Levofloxacin 300 mg Once-daily Versus Levofloxacin 100 mg Three-times-daily in the Treatment of Respiratory Tract Infections in Elderly Patients

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Background & Aims : Levofloxacin (LVFX) is a newly synthesized quinolone antibiotic, and although LVFX 500 mg once-daily has been reported to have good efficacy against with respiratory tract infections in the US and other countries, once-daily the regimen seldom been used in Japan. **Methods :** This randomized, parallel-group, open, multicenter clinical study was designed to compare a 7-day course of LVFX 300 mg once-daily with LVFX 100 mg three-times-daily in elderly patients with respiratory tract infections. Between February 2002 and March 2003, a total of 63 patients with significant respiratory tract infections were enrolled in this study. **Results :** Data were available for 49 patients. The clinical cure rate was 76.0% (19/25) in the LVFX 300 mg once-daily group and 83.3% (20/24) in the LVFX 100 mg three-times-daily group. The overall clinical cure rates and overall incidences of adverse reactions were similar in both groups. There was also no significant difference in compliance between the groups. **Conclusions :** LVFX 300 mg once-daily is as effective and safe as LVFX 100 mg three-times-daily in elderly patients with respiratory tract infections. (Kitakanto Med J 2003 ; 53 : 251~255)

Key words : Levofloxacin (LVFX), elderly patients, respiratory tract infections, clinical study, three-times-daily versus once-daily

Introduction

Levofloxacin (LVFX) is a newly synthesized quinolone antibiotic that has dose-dependent and concentration-dependent antibacterial efficacy.^{1~7} Since LVFX 300 mg once-daily yields higher serum concentrations than LVFX 100 mg three-times-daily, LVFX 300 mg once-daily should have greater efficacy than LVFX 100 mg three-times-daily. Although LVFX 500 mg once-daily has been reported to have good efficacy against respiratory tract infections in the US and other countries,^{8~12} once-daily administration has seldom been used in Japan.

The present study analyzed the efficacy of a 7-day course of LVFX 300 mg once-daily and LVFX 100 mg three-times-daily for the treatment of respiratory tract

infections in elderly patients.

Methods

Subjects

Male and female patients aged 60 years or over who had a respiratory tract infection were entered into the trial. To be included patients had to have at least one of the following symptoms of respiratory tract infection: cough, sputum, dyspnea, sore throat, pain on swallowing, rhinorrhea.

Exclusion criteria were treatment with systemic antibacterial agents for more than 72 h prior to enrollment in the study; known hypersensitivity to fluoroquinolones; known central nervous system disorders that might predispose to seizures or lower the seizure threshold; the use of corticosteroids (prednisolone 10

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mg over); use of interacting drugs (antacids, sucralate, metal cations, multivitamins, theophylline, warfarin, cyclosporine, digoxin, probenecid, cimetidine, non-steroidal anti-inflammatory drugs, or antidiabetic agents).

Patients were recruited by 4 centers in Japan: Gunma University Hospital, Maebashi Kyouritsu Hospital, Tomioka Public Hospital, Kiryu Public Hospital, and obtained the approval of the ethics committee of those hospitals. All subjects gave their informed consent to the study.

Study design

The trial was designed as a randomized, parallel-group, open, multicenter clinical study to compare a 7-day course of LVFX 300 mg once-daily with LVFX 100 mg three-times-daily in Japan in elderly patients with respiratory tract infections. Randomization was performed by drawing cards (numbers 1 or 3). LVFX 300 mg once-daily was prescribed for patients who drew 1 and LVFX 100 mg three-times-daily for patients who drew 3. We had the patients fill out questionnaires (compliance and visual analogue scale for health status and appetite) on each of the 7 days after the start of administration, and patients were asked to answer yes or no on a questionnaire to determine whether they had experienced adverse reactions (epigastric pain, heartburn, nausea, vomiting, abdominal pain, bloating, soft stools, diarrhea, constipation, stomatitis, rash, skin spots, urticaria, pruritus, headache, heavy headedness, vertigo, dizziness, insomnia, palpitations, general fatigue, taste disorders, arthralgia, and tremor). On the day of entry and on the final day of the study, we examined the patients for signs and symptoms.

A clinical response was defined as "clinical cure," meaning resolution of acute signs and symptoms related to infection with no need for further antibiotic therapy.

