Pharmacokinetics and Pharmacodynamics of Olprinone after Cardiac Surgery

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Abstract

Background

Phosphodiesterase type Ⅲ inhibitors are often delivered by continuous intravenous infusion without initial loading to prevent hypotension, i.e., by "slow induction". We evaluated the pharmacokinetics (PK) and pharmacodynamics (PD) of olprinone slow induction after open-heart surgery.

Methods

Olprinone was infused at a rate of 0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ in seven patients post operatively after elective cardiac surgery. Olprinone plasma concentration was determined by HPLC. PK parameters were calculated from concentrations at 90 and 180 minutes after start of infusion. PD data were analyzed by collected E_{max} model using SAAMII® PC programs.

Results

Systemic vascular resistance index initially decreased about 20 ng/mL and then cardiac index increased. Initially, a vasodilating effect occurs and then inotropic effect follows. Systemic hypotension may induced by the different EC_{50} between inotropic and vasodilating action. Moreover, much vasodilating effect will be observed with olprinone than with milrinone, based on our previous data.

Conclusions

Olprinone slow induction is useful and safe for critically ill patients.

Key Words: Pharmacokinetics-pharmacodynamics-olprinone-cardiac surgery

Introduction

Olprinone is a PDE-Ⅲ (Phosphodiesterase type Ⅲ) inhibitor with positive inotropic and vasodilatory effects but minimal effects on myocardial oxygen consumption. The effects of olprinone are mediated through β-adrenergic receptors, yielding an increase in cyclicAMP level that may enhance the effects of catecholamines and decrease the dose of it[1].

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Other PDE-Ⅲ inhibitors, milrinone and amrinone, are widely used after open-heart surgery with reported efficacy[2,3]. However, PDE-Ⅲ inhibitors may produce severe hypotension, especially at initial loading injection. PDE-Ⅲ inhibitors have recently often used by continuous intravenous infusion without initial loading injection to prevent such hypotension, i.e., by slow induction[4,5].

It may cause an alternation of pharmacokinetics and pharmacodynamics of PDE-Ⅲ inhibitors in critically ill patients[6]. We previously reported the pharmacokinetics and pharmacodynamics of milrinone slow induction after coronary artery bypass grafting[7]. But pharmacokinetics and pharmacodynamics of olprinone slow induction had not been investigated previously. The aim of study was to evaluate the pharmacokinetics and pharmacodynamics of olprinone slow induction, with the discussion of differences from milrinone[8].

Materials and Methods

Seven elective open-heart surgery patients were included. The criteria for use of olprinone were that cardiac index was between 2 and 3 $L \cdot min^{-1} \cdot m^{-2}$ and the doses of dopamine and dobutamine were less than 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ at the beginning of olprinone infusion after operation. Patients who required IABP (Intra Aortic Balloon Pumping), electrical pacing or hemodialysis support postoperatively were excluded (Table 1).

Continuous intravenous infusion of olprinone was started at the rate of 0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ without bolus initial loading injection after the difference between central and peripheral temperatures was less than 2℃. No other vasoconstrictive or vasodilatory agents were used, and the rates of infusion of catecholamines and sedative drugs were not changed. Transfusion or plasma protein infusion was performed to prevent the hypotension and to keep central venous pressure above 10 mm Hg. No severe hypotension or arrhythmia was observed in this study.

Assay of olprinone

Blood samples were collected through a radial artery catheter at 90 and 180 minutes after administration of olprinone, centrifuged immediately at 3000 rpm for 10 minutes for serum separation and then frozen at −70℃ until assay. Plasma concentrations were determined by high-performance liquid chromatography (HPLC) with a 5 μm ultra sphere C18 column (TSK-GEL® ODS-80TS, TOSOH). HPLC was performed with an isocratic mobile phase consisting of acetonitrile: potassium phosphate buffer (10 mM, Ph 7.0) 15:85 (v/v). The coefficient of variation of HPLC was 6.31% at 40 ng/mL and 6.31% at 60 ng/mL.

