Cardiovascular Effects of Continuous Propofol Infusion in Horses

Kazuomi OKU[1)]*, Minoru OHTA[1)], Tomohiro KATOH[1)], Hidekazu MORIYAMA[1)], Kanichi KUSANO[1)] and Toru FUJINAGA[2)]

[1)]*Racehorse Clinic, Miho Training Center, Japan Racing Association, 2500–2 Oaza-Mikoma, Mihomura, Inashiki-gun, Ibaraki 300–0439* and [2)]*Laboratory of Veterinary Surgery, Department of Veterinary Clinical Sciences, Graduate School of Veterinary Medicine, Hokkaido University, Sapporo 060–0818, Japan*

ABSTRACT. We examined the influence of propofol infusion on cardiovascular system at the rate of 0.14, 0.20 and 0.30 mg/kg/min in six adult Thoroughbred horses. The cardiovascular parameters were heart rate (HR), mean arterial pressure (MAP), mean right atrial pressure (MRAP), stroke volume (SV), cardiac output (CO), systemic vascular resistance (SVR), pre-ejection period (PEP) and ejection time (ET). In order to keep the ventilation conditions constantly, intermittent positive pressure ventilation was performed, and the partial arterial CO_2 pressure was maintained at 45 to 55 mmHg during maintenance anesthesia. SV showed a significant dose-dependent decrease however, CO did not show significant change. SVR decreased significantly at higher dose. PEP was prolonged and PEP/ET increased significantly at the highest dose. From these results, it became clear that SV decreases dose-dependently due to decrease of cardiac contractility during anesthesia with continuous propofol infusion in horses. On the other hand, since MAP and CO did not show significant changes, total intravenous anesthesia with propofol was suggested to be suitable for long-term anesthesia in horses.
KEY WORDS: anesthesia, equine, hemodynamics, propofol, Pulsed Doppler echocardiography.

Propofol (2,6-diisopropylphenol), a new intravenous anesthetic, fulfills many of the conditions required for total intravenous anesthesia (TIVA), i.e. short duration of action with little cumulative effects, easiness of anesthetic depth control and rapid recovery [13, 26]. For this reason, TIVA using propofol became widely performed in people [7] and animals including horses [3, 10, 15, 19, 20, 22] in recent years.

Many of anesthetic agents generally induce profound cardiovascular depression [17, 23]. In human propofol anesthesia, the decreases of arterial blood pressure, stroke volume, cardiac indices, systemic vascular resistance and left cardiac work indices are reported [13]. In horses, the incidence of postanesthetic complications such as myopathy, lameness, and colitis-X are increased by cardiovascular depression during anesthesia [12, 14]. Therefore, in order to carry out TIVA safely using this anesthetic agent in horses, it is essential to understand the influence of continuous propofol infusion on the cardiovascular system. However, in horses, there are few reports that evaluate the changes in cardiovascular system during TIVA using propofol based on the measurement of cardiac output (CO) [2, 4, 15]. Moreover, in all of these reports, medetomidine [2, 4] or xylazine [15] was infused in conjunction with propofol, therefore these drugs had no small effect on the results. Additionally, only one report evaluated the relationship between propofol infusion rate and the degree of cardiovascular depression [15]. According to this report, cardiodepressive effect at high propofol infusion rate was masked by the indirect sympathomimetic effects attributed to the dose-dependent respiratory depression. Thus, the relationship between propofol infusion rate and the degree of cardiovascular depression in horses during TIVA with propofol has not been clarified yet.

The purpose of this study was to collect basic cardiovascular data for TIVA using propofol in horses. Meanwhile, for the purpose, it is desirable not only to maintain, but also to induce anesthesia with propofol alone. However, to ensure safety of horses and personnel, xylazine only was used for premedication. We examined the relationship between propofol infusion rate and cardiovascular parameters such as heart rate (HR), arterial blood pressure and cardiac output (CO) etc. during TIVA after premedication with xylazine under a constant ventilated condition.

MATERIALS AND METHODS

Horses: Six healthy Thoroughbred horses (4 males and 2 females) were used. Four of these horses were 3 years old and 2 were 4 years old (mean ± standard deviation (SD), 3.5 ± 0.6 years old). Their mean weight was 450 ± 15 kg. Horses were fasted for 12 hr before anesthesia but had free access to water. Experiments were conducted according to the Guidelines for Animal Experiments at Equine Research Institute, Japan Racing Association.

