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Clinical Study on Concentrations of Lomefloxacin in Pleural Fluid

Toshiharu MATSUSHIMA, Junichi NAKAMURA and Masayoshi KAWANISHI

Department of Medicine, Kawasaki Hospital, Kawasaki Medical School, Okayama 700, Japan

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ABSTRACT. A single dose of lomefloxacin, a new oral antibacterial agent with excellent antibacterial potency and spectrum and safety profile, was administered at 200 mg, the recommended dose, to 6 patients with accumulated pleural fluid in order to determine drug concentrations in the pleural fluid over time after treatment.

Lomefloxacin appeared in the pleural fluid 1 hr after oral treatment in some cases. The mean concentration increased gradually from 0.49 μg/ml 2 hrs after treatment to 0.81, 1.00 and 1.16 μg/ml, respectively, 3, 4 and 6 hrs after treatment. A concentration of 0.45 μg/ml was still present 24 hrs after treatment. The AUC determined up to 24 hrs after treatment was 18.51 μg hr/ml. Concentrations reached in the pleural fluid 2 hrs after treatment, in particular those reached 3 hrs after treatment, were higher than MICs of lomefloxacin for most bacteria against which the drug has been found to be effective, and concentrations remained above MICs over a long period of time.

In addition, concentrations in the pleural fluid obtained in different patients showed very little variability, although the drug was orally administered. This finding suggests that the drug's absorption from the intestine and the passage through the pleura are very stable. Therefore, lomefloxacin seems to be a drug of choice for use in studies on passage of drugs through various barriers.

Key words : lomefloxacin — new quinolone — pleural fluid — drug concentration

Although a great variety of antibacterial agents are available at present, new quinolones with excellent antibacterial activity are being actively development in recent years.

Lomefloxacin is a new quinolone antibacterial agent developed by Hokuriku Seiyaku Co., Ltd. It has a very broad antibacterial spectrum which covers not only Gram-positive cocci but also Gram-negative bacilli. It has been found to be a very useful drug which is associated with only a few side effects.[1)]

In the present study, we determined concentrations of this drug in the pleural fluid in order to determine whether or not concentrations effective for the treatment of pleural inflammatory diseases can be achieved, as well as to evaluate the role of the pleura as a barrier against drug penetration. Only

松島敏春，中村淳一，川西正泰

a few studies have been carried out with respect to concentrations of antibacterial agents, in particular new quinolones, in the thoracic cavity. Interesting findings were obtained in the present study.

SUBJECTS AND METHODS

Included in the present study were 6 patients with pleurisy, 4 males and 2 females aged between 23 and 85 years (mean: 68 years) who were admitted to the Second Department of Medicine of Kawasaki Medical School, Kawasaki Hospital between July, 1987 and January, 1989. The underlying diseases which caused pleurisy were metastasis of malignant tumors (pleural mesothelioma, malignant lymphoma, lung cancer and liver cancer) to the pleura and resulting accumulation of the pleural fluid in 4 patients, inflammatory accumulation of the pleural fluid for unknown cause in 1 and accumulation of the pleural fluid due to heart failure in the other.

Table 1 shows information related to the pleural fluid. Drug concentrations in the pleural fluid were generally determined within 15 days after the confirmation of the accumulation of the pleural fluid, although 1 to 1.5 months elapsed until concentrations were determined in some cases. The amount of accumulated pleural fluid as determined based on chest X-ray films was "slight" in 2 cases, "moderate" in 3 and "marked" in 1. The protein concentration in the pleural fluid ranged between 2.6 and 4.8 g/dl (mean: 4.2 g/dl). Only the pleural fluid obtained from Case 5 who had heart failure was transudate and contained only a small amount of protein. The color was yellow or bloody and turbid. Findings obtained by cell classification and cytological diagnosis conducted using pleural fluid sediments are also shown in Table 1.

A single dose of lomefloxacin (two 100 mg capsules) was administered after a meal. Pleural fluid samples were obtained at hourly intervals after administration of the drug from thoracotube. The number of samples obtained varied from 1 to 7. Administration of drug, and drawing of blood and/or pleural fluid were performed with patient's permission, so serum concentrations were determined in only 3 cases. Pleural fluid samples were frozen after collection and thawed immediately before determination.

Concentrations of lomefloxacin were determined by bioassay using paper discs and Escherichia coli KP as the test organism.

