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ORIGINAL ARTICLE

Remimazolam anesthesia in pediatric patients undergoing cardiac catheterization for congenital heart disease: a retrospective observational study

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Abstract

Background Benzodiazepines are used in pediatric patients with congenital heart disease (CHD) because of their mild hemodynamic depressant effects. A novel short-acting benzodiazepine, remimazolam, is expected to be suitable for these patients. We examined the characteristics of remimazolam anesthesia in pediatric patients with CHD undergoing cardiac catheterization.

Methods This single-center retrospective study included pediatric patients undergoing cardiac catheterization for CHD. The primary outcome was the remimazolam dose for loss of consciousness. Secondary outcomes included the mean maintenance remimazolam dose, recovery time from anesthesia, predicted remimazolam concentration at emergence, decrease in blood pressure and heart rate, vasopressor administration during anesthesia, electroencephalogram index (bispectral index: BIS or patient state index: PSI), and life-threatening adverse events.

Results Thirty-nine patients, aged 2 months to 16 years, were included. Thirty-three patients received a median [interquartile] midazolam dose of 0.10 [0.10–0.10] $mg.kg^{-1}$ in the pre-anesthesia room. The remimazolam dose for loss of consciousness was 0.34 [0.26–0.45] $mg.kg^{-1}$. The mean maintenance dose was 1.0 [0.8–1.4] $mg.kg^{-1}.h^{-1}$. The recovery time was 15 [12–17] min. The predicted remimazolam concentration at emergence was 0.4–1.2 $\mu g.ml^{-1}$ in 3–6-year-old patients. Blood pressure and heart rate decreased by 30% in 15 and 6 patients, respectively. Vasopressors were administered as a bolus in 8 patients. The BIS or PSI did not fall ≤ 60 or ≤ 50, respectively, in 51% of patients before tracheal intubation. No life-threatening adverse events were reported.

Conclusions Remimazolam is a good alternative anesthetic agent for pediatric patients undergoing cardiac catheterization for CHD.

Keywords Cardiac catheterization · Congenital heart disease · Intravenous anesthesia · Pediatric · Remimazolam

Introduction

Pediatric patients with congenital heart disease often experience hypotension during general anesthesia [1, 2]. Although hypotension is not necessarily a clinically dangerous condition, it is generally treated to prevent organ hypoperfusion, which can cause complications [3]. In this context, benzodiazepines offer an advantage in patients at risk of hemodynamic instability during general anesthesia, because they generally have only a mild hemodynamic depressant effect [4].

Remimazolam is a novel, short-acting, intravenous benzodiazepine that has been shown to have a less hypotensive effect than that of propofol in adult clinical trials [5, 6]. As remimazolam maintained hemodynamic variables, including mean arterial pressure, heart rate, cardiac output, and systemic vascular resistance, after a remimazolam bolus of 0.2 mg in elderly patients [7], remimazolam might also have advantages in pediatric patients with congenital heart disease whose hemodynamic can be unstable during general anesthesia. Additionally, benzodiazepines do not pose the

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risk of developing propofol infusion syndrome [8] and do not trigger malignant hyperthermia [9]. Accordingly, remimazolam may be an alternative to general anesthesia in pediatric patients with congenital heart disease. However, limited information is currently available on remimazolam anesthesia in pediatric patients, given that it is used off-label [10], particularly in patients with congenital heart disease [11].

We here conducted a retrospective study to examine remimazolam anesthesia in pediatric patients undergoing cardiac catheterization for congenital heart disease, to determine the remimazolam dose required to achieve loss of consciousness and for maintenance of anesthesia, hemodynamic characteristics, and the time course of the electroencephalogram (EEG) index. Additionally, the time course of remimazolam concentration during anesthesia and the remimazolam concentration at recovery from anesthesia were predicted in 3–6-year-old patients, using a published remimazolam pharmacokinetic model for this age group [10].

Methods

This was a retrospective, single-center, observational study involving children who underwent cardiac catheterization under remimazolam anesthesia at the Showa University Hospital (Tokyo, Japan). For the off-label use of remimazolam for general anesthesia in pediatric patients, we obtained approval from Showa University Hospital (Showa University Medical Safety Management section, Reference No. 2102T00044). We obtained written informed consent from the parents or legal guardians of the children before remimazolam was administered to the patients in clinical practice. Anesthesia records were extracted after institutional review board approval (Showa University School of Medicine, Reference No. 22-028-B) was obtained, and the need for obtaining informed consent for data use from the patients and their parents/guardians was waived.

Patients were included if they were aged < 18 years and underwent cardiac catheterization under remimazolam anesthesia between April and September 2022. The exclusion criteria were as follows: contraindications to benzodiazepines, fentanyl, remifentanil, or rocuronium; history of long-term benzodiazepine use; and severe liver or renal dysfunction.