Anesthesia: At 10 min after premedication with xylazine (1.0 mg/kg; Celactar, Bayer, Tokyo, Japan), each horse was restrained in a swing-door induction system and was induced with the intravenous injection of 1% propofol (3.0 mg/kg; Rapinovet, Mallinckrodt Veterinary, Mundelein, IL, 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. Continuously, horses

* CORRESPONDENCE TO: OKU, K., Clinical Sect., Racehorse Hospital, Ritto Training Center, Japan Racing Association 1028, Misono, Ritto-shi, Shiga 520–3085, Japan.

Table 1. The sequence of changing propofol infusion rates in each horse

Horse No.	Duration after the start of propofol infusion (min)											
	50		70		75		95		100		120	
	Propofol infusion rate (mg/kg/min)											
1	0.14	→	0.14	→	M	→	0.20	→	M	→	0.30	→ M
2	0.14	→	0.14	→	M	→	0.30	→	M	→	0.20	→ M
3	0.14	→	0.20	→	M	→	0.14	→	M	→	0.30	→ M
4	0.14	→	0.20	→	M	→	0.30	→	M	→	0.14	→ M
5	0.14	→	0.30	→	M	→	0.14	→	M	→	0.20	→ M
6	0.14	→	0.30	→	M	→	0.20	→	M	→	0.14	→ M

M: measurement of cardiovascular parameters.

were endotracheally intubated and transported to operation room by hoist and placed on a mat in right lateral recumbency.

Following induction by the 3.0 mg/kg propofol injection, continuous infusion of propofol using intravenous infusion pump (Star-Flow 592, IVAC, San Diego, CA, U.S.A.) was started for maintaining anesthesia. The initial infusion rate was set at 0.14 mg/kg/min which is equivalent to the 95% effective dose of propofol infusion [21]. In order to mitigate the influence of premedication as much as possible, infusion at such rate was continued for 50 min, equal to the systemic half-life of xylazine [11]. Subsequently, the cardiovascular parameters at three infusion rates, 0.14, 0.20 and 0.30 mg/kg/min, were measured. After maintaining each infusion rate for 20 min, the parameters were measured over approximately 5 min. There are 6 possible sequences of 3 different infusion rates and each of these 6 sequences was applied to each of 6 horses respectively, and randomly (Table 1). During anesthesia, the endotracheal tube was connected to a large animal circle breathing device (MOK94, Silver Medical Co., Tokyo) fitted with a time cycle ventilator (Compos-β EV, Silver Medical Co.) and supplied with 100% oxygen. The oxygen flow rate was set at 6 *l*/min. Horses were allowed to breathe spontaneously for the first 5 min of maintenance anesthesia and respiratory rate was measured to check for apnea more than 30 sec. Continuously, ventilation was controlled by intermittent positive pressure ventilation (IPPV) to maintain partial arterial CO_2 pressures ($PaCO_2$) of 45 to 55 mmHg.

Arterial blood gases: Arterial blood gases were measured at 15, 30 and 45 min after the start of maintenance anesthesia and at 15 min after each change of infusion rate. Blood samples for the measurement were collected anaerobically from the arterial catheter and analyzed for PaO_2 and $PaCO_2$ using a calibrated arterial blood gas analyzer (288 Blood Gas System, Ciba-Corning, Tokyo).

Mean arterial pressure (MAP) and mean right atrial pressure (MRAP): MAP and MRAP were measured with a 20 G catheter positioned within the facial artery and a Swan-Ganz catheter (93A-191-8F, Baxter Co., Tokyo) introduced into the right atrium via the left jugular vein, respectively. These catheters were connected to the pressure transducers of the multipurpose monitoring system (M1166A, Hewlett Packard, Palo Alto, CA, U.S.A.). Transducer 0-level was placed at the level of the sternum.

Pulsed Doppler echocardiographgy: HR, stroke volume (SV), pre-ejection period (PEP) and ejection time (ET) were measured using the Pulsed Doppler echocardiography [27]. CO, cardiac index (CI), systemic vascular resistance (SVR) and ratio of pre-ejection period to ejection time (PEP/ET) were calculated from these parameters. The Pulsed Doppler echocardiography was reported to be useful for measuring CO non-invasively, to provide data closely correlated with those of the dye dilution or thermo dilution methods in horses [16].

