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ORIGINAL ARTICLE

Pharmacokinetics of olmesartan medoxomil in hemodialysis patients: little effect of dialysis upon its pharmacokinetics

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Abstract Olmesartan medoxomil is a new angiotensin-2 receptor blocker (ARB). Its pharmacokinetics in hemodialysis patients has not been investigated. We evaluated the pharmacokinetics of olmesartan medoxomil in six patients on maintained hemodialysis. We divided these six patients into two groups; one group ($n = 3$) took the drug when hemodialysis started (HD day group), and the other group ($n = 3$) took in the morning on non-dialysis day (non HD day group). In each group, plasma concentrations of olmesartan were evaluated seven points after drug administration. In each point, blood pressure and heart rate were also measured. On HD day group, plasma concentrations in upstream of dialyser were compared with those in downstream of dialyser in three points. The area under the plasma concentration–time curve (AUC) in HD day group had no remarkable difference from those in non-HD day group. Another pharmacokinetic parameter, such as maximum plasma drug concentration (C_{max}), biological half-life ($t_{1/2}$) and time to reach C_{max} (t_{max}), were almost similar in both groups. Blood pressure and heart rate showed the same consequence as well. This result suggests that plasma concentration of olmesartan medoxomil does not decrease during hemodialysis, and that it is not necessary to change prescription on hemodialysis day or not.

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Introduction

ARB is known as not only to depress blood pressure but also to repress vascular injury [1]. In addition, many ARBs are preferentially excreted in bile. From these points, ARBs are recommended to apply to patients with the end stage renal disease (ESRD) [2]. In addition, the most ARBs show high affinity with serum proteins such as albumin, therefore systemic exposures are not reduced during hemodialysis, resulting in that the hemodialysis do not affect efficacy of ARBs [3]. ARBs are preferable for blood pressure control on hemodialysis patients. Moreover, recently several reports suggested ARB upon hemodialysis patients might improve their mortality [4, 5]. Olmesartan medoxomil is a new ARB developed by DaiichiSankyo Co, Ltd. and being used widely for the patient with several kinds of hypertension. However, pharmacokinetic profile in hemodialysis patients has not been investigated so far. In this study, we evaluated pharmacokinetics of olmesartan medoxomil in six patients with ESRD both on and off hemodialysis.

Patients and methods

This study enrolled six volunteers with severe, dialysis-dependent renal insufficiency. The patients were suffering from the following the underlying renal diseases: chronic glomerulonephritis, diabetic nephropathy, nephrosclerosis, ANCA-related crescentic glomerulonephritis. All patients gave their written informed consent to participate in the study. The Ethical Committee at the Osaka University,

Graduate School of Medicine approved this study protocol. We randomly divided these six patients into two groups: one group took the drug when hemodialysis started, after breakfast (HD day group), and the other group took in the morning non-dialysis day (non-HD day group) after breakfast. All patients received anti-hypertensive medication. Other ARB was switched to olmesartan medoxomil on the study day, but any other anti-hypertensive drugs, including ACEi (angiotensin converting enzyme inhibitor) were continued. The characteristics of these patients are shown in Table 1. No significant difference was shown between the HD day group and non-HD day group. In the HD day group, olmesartan medoxomil was orally administered as a 20-mg single dose when hemodialysis started after breakfast, and they underwent regular hemodialysis (3–4 h) after administration. On non-HD day group, it was administered in a same way after the breakfast. Pharmacokinetics of olmesartan medoxomil was not affected by food intake in healthy subject [6, 7], thus we considered postprandial administration was adequate in this study.

In each group, plasma concentrations of olmesartan were evaluated seven points after drug administration. Blood samples were obtained immediately before administration and 0.5, 1, 2, 3, 6, 12, and 24 h after drug administration. In each sampling point, blood pressure and heart rate were also measured.

On HD day group, plasma concentrations in upstream of dialyser were compared with those in downstream of dialyser (0.5, 1, and 3 h after hemodialysis started).