Anesthetic management and monitoring

Standard anesthetic management and monitoring were performed as follows. An intravenous catheter was placed in the ward. Midazolam was administered to treat patients who cried, were agitated, or were anxious in the pre-anesthesia catheterization room, if necessary. Standard monitoring was performed, including non-invasive blood pressure, electrocardiogram, pulse oxygen saturation, and EEG monitoring using BIS® (Medtronic, Minneapolis, MN, USA) or SedLine® (version 2.3.3.7, Masimo, Irvine, CA, USA). After recording baseline vital signs, oxygen (FiO_2 0.21–1.0) was delivered via a face mask. Remimazolam besylate, fentanyl, and remifentanil were administered to induce anesthesia. After rocuronium administration, the trachea of the patients was intubated. During the maintenance of anesthesia, the administration of remimazolam and opioids was adjusted with reference to vital signs, EEG waveforms, especially the presence of spindle waves, and EEG index (bispectral index [BIS] value or patient state index [PSI]). Vasopressors were administered at the discretion of the attending anesthesiologist. After confirming hemostasis at the sheath puncture site, remimazolam administration was terminated. The trachea was extubated after spontaneous breathing resumed with eyes open. Flumazenil was used for insufficient recovery from anesthesia, such as cases with somnolence or inadequate respiratory status.

Outcomes and statistical analysis

The primary outcome was the dose of remimazolam required to achieve loss of consciousness. In this study, we defined the time of the first dose of muscle relaxant as the time of loss of consciousness, because muscle relaxants were administered immediately after confirming the loss of consciousness in our standard practice. The secondary outcomes included the mean maintenance remimazolam dose, the time for recovery from remimazolam anesthesia (defined as the time from the termination of remimazolam infusion to extubation), blood pressure and heart rate decrease by 30% in two consecutive measurements, time courses of hemodynamics and EEG index, number of patients administered vasopressors during anesthesia, and life-threatening adverse events including severe hemodynamic change requiring resuscitation and anaphylaxis.

Additionally, we examined the time course of the predicted plasma concentration (Cp) of remimazolam during anesthesia and the remimazolam Cp at emergence. The remimazolam Cp was estimated for 3–6-year-old patients only, because the pediatric pharmacokinetic model (the Gao model) was available only for this age group [10]. Cp was estimated using NONMEM 7.5 (ICON Development Solution, Ellicott City, MD, USA) and PLT Tools 6.4.0 (PLT soft, San Francisco, CA, USA).

We divided the patients into four age groups: ≤ 11 months, 1–5 years, 6–12 years, and ≥ 13 years, to summarize and analyze the data. Data are expressed as median [25th–75th percentile] or number (percentage). Statistical analyses were performed using GraphPad Prism 9 (GraphPad Software, Boston, MA, USA).

Results

Thirty-nine patients were included in the study. The patient characteristics are shown in Table 1. Each age group included six cases in the ≤ 11-month-old group, 20 cases in the 1–5-year-old group, 10 in the 6–12-year-old group, and three cases in the ≥ 13-year-old group. One patient was anesthetized twice at 2 years, and another patient was anesthetized once at the age of 5 and once at the age of 6 years. Three patients received dexmedetomidine during the last phase of the procedure in the postoperative period. Cyanosis was present in 31% of all patients. Congenital heart diseases were repaired in most patients in the 6–12- and ≥ 13-year-old groups (90% and 100%, respectively), whereas most patients in the ≤ 11 months group (83%) had not yet undergone surgery. None of the patients required a switch from remimazolam to another anesthetic. None of the patients experienced life-threatening adverse events, such as severe bradycardia, severe arrhythmia, or anaphylactic reactions during the anesthetic or postoperative periods, which could have been related to general anesthesia.

A summary of remimazolam anesthesia, including adverse events, is shown in Table 2. Before remimazolam anesthesia, intravenous midazolam of 0.10 [0.10–0.10] $mg.kg^{-1}$ was administered in 33 patients before the start of remimazolam infusion in the pre-anesthesia room. For general anesthesia, remimazolam was initially infused at a rate of 1–3 $mg.kg^{-1}.h^{-1}$. Some patients received an additional bolus of 0.1–0.2 $mg.kg^{-1}$ remimazolam one-to-three times until the patient lost consciousness. Fentanyl of 4 $\mu g.kg^{-1}$ was also administered for anesthesia induction in all but one patient. After loss of response to calling the patients name and tapping on their shoulder, rocuronium 1 $mg.kg^{-1}$ was administered intravenously and patients underwent tracheal intubation. The remimazolam dose for loss of consciousness was 0.34 [0.26–0.45] $mg.kg^{-1}$ in all patients, and 0.33 [0.26–0.46] $mg.kg^{-1}$ in the 33 patients who had been administered midazolam. Figure 1A shows the remimazolam dose required for loss of consciousness in each patient. During anesthesia maintenance, the mean infusion rate of remimazolam was 1.0 [0.8–1.4] in patients overall, and 0.8 [0.8–1.0], 1.0 [0.9–1.5], 1.3 [1.1–1.6], and 0.9 [0.9–1.0] $mg.kg^{-1}.h^{-1}$ in the ≤ 11-month-old, 1–5-year-old, 6–12-year-old, and ≥ 13-year-old groups, respectively (Fig. 1B).

The non-invasive blood pressure and heart rate measurements are shown in Fig. 2. In the 6–12-year-old and ≥ 13-year-old groups, both mean blood pressure and heart rate decreased gradually after the start of remimazolam administration. Blood pressure and heart rate decreased in 15 (38%) and six (15%) patients, respectively, during the maintenance of anesthesia.