SV was calculated according to the previous report [16] using an ultrasound imaging system (Logiq TM 500, Yokogawa Medical Systems, Tokyo) with a 2.5 MHz sector-type probe. The left thoracic wall between the 5th and 6th ribs was scanned by the sound to produce a B-mode image of the aortic sinus, and the cut-surface area at a systolic stage was calculated by measuring the inside diameter of the outflow passage of the left ventricle. The sampling point of the aortic blood flow was immediately above the aortic valve in the center of the ascending aorta. The aortic blood flow was continuously imaged at an incoming angle of 15° or less against the flow direction of doppler. The typical and distinguished velocity waves of the aortic blood flow in successive 5 strokes were selected from the diagnostic images. Then SV was calculated by multiplication of the time integral value measured by tracing these velocity waves and the cut surface areas of the cardiac outflow passage. In addition, from the wave shape of the aortic blood flow velocity and of electrocardiogram (Base-apex lead), HR, PEP (time from the onset of the QRS complex to the onset of ejection) and ET (time from the onset to the end of ejection) were calculated. PEP and ET can be used as an index of the cardiac contractility in human [25] and horses [27,29]. Subsequently the CO, CI, PEP/ET (more accurate indicator of left ventricular function [6]) and SVR were calculated as follows:

CO (*l*/min) = SV (*l*) × HR (beats/min)
CI (*l*/min/kg) = CO (*l*) / Body weight (kg)
PEP/ET = PEP (msec) / ET (msec)
SVR (dynes·sec/cm^5)
= 60 × [MAP(mmHg) – MRAP(mmHg)] × 1332/ [CO(*l*/min) × 1000] [5]

Statistics: The data sets of cardiopulmonary measurement were analyzed with repeated measure analysis of variance to determine the effects of anesthesia duration and infusion rate. When appropriate, values between different infusion rates or different measurement time points were examined by Student-Newman-Keuls test. The level of statistical significance was less than 0.05.

RESULTS

Anesthesia: Time from the start of 3.0 mg/kg propofol administration for induction to sternal recumbency in swing-door was 2.4 to 3.0 (mean ± SD, 2.6 ± 0.2) min. The time required from the end of 3.0 mg/kg propofol administration to the start of continuous propofol infusion for maintaining anesthesia was 5 to 14 (8.8 ± 3.7) min, and during this period, horses were intubated and transported to operation room. The duration of maintaining anesthesia by continuous infusion of propofol was 124 to 131 (127.8 ± 2.9) min. The measurement of parameters was performed at approximately 70, 95 and 120 min, respectively, after the start of propofol infusion. No abnormal findings that required emergency treatment were noted in any of the horses during anesthesia.

Respiratory rate and arterial blood gases: Respiratory rate was 6.2 ± 2.6 breathes/min under spontaneous breathing at 5 min after the start of maintenance anesthesia, and apnea of 30–60 sec was observed in two horses. After applying IPPV, $PaCO_2$ was maintained at the targeted level of 45–55 mmHg.

Changes of the cardiovascular parameters related to the change of propofol infusion rate: Measurements of cardiovascular variables at three infusion rates are shown in Table 2. Mean HR was in the range of 32.0–32.9 beats/min, showing no significant change. SV decreased with the increase of infusion rate. SV at 0.20 and 0.30 mg/kg/min (703.3 and 694.7 m*l*, respectively) was significantly lower than that of

0.14 mg/kg/min (744.7 m*l*). CO and CI were in the ranges of 22.6–23.7 *l*/min and 50.5–52.8 m*l*/kg/min, respectively. MAP and MRAP were in the range of 96–105 and 6.0–6.7 mmHg, respectively. SVR at 0.30 mg/kg/min (315.9 dynes·sec/cm^5) was significantly lower than that of 0.20 mg/kg/min (350.0 dynes·sec/cm^5). PEP was prolonged dose-dependently, and the value at 0.30 mg/kg/min (163.4 msec) was significantly longer than that of 0.14 mg/kg/min (128.4 msec). ET was in the range of 532.2–554.9 msec. PEP/ET at 0.30 mg/kg/min (0.31) was significantly larger than that of 0.14 mg/kg/min (0.23).

Changes of the cardiovascular parameters over time during propofol infusion: Chronological changes in cardiovascular variables during maintenance of anesthesia are shown in Table 3. Mean HR increased significantly with time. HR at 120 min (33.6 beats/min) was significantly higher than that of 70 min (30.9 beats/min). SV changed within the range of 693.7–727.0 m*l*, showing no significant change. CO and CI at 95 min (23.4 *l*/min and 52.2 m*l*/kg/min, respectively) and at 120 min (24.4 *l*/min and 54.5 m*l*/kg/min, respectively) were significantly higher than those of 70 min (21.4 *l*/min and 47.9 m*l*/kg/min). MAP was in the range of 97–104 mmHg. MRAP, SVR, PEP, ET and PEP/ET also showed no significant change.

