Clinical Observations during Induction and Recovery of Xylazine–Midazolam–Propofol Anesthesia in Horses

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ABSTRACT. To evaluate clinical usefulness of xylazine (1.0 mg/kg)-midazolam (20 µg/kg)-propofol (3.0 mg/kg) anesthesia in horses, 6 adult Thoroughbred horses were examined. The quality of induction varied from poor to excellent and 5 out of 6 horses presented myotonicus in the front half of the body. However, paddling immediately after induction observed in other reports of equine propofol anesthesia was not observed. Recovery time was 35.3 ± 9.3 min and the quality of recovery was calm and smooth in all horses. Respiration rate decreased after induction and hypoxemia was observed during lateral recumbency. Heart rate also decreased after induction, however mean arterial blood pressure was maintained above approximately 100 mmHg.

KEY WORDS: equine, intravenous anesthesia, propofol.

The intravenous anesthetic, propofol (2,6-diisopropylphenol) has been widely used for total intravenous anesthesia of human beings [12, 20, 22] and some animals [9, 11, 13]. The drug is characterized by short duration of action with little cumulative effects, easiness of anesthetic depth control and rapid recovery [4, 12]. There is a number of reports of anesthesia using propofol also in horses [1, 3, 15–18], in many of these reports, undesirable anesthesia-induction characteristics, i.e., excitement, increased muscle activities and paddling in the early recumbent phase were observed [3, 15–17]. For anesthesia induction in horses, safety of both personnel and horse is an important subject. Therefore, establishment of the anesthesia method without such undesirable characteristics is necessary for the clinical application of propofol to horses.

In this research, midazolam, a benzodiazepine derivative, was used together with xylazine for premedication of propofol anesthesia of a horse, and the behavior of horses during anesthetic induction and recovery and their effects on the cardiopulmonary function were characterized.

Six male 2-years-old (28 ± 1 months of age) healthy Thoroughbred horses trained for rearing weighing 469 ± 24 kg were used. Horses were fasted for 12 hr before anesthesia and freely given water. The experiments were conducted according to the guidelines established by the Experimental Animal Committee, Japan Racing Association.

Five min after premedication with xylazine (1.0 mg/kg; Celactar, Bayer, Tokyo, Japan) followed by midazolam (20 µg/kg; Dormicum, Yamanouchi, Tokyo, Japan) 10 min later, horses received a 3 min in duration intravenous injection of 1% propofol (3.0 mg/kg; Rapinovet, Mallinckrodt Veterinary, Mundelein, U.S.A.) solution.

Horses were restrained by a swing-door induction system and propofol was administered. After the horses attained a sternal recumbency, the swing-door was opened and horses were turned to lateral recumbency. Following endotracheal intubation, horses were transported to the recovery room by hoist. In the recovery room, horses were placed in right lateral recumbency on a mat and spontaneously inhaled room air. After appearance of the swallowing reflex the endotracheal tube was removed and recovery was awaited without any stimulation or assistance.

The quality of induction and recovery were quantified using a score of 1 to 5 (1, poor; 2, marginal; 3, fair; 4, good; 5, excellent) according to a description by Mama et al. [15, 16]. The time to sternal recumbency from the start of propofol administration, as well as the time to attain a sternal recumbency and to stand in the recovery room from the end of administration were measured.

Respiratory rate (RR), heart rate (HR), arterial blood pressures (ABP) and arterial partial pressures of O2 and CO2 (PaO2 and PaCO2) were measured. The ABP was obtained using a multipurpose monitoring system (M1166A, Hewlett Packard, Palo Alto, U.S.A.) connected via a transducer with a 20 G catheter placed in the facial artery. The transducer 0-level was placed at the level of the sternum. Blood samples collected from the arterial catheter were analyzed for PaO2 and PaCO2 using a calibrated arterial blood gas analyzer (288 Blood Gas System, Ciba-Corning, Tokyo, Japan). The measurements were obtained before medication, just after administration of propofol, 10, 15 and 20 min after administration of propofol as well as immediately after, 10, 20 and 30 min after standing-up.

