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Original Article

Factors Affecting the Absorption of Midazolam to the Extracorporeal Membrane Oxygenation Circuit

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Sedatives are administered during extracorporeal membrane oxygenation (ECMO) therapy to ensure patient safety, reduce the metabolic rate and correct the oxygen supply-demand balance. However, the concentrations of sedatives can be decreased due to absorption into the circuit. This study examined factors affecting the absorption of a commonly used sedative, midazolam (MDZ). Using multiple *ex vivo* simulation models, three factors that may influence MDZ levels in the ECMO circuit were examined: polyvinyl chloride (PVC) tubing in the circuit, use of a membrane oxygenator in the circuit, and heparin coating of the circuit. We also assessed changes in drug concentration when MDZ was re-injected in a circuit. The MDZ level decreased to approximately 60% of the initial concentration in simulated circuits within the first 30 minutes. The strongest factor in this phenomenon was contact with the PVC tubing. Membrane oxygenator use tended to increase MDZ loss, whereas heparin circuit coating had no influence on MDZ absorption. Similar results were obtained when a second dose of MDZ was injected to the second-use circuits.

Key words: sedatives, ECMO, polyvinyl chloride, pharmacokinetics, pharmacodynamics

Extracorporeal membrane oxygenation (ECMO) is a powerful support therapy that has been demonstrated to increase survival in patients with potentially reversible respiratory and circulatory failure [1,2]. Various medications are used to manage the underlying illness or complications caused by ECMO therapy [3-5]. Sedatives are administered to ensure patient safety, reduce the metabolic rate and correct the oxygen supply-demand balance. Among the available sedatives for ECMO treatment, midazolam (MDZ) is the most commonly used [6] because of its low cost and physicians' familiarity with the drug in intensive care.

In ECMO patients, the distribution volume and clearance of administered drugs generally increase as the drugs are absorbed by the polyvinyl chloride (PVC) tubing and/or membrane oxygenator, which remarkably complicates the pharmacokinetics of the injected agents [7-9]. Additionally, only a few studies have reported on preventive measures to reduce the absorp-

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tion caused by heparin coating of the circuit [10, 11]. Only a small number of published studies have investigated the pharmacokinetic or pharmacodynamic profiles of MDZ in ECMO patients (for review, see [12]). Moreover, clinical research has been limited by differences in the conditions and metabolism among studied patients, and differences in the ECMO equipment and techniques used.

We hypothesized that three major factors, PVC tubing in the circuit, use of a membrane oxygenator in the circuit, and heparin coating of the circuit, effected the loss of MDZ in the circuit. Using multiple *ex vivo* simulation models, this study aimed to assess the impact of each of these three factors on MDZ levels in the ECMO circuit. We also assessed changes in the concentration of MDZ upon re-injection into the same circuits.

Materials and Methods

Because this was an experimental simulation study and did not include any patients, the ethical committee waived study approval and patient consent. 4 types of simulated ECMO circuits were prepared using a reservoir, PVC tubing with or without heparin-coating, and a membrane oxygenator with or without heparin coating.

Preparation of ECMO circuits. We prepared 4 types of closed simulated ECMO circuits. Circuits were designed by connecting the arterial and venous cannulas to a reservoir bag, permitting continuous flow of priming fluid around the circuit.

Circuits were categorized into 4 groups as follows (Table 1). Group 1: circuits with a heparin-coated membrane oxygenator and tubes; Group 2: circuits with a non-heparin-coated membrane oxygenator and tubes; Group 3: circuits with only heparin-coated tubes; and Group 4: circuits with only non-heparin-coated tubes. Each group consisted of 4 identically prepared circuits.

Table 1 The 4 kinds of simulation circuits studied

	Membrane oxygenator	Heparin coating
Group 1	Yes	Yes
Group 2	Yes	No
Group 3	No	Yes
Group 4	No	No

Simulation circuits were categorized into 4 groups. Group 1 circuits were with heparin-coated membrane oxygenator and tubes, Group 2 circuits were with non-heparin-coated membrane oxygenator and tubes, Group 3 circuits were with only heparin-coated tubes, and Group 4 circuits were with only non-heparin-coated tubes.

