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Comparison of dose doubling with probenecid for sustaining serum cefuroxime levels

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Serum cefuroxime concentrations were measured over a 12 h period in ten healthy adults following three iv dosing regimens: 750 mg cefuroxime, 1.5 g cefuroxime, and 750 mg cefuroxime with 1 g of probenecid given orally 3 h before the cefuroxime infusion. Probenecid prolonged the serum cefuroxime half-life by 63% ($P < 0.05$) with a significant increase in the mean time for which serum cefuroxime concentrations exceeded the MIC_{90} for common respiratory pathogens (2 mg/L) compared with either 750 mg cefuroxime (2.2 h, $P < 0.05$) or 1.5 g of cefuroxime (0.9 h, $P < 0.05$) without probenecid. The cost of the 750 mg cefuroxime dose plus probenecid is approximately half that of a 1.5 g cefuroxime dose.

Introduction

The efficacy of β-lactam antibiotics is optimized by maintaining serum concentrations above the MIC for the target organisms. Since these antimicrobial agents have little, if any, post-antibiotic effect against Gram-negative organisms, maintaining concentrations above the MIC for the majority of the dosing interval is a major determinant of efficacy.[1] The length of time for which the serum concentration of cefuroxime remains above the MIC is influenced by the the dose given,[2] the extent of distribution within the body and the rate of elimination from the body. Cefuroxime is cleared by the kidney, by both glomerular filtration and tubular secretion.[3] Blocking tubular secretion with probenecid has been shown to decrease the elimination of cefuroxime.[2]

To determine an optimal regimen for maximizing the time above MIC for common respiratory pathogens while minimizing the cost of treatment, we compared three cefuroxime dosing regimens. The regimens chosen permitted a direct comparison of increasing the dose with decreasing the elimination rate in the same subjects.

Patients and methods

The study was approved by the Research Ethics Board for Human Experimentation of the hospital and all volunteers provided signed consent to participate. The ten volunteers (five female and five male) ranged in age from 18 to 48 years (mean 32 years). Their mean weight was 72 kg (range 54–94 kg) and their mean height was 172 cm (range 158–182 cm). Results of physical examinations and screening laboratory tests, including urinalysis, complete blood count, serum alanine aminotransferase, alkaline phosphatase, creatinine and total bilirubin, were normal prior to starting the study. Female patients were postmenopausal, surgically sterile or using a highly effective method of contraception. All women of childbearing potential had a negative urine pregnancy test.

Volunteers with a history of gout or cephalosporin allergy or with a body weight differing from the ideal by >30% were excluded. During the study, patients were allowed no alcohol or medications in addition to their study medications with the exception of oral contraceptives and levothyroxine.

All volunteers received each of the three regimens of iv cefuroxime, namely 1.5 g, 750 mg, and 750 mg with 1 g of probenecid, with 1 week between each dose. The sequence of study regimens was randomly allocated to each participant. All the iv doses were given over 20 min via an infusion pump and probenecid was given orally 3 h before the cefuroxime infusion started. Volunteers were requested to take their probenecid at 5 a.m. on an empty stomach. Blood samples were drawn from a venous catheter in the arm

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opposite the iv infusion site at time 0, 10 and 20 min after the start of infusion and 5, 10, 20, 30 and 45 min and 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10 and 12 h after completion of the infusion.

Cefuroxime concentrations were measured with a bioassay using *Streptococcus pyogenes* ATCC 19615 as the indicator. An overnight broth culture of the indicator strain prepared in Brain Heart Infusion broth (Nepean, Ontario, Canada) with 5% yeast extract was diluted 1 in 100 in sterile Mueller–Hinton agar (BBL) cooled to 50°C and poured into 150 × 15 mm Petri dishes. Standard concentrations of cefuroxime were diluted in pooled human serum that had been shown not to have any antimicrobial activity against the indicator strain. Ten microlitres of each standard was applied to sterile 6 mm paper discs, allowed to dry at room temperature for 10 minutes and applied in duplicate to the surface of the agar. The concentration range for the standards was 0.15–320 mg/L in doubling concentrations, and the assay was linear between 0.5 and 100 mg/L, based on logarithmic concentration. Serum was applied in the same manner as the standards, and an internal control of 1.25 mg/L of cefuroxime was included on each plate. Serum samples expected to contain >10 mg/L of cefuroxime were first diluted 1 in 5 and 1 in 10 and applied in duplicate. After overnight incubation at 35°C, the zone diameters of inhibition were measured with digital calipers. Two technologists read the plates separately, the results were averaged and the zone diameters were interpolated in the standard curve.

The pharmacokinetic assessment used a noncompartmental, first-order elimination model. The elimination rate constant for each patient was calculated by linear regression analysis of the measured concentrations. The apparent volume of distribution was calculated as the product of the clearance and the mean residence time.[4] Values were compared using repeated measures analysis of variance followed by the Newman–Keuls test for multiple comparisons with a significance level of 0.05. The sample size of ten subjects was sufficient to detect a difference of at least one standard deviation.

