J Anesth (2013) 27:243–250
DOI 10.1007/s00540-012-1505-4

ORIGINAL ARTICLE

Population pharmacokinetics of olprinone in patients undergoing cardiac surgery with cardiopulmonary bypass

Tsunehisa Tsubokawa · Syuichi Ishizuka · Kyoko Fukumoto · Kazuyuki Ueno · Ken Yamamoto

Received: 31 October 2011 / Accepted: 9 October 2012 / Published online: 23 October 2012
© Japanese Society of Anesthesiologists 2012

Abstract
Purpose Olprinone, a phosphodiesterase type III inhibitor, is a strong inotrope and vasodilator that does not increase oxygen consumption and is often used during weaning from cardiopulmonary bypass (CPB). To control the pharmacological effects of olprinone, pharmacokinetic information is essential; however, there is little published information on the pharmacokinetics of olprinone in a large population. Therefore, the purpose of this study was to determine olprinone pharmacokinetic parameters in a large population undergoing cardiac surgery with CPB.
Methods Olprinone was infused at a rate of 0.2 μg/kg/min when weaning from CPB was started. Whole blood samples were periodically obtained to determine the olprinone concentrations using high-performance liquid chromatography. Measured olprinone concentrations were analyzed with a one-compartment model via a population approach.
Results A total of 86 blood samples from 26 patients were used for pharmacokinetic analysis. The calculated clearance, volume of distribution (V_d), and elimination half-life were 378 ml/min, 40.7 l, and 97.1 min, respectively. Olprinone clearance depended on weight and creatinine clearance, whereas V_d depended only on weight.
Conclusion We investigated the pharmacokinetic parameters of olprinone in patients undergoing cardiac surgery with CPB. Olprinone clearance depended on weight and creatinine clearance, whereas V_d depended only on weight. When olprinone is infused according to the recommended dosing regimen, it takes more than 60 min to reach the target concentration (20 ng/ml). However, there is a possibility that a lower concentration is sufficient for weaning from CPB in combination with a continuous infusion of dopamine.

Keywords Olprinone · Cardiac surgery · Cardiopulmonary bypass · Population pharmacokinetics

T. Tsubokawa (✉) · K. Yamamoto
Department of Anesthesiology, Faculty of Medicine, Institute of Medical, Pharmaceutical and Health Sciences, Kanazawa University Hospital, Kanazawa University, 13-1 Takaramachi, Kanazawa, Ishikawa 920-8641, Japan
e-mail: tsune@med.kanazawa-u.ac.jp

S. Ishizuka
Department of Anesthesiology, Ishikawa Prefectural Central Hospital, Kanazawa, Japan

K. Fukumoto · K. Ueno
Department of Pharmaceutical Sciences, Niigata University of Pharmacy and Applied Life Sciences, Niigata, Japan

Introduction

Phosphodiesterase type III inhibitors (PDEIs) have strong inotropic and vasodilatory effects [1–3] without increasing oxygen consumption in cardiomyocytes [4, 5]. They are also effective when there is downregulation of beta receptors [6]. These agents are often used in cardiac surgery to increase cardiac output for withdrawal from cardiopulmonary bypass (CPB) [7, 8]. Pharmacokinetic information is essential to control the olprinone concentration. There are few published reports on olprinone pharmacokinetics. Arata et al. [9] investigated olprinone pharmacokinetics in seven healthy volunteers and reported a volume of distribution (V_d) and clearance of 126–249 ml/kg and 7.8–9.7 ml/kg/min, respectively. Mori et al. [10] also studied this drug in seven patients undergoing cardiac surgery with CPB and found that the V_d and clearance were 335 ml/kg and 4.7 ml/kg/min, respectively. Both these

studies enrolled only seven patients each. Furthermore, the subjects were healthy volunteers in the former study, and there was an analytical problem in the latter study.

The purpose of this study was to determine olprinone pharmacokinetic parameters using a population pharmacokinetic analysis in a large sample of patients undergoing cardiac surgery with CPB.

Methods

After approval by the ethics committee of our institute, we recruited consecutive patients scheduled for cardiac surgery with CPB from February 1, 2005 to January 31, 2007. Written informed consent was obtained from all subjects at the time of study enrollment. Patients who had renal or hepatic dysfunction based on preoperative evaluations were excluded.