A PVC tube (Senko Medical Instruments, Tokyo) of 120 cm length (3/8 inch diameter; 3/32 inch thickness) was used. Heparin coating was applied to the tubes used for Groups 1 and 3. For the membrane oxygenator, a silicon-coated external-perfusion hollow-fiber polypropylene porous membrane was used; its surface area was 2.3 m^2. Heparin coating was applied to the membrane oxygenators that were used for Group 1. In each circuit, a roller pump (HAD-11; Senko Medical Instrument) was used to maintain flow. Each ECMO circuit was maintained at 37°C using a temperature control unit for artificial heart-lung apparatuses (HHC-51; Senko Medical Instrument).

Study Phase I: Short-term MDZ absorption. Short-term MDZ loss was examined in Phase I. Ten mg of MDZ was dissolved in 500-ml normal saline. The concentration of MDZ at this time was defined as P0 (20 μg/ml). The total volume of solution was injected into the simulated ECMO circuit and priming was conducted. We maintained flow at 2.0 l/min using a roller pump and obtained 1 ml samples from each circuit at each of 6 time points: 0.5 h (P1), 1 h (P2), 3 h (P3), 6 h (P4), 12 h (P5), and 24 h (P6) after injection. Each sample was passed through a membrane filter into a glass container and cryopreserved at −84°C until analysis. MDZ absorption and the interactions of MDZ with the PVC tubing circuit, the membrane oxygenator in the circuit, and the heparin circuit coating were assessed.

In this paper, Groups 1 and 2 are collectively referred to as the "membrane oxygenator category" and Groups 3 and 4 are collectively referred to as the "non-membrane oxygenator category." Similarly, Groups 1 and 3 are collectively referred to as the "heparin-coated category (in Phase I)" and Groups 2 and 4 are collectively referred to as the "non-heparin-coated category (in Phase I)." Each category encompasses eight circuits.

Study Phase II: Long-term MDZ loss and effect of MDZ re-injection to the circuit. For the Phase II study, we first quantified the long-term loss of MDZ. The circuits from Groups 1 and 2 in Phase I were stored at normal temperature for approximately one month; these were designated the Group 1' and Group 2' circuits. Then 1 ml of sample was obtained from each circuit and the MDZ concentration was measured (P'

base line, P'BL). Next, these circuits were used to determine whether a circuit which had already absorbed MDZ would similarly absorb MDZ a second time. In this experiment, 10 mg of MDZ was dissolved in the circuit again, and P'0 was set as 20 μg/ml above the P'BL level. As in Phase I, we maintained flow at 2.0 l/min using the same roller pump and obtained 1 ml samples from each circuit at six time points: 0.5 h (P'1), 1 h (P'2), 3 h (P'3), 6 h (P'4), 12 h (P'5), and 24 h (P'6) after MDZ injection. Each sample was cryopreserved using the same method.

Groups 1 and 2 are collectively referred to as the "first-use category" and Groups 1' and 2' are collectively referred to as the "second-use category." Similarly, Groups 1 and 1' are collectively referred to as the "heparin-coated category (in Phase II)" and Groups 2 and 2' are collectively referred to as the "non-heparin-coated category (in Phase II)." Each category encompasses eight circuits.

Measurement of MDZ concentration. High performance liquid chromatography was used for quantitative determination of MDZ levels. A Supersphere 100RP-18 (e) column was used under the following conditions: column temperature of 35°C; mobile phase of acetonitrile, methanol, phosphate buffer (pH 5.0) = 1 : 1 : 1; flow rate of 1.3 ml/min; and single-dose injection of 30 μl. Isopropylantipyrine was used as an internal standard substance.

Statistical analysis. Data were expressed as mean ± standard deviation. We used a two-way repeated measures analysis of variance (ANOVA) to account for repetitions within each circuit. We used the MDZ value as a dependent variable and entered the time (*i.e.*, time comparison), the conditions (presence or absence of a membrane oxygenator; use or non-use of heparin-coated tubes; or first or second use of the circuit) (*i.e.*, group comparison), and an interaction term between the time and the conditions (*i.e.*, time and group interaction) into the model as independent variables. We used the interaction term between dependent variables to explore whether changes in the MDZ value between time periods differed depending on each condition. Statistical analysis was performed using STATA version 15 (StataCorp LP, College Station, TX, USA). The "anova" command was used for the first run and the "regress" command thereafter in order to fit the underlying regression model to an ANOVA model using the "anova" command. A p-value below 0.05 was considered statistically significant.

