Optimizing ceftazidime pharmacodynamics in patients with acute exacerbation of severe chronic bronchitis

Annette Lubasch¹, Stefan Lück¹, Hartmut Lode¹*, Harald Mauch², Joachim Lorenz³, Pal Bölcskei⁴, Tobias Welte⁵ and the COPD study group

Zentralklinik Emil v. Behring, Department Lungenklinik Heckeshorn, ¹Pneumologie I and ²Institute of Medical Microbiology and Immunology, affil. Freie Universität Berlin, Zum Heckeshorn 33, D-14109 Berlin; ³Department of Internal Medicine, Kreiskrankenhaus Lüdenscheid, Paulmannshöher Str. 14, 58515 Lüdenscheid; ⁴Klinikum Nord, Medizinische Klinik I, Department of Pneumologie, Prof.-Ernst-Nathan-Str. 1, 90419 Nürnberg; ⁵Medizinische Klinik und Poliklinik, Universitätsklinikum Magdeburg, Otternweg 7, 39120 Magdeburg, Germany

Received 19 June 2002; returned 25 August 2002; revised 5 October 2002; accepted 3 December 2002

Objectives: Implementation of current pharmacodynamic knowledge could enhance clinical results, avoid resistance development and reduce treatment costs. In this open, randomized, multicentre study, we evaluated the clinical and bacteriological outcome and pharmacokinetic as well as pharmacodynamic parameters of two ceftazidime therapy regimens in patients with acute exacerbation of severe chronic bronchitis (AECB).

Methods: Eighty-one patients (56 males, 25 females, age 65.3 ± 10.1 years) with AECB were included. A subgroup of 21 patients underwent pharmacokinetic and pharmacodynamic examination. The patients received either ceftazidime 2 g every 8 h (C³ × ²) or ceftazidime 2 g as a loading dose, followed by ceftazidime 2 g over 7 h every 12 h (C² × ²) for 8–14 days. Clinical and bacteriological responses were monitored at day 8 or 9, and 72 h after the end of therapy (EOT).

Results: At EOT, clinical success was recorded in 90% and 90.2% of clinically evaluable patients receiving C³ × ² and C² × ², respectively. Bacteriological success at EOT was achieved in 87.5% and 90.2% of evaluable patients treated with C³ × ² and C² × ², respectively. Cmax (mg/L) varied between 168.9 ± 34.1 and 144.0 ± 9.8 in the C³ × ² group, and between 60.1 ± 34.1 and 54.2 ± 30.4 at steady-state in the C² × ² group. Minimal concentrations were between 9.1 and 13.4 mg/L in the C³ × ² group, and between 16.6 and 17.7 mg/L in the C² × ² group. Concentrations >4–5 × MIC were seen in all pathogens, except Staphylococcus aureus, during 100% of infusion time.

Conclusion: The 2 × 7 h infusion of ceftazidime 2 g (C² × ²) was clinically and bacteriologically as effective as the usual 3 × 2 g ceftazidime short-term infusion in the treatment of AECB, and demonstrated advantages in terms of pharmacodynamic parameters compared with the C³ × ² regimen.

Keywords: ceftazidime, AECB, pharmacokinetic, pharmacodynamic

Introduction

Ceftazidime is a well-known parenteral cephalosporin, which is characterized by a broad antibacterial spectrum, including Pseudomonas aeruginosa.β-Lactam antibiotics are commonly administered as an intermittent short course infusion. Previous studies have demonstrated that the effect of ceftazidime is time dependent, without a significant post-antibiotic effect.² Therefore, the important determinant of β-lactam antibiotic efficacy is the time of serum drug concentration above MIC (τ > MIC) in the pathogens during the dosing interval.²,³ Maximal destruction would be achieved at concentrations at least four to five times greater than the organism’s MIC.²,⁴,⁵ Because of this, a continuous application of β-lactams, which need a lower total dose of antibiotics, is an attractive alternative antibacterial treatment.

*Corresponding author. Tel: +49-30-8002-2222; Fax: +49-30-8002-2623; E-mail: halocheck@zedat.fu-berlin.de

© 2003 The British Society for Antimicrobial Chemotherapy
Recent studies, with a continuous infusion of ceftazidime 2 or 3 g over 24 h, demonstrated the effectiveness of continuous infusion in patients with cystic fibrosis or Gram-negative infections, or in febrile neutropenic patients with acute myeloid leukaemia or in nosocomial infections.6–12 Until now, no clinical study has analysed whether the modern pharmacodynamic approach of rational antibiotic dosing is also effective in severe chronic bronchitis patients.