Table 1. Patient characteristics

No	Age	Sex	Height (cm)	Weight (kg)	Operation	Scre (μg/mL)
1	69	male	164	64	MVR+CABG	1.27
2	73	female	160	50	Bentall	0.97
3	66	male	156	68	GR	1.36
4	53	male	160	67	CABG	0.8
5	68	male	154	54	CABG	0.9
6	77	male	166	80	CABG	1.2
7	58	male	161	50	AVR	0.8
mean	66.2	M:6 F:1	160.1	61.9		1.04
SD	8.3		4.2	11.1		0.23

MVR, mitral valve replacement; CABG, coronary artery bypass grafting; GR, graft replacement; AVR, aortic valve replacement; and Scre, serum creatine level.

Pharmacokinetic analysis

A one compartment open model was applied to olprinone slow induction, because olprinone infusion rate was very low and distributed uniformly in the central and peripheral compartments.

Pharmacokinetic analysis was performed with concentrations at the two points (90 and 180 minutes) with the following equation (Appendix). Conc 1 is the concentration at 90 minutes and Conc 2 is that at 180 minutes after start infusion of olprinone. The theoretically expected plasma concentrations were calculated using the obtained parameters.

Pharmacodynamic analysis

In all cases, a continuous cardiac output/oximetry thermodilution catheter (Swan-Ganz CCOmbo CCO/SvO_2®, 7.5 Fr, Baxter Corporation) was inserted via a right jugular vein before the beginning of operation. It was connected to the oximetry monitor (Vigilance®, Baxter Corporation) and PC data recorder (Vigilance Data Preserver®, Baxter Corporation). Cardiac index (CI) and systemic vascular resistance index (SVRI) were automatically recorded as indicators of inotropic and vasodilatory effects every two minutes, data at 30, 60, 90, 120, 180, 240, and 360 minutes after infusion are recorded. The CI and SVRI data were plotted on a sheet with the theoretically expected plasma concentrations and each value. Non-linear regression was performed using the SAAMII® program with the following equation (Table 3). The reliability of fit was evaluated by Akaike's information criteria (AIC)[9].

Results

No patients had hepatic and renal dysfunction before operation. Transient impairment of renal function was observed in one case (Case No. 1 in Tables and Figs) after operation, but creatinine clearance was above 30 mL/min. No vasoconstrictive agent was needed to maintain systemic blood pressure.

Pharmacokinetic parameters are shown in Table 2, and the time-concentration curve was calculated using these parameters (Fig. 1). Arrival time for yielding 20 ng/mL, the minimum effective concentration of olprinone, was 46.8±17.87 minutes.

Pharmacodynamic parameters are shown in Table 3, and the regression curves for concentration and effects were well fitted by both parameters, CI and SVRI. An inotropic effect was observed following a vasodilatory effect in all cases. EC_{50} was 38.38±8.26 ng/mL for CI and 31.95±6.70

Table 2. Pharmacokinetic parameters

No	CL ($mL \cdot kg^{-1} \cdot min^{-1}$)	Ke (/min)	Vd (mL/kg)	Conc 1 (ng/mL)	Conc 2 (ng/mL)	Arrival time for yielding 20 ng/mL in olprinone plasma concentration (min)
1	2.76	0.0092	300.88	40.70	58.50	35.22
2	5.45	0.0224	243.47	31.80	36.04	35.18
3	4.17	0.0199	209.91	39.95	46.64	27.16
4	7.18	0.0164	437.11	21.50	26.40	77.09
5	4.11	0.0127	324.64	33.10	43.70	41.80
6	4.54	0.0130	349.08	30.40	39.84	46.51
7	4.64	0.0096	481.21	25.01	35.51	64.67
mean	4.69	0.0147	335.19	31.78	40.95	46.80
SD	1.36	0.0050	97.72	7.09	10.12	17.87

CL, clearance; Ke, elimination constant; Vd, volume of distribution; Conc 1 and 2, olprinone concentrations at 90 and 180 minutes after the start of infusion; and Arrival time for yielding 20 ng/mL, calcurated time that olprinone plasma concentration yield 20 ng/mL.