Results

A temperature of 37°C was maintained throughout the experiments. ECMO flow was stable and constantly maintained at 2.0 l/min.

Study phase I. In Phase I, the experiment was performed using 4 circuits in each of the 4 groups, and 6 samples were obtained from each circuit; thus a total of 96 samples were analyzed.

In every group, MDZ levels declined over time (Group 1: P1 = 9.9 ± 3.4 μg/ml (50%) to P6 = 5.8 ± 3.1 μg/ml (29%); Group 2: P1 = 11.0 ± 3.3 μg/ml (55%) to P6 = 6.9 ± 3.0 μg/ml (35%); Group 3: P1 = 11.6 ± 2.0 μg/ml (58%) to P6 = 8.7 ± 4.0 μg/ml (44%); Group 4: P1 = 10.7 ± 5.1 μg/ml (54%) to P6 = 10.0 ± 1.9 μg/ml (50%).

To observe MDZ absorption into the PVC circuit, the reductions in MDZ in Groups 3 and 4 (non-membrane oxygenator category) were examined. The MDZ levels declined by approximately 60% at 0.5 h after initiation of the experiment. Thereafter the decline was less pronounced: at 24 h after initiation of the experiment, the MDZ level was 47% lower (P6 = 9.3 μg/ml) compared to that at initiation (P0) of the experiment.

As shown in Fig. 1A, the presence of a membrane oxygenator seemed to have an impact on changes in MDZ level, although the interaction term between time and the presence of a membrane oxygenator did not reach statistical significance ($p = 0.20$). The subsequent "regress" command suggested some meaningful interactions (between time and the presence of a membrane oxygenator) at P2 ($p = 0.017$) and P6 ($p = 0.06$) — *i.e.*, the declines in MDZ level after one or 24 h tended to be larger in the presence of a membrane oxygenator compared to those in the absence of a membrane oxygenator. Finally, as shown in Fig. 1B, heparin coating of the circuit had no influence on the changes in MDZ level, and the interaction term was not statistically significant ($p = 0.79$).

Study phase II. After the final MDZ measurement (P6), all the circuits for Groups 1 and 2 were stored at normal temperature for 1 month, and then the drug concentration was measured again. The mean MDZ levels for the 4 circuits after one-month storage were 3.0 ± 2.8 μg/ml (15%) and 2.7 ± 3.1 μg/ml (14%) in Groups 1 and 2, respectively, and both values were

approximately 15% lower than the corresponding P6 levels. In Phase II, 6 samples were obtained from each circuit (2 circuits for each group); a total of 48 samples were analyzed. The MDZ levels declined over time in both groups: Group 1', P1' = 12.3 ± 5.1 μg/ml (62%) to P6' = 9.5 ± 6.1 μg/ml (48%); Group 2', P1' = 13.7 ± 5.2 μg/ml (69%) to P6' = 9.3 ± 6.1 μg/ml (47%). The decline in MDZ in the groups of the second-use circuit category (Groups 1' and 2') was similar to that of the first-use circuit category. The final MDZ measurement in the Group 1' and 2' circuits was slightly (10%) but not significantly higher than that of the first-use circuits.

Using the Phase I (Groups 1 and 2) and Phase II data, the factors that may influence MDZ levels within a circuit (*i.e.*, first- or second-use circuit; presence or absence of heparin coating inside a circuit) were examined. There was a 10% difference in MDZ absorption when comparing the first- or second-use circuit categories, but the interaction term did not reach statistical significance ($p = 0.44$) (Fig. 1C). Circuit heparin coating also had no influence on changes in MDZ level, and this interaction term was also not significant (heparin-coated category vs. non-heparin-coated category) ($p = 0.64$) (Fig. 1D).