Our study, therefore, aimed to evaluate the clinical outcome, bacteriological efficacy, and pharmacokinetic and pharmacodynamic parameters of ceftazidime. The dosing was: 3 × 2 g as a short infusion of 30 min, compared with 2 × 2 g, as a 7 h infusion, in hospitalized patients with acute exacerbation of severe chronic bronchitis (AECB).

Materials and methods

Patients

Eighty-one Caucasian patients (56 males, 25 females), age [mean ± s.d. (range)] 65.3 ± 10.1 (40–87) years, height 169.4 ± 8.9 (149–192) cm, weight 72.2 ± 16.7 (43–111.3) kg, body mass index 25.2 ± 5.7 (15.3–40.9), with purulent exacerbation of severe chronic bronchitis (FEV1 < 50% of predicted value in stable phase) were included in this study between September 1998 and January 2000. All patients were current or ex-smokers. The inclusion criteria were: age > 40 years; in females patients, a negative pregnancy test, or post-menopause; written informed consent; known chronic bronchitis with an FEV1 < 50% of predicted value; signs of acute exacerbation [at least two of the following symptoms: (i) dyspnoea or increased dyspnoea; (ii) increased sputum volume; (iii) increased cough; (iv) increased sputum purulence; (v) increased bronchial retention of secretion; and (vi) fever ≥37.8°C and/or chills]. Exclusion criteria were: pregnancy or lactation period; beta-lactams and/or aminoglycosides; antibiotic pre-treatment within last 72 h; progressive lethal disease, or life expectancy <1 month; alcohol or drug abuse; creatinine >2.5 mg/L or creatinine clearance <40 mL/min/1.73 m²; shock; mechanical ventilation; neutropenic patients (<2000 granulocytes/mm³); uncooperative patient; or participation in a clinical trial within the last 4 weeks. The study was approved by the Ethics Committee of the Freie Universität, Berlin, and informed consent was obtained for all patients prior to study participation.

Study design

This study design was open, randomized and multicentred. Patients received either ceftazidime 2 g intravenously (iv) every 8 h (C3 × 2; n = 40), or ceftazidime 2 g iv as a loading dose, followed by ceftazidime 2 g iv over 7 h every 12 h (C2 × 2; n = 41). Ceftazidime (GlaxoSmithKline, Munich, Germany) was prepared according to the manufacturer’s guidelines. For both therapeutic regimens, ceftazidime was dissolved in 40 mL of sterile water. For the short infusion, it was given over a 30 min period via an infusion pump (Infusomat; Braun, Melsungen, Germany); for the 7 h infusion, ceftazidime was given via a transportable infusion pump (Perfusor; Braun, Melsungen, Germany).

Clinical assessment, lung function, and laboratory, sputum and bacteriological examinations were performed before treatment, between days 3 and 5, between days 8 and 9, and within 72 h of the end of treatment (EOT). Criteria for validity of sputum samples corresponded to the American Society for Microbiology criteria >10 leucocytes and <25 squamous cells per high power field. In all centres, tests for susceptibility were conducted by Etest.

A subgroup of 21 patients [17 males, four females, age 62.8 ± 8.7 years; n = 10 (C2 × 2), n = 11 (C3 × 2)] in one centre (Berlin) underwent pharmacokinetic examinations.

Blood sampling

Blood samples (5 mL) for pharmacokinetic and pharmacodynamic analyses were obtained before first dosing and 0.5, 1, 2, 4, 6, 8, 10, 12, 14 and 16 h after first dosing. Between days 3 and 5 samples were taken before the morning dose, and after 0.5, 1, 2, 4, 6, 8, 10 and 16 h. At EOT, samples were taken before last dose, and 0.5, 1, 2, 4, 6, 8, 12 and 24 h after the last dose. All blood samples were taken through an indwelling cannula. After blood collection to obtain serum, the serum, which was then shock frozen at −30°C, was stored at room temperature for −30 min. All samples were centrifuged for 10 min at 1000g and 21°C to separate the serum, which was then shock frozen at −20°C.

Bioassay method

The bioassay method was based on an agar plate diffusion technique previously described in detail by Reeves & Bywater.13 This method was used to determine concentrations of ceftazidime in serum. Serum samples were assayed against standards prepared in activity-free pooled human serum. On each agar plate, four serum samples, one control sample and five standard samples were tested in triplicate. After pre-diffusion for 30 min at room temperature, the agar plates were incubated for 18 h at 30°C. The test strain was Escherichia coli (ATCC 25922), and N-agar (pH 7.4) was used. The detection limit was 0.78 mg/L. The coefficient of variation...
was 3.41%, determined on three different days between concentrations of 3 and 40 mg/L.