The data were grouped within categories and summarized as mean ± standard deviation. The data of cardiopulmonary measurement were analyzed for repeated measure ANOVA
were turned from sternal to lateral recumbency. Endotracheal movement when the swing-door was opened and the horses movement was observed. Neither of the horses showed leg severely in Horse Nos. 3 to 6 and moderately so in Horse No. 1. In Horse No. 6, extended forelegs with some leg head elevation and forelegs extension was observed myotonus of the neck and the forelegs which leads to the appeared at the caudal half of the body, whereas transient difference was observed in the quality of induction and there were excitement and transiently increased muscle activities during the induction of anesthesia [15–17]. Then, paddling was a common feature early in the recumbent phase in those studies [3, 15–17]. Induction appears to be improved when guaiacol glycerin ether (GGE) is used together with propofol in Brazilian horses [1]. The use of GGE appears to facilitate endotracheal intubation and decrease the amount of propofol used. However, GGE preparations might contain something impure or be contaminated, since GGE for injection is not yet commercially available in Japan and therefore preparations might contain something impure or be contaminated, since GGE for injection is not yet commercially available in Japan and therefore might be prepared personally. Endophlebitis and thrombophlebitis were reported to occur after rapid intravenous injection of 5 to 10% GGE [6, 10]. For the above reasons, GGE was not used in this study. On the other hand, midazolam, a benzodiazepine derivative, is known to reduce dosage of anesthetic for induction in dogs [26] as well as to inhibit abnormal excitement and enhance muscular relaxation in horses treated with ketamine [2]. So midazolam comparing between the time stages. In cases with significant difference between time stages of RR and HR measurement, the values at different time stages as well as predrug value were examined by the Wilcoxon U test. The level of statistical significance was 0.05 or less.

Anesthetic induction and recovery scores are shown in Table 1. Anesthetic induction scores were variable. In all the horses except Horse No. 2, the muscle relaxation first appeared at the caudal half of the body, whereas transient myotonus of the neck and the forelegs which leads to the head elevation and forelegs extension was observed severely in Horse Nos. 3 to 6 and moderately so in Horse No. 1. In Horse No. 6, extended forelegs with some leg movement was observed. Neither of the horses showed leg movement when the swing-door was opened and the horses were turned from sternal to lateral recumbency. Endotracheal intubation was easy and no rigidity of masseter muscle or swallowing movements were seen. No horses moved in response to hoisting of the horse body, whereas brisk palpebral and corneal reflexes were observed.

The time from the beginning of propofol administration to sternal recumbency in the swing door was 1.9 ± 0.1 min. The time from the end of administration to sternal recumbency in the recovery room was 26.1 ± 5.7 min, while the time from the end of administration to standing-up was 35.3 ± 9.3 min.

Recovery from anesthesia was calm and smooth in all horses. Horse No. 6 which showed some ataxia at the time of standing-up had the shortest time (22.1 min) to standing-up as well as the lowest anesthetic induction score.

Recorded cardiopulmonary measurements are presented in Table 2. The RR decreased from 17.3 ± 4.5 breaths/min at rest to 9.0 ± 4.2 breaths/min immediately after administration of propofol. Thereafter, the RR increased with time during recumbency and decreased again after standing-up.

The PaCO2 and PaO2 during recumbency were 45 to 55, 55 to 65 mmHg. Hypoxemia (defined as a PaO2 <60 mmHg) was observed in 4 horses immediately after induction, in 2 horses at 10 and 15 min after induction and in 4 horses at 20 min after induction. Hypoxemia was not observed after standing-up in all horses.

The HR during most of recumbency was 30 to 35 and significantly less than the predrug value. The HR once increased immediately after standing-up and decreased again after that.

During recumbency, the systolic (SABP), diastolic (DABP) and mean arterial blood pressures (MABP) were approximately 120, 90 and 100 mmHg, respectively.