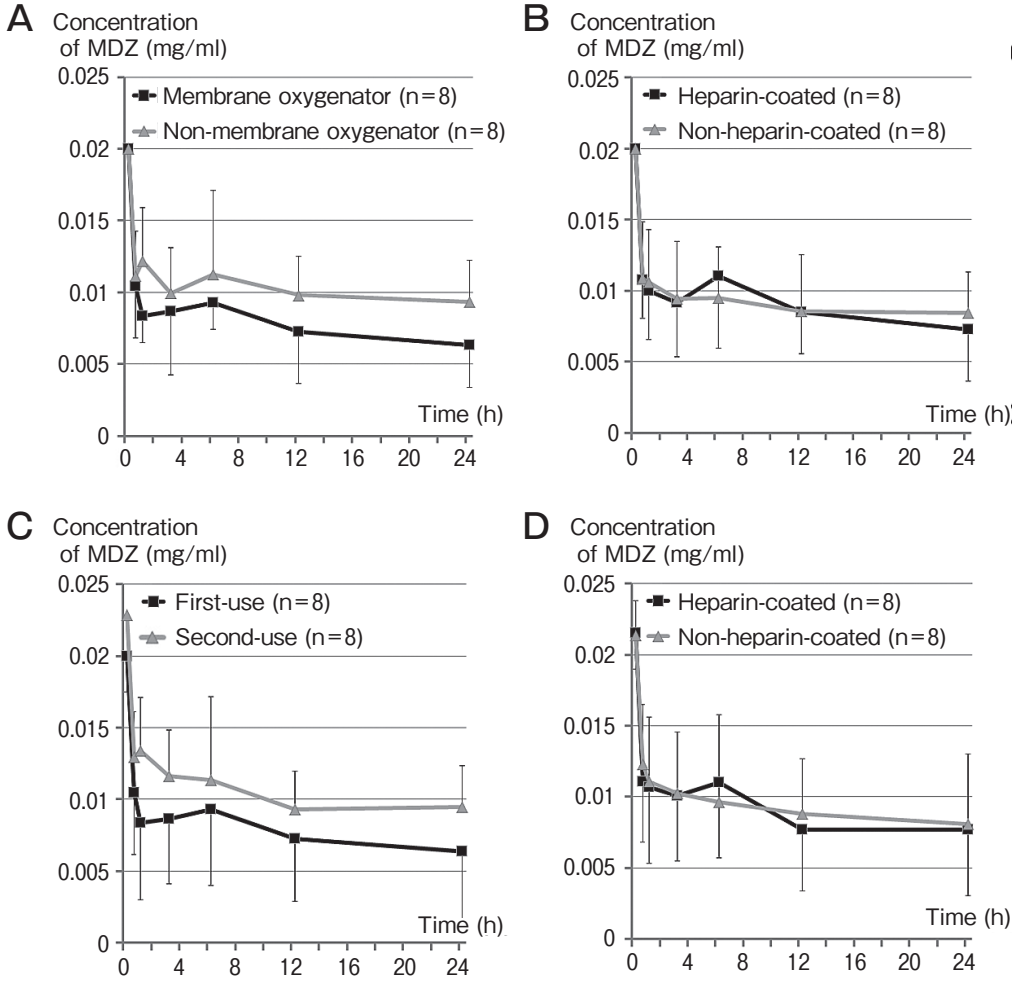

Fig. 1 **A**, Comparison of MDZ levels between groups with or without membrane oxygenators. Each category contained 8 circuits and the interaction terms were statistically significant at 1 h after administration (P2) ($p = 0.017$); **B**, Comparison of MDZ levels between groups with or without heparin coating. Each category contained 8 circuits and the interaction terms were not significant; **C**, Comparison of MDZ levels between a first-use and second-use ECMO circuit. Each category contained 8 circuits and the interaction terms were not significant; **D**, Comparison of MDZ levels between groups with or without heparin-coating in the second-use circuits. MDZ: midazolam. Each category contained 8 circuits and the interaction terms were not significant.