Oral intake of food and water was prohibited for at least 6 h before surgery, and patients walked into the operating theater without any premedication. Following the placement of monitors for direct arterial pressure via the radial artery, electrocardiogram, pulse oximetry, and bispectral index, anesthesia was induced with 6–10 μg/kg fentanyl, 3–5 mg midazolam, and sevoflurane. Tracheal intubation was performed after administration of vecuronium. After anesthetic induction, a pulmonary catheter was placed via the right jugular vein, and a transesophageal echocardiography probe was inserted. Anesthesia was maintained with 1–2 % sevoflurane before and after CPB. During CPB, anesthesia was changed to propofol using a target-controlled infusion system. Patients were ventilated in a pressure-controlled mode to maintain end-tidal carbon dioxide between 35 and 40 mmHg. Thirty minutes before the end of surgery, 200 μg fentanyl was administrated and followed by patient-controlled analgesia with fentanyl (25 μg/h + 25 μg/rescue; lockout time = 30 min).

Olprinone was infused via a central venous catheter at a rate of 0.2 μg/kg/min when withdrawal from CPB started, and this infusion rate was basically fixed until the patient was transferred to the intensive care unit. However, we had decided to use NONMEM (ver. VII; Globomax LIC, Hanover, MD, USA) for pharmacokinetic analysis because it has a flexible analytical architecture and does not require regular drug administration or blood sampling for determination of drug concentration. Therefore, the anesthesiologists were allowed to modify the olprinone infusion rate. The anesthesiologists recorded the time on the anesthesia record when they changed the infusion rate or when blood samples were obtained for olprinone assay. When cardiac output fell below 2.0 l/min, the dopamine infusion rate was increased, and rapid volume loading or transfusion was performed based on the central venous pressure, pulmonary pressure, and the results of transesophageal echocardiography. If systolic blood pressure could not be maintained above 80 mmHg, then up to three boluses of 0.1 mg phenylephrine were administered. When it was difficult to keep the systolic pressure above 80 mmHg despite phenylephrine boluses, noradrenaline was administered at a rate of 0.05 μg/kg/min, and the olprinone infusion rate was decreased or stopped at the anesthesiologist's discretion. After the termination of surgery, patients were transferred to the intensive care unit under sedation.

Blood sampling and olprinone measurement

Whole arterial blood samples for olprinone assay were initially aspirated into heparinized syringes and centrifuged at 3,000 *g* for 10 min. Plasma was transferred into tubes and stored at −70 °C until analysis. Olprinone concentrations were determined using high-performance liquid chromatography [10] at the Niigata University of Pharmacy and Applied Life Science. To minimize the effect of CPB on the pharmacokinetic analysis, cases in which withdrawal from CPB required more than 30 min were excluded from the analysis.

Pharmacokinetic analysis

A population approach was used to analyze the olprinone concentration–time data that employed a first-order conditional estimation method with interaction (FOCE-I) method implemented in the NONMEM VII program with the PREDPP subroutines, ADVAN1 and TRANS1. A one-compartment model was selected to fit the pharmacokinetic data. Exponential and proportional error models were used to describe the intra- and interindividual variability, respectively. We considered gender, age, height, weight, body mass index, CPB time, and creatinine clearance as parameters in the model. In the forward step of model construction, the chi-square test was used to compare the objective function (−2 × logarithm of the likelihood of the results); $P < 0.05$ was considered as significant in the forward step and $P < 0.01$ as significant in the backward step. In addition, goodness of fit between observed values and predicted values was evaluated by visual inspection of the graphs.

Simulation study

The currently recommended infusion regimen for olprinone is 2.0 μg/kg/min for 5 min followed by continuous infusion at a rate of 0.2 μg/kg/min. Simulation studies were performed using the individual parameters obtained in the base model by Bayesian estimation [11].

Results

Thirty-seven patients were enrolled in this study; all gave written informed consent. A total of 123 blood samples were obtained from the 37 patients in the study. However, more than 30 min was needed for withdrawal from CPB in 8 cases, and thus samples obtained from these 8 cases were excluded from the analysis. Three other cases were also excluded from the analysis because the olprinone infusion was stopped at the anesthesiologist's discretion before the end of surgery. Consequently, 85 samples obtained from 26 patients were used for the pharmacokinetic analysis. The demographic data of the 26 patients included in the analysis are shown in Table 1. Aortic valve replacement was performed in 59 % of the patients, whereas 21 % had a mitral valve procedure. Three patients received aortic arch replacement. Other procedures were simultaneous replacement of the aortic and mitral valves, mitral valve plus left ventricular patch plasty, and removal of a pulmonary artery thrombus.