Pharmacokinetic analysis

Several pharmacokinetic parameters were analysed by standard methods: peak serum concentration (Cmax) and area under the concentration–time curve (AUC).14,15 AUC24 were calculated by 3 × AUC for 8 h (C3 × 2), and/or 2 × AUC for 12 h (C2 × 2).

Pharmacodynamic analysis

The presumable efficacy of an antibiotic therapy regimen can be expressed as AUC/MIC ratio, or ratio of peak/MIC.16,17

Statistical analysis

Differences between the therapy regimens were identified by the Wilcoxon test. A value of <0.05 was considered significant.

Clinical success

Clinical success was defined as cure or improvement (recurrence to the situation before exacerbation).

Results

Clinical outcome

Mean treatment duration was 9 ± 2.8 days in the C2 × 2 group, and 11 ± 5.4 days in the C3 × 2 group. Dyspnœa at rest was improved from 61% (n = 25) to 4.9% (n = 2), and from 55% (n=22) to 2.5% (n = 1) in patients receiving C2 × 2 and C3 × 2, respectively. Thirty-seven patients in the C2 × 2 group and 35 in the C3 × 2 group had sputum production before therapy; 35 of them in each group had purulent sputum. Sputum volume >30 mL/24 h decreased from 43.9% (n = 18) to 2.4% (n = 1) in the C2 × 2 group, and from 47.5% (n = 19) to 7.5% (n = 3) in the C3 × 2 group. The severity of cough (moderate and severe) was reduced from 68.3% (n = 28) to 4.9% (n = 2), and from 70% (n = 28) to 5% (n = 2) in patients receiving C2 × 2 and C3 × 2, respectively.

No significant changes were observed in lung function before and after therapy. FEV1 (% predicted) was 41.9 ± 15.7 before and 45.4 ± 22.1 after antibiotic therapy in the C2 × 2 group, and 42.3 ± 13.9 and 41.5 ± 11.0 in the C3 × 2 group.

Peak flow increased from 196.3 ± 56.2 L/min to 239.1 ± 84.9 L/min in the C2 × 2 group, and from 190.4 ± 64.5 L/min to 206.1 ± 72.2 L/min in the C3 × 2 group.

At EOT, clinical success (cure or improvement) was recorded in 90.2% (n = 37) and 90% (n = 36) of clinically evaluable patients receiving C2 × 2 and C3 × 2, respectively. No statistically significant differences were found between the therapy regimens as regards clinical success.

Bacteriological outcome

A total of 61 pre-treatment pathogens were isolated in 38 patients [22 pathogens in the C2 × 2 group (16 patients) and 39 in the C3 × 2 group (22 patients)]. The primary pathogens were Pseudomonas aeruginosa (10), Streptococcus pneumoniae (nine), Staphylococcus aureus (seven) and Haemophilus influenzae (six). In no case of P. aeruginosa was a combination therapy with aminoglycosides used. All documented P. aeruginosa infections were clinically cured or improved. Also, all infections caused by S. pneumoniae, H. influenzae or S. aureus were recorded as clinical successes (cured or improved). In total, bacteriological success, or presumed eradication at EOT, was achieved in 90.2% and 87.5% of evaluable patients treated with C2 × 2 and C3 × 2, respectively.

Pharmacokinetic results

After first dosing, maximal concentrations of ceftazidime in serum were observed at the end of the 30 min infusion in both therapy groups [Cmax 144 ± 9.8 mg/L in C3 × 2; Cmax 138.2 ± 35.7 mg/L in C2 × 2 (initial loading dose)]. Minimal ceftazidime concentrations in the C3 × 2 group were measured 8 and 16 h after the first infusion before the next dosing (10.2 ± 7.4 and 13.0 ± 8.5 mg/L). In the C2 × 2 group, minimal concentrations were measured 12 h after first dosing immediately before the second 7 h infusion was started (17.7 ± 15 mg/L). Between days 3 and 5, minimal concentrations in C3 × 2 varied from 11.1 ± 9.0 mg/L to 13.4 ± 9.8 mg/L; maximal concentrations were observed 30 min after the short infusion (Cmax 157.9 ± 22.5 mg/L). In the C2 × 2 group, Cmax (60.1 ± 34.1 mg/L) was seen 6 h after infusion start; minimal concentrations were 17.5 ± 10.2 mg/L. Minimal concentrations before final dosing were 9.2 ± 6.9 and 16.6 ± 12.8 mg/L in the C3 × 2 and C2 × 2 groups, respectively. Cmax was observed 4 h after infusion start in the C2 × 2 group (54.2 ± 30.37 mg/L), or at the end of the short infusion in the C3 × 2 group (168.9 ± 34.12 mg/L). Twelve hours after the last dosing, ceftazidime concentrations were 9.91 ± 8.8 and 3.99 ± 4.23 mg/L in the C2 × 2 and C3 × 2 groups, respectively.

