KAWASAKI MED. J. VOL. 15 : NO. 2, 59-63 (1989)

Serum Concentration of Flomoxef in Administration of One Hour Infusion Every Eight Hours a Day

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Accepted for publication on September 13, 1989

ABSTRACT. Flomoxef (FMOX) is a new, parenteral oxacephem antibiotic with strong, broad-spectrum antimicrobial activity. To compensate for short half time of this drug, multi-divided administration of the drug was attempted, and the concentrations of FMOX in the blood were determined.

The treatment by dripping intravenous infusion of FMOX thrice daily or one hour infusion every eight hours were carried out in six patients with an indwelling intravenous catheter. Four patients had pneumonia and the other two suffered from respiratory infections with lung cancer. With the patient's permission, six blood samples were drawn from each patient just before and after infusions, and the concentration of FMOX was determined by bioassay. The mean serum concentration in the six patients ranged between three troughs just before infusion and three peaks just after infusion, being 1.40 μg/ml, 2.59 μg/ml and 1.84 μg/ml, and 47.32 μg/ml, 52.17 μg/ml and 50 μg/ml, respectively. These concentrations, even troughs, were higher than the MIC_{90} of almost all bacteria considered to be sensitive to FMOX. In fact, five out of six patients showed a good response to this treatment. No side effects were observed, except mild and transient elevation of transaminase in one case.

In conclusion, we recommend the administration of FMOX thrice daily for patients with severe pulmonary infections, especially from the standpoint of its blood concentration.

Key words : Flomoxef (FMOX) — blood concentration — respiratory infection — multi-divided administration

FMOX, a new parenteral oxacephem antibiotic, has strong and broad-spectrum, antimicrobial activity.[1,2] A high serum concentration of FMOX following parenteral administration has been reported in several studies,[3,4] but its half time has also been reported to be less than one hour. In order to compensate for this short half time and the short postantibiotic effect[5] in cephalosporines, multi-divided infusion of FMOX was considered to be ideal. The present investigation was designed to determine the serum concentration of FMOX following administration thrice daily.

PATIENTS AND METHODS

The six patients in the present study included four patients with pneumonia and two patients with lung cancer and lower respiratory tract infections.

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These patients, four males and two females, who ranged in age from 47 to 83 years old (Mean: 59.7), were admitted to our department of Kawasaki Medical School, Kawasaki Hospital between August 1988 and February 1989. Since these severely ill patients were receiving continuous nourishment through indwelling intravenous catheters, multi-divided administration of antimicrobial agents (FMOX) was employed (Table 1).

TABLE 1. Patient's characteristics

Case No.	1	2	3	4	5	6
Age, Sex	67, F	57, M	47, M	52, M	52, M	83, F
Disease	Pneumonia	Pneumonia	LRTI	Pneumonia	LRTI	Pneumonia
Underlying Disease	Bronchi-ectasis	CVD	Lung Ca. Hepatitis	D. M.	Lung Ca.	Perkinson
Isolated bacteria	S. aureus	E. coli	Unknown	Unknown	S. pneu-moniae	Unknown
FMOX (g×time×day)	1.0×3×8	1.0×3×15	1.0×3×5	1.0×3×14	1.0×3×14	1.0×3×12
Clinical Effect	good	good	poor	excellent	good	excellent
Adverse reaction	—	—	GOT↑,GPT↑	—	—	—
Body weight	62	n. d.	43	58	66	41
Activity	bed rest	bed rest	normal	normal	bed rest	bed rest
Serum protein	7.1	7.2	6.9	6.6	5.2	6.4
RBC ($\times 10^4$)	346	414	302	351	358	336
WBC ($\times 10^3$)	10.1	16.4	18.5	8.6	9.9	8.3
GOT (IU/l)	14	18	39	25	102	55
GPT (IU/l)	11	13	26	16	104	56
Al-P (IU/l)	240	157	1315	164	520	192
Urine (ml/day)	1400	1150	2500	1600	1600	1130
Proteinuria	—	—	—	+	±	—
BUN (mg/dl)	13	12	8	20	17	17
Cr (mg/dl)	0.5	0.4	0.5	0.5	1.0	0.5
Ccr (ml/min)	139.2	184	80.9	n. d.	75	n. d.