When propofol was given to horses singly or together with an α2-agonist such as xylazine, remarkable individual difference was observed in the quality of induction and there were excitement and transiently increased muscle activities during the induction of anesthesia [15–17]. Then, paddling was a common feature early in the recumbent phase in those studies [3, 15–17]. Induction appears to be improved when guaiacol glycerin ether (GGE) is used together with propofol in Brazilian horses [1]. The use of GGE appears to facilitate endotracheal intubation and decrease the amount of propofol used. However, GGE preparations might contain something impure or be contaminated, since GGE for injection is not yet commercially available in Japan and therefore might be prepared personally. Endophlebitis and thrombophlebitis were reported to occur after rapid intravenous injection of 5 to 10% GGE [6, 10]. For the above reasons, GGE was not used in this study. On the other hand, midazolam, a benzodiazepine derivative, is known to reduce dosage of anesthetic for induction in dogs [26] as well as to inhibit abnormal excitement and enhance muscular relaxation in horses treated with ketamine [2]. So midazolam

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Induction</th>
<th>Recovery</th>
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<tbody>
<tr>
<td>1</td>
<td>5</td>
<td>5</td>
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<td>2</td>
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<td>3</td>
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<td>5</td>
<td>3</td>
<td>5</td>
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<tr>
<td>6</td>
<td>1</td>
<td>4</td>
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</tbody>
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Table 1. Induction and recovery scores of each horse receiving xylazine-midazolam-propofol

<table>
<thead>
<tr>
<th>Variable</th>
<th>Minutes after induction</th>
<th>Minutes after standing-up</th>
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<tbody>
<tr>
<td>RR</td>
<td>17.3±4.5</td>
<td>9.0±3.7</td>
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<tr>
<td>PaCO2</td>
<td>53.1±2.1</td>
<td>49.2±2.6</td>
</tr>
<tr>
<td>PaO2</td>
<td>58.1±10.9</td>
<td>63.0±7.2</td>
</tr>
<tr>
<td>pHa</td>
<td>37.7±0.032</td>
<td>7.41±0.02</td>
</tr>
<tr>
<td>HR</td>
<td>37.7±5.0</td>
<td>33.7±4.5</td>
</tr>
<tr>
<td>SAP</td>
<td>NM 122.3±11.1</td>
<td>120.3±11.7</td>
</tr>
<tr>
<td>DAP</td>
<td>NM 93.3±7.5</td>
<td>90.3±7.7</td>
</tr>
<tr>
<td>MAP</td>
<td>NM 104.7±8.2</td>
<td>102.0±8.5</td>
</tr>
</tbody>
</table>

* P<0.05 from predrug value.

Data are expressed as mean ± SD.
P=predrug values; I=immediately after induction; S=immediately after standing-up; RR=respiratory rate (breaths/min); PaCO2=arterial carbon dioxide tension (mm of Hg); PaO2=arterial oxygen tension (mm of Hg); HR=heart rate (beats/min); SAP=systolic arterial pressure (mm of Hg); DAP=diastolic arterial pressure (mm of Hg); MAP=mean arterial pressure (mm of Hg); NM=values not measured.
was used for premedication in this study in addition to xylazine.

In this study, myotonus at the front half of the body was also seen during induction and the induction scores varies between individuals. Even in horses premedicated with xylazine plus midazolam, behavior after propofol is unpredictable and the quality of anesthetic induction is not always good. However, increased muscle activities in the forelegs was observed only in one horse and paddling in the early recumbent phase was not observed in any horses of this study. The dose of propofol in this study (3.0 mg/kg) was more than that in other reports. However, in another study of us, all of 6 horses administered xylazine 1.0 mg/kg without midazolam followed by propofol 3.0 mg/kg, the same dose as this study, showed paddling immediately after becoming lateral recumbency (unpublished observation). From this, it was considered that control of the paddling was not attributed to combination with mydazolam rather than the difference of the dose of propofol. Thus premedication with xylazine / midazolam combination seemed to be available.

