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ORIGINAL ARTICLE

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Evaluation of clinical dosage of gatifloxacin for respiratory tract infections in elderly patients based on pharmacokinetics/pharmacodynamics (PK/PD)

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Abstract The efficacy and safety of gatifloxacin (GFLX) was evaluated for elderly patients with respiratory infections. Each patient received one-half (100 mg b.i.d.) or one-quarter (100 mg q.d.) of the conventional dosage of 200 mg b.i.d., after a tentative clinical dosage for GFLX was estimated based on the patient's age and body weight. The subjects were 34 patients aged 65 years or older with mild to moderate acute bronchitis, pneumonia, or chronic respiratory tract infections. The serum concentration of GFLX was measured for each patient, and population and pharmacokinetic (PPK) analysis was performed, using the Bayesian method, to calculate the AUC and maximum drug concentration (Cmax). The overall efficacy rate of GFLX for 33 patients was 87.9% (29/33 patients). GFLX was effective for 75.0% (6/8 patients) in the 100-mg dosage group and 92.0% (23/25 patients) in the 200-mg dosage group. The clinical efficacy was 90.0% (9/10 patients) for acute bronchitis, 86.7% (13/15 patients) for pneumonia, and 87.5% (7/8 patients) for chronic respiratory tract infections. The bacterial eradication rate was 85.7% (12/14 patients). No adverse events or laboratory abnormalities were observed. The AUC values were 11.2–37.5 μg·h/ml and 12.7–111 μg·h/ml for the 100-mg and 200-mg dosage groups, respectively, and the Cmax values were 1.28–3.02 μg/ml and 0.72–6.35 μg/ml, respectively, for the two groups. These results suggest that the dosage of GFLX examined in this study is clinically useful in elderly patients aged 65 or older with acute bronchitis, pneumonia, or chronic respiratory tract infections. The results of PPK analysis with the dosage management also support the efficacy of GFLX.

Key words Gatifloxacin · Elderly · Respiratory tract infection · Dosage · Pharmacokinetics/pharmacodynamics (PK/PD)

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Introduction

Gatifloxacin (GFLX) has a broad antibacterial spectrum and strong antibacterial activity against causative organisms of various respiratory infections. These causative organisms include *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Mycoplasma pneumoniae*, and Chlamydophila. GFLX is a fluoroquinolone antibacterial agent (new quinolone [NQ]) with high penetration into sputum and respiratory tissues.[1] The efficacy of GFLX against respiratory infections was previously reported to exceed 90%, and GFLX is considered to be a valuable agent for the treatment of these infections.

Ever since GFLX has been on the market, it has been reported to have side effects of hypo- and hyperglycemia, which are common to NQs. Based on an analysis of the side effects of GFLX, diabetes, renal dysfunction, and aging (65 years or more) were revealed as risk factors.[2] GFLX is contraindicated in patients with diabetes. For patients with renal dysfunction, an adjusted dosage is recommended

based on creatinine clearance (Ccr) levels, and thus the occurrence of the side effects can be decreased by reducing the dosage.

In the elderly, a decrease in renal function is generally observed with aging. For drugs eliminated renally, such as GFLX, prolonged serum half-life, elevation in the maximum serum concentration, and increase in the AUC are occasionally observed.[3] Therefore, dosage management with consideration for both efficacy and safety is recommended.

In this study, patients received a half (100 mg b.i.d.) or a quarter (100 mg q.d.) of the conventional dosage of 200 mg b.i.d., after a tentative clinical dosage of GFLX was established based on patients' body weight and age. The efficacy and safety of these dosages for respiratory infections were examined and discussed using population and pharmacokinetic (PPK) analysis.

Patients and methods

Patients

The subjects of our study were male and female patients aged 65 years or older with mild or moderate acute bacterial bronchitis, community-acquired pneumonia (bacterial pneumonia and atypical pneumonia), or chronic respiratory tract infections (such as pulmonary emphysema, chronic bronchitis, bronchiectasis, and bronchial asthma). Thirty four patients were examined at the trial sites between November 2004 and June 2006. Patients with diabetes mellitus and patients testing positive for glucose in the urine were excluded.