The basic population pharmacokinetic analysis showed the clearance and V_d were 378 ml/min [95 % confidence interval (CI), 191–565], and 40.7 l (95 % CI, 29.2–42.2), respectively. The model-based estimate of olprinone half-life in this group was 97 min. The patient distributions for the individual clearance (ml/kg/min) and V_d (ml/kg) data are shown in Fig. 1.

After the primary pharmacokinetic analysis, we then explored the relationships among the covariates and pharmacokinetic parameters using Pearson's correlation analysis. This analysis showed that weight was positively correlated with both clearance and V_d (Figs. 2, 3). Creatinine clearance showed a positive correlation with total olprinone clearance (Fig. 4); there was a weak negative correlation between creatinine clearance and age, because age is a factor used to calculate creatinine clearance from serum creatinine concentration. Body mass index (BMI) and height showed a weak positive relationship with weight. Based on these findings, gender, weight, CPB time, and creatinine clearance were included as covariates in the full pharmacokinetic model.

In the forward step, gender and CPB time were excluded from the final model. Weight and creatinine clearance remained as significant covariates of the final model after the backward step. Our final model is shown in Table 2. Creatinine clearance and weight were covariates that influenced olprinone clearance, whereas only weight influenced V_d. The observed values plotted against the predicted values based on the final model are shown in Fig. 5. In addition, the observed values plotted against the predicted values for the individual pharmacokinetic parameters (calculated by the NONMEM option) are shown in Fig. 6. Figure 7 shows a goodness-of-fit plot of predicted concentrations of olprinone and weighted residuals (w_{res}). Most of the data fall between −3 and +3 throughout the full concentration range, which indicates that this model is acceptable.

Table 1 Demographic data

	Values	Range
Gender (female/male)	13/13	
Age (years)	64.9 ± 7.4	29–77
Height (cm)	158.5 ± 6.9	146–178
Weight (kg)	55.4 ± 7.0	39.6–76.5
Body mass index (kg/m^2)	22.1 ± 2.5	15.1–30.6
Operation		
AVR	14	
MVR or MVP	6	
Aortic arch replacement	3	
Others	3	
GPT (IU/l)	23.0 ± 8.8	10–50
Serum creatinine (mg/dl)	0.86 ± 0.16	0.52–1.50
Creatinine clearance (ml/min)	56.6 ± 12.9	34–81
Total protein (g/dl)	6.9 ± 0.5	4.8–8.5
Anesthetic time (min)	377 ± 84	250–685
Operation time (min)	289 ± 69	185–515
Cardiopulmonary bypass time (min)	126 ± 38	55–320

Values are expressed in mean ± SD

Creatinine clearance was calculated using the Cockcroft–Gault equation

AVR aortic valve replacement, *MVR* mitral valve replacement, *MVP* mitral valve plasty, *GPT* glutamate pyruvate transaminase

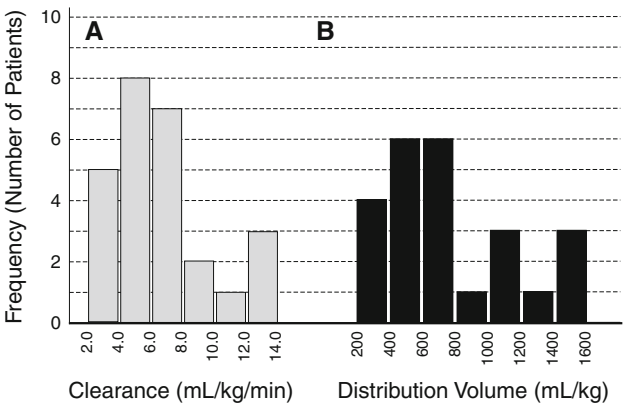

Fig. 1 Distributions of total clearance (ml/kg/min) and V_d (ml/kg) in individual patients. These data were calculated by NONMEM post hoc in the basic model. The population mean clearance and V_d were 325 ml/min (95 % CI, 214–436 ml) and 38.6 l (95 % CI, 27.6–49.6), respectively. These data were calculated by NONMEM post hoc in the basic model. Average clearance and V_d calculated individually in NONEMEM post hoc were 7.15 ± 3.06 ml/kg/min and 802 ± 385 ml/kg, respectively

