A Pharmacokinetic and Pharmacodynamic Study on Intravenous Cefazedone Sodium in Patients with Community-acquired Pneumonia

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Abstract

Background: As a time-dependent antibiotic, the time of cefazedone concentration exceeds the minimum inhibitory concentration (MIC) is the key pharmacokinetic-pharmacodynamic (PK-PD) variable associated with the killing of pathogens. The purpose of the study was to evaluate the clinical regimen rationality of intravenous cefazedone sodium in the treatment of community-acquired pneumonia (CAP) by PK/PD study.

Methods: Ten patients with mild to moderate CAP were enrolled to receive intravenous cefazedone sodium (2 g q12 h) for 7–14 days. Blood samples were collected in any day during day 5–7. Sputum specimens were collected before treatment for bacteria isolated, and susceptibility to cefazedone determined. PK-PD analysis was performed using the noncompartmental analysis of Phoenix WinNolin software (version 6.1, Pharsight Corporation, CA, USA). The maximal time above MIC (ƒT > MIC) was calculated, and its correlation with clinical efficacy was analyzed.

Results: All 10 patients completed the study and 8 of them were cured. Six strains were isolated from patients before treatment (one for each patient) and all susceptible to cefazedone. Five patients of six in culture positive group were cured. All pathogens were cleared at the end of therapy. The MICs were between 0.25 and 1 mg/L. The main PK parameters were Cmax = 175.22 ± 36.28 mg/L; T1/2 = 1.52 ± 0.23 h; AUC(0–∞) = 280.51 ± 68.17 mg·L⁻¹·h⁻¹; CL 7.37 ± 1.84 L/h; Vd 16.06 ± 4.42 L. The average ƒT > MIC was 55.45 ± 8.12%.

Conclusions: Intravenous injection of cefazedone sodium with 2 g q12 h dosage regimen is used in the treatment of CAP caused by sensitive bacteria, either ƒT > MIC or clinical efficacy shows that such dosing regimen is reasonable.

Key words: Cefazedone; Community-acquired Pneumonia; Pharmacodynamic; Pharmacokinetic

Introduction

Cefazedone, a first-generation cephalosporin with activity against Gram-positive and Gram-negative bacteria,[1-3] has been shown to be effective in the treatment of infections caused by sensitive bacteria.[4-7] As a time-dependent antibiotic, the time of cefazedone concentration exceeds the minimum inhibitory concentration (MIC) is the key pharmacokinetic-pharmacodynamic (PK-PD) variable associated with the killing of pathogens. The purpose of the study was to evaluate the clinical regimen rationality of intravenous cefazedone sodium in the treatment of mild to moderate community-acquired pneumonia (CAP) by PK/PD study.

Methods

Study design

This is an open-label, noncontrolled clinical study approved by the Independent Ethics Committee of Beijing University First Hospital. All subjects provided written informed consent. Studies were conducted in accordance with the guidelines for Good Clinical Practices and the ethical principles of the Declaration of Helsinki.

Patients

Ten patients aged between 18 and 70 years, were enrolled in this study. All subjects met the criteria of mild or moderate CAP according to the Guide for Diagnosis and Treatment of Community-acquired Pneumonia in Adults issued by the Chinese Medical Association Respiratory branch. The exclusion criteria included subjects who were:
Pregnancy, nursing women; allergic to test drug; with severe life-threatening diseases, such as severe heart, lung, liver, kidney dysfunction; leucopenia; presence of an infection or a complication that required nonstudy systemic antibacterial therapy, *et al.* Or researchers believed that the patients were not eligible into the study.

**Drug administration**

Cefazedone was administered at a dosage of 2 g every 12 h via a 30 min intravenous infusion for 7–14 days. Unless medical needs, any other drugs should be avoided.

**Clinical and microbiological assessment**

Clinical assessments, including the symptoms and signs, were performed throughout the medication period. Laboratory assessments, including routine hematology, chemistry and urinalysis profiles, electrocardiogram, chest X-ray, and cultures of expectorated sputum were performed at the time of enrollment and 1 day after the completion of the therapy. The patients with a cured or failed clinical outcome were followed-up on 7–14 days after the treatment for microbiological and efficacy assessments.

