THE KINETICS OF OXACEPHEMS IN PLEURAL EFFUSION

HOZUMI YAMADA, OSAMU KATOH, YOSUKE AOKI, SHIGETAKA KUROKI, TSUNEKO YAMAGUCHI and KENYA HIURA

Department of Internal Medicine, Saga Medical School, Nabeshima, Nabeshima-cho, Saga 840-01, Japan

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We studied serum and pleural fluid concentrations in 14 patients after intravenous infusion of 2 g of LMOX or FMOX. Eight patients received LMOX and six FMOX.

The pharmacokinetic parameters of both drugs in serum were : (1) a peak concentration of 104 ± 31 μg/ml (LMOX) and 76 ± 16 μg/ml (FMOX) at the end of infusion ; (2) an elimination half-life of 2.5 ± 0.5 h (LMOX) and 1.3 ± 0.1 h (FMOX) ; (3) an area under the concentration curve of 332 ± 94 μg·h^{-1} ml (LMOX) and 157 ± 30 μg·h^{-1} ml (FMOX). These data suggest that FMOX was cleared more rapidly from serum.

On the other hand, both drugs when given intravenously penetrated slowly into pleural fluid after initiation of drug infusion, and the pleural fluid concentration reached a peak of 31 ± 20 μg/ml at 4 h for LMOX and 21 ± 14 μg/ml at 2 h for FMOX. The elimination half-lives in pleural fluid for LMOX and FMOX were 7.4 ± 1.2 h and 5.4 ± 1.4 h.

In addition, the multiple-dose administration given in twice daily infusions of either oxacephem did not increase serum or pleural fluid concentrations.

These data suggest that both oxacephems penetrated into pleural fluid at a high rate of 27.5%, and that their elimination half-lives were 3-4 times longer in pleural fluid than in serum. We believe that the pharmacokinetics of both drugs may be of great advantage for the treatment of pleural space infections.

Key words : Latamoxef, Flomoxef, Blood concentration, Pleural fluid concentration, **Pharmacokinetic parameters**

INTRODUCTION

There are two different types of oxacephem antibiotic. We have studied the pharmacokinetics of latamoxef (LMOX) in pleural fluid after single-dose administration in an earlier study[1].

In the present study, we determined the penetration into pleural fluid of a newer oxacephem, flomoxef (FMOX), given by single and multiple injections, and made a pharmacokinetic comparison of both oxacephems.

MATERIALS AND METHODS

The study group consisted of 14 patients (12 men and 2 women ; 38-83 y. o., body weight 47-77 kg) with pleural effusion (Table 1). All subjects were tested from May 1983 to August 1987 at Saga Medical School. Twelve patients (No's. 2-5, 7-10, 12, 14) had cytologically proven carcinomatous pleural effusion, and four (1, 6, 11, 13) suffered from tubercular pleural effusion which was either confirmed by pleura biopsy(1, 13) or suspected from response to antitubercular drugs (6, 11).

Each subject had 300-2,300 ml of pleural fluid containing 3.2-6.8 g of protein per dl at the time of testing. Eight patients had hemorrhagic pleural fluid, and six yellowish clear effusion. All subjects had normal liver and kidney functions during the study. Each patient had a thoracic catheter (trocar catheter, size 10-12 F) implanted before the study, the exposed end of which was always clamped except during sampling. Just before drug administration, 20-500 ml of pleural fluid and 10 ml of venous blood were obtained as control samples.

In the single-dose administration study, 2 g of

Table 1. Patients studied for penetration of LMOX or FMOX into pleural fluid

Patient No.	Age	Sex	Body weight	Disease	Pleural fluid	
					volume (ml)	protein (g/dl)
1	45	M	65	tuberculosis	650	4.8
2	83	F	47	lung cancer	1,100	6.8
3	69	M	50	lung cancer	900	3.2
4	48	M	48	lung cancer	1,800	4.8
5	69	M	56	lung cancer	1,400	4.9
6	83	M	47	tuberculosis	460	4.5
7	55	F	50	lung cancer	820	5.3
8	38	M	77	lung cancer	370	4.2
9	68	M	52	lung cancer	530	3.4
10	68	M	50	lung cancer	1,400	3.3
11	82	M	47	tuberculosis	470	5.3
12	59	M	58	lung cancer	920	5.4
13	78	M	51	tuberculosis	300	4.4
14	57	M	49	lung cancer	1,200	4.7

