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The Minimum Infusion Rate (MIR) of Propofol for Total Intravenous Anesthesia after Premedication with Xylazine in Horses

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ABSTRACT. To investigate an adequate infusion rate of propofol for total intravenous anesthesia (TIVA) in horses, the minimum infusion rate (MIR) comparable to the minimum alveolar anesthetic concentration (MAC) of inhalation anesthetic was determined under constant ventilation condition by intermittent positive pressure ventilation (IPPV). In addition, arterial propofol concentration was measured to determine the concentration corresponding to the MIR (concentration preventing reaction to stimulus in 50% of population, Cp_{50}). Further, 95% effective dose (ED_{95}) was estimated as infusion rate for acquiring adequate anesthetic depth. Anesthetic depth was judged by the gross purposeful movement response to painful stimulus. MIR and Cp_{50} were 0.10 ± 0.02 mg/kg/min and 5.3 ± 1.4 μg/m*l*, respectively. ED_{95} was estimated as 0.14 mg/kg/min (1.4MIR).

KEY WORDS: anesthesia, equine, MIR, propofol.

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Total intravenous anesthesia (TIVA) using propofol (2,6-diisopropylphenol), a new intravenous anesthetic, for maintaining anesthesia became widely performed in people [6] and some animals [2–4, 7, 9, 16, 17, 20]. However, in animals including horses, the infusion rate of propofol is mainly determined based on clinical experience of a researcher. Consequently, examination of infusion rate based on objective assessment of anesthetic depth is still unsatisfactory.

One of the most useful indices for assessing the anesthetic depth is considered as a body movement in response to painful stimulus [10]. As a concept of anesthetic depth using this index, minimum alveolar anesthetic concentration (MAC) of inhalation anesthetic is well known, and it is defined as concentration of anesthetic in the alveolar gas which prevents gross purposeful movement in response to supramaximal painful stimulus in 50% of subjects, i.e. 50% effective dose (ED_{50}) [8]. Since MAC is the most basic objective indicator of efficacy of inhalation anesthetics, it is indispensable for determining the adequate dose (concentration) of inhalation anesthetic in clinical application.

As a concept comparable to MAC, Cp_{50} [10] and minimum infusion rate (MIR) [10, 19, 22], the plasma concentration and the infusion rate of intravenous anesthetic preventing reaction to stimulus in 50% of population, respectively, has been introduced for intravenous anesthetic agents. Cp_{50} can be helpful in comparing anesthetic potency and individual sensitivity to an anesthetic and delivering anesthesia that is adequate to the patient and the procedure [10]. However, since it is very difficult to measure plasma drug concentration in real time, Cp_{50} is not necessarily useful in clinical anesthesia. On the other hand, generally, it is considered that MIR concept is not so useful as MAC concept because pharamacokinetics of intravenous anesthetic remarkably differs from that of inhalation anesthetic [10]. However, metabolism of propofol is rapid and its cumulative effects is little [15, 28]. Furthermore, it is known that propofol is characterized by rapid onset and short duration of action [5, 15]. Because of these characteristics, change of infusion rate quickly reflects the change of anesthetic depth in propofol anesthesia. Therefore, it is inferred that the MIR of propofol has usefulness in clinical anesthesia close to the MAC of inhalation anesthetic. Moreover, MIR is measured by judging anesthetic depth objectively based on response to painful stimulus. Accordingly, MIR is an important index for evaluating the potency and determining the adequate dose of intravenous anesthetics such as propofol used for TIVA, as is the case with the MAC concept. However, in horses, only MIR of propofol in combination with infusion of xylazine or medetomidine has been reported [3, 4, 16].

In this research, we determined the MIR for infusion of propofol alone in horses premedicated with xylazine as well as examined the adequate dose of propofol for continuous infusion to maintain anesthesia.

MATERIALS AND METHODS

Horses: Six healthy Thoroughbred horses (4 males, 1 female and 1 gelding) were used. Three of these horses were 4 years old, 2 were 6 years old and 1 was 7 (mean ± SD, 5.2 ± 1.3) years old . Their mean body weight was 450 ± 15 kg. Horses were fasted for 12 hr before anesthesia and freely given water. Experiments were conducted according to the guidelines established by the Experimental Animal Committee, Japan Racing Association.