Cardiovascular agonists were also administered to some patients (Table 2). During the induction of anesthesia, atropine and ephedrine were administered to treat bradycardia in four and one case, respectively, and phenylephrine and calcium chloride were administered to treat

Table 1 Patient characteristics

	Group			
	≤ 11-month-old (*n* = 6)	1–5-year-old (*n* = 20)	6–12-year-old (*n* = 10)	≥ 13-year-old (*n* = 3)
Age	2–11 months	1–5 years	6–12 years	13–16 years
Sex (male/female)	2 / 4	10 / 10	5 / 5	1 / 2
Height (cm)	65 [64–69]	81 [75–97]	110 [104–120]	158 [155–162]
Weight (kg)	6 [6–7]	10 [10–7]	18 [16–20]	51 [46–52]
ASA physical status I/II/III	0 / 4 / 2	0 / 13 / 7	1 / 7 / 2	0 / 2 / 0
Cyanosis	2 (33)	6 (30)	3 (30)	1 (33)
Single ventricle physiology	0 (0)	4 (20)	2 (20)	1 (33)
Pulmonary hypertension	1 (17)	1 (5)	3 (30)	0 (0)
Genetic syndrome	1 (17)	5 (25)	3 (30)	0 (0)
Status of congenital heart disease				
Native	5 (83)	8 (40)	1 (10)	0 (0)
Palliated	1 (17)	4 (20)	0 (0)	0 (0)
Repaired	0 (0)	8 (40)	9 (90)	3 (100)
Procedure				
Diagnostic	3 (50)	11 (55)	2 (20)	2 (67)
Interventional	3 (50)	9 (45)	8 (80)	1 (33)

ASA: American Society of Anesthesiologists. Values are presented as *n* (% of the group) or median [25th–75th percentile]

Table 2 Summary of remimazolam anesthesia

	All ($n=39$)	Age group			
		≤11-month-old ($n=6$)	1–5-year-old ($n=20$)	6–12-year-old ($n=10$)	≥13-year-old ($n=3$)
Duration of anesthesia (min)	154 [138–181]	130 [123–138]	155 [146–168]	185 [135–219]	181 [166–191]
Duration of procedure (min)	87 [72–110]	75 [59–82]	86 [70–102]	105 [80–141]	114 [98–123]
Midazolam dose prior to anesthesia* ($mg.kg^{-1}$)	0.10 [0.10–0.10] ($n=33$, 85%)	0.10 [0.10–0.13] ($n=3$, 50%)	0.10 [0.10–0.10] ($n=17$, 85%)	0.10 [0.10–0.10] ($n=10$, 100%)	0.05 [0.05–0.05] ($n=3$, 100%)
Drug doses for loss of consciousness					
Remimazolam ($mg.kg^{-1}$)	0.34 [0.26–0.45]	0.40 [0.33–0.47]	0.38 [0.30–0.48]	0.31 [0.24–0.41]	0.13 [0.13–0.20]
Remimazolam in patients administered midazolam ($mg.kg^{-1}$)	0.33 [0.26–0.46]	0.33 [0.24–0.40]	0.37 [0.30–0.48]	0.31 [0.24–0.41]	0.13 [0.13–0.20]
Fentanyl ($\mu g.kg^{-1}$)	4.0 [3.8–4.1]	4.0 [3.8–4.1]	4.0 [3.9–4.1]	4.0 [3.9–4.1]	3.7 [1.9–3.8]
Remifentanil infusion rate ($\mu g.kg^{-1}.min^{-1}$)	0.0 [0.0–0.0]	0.0 [0.0–0.0]	0.0 [0.0–0.0]	0.0 [0.0–0.0]	0.0 [0.0–0.15]
Anesthetic and analgesics during anesthesia					
Remimazolam infusion rate ($mg.kg^{-1}.h^{-1}$)	1.0 [0.8–1.4]	0.8 [0.8–1.0]	1.0 [0.9–1.5]	1.3 [1.1–1.6]	0.9 [0.9–1.0]
Fentanyl dose ($\mu g.kg^{-1}.h^{-1}$)	0.0 [0.0–0.7]	0.0 [0.0–0.8]	0.0 [0.0–0.6]	0.2 [0.0–0.6]	0.0 [0.0–0.4]
Remifentanil infusion rate ($\mu g.kg^{-1}.min^{-1}$)	0.16 [0.04–0.30]	0.09 [0.00–0.20]	0.17 [0.04–0.31]	0.16 [0.10–0.20]	0.20 [0.12–0.30]
Hemodynamic changes during anesthesia					
30% decrease in blood pressure	15 (38%)	2 (33%)	7 (35%)	4 (40%)	2 (66%)
30% decrease in heart rate	6 (15%)	0 (0%)	5 (25%)	1 (10%)	0 (0%)
Cardiovascular agonists and flumazenil during anesthesia					
Vasopressors	8 (21%)	1 (17%)	4 (20%)	2 (20%)	1 (33%)
During anesthesia induction	4 (10%)	0 (0%)	1 (5%)	2 (20%)	1 (33%)
During anesthesia maintenance	6 (15%)	1 (17%)	3 (15%)	1 (10%)	1 (33%)
Ephedrine	1 (3%)	0 (0%)	0 (0%)	1 (10%)	0 (0%)
Phenylephrine	6 (15%)	1 (17%)	3 (15%)	1 (10%)	1 (33%)
Calcium chloride	4 (10%)	0 (0%)	3 (15%)	1 (10%)	0 (0%)
Dobutamine**	1 (3%)	0 (0%)	1 (5%)	0 (0%)	0 (0%)
Atropine	6 (15%)	0 (0%)	5 (25%)	1 (10%)	0 (0%)
Flumazenil	6 (15%)	1 (17%)	3 (15%)	1 (10%)	1 (33%)
Time from termination of remimazolam administration to extubation (min)	15 [12–17]	15 [12–16]	15 [12–17]	13 [12–17]	16 [12–18]
Adverse event during anesthesia and postoperative period					
Postoperative nausea and vomiting	7 (18%)	1 (17%)	4 (20%)	2 (20%)	0 (0%)
Life-threatening adverse events#	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Values are presented as n (% of the group) or median [25th–75th percentile].* Midazolam dose administered prior to anesthesia. **Administered for a stress test, but not to treat hemodynamic instability. # Life-threatening adverse events, such as severe bradycardia, severe arrhythmia, or anaphylactic reactions during the anesthetic or postoperative period that could have been related to general anesthesia