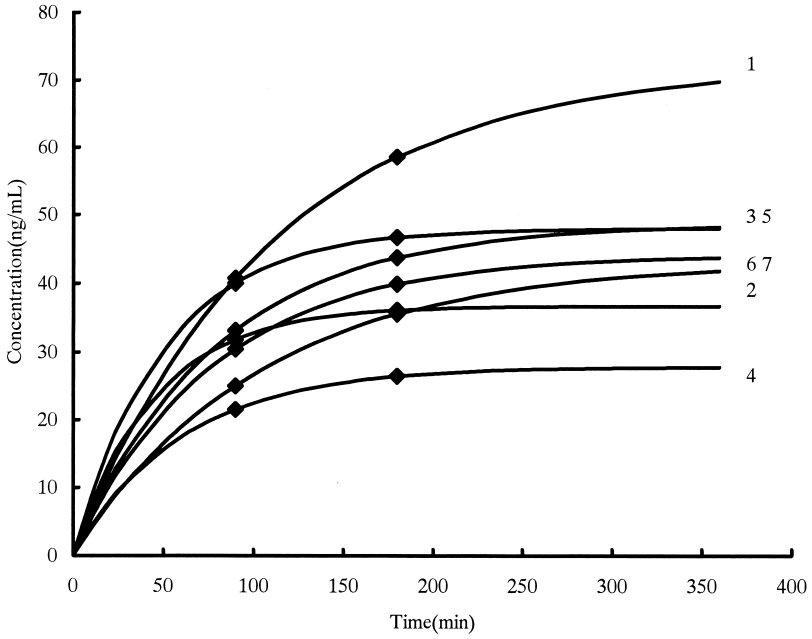

Figure 1. The theoretically expected olprinone plasma concentrations. Numbers in figure shows each patient's number in previous table.

Table 3. Pharmacodynamic parameters

	CI						SVRI					
No	E_{max}	EC_{50}	γ	α	cE_{max}	AIC	E_{max}	EC_{50}	γ	α	cE_{max}	AIC
1	1.23	47.60	4.80	2.14	3.37	−1.29	1188	37.00	5.68	2396	1208	6.57
2	1.19	38.71	5.69	2.04	3.23	−1.38	1114	30.97	5.90	2337	1223	6.05
3	2.11	41.66	7.47	2.95	5.06	−4.01	666	38.43	5.97	1425	759	5.68
4	2.84	24.73	5.14	2.44	5.28	−4.00	1187	22.06	6.05	1868	681	5.13
5	0.88	42.18	3.94	2.56	3.44	−4.81	714	35.15	4.84	1980	1265	5.82
6	1.84	44.25	5.16	2.17	4.01	−5.53	1616	36.54	4.52	2774	1158	6.02
7	1.26	29.53	4.53	2.74	4.00	−7.56	1083	23.50	2.89	2594	1511	5.80
mean	1.62	38.38	5.25	2.43	4.06		1081.2	31.95	5.12	2196.2	1115.0	
SD	0.68	8.26	1.12	0.34	0.82		320.6	6.70	1.15	465.7	293.4	

$CI=\alpha+E_{max}\cdot C^{\gamma}/(EC_{50}^{\gamma}+C^{\gamma})$ $SVRI=\alpha-E_{max}\cdot C^{\gamma}/(EC_{50}^{\gamma}+C^{\gamma})$