Table 1 Patients' characteristics

	HD day group	Non HD day group
n	3	3
Male:female	1:2	1:2
Age (year)	62 ± 15	66 ± 4
Height (cm)	155.3 ± 12.7	156.7 ± 12.4
Body weight (kg)	53.5 ± 1.9	49.5 ± 12.3
sBP (mmHg)	161 ± 12	138 ± 24
dBP (mmHg)	87 ± 15	70 ± 15
HR (beats/min)	76 ± 16	66 ± 5
eGFR (ml/min)	7.0 ± 1.6	6.7 ± 4.4
Cr (mg/dl)	6.9 ± 1.6	8.7 ± 4.9
Alb (g/dl)	3.7 ± 0.2	3.4 ± 0.1
Dulation of HD[a]	1	1
(Month)[b]	(1–31)	(1–4)

The values show arithmetic mean of three patients in two groups shown (±SD). eGFR (estimated GFR) was calculated from MDRD formula [13]. HD duration is expressed median and range because of these parameters distortion, all parameters of each group were no statistically significant tested by Wilcoxon test

[a] Median

[b] Range

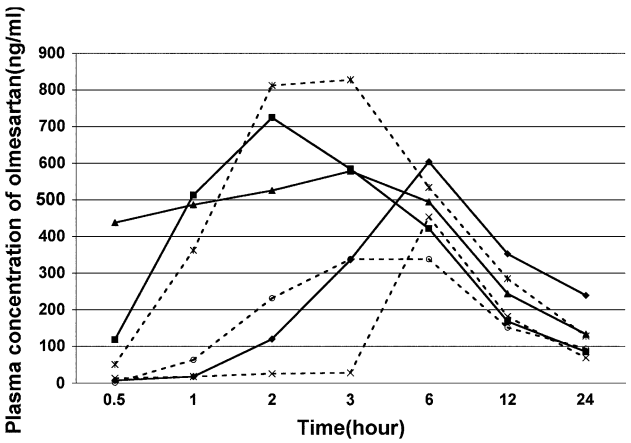

Fig. 1 Plasma concentration–time curve of olmesartan in hemodialysis patients. Individual plasma concentration–time curve of olmesartan in hemodialysis patients after administration of a single oral dose of olmesartan medoxomil 20 mg on non-dialysis days and on dialysis day. The *broken lines* represent non-HD day group (+), the *solid lines* represent HD day group (x)

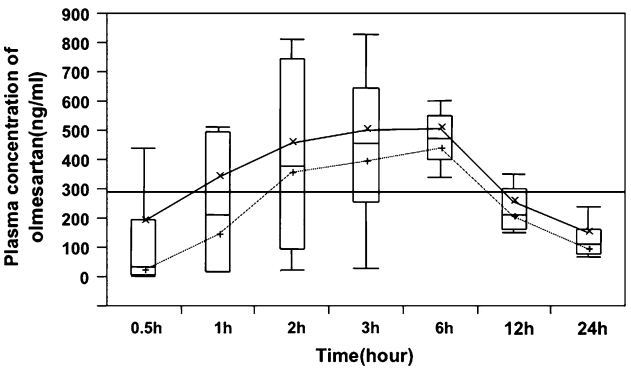

Fig. 2 Average of plasma concentration–time curve. Averages of plasma concentration–time curve of olmesartan in each group was shown. There was no significant difference between two groups. The *broken line* represents non-HD day group, the *solid line* represents HD day group

Duration of hemodialysis treatment ranged from 3 to 4 h. Polysulfone hollow-fiber dialysis filters ("TORAYSULFONE", TORAY, Chuo-ku, Tokyo, Japan) were used for all hemodialysis sessions.

Blood samples were collected into glass tubes with heparin as an anticoagulant and then centrifuged at 1,500 rpm for 10 min to obtain plasma and at −20°C until analysis. Plasma concentrations of olmesartan were measured by a validated method using high-performance liquid chromatography at Science and Technology Institute (Shinagawa, Tokyo, Japan). A series of model-independent pharmacokinetic parameters was calculated such as area under the plasma concentration–time curve from 0 to 24 h after drug administration ($AUC_{0-24\ h}$), maximum plasma drug concentration (C_{max}), biological half-life ($t_{1/2}$) and time to reach C_{max} (t_{max}).