The causes of excitement, myoclonic activity and limb movements appearing after propofol administration remain unknown, although myoclonic activity in dogs and goats were reported to be manifestations of excitement related to a light plane of anesthesia [19, 27]. In man and dogs, it is known that the localized pain some times follows propofol administration [12, 23, 24] into small vessels. Its incidence was lower when administered via larger vessels [12]. These reports suggest that there are low possibility for pain on injection to cause myotonus of this study where propofol was injected slowly into a relatively large vessel, i.e. jugular vein.

It is reported that induction dose of propofol for premedicated horses with α2-agonist is 2.0 mg/kg [1, 3, 16–18]. However, in our preliminary experiment using 3-years-old Thoroughbred horses, anesthetized state after administration of 2.0 mg/kg propofol was not deep enough to realize easy endotracheal intubation or transport by the hoist (unpublished observation). Therefore, in this research, induction dose of propofol was set as 3.0 mg/kg. The cause that a higher propofol dose was required for anesthetic induction in our research than other reports is not clear. However, it is also guessed as one of the causes that the horse used in this research was a young Thoroughbred, while the old horse [16] or the non-Thoroughbred [1, 3, 18] was used in other reports. In man, dose requirements of propofol were reduced in older patients [12]. Moreover, in Greyhound dogs, a higher propofol dose was required for induction as compared with non-Greyhound dogs [21].

Rapid and smooth recovery from propofol anesthesia is reported in man [12, 22, 23], goats [5], sheep [13] and horses [15–18]. Time required for recovery in this study approximated to that of the horse administered xylazine 1.0 mg/kg followed by propofol 2.0 mg/kg in other study [16], and recovery was calm and smooth like other reports. Therefore, premedication with xylazine-midazolam combination was considered not to lead to delay or deterioration of the quality of recovery.

The effects of propofol on respiratory system were reported to decrease RR and apnea in horses [15, 16], ponies [18], dogs [21, 24], goats [5, 19] and man [12]. Also in this study, the RR decreased after anesthetic induction and the horses showed PaO2 of about 60 mmHg during lateral recumbency. The PaCO2 during lateral recumbency was slightly higher than normal values in awake [25]. Since PaCO2 had not increased markedly, such hypoxemia was presumed the result of ventilation/perfusion abnormalities caused by recumbent posture rather than hypoventilation [7]. On the other hand, the higher incidence of apnea was reported in propofol-treated dogs and goats [19, 24]. In particular after bolus administration, the incidence was higher because of a transient increase of blood concentration of the drug [19]. Perhaps no apnea occurred in this study because propofol was injected slowly (i.e., 1.0 mg/kg/min).

In the present study, the HR and ABP during recumbency were lower compared with those of conscious animals [25], however they approximated to those of horses administered propofol after premedication with α2-agonist in other reports [16, 17]. It is known that propofol reduces cardiac output and ABP in combination with α2-agonists in horses [3, 18]. On the other hand, midazolam was considered to have only a slight effect on the cardiovascular system [2]. Therefore, it was thought that the cardiovascular depression by xylazine and propofol was not further strengthened by midazolam. It has been suggested that MABP required to prevent postanesthetic complications is 65 to 70 mmHg or more [8, 14]. The MABP in this study was maintained more highly than this value. Therefore, it was thought that ABP was maintained in the safe range.

In equine propofol anesthesia, premedication with midazolam in addition to xylazine was considered to be effective for the improvement of the quality of induction. Furthermore, recovery from xylazine-midazolam-propofol anesthesia by horses in this study was excellent. In equine anesthesia, it is an important issue to ensure the safety of horses and personnel during induction and recovery. The depressant effect of xylazine-midazolam-propofol on the cardiopulmonary system was permissible except for hypoxemia. From the above things, it is considered that clinical application is possible for xylazine-midazolam-propofol anesthesia in horses when a means of oxygen supplementation is available. However, it is desired that further investigation is made in order to ease the transient myotonus during the induction period.

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REFERENCES