DISCUSSION

In TIVA of horses, propofol has been combined with infusion of xylazine [15], medetomidine [3, 4], and ketamine [20] to improve anesthesia quality. However, there have been no definite conclusions yet about the agents to combine with propofol in horses due to problems such as hypoxaemia, hypercapnia etc. Therefore, to collect basic data about propofol for TIVA in horses, anesthesia was maintained with infusion of propofol alone in this research.

Anesthetic induction of horses with propofol alone is dangerous since marked limb paddling movement appears

Table 2. Changes in cardiovascular variables at three infusion rates during propofol anesthesia

Variables	Infusion rates (mg/kg/min)		
	0.14	0.20	0.30
Heart rate (beats/min)	32.0 ± 7.9	32.1 ± 6.0	32.9 ± 6.1
Stroke volume (m*l*)	744.7 ± 38.5	703.3 ± 39.2[a)]	694.7 ± 35.5[a)]
Cardiac output (*l*/min)	23.7 ± 5.6	22.6 ± 4.3	22.9 ± 4.8
Cardiac index (m*l*/kg/min)	52.8 ± 8.9	50.5 ± 7.1	51.2 ± 8.4
Mean arterial blood pressure (mmHg)	105 ± 11	104 ± 14	96 ± 15
Mean right atrial pressure (mmHg)	6.3 ± 4.7	6.3 ± 3.8	6.0 ± 4.9
Systemic vascular resistance (dynes·sec/cm^5)	341.6 ± 60. 0	350.0 ± 49.4	315.9 ± 30.9[b)]
Pre-ejection period (msec)	128.4 ± 33.3	145.7 ± 36.3	163.4 ± 47.7[a)]
Ejection time (msec)	554.9 ± 48.6	547.2 ± 43.2	532.2 ± 29.7
Pre-ejection period/Ejection time (PEP/ET)	0.23 ± 0.06	0.27 ± 0.05	0.31 ± 0.08[a)]

$p < 0.05$. a) *versus (vs.)* 0.14 mg/kg/min. b) *vs.* 0.20 mg/kg/min.

Table 3. Chronological changes in cardiovascular variables during propofol anesthesia

Variables	Duration of propofol infusion (min)		
	70	95	120
Heart rate (beats/min)	30.9 ± 5.8	32.5 ± 7.4	33.6 ± 6.7[a]
Stroke volume (m*l*)	693.7 ± 59.1	722.0 ± 28.2	727.0 ± 30.7
Cardiac output (*l*/min)	21.4 ± 4.3	23.4 ± 4.9[a]	24.4 ± 5.1[a]
Cardiac index (m*l*/kg/min)	47.9 ± 7.4	52.2 ± 7.7[a]	54.5 ± 7.9[a]
Mean arterial blood pressure (mmHg)	97 ± 18	103 ± 11	104 ± 12
Mean right atrial pressure (mmHg)	6.7 ± 4.3	6.0 ± 4.7	6.0 ± 4.5
Systemic vascular resistance (dynes·sec/cm^5)	340.8 ± 49.6	340.7 ± 62.7	326.0 ± 34.4
Pre-ejection period (msec)	147.9 ± 45.0	137.9 ± 25.3	151.8 ± 51.5
Ejection time (msec)	542.8 ± 39.1	546.7 ± 45.2	544.9 ± 43.0
Pre-ejection period/Ejection time (PEP/ET)	0.27 ± 0.08	0.25 ± 0.03	0.38 ± 0.09

$p < 0.05$. a) *vs.* 70 min.

in lateral recumbency immediately after induction (unpublished data). For this reason, minimal premedication with xylazine alone was performed to ensure the safety of horses and personnel. Therefore, the influence of xylazine cannot be denied in this research. However, cardiovascular parameters were measured at approximately 80 min or later after xylazine administration. After 80 min from intravenous administration of 1.0 mg/kg xylazine, it is known that MAP, CI, SV, SVR and HR showed no significant change [28]. In consequence, the influence of premedication on measurements obtained in this research was presumably small.

It would be reasonable to suppose that the influence of propofol infusion on cardiovascular function would tend to be more pronounced in the latter parts of TIVA. In this research, to control the influence of such time factor, each of 6 possible sequences of 3 different infusion rates was applied to each of 6 horses respectively and randomly. Therefore, it can be considered that the influence of time factors would be evenly distributed throughout the 6 horses. Moreover, any effects attributable to the difference of infusion rate at each measurement time point would also be evenly distributed throughout the 6 horses.