Anesthesia: Ten min after premedication with xylazine

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(1.0 mg/kg; Celactar, Bayer, Tokyo, Japan), each horse was restrained in a swing-door induction system and induced with the intravenous injection of 1% propofol (3.0 mg/kg; Rapinovet, Mallinckrodt Veterinary, Mundelein, Illinois, U.S.A.) solution at a 3 min duration. After horses attained a sternal recumbency, the swing-door was opened and horses were turned to lateral recumbency. Following endotracheal intubation, horses were transported to operation room by hoist and placed on a mat in right lateral recumbency. Anesthesia was maintained with infusion of propofol using IV pump (Star-Flow 592, IVAC, San Diego, U.S.A.). The initial infusion rate was set as 0.20 mg/kg/min in Horse No.1 and reduced to 0.14 mg/kg/min in Horse Nos.2 to 6 based on the result of Horse No. 1. Infusion of propofol at such initial infusion rate was continued for 45 min to minimize the influence of premedication, then measurement of MIR was initiated. The endotraceal tube was connected to a large animal circle breathing device (MOK94, Silver Medical Co., Tokyo, Japan) fitted with a time cycle ventilator (Compos-β EV, Silver Medical) and supplied with 100% oxygen. The oxygen flow rate was set at 6 *l*/min. Horses were allowed to breath spontaneously for the first 5 min of maintaining anesthesia and respiratory rate was measured to check for apnea (>30 sec). Then, intermittent positive pressure ventilation (IPPV) was performed to maintain partial arterial CO_2 pressures ($PaCO_2$) between 45 and 55 mmHg.

Measurement of MIR: The MIR was measured according to previous reports measuring MAC in horses [1, 24]. The MIR was measured by judging the gross purposeful movement response to painful stimulus in various infusion rates of propofol, while increasing or decreasing the infusion rate in 0.02 mg/kg/min steps from 0.20 (in Horse No. 1) or 0.14 (in Horse Nos. 2 to 6) mg/kg/min. Painful stimulus were produced by stimulating the upper oral mucosa with electric currents (50 V, 5 Hz, 10 ms, 60 sec), using an electrical stimulator (DSP-06, Diamedical System, Tokyo). Responses to electrical stimulus were judged by either (+) or (–). The response was judged as (+) only when gross purposeful movement (eg, head elevation or leg escape movement) was observed, and it was judged as (–) when no reaction or other reactions such as increase in heart rate (HR) or arterial blood pressure (ABP) were observed. In addition, when a spontaneous movement was observed before giving an electrical stimulus, it was judged as (+). Infusion rate of propofol was decreased when (–) response was detected and increased when (+) response was detected. After maintaining for 20 min at each infusion rate, response to an electrical stimulus was judged again. Change of the response from (+) to (–) or (–) to (+) was defined as a pair, and the stimulation was repeated at different infusion rates until 3 pairs of responses were recorded. Mean value of two infusion rates was obtained for each pair of responses. MIR was determined as the average of these three mean values.

Measurement of arterial propofol concentration: Arterial blood samples of each infusion rate was collected at 15 and 20 min after changing infusion rate from the arterial catheter positioned within the facial artery for determination of plasma drug concentration of propofol. Moreover, the arterial propofol concentration corresponding to MIR, i.e. Cp_{50}, was determined by the same method as determination of MIR. For determination of Cp_{50}, the measured values at 20 min after changing infusion rate were used except for the case where the measurement at 20 min was impossible due to advent of spontaneous movement and the value at 15 min was used. Blood was collected in EDTA tubes and briefly stored on ice, then plasma was separated by centrifugation. Plasma samples were then stored at –20°C until later analysis. Propofol concentration in plasma was measured by high performance liquid chromatography (HPLC) system consisting of a pump, auto sampler, column oven, gradient unit, UV/VIS detector, degasser and system controller (880-PU, 851-AS, 860-CO, 880-02, 875-UV, 880-50 and 802-SC, respectively, JASCO Corp., Tokyo, Japan) and an integrator (C-R4A, Shimadzu Corp., Kyoto, Japan) in the commercial laboratory (SRL, Tokyo, Japan) for human. The limit of detection was 0.1 μg/m*l*.