Discussion

Previous pharmacokinetic clinical studies on MDZ have been limited by differences among ECMO techniques and devices, variations in patient clinical backgrounds, and small sample sizes. In addition, because these studies were conducted in an *in vivo* environment, the effects of drug interactions and internal metabolism could not be excluded. In this study, using a simulated ECMO circuit, we investigated factors that influence the absorption of MDZ by the circuit. The system used in this experiment allowed us to examine influences on the ECMO circuit alone, excluding any potential biological influences.

Our results showed that the use of a membrane oxygenator may contribute to a decrease in MDZ concentration, and second-use circuits appear to make a similar contribution to the decrease in MDZ. The membrane oxygenator used in our study was made of polypropylene with a 2.2 m^2 surface area. Polypropylene-based membrane oxygenators have been reported to absorb a smaller quantity of drugs than silicone-based membrane oxygenators [13]. However, the surface area of a circuit with a membrane oxygenator is 65 times larger than that of a circuit without a membrane oxygenator, and a larger circuit surface area generally absorbs larger amounts of injected agents. Due to the large surface area of the membrane oxygenator, we expected a more dramatic decrease in MDZ level in the circuit with the membrane oxygenator. However, the difference between the membrane oxygenator and non-membrane oxygenator groups at 24 h was only 15%. The polypropylene-based membrane oxygenator in the circuit had some impact on the absorption of MDZ, but its effect seemed to be much less than that of the absorption to PVC.

PVC is the most commonly used material for conduit tubing because of its flexibility, precise connectability, and cost-effectiveness. It has been reported that PVC tubing absorbs lipid-soluble agents, including sedatives [14]. In particular, lipid-soluble drugs with high octanol water partition coefficients are very readily absorbed into the ECMO circuit [6, 15, 16]. MDZ is a highly lipid-soluble drug with a protein binding rate of 97% and a high octanol/water partition coefficient of 1688.

The mechanism underlying the decrease in lipid soluble drug in the ECMO circuit is absorption (*i.e.*, incorporation of the drug into the material) into the plasticizer of the PVC circuit tubing, not adsorption (*i.e.*, adherence of the agent to the surface of the material). Generally, diethylhexyl phthalate (di (2-ethylhexyl) phthalate; DEHP) or trimellitic acid tris (2-ethylhexyl) trimellitate (TOTM) are used as plasticizers for PVC. In the present study, the tubing plasticizer was DEHP. Previous studies have indicated that MDZ molecules are absorbed upon exposure to the molecules of the DEHP plasticizer [17, 18].

These chemical properties are considered to contribute to the decrease in the MDZ concentration due to absorption by a PVC tube. Similar to our experiment, MDZ absorption to the entire ECMO circuit, including the membrane oxygenator, has been reported in other research (30 min: 56% absorption; 24 h: 89% absorption) [19]. Our study showed that even without a membrane oxygenator, the PVC circuit absorbed approximately 60% of the MDZ within 30 min. PVC tubing thus seems to be the most determinative factor of MDZ absorption in ECMO components.

In general, coating ECMO circuits with heparin decreases neurological or systemic hemorrhagic complications and shortens hospitalization duration [20]. Such coating can suppress the absorption of certain agents, such as morphine [11], although the absorption rate varies depending on whether heparin or some other coating agent is used. In addition, other agents such as propofol are absorbed to PVC regardless of whether or not the circuit is heparin-coated [10]. Indeed, our results indicated that heparin coating did not prevent the absorption of MDZ to the ECMO circuit.

We further compared MDZ absorption between a first-use and second-use ECMO circuit. The concentration of MDZ following a second administration in a previously second-use circuit decreased to the same extent as the MDZ concentration following the first administration. Mulla *et al.* reported that when a dose of MDZ to an ECMO circuit exceeded approximately 30 mg in an *in vivo* experiment, the absorption to the circuit decreased and the circuit became saturated [21]. After saturation, a utilized circuit seems to absorb less agent over time [22]. In our present experiments, the full 20 mg dose of MDZ was absorbed without the PVC tube becoming saturated. It is known that MDZ dose adjustments and thorough monitoring are required for patients with ECMO [23], especially in the early phase of sedation.