Design of GFLX dosage

Gatifloxacin (GFLX) 100-mg tablets (Kyorin Pharmaceutical, Tokyo, Japan) were used. GFLX 100 mg was administered orally either once or twice per day for 3–14 days, as indicated in Table 1.

Criteria for estimation of dosage

The dosage was considered based on the serum pharmacokinetics and antibacterial activities of GFLX. The AUC was calculated to obtain both efficacy against *S. pneumoniae* and safety in patients with dysglycemia. The AUC reference value for efficacy was defined as follows. The lower limit (minimum AUC) was defined as the level needed to obtain sufficient efficacy; this corresponded to an AUC/minimum inhibitory concentration (MIC) of more than 30, indicative of NQ efficacy against *S. pneumoniae*.[4] An MIC of 0.39 μg/ml was used for *S. pneumoniae*, calculated based on the MICs of 134 strains isolated from patients in clinical trials. Thus, an AUC of more than 11.7 μg·h/ml was regarded as the reference value for efficacy (Fig. 1). The upper limit (maximum AUC) was defined as an AUC of less than 60 μg·h/ml, which was previously reported to be the lowest level among ten patients with hyperglycemia.[5] Because the AUC values for patients with hypoglycemia were unknown, they were not reflected in the reference value. The maximum drug concentration (Cmax) of hypoglycemic patients was within the range of 4.21 to 5.80 μg/ml, and thus a Cmax of less than 4 μg/ml, the lowest Cmax level detected in the patients, was defined as the criterion for safety.[5]

Table 1. Dosages of gatifloxacin used in this study

	Age (years)		
	65–74	75–84	85≦
Body weight (kg)			
≦40	100 mg × 1	100 mg × 1	100 mg × 1
41–60	100 mg × 2	100 mg × 2	100 mg × 1
61≦	100 mg × 2	100 mg × 2	100 mg × 2

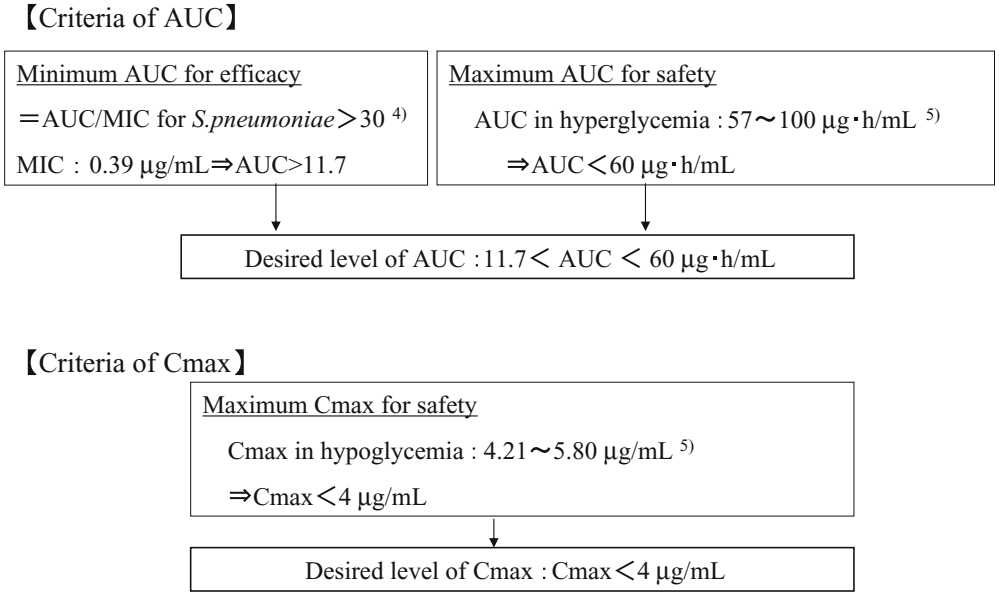

Fig. 1. Criteria of AUC and Cmax in this study. *MIC*, minimum inhibitory concentration; *Cmax*, maximum drug concentration