Concentrations of ceftazidime, based on the measured values, were calculated over a 24 h period and are shown in Figure 1.

AUC12 (mg·h/L) in the C2 × 2 group was 642.7 ± 240.6 after the first dosing, 370.1 ± 184.8 between days 3 and 5, and 347.2 ± 165.2 at the last dosing. In the C3 × 2 group, AUC8 (mg·h/L) varied between 347.9 ± 108.6 (first dosing), 390.6 ± 99.7 (days 3–5) and 364.3 ± 64.2 at last infusion. AUC24 (mg·h/L) was calculated using 2 × AUC12 in the C2 × 2 group, and 3 × AUC12 in the C3 × 2 group. AUC24 calculations resulted in 888.8 ± 420.2 mg·h/L, and 1092 ± 192.5 mg·h/L, in the C2 × 2 and C3 × 2 groups, respectively.
In one centre (Berlin), 14 pathogens from 12 patients were isolated. MICs were determined by Etest. The ceftazidime MIC for *S. pneumoniae* varied between 0.094 and 0.125 mg/L, for *Moraxella catarrhalis* between 0.023 and 0.125 mg/L, and for *H. influenzae* between 0.064 and 0.094 mg/L. The MIC for *S. aureus* was 8.0 mg/L, for *P. aeruginosa* 1.5 mg/L, for *Enterobacter cloacae* 0.125 mg/L and for *Burkholderia cepacia* 4.0 mg/L.

Pharmacodynamic results

Peak/MIC ratios observed in *S. aureus* (C2 × 2 group) were between 6.8 and 17.2. Also, in *B. cepacia* (C2 × 2 group) the peak/MIC ratios were lower compared with the other pathogens (13.6–69.1). In *P. aeruginosa* (C3 × 2 group), the peak/MIC ratio ranged between 96 and 112.6. In all other pathogens, the peak/MIC ratio was >500.

AUC24/MIC was the lowest in *S. aureus* (C2 × 2 group) with 111.1, followed by *B. cepacia* (C2 × 2 group) with 222.2 and *P. aeruginosa* (C3 × 2 group) with 728. All other AUC/MIC values were >8000.

Ceftazidime concentrations in the C2 × 2 and C3 × 2 groups, in comparison with MIC, are demonstrated in Figure 1.

Throughout the treatment, ceftazidime concentrations in both therapy regimens were greater than 4 × to 5 × MIC in *M. catarrhalis, H. influenzae, S. pneumoniae, E. cloacae* and *P. aeruginosa*. For *S. aureus* (MIC 8.0 mg/L), ceftazidime concentrations were greater than 5 × MIC in the C2 × 2 group for 12 h per day (50% of therapy time), and between 10 and 12 h per day in the C3 × 2 group. Ceftazidime concentrations in the C2 × 2 group were greater than 5 × MIC for *B. cepacia* (MIC 4.0 mg/L) throughout the treatment; in the C3 × 2 group, concentrations greater than 5 × MIC were observed for 18 h per day (75% of therapy time).

Side-effects

The tolerance of ceftazidime in both therapy regimens in general was good. The most frequent side-effects were mild-to-moderate gastrointestinal (18.5% of patients) and CNS disorders (4.9% of patients), but probably only two cases were connected with the study medication.

Discussion

The purpose of our study was to evaluate the clinical outcome, bacteriological efficacy and pharmacokinetic as well as pharmacodynamic parameters of two different ceftazidime treatment regimens, in patients with AECB.