Sputum specimens were obtained, and bacterial cultures were done prior to the initial treatment and on the day after the completion of the therapy. Susceptibility of clinical isolates to cefazedone was determined using Kirby-Bauer disc diffusion method (for susceptibility determination of cefazedone) at the beginning of treatment, and only patient infected by sensitive strains were eligible, and the broth dilution method (for minimum inhibitory assay and PK/PD analysis) after the end of all study. Microbiological susceptibility was determined according to the CLSI 2009 guidelines.

The clinical efficacy, bacteriological efficacy were evaluated based on “Antibacterial Clinical Trials Technical Guidelines” issued by CDE of CFDA in March 2007.

Cure was defined as resolution of the clinical signs and symptoms and laboratory tests of infection with no further need for antibiotic therapy at the termination of treatment. Criteria for failure included at least one abnormality remained at the termination of treatment; clinical manifestations remained or aggravated after 72 h of treatment.

Bacteriological response was evaluated as follows: Eradication, assumed eradication, partial or no eradication, superinfection or re-infection.

**Blood sample detection and method validation**

Blood samples were taken predose and at 0.5, 1, 2, 4, 6, and 8 h postdose in any day during day 5–7 of treatment. The drug concentrations were determined using high-performance liquid chromatography (HPLC) method.

Briefly, the HPLC system (Shimadzu Prominence UFLC Chromatographic Analyzer, Shimadzu, Japan) consisted of two LC-20ADXR 501 pumps, an SIL-20ACXR Plus Autosampler and an SPD-20A ultraviolet detector operated at 278 nm. The stationary phase was an Alltima C18 column (150 mm × 4.6 mm, 5 μm, Alltech, USA), the mobile phase used was acetonitrile/0.020 mol/L potassium dihydrogen phosphate (13:87, v/v) at a flow rate of 1.0 ml/min. After 50 μl of the internal standard solution was added, 200 μl plasma samples were precipitated with 300 μl of acetonitrile, vortexed and centrifuged at 12,000 r/min for 5 min, the supernatant, after concentrated with dichloromethane, was analyzed with UFLC.

Prior to the analysis of cefazedone in human plasma, the analytical method was fully validated for its specificity, linearity, recovery, intra- and inter-run precisions, and stability in the analytical conditions. The results showed cefazedone was not interfered with endogenous substances in plasma and internal standard [Figure 1], the method was linear over the range of 0.53–385.1 μg/ml, and the low limit of quantitation was 0.53 μg/ml. The intra- and inter-run coefficients of variation for the three quality control standards were <10.2%, the absolute recoveries were >82.0%.

**Pharmacokinetic and pharmacodynamic analysis**

Pharmacokinetic parameters, including maximum observed serum concentration ($C_{\text{max}}$), area under the concentration-time curve with extrapolation to infinity after a single dose ($\text{AUC}_{0-\infty}$), clearance (CL), volume

![Figure 1: (a) Blank plasma chromatogram and (b) human plasma sample chromatogram.](image_url)
of distribution (V), terminal half-life (t₁/₂), and renal clearance (CLR) were calculated by noncompartmental analysis using Phoenix WinNonlin (version 6.1, Pharsight Corporation, CA, USA).

Pharmacodynamic parameters (T > MIC) were calculated by the formula as following: $fT > MIC\% = \ln\left(\frac{[Dose \times f]}{[V_o \times MIC]}\right) \times \left(t_1/2 / 0.693\right) \times (100/DI)$.\[8\]

The PK/PD correlation analysis between $fT > MIC$ and clinical efficacy will be conducted.

**Results**

**Subjects**

Ten patients with mild to moderate CAP were enrolled in this study. All subjects completed the trials as planned. The demographic details are presented in Table 1.