Numerous other factors influence the pharmacokinetics in patients treated with ECMO, and can inhibit accurate dosing estimation and injection. Hemodilution with the priming solution at induction, increased distribution of volume-by-volume load to maintain intravascular volume after induction [24], and decrease in drug consumption [8] all can influence pharmacokinetics during ECMO. The decrease in drug levels in an ECMO circuit is also dependent on the individual chemical properties of each drug [7, 25-27] and on drug interactions. The temperature in the ECMO circuit may influence drug absorption [6]. The type of driving pump may also be an influencing factor: lipid-soluble drugs have shown lower absorption in centrifugal pumps. Exposure to oxygen may facilitate decreased drug concentration in the circuit [16]. Finally, MDZ absorption may become saturated through long-term continuous infusion to the ECMO circuit [28].

In future studies, it will be necessary to examine other dosing (concentrations) and continuous infusion, or a circuit saturated with MDZ. In addition, although the effects on patients were well-predicted by our *ex vivo* experiments, it will be necessary to perform an *in vivo* study to definitively demonstrate these effects. Studies on adult patients are required due to the lack of published literature describing pharmacokinetic variations during ECMO [8] in adult patients; studies on neonates/infants are needed as well. Finally development of alternative flexible circuits formed of materials other than PVC and/or development of plasticizers that do not absorb MDZ or other agents will be needed.

In conclusion, the MDZ level rapidly (within 30 min) decreased from its initial concentration, mainly due to absorption into PVC. The silicone-based membrane oxygenator in the circuit also tended to have an impact on the absorption of MDZ. MDZ injected as a second dose was absorbed in the circuit in a manner similar to the primary injection. Considering the various factors that influence drug absorption, further *in vivo* research is necessary.

References

1. Green TP, Timmons OD, Fackler JC, Moler FW, Thompson AE and Sweeney MF: The impact of extracorporeal membrane oxygenation on survival in pediatric patients with acute respiratory failure. Pediatric Critical Care Study Group. Crit Care Med (1996) 24: 323–329.
2. Lequier L: Extracorporeal life support in pediatric and neonatal critical care: a review. J Intensive Care Med (2004) 19: 243–258.
3. Rais-Bahrami K and Short BL: The current status of neonatal extracorporeal membrane oxygenation. Semin Perinatol (2000) 24: 406–417.
4. Champion MP, Murdoch I, Sajjanhart T and Marsh MJ: Extracorporeal membrane oxygenation in refractory shock in fulminant meningococcaemia. Lancet (1996) 347: 201–202.
5. Rais-Bahrami K, Short BL: Citrobacter sepsis and severe newborn respiratory failure supported with extracorporeal membrane oxygenation. J Perinatol (2000) 20: 265–266.
6. Wildschut ED, Ahsman MJ, Allegaert K, Mathot RA and Tibboel D: Determinants of drug absorption in different ECMO circuits. Intensive Care Med (2010) 36: 2109–2116.
7. Buck ML: Pharmacokinetic changes during extracorporeal membrane oxygenation: implications for drug therapy of neonates. Clin Pharmacokinet (2003) 42: 403–417.
8. Shekar K, Fraser JF, Smith MT and Roberts JA: Pharmacokinetic changes in patients receiving extracorporeal membrane oxygenation. J Crit Care (2012) 27: e9–18.
9. Shekar K, Roberts JA, Ghassabian S, Mullany DV, Ziegenfuss M, Smith MT, Fung YL and Fraser JF: Sedation during extracorporeal membrane oxygenation-why more is less. Anaesth Intensive Care (2012) 40: 1067–1069.
10. E Hammaren, PH Rosenberg and M Hynynen: Coating of extracorporeal circuit with heparin does not prevent sequestration of propofol in vitro. Br J Anaesth (1999) 82: 38–40.
11. Preston TJ, Ratliff TM, Gomez D, Olshove VE Jr, Nicol KK, Sargel CL and Chicoine LG: Modified surface coatings and their effect on drug adsorption within the extracorporeal life support circuit. J Extra Corpor Technol (2010) 42: 199–202.
12. Rayyan M and Allegaert K: Pharmacotherapy during neonatal extracorporeal membrane oxygenation: toward an evidence-based approach. Crit Care (2007) 11: 107.
13. DA Rosen, Rosen KR and Silvasi DL: In vitro variability in fentanyl absorption by different membrane oxygenators. J Cardiothorac Anesth (1990) 4: 332–335.
14. Mulla H, Lawson G, von Anrep C, Burke MD, Upton DU, Firmin RK and Killer H: In vitro evaluation of sedative drug losses during extracorporeal membrane oxygenation. Perfusion (2000) 15: 21–26.
15. Lemaitre F, Luyt CE, Roullet-Renoleau F, Nieszkowska A, Zahr N, Corvol E, Fernandez C, Antignac M, Farinotti R and Combes A: Impact of extracorporeal membrane oxygenation and continuous venovenous hemodiafiltration on the pharmacokinetics of oseltamivir carboxylate in critically ill patients with pandemic (H1N1) influenza. Ther Drug Monit (2012) 34: 171–175.
16. Lemaitre F, Luyt CE, Roullet-Renoleau F, Nieszkowska A, Zahr N, Fernandez C, Farinotti R and Combes A: Oseltamivir carboxylate accumulation in a patient treated by haemodiafiltration and extracorporeal membrane oxygenation. Intensive Care Med (2010) 36: 1273–1274.
17. Kawano K, Matsunaga A, Nakazawa K, Komatsu R and Nakajima S: The Effect of pH in the Solutions on the sorption of Midazolam into a Plastic Container or an Administration Set. Jpn J Hosp Pharm (1992) 18: 449–453 (in Japanese).
18. Senshu K, Takenaka M, Miyahara Y, Ichiishi M and Koyama S: Study on Drug Sorption of Polyvinyl Chloride-Infusion Line Containing Tris (2-ethylhexyl) trimellitate as the Plasticizer and Release Behavior of the Plasticizer. Jpn J Pharm Health Care Sci (2004) 30: 136–142 (in Japanese).
19. Lemaitre F, Hasni N, Leprince P, Corvol E, Belhabib G, Fillatre P,