In recent years, the importance of pharmacodynamic and pharmacoeconomic parameters of antibiotic agents has been emphasized. The optimal dosing of β-lactam antibiotics was analysed because the most important pharmacodynamic parameter for β-lactam agents has been shown to be $t > \text{MIC}$. Several methods are possible to maximize the $t > \text{MIC}$; however, the use of continuous infusions appears to be an attractive option. Concentrations of 4 × to 5 × above the MIC for the infecting pathogen should be the target concentration. Adequate concentrations (4 × to 5 × above the MIC for the pathogens) of ceftazidime could be achieved by
continuous infusion over 24 h, with a daily dose of ceftazidime 3 g or 2 g. In our study, the recommended C_max/MIC ratio for bacteriological efficacy (>8–10 in Gram-positive and 10–12.2 in Gram-negative bacteria) were achieved in all isolated pathogens, except for S. aureus in the C2 × 2 regimen (7.5 and 6.8). The AUC/MIC was greater in all cases than the recommended values (>125 in Gram-negative and >100 in Gram-positive bacteria).

Ceftazidime concentrations greater than 4 × 5 × MIC were achieved in both therapy regimens over the treatment period for M. catarrhalis, H. influenzae, S. pneumoniae, E. cloacae and P. aeruginosa. For S. aureus, the required ceftazidime concentration of 4 × 5 × MIC was observed for 50% of the therapy time in the C2 × 2 group, and for 10–12 h per day in the C3 × 2 group. In B. cepacia, ceftazidime concentrations 4 × 5 × MIC were achieved only for 75% of the therapy time in the C3 × 2 group, compared with 100% of therapy time in the C2 × 2 group. In essence, the C2 × 2 regimen achieved better results in regard to the key parameter of efficacy (time of ceftazidime concentration 4 × 5 × MIC) compared with the standard therapy regimen, with intermittent bolus application of ceftazidime 2 g every 8 h. Our results confirm previously published findings, that a longer infusion time improves the pharmacodynamic profile of ceftazidime.

In our study, maximal serum concentrations of ceftazidime (144 ± 9.8 mg/L to 168.9 ± 34.1 mg/L) at the end of a 30 min infusion in the C3 × 2 regimen, and pre-dose concentrations (9.14 and 13.4 mg/L), were in good agreement with the values reported previously. Maximal ceftazidime concentrations in the C2 × 2 group were observed between 4 and 6 h after the start of infusion (54.2 ± 60.1 mg/L); pre-dose concentrations varied between 16.6 and 17.7 mg/L. These pre-dose concentrations were again in excellent agreement with the steady-state concentration of ceftazidime 3 g applied in a 24 h infusion (18.2 ± 4.5 mg/L). In 2 g continuous therapy regimens, the steady-state concentrations were lower (12.8 ± 3.0 mg/L).

Ceftazidime is an effective antibiotic agent in the treatment of AECB. In all published studies in patients with chronic bronchitis the standard application (0.5–2 g two or three times daily as short infusions) or the intramuscular application was used. A continuous infusion of ceftazidime is described in critically ill patients with Gram-negative infections, in patients with septicemia or meningitis, in febrile neutropenic patients with acute myeloid leukemia, in patients with nosocomial infections and in cystic fibrosis patients, but not in patients with AECB. In studies in which standard dosing was compared with continuous infusion, continuous infusion was as effective as the standard application with regard to optimizing the pharmacodynamic and pharmacoeconomic profile of ceftazidime. In our study we found no significant difference in clinical or bacteriological outcome between either therapy regimen (C2 × 2 versus C3 × 2). These results emphasize the efficacy of therapy regimens with long infusion times; they reduce the total daily dose and therefore also therapy costs. The difference in our study compared with previous studies with continuous infusion was that we applied ceftazidime but over a 14 h (2 × 7 h/day) period, and not over a 24 h period. This appears to be an advantage for patients.

In summary, the results of our study have demonstrated that a therapy regimen with a ceftazidime 2 g loading dose, followed by ceftazidime 2 g over two 7 h infusions (C2 × 2) per day, is clinically and bacteriologically as effective as the standard application of ceftazidime 2 g every 8 h (C3 × 2) as a short infusion (30 min) in patients with acute exacerbation of severe chronic bronchitis. Also, the pharmacodynamic parameters showed advantages within the C2 × 2 therapy regimen. The key parameter for efficacy (time of ceftazidime concentration above 4 × 5 × MIC) was achieved by all isolated pathogens, except for S. aureus, in 100% of therapy time in this regimen. The twice-daily 2 g infusion of 7 h each seems to be effective, resulting in a lower total dose and therefore lower treatment costs.

Acknowledgements

This study was sponsored by GlaxoSmithKline.

References