Measurement of HR, ABP and arterial blood gases: During anesthesia, HR, ABP and arterial blood gases were measured at each infusion rate. Measurement was performed just before the electrical stimulation at 20 min after changing infusion rate. HR and ABP were measured using a multipurpose monitoring system (M1166A, Hewlett Packard, Palo Alto, U.S.A.). ABP was measured by the pressure transducer of the multipurpose monitoring system connected to a 20 G catheter placed into the facial artery. Transducer 0-level was placed at the level of the sternum. Blood samples collected anaerobically from the arterial catheter were analyzed for PaO_2 and $PaCO_2$ using a calibrated arterial blood gas analyzer (288 Blood Gas System, Ciba-Corning, Tokyo, Japan).

Statistics: Data of cardiopulmonary measurement was analyzed with repeated measure ANOVA to determine the effects of time and infusion rate. The relationship between MIR and Cp_{50} as well as infusion rate and arterial concentration of propofol were evaluated by Spearman rank correlation test. The relationship between propofol infusion rate and the probability of preventing body movement to stimulus, i.e. the proportion of the number of (–) response occurring to the total numbers of (+) response and (–) response occurring at each infusion rate in 6 horses, were also evaluated by the same test. The level of statistical significance was 0.05 or less.

RESULTS

Duration of anesthesia: The time required from the end of 3.0 mg/kg propofol administration to the start of propofol infusion for maintaining anesthesia was 7 to 9 (8.5 ± 0.8) min, and during this period, horses were intubated and transported to operation room. The duration of maintaining anesthesia by continuous infusion of propofol was 140 to 200 min. The responses to electrical stimulus were judged in the period from 45 to 200 min in Horse No. 1 and to 140–165 min in Horse Nos. 2–6 after the start of propofol infusion.

Response to electrical stimulus: Responses to electrical stimulus, arterial propofol concentrations, HR and mean ABP at 15 and 20 min after changing propofol infusion rate at various infusion rates in addition to MIR and Cp_{50} of each horse are shown in Table 1. No horse showed gross purposeful movement in response to electrical stimulus at 0.14 mg/kg/min, while all the horses showed the movement at 0.06 mg/kg/min. As well, brisk palpebral and corneal reflexes were observed at all infusion rates of 0.06–0.20 mg/kg/min.

MIR and Cp_{50}: MIR of each horse was in the range of 0.08 to 0.12 mg/kg/min, and the great interindividual difference was not observed. The mean ± SD of MIR was 0.10 ± 0.02 mg/kg/min. On the other hand, Cp_{50} ranged from 3.8 to 7.8 μg/m*l* with large individual difference, and mean ± SD of Cp_{50} was 5.3 ± 1.4 μg/m*l*. No significant correlation was

Table 1. Responses to electrical stimulus, arterial propofol concentrations, and cardiovascular measurements at various propofol infusion rates in 6 horses