RESULTS

Concentrations of lomefloxacin determined in the pleural fluid and serum are shown in Table 2. Pleural fluid concentrations were below the limit of detection in most cases 0.5 and 1 hr after oral treatment but increased to measurable levels by 2 hrs after treatment in all cases. Concentrations continued to increase thereafter until a peak was observed between 4 and 6 hrs after treatment. Significant residual concentrations were still observed 24 hrs after treatment. Changes in pleural fluid concentrations are illustrated in Fig. 1. The curve which was drawn by connecting the mean obtained at each time point-data shown by closed circles were excluded as they were obtained from only one patient-clearly delineated changes in concentrations of lome-

TABLE 1. Characteristics of pleural fluid

No.	sex	age	underlying disease	duration (Mon.)	volume	protein (g/dl)	color	sediment (%)			markers	cytology
								Seg.	Lym.	malig.		
1	F	38	pleural mesothelioma	1.5	L	4.5	yellow	32	61	0	ADA 59.7	II
2	M	80	lung ca. (epi)	0	S	4.3	sl. bloody	—	—	—	not remarkable	V
3	M	23	malignant thymoma	0	M	4.3	yel-brow	0	8	80	ADA 150	V
4	F	80	pleuritis (unknown)	1.2	M	4.8	bloody	12	87	0	not remarkable	II
5	M	85	CHF, pneumonia	1/3	S	2.6	sl. yellow	3	42	0	not remarkable	II
6	M	67	metastatic (hepatoma)	1/2	M	4.8	bloody	35	46	2	α-feto 77×10^3	V

TABLE 2. Pleural fluid concentrations (μg/ml) of lomefloxacin after a single oral administration of 200 mg

Time (h.) / No.	1/2	1	2	3	4	5	6	12	24
1	N.D.	0.23	0.56 (2.83)	0.83	1.19 (2.19)		1.36	1.50	
2	N.D.	N.D.	0.34 (2.85)	0.63	0.94 (2.58)	1.08	1.30		
3	N.D.	N.D.	0.33	0.61	0.76	0.78	0.66		
4							1.47		0.64
5				0.85 0.99					
6	0.23 (3/4 h.)		0.74	0.96 (2.08)	1.12 (1.42)		1.03		0.26
Mean		0.08	0.49	0.81	1.00	0.93	1.16		0.45

N.D. : $<$ 0.1 μg/ml, ( ) : Serum concentration (μg/ml)

TABLE 3. Characteristics of pleural fluid of case No. 5

	right	left
Color	sl. yellow	sl. yellow
Turbidity	+	+
pH	8.0	8.0
Specific gravity	1.022	1.021
Protein (g/dl)	2.6	2.6
Sediment (%)		
RBC	5~10	many
WBC	0~ 1	many
Neu.	1	3
Lym.	96	42
Other	3	55
Lomefloxacin concentrations 3 hrs after treatment (μg/ml)		
Pleural fluid	0.85	0.99
Serum	2.08	

floxacin in the pleural fluid. Differences in concentrations obtained from different patients were very slight at all time points.

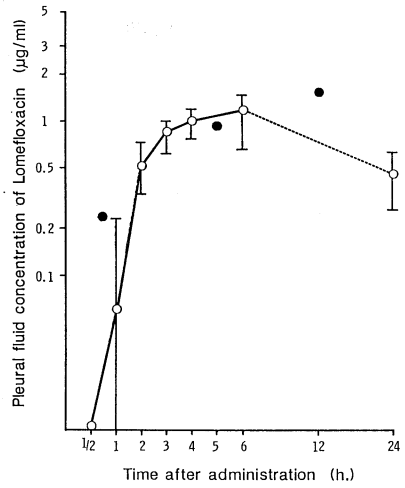

Fig. 1. Pleural fluid concentrations of lomefloxacin after a single oral administration of 200 mg

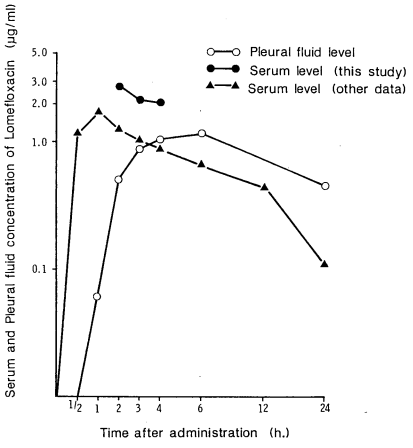

Fig. 2. Comparison of serum and pleural fluid level after a single oral dose of 200 mg (▲—▲ : published data by R. Saito, Hokkaido Univ.)

Fig. 2 compares concentrations of lomefloxacin in the pleural fluid and serum obtained in 3 patients. Serum concentrations were thought to peak about 2 hrs after treatment in the present study because a single 200 mg dose was orally administered after a meal. In fact, values found were the highest at 2 hrs after treatment and decreased gradually 3 and 4 hrs after treatment. In contrast, concentrations in the pleural fluid continued to increase 4 hrs after treatment and showed a peak about 6 hrs after treatment.

Fig. 3 illustrates changes in lomefloxacin concentrations in the pleural fluid

and serum in Case 6 in whom determinations were made the most frequently. Overall, changes observed in this case are very similar to those in mean values obtained in the 6 cases.

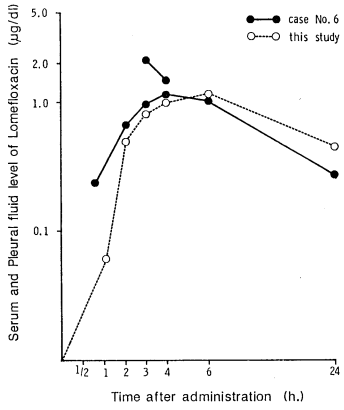

Fig. 3. Pleural fluid and serum level of lomefloxacin in Case No. 6 compared with mean level of this study

Table 3 compares drug concentrations in the pleural fluid obtained from the left and right thoracic cavities in Case 5. This patient, a 85-year-old male admitted for the treatment of anxiety neurosis, had heart failure due to arteriosclerotic cardiopathy during hospitalization and had accumulation of the pleural fluid in the left and right thoracic cavities. Although the pleural fluid samples obtained from the left and right thoracic cavities were similar, differences were noted with respect to cell counts and composition.