hypotension in two and two cases, respectively. During the maintenance of anesthesia, atropine was administered in one case, and phenylephrine and calcium chloride were administered in five and three cases, respectively. After extubation, atropine was administered to one patient. None of the patients received continuous administration of a cardiovascular agonist to treat hemodynamic instability. Additionally, dobutamine was administered to one patient for the dobutamine stress test, but not for hemodynamic instability. The diseases of these patients receiving cardiovascular agonists are listed in Supplemental Table 1.

The individual time courses of the BIS ($n=7$) and PSI ($n=29$) values are shown in Fig. 2. The EEG index was missed due to technical problems in the one patient each in the ≤11-month-old, 1–5-year-old, and 6–12-year-old groups. Patients with BIS values above 60 or PSI values above 50 for most of the time during surgery were four out of eight patients or 18 out of 28 patients, respectively. (Fig. 2).

The recovery time from remimazolam anesthesia was 15 [12–17] min in patients overall, and 15 [12–16], 15 [12–17], 13 [12–17], and 16 [12–18] min in the ≤11-month-old, 1–5-year-old, 6–12-year-old, and ≥13-year-old groups,

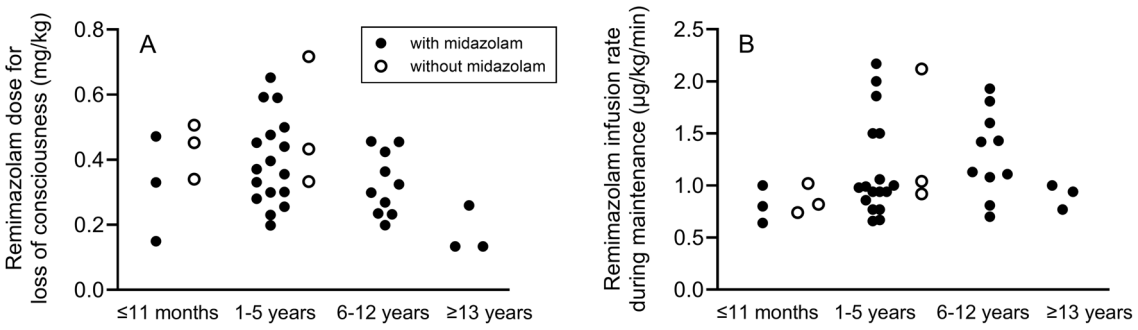

Fig. 1 Remimazolam dose for loss of consciousness. **A** Each filled or open circle indicates (**A**) the remimazolam cumulative dose at which a patient lost consciousness and (**B**) the mean remimazolam infusion rate during maintenance of anesthesia, with or without midazolam administration in the pre-anesthesia room

respectively (Table 2). Flumazenil was administered after the remimazolam infusion was terminated and after spontaneous respiration resumed in six patients. Details of the infusion rate and dose of remimazolam, remifentanil, and flumazenil and the trend of BIS or PSI value in each case are shown in Supplemental Fig. 1.

The infusion history and individual time course of the predicted remimazolam Cp in the 4–6 year patients are shown in Fig. 3. Remimazolam Cp was maintained between 1 and 2 $\mu g.ml^{-1}$ during anesthesia in eight out of ten patients. Predicted remimazolam Cp at emergence ranged from 0.4 to 1.2 $\mu g.ml^{-1}$ without flumazenil administration, and from 0.2 to 0.4 $\mu g.ml^{-1}$ with flumazenil administration.

Discussion

Remimazolam was administered concomitantly with fentanyl and remifentanil to pediatric patients undergoing cardiac catheterization for congenital heart disease. All patients lost consciousness and their hemodynamics were generally stable during the procedure, with vasopressor use. No life-threatening adverse events were observed.