IR	T	R	MVI	PC	MVC	HR	ABP	IR	T	R	MVI	PC	MVC	HR	ABP
Horse No.1								Horse No.4							
0.20	45	–		NM		29	95	0.14	45	–		5.2		28	102
0.18	20	–		NM		29	85	0.12	15			4.5		31	105
0.16	20	–		NM		31	84	↓	20	–		4.5	4.3	31	104
0.14	20	–		9.7		30	81	0.10	15	+[a)]	0.11	4.1		31	103
0.12	15			9.4		29	86	0.12	15			5.1		31	103
↓	20	–		9.3		30	86	↓	20	+		4.9		31	101
0.10	15			8.3		28	85	0.14	15		0.13	5.6	5.3	43	112
↓	20	–		8.2		29	86	↓	20	–		5.7		40	115
0.08	15		0.09	7.4	7.9	30	93	0.12	15		0.13	5.6	5.7	44	113
↓	20	+		7.5		30	98	↓	20	+		5.6		48	117
0.10	15		0.09	8.3	7.9	28	91	MIR=0.12				Cp_{50}=5.1			
↓	20	–		8.3		28	90								
0.08	15	+[a)]	0.09	7.0	7.7	40	99								
MIR=0.09				Cp_{50}=7.8											
Horse No.2								Horse No.5							
0.14	45	–		5.1		28	94	0.14	45	–		4.4		28	88
0.12	15			4.7		29	92	0.12	15			3.9		28	91
↓	20	–		4.9		29	93	↓	20	–		3.9		29	95
0.10	15			4.4		32	101	0.10	15		0.11	3.3	3.8	30	107
↓	20	–	0.09	4.4	4.2	33	103	↓	20	+		3.7		28	108
0.08	15	+[a)]		4.0		34	105	0.12	15			4.6		28	112
0.10	15	+[a)]		4.6		33	91	↓	20	+		4.8		28	111
0.12	15		0.11	5.3	5.1	32	94	0.14	15		0.13	6.4	5.6	28	107
↓	20	–		5.5		33	95	↓	20	–		6.4		30	105
0.10	15		0.11	5.2	5.4	36	100	0.12	15		0.13	5.4	6.1	28	116
↓	20	+		5.2		33	108	↓	20	+		5.7		28	108
MIR=0.10				Cp_{50}=4.9				MIR=0.12				Cp_{50}=5.2			
Horse No.3								Horse No.6							
0.14	45	–		5.0		27	91	0.14	45	–		5.4		20	91
0.12	15			4.6		27	90	0.12	15			4.6		21	94
↓	20	–		4.7		28	90	↓	20	–		4.7		21	94
0.10	15			4.2		28	89	0.10	15			4.0		22	96
↓	20	–		3.3		29	92	↓	20	–		3.9		24	99
0.08	15		0.09	3.7	3.5	29	97	0.08	15		0.09	3.3	3.6	30	115
↓	20	+		3.7		30	99	↓	20	+		3.3		36	120
0.10	15		0.09	4.5	4.2	29	100	0.10	15	+[a)]		4.6		40	123
↓	20	–		4.6		30	100	0.12	15		0.11	5.9	5.3	35	119
0.08	15			4.0		30	102	↓	20	–		5.9		35	120
↓	20	–		4.0		30	102	0.10	15		0.11	5.3	5.7	40	126
0.06	15		0.07	3.2	3.7	30	109	↓	20	+		5.4		41	127
↓	20	+		3.3		27	110	MIR=0.10				Cp_{50}=4.8			
MIR=0.08				Cp_{50}=3.8											

IR: Infusion rate of propofol (mg/kg/min). T: Time after changing infusion rate (min). R: Response to electrical stimulus. MVI: Mean value of the infusion rates for the pair of responses (mg/kg/min). MIR: Minimum infusion rate (mg/kg/min), the average of MVIs. PC: Arterial propofol concentration (μg/m*l*). MVC: Mean value of the arterial propofol concentration for the pair of responses (μg/m*l*). Cp_{50}: Concentration preventing reaction to stimulus in 50% of population (μg/m*l*), the average of MVCs. HR: Heart rate (bpm). ABP: Mean arterial blood pressure (mmHg). NM: Not measured. a) The movement of the head or leg was observed before giving an electrical stimulation.

Table 2. Arterial propofol concentration in relation to infusion rates of propofol in 6 horses

Horse Number	Infusion rate of propofol (mg/kg/min) 0.14	0.12	0.10	0.08
	Arterial propofol concentration (μg/m*l*)			
1	9.7	9.3	8.3	7.3
2	5.1	5.2	4.7	4.0
3	5.0	4.7	4.0	3.9
4	5.5	5.0	4.1	ND
5	5.4	4.8	3.7	ND
6	5.4	5.3	4.6	3.3
Mean ± SD*	5.3 ± 0.2	5.0 ± 0.3	4.2 ± 0.4	3.7 ± 0.4

*: Excluding Horse No. 1 in which arterial propofol concentration was maintained at a higher value as compared with other horses. ND: Not detected. Significant correlation was detected between infusion rate and arterial concentration. r=0.62, P<0.01.

detected between MIR and Cp_{50}.

Arterial propofol concentrations: In both the case of an increase and decrease of infusion rate, the difference was not detected between the arterial propofol concentrations at 15 and 20 min after changing infusion rate. In addition, arterial propofol concentration of Horse No. 1 was maintained at a higher value as compared with those of other five horses. Arterial propofol concentrations in relation to infusion rates are shown in Table 2. There was no large individual difference between horses in the arterial propofol concentrations at each infusion rate except for Horse No. 1 which maintained higher concentration. Mean value of arterial propofol concentration excluding Horse No. 1 was 5.3 and 3.7 μg/m*l* at infusion rate of 0.14 and 0.08 mg/kg/min, respectively. Arterial propofol concentration was significantly correlated with propofol infusion rate (r=0.62, p<0.01).