**Concentrations of cefazedone in serum**

The mean serum concentration-time curve was calculated following intravenous administration 2.0 g q12 h of cefazedone [Figure 2].

**Noncompartmental pharmacokinetic analysis**

Pharmacokinetic parameters were calculated using the noncompartmental method as follows: The $C_{max}$ was obtained directly from the concentration-time data. The $C_{max}$ for individuals ranged from 117.25 to 239.04 mg/L. The $t_{1/2}$, AUC₀–∞, V, and CL were 1.52 h (range, 1.28–2.02 h), 280.51 mg·L⁻¹·h⁻¹ (range, 172.81–431.20 mg·L⁻¹·h⁻¹), 16.06 L (range, 12.32–25.51 L) and 7.37 L/h (range, 4.31–11.37 L/h), respectively. The PK parameters are summarized in Table 2.

**Clinical and microbiologic responds**

In 10 patients with CAP, 8 cases were cured, and 2 cases were failure after receiving injections of cefazedone sodium. Among all patients, 6 cases were culture positive before treatment and cured after treatment. All the pathogens were eradicated or presumed eradicated. Details are shown in Table 3.

**In-vitro drug susceptibility assay**

Minimum inhibitory concentration assays were conducted for all isolates. The results are shown in Table 4.

**Pharmacokinetic and pharmacodynamic parameters**

It was reported that cefazedone sodium presents high serum protein binding rate (93–96%), therefore, the free drug concentration in the blood plasma would be 4–7% of the actual measurement. In this study, 5% of actual measurement drug concentration as free drug concentration ($f$) was applied for calculating $fT > MIC$.

The calculation of $fT > MIC$ was based on the PK parameters of six patients (bacterial culture positive), the free drug ratio ($f$), the MIC results of clinical isolates and dose regimen of cefazedone. The results are shown in Table 4 and Figure 3.

**Discussion**

This is a PK/PD study of cefazedone in CAP patients. As a cephalosporin antibiotic, cefazedone belongs to a time-dependent antibiotic. Time above MIC of free drug concentrations ($fT > MIC$) is an important PK-PD parameter for evaluating the rationality of dose regimens.\[9\] In most study, the PK/PD studies were completed in healthy volunteers. As known, study design and volunteer physical condition between healthy people and patients may be different. So in this study, we applied PK/PD method to evaluate treatment programs rationality of the first generation cephalosporin-cefazedone in patients suffered from CAP.

According to the characteristics of time-dependent antibiotics, $fT > MIC$ of cephalosporin needs to reach the dosing interval of 40–60% in order to get a good clinical efficacy.\[10,11\] For CAP, $fT > MIC$ of cephalosporin should reach more than 40% of the dosing interval to get a good clinical efficacy.\[12\] Since the majority of the clinical infection diseases need to be treated empirically, $fT > MIC$ of β-lactam antibiotics including cephalosporin is needed to reach or exceed 50% of the dosing interval to clinical common pathogens (including moderately sensitive pathogens) in order to achieve good effect.\[13\]

It is reported that\[14\] in Chinese healthy volunteers receiving intravenous continuously injection of cefazedone sodium administered 2 g q12 h for 7 days, the PK parameters were $C_{max}$ 228.82 ± 40.71 mg/L, $t_1/2β$ 1.61 ± 0.16 h, AUC₀–t 441.93 ± 80.78 mg·L⁻¹·h⁻¹, Vd 10.63 ± 1.61 L, CL 4.62 ± 0.87 L/h. Compared with that in healthy subjects, $C_{max}$ and AUC₀–t in 10 CAP patients was
Table 1: Demographic characteristics of ten patients with mild to moderate community-acquired pneumonia