CI, cardiac index; SVRI, systemic vascular resistance index; C, olprinone plasma concentration; γ, parameter describing the steepness of the curves, means a number of recepters; α, collecting items, means the data at the beginning of infusion; EC_{50}, olprinone plasma concentration associated with a 50% increase for CI and decrease for SVRI; E_{max}, maximum increase for CI and decrease for SVRI based on the collecting items; and cE_{max}, $\alpha+E_{max}$ for CI and $\alpha-E_{max}$ for SVRI.

ng/mL for SVRI. E_{max} was 1.62±0.68 $L\cdot min^{-1}\cdot m^{-2}$ for CI and 2196.2±465.7 $dynes\cdot sec\cdot m^{2}\cdot cm^{-5}$ for SVRI. γ was 5.25±1.12 for CI and 5.12±1.15 for SVRI.

Discussion

PDE-Ⅲ inhibitor slow induction has been discussed, and some reports have shown the efficacy and safety of this technique[10]. Baruch et al found that non-bolus infusion of milrinone did not differ from continuous infusion with bolus loading in plasma concentration over 3 hours[11]. In our study 0.2 $\mu g\cdot kg^{-1}\cdot min^{-1}$ olprinone slow induction yielded a level of 20 ng/mL in 46.8±17.87 minutes and maintained an effective concentration throughout the study period.

There are few reports an olprinone because it has been used only in Japan. In this study, we

could calculate the pharmacokinetic parameters only at two points blood sampling. Our acquired parameters, Ke, Vd, and plasma concentration, differed little already-reported data. It have been reported that Ke was 0.89/hr (0.0148/min) and Vd was 249 mL/kg. Yamamura K. reported that 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ olprinone infusion yielded a 26 ng/mL plasma concentration, while 0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ infusion yielded 53 ng/mL[12,13]. This two-points blood sampling method feels convenient and reliable in clinical PK approach, if the blood sampling volume is so little the better.

Much olprinone will be excreted through the kidney and the liver will metabolize little of it. Renal insufficiency may result in decrease of Ke and CL and increase in olprinone plasma concentration, as suggested by our results[14,15]. This result indicates that for patients with renal dysfunction or who require hemodialysis therapy olprinone infusion rate should be reduced. Adverse effects of olprinone readily occur in patients with renal insufficient even when slow induction is selected.

PDE-III inhibitors have vasodilatory and inotropic effects, and both effects will diminish oxygen consumption by heart muscle[16]. However, the two effects are mediated by different pathway, since Figure 2 and Table 3 show that γ and curve differ for the two. This indicates that the inotropic effect of olprinone did not result from vasodilatory effect and volume loading. Moreover, E_{max} for CI and SVRI exhibited much variation in each case, indicating that the degrees of inotropic and vasodilatory effect of olprinone are not constant and are influenced by many factors, including myocardial function, compliance of vessels, sensitivity of receptors, etc. In fact, the vasodilating effect and inotropic effect are complementary. CI and SVRI may not be a pure indicator of those two effects. But we recognized that in this study CI and SVRI was the outcome caused after vasodilating and inotropic effect was expressed, and the periodic discrepancy between CI and SVRI must be mentioned. The hypotension induced by PDE-III inhibitors is thought to be due to the time lag between vasodilatory and inotropic effects, and our study found different EC_{50} values for CI and SVRI (Table 2 and Fig. 2). To prevent hypotension, infusion by bolus injection may be better pharmacokinetically, because it will rapidly increase olprinone concentration and shorten the above time lag. However, particularly in critical ill patients who often have poor cardiac function and peripheral circulatory disorder, this method may result in more severe hypotension.

In this study, we prevented severe hypotension by volume loading alone until an inotropic effect appeared. However volume-loading therapy may have other adverse effects in critically ill patients, since such patients exhibit various changes in there vascular beds. Adequate use of vasoconstrictors will be more useful for control of hemodynamics[17].