Luyt CE, Leven C, Farinotti R, Fernandez C and Combes A: Propofol, midazolam, vancomycin and cyclosporine therapeutic drug monitoring in extracorporeal membrane oxygenation circuits primed with whole human blood. Critical Care (2015) 19: 40.
20. Wendel HP and Ziemer G: Coating-techniques to improve the hemocompatibility of artificial devices used for extracorporeal circulation. Eur J Cardiothorac Surg (1999) 16: 342–350.
21. Mulla H, Lawson G, Peek GJ, Firmin RK and Upton DR: Plasma concentrations of midazolam in neonates receiving extracorporeal membrane oxygenation. ASAIO J (2003) 49: 41–47.
22. Dagan O, Klein J, Gruenwald C, Bohn D, Barker G and Koren G: Preliminary studies of the effects of extracorporeal membrane oxygenator on the disposition of common pediatric drugs. Ther Drug Monit (1993) 15: 263–266.
23. Ahsman MJ, Hanekamp M, Wildschut ED, Tibboel D and Mathot RA: Population Pharmacokinetics of Midazolam and Its Metabolites during Venoarterial Extracorporeal Membrane Oxygenation in Neonates. Clin Pharmacokinet (2010) 49: 407–419.
24. Bartlett RH: Extracorporeal life support for cardiopulmonary failure. Curr Probl Surg (1990) 27: 621–705.
25. Smith JC, Davies MC, Melia CD, Denyer SP and Derrick MR: Uptake of drugs by catheters: the influence of the drug molecule on sorption by polyurethane catheters. Biomaterials (1996) 15: 1469–1472.
26. Mehta NM, Halwick DR, Dodson BL, Thompson JE and Arnold JH: Potential drug sequestration during extracorporeal membrane oxygenation: results from an ex vivo experiment. Intensive Care Med (2007) 33: 1018–1024.
27. Bhatt-Meht V and Annich G: Sedative clearance during extracorporeal membrane oxygenation. Perfusion (2005) 20: 309–315.
28. Ahsman MJ, Hanekamp M, Wildschut ED, Tibboel D and Mathot RA: Population pharmacokinetics of midazolam and its metabolites during venoarterial extracorporeal membrane oxygenation in neonates. Clin Pharmacokinet (2010) 49: 407–419.