Statistical analysis

Data are expressed as means $\pm$ SD. The significance of differences within and between groups was

Fig.1. Trial population profile. LVFX: Levofloxacin.

analyzed by the t-test. Differences between LVFX 300 mg once-daily group and LVFX 100 mg three-times-daily group were statistically analyzed by repeated measures analysis of variance (ANOVA). Probability values <0.05 were considered significant.

Results

Efficacy

Between February 2002 and March 2003, 63 patients with significant respiratory tract infections were enrolled in this study (Figure 1). Essential data for 14 patients were missing or invalid (Figure 1), and complete data were available for 49 patients (Figure 1). There were no significant differences between patient characteristics in the LVFX 300 mg once-daily group and LVFX 100 mg three-times-daily group (Table 1).

The clinical cure rate was 76.0% (19/25) in the LVFX 300 mg once-daily group and 83.3% (20/24) in the LVFX 100 mg three-times-daily group. The overall clinical cure rate was similar in both groups.

Adverse events

The majority of adverse events were assessed by the patients as mild in severity (Table 2). Adverse events judged by the investigator to be possibly or definitely drug-related were reported in 13 patients (52.0%) in the LVFX 300 mg once-daily group and in 15 patients (62.5%) in the LVFX 100 mg 3 three-times-daily

Table 1 Baseline characteristics of patients

Characteristic	Mean $\pm$ SD (No. [%] of patients)	
	Levofloxacin 300 mg once-daily (n = 25)	Levofloxacin 100 mg three-times-daily (n = 24)
Male	11	14
Female	14	10
Age (years)	67.1 $\pm$ 6.3	72.3 $\pm$ 9.5
Temperature ($^{\circ}$ C)	36.5 $\pm$ 0.4	36.4 $\pm$ 0.6
Cough	21 (84.0%)	23 (95.8%)
Sputum	15 (60.0%)	14 (58.3%)
Dyspnea	3 (12.0%)	5 (20.8%)
Sore throat	12 (48.0%)	6 (25.0%)
Pain on swallowing	4 (16.0%)	1 (4.2%)
Rhinorrhea	1 (4.0%)	4 (16.7%)

Table 2 Number of patients with adverse events (No. [%] of patients)

Adverse events	Levofloxacin 300 mg once-daily (n=25)	Levofloxacin 100 mg three-times-daily (n=24)
Epigastric pain	1 (4.0%)	2 (8.3%)
Heartburn	2 (8.0%)	2 (8.3%)
Nausea	2 (8.0%)	1 (4.2%)
Vomiting	0 (0.0%)	0 (0.0%)
Abdominal pain	1 (4.0%)	1 (4.2%)
Bloating	5 (20.0%)	3 (12.5%)
Soft stools	9 (36.0%)	4 (16.7%)
Diarrhea	1 (4.0%)	0 (0.0%)
Constipation	2 (8.0%)	2 (8.3%)
Stomatitis	1 (4.0%)	0 (0.0%)
Rash	0 (0.0%)	0 (0.0%)
Skin spots	0 (0.0%)	0 (0.0%)
Urticaria	0 (0.0%)	0 (0.0%)
Pruritus	2 (8.0%)	2 (8.3%)
Headache	5 (20.0%)	1 (4.2%)
Heavy headedness	3 (12.0%)	2 (8.3%)
Vertigo	2 (8.0%)	2 (8.3%)
Dizziness	2 (8.0%)	2 (8.3%)
Insomnia	1 (4.0%)	1 (4.2%)
Palpitation	1 (4.0%)	1 (4.2%)
General fatigue	2 (8.0%)	1 (4.2%)
Taste disorder	1 (4.0%)	0 (0.0%)
Arthralgia	1 (4.0%)	1 (4.2%)
Tremor	3 (12.0%)	0 (0.0%)

Table 3 Visual analogue scale for health status

Mean $\pm$ SD		
Days	Levofloxacin 300 mg once-daily (n=25)	Levofloxacin 100 mg three-times-daily (n=24)
0	73.5 $\pm$ 24.0	70.7 $\pm$ 24.5
1	74.9 $\pm$ 21.2	72.6 $\pm$ 24.5
2	77.2 $\pm$ 20.6	75.4 $\pm$ 23.0
3	80.5 $\pm$ 15.9	80.3 $\pm$ 17.0
4	82.5 $\pm$ 15.7	83.8 $\pm$ 12.1
5	85.5 $\pm$ 12.5	86.3 $\pm$ 9.6
6	86.6 $\pm$ 11.6	87.9 $\pm$ 9.0
7	87.3 $\pm$ 12.4	87.0 $\pm$ 12.0