| Subjects | Sex | Age (years) | Weight (kg) | Height (cm) | BMI (%) | Period of treatment (days) | Total amount of drugs (g) |
|----------|-----|-------------|-------------|-------------|---------|---------------------------|--------------------------|
| 01       | Male| 31          | 71.0        | 173         | 23.72   | 7.0                       | 28                       |
| 02       | Male| 33          | 60.0        | 177         | 19.15   | 7.5                       | 30                       |
| 03       | Female| 39        | 52.0        | 150         | 23.11   | 11.0                      | 44                       |
| 04       | Male| 55          | 64.0        | 170         | 22.15   | 9.0                       | 36                       |
| 05       | Female| 62        | 55.0        | 160         | 21.48   | 7.0                       | 28                       |
| 06       | Female| 61        | 59.0        | 154         | 24.88   | 11.0                      | 44                       |
| 07       | Male| 28          | 80.0        | 170         | 27.68   | 7.0                       | 28                       |
| 08       | Female| 43        | 60.0        | 160         | 23.44   | 7.0                       | 28                       |
| 09       | Female| 68        | 46.5        | 155         | 19.35   | 7.5                       | 30                       |
| 10       | Female| 32        | 65.0        | 164         | 24.17   | 7.0                       | 28                       |

Mean - 45.20 61.25 163.30 22.91 8.10 32.40
SD - - 14.95 9.54 8.98 2.55 1.65 6.59
Minimum - 28 46.5 154 19.15 7 28
Maximum - 68 80 177 27.68 11 44

BMI = Weight (kg)/高度 (m²). BMI: Body mass index; SD: Standard deviation.

Table 2: Noncompartmental pharmacokinetic parameter estimates of cefazedone

| Subjects | T₁/₂ (h) | Cmax (mg/L) | AUC₀‑t (mg·L⁻¹·h⁻¹) | VD (L) | CL (L/h) |
|----------|----------|-------------|-----------------------|--------|----------|
| 01       | 1.79     | 170.51      | 225.37                | 22.53  | 8.74     |
| 02       | 1.28     | 146.56      | 295.14                | 12.32  | 6.69     |
| 03       | 1.39     | 176.45      | 258.58                | 15.32  | 7.65     |
| 04       | 1.56     | 117.25      | 172.81                | 25.51  | 11.37    |
| 05       | 1.41     | 158.38      | 275.73                | 14.52  | 7.15     |
| 06       | 1.46     | 224.41      | 325.13                | 12.83  | 6.08     |
| 07       | 1.32     | 196.04      | 254.31                | 14.76  | 7.78     |
| 08       | 1.53     | 239.04      | 306.51                | 14.19  | 6.44     |
| 09       | 2.02     | 167.56      | 431.21                | 12.59  | 4.31     |
| 10       | 1.48     | 156.01      | 260.31                | 16.04  | 7.53     |

Mean - 1.52 175.22 280.51 16.06 7.37
SD - 0.23 36.28 68.17 4.42 1.84
RSD - 14.92 20.7 24.3 27.52 24.99

SD: Standard deviation; RSD: Relative standard deviation.

Table 3: Summary of the clinical response

| Subjects | Severity | Bacterial culture | Clinical efficacy | Bacteriological response |
|----------|----------|-------------------|-------------------|-------------------------|
| 01       | Mild     | Positive          | Clinical cure     | Assumed eradication     |
| 02       | Moderate | Negative          | Clinical cure     | -                       |
| 03       | Moderate | Negative          | Clinical cure     | -                       |
| 04       | Moderate | Negative          | Clinical failure  | -                       |
| 05       | Mild     | Negative          | Clinical cure     | -                       |
| 06       | Moderate | Positive          | Clinical cure     | Eradication             |
| 07       | Moderate | Positive          | Clinical cure     | Eradication             |
| 08       | Moderate | Positive          | Clinical cure     | Eradication             |
| 09       | Moderate | Positive          | Clinical failure  | Assumed eradication     |
| 10       | Moderate | Positive          | Clinical cure     | Eradication             |