Relationship between infusion rate and response to stimulus: Relationship between infusion rate of propofol and the probability of preventing body movement to stimulus, i.e. the proportion of (–) response occurring, is shown in Fig. 1. The proportion of (–) response was highly significantly correlated with propofol infusion rate (r = 0.98, p<0.01) in the following regression equation; y = 12.5x – 0.78 (y; proportion of the (–) response, x; propofol infusion rate).

HR and ABP: HR and mean ABP increased significantly with time. HR and mean ABP according to infusion rates are shown in Table 3. Mean ABP tended to increase with decrease of infusion rate, p=0.057, although the changes of HR and ABP in relation to infusion rate were not significant.

Respiratory rate and arterial blood gases: Respiratory rate decreased from 14.2 ± 4.7 breath/min before induction to 8.3 ± 5.0 breath/min at 5 min after the start of propofol infusion. In addition, apnea was observed in two horses, and the duration of apnea was 30 sec or more in one horse and 60 sec or more in another horse. $PaCO_2$ and PaO_2 were 58.6 ± 6.7 and 239.7 ± 73.7 mmHg, respectively under spontaneous respiration at 5 min after the start of propofol infusion. After IPPV was performed, they were maintained at 45–55 mmHg and 350–550 mmHg, respectively.

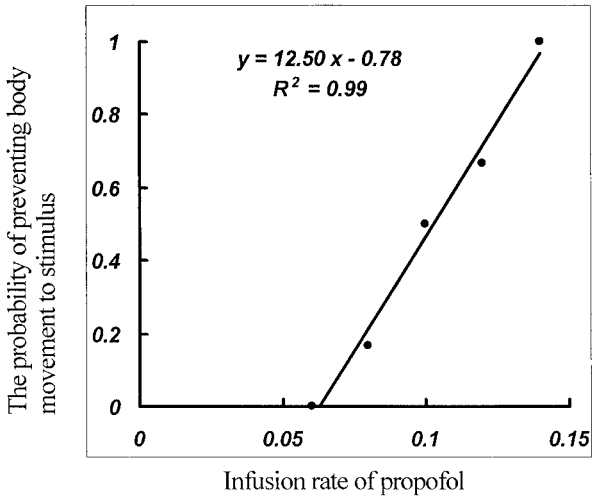

Fig. 1. Relationship between infusion rate of propofol and the probability of preventing body movement to stimulus. The fitted infusion rate—response line is also indicated. r = 0.977, P<0.01.

Table 3. Heart rate and mean arterial blood pressure according to infusion rates of propofol in 6 horses

	Horse Number	Infusion rate of propofol (mg/kg/min) 0.14	0.12	0.10
Heart rate (bpm)	1	30.0	30.0	28.5
	2	28.0	31.0	33.0
	3	27.0	28.0	29.5
	4	34.0	36.7	31.0
	5	29.0	28.3	28.0
	6	20.0	28.0	35.0
	Mean ± SD	28.0 ± 4.6	30.3 ± 3.3	30.8 ± 2.7
Mean arterial blood pressure (mmHg)	1	81.0	86.0	88.0
	2	94.0	94.0	100.7
	3	91.0	90.0	96.0
	4	108.5	107.3	103.0
	5	96.5	104.7	108.0
	6	91.0	107.0	111.0
	Mean ± SD	93.7 ± 9.0	98.2 ± 9.3	101.1 ± 8.3

DISCUSSION

For measurement of MIR, it is desirable to induce anesthesia with measuring object anesthetic alone to eliminate the influence of premedication. However, since we had observed marked limb paddling in lateral recumbency immediately after induction with propofol (3.0 mg/kg) alone in the pilot study (unpublished data), premedication with xylazine was performed for the purpose of the safe reservation during induction in this research. In this regard, in order to mitigate the influence of premedication as much as possible, the measurement of MIR was initiated at 45 min after the start of propofol infusion, i.e. approximately 65 min after xylazine administration. Since this interval of 65 min was longer than the systemic half-life of xylazine of 50

min [11], the influence of premedication was presumably small. However, the MAC of isoflurane in horses is known to be reduced by 35 and 15% at 70 and 150 min, respectively, after administration of xylazine at 1.0 mg/kg [27]. Hence, the influence of xylazine to MIR obtained in this research cannot be denied.