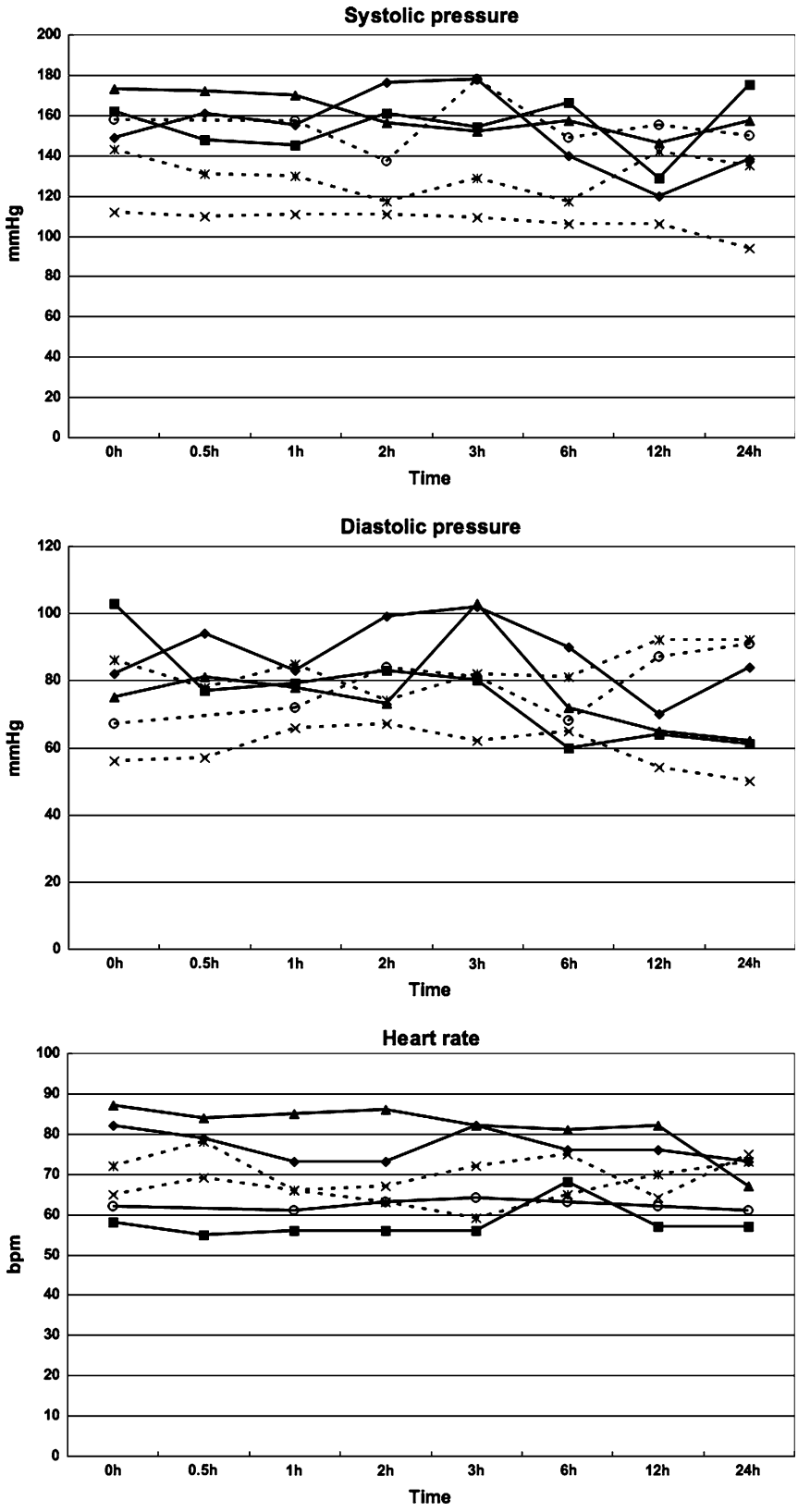

Fig. 3 Time course of blood pressure and heart rate. Time course of blood pressure and heart rate of each patient. The *broken line* represents non-HD day group, the *solid line* represents HD day group. There was no relationship between the two groups