This study clarified that the dose of remimazolam required for achieving loss of consciousness was 0.34 [0.26–0.45] $mg.kg^{-1}$, with a concomitant dose of opioid, in patients aged 2 months to 16 years, with congenital heart disease undergoing cardiac catheterization. In adult patients, the 50% and 95% effective doses (ED50 and ED95) of remimazolam for loss of consciousness without opioid administration were 0.11 and 0.19 $mg.kg^{-1}$ in patients aged 21–88 years, respectively [12]. In older adult patients with severe aortic stenosis, the median remimazolam dose with concomitant remifentanil for achieving loss of consciousness was 0.13 $mg.kg^{-1}$ [13]. Although midazolam was administered before remimazolam infusion in our pediatric patients, the remimazolam dose required for achieving loss of consciousness was higher in pediatric patients than that required in adults. Similar to other anesthetics, a higher dose of remimazolam may be required for loss of response in pediatric patients than in adults [14, 15]. In adolescents aged ≥ 13 years ($n = 3$), 0.13 [0.13–0.20] $mg.kg^{-1}$ of remimazolam was infused to achieve loss of consciousness, with a concomitant dose of opioid after administering 0.05 $mg.kg^{-1}$ of midazolam. As the ED50 and ED95 of remimazolam for loss of consciousness, without opioid administration, were 0.19 and 0.33 $mg.kg^{-1}$, respectively, in patients in their twenties [12], remimazolam requirements for achieving loss of consciousness may be similar in adolescents and young adults. The infusion rate of remimazolam in our study varied from 1 to 3 mg/kg/h during induction, which would have affected the induction dose of remimazolam [6], i.e., a lower infusion rate could result in a higher induction dose due to its pharmacological profile including rapid offset of action[5].

During anesthesia maintenance, remimazolam was infused at 0.8 [0.8–1.0], 1.0 [0.9–1.5], 1.3 [1.1–1.6], and 0.9 [0.9–1.0] $mg.kg^{-1}.h^{-1}$ in patients aged ≤ 11 months, 1–5 years, 6–12 years, and ≥ 13 years, respectively. These doses were similar to those administered in a phase IIb/III trial in adult patients with American Society of Anesthesiologists physical status (ASA-PS) I or II who received a mean remimazolam dose of 1.0 $mg.kg^{-1}.h^{-1}$ [6]. Although the appropriate maintenance infusion rate of remimazolam in pediatric patients may appear to be similar to that in adults, this conclusion is premature. The context-sensitive decrement time was longer in pediatric patients, as calculated using the Gao model, than in adults, as calculated using the Masui model (Fig. 4) [10, 16]. If the ratio of the remimazolam concentration during anesthesia maintenance to the remimazolam concentration at extubation is similar between children and adults, the time from the termination of the remimazolam infusion to extubation will be longer in children than in adults. However, the time from the termination to extubation of 15 min in our patients was shorter than that of 19 min in adult patients of the phase IIb/III trial.