Blood and left and right pleural fluid samples were obtained 3 hrs after oral administration of 200 mg of lomefloxacin for the comparison of drug concentrations. The lomefloxacin concentration was 0.99 and 0.85 μg/ml, respectively, in the left and right pleural fluid samples, suggesting that the drug concentration is similar in the left and right pleural fluid samples.

DISCUSSION

In the present study, we determined concentrations of lomefloxacin in the pleural fluid to answer two questions.

The first question was whether or not drug concentrations in the pleural fluid reached after oral administration of a single 200 mg dose, the recommended dose, were high enough to inhibit the growth of bacteria. The lomefloxacin concentration in the pleural fluid was found to be 0.33 μg/ml or higher (mean: 0.49 μg/ml) 2 hrs after oral administration of a single 200 mg dose. It increased to 0.61 μg/ml or higher (mean: 0.81 μg/ml) 3 hrs after treatment, 0.76 μg/ml or higher (mean: 1.00 μg/ml) 4 hrs after treatment and 0.66 μg/ml or higher (mean: 1.16 μg/ml) 6 hrs after treatment. The mean concentration was still 0.45 μg/ml 24 hrs after treatment. The highest concentration (1.50 μg/ml) was obtained 12 hrs after treatment. According to Hirose,[2] the MIC

(inoculum size, 10^6 CFU/ml) of lomefloxacin is 0.78 μg/ml for *S. aureus* FDA209P JC-1, 3.13 μg/ml for *S. pyogenes* Cook, 0.20 μg/ml for *E. coli* NIHJ JC-2, 0.10 μg/ml for *K. pneumoniae* PCI-602, 0.10 μg/ml for *S. typhi* 901, 0.39 μg/ml for *E. aerogenes* ATCC13048, 0.39 μg/ml for *E. cloacae* 963, 0.39 μg/ml for *P. mirabilis* IFO3849, 0.05 μg/ml for *P. vulgaris* OX-19, 0.10 μg/ml for *M. morganii* IFO3848, 0.39 μg/ml for *S. marcescens* IAM1184, 1.56 μg/ml for *P. aeruginosa* IFO3445 and 0.78 μg/ml for *P. aeruginosa* NCTC 10490. Lomefloxacin concentrations in the pleural fluid determined in the present study are therefore higher than MICs with respect to most Gram-negative organisms from 2 to 24 hrs after treatment and with respect to *S. aureus* and almost all Gram-negative rods between 3 and 6 hrs after treatment. Lomefloxacin orally administered at the recommended dose was thus found to produce concentrations in the pleural fluid which are higher than MICs with respect to various organisms against which it has been found to be effective and to maintain concentrations above MICs over a long period of time.

In general, drug concentrations in the serum and pleural fluid are maintained at high levels over a long period of time in patients with renal dysfunction.[3] In the present study, however, only Case 5 had heart failure, and serum BUN and creatinine levels were normal in all cases.

Only a few studies have been conducted regarding the penetration of antibacterial agents into the pleural fluid. The number of clinical studies is particularly limited on concentrations of antibacterial agents in the pleural fluid. In addition, the limited number of recent studies focus mostly on cephalosporins[3–5] and only rarely on AGs.[6] There is virtually no study on new quinolones whose efficacy has been highlighted in recent years. Therefore, our study, which showed that lomefloxacin, a new quinolone, was able to produce effective concentrations in the pleural fluid, is very useful.

The second question was what role the pleura plays as a barrier against the penetration of the drug into pleural fluid. In general, barriers become looser in the presence of inflammation than in the normal condition. This is also true with respect to the pleura as demonstrated by our study in animals.[7] In the present study, the pleural fluid was exudative in 5 cases and transudative in the remaining 1 case, and the concentrations obtained in the transudate were similar to those obtained in the exudate. Since transudative pleural fluid was obtained in only one case in the present study, further studies are needed as to whether this finding is specific to lomefloxacin or is an exceptional finding obtained in this specific case.

Many studies suggest that the penetration of a drug through the pleura in patients with pleurisy is related to the protein binding rate for that drug and that the lower the protein binding rate, the greater is the penetration.[8] In fact, the maximum pleural fluid concentration/maximum serum concentration ratio has been shown to be inversely related to the serum protein binding rate for CER.[9] Since the serum protein binding rate of lomefloxacin has been found to be about 20%,[10] high concentrations in various organs may be explained by this low protein binding rate. Incidentally, lomefloxacin concentrations in sputum were also found to be comparable to or apparently higher than maximum serum concentrations in humans,[11] suggesting that the drug easily crosses the blood-bronchus barrier, a barrier similar to the pleura.

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