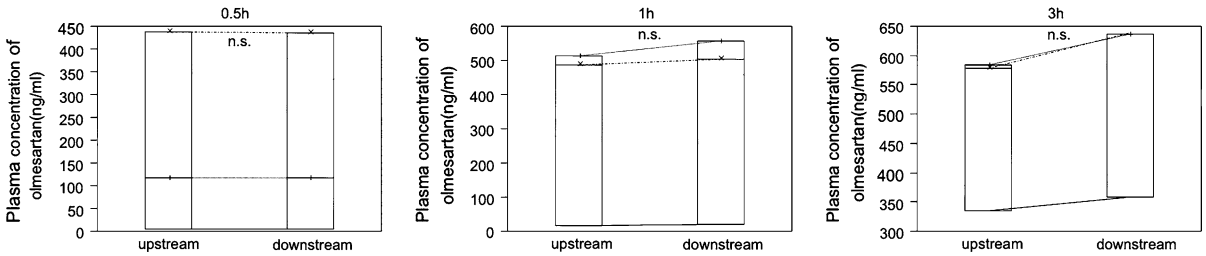

Fig. 4 Comparison of plasma concentration of olmesartan at the upstream of dialyser membrane and that of the downstream. *Left side* shows the plasma concentration of olmesartan of at the upstream of dialyser membrane; *right side* is the same concentration at the downstream. This result suggested olmesartan is not eliminated during hemodialysis. There is increasing tendency of plasma concentration during HD but no statistical significance was shown when tested by Wilcoxon signed-ranks test

Results

Figure 1 shows the individual plasma concentrations of olmesartan in hemodialysis patients after administration of a single oral dose of olmesartan Medoxomil 20 mg on the nondialysis and dialysis days, respectively. There was no significant difference between HD day group and non HD day group. Figures 2, and 3 show the average time course of plasma concentration of olmesartan in each group. There was no difference in the two groups. The time courses of blood pressure and heart rate had no significant difference as well (data not shown). Figure 4 shows a comparison of plasma concentration of olmesartan in the upstream of dialyser membrane with that in the downstream. Plasma concentration of olmesartan was not reduced by hemodialysis. This suggested that the antihypertensive effect of olmesartan medoxomil was not reduced by hemodialysis. Table 2 shows pharmacokinetic parameters of the olmesartan in patients on and off hemodialysis. Between HD day group and non-HD day group, any significant difference was not observed.

Discussion

In this study we examined hemodialyzability of olmesartan using the generally applied polysulfone hollow-fiber in patients with ESRD and found that there was no difference in the pharmacokinetic profile of olmesartan between the HD day and the non-HD day groups. There was also no remarkable difference between upstream of dialyzer and downstream. These results imply that hemodialysis hardly eliminates olmesaltan and thus does not affect pharmacokinetics in HD patients.

Olmesartan medoxomil is categorized into a class of preferential biliary elimination. In normal human, 77.2% of olmesartan was excreted in the feces, while 12.6% was found in urine after a single oral dose. It was reported that olmesartan oral clearance was slightly decreased by sever renal impairment, older age [8], and because of this, this type of drug was used safely and widely even in patients with renal failure [9], and at the first administration, dose control was not required [10]. However, the effect of hemodialysis has not been elucidated. From comparison of plasma concentration between both sides of the dialyzer membrane, olmesartan is not eliminated during hemodialysis using the commonly used membrane filter. The slight increase of olmesartan concentrations after the dialyser may be caused by the ultra filtration of water.

As olmesartan shows high affinity with serum proteins such as albumin (99.6%). This might be a possible reason for relatively lower clearance by hemodialysis and higher plasma levels concentration during hemodialysis. In addition, there is no significant difference that plasma concentration–time curve between in HD day group and in non HD day group.

In another study about Telmisartan, pharmacokinetic parameters of Telmisartan (AUC and, C_{max}) were slightly decreased during hemodialysis [11]. Hemodialysis also caused a significant reduction of serum protein binding of Telmisartan [11]. A similar phenomenon might also be speculated for olmesartan medoxomil, however in our

Table 2 Pharmacokinetic parameters of olmesartan in the patients under hemodialysis

	C_{max} (μg/l)	T_{max} (h)	$T_{1/2}$ (h)	$AUC_{0-24\ h}$ (ng × h/ml)
HD day group	634.4 (±78.2)	3.7 (±2.1)	10.8 (±3.1)	7268.0 (±952.3)
Non HD day group	538.7 (±256.1)	5 (±1.7)	8.7 (±1.8)	5639.2 (±2457.2)