When the relation between infusion rate and the response to a painful stimulus is examined, sufficient time is required from changing infusion rate to a stimulation in order to stabilize the propofol concentration in arterial blood. The result that there was no difference between the arterial propofol concentrations at 15 and 20 min after changing infusion rate supports the possibility that the change of the propofol concentration plateaued after 15 min. Therefore, it can be safely said that the MIR was measured under the condition where the propofol concentration in blood was almost stabilized in this research.

It is reported in horses that MIR of propofol in combination with the infusion of 3.5 μg/kg/hr of medetomidine after premedication with 7 μg/kg of medetomidine ranged from 0.06 to 0.1 [3] or 0.89 to 0.1 [4] mg/kg/min, and MIR in combination with the infusion of 35 μg/kg/min of xylazine after premedication with 0.75 mg/kg of xylazine was slightly below 0.15 mg/kg/min [16]. The MIR of 0.10 mg/kg/min obtained in this research is approximated to these values in combination with infusion of α_2-agonist and can be considered as a low value for the MIR for infusion of propofol alone. This is probably attributed to the difference between the rates of anesthetic agent removal from blood in this research and the previous reports as described later.

Arterial propofol concentration corresponding to MIR, i.e. Cp_{50}, was 5.3 μg/m*l* in this research. Meanwhile, it is reported that the value considered as Cp_{50} of propofol in combination with infusion of medetomidine 3.5 μg/kg/hr after premedication with 7 μg/kg of medetomidine was 2.3 to 3.5 μg/m*l* [2] and the value in combination with infusion of xylazine 35 μg/kg/min after premedication with 0.75 mg/kg of xylazine was slightly below 4.3 to 4.7 μg/m*l* [16]. The Cp_{50} obtained in this research was a little higher than those values in combination with infusion of α_2-agonist. From this, it is likely that the value obtained in this research is valid for the Cp_{50} for infusion of propofol alone.

As mentioned above, MIR and Cp_{50} in this research showed a different tendency as compared with the previous reports, the former was low and the latter was valid. Additionally, there was no significant correlation between MIR and Cp_{50}. This is probably attributed to the difference between their physiological meanings. Cp_{50} can be considered as the propofol concentration in blood required for changing the state of consciousness in horses from alert to anesthetic. Whereas MIR can be considered as the dosage of propofol required in order to compensate for propofol removed from blood and maintain an anesthesia state. It is presumed that since the former mainly reflects the tolerance for propofol in a horse and the latter reflects not only the tolerance but also the removal rate of propofol from blood, there was no significant correlation between the two. Moreover, the difference of the degree of individual variability between Cp_{50} and MIR, the former was large and the latter was small, also suggest the difference between what Cp_{50} and MIR reflects.

The rate of anesthetic agent removal from blood is influenced by the degree of distribution of anesthetic agent in the peripheral tissues and the metabolic rate of the agent [21]. In this research, it is likely that the degree of distribution of propofol in the peripheral tissues was increased by the higher induction dose and the longer infusion period of propofol as compared with the previous reports and the metabolic rate of propofol was decreased by IPPV. Consequently, there is a fair possibility that the MIR in this research was reduced by the reduction of the removal rate of propofol from blood attributed to these factors, i.e. higher induction dose, longer infusion period and IPPV.

In this research, induction dose of propofol was 3.0 mg/kg which is reported as an appropriate dose for young Thoroughbred [18]. On the other hand, induction dose of propofol was 2.0 mg/kg in the previous reports in which elder aged horses were used [16]. Moreover, in this research, in order to reduce the influence of premedication, measurement of MIR and arterial propofol concentration was initiated 45 min after propofol infusion started. Thus, total dose of propofol administered until the initiation of MIR measurement in this research was larger than that of the previous reports. It is probable that accumulation to body tissue of such propofol infused during the period before MIR measurement initiation have caused the reduction of MIR. Considering the infusion rate, arterial propofol concentration in this research was relatively higher than that of previous report, 6.3–6.7 and 4.3–4.7 μg/m*l* at the infusion rate of 0.25 and 0.15 mg/kg/min, respectively [16]. This result suggests the possibility of accumulation in the peripheral tissues. Propofol accumulation caused by this 45 min infusion can be supported from the arterial propofol concentration of Horse No.1. The initial infusion rate of Horse No.1 was higher than other five horses, which its arterial propofol concentration was maintained at a higher value as compared with those of others.