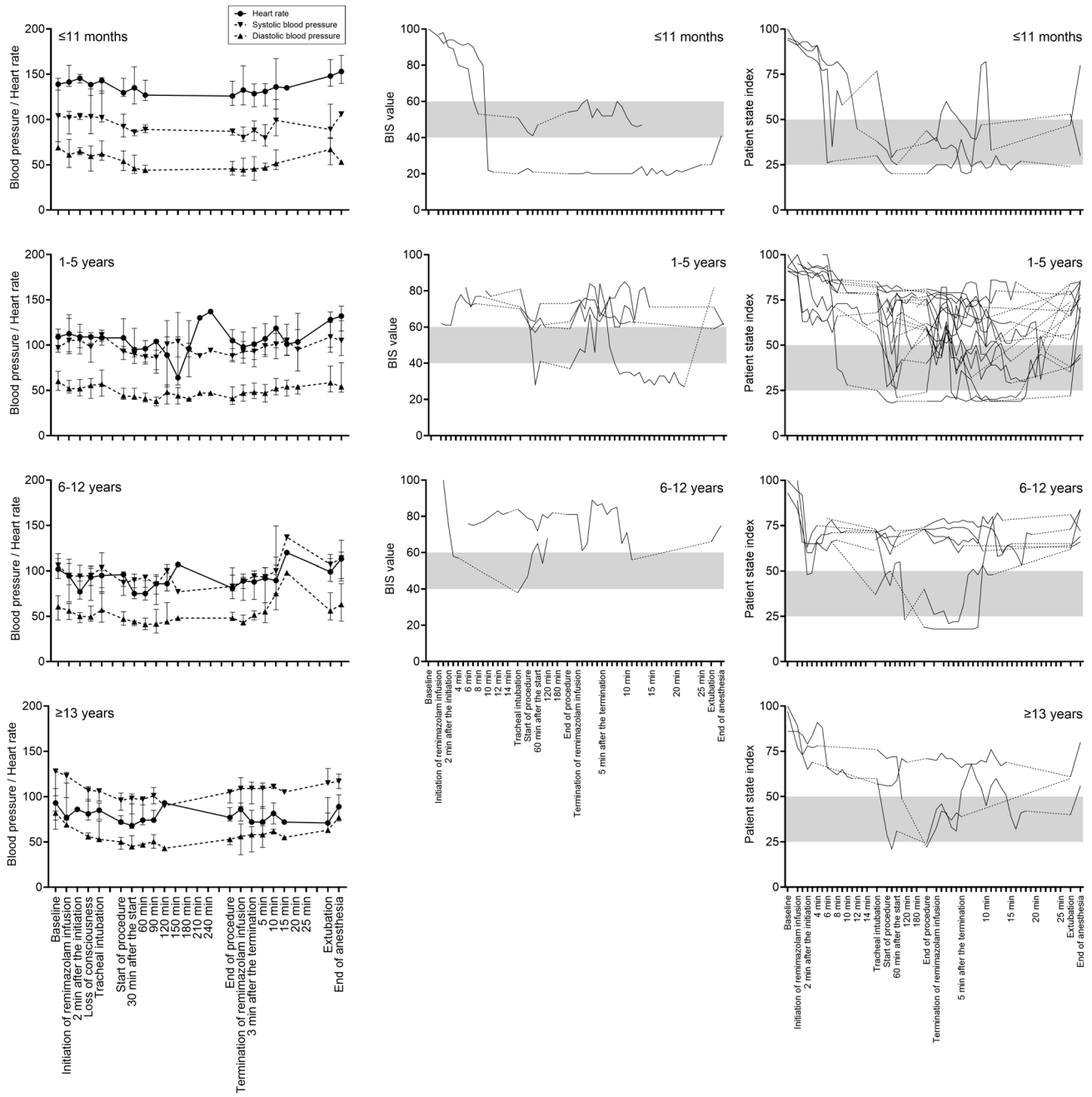

Fig. 2 Time courses of blood pressure, heart rate, and electroencephalogram index. The figures in the left column show the time courses of the blood pressure and heart rate. The black triangle and error bars show the mean and range of non-invasive blood pressure, and the black circles and error bars show the mean and range of heart rate, respectively. The figures in the middle and right columns show the time courses of the bispectral index (BIS) values and patient state index (PSI), respectively. Each line indicates the time courses in an individual. The grey band represents the range that suggests appropriate anesthesia for propofol and inhalation anesthesia

These results suggest that the adequate remimazolam infusion rate for anesthesia maintenance is higher in children than adults. Additionally, the mean remimazolam infusion rate of 1.0 $mg.kg^{-1}.h^{-1}$ in our patients, whose ASA-PS was III in 11 of our 39 patients (28%), was higher than that of 0.6 $mg.kg^{-1}.h^{-1}$ in a clinical trial for general anesthesia in adult patients with ASA-PS III [17]. In the current study, all patients who received > 1.2 $mg.kg^{-1}.h^{-1}$ remimazolam were 1–12 years old ($n = 11$; 28% of all patients; 37% of 1–12-year-old patients). The immaturity of neonatal metabolism may be one reason for the skewed distribution of the maintenance dose. Remimazolam is mainly metabolized by