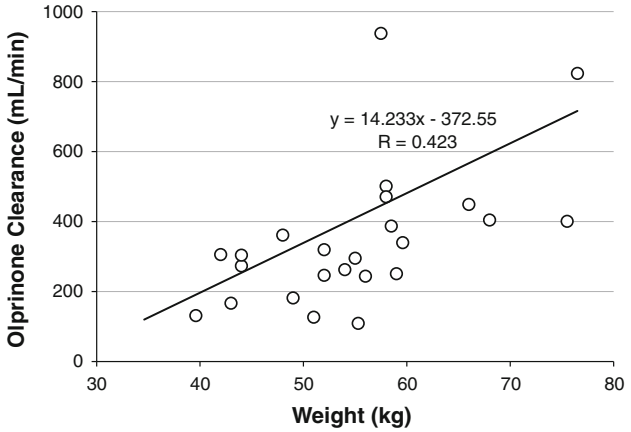

Fig. 2 Relationship between weight and creatinine clearance was positive (Pearson's $R = 0.423$, $P = 0.031$)

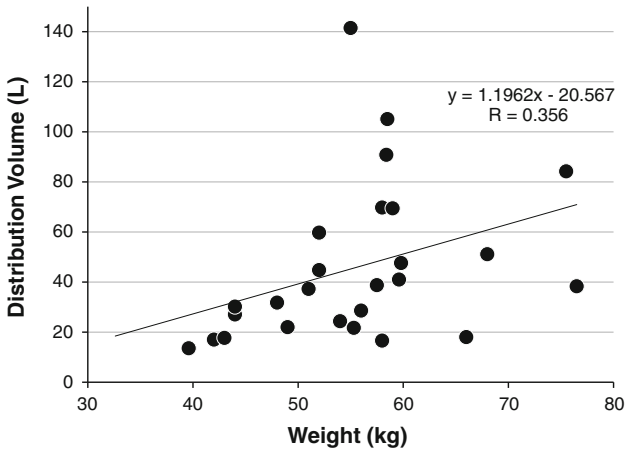

Fig. 3 Relationship between weight and distribution volume (V_d) was weakly positive (Pearson's $R = 0.356$, $P = 0.074$)

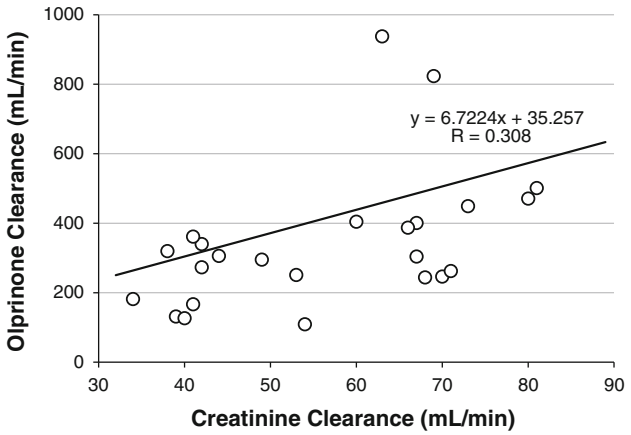

Fig. 4 Relationship between creatinine clearance and olprinone clearance was weakly negative (Pearson's $R = 0.395$). There was also a weakly positive relationship (Pearson's $R = 0.308$, $P = 0.126$)

The simulation results for this study and currently recommended regimens are displayed in Figs. 8 and 9, respectively. Figure 8 shows the expected response when olprinone is infused at a rate of 0.2 μg/kg/min without loading (this study condition), whereas Fig. 9 shows the expected response when olprinone is administrated according to the recommended regimen (2.0 μg/kg/min for 5 min followed by 0.2 μg/kg/min) [11]. Three patients in this graph show high olprinone concentrations (>60 ng/ml), and their demographic data are shown in Table 3.

Table 2 Final model

Parameters	Population mean (SE)	Interindividual variability (% SE)
CL (ml/min) = $\theta 1 \times (\text{weight}/56)^{\theta 2} \times \text{creatinine clearance}^{\theta 3}$	$\theta 1 = 378$ (95.3)	36.2 % (58.6)
	$\theta 2 = 2.48$ (0.674)	
	$\theta 3 = 0.819$ (0.271)	
V_d (ml) = $\theta 4 \times (\text{weight}/56)^{\theta 5}$	$\theta 4 = 40700$ (5850)	66.0 % (29.0)
	$\theta 5 = 1.68$ (0.645)	
Residual variability	23.9 (19.9)	