Another factor which is possible to have reduced the MIR in this research is IPPV. Even with 100% oxygen supplementation, hypercapnia [9, 16, 17] and hypoxemia [3, 9, 17] have been reported in spontaneously breathing horses anesthetized with TIVA using propofol. Therefore, ventilation was controlled by IPPV to prevent hypercapnia and hypoxemia during anesthesia. It is known that IPPV depresses the cardiovascular system [12, 26]. Moreover, it is reported in horses that cardiac output was increased due to sympathomimetic effect associated with respiratory depression in TIVA using propofol under spontaneous respiration [16]. Therefore, it is reasonable to suppose that there is a considerable gap between the cardiovascular system function in the previous reports under spontaneous respiration [2–4, 9, 16, 17] and this research under IPPV. Meanwhile, it is reported in swine that plasma propofol concentrations can be influenced by blood flows of organs, such as a liver

which metabolizes propofol, and there is an inverse relation between cardiac output and plasma propofol concentrations during constant infusion [14]. From this, the possibility cannot be denied that the depression of cardiovascular system as compared with other reports attributed to IPPV influenced the propofol metabolism in this research and consequently reduced MIR.

Since MIR is the infusion rate at which 50% subjects show gross purposeful movement in response to painful stimulus, i.e. ED_{50}, the MIR is inadequate as an infusion rate for clinical application. In inhalation anesthetic mainly used for prolonged anesthesia of horses, 1.2 to 1.4 MAC is recommended as adequate dosage for maintaining anesthesia [26]. However it is not clear if the same applies to the MIR concept of intravenous anesthetic. Generally, the anesthetic dosage required for surgical procedure is estimated to be 95% effective dose, i.e. ED_{95} [23]. Then, ED_{95} of propofol was calculated using regression line, $y = 12.50 x - 0.78$, for the probability of preventing gross purposeful movement to stimulus and propofol infusion rate. Consequently, ED_{95} was estimated at 0.138 mg/kg/min. Therefore, approximately 0.14 mg/kg/min (1.4 MIR) is considered to be adequate for basic infusion rate of propofol required for a surgical operation in TIVA of horses.

In inhalation anesthesia of horses, the palpebral and cornea reflex are important to assess anesthetic depth, and the former is generally depressed, and the latter is always present at adequate depth of anesthesia [13]. In this research, brisk palpebral and corneal reflexes were observed at the infusion rates at which no gross purposeful movement in response to painful stimulus was observed, in other words, the anesthetic depth was sufficient. This observation suggested the difficulties of assessing anesthetic depth of propofol anesthesia by these ocular reflex activities.

In this research, mean ABP during anesthesia was lower compared with those of conscious animals [25] although HR and ABP increased significantly with time. Xylazine used for premedication depresses cardiovascular function [29]. Therefore, one of the causes for the lower ABP is xylazine, and increase of HR and ABP with time is probably due to the attenuation of cardiovascular depressant effect of xylazine with time. Besides, it is known that poropfol also depresses the cardiovascular system [15, 28]. The ABP in this research tended to be lower at the higher infusion rate although the difference was not significant. This result suggests a possibility that propofol will produce a dose-dependent cardiovascular depression in horses. On the other hand, in a study of TIVA which used propofol and xylazine under spontaneous respiration, heart rate and cardiac output was greater for the higher propofol infusion rate [16]. This was explained by indirect sympathomimetic effects of the dose-dependent respiratory depression. Therefore, in order to examine the direct influence of propofol on the cardiovascular system, it is necessary to clarify relation between infusion rate and cardiovascular function under constant ventilatory conditions by IPPV.

In conclusion, MIR and Cp_{50} of propofol were 0.10 mg/kg/min and 5.3 μg/m*l*, respectively, for TIVA after premedication with 1.0 mg/kg of xylazine in Thoroughbred horses. Moreover, ED_{95} for preventing gross purposeful movement to electrical stimulus was estimated at approximately 0.14 mg/kg/min. Additionally, brisk palpebral and corneal reflex were always observed at all infusion rate of 0.08 to 0.20 mg/kg/min. For safer TIVA with propofol in horses, it is necessary to characterize the influence of propofol on cardiovascular system, especially relation between infusion rate and cardiovascular depression.

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