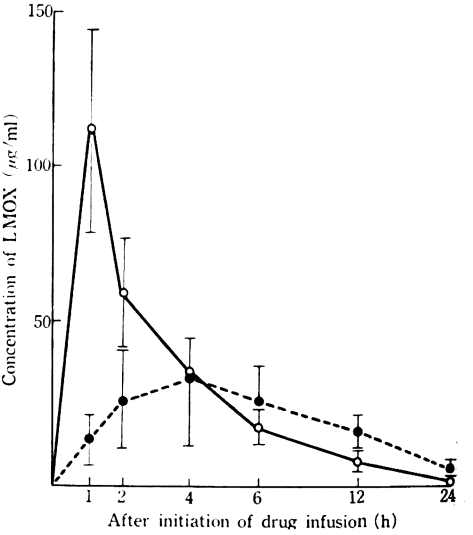
Six patients (No's. 1~6) received 2g of LMOX by single injection and three patients (No's. 6~8) received LMOX five times twice daily. Six patients (No's. 9~14) received 2g of FMOX by single and multiple injections.

LMOX (1-6) or FMOX (9-14) were infused intravenously over a 1-hour period. Venous blood (5-10 ml) and pleural fluid (10-20 ml) were obtained at 1, 2, 4, 6, 12 and 24 h after initiation of drug administration.

For the multiple-dose administration study, a total of five injections of LMOX (6-8) or FMOX (9-14) were administered. The subjects received an infusion twice a day, at the end of which venous blood was obtained, and pleural effusion was sampled at 2, 4 and 6 h after each injection.

Pleural fluid was drained off completely after the last sampling for estimation of total fluid volume. All samples were centrifuged, and serum and pleural fluid supernatants were stored at below −20°C until assayed. The concentrations of both oxacephems in serum and pleural fluid were determined by bioassay with the agar diffusion method. Serum samples were diluted with standard human serum, and pleural fluid was diluted with 20 M phosphate buffer (pH 7.0). *Escherichia coli* 3437 was used as the test organism.

The elimination half-lives of both drugs were calculated from the time of peak concentration to 6 h in serum and to 12 h in pleural fluid after initiation of drug infusion. The area under the serum concentration curve was calculated by the trapezoidal rule[2] and the penetration rate as the ratio of pleural fluid peak concentration to serum peak concentration of the drugs.



Six patients (No's. 1~6) received 2g of LMOX by intravenous infusion over one hour. Each point represents the mean concentration, and vertical bars indicate standard deviation (SD) of the means.

Fig. 1. Serum (solid line) and pleural fluid (broken line) concentrations of LMOX after single-dose administration

Table 2. Pharmacokinetic parameters of LMOX given by 2g infusion over one hour in patients with pleural fluid

Patient No.	Penetration rate (%) (peak of pleural fluid /peak of serum)	Elimination half-life (h)		Area under the serum concn. curve ($\mu g \cdot h^{-1} ml$)
		serum	pleural fluid	
1	(10/107) 9.3	2.3	8.1	303
2	(13/104) 12.5	2.6	6.7	375
3	(9/43) 20.9	2.4	6.8	167
4	(35/118) 29.7	3.0	9.1	322
5	(34/122) 27.9	1.7	8.0	395
6	(59/128) 46.1	2.9	5.7	434
7	(26/88) 29.5	NT	NT	NT
8	(36/82) 43.9	NT	NT	NT
mean±SD	27.5±13.2	2.5±0.5	7.4±1.2	332±94

Elimination half-life was calculated from the time of peak concentration to 6 h (serum) or 12 h (pleural fluid) after initiation of drug administration.
The area under the serum concentration curve (AUC) was calculated by the trapezoidal rule.
NT : not tested, SD : standard deviation.

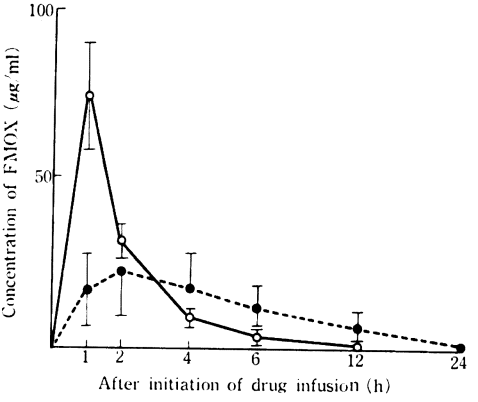
RESULTS

Single-dose administration

(1) LMOX : Six patients (No's. 1-6) received intravenous infusion of 2 g LMOX. Serum and pleural fluid concentrations after a single injection are shown in Fig. 1. The serum concentration of LMOX was 104 ± 31 μg/ml (mean ± SD) at the end of infusion, 56 ± 16 μg/ml at 2 h, and 17 ± 6 μg/ml at 6 h. Elimination half-life, area under the serum concentration curve and penetration rate of LMOX are presented in Table 2. The elimination half-life of LMOX in serum was 2.5 ± 0.5 h (mean ± SD), when calculated from the time of peak concentration to 6 h, and the area under the serum concentration curve, calculated by the trapezoidal rule, was 332 ± 94 $\mu g \cdot h^{-1}$ ml (mean ± SD).