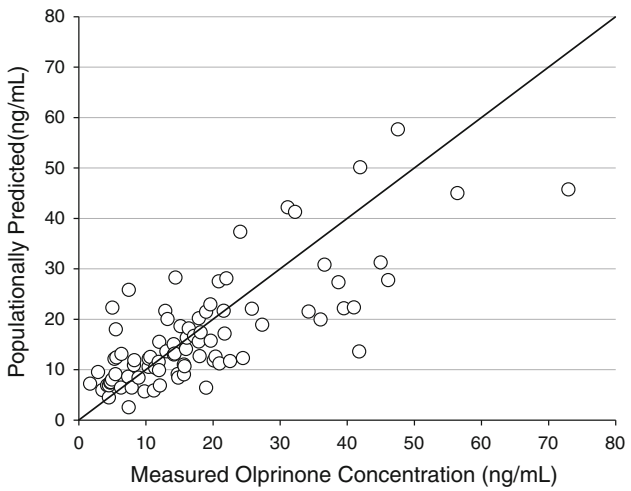

Fig. 5 Goodness-of-fit plots between measured concentrations and olprinone concentrations predicted by population analysis

Discussion

In this study, clearance, V_d and elimination half-life individually estimated in the basic model were 378 ml/min (= 7.13 ml/kg/min), 40.7 l (= 802 ml/kg), and 97.1 min, respectively. Mori et al. [10] reported that clearance, V_d, and half-life were 4.69 ml/kg/min, 335 ml/kg, and 46.8 min, respectively. All these parameters in the present study were larger than the previously reported values. Mori

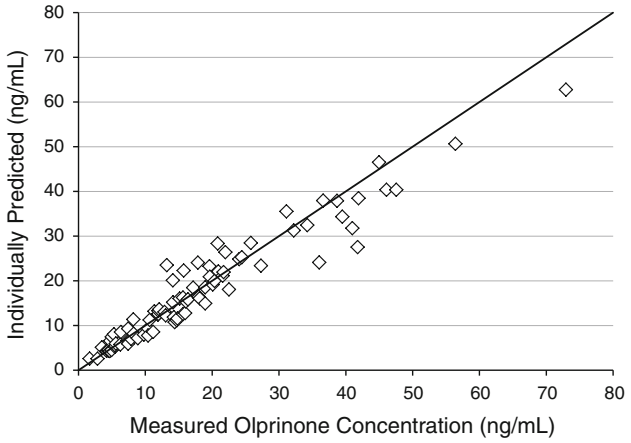

Fig. 6 Goodness-of-fit plots between measured concentrations and those predicted by individual Bayesian estimation

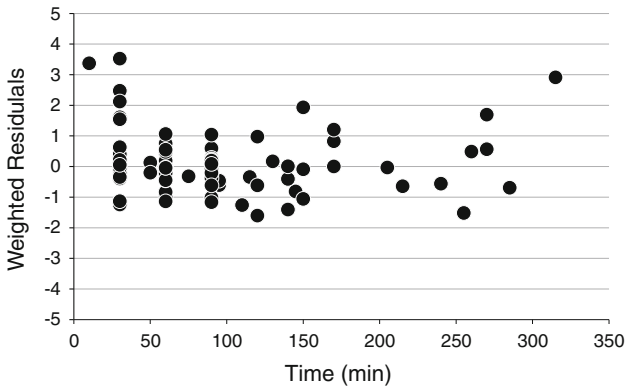

Fig. 7 Goodness-of-fit plots between time and weighted residuals (w_{res}). W_{res} was automatically calculated by NONMEM. Most data fall between -3 and $+3$ throughout the full concentration range

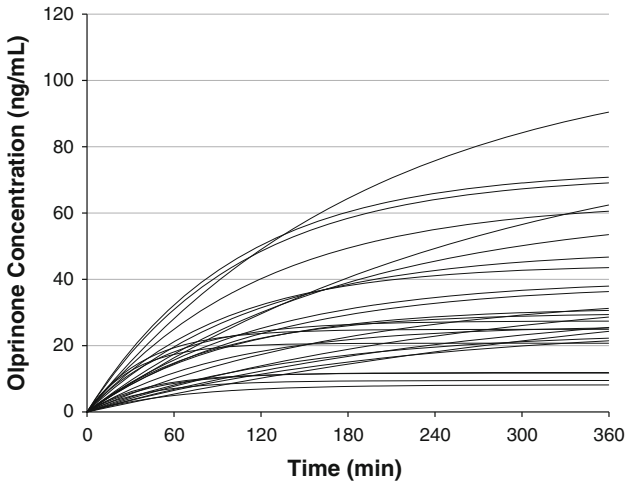

Fig. 8 Simulation results when olprinone is continuously infused without loading at a rate of 0.2 μg/kg/min (this study condition)