The published MIC_{90}s of cefuroxime for the common respiratory pathogens *Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, Klebsiella pneumoniae* and *Staphylococcus aureus* are below 2 mg/L.[5] This concentration was chosen as the minimum effective concentration of cefuroxime for the purposes of this study.

Results

The coefficient of variation of the internal cefuroxime standard (1.25 mg/L) was 2.9%. The mean concentration of samples diluted 1:5 and 1:10 were not significantly different, and the coefficients of variation for all diluted samples were 9.4% and 9.5% respectively for 1:5 and 1:10 dilutions.

The mean serum cefuroxime concentrations obtained with each of the regimens examined are illustrated in the Figure. Three hours after the infusions were complete, the mean concentration obtained with the addition of probenecid to the 750 mg dose of cefuroxime exceeded that obtained with the 1.5 g dose given alone.

The pharmacokinetic parameters obtained for each regimen are shown in the Table. Probenecid decreased the clearance of cefuroxime from 10.1 L/h to 7.2 L/h ($P < 0.05$) while having no significant effect on the apparent volume of distribution. The mean serum half-life for the 750 mg dose was 0.8 h which probenecid increased by 63% to 1.3 h ($P < 0.05$). The addition of probenecid to the 750 mg dose increased the area under the concentration–time curve (AUC) by 44% ($P < 0.05$).

Doubling the dose of cefuroxime to 1.5 g significantly increased the mean maximum serum concentration (C_{max}) and AUC without significantly affecting clearance. Doubling the dose resulted in statistically significant increases in serum half-life and volume of distribution; the increases were only 25% and 30% respectively.

The mean serum cefuroxime concentrations with the 750 mg plus probenecid combination remained above 2 mg/L

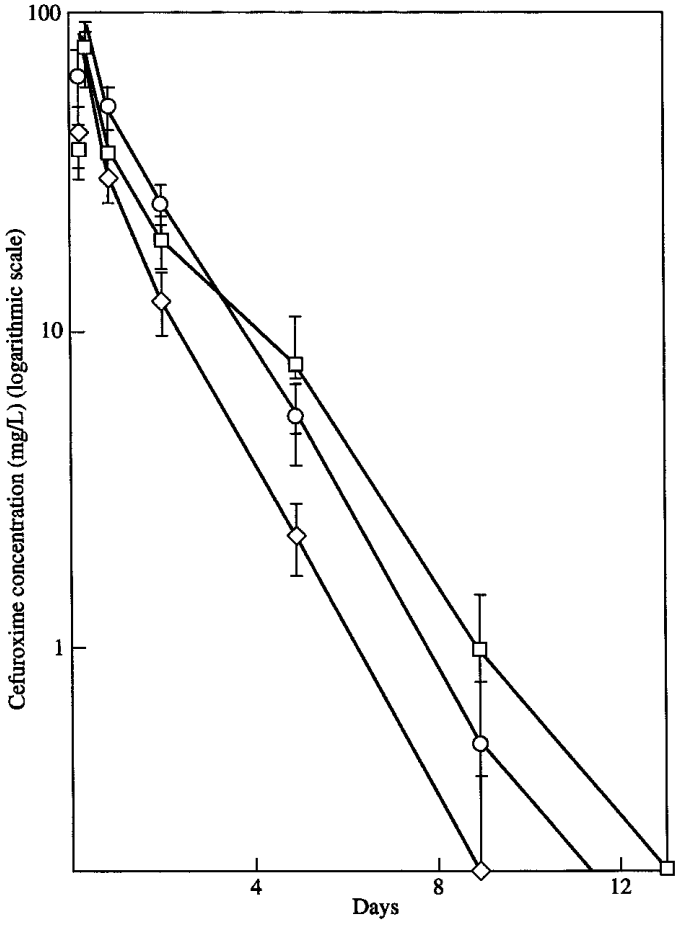

Figure. Serum cefuroxime concentrations achieved with 750 mg cefuroxime (◇); 1.5 g cefuroxime (○) and 750 mg cefuroxime with a prior dose of 1 g probenecid (□). Bars depict the S.E.M.