On the other hand, the pleural fluid concentration of LMOX increased to 12 ± 7 μg/ml at the end of infusion and reached a peak of 31 ± 20 μg/ml at 4 h. The elimination half-life of LMOX was 7.4 ± 1.2 h in pleural fluid, and the penetration rate of LMOX ranged from 9.4% to 46.1% (mean 27.5%).

(2) FMOX : 2 g of FMOX was given intravenously to 6 patients (9-14). Serum and pleural fluid concentrations of FMOX after a single injection are shown in Fig. 2. The serum concentrations of FMOX were 76 ± 16 μg/ml at the end of infusion, 31 ± 5 μg/ml, and 3 ± 1 μg/ml at 6 h.



Six patients (No's.9 ~14) received 2g of FMOX by intravenous infusion over one hour. Each point represents the mean concentration, and vertcal bars indicate standard deviation (SD) of the means.

Fig. 2. Serum (solid line) and pleural fluid (broken line) concentrations of FMOX after single-dose administration

The serum peak concentration of FMOX was significantly lower than that of LMOX given under the same management ($p<0.05$). Elimination half-life, area under the serum concentration curve and penetration rate of FMOX are presented in Table 3. The serum elimination half-life of 1.3 ± 0.1 h was significantly shorter than 2.5 ± 0.5 h for LMOX ($p<0.01$), and the area under the serum concentration curve of 157 ± 30 $\mu g \cdot h^{-1}$ ml was also significantly smaller than 332 ± 94 $\mu g \cdot h^{-1}$ ml

Table 3. Pharmacokinetic parameters of FMOX given by 2g infusion over one hour in patients with pleural fluid

Patient No.	Penetration rate (%) (peak of pleural fluid /peak of serum)	Elimination half-life (h)		Area under the serum concn. curve ($\mu g \cdot h^{-1} ml$)
		serum	pleural fluid	
9	(4/78) 5.1	1.2	5.4	148
10	(21/81) 25.9	1.2	5.5	164
11	(27/81) 33.3	1.2	3.0	180
12	(44/96) 45.8	1.3	4.6	188
13	(18/68) 26.5	1.4	7.0	158
14	(13/46) 28.3	1.5	6.7	104
Mean±SD	27.5±13.2	1.3±0.1	5.4±1.4	157±30

Elimination half-life was calculated from the time of peak concentration to 6 h (serum) or 12 h (pleural fluid) after initiation of drug administration.
The area under the serum concentration curve (AUC) was calculated by the trapezoidal rule.
SD : standard deviation.

Table 4. Serum and pleural fluid peak concentrations of LMOX and FMOX after multiple-dose administration

Infusion	Peak concentrations of LMOX		Peak concentrations of FMOX	
	serum (n = 3)	pleural fluid (n = 3)	serum (n = 6)	pleural fluid (n = 6)
1 st	99±25	42±16	76±16	21±14
2 nd	139±43	49±22	82±21	17±9
3 rd	132±27	46±19	78±23	18±7
4 th	105±18	41±17	78±40	19±6
5 th	104±11	43±13	77±27	14±8

Either drug (2g) was given five times in twice daily infusions.
Three patients (No's. 6~8) received LMOX and six patients (No's. 9~14) received FMOX.

for LMOX ($p<0.01$). FMOX injected intravenously penetrated into pleural fluid more quickly than did LMOX. The pleural fluid concentration of FMOX increased to 17 ± 11 μg/ml at the end of infusion, and reached a peak of 21 ± 14 μg/ml at 2 h. This peak level in pleural fluid was lower than 31 ± 20 μg/ml for LMOX (NS). However, the penetration rate of FMOX ranged from 5.1%-45.8% (mean 27.5%). This mean was the same as that for LMOX. The elimination half-life of FMOX was 5.4 ± 1.4 h in pleural fluid. This half-life was significantly shorter than 7.4 ± 1.2 h for LMOX ($p<0.05$).

Multiple-dose administration

LMOX and FMOX were given five times in twice daily infusions to 3 patients (6-8) and to 6 patients (8-14), respectively. The peak serum and pleural fluid concentrations after each injection are shown in Table 4. The peak serum level of LMOX ranged from 99 ± 25 μg/ml to 139 ± 42 μg/ml, and the highest concentration in pleural fluid ranged from 41 ± 17 μg/ml to 49 ± 22 μg/ml at 4 h. On the other hand, the peak serum and pleural fluid concentrations ranged from 76 ± 16 μg/ml to 82 ± 20 μg/ml and from 14 ± 8 μg/ml to 21 ± 14 μg/ml, respectively. Multiple injections of either oxacephem did not increase concentrations in serum and pleural fluid.