On the third day after the start of every eight hours administration of FMOX against respiratory infections, blood samples were drawn with the patient's permission or the family's in one case, just before and after one hour dripping intravenous infusion. Infusion was done for exactly one hour, so the serum level of the drug was expected to be lowest (trough) at the starting point, and highest (peak) at the end. Each blood sample was centrifuged at 3,000 g for 10 minutes and then serum was extracted and frozen. The sera were thawed immediately before determination. Concentrations of FMOX were determined by a bioassay method using the band culture method and E. coli 7,437 strain as the test organism.[6]

RESULTS

The serum concentrations of FMOX in the six cases just before the start of the first drip infusion on the morning of the third therapeutic day ranged

between 0.17 μg/ml and 3.08 μg/ml (Mean: 1.40 μg/ml). Just after one hour's infusion it rose to between 35.40 μg/ml and 63.60 μg/ml (Mean: 47.32 μg/ml). After that the serum concentrations decreased until the next infusion, or a trough appeared seven hours after the end of the first infusion. The second trough level ranged from 0.28 μg/ml to 10.00 μg/ml (Mean: 2.59 μg/ml). The peak levels just after the end of the second infusion ranged from 28.70 μg/ml to 73.70 μg/ml (Mean: 42.65 μg/ml). The third trough level ranged from 0.29 μg/ml to 5.06 μg/ml (Mean: 1.84 μg/ml) and the third peak levels ranged from 52.17 μg/ml to 67.20 μg/ml (Mean: 52.17 μg/ml), as shown in Table 2. The serum concentrations of FMOX in the three troughs and three peaks were 1.94 μg/ml and 47.38 μg/ml respectively.

Fig. 1 shows a hypothetical daily curve of changes in serum FMOX levels based on the mean trough and peak concentrations in this study and with reference to a previously reported pharmacokinetic study.[3] The daily concentration of FMOX following each eight hour infusion, which ranged from about 1 μg/ml to about 50 μg/ml on the whole, is also shown.

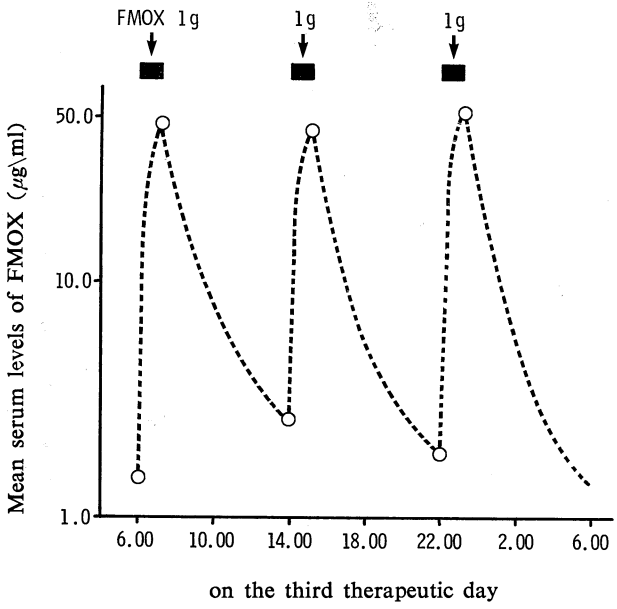

Fig. 1. Schematic curve of daily serum levels of FMOX administered thrice daily

DISCUSSION

Parenteral antibiotic administration is usually performed twice a day. This is basically because of the pain caused by injection or restricted action for long time due to drip intravenous infusion. But if the patient has an indwelling intravenous catheter supplying nutritious, meneral, or aqueous solutions to the body, it is very easy to administer antimicrobial agents several times. We decided to administer FMOX thrice daily to six patients with severe pulmonary infection, and then determined serum concentrations. Multi-divided

administration was considered to be more suitable for FMOX, since this antibiotic has been reported to have a short half time and short postantibiotic effects.