Olprinone has a strong vasodilatory effect than other PDE-III inhibitors. It is difficult to determine which PDE-III inhibitor has strong inotropic or vasodilatory effects, since each PDE-III inhibitor is used at a different dosage. Some investigators reported that milrinone has the strongest inotropic and olprinone the strongest vasodilatory effect among PDE-III inhibitors[18]. We reported that E_{max} was 4.39 $L \cdot min^{-1} \cdot m^{-2}$ for CI and 1952.8 dynes $\cdot$ sec $\cdot$ $m^{-2} \cdot cm^{-5}$ for SVRI when milrinone slow induction was used (0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ infusion without bolus)[7]. Our results suggest that milrinone has a higher E_{max} for CI than olprinone and that olprinone has a higher E_{max} for SVRI than milrinone. Another investigator reported that 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ olprinone infusion without bolus injection yielded a plasma concentration of only 20 ng/mL[19]. Only a

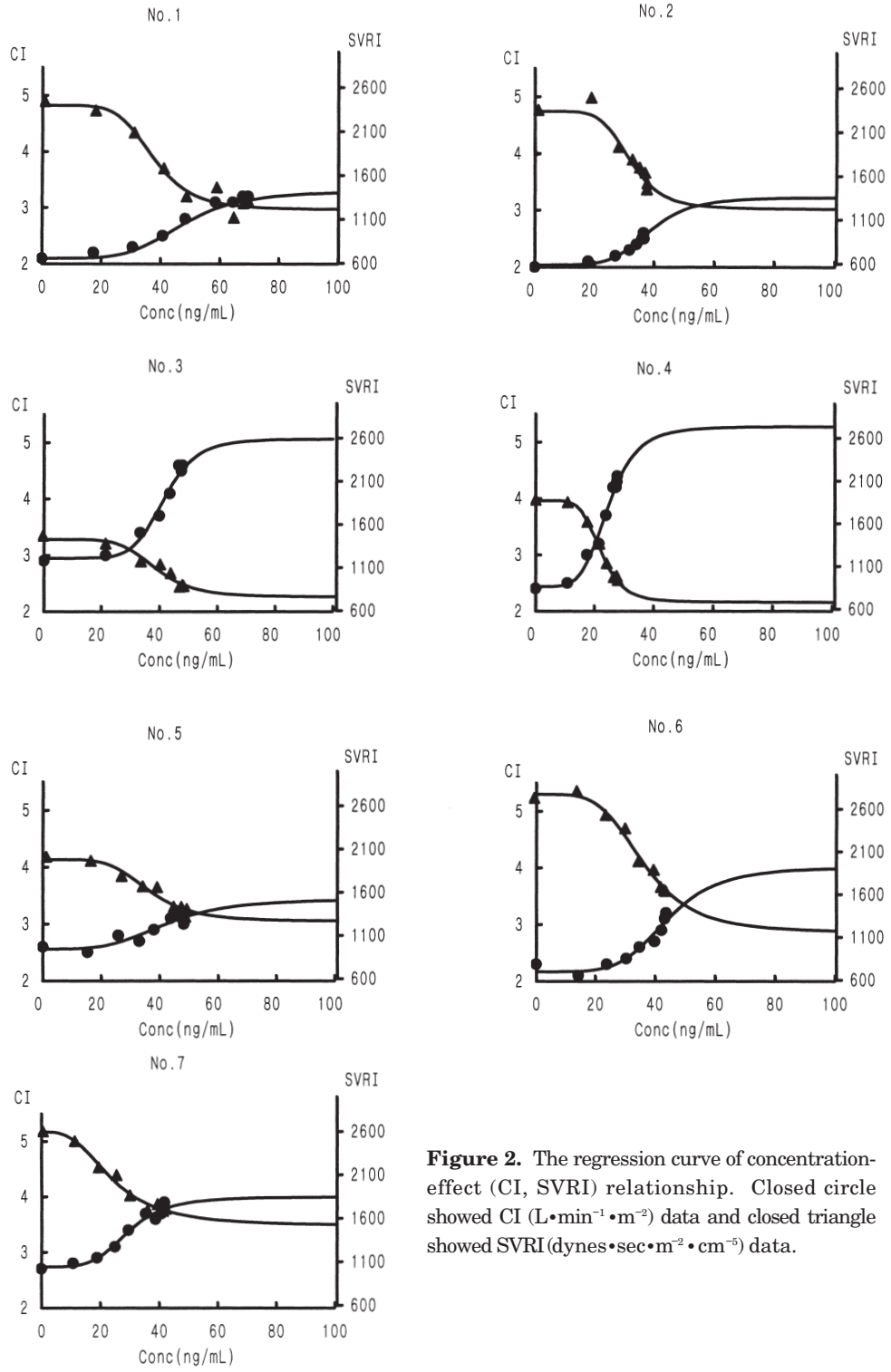

Figure 2. The regression curve of concentration-effect (CI, SVRI) relationship. Closed circle showed CI ($L \cdot min^{-1} \cdot m^{-2}$) data and closed triangle showed SVRI ($dynes \cdot sec \cdot m^{-2} \cdot cm^{-5}$) data.

vasodilatory effect will be observed at this concentration. Low dose infusion of olprinone may induce only hypotension without an inotropic effect. Our results showed that 40 ng/mL plasma olprinone concentrations was the minimum concentration for efficacy and the maximum effect was obtained at about 60 ng/mL. It was concluded from our results that olprinone effective plasma concentration is over the range 40 to 60 ng/mL, and that 20 ng/mL was the concentration yielding onset of effects.

