17.003
Optimal Administration Method of Cefepime for Febrile Neutropenia Based on Pharmacokinetic and Pharmacodynamic Findings

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Objectives: Cefepime (CFPM) is being used worldwide for febrile neutropenia (FN) with three administrations per day (q8h), but because no population pharmacokinetics analysis has been performed yet, the optimal CFPM administration method remains unknown.

Methods: We conducted a prospective clinical trial of CFPM among adult hematological patients with FN. CFPM was administered with a daily dose of 4 g (1 g at 10:00, 1 g at 16:00, 2 g at 22:00 hours). NONMEM software was used for the population pharmacokinetic analysis. Monte Carlo simulation was performed based on the data of minimum inhibitory concentration (MIC) frequency distribution of main bacteria strains gathered at our institute.

Results: Intravenous CFPM was administered for 101 episodes of FN. A high percentage of these episodes was treated successfully (69.2%). The NONMEM program demonstrated that a 2-compartment model with CL of 4.23 (L/hr), V1 of 12.0 (L), Q of 3.98 (L/hr), and V2 of 3.40 (L) fits the data best. Monte Carlo simulation indicated that the proportion of simulated patients with probability of attainment above target (time above MIC = 70%) was greater among those treated with the thrice-a-day method than with the twice-a-day method. Time above MIC for administration at irregular time intervals was similar to that for q8h administration.

Conclusions: Our administration method appears to be the most suitable for FN patients. With this method, late night and early morning drip infusion as well as the inconvenience of maintaining exact 8 h intervals can be avoided.

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17.005
Fluoroquinolone Resistance in Clinical Isolates of Klebsiella oxytoca

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Background: Prevalence of fluoroquinolone-resistant Klebsiella oxytoca has been reported worldwide.

Methods: We recovered twelve clinical K. oxytoca isolates from patients with acute urinary tract infections, asymptomatic bacteriuria or acute bacillary diarrhea in Japan. Fluoroquinolone resistance was characterized genetically by PCR and DNA sequencing methods. Outer membrane protein (OMP) profiles were determined by SDS-PAGE.

Results: In 11 clinical isolates of levofloxacin-resistant K. oxytoca, nucleotide sequences in the quinolone resistance-determining regions showed amino acid mutations such as Thr83Ile and Asp87Gly in GyrA and Ser80Ile in ParC. Combined effects of reduced 36-kDa OMP production and amino acid mutations in GyrA and ParC were shown by four K. oxytoca isolates exhibiting higher MICs for fluoroquinolones than other fluoroquinolone-resistant isolates.

Conclusion: We identified multiple mechanisms of fluoroquinolone resistance in K. oxytoca clinically isolated in Japan, including reduction of 36-kDa OMP production as well as GyrA and ParC mutations.

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