The mean serum concentrations of FMOX administered thrice daily resulted in a curve with three peaks and three troughs ranging between about 50 μg/ml (peak level) and about 1 μg/ml (trough level). This level is an effective one against common organisms in respiratory infections, based on the reported MIC_{90} of FMOX against clinically isolated bacteria[1]; i.e., 0.39 μg/ml in 74 strains of S. aureus, 0.19 μg/ml in 24 strains of S. pneumoniae, 0.78 μg/ml in 77 strains of H. influenzae, 0.19 μg/ml in 95 strains of E. coli, 0.05 μg/ml in 44 strains of K. pneumoniae, over 100 μg/ml in 100 strains of P. aeruginosa, and 0.39 μg/ml in B. catarrhalis.[7] In summary, even the trough levels of FMOX obtained in the present study were higher than the previously reported MIC_{90} of S. aureus, S. pneumoniae, H. influenzae, B. catarrhalis, K. pneumoniae and E. coli, which are common pathogens in respiratory infections. The only exception of that is a P. aeruginosa. These results seem to indicate that thrice method of administration would be useful in the treatment of respiratory infection. In fact, FMOX administered by thrice daily was effective in five out of six severe respiratory infections (83%) in various underlying disease in this study (Table 2).

TABLE 2. Serum levels after one-hour intravenous drip infusion of 1,000 mg FMOX

	Serum level (μg/ml) of FMOX					
drawing time of blood / Case No.	Infusion		Infusion		Infusion	
	6.00	7.00	14.00	15.00	22.00	23.00
1	0.25	49.50	2.53	28.70	5.06	52.50
2	2.53	36.40	0.34	37.40	0.29	33.30
3	1.33	60.60	1.65	42.40	1.53	69.70
4	0.17	35.40	0.28	33.30	0.33	34.20
5	3.08	38.40	10.00	40.40	2.86	55.60
6	1.02	63.60	0.72	73.70	0.94	67.70
Mean	1.40	47.32	2.59	42.65	1.84	52.17

The high plasma level of antimicrobial agents is commonly considered to be useful in the treatment of infections with an immunocompromised host, but this may also cause adverse effects. In the present study, there were no side effects with the exception of a mild, and transient elevation of transaminase observed in one case with chronic hepatitis. Cumulation of the drug was not recognized by administration thrice daily.

In conclusion, we believe administration of FMOX thrice daily should be attempted in the treatment of severe pulmonary infections, especially in the patients with an indwelling intravenous catheter.

REFERENCES

1) Iyobe, S., Kubota, T. and Mitsuhashi, S.: In vitro and in vivo antibacterial activities of 6315-S (Flomoxef). Chemotherapy **35** (S-1) : 22-32, 1987
2) Goto, S., Ogawa, M., Kaneko, Y., Miyazaki, S., Tsuji, A. and Kuwahara, S.: Bacteriological evaluation of a new oxacephem antibiotic, 6315-S (Flomoxef). Chemotherapy **35** (S-1) : 1-22, 1987
3) Saito, A.: 6315-S (Flomoxef). Chemotherapy **35** (S-1) : 523-540, 1987
4) Yasunaga, K., Okamoto, Y. and Yamada, H.: Phase-I clinical study on 6315-S (Flomoxef). Chemotherapy **35** (S-1) : 494-517, 1987
5) Baquero, F., Culebras, E., Patrōn, C., Péréz-Diaz, J.C., Medrano, J.C. and Vincente, M.F.: Postantibiotic effect of imipenem on gram-positive and gram-negative micro-organisms. J. Antimicrob. Chemother. **18** (S-E) : 47-49, 1986
6) Kimura, Y., Nakano, M. and Yoshida, T.: Microbiological assay methods for 6315-S (Flomoxef) concentrations in body fluid. Chemotherapy **35** (S-1) : 129-136, 1987
7) Nagatake, T., Matsumoto, K. and Rikitomi, N.: Laboratory and clinical evaluation of 6315-S (Flomoxef) in respiratory infections. Chemotherapy **35** (S-1) : 727-738, 1987