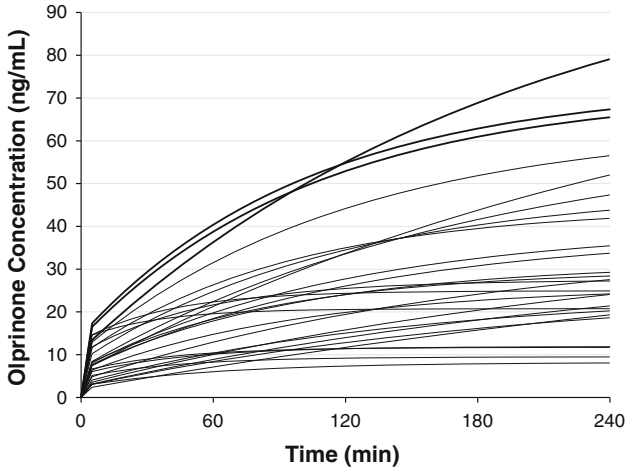

Fig. 9 Simulation results when olprinone is infused according to the recommended dosing regimen. Olprinone is infused at a rate of 2.0 μg/kg/min for 5 min, and then the infusion rate is changed to 0.2 μg/kg/min. Three patients showed more than 60 ng/ml of olprinone concentration: their pharmacokinetic data are shown in Table 3

et al. also enrolled clinical cases undergoing open heart surgery with CPB, but they obtained only two blood samples per patient ($n = 7$) and did not use population pharmacokinetic techniques. These differences may well account for the higher values of our study. However, the time–concentration curves were similar in comparing their study with our study.

Pharmacokinetic models

A one-compartment model was used to analyze olprinone pharmacokinetics in the present study. There were two reasons for this. The first is that we started olprinone infusion at the beginning of weaning from CPB. The hemodynamic condition during CPB is far from normal; the V_d is increased by the CPB circuit, drug protein binding is reduced by a lower plasma protein concentration, and drug clearance may be reduced by lower renal blood flow. Therefore, these confounding variables would most certainly alter the parameters in the model. It might be possible to build pharmacokinetic models considering the effects of CPB; however, it would be difficult to express the dynamic changes that occur when a normal state is achieved after withdrawal of CPB. In the clinical setting, we were not able to sample blood frequently enough to build a multi-compartment model.

Another option to build a multi-compartment model would be to obtain blood samples during the decay phase after stopping the infusion. It was not possible to obtain samples during the decay phase because our study was a clinical study and the decision to stop the infusion after surgery was made by the cardiac surgeons in the intensive

Table 3 Characteristics of three patients who showed high olprinone concentration in s simulation study

	Parameters								
	Clearance (ml/min)	V_d (l)	Age (years)	Gender	Weight (kg)	Height (cm)	BMI (kg/m^2)	CPB (min)	CCL (ml/min)
Case 1	162	17.3	75	Female	43.0	146	20.2	90	41
Case 2	120	12.3	70	Female	39.6	150	17.6	110	39
Case 3	104	22.3	77	Female	55.3	157	22.4	110	54
Average[a]	267	44.3	64.9	1:1	55.4	158.5	22.1	126	57

V_d distribution volume, *BMI* body mass index, *CPB* cardiopulmonary bypass time, *CCL* creatinine clearance

[a] Average means the average value of whole group

care unit. Because we could not collect samples during the decay phase, we decided to analyze the data with a simple, one-compartment model.

Creatinine and olprinone clearances

Because 80 % of olprinone is eliminated unchanged by the kidney [9], renal function and blood flow are major factors that influence olprinone clearance. In this study, olprinone clearance was larger compared to the previous data obtained in nonsurgical populations. During or after withdrawal from CPB, increase in urinary output resulting from osmotic diuresis or dopamine infusion is normally observed. This enhancement of renal function might contribute to large olprinone clearance in the present study.

Kimata et al. [12] reported a positive correlation between serum creatinine concentration and olprinone elimination half-life. In this study, there was a positive relationship between creatinine clearance and olprinone clearance similar to that reported by Kimata, and creatinine clearance remained as a covariate in the final model.

In Fig. 9, three patients showed high olprinone concentrations; Table 3 shows the demographic data of these three patients. Small, elderly female patients with low creatinine clearance are likely to experience overdosing, and attention is required to administer olprinone to these patients. Figure 10 shows the result of a simulation study to evaluate the effect of creatinine clearance on olprinone concentration. In the case that creatinine clearance is less than 30 ml/h, the olprinone infusion rate should be reduced.