DISCUSSION

In numerous clinical studies, it has been demonstrated that LMOX and FMOX are very useful for the treatment of lung and pleural space infections[3,4,5]. In particular, these drugs are often used as first choice antibiotics for empyema because of their excellent antibiotic effect on anaerobic bacteria[6,7,8]. We therefore thought it important to determine the pharmacokinetics in pleural fluid of both oxacephems, and in the present study, we

investigated their distribution in pleural fluid when infused intravenously by single or multiple injections.

In the single-dose study, 2 g infusion of LMOX or FMOX produced the serum concentration curves shown in Fig's. 1 and 2. The peak concentration of each oxacephem was 104 ± 31 μg/ml and 76 ± 16 μg/ml, respectively. Both peak levels were lower than those of other newer cephems : cefoperazone 209 μg/ml, ceftizoxime 124 μg/ml, and cefmenoxime 107 μg/ml, under the same management of 2 g infusion over 1 h[1,9,10]. Comparing both oxacephems, the peak concentration of LMOX was significantly higher than that of FMOX ($p<0.05$). The area under the serum concentration curve and the elimination half-life in serum of LMOX were about two times greater than those of FMOX ($p<0.01$). These data suggest that FMOX is cleared more rapidly from serum. Probably this rapid clearance of FMOX from serum can be attributed to the pharmacological characteristics of the drug, especially its lower protein binding capacity (30%) as compared to that of LMOX (53%)[11,12].

The concentration curves of LMOX and FMOX in pleural fluid (Fig's. 1 and 2) suggest that FMOX penetrated into pleural fluid more quickly, but that its peak level was lower than that of LMOX. The peak levels of both oxacephems in pleural fluid correlated with their peak serum concentrations, area under the serum concentration curves and elimination half-lives in serum. There was no significant difference in patients' condition (age, body weight, disease, fluid volume, fluid protein) in each group. Consequently, the pharmacological characteristics of both oxacephems, especially their protein binding capacities, may be one of the most important factors limiting their penetration into pleural fluid.

There have been several studies dealing with penetration rates of cephems into pleural fluid. TAKAMOTO et al.[13] reported penetration rates for cefazolin (6.9%) and ceftizoxime (15.8%), and we determined the penetration rate of cefoperazone (8.2%) in a previous study[1]. The penetration rates of both oxacephems (27.5%) are considerably higher than those of other cephems. The high penetration rates of both oxacephems may be of great advantage for the treatment of pleural space infections.

GERDING et al.[14] have also reported that multiple injections of cephems significantly increased their peak concentrations in ascites. In this study, however, twice daily infusions of either oxacephem did not increase its peak concentration levels in serum and pleural fluid.

Our data suggest that LMOX and FMOX, given intravenously, penetrated into pleural fluid sufficiently to exceed reported MICs for most susceptible organisms, and that the elimination half-lives of both oxacephems were three to four times longer in pleural fluid than in serum. These pharmacokinetics in pleural fluid of LMOX and FMOX may be of great advantage in fighting infection in the pleural space.

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Oxacephem 剤の胸水内動態

山田穂積・加藤　収・青木洋介
黒木茂高・山口常子・日浦研哉
佐賀医科大学内科*

LMOX と FMOX の 2 g 点滴静注時の薬剤胸水移行を 14 名の患者で検討した。両薬剤の最高血中濃度は LMOX 104 ± 31 μg/ml と FMOX 76 ± 16 μg/ml であり，血中半減期は LMOX 2.5 ± 0.5 h と FMOX 1.3 ± 0.1 h であった。また，AUC (area under the serum concentration curve) は LMOX 332 ± 94 μg·h^{-1}ml と FMOX 157 ± 30 μg·h^{-1}ml であった。一方，胸水内濃度は，点滴開始後に徐々に上昇し，LMOX は 4 h で最高値 31 ± 20 μg/ml，FMOX は 2 h で最高値 21 ± 14 μg/ml を示した。また，胸水内半減期はそれぞれ 7.4 ± 1.2 h と 5.4 ± 1.4 h であった。なお，両薬剤の血中および胸水の pharmacokinetic parameters は胸水内最高濃度を除いて，いずれも有意の差であった。また，1 日 2 回の連続投与を 9 名に行なったが，血中と胸水内濃度に有意の変化を認めなかった。今回の成績は，LMOX と FMOX が高い胸水移行率 (27.5%) を有し，しかも胸水内半減期は血中よりも著しく長いことを示すものであった。両薬剤は抗菌力ばかりでなく，このような薬理学的特徴からも，胸腔内感染の治療に極めて有利な薬剤と考えられる。

* 佐賀市鍋島町大字鍋島三本杉