It is known that the change of the arterial propofol concentration in relation to the change of infusion rate plateaued at 15 min after changing the rate [21]. Therefore, in this research, cardiovascular parameters were measured after maintaining each infusion rate for 20 min.

It is reported that SV and CO decreased during propofol anesthesia in human [13], pig [9] and dog [18] similar to other anesthetics. However, there is another report in human where propofol did not influence SV or CO probably because some depressive effects of propofol on cardiovascular system was masked by the effects of increased $PaCO_2$ caused by moderate respiratory impairment [8]. Moreover, in a study of horses, profound hypercapnia at high propofol infusion rate (0.25 mg/kg/min) was associated with higher CI (62 m*l*/kg/min), compared with the lower infusion rate

(0.15 mg/kg/min) that was associated with lower $PaCO_2$ and CI (35 m*l*/kg/min) [15]. In order to avoid such indirect influence of respiratory depression, IPPV was performed in this research to maintain constant $PaCO_2$ at 45 to 55 mmHg. As a result, in contrast with the above report of horses, SV decreased significantly in a dose-dependent manner, although HR and CO did not change. Therefore, it was confirmed that propofol infusion depresses cardiac function in horses dose-dependently under the condition without the influence of respiratory depression by itself.

In this research, SV decreased significantly in a dose-dependent manner during propofol infusion, however CO did not decrease. CO is simply calculated by multiplying SV by HR. Therefore, it follows that the decrease in SV was compensated by the slightly increase in HR though HR did not change significantly. The cause of this compensation for decreased SV by slightly increased HR is not clear. However, it is known that propofol dose not impair the baroreceptor reflex sensitivity [8]. Therefore, the cause for which CO did not change in spite of decrease in SV may include the baroreceptor reflex control of HR.

In this research, although MAP and CO did not change significantly, MAP tended to decrease, $p = 0.088$, and SVR decreased significantly at higher dose. It is reported that the decrease of SVR associated with a central depression of sympathetic outflow resulted in the decrease of arterial pressure during TIVA with propofol [8]. Consequently, also in this research, the decrease of SVR may have influenced MAP in some degree.

In this research, PEP was prolonged and PEP/ET increased significantly with increase of infusion rate. In addition, PEP and ET obtained in this research were longer than those reported in conscious horses, 70 and 480 msec, respectively [29]. PEP is known to be prolonged due to increase in afterload and decrease in preload and cardiac contractility [6, 24, 30]. PEP/ET increases due to increased HR and decrease in preload and cardiac contractility [6, 24].

In this research, MRAP, an indicator of preload [5], and HR did not change significantly. SVR, an indicator of afterload, significantly decreased. Therefore, it can be safely said that the significantly prolonged PEP and increased PEP/ET reflect the decrease in cardiac contractility.

In anesthetized horses with sevoflurane, CI, SV and MAP are reported to be 47 ± 6 ml/kg/min, 619 ± 70 ml and 65 ± 12 mmHg at 1.5 minimum alveolar concentration (MAC) and 32 ± 7 ml/kg/min, 419 ± 91 ml and 43 ± 6 mmHg at 2.0 MAC, respectively [1]. The CI, SV and MAP in this research were maintained higher than these values even at the highest infusion rate. On the other hand, the depth of anesthesia produced by 1.2 to 1.4 MAC of inhalation anesthetic is almost equivalent to the depth produced by propofol infusion of 0.14 mg/kg/min, the lowest rate in this research, [21]. Therefore, CI, SV and MAP in this research were higher than those in horses anesthetized with sevoflurane in comparison at almost the same anesthetic depth.

SV and MAP did not change, and HR, CO and CI increased significantly with time in this research. From the above, it can be inferred that the accumulation of propofol did not contribute to increased cardiovascular depression in the latter parts of TIVA. As the cause of increase in HR, CO and CI with time, the chronological reduction of cardiovascular depressant effect by xylazine used for premedication can not be denied. However, as has been mentioned, the influence of xylazine on measurements was presumably small. Another possible cause of chronological increase in HR, CO and CI is the time-related increase of sympathetic nervous system activity as suggested in inhalation anesthetics [23].

It was found from the result that, during TIVA with propofol of 0.14 to 0.30 mg/kg/min in horses, SV decreased dose-dependently caused by the depression of cardiac contractility without CO decrease. Although SVR decreased dose-dependently, MAP did not decrease. Moreover, it is inferred that the degree of cardiovascular depression during TIVA with propofol is less than those of inhalation anesthesia. It is concluded that these results indicate a high safety of TIVA with propofol for clinical applications in horses.

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