The effectiveness of olprinone

Murakami et al. [13] reported that the minimum effective concentration of olprinone was 20 ng/ml, and this value was determined in patients with acute cardiac failure rather than surgical cases. In the present study, olprinone concentration did not reach 20 ng/ml [13] in most of the cases; however, olprinone was considered to be effective by

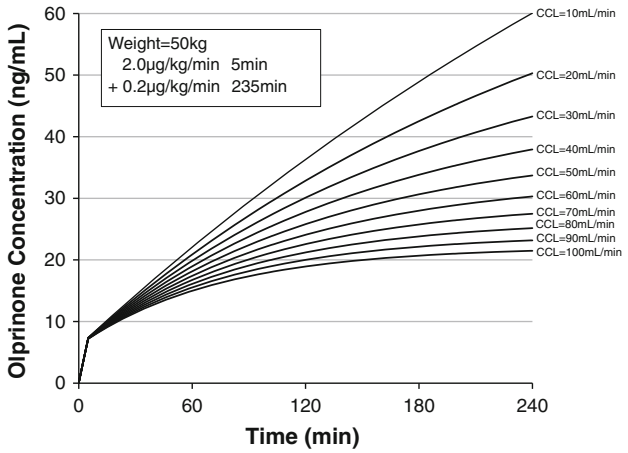

Fig. 10 Simulation results showing the effect of creatinine clearance on time–concentration curves. Olprinone is infused at a rate of 2.0 μg/kg/min for 5 min, and then the infusion rate is changed to 0.2 μg/kg/min

retrospective inspection. One possible reason was that we routinely used dopamine as an inotropic agent, and there is probably a synergistic effect between olprinone and dopamine; therefore, an olprinone concentration below the target concentration could be effective. Another possible reason was that the previously reported value of 20 ng/ml may not be accurate, and a lower concentration might be enough to improve cardiac function in cardiac anesthesia. To clarify these mechanisms, further experiments including pharmacodynamic evaluation is necessary.

Study limitations

The main aim of this study was to obtain pharmacokinetic parameters in open heart surgery; however, the effect of CPB made it difficult to evaluate these parameters. In this study, V_d was larger than the values in previous reports. To minimize the effect of CPB on the analysis, we excluded cases that required more than 30 min to wean from CPB, and we did not include any blood samples obtained before the completion of withdrawal from CPB. Figure 7 shows

the relationship between time and w_{res}. There was no specific tendency for negative values of w_{res} before 60 min, which might show the effect of CPB was successfully suppressed. Clearance obtained in this study was also greater compared to previous reports. When a drug is continuously infused, the concentration at steady state is determined by the ratio of infusion rate and clearance; thus, clearance is the most important factor to predict drug concentration near steady state. Furthermore, the dilutive effects of CPB on drug concentrations should not have much impact on clearance. Thus, the value of clearance in this study contains less bias compared with V_d. When drug concentration is kept at a steady state, the concentration is determined by the ratio between infusion rate and clearance, and V_d is not included. Clearance information is more important for continuous infusion.

PDEIs, including olprinone, are usually used to support withdrawal from CPB similar to this study condition. The data obtained in this study might include some bias and the parameters might not be correct as standard data for normal healthy individuals undergoing noncardiac surgery without CPB. However, in cardiac cases with CPB, our data would be more useful for anesthesiologists than standard values.

In the present study, we did not record hemodynamic values periodically, and we could not perform pharmacodynamics analysis. The present minimum effective concentration (= 20 ng/ml) was defined as the concentration to reduce pulmonary artery wedge pressure by 20 % in patients with acute heart failure [13]. Further studies are necessary to obtain proper effective concentration for anesthetic management in cardiac surgery cases.

Comparison with milrinone

Milrinone is another PDEI that has a similar inotropic effect but a lesser vasodilatory effect than olprinone. Because milrinone causes less hypotension than olprinone [14], it may be preferred at the time of weaning from CPB. There are some reports that investigated the pharmacokinetic parameters of milrinone. The elimination half-life of milrinone is about 100 min [15–17], which is comparable to 97 min in the present study. Although there are some studies that compared the pharmacodynamic effects of olprinone and milrinone [18, 19], there are no studies comparing the pharmacokinetic parameters of these two drugs. Further studies are necessary to determine which drug is easier to control during weaning from CPB.

In conclusion, we investigated the pharmacokinetic parameters of olprinone in patients undergoing cardiac surgery with CPB and estimated the clearance and V_d of olprinone based on a one-compartment model. Olprinone clearance depended on weight and creatinine clearance, whereas V_d depended only on weight. When olprinone is infused according to the recommended dosing regimen, more than 60 min is needed to reach the target concentration (20 ng/ml). However, there is a possibility that a lower concentration is sufficient for weaning from CPB in combination with a continuous infusion of dopamine.