Table 4 Visual analogue scale for appetite

Mean $\pm$ SD		
Days	Levofloxacin 300 mg once-daily (n=25)	Levofloxacin 100 mg three-times-daily (n=24)
0	83.9 $\pm$ 21.0	85.6 $\pm$ 18.6
1	85.2 $\pm$ 19.6	84.5 $\pm$ 20.1
2	84.0 $\pm$ 17.1	85.7 $\pm$ 18.6
3	87.0 $\pm$ 15.4	90.3 $\pm$ 10.1
4	89.8 $\pm$ 11.9	91.7 $\pm$ 9.1
5	90.5 $\pm$ 11.7	93.6 $\pm$ 4.5
6	91.6 $\pm$ 11.6	94.3 $\pm$ 4.0
7	91.7 $\pm$ 11.5	94.9 $\pm$ 3.9

group. Although there were no significant differences between the incidence of adverse events in the LVFX 300 mg once-daily group and the LVFX 100 mg three-times-daily group (Table 2), the numbers of patients with soft stools, headache, and tremor on LVFX 300 mg once-daily tended to be higher than on LVFX 100 mg three-times-daily.

Compliance

Compliance tended to be better in the LVFX 300 mg once-daily group (89.1 $\pm$ 23.4%) than in the LVFX 100 mg three-times-daily group (86.0 $\pm$ 25.6%), but the difference was not significant.

Visual analogue scales for health status and appetite

There were no significant differences between health status and appetite in the LVFX 300 mg once-

daily group and LVFX 100 mg three-times-daily group during the 7 days after the day of entry the first day of administration (Tables 3 and 4).

Discussion

This study compared 7 days of LVFX 300 mg once-daily with 7 days of LVFX 100 mg three-times-daily in elderly patients with respiratory tract infections.

Clinical efficacy of LVFX was previously reported in 13 elderly patients with respiratory tract infections.¹³ Although the clinical response was good in all patients in their study, and their efficacy rate was high, 100%,¹³ the clinical "cure" rate in the present investigation was 76.0% in the LVFX 300 mg once-daily group and 83.3% in the LVFX 100 mg three-times-daily group. This discrepancy may be due to a difference in definition between the clinical "response" rate and the clinical "cure" rate.

In the previous study of LVFX treatment for respiratory tract infections in elderly patients, eosinophilia was detected in 1 out of the 13 patients (7.7%),¹³ but it was mild, and no severe adverse events attributable to the drug were observed. As shown in Table 2, the majority of adverse events in the present study were also judged to be mild in severity, but they were reported in 13 of the 25 (52.0%) patients in the LVFX 300 mg once-daily group and in 15 of the 24 (62.5%) patients in the LVFX 100 mg three-times-daily group. The incidence of adverse events may have been higher in the present study, because the patients answered yes or no to the questions on adverse reactions.

As shown in Table 2, the number of patients with soft stools may have been higher in the LVFX 300 mg once-daily group ($n = 9$; 36.0%) than in the LVFX 100 mg three-times-daily group ($n = 4$; 16.7%), because LVFX 300 mg once-daily may have a more potent effect than LVFX 100 mg three-times-daily, not only on the respiratory tract but on the gastrointestinal tract. The numbers of patients with headache and tremor also tended to be higher in the LVFX 300 mg once-daily group ($n = 5$; 20.0%, $n = 3$, 12.0%) than in the LVFX 100 mg three-times-daily group ($n = 1$; 4.2%, $n = 0$; 0.0%), because LVFX 300 mg once-daily had a more potent effect on the central nervous system than LVFX 100 mg three-times-daily.

Compliance on once-daily medications is better than on twice-daily¹⁴⁻¹⁷ or three-times-daily¹⁸ medications, and in this study compliance in the LVFX 300 mg once-daily group (89.1%) was better than in the LVFX 100 mg three-times-daily group (86.0%).

As shown in Tables 3 and 4, both health status and appetite during the 7 days after the day of entry were similar in both groups, and the overall results were

generally similar in both groups.

In summary, LVFX 300 mg once-daily is as effective and safe as LVFX 100 mg three-times-daily in elderly patients with respiratory tract infections.

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