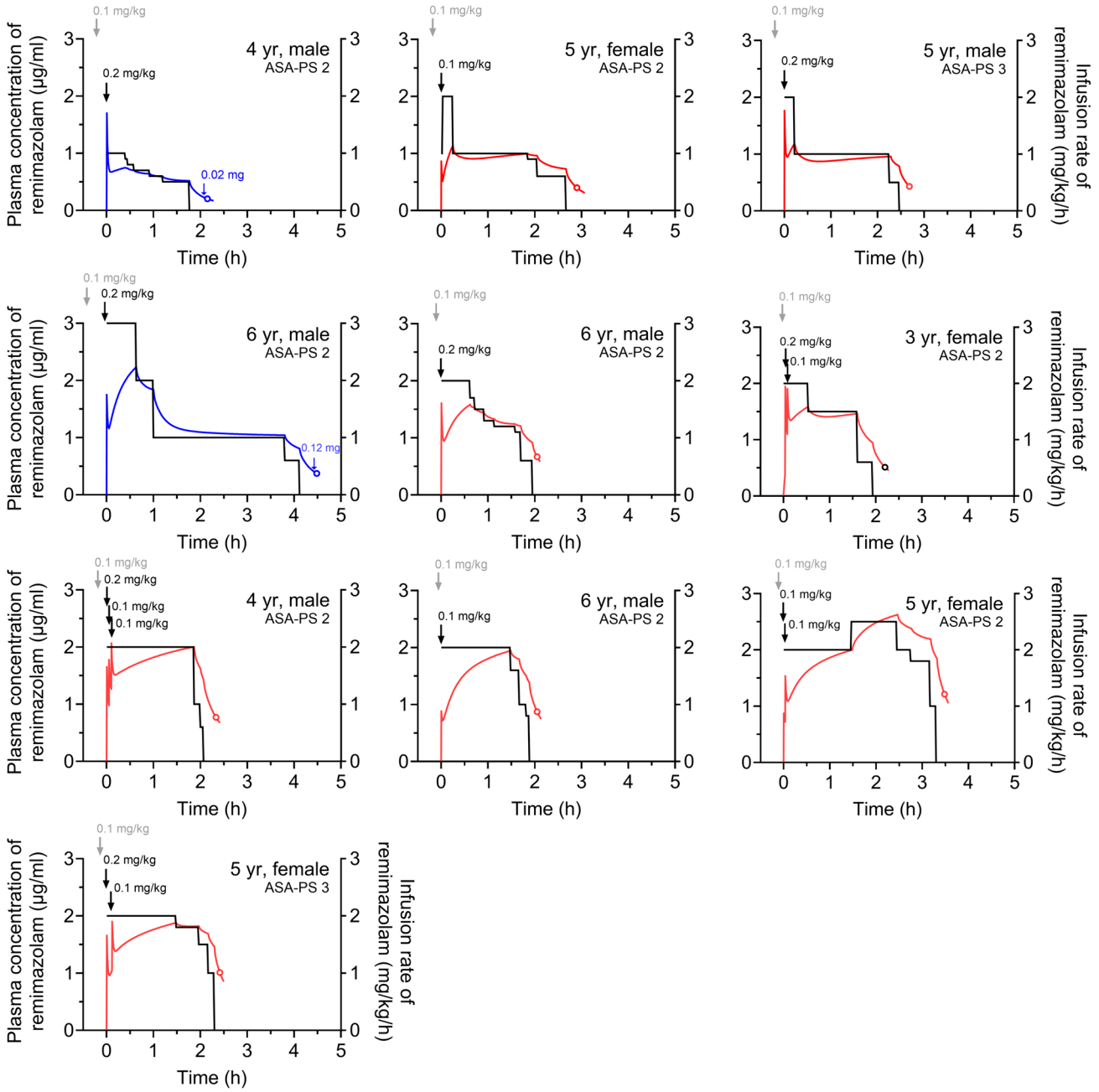

Fig. 3 Time courses of remimazolam infusion rate and predicted plasma concentration of remimazolam in 3–6-year-old patients. The black line represents the remimazolam infusion rate. Red and blue lines indicate the predicted plasma concentrations of remimazolam in patients receiving and not receiving flumazenil, respectively. The open circles indicate the plasma concentration at extubation. Black and grey arrows indicate remimazolam and midazolam boluses, respectively

hepatic carboxylesterase 1 [18, 19], the expression of which is lower in neonates and infants than in those aged ≥ 1 year [20] and which is comparable among 1–5-year-old, 6–11-year-old, and 12–18-year-old age groups. Nonlinear regression analysis showed that the carboxylesterase 1 expression increased in an age-dependent manner, exceeding 50% of the adult level by 7 months of age [19]. If the effective concentration of remimazolam is similar in neonates/infants and older children, the infusion rate of remimazolam should be lower in neonates/infants than in older children. Further studies are required to determine the optimal maintenance dose of remimazolam. Congenital heart disease-specific high-flow shunt might influence the pharmacokinetics of remimazolam. However, the clearance of morphine, which is mainly metabolized in the liver, similar to remimazolam, is not influenced by congenital heart disease [21].

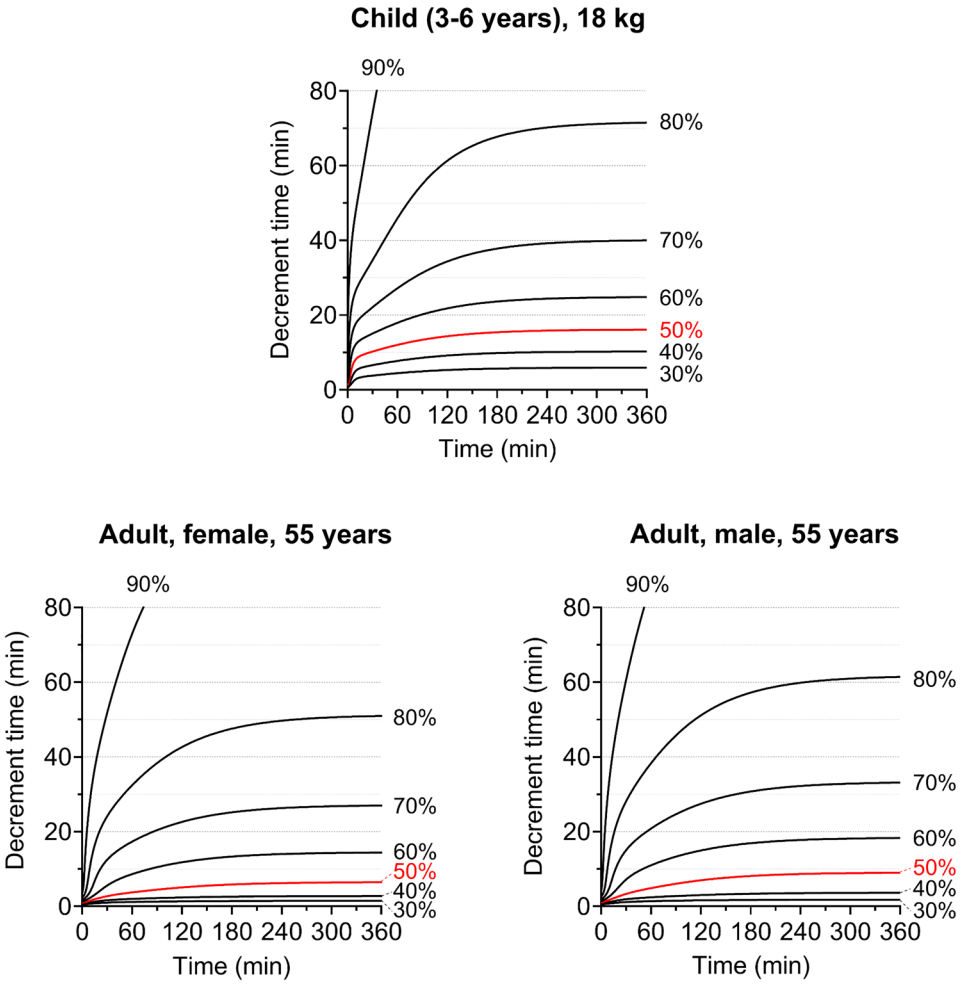

Fig. 4 Context-sensitive decrement times of plasma concentration of remimazolam in a 3–6-year-old child weighing 18 kg (upper figure), in a male adult aged 55 years (lower left figure), and in a female adult aged 55 years (lower right figure). The context-sensitive decrement times of remimazolam were calculated using the Gao model [10] (upper panel) and the Masui model [16] (lower panel)