References

1. George M, Lehot JJ, Estanove S. Haemodynamic and biological effects of intravenous milrinone in patients with a low cardiac output syndrome following cardiac surgery: multicentre study. Eur J Anaesthesiol Suppl. 1992;5:31–4.
2. Mizushige K, Ueda T, Yukiiri K, Suzuki H. Olprinone: a phosphodiesterase III inhibitor with positive inotropic and vasodilator effects. Cardiovasc Drug Rev. 2002;20:163–74.
3. Young RA, Ward A. Milrinone. A preliminary review of its pharmacological properties and therapeutic use. Drugs. 1988;36:158–92.
4. Monrad ES, Baim DS, Smith HS, Lanoue AS. Milrinone, dobutamine, and nitroprusside: comparative effects on hemodynamics and myocardial energetics in patients with severe congestive heart failure. Circulation. 1986;73:III168–74.
5. Adachi H, Tanaka H. Effects of a new cardiotonic phosphodiesterase III inhibitor, olprinone, on cardiohemodynamics and plasma hormones in conscious pigs with heart failure. J Cardiovasc Pharmacol. 1997;29:763–71.
6. Sasayama S, Asanoi H, Ishizaka S. Mechanics of contraction and relaxation of the ventricle in experimental heart failure produced by rapid ventricular pacing in the conscious dog. Eur Heart J 1991;12(suppl C):35–41
7. Yamada T, Takeda J, Katori N, Tsuzaki K, Ochiai R. Hemodynamic effects of milrinone during weaning from cardiopulmonary bypass: comparison of patients with a low and high prebypass cardiac index. J Cardiothorac Vasc Anesth. 2000;14:367–73.
8. Orime Y, Shiono M, Hata H, Yagi S, Tsukamoto S, Okumura H, Kimura S, Hata M, Sezai A, Obana M, Sezai Y. Effects of phosphodiesterase inhibitors after coronary artery bypass grafting. Jpn Circ J. 1999;63:117–22.
9. Arata H, Sasaki H, Ohsaka M, Sasaki Y, Hayakawa H, Tomono Y, Morishita N. A phase 1 study of E-1020: intravenous injection (in Japanese). Jpn J Clin Pharmacol Ther. 1990;21:613–21.
10. Mori M, Nishi S, Asada A. Pharmacokinetics and pharmacodynamics of olprinone after cardiac surgery (in Japanese). Osaka City Med J. 2004;50:1–8.
11. Product Note: "Coretec.®" Eizai Co., Ltd.
12. Kimata S, Hirosawa K, Kasanuki H, Takano T, Serizawa T, Shinoyama S, Kumata T, Hori S, Hiramori K. Clinical evaluation of E-1020 in patients with acute heart failure (in Japanese). Rinsho to Kenkyu. 1992;69:2260–74.
13. Murakami R, Ishibashi Y, Morioka S, Moriyama K. Comparison of E-1020 and dobutamine in patients with acute heart failure (in Japanese). Rinsho to Kenkyu. 1993;70:1265–72.
14. Onomoto M, Tsuneyoshi I, Yonetani A, Suehiro S, Matsumoto K, Sakata R, Kanmura Y. Differential pharmacologic sensitivities of phosphodiesterase-3 inhibitors among human isolated gastroepiploic, internal mammary, and radial arteries. Anesth Analg. 2005;101:950–956 (table of contents).
15. Das PA, Skoyles JR, Sherry KM, Peacock JE, Fox PA, Woolfrey SG. Disposition of milrinone in patients after cardiac surgery. Br J Anaesth. 1994;72:426–9.
16. Benotti JR, Lesko LJ, McCue JE, Alpert JS. Pharmacokinetics and pharmacodynamics of milrinone in chronic congestive heart failure. Am J Cardiol. 1985;56:685–9.

17. Butterworth JF 4th, Hines RL, Royster RL, James RL. A pharmacokinetic and pharmacodynamic evaluation of milrinone in adults undergoing cardiac surgery. Anesth Analg. 1995;81:783–92.
18. Hirabayashi Y, Igarashi T, Saitoh K, Fukuda H, Suzuki H, Shimizu R. Comparison of the effects of amrinone, milrinone and olprinone in reversing bupivacaine-induced cardiovascular depression. Acta Anaesthesiol Scand. 2000;44:1128–33.
19. Iribe G, Yamada H, Matsunaga A, Yoshimura N. Effects of the phosphodiesterase III inhibitors olprinone, milrinone, and amrinone on hepatosplanchnic oxygen metabolism. Crit Care Med. 2000;28:743–8.