Effects will not disappear immediately if olprinone infusion is discontinued, because the effects of PDE-Ⅲ inhibitors depend on intracellular cyclicAMP concentration. The intracellular cyclicAMP concentration could not be determined in our study, but bolus injection will result in large discrepancies between plasma olprinone concentration and intracellular cyclicAMP concentration. If olprinone infusion must be stopped unfortunately, higher intracellular cyclicAMP concentration will induce the delayed pharmacological effects. On the other hand, slow induction may result in small discrepancies between those. The slow induction method will be useful and safe in preventing hypotension and other adverse effects of olprinone in critically ill patients.

Conclusion

From the clinical pharmacokinetic and pharmacodynamic standpoint, olprinone slow induction is useful and safe for critically ill patients, and will be more effective when hemodynamic monitoring and vasoconstrictive agents are used.

Appendix

$$Conc\ 1=\frac{R}{CL}\cdot(1-e^{-90\cdot Ke})$$

$$Conc\ 2=\frac{R}{CL}\cdot(1-e^{-180\cdot Ke})=\frac{R}{CL}\cdot(1+e^{-90\cdot Ke})\cdot(1-e^{-90\cdot Ke})$$

$$Ke=-\frac{1}{90}\cdot\ln\left(\frac{Conc\ 2}{Conc\ 1}-1\right)$$

CL is clearance, Ke the elimination constant, and R the infusion rate (0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$). Conc 1 and 2 is the olprinone plasma concentrations at 90 and 180 minutes after the start of infusion.