In this study, 10 patients with CAP provided PK blood samples and six of them had pathogen isolated from the lower respiratory tract, which are within the scope of the antibacterial spectrum of cefazedone, and sensitive to the drug. MIC determination showed that the MICs of cefazedone to these pathogens were between 0.25 and 1 mg/L, far below the mean peak serum drug concentration (175.22 ± 36.28 mg/L) of the 10 subjects. Although the serum protein binding of cefazedone is up 93–96% and the concentration of free drug in the blood serum is only 4–7% of the measured concentration of drug, the MICs to these pathogens are still below the mean peak serum concentration of free drug. fT > MIC of cefazedone in all six patients, from whom pathogens were isolated, were higher than 40% and in five of six patient was even over 50%. The average fT > MIC was 55.45 ± 8.12%. Ten patients with CAP accepted cefazedone sodium intravenous therapy, 2 g q12 h, the average duration of treatment was 8.1 days and achieved good clinical efficacy, which clinical cure in eight cases.

In this study, the clinical efficacy of two cases was clinical failure, one case of male patients, sputum culture negative, cough, sputum, and other symptoms improved after treatment, but still high fever, chest computed tomography showed 8–9 thoracic vertebral destruction, disc space narrowing, consider chest eight, nine intervertebral infection; Another one case of female patient, sputum culture positive, with a history of rheumatic heart disease and mitral stenosis, cough, sputum, and other symptoms improved after treatment, Pleural effusion, heart, and lung changes occur in X-ray, consider cardiac dysfunction, UCG shows rheumatic heart disease, mitral stenosis and regurgitation, left atrial thrombus, the patient needed continuous treatment. Because of complications, these two patients were evaluated for clinical failure.
Intravenous injection of cefazedone sodium with 2 g q12 h dosage regimen is used in the treatment of CAP caused by sensitive bacteria, either \( t > \text{MIC} \) or clinical efficacy shows that such dosing regimen is reasonable.

### Table 4: Injection cefazedone \( t > \text{MIC} \) results

| Subjects | Isolates                        | \( t_{1/2} \) (h) | VD (ml) | \( f \) | MIC (mg/L) | Dose (mg) | DI (h) | \( t > \text{MIC} \) (%) |
|----------|--------------------------------|------------------|--------|------|------------|-----------|--------|------------------------|
| 01       | *Haemophilus influenzae*       | 1.79             | 22.53  | 0.05 | 0.25       | 2000      | 12     | 61.92                  |
| 02       | -                              | 1.28             | 12.32  | 0.05 | -          | 2000      | 12     | -                      |
| 03       | -                              | 1.39             | 15.32  | 0.05 | -          | 2000      | 12     | -                      |
| 04       | -                              | 1.56             | 25.51  | 0.05 | -          | 2000      | 12     | -                      |
| 05       | -                              | 1.41             | 14.52  | 0.05 | -          | 2000      | 12     | -                      |
| 06       | *Staphylococcus aureus*        | 1.46             | 12.83  | 0.05 | 0.25       | 2000      | 12     | 60.39                  |
| 07       | *Haemophilus influenzae*       | 1.32             | 14.76  | 0.05 | 0.5        | 2000      | 12     | 41.37                  |
| 08       | *Staphylococcus aureus*        | 1.53             | 14.19  | 0.05 | 0.25       | 2000      | 12     | 61.43                  |
| 09       | *Klebsiella pneumoniae*        | 2.02             | 12.59  | 0.05 | 1          | 2000      | 12     | 50.34                  |
| 10       | *Streptococcus pneumoniae*     | 1.48             | 16.04  | 0.05 | 0.25       | 2000      | 12     | 57.25                  |
| Mean     |                                | 1.52             | 16.06  | 0.05 | 0.42       | 2000.00   | 12.00  | 55.45                  |
| SD       |                                | 0.23             | 4.42   | 0.00 | 0.30       | 0.00      | 0.00   | 8.12                   |
| CV%      |                                | 14.92            | 27.52  | 0.00 | 72.66      | 0.00      | 0.00   | 14.64                  |

SD: Standard deviation; CV: Coefficient of variation; MIC: Minimum inhibitory concentration.

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### Table 4: Injection cefazedone \( t > \text{MIC} \) results

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