Table. Pharmacokinetic data

Parameter	Mean (S.D.) 750 mg	1.5 g	750 mg + P[a]	750 mg vs 1.5 g % change	*P*	750 mg vs 750 mg + P % change	*P*	1.5 g vs 750 mg + P % change	*P*
Mean AUC[b] (mg/L/h)	77(10)	137(20)	111(22)	79	<0.05	44	<0.05	−19	<0.05
Mean serum half-life (h)	0.8(0.1)	1.0(0.1)	1.3(0.2)	25	<0.05	63	<0.05	30	<0.05
Mean volume of distribution (L)	12.5(3.0)	16.2(2.3)	13.5(2.2)	30	<0.05	8	NS	−17	<0.05
Mean time > 2 mg/L[c] (h)	3.8(0.8)	5.1(0.6)	6.0(1.0)	34	<0.05	58	<0.05	18	<0.05
Mean C_{max} (mg/L)	74(14.7)	114(9.4)	79.7(16.1)	54	<0.05	8	NS	−30	<0.05
Clearance (L/h)	10.1(1.4)	11.4(1.6)	7.2(1.3)	13	NS	−29	<0.05	−37	<0.05

[a] P = probenecid.
[b] Area under the serum concentration–time curve.
[c] Mean time for which serum cefuroxime concentrations exceeded 2 mg/L

for 6.0 h. This is a 58% increase over the 3.8 h attained with the cefuroxime 750 mg dose alone and an 18% increase over the 5.1 h attained after 1.5 g of cefuroxime, both of which differences are statistically significant.

The adverse effects reported in all arms of the study were minimal. One subject reported feeling drowsy after taking the probenecid but the remainder of the patients were free of adverse effects.

Discussion

β-Lactam antibiotics are most effective when the serum concentration is maintained above the MIC for the target organisms.[1] Cefuroxime, a second-generation cephalosporin, is commonly used to treat community-acquired pneumonia requiring hospitalization.[6,7] Although 2 mg/L was chosen as the minimum effective concentration of cefuroxime for this study, the MIC for most respiratory pathogens is <2 mg/L, so that the time for which serum cefuroxime concentrations exceed the MIC for most community-acquired respiratory pathogens will usually be longer than the times reported here. The probenecid–cefuroxime regimen maintained these concentrations for the longest time period.

The usual dose given for mild-to-moderate infections is 750 mg iv. This dose has been reported to maintain serum cefuroxime levels above 2 mg/L for approximately 4 h.[3] For serious infections, the product monograph suggests increasing the dose to 1.5 g every 8 h, which doubles the cost of therapy.

Probenecid inhibited renal excretion of cefuroxime thereby maintaining serum concentrations above 2 mg/L for 6.0 h which is a 58% increase over the 3.8 h attained with the 750 mg dose of cefuroxime and an 18% increase over the 5.1 h attained with the 1.5 g dose. In all subjects, serum cefuroxime concentrations exceeded 2 mg/L in the probenecid treatment for at least the same length of time as with the 1.5 g dose.

Age may account, in part, for variations in cefuroxime excretion when probenecid is added to the 750 mg dose. When the subjects had taken probenacid, the average increase in the time for which serum cefuroxime concentration remained above 2 mg/L was 1.6 h in the five subjects under 25 years of age but 2.8 h in the five subjects over the age of 25.

We have demonstrated that oral administration of probenecid 3 h before iv infusion of cefuroxime significantly increases the time for which serum cefuroxime levels remain above the MICs for common respiratory pathogens, using a single dose of each drug. The addition of probenecid provided more sustained serum cefuroxime levels than doubling the cefuroxime dose, without doubling the cost of therapy. In single-dose cefuroxime prophylaxis, the period of antibiotic coverage could be extended, allowing for adequate antibiotic levels at the time of wound clo-

sure in longer operative procedures. Our study did not examine the use of multiple doses of cefuroxime and probenecid, nor did it assess clinical efficacy. Given the potential for significant cost savings, the efficacy and tolerance of multiple dosing of cefuroxime and probenecid is worthy of study.

Acknowledegements

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References

1. Craig, W. (1993). Pharmacodynamics of antimicrobial agents as a basis for determining dosage regimens. *European Journal of Clinical Microbiology and Infectious Diseases* **12**, *Suppl. 1*, 6–8.

2. Foord, R. D. (1976). Cefuroxime: human pharmacokinetics. *Antimicrobial Agents and Chemotherapy* **9**, 741–7.

3. Gower, P. E. & Dash, C. H. (1977). The pharmacokinetics of cefuroxime after intravenous injection. *European Journal of Clinical Pharmacology* **12**, 221–7.

4. Benet, L. Z. & Galeazzi, R. L. (1979). Noncompartmental determination of the steady state volume of distribution. *Journal of Pharmaceutical Sciences* **68**, 1071–4.

5. Brogden, R. N., Heel, R. C., Speight, T. M. & Avery, G. S. (1979). Cefuroxime: a review of its antibacterial activity, pharmacological properties and therapeutic use. *Drugs* **17**, 233–66.

6. The British Thoracic Society. (1993). Guidelines for the management of community-acquired pneumonia in adults admitted to hospital. *British Journal of Hospital Medicine* **49**, 346–50.

7. Niederman, M. S., Bass, J. B., Campbell, G. D., Fein, A. M., Grossman, R. F., Mandell, L. A. *et al.* (1993). Guidelines for the initial management of adults with community-acquired pneumonia: diagnosis, assessment of severity, and initial antimicrobial therapy. *American Review of Respiratory Disease* **148**, 1418–26.

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