References

1. Satou H, Endou M. Effects of a New Cardiotonic Agent 1,2-Dihydro-6-methyl-2-oxo-5[imidazo (1,2-a) pyridin-6-yl]-3-pyridine Carbonitrile Hydrochloride Monohydrate (E-1020) on Contractile Force and Cyclic AMP Metabolism in Canine Ventricular Muscle. Jpn J Pharmacol 1990;52:215-224.
2. Bailey J M. The effect of Milrinone on hemodynamics and left ventricular function after emergence from cardiopulmonary bypass. Anesth Analg 1997;85:16-22.
3. Levy JH, Bailey JM, Deeb GM. Intravenous Milrinone in cardiac surgery. Ann Thorac Surg 2002;73:325-350.
4. Orime Y, Shiono M, Hata M, Sezai Y. Effects of Phosphodiesterase Inhibitors After Coronary Artery Bypass Grafting. Jpn Circ J 1996;63:117-122.
5. Shibata T, Suehiro S, Sasaki Y, Hosono M, Nishi S, Kinoshita H. Slow induction of milrinone after coronary artery bypass grafting. Ann Thorac Surg 2002;73:325-350.
6. Borrás-Blasco J, Rosique-Robles JD, Peris-Martí J, Santos-Calle FJ, Navarro-Ruiz A, Gonzalez-Delgado M. Kinetic alteration of theophylline at therapeutic doses. Int J Clin Pharm Th 2000;38(9):457-460.
7. Nishi S, Azuma K, Asada A. Pharmacokinetics and pharmacodynamics of milrinone slow induction after cardiac surgery. Pharmacol Toxicol 2001;89(suppl):89.
8. Butterworth JF, Hines RL, Royster RL, James RL. A Pharmacokinetics and Pharmacodynamic Evaluation of Milrinone in Adaluts Undergoing Cardiac Surgery. Anesth Analg 1995;81:783-792.
9. Akaike H. A new look at the Statistical Model Identification. IEEE T Automat Contr 1974;AC-19(6):716-723.
10. Orime Y, Shiono M, Hata H, Yagi S, Tukamoto S, Kimura S, et al. Post-operative effects of olprinone after coronary bypass grafting. Annals of Thoracic & Cardiaovascular Surgery 1998;4(6):340-346.
11. Baruch L, Patacsil P, Hameed A, Pina I, Loh E. Pharmacodynamic effects of milrinone with and without a

bolus loading infusion. Am Heart J 2001;141(2):266-273.
12. Yamamura K, Akiyoshi K, Irita K, Taniyama T, Takahashi S. Effects of olprinone, a new Phosphodiesterase inhibitor, on gastric intramucosal acidosis and systemic inflammatory responses following hypothermic cardiopulmonary bypass. Acta Anaesth Scand 2001;45:427-434.
13. Atarashi H, Sasaki H, Ohsaka M, Sasaki Y, Hayakawa H, Tomono Y, et al. A Phase I Study of E-1020 -Intravenous injection. Jpn J Pharmacol Ther 1990;21(3):613-621.
14. Taniguchi T, Shibata K, Saito S, Matsumoto H, Okeie K. Pharmacokinetics of milrinone in patients with congestive heart failure during continuous venovenous homofiltration. Intens Care Med 2000;26(8):1089-1093.
15. Amenomori H, Sakaki S, Hiraoka K, Morimoto Y, Gando S, Kemmotsu O. Phosphodiesterase **Ⅲ** inhibitor olprinone chlorate is not significantly removed by continuous venovenous hemodiafiltration. ASAIO J 2000;46(5):635-638.
16. Prielipp RC, MacGregor DA, Butterworth JF, Meredith JW, Levy JH, Wood KE, et al. Pharmacodynamics and pharmacokinetics of milrinone administration to increase oxygen delivery in critically ill patients. Chest 1996;109(5):1291-1301.
17. Gold J, Cullinane S, Chen J, Seo S, Oz MC, Oliver JA, et al. Vasopressin in the treatment of milrinone-induced hypotention in severe heart failure. Am J Cardiol 2000;85(4):506-508.
18. Sha K, Shimaoka M, Kawaraguchi Y, Takahashi M, Yanaidani F, Kitaguchi K, et al. Differences in hemodynamic effects of amrinone, milrinone and olprinnone in valvular cardiac surgery. Masui-Japanese Journal of Anesthesiology 2000;49(9):981-986.
19. Arai T, Takano Y, Mizukami S, Sato I. The effect of olprinone administered after cardio-pulmonary bypass grafting open heart surgery, evaluated by its plasma concentration and hemodynamic changes. Masui-Japanese Journal of Anesthesiology 1999;48(10):1083-1990.