Pharmacokinetic parameters of each group. All values are expressed mean ± SD. C_{max}, T_{max}. All parameters were no statistically significant between two groups. Each parameter tested with Wilcoxon test

study, the plasma concentration profile of olmesartan was not altered by HD. No clinically undesirable signs or symptoms attributable to olmesartan were recognized during the study period. The phamacokinetic parameters of this study were higher compared with healthy adults who took the same dose, but almost same when compared to those who took 40 mg [8]. After hemodialysis, there were no remarkable changes of the trend of elimination between HD day and non-HD day groups. These results might suggest that there is no necessity of special attention to the dosage regimens of this drug though it is the hemodialysis day or not.

It is noteworthy that the systemic exposures of olmesartan in ESRD patients in this study were about 2–3 times higher than those estimated for patients with normal renal function [8]. One possible explanation for this might be the concomitant decrease of hepato-biliary transporters such as OATP1B and/or MRP2 activity in patients with ESRD to eliminate of olmesartan [12]. This observation brings a different question whether any dose adjustment program for ESRD patients should be required comparing to patients with normal renal function. According to the results of the post-marketing surveillance of olmesartan medoxomil, the occurrence frequency of the major adverse events was almost comparable between the two populations, namely one was taking from 10 to 20 mg as a daily dose and the other was taking more than 20 mg daily. If we assume that pharmacokinetics in this study is applicable for calculation of a scaling factor to adjust dose size and the safety observations derived from above post-marketing surveillances is reasonable, the adequate dose for ESRD patients would be estimated as between 5 and 20 mg.

In conclusion, olmesartan medoxomil is effectively and safely applicable for hemodialysis patients without any special concern except for dose size.

References

1. Schmieder RE. Mechanisms for the clinical benefits of angiotensin II receptor blockers. Am J Hypertens. 2005;18(5 Pt 1):720–30.
2. Sica DA. Renal handling of angiotensin receptor blockers: clinical relevance. Curr Hypertens Rep. 2003;5(4):337–9.
3. Pfister M, et al. Pharmacokinetics and haemodynamics of candesartan cilexetil in hypertensive patients on regular haemodialysis. Br J Clin Pharmacol. 1999;47(6):645–51.
4. Takahashi A, et al. Candesartan, an angiotensin II type-1 receptor blocker, reduces cardiovascular events in patients on chronic haemodialysis—a randomized study. Nephrol Dial Transplant. 2006;21(9):2507–12.
5. Pun PH, et al. Predictors of survival after cardiac arrest in outpatient hemodialysis clinics. Clin J Am Soc Nephrol. 2007;2(3):491–500.
6. Wehling M. Can the pharmacokinetic characteristics of olmesartan medoxomil contribute to the improvement of blood pressure control? Clin Ther. 2004;26(Suppl A):A21–7.
7. Tanaka T, et al. Influence of food intake on pharmacokinetics of CS-866 (olmesartan medoxomil), an angiotensin II receptor antagonist. J Clin Ther Med. 2003;19(11):1283–1295.
8. Yoshihara K, et al. Population pharmacokinetics of olmesartan following oral administration of its prodrug, olmesartan medoxomil: in healthy volunteers and hypertensive patients. Clin Pharmacokinet. 2005;44(12):1329–42.
9. Laeis P, Puchler K, Kirch W. The pharmacokinetic and metabolic profile of olmesartan medoxomil limits the risk of clinically relevant drug interaction. J Hypertens Suppl. 2001;19(1):S21–32.
10. von Bergmann K, et al. Olmesartan medoxomil: influence of age, renal and hepatic function on the pharmacokinetics of olmesartan medoxomil. J Hypertens Suppl. 2001;19(1):S33–40.
11. Stangier J, et al. Pharmacokinetics of single-dose telmisartan 120 mg given during and between hemodialysis in subjects with severe renal insufficiency: comparison with healthy volunteers. J Clin Pharmacol. 2000;40(12 Pt 1):1365–72.
12. Nakagomi-Hagihara R, et al. OATP1B1, OATP1B3, and mrp2 are involved in hepatobiliary transport of olmesartan, a novel angiotensin II blocker. Drug Metab Dispos. 2006;34(5):862–9.
13. Levey AS, et al. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med. 2006;145(4):247–54.