PK–PD parameters of CPFX IV in Japanese. Matsuo et al. [6] stressed the need for revalidation of the target value reported by Forrest et al. [1] because the mean AUC/MIC in Japanese patients with pneumonia who responded

to CPFX IV (300 mg twice daily) was 87.8; however, no prospective study of CPFX IV for the treatment of intra-abdominal infection has been reported.

Therefore, our objective was to investigate the relationship between the clinical efficacy and AUC/MIC of CPFX IV (300 mg twice daily, the approved dose in Japanese) in patients with intraabdominal infection.

Case report

Sixteen patients were admitted to Gifu University Hospital from January 2006 to May 2008 for the treatment of primary or secondary intraabdominal infections of mild to moderate severity; some of these patients required surgical intervention. This study was approved by the IRB. Before the study, voluntary written informed consent to participate in the study was obtained from each patient (or his/her representative) after the objectives and methods of the study and potential benefits and risks had been fully explained using an information document.

Intravenous ciprofloxacin (CPFX IV) was administered via intravenous infusion for 1 h at a dose of 300 mg twice daily for 7 days; this regimen corresponded to the approved dose in Japan. All the patients were given no antimicrobial agent other than CPFX IV during the study.

Causative organisms were isolated from ascites fluid and identified before treatment with CPFX IV. Susceptibility to CPFX was measured for each isolate by microdilution in Mueller–Hinton broth (Difco) supplemented with Ca^{2+} (20 mg/l) and Mg^{2+} (25 mg/l) according to the Standard Method of the Japan Society of Chemotherapy [7]. MICs were measured after incubation for 18–20 h at 37 °C with a bacterial inoculum of 10^4 colony-forming units (CFU)/ml [7].

Blood samples were collected from all patients 1 h (after administration) and about 2 or 4 h after the fifth dose of CPFX IV. Plasma was separated from blood by centrifugation, and the plasma-free, protein-unbonded drug concentration was measured by a bioassay using *Escherichia coli* Kp as the test organism [8]. The calibration curve of ciprofloxacin was utilized from the study with the same bioassay method of ciprofloxacin concentration in our study (concentration range, 0.025–1.6 μg/ml, $r > 0.99$; detectable lower limit, 0.02 μg/ml) [8].

Clinical response was evaluated as either "good response" or "no response" on the basis of improvement of the general condition, clinical manifestations, and test data during the 7 days after the first administration of CPFX IV.

With the obtained plasma concentration, individual pharmacokinetic parameters were estimated by the empirical Bayes approach using NONMEM (version 7.1.2) [9], and the individual plasma concentration profile was calculated. A two-compartment linear model with elimination from the central compartment (ADVAN3 TRAN4) was used. Population pharmacokinetic parameters were utilized from the mean on day 7 in a Japanese phase I study, in which 300 mg CPFX was administrated via intravenous infusion over 1 h twice daily for 7 days [10]. Each population mean parameter was configured as 34.6 l/h for clearance (CL), 19.8 l for volume of the central compartment (V1), 82.1 l for peripheral volume of distribution (V2), and 72.9 l/h for intercompartmental clearance (Q), respectively. The equations for the estimation of population mean parameter were as follows: $V2 = Vdss - Vc = 101.9 - 19.8 = 82.1$ (L). $Q = k_{21} * V2 = 0.8875 * 82.1 = 72.9$ (L) and $K_{21} = \alpha * \beta * AUC_{0-\infty} / (A + B) = \alpha * \beta * AUC_{0-\infty} / (Dose/Vc) = 5.99 * 0.25 * 8.98 / (300/19.8) = 0.8875$, respectively.

The interindividual variabilities of V2 and Q were configured to be 0, and the intraindividual variability was configured to be 0. With those parameters fixed, observed sparse plasma concentration data were applied to NONMEM, and the interindividual variabilities of CL and V1 were estimated as 27.9 and 37.0 %, respectively.

From the limited number of plasma concentrations, individual AUCs were calculated with the noncompartment analysis method using PHOSTOC estimate [8] of individual plasma CPFX concentrations from 0 to 24 h every 0.5 h derived from the CPFX population pharmacokinetic model and individual observations of plasma CPFX concentration.

The PK–PD parameters AUC_{0-24}/MIC were employed as predictors of the likelihood of clinical and microbiological response.

In this study, 16 patients with peritonitis were enrolled; 8 patients were male, 8 were female, and the mean age was 60.3 years (range, 46–72). No patient had particularly abnormal renal function (serum creatinine level before CPFX IV administration, 0.35–1.13 mg/dl) and had other antimicrobial agents concomitantly. For all patients, the causative organism was identified in ascites fluid as a gram-negative organism. Fourteen patients were infected with a single organism: 4 with *E. coli*, 1 with *Klebsiella pneumoniae*, 1 with *Citrobacter freundii*, 1 with *Enterobacter cloacae*, and 7 with *Pseudomonas aeruginosa*. Two patients were infected with more than one organism: 1 with *P. aeruginosa* and *Bacteroides fragilis*, and 1 with *E. coli* and *P. aeruginosa* (Table 1).

Susceptibility (MIC) to CPFX was 0.008–4 mg/l for *E. coli* (5 strains), 0.016 mg/l for *K. pneumoniae*, 0.03 mg/l for *C. freundii*, 0.06 mg/l for *E. cloacae*, 0.004–2 mg/l for *P. aeruginosa* (9 strains), and 12.5 mg/l for *B. fragilis* (Table 1).

Evaluation of the clinical response over 7 (±2) days after the administration of CPFX IV revealed that 9