Vasopressors were administered as boluses, but not as continuous infusions, to treat hemodynamic instability in 21% of pediatric patients undergoing cardiac catheterization in our study. Among pediatric patients with congenital heart disease undergoing noncardiac surgery under general anesthesia ($n = 2{,}966$; 96% of patients were anesthetized using isoflurane or sevoflurane), 11.5% received continuous infusions of inotropic agents during anesthesia [22]. Because our patients did not receive a continuous infusion of vasopressors, remimazolam anesthesia may have resulted in a more stable blood pressure than that achieved with inhalation anesthesia.

The BIS and PSI values did not decrease below 60 and 50, respectively, in 51% of our patients until tracheal intubation, although loss of consciousness was confirmed immediately before the initial dose of rocuronium in our clinical practice. In a previous study, BIS and PSI values were > 60 and > 50, respectively, in most patients with a Modified Observer's Assessment of Alertness and Sedation scale of 1 [23]. A prospective study in adults showed that remimazolam anesthesia maintained a BIS value between 60 and 80, with no evidence of explicit or implicit memory formation [24]. BIS values in pediatric patients have been reported with remimazolam anesthesia. A 5-year-old patient with medium-chain acyl-coenzyme A dehydrogenase deficiency, who received remimazolam at 1–2 $mg \cdot kg^{-1} \cdot h^{-1}$, with a BIS value between 60 and 70, had a time to emergence of > 30 min from the termination of remimazolam infusion [25]. Another 4-year-old patient with Duchenne muscular dystrophy, weighing 16 kg, received remimazolam at 15 $mg \cdot h^{-1}$ with a BIS value between 70 and 80. Although the infusion rate of remimazolam was reduced to 5 $mg \cdot h^{-1}$, it took 20 min from the termination of the remimazolam infusion to emergence [26]. Although overall BIS and PSI values during maintenance of anesthesia were > 60 and > 50, respectively, in 60% of our pediatric patients (Supplemental Fig. 1), the recovery time from remimazolam anesthesia was 15 [12–17] min. These results suggested that BIS > 60 and PSI > 50 are likely to be observed with adequate levels of remimazolam anesthesia. (Fig. 2) [27]. The observations of unprocessed EEG and EEG spectrogram may be essential for evaluating the effect of remimazolam anesthesia [27].

This study had several limitations. First, because we did not estimate the loss of response using a sedation scale, we defined the period when the muscle relaxant was administered as the time of loss of response. In our daily anesthesia practice, muscle relaxants are administered immediately after confirming the absence of a response to calling the patient's name and light tapping on the shoulder. Second, most patients received intravenous midazolam before the start of anesthesia, which influenced the remimazolam dose required for induction. This is a common practice in children with congenital heart disease, to ease separation from their parents, reduce crying, and decrease oxygen consumption [28]. Third, our patients were mechanically ventilated during the procedure. Hemodynamic variables may be more stable in patients with spontaneous respiration during the catheterization.

In conclusion, remimazolam anesthesia was administered to pediatric patients undergoing cardiac catheterization for congenital heart disease. The initial dose of remimazolam required for loss of consciousness was 0.34 [0.26–0.45] $mg.kg^{-1}$, with concomitant opioid use, in patients aged 2 months to 16 years. Overall, 85% of all patients received intravenous midazolam prior to anesthesia induction. During the maintenance of remimazolam anesthesia, hemodynamics were stable, with only 21% of the patients receiving a vasopressor bolus, and none requiring a continuous infusion of vasopressor. The recovery time from remimazolam anesthesia was 15 [12–17] min. Our results indicated that remimazolam is a good alternative anesthetic agent for pediatric patients undergoing cardiac catheterization for congenital heart disease. The EEG index might be higher during remimazolam anesthesia than during propofol or inhalation anesthesia at the same level of anesthesia, because the BIS and PSI values were above 60 and 50, respectively, until tracheal intubation in 51% of the patients. Further studies are warranted to examine the appropriate remimazolam dose for loss of consciousness and maintenance of anesthesia, and the influence of age on the pharmacodynamic effects in pediatric patients.

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Author contributions MH and KM contributed equally to this work. MH contributed to the study design, analysis and interpretation of the data, drafted and revised the manuscript critically for important intellectual content, and approved the submission of the manuscript. YT and TU contributed to the study design and data curation, critically revised the manuscript for important intellectual content and approved the submitted manuscript. KO contributed to the critical revision of the manuscript for important intellectual content and approved the submitted manuscript. KM contributed to the study design, analysis, and interpretation of the data; critically revised the manuscript for important intellectual content; and approved the submitted manuscript.

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Declarations

Conflict of interest Kenichi Masui received payment for delivering domestic lectures from Mundipharma K.K. and a section editor of Journal of Anesthesia and JA Clinical Reports. The other authors declare no conflicts of interest.

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