Effects of Intravenous Fentanyl Administration on End-Tidal Sevoflurane Concentrations in Thoroughbred Racehorses undergoing Orthopedic Surgery

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ABSTRACT. To evaluate the effects of IV fentanyl administration on the end-tidal sevoflurane concentration (ETSEVO) in thoroughbred racehorses, the ETSEVO required for internal fixation of longitudinal fractures was compared between horses anesthetized with sevoflurane-fentanyl (Group SF; n=9) and those anesthetized with sevoflurane alone (Group S; n=9). The loading dose of fentanyl (5.0 μg/kg) was administered over 15 min followed by a maintenance dose of fentanyl (0.1 μg/kg/min) throughout the operation in Group SF. The mean ETSEVO during the operation in Group SF (2.6 ± 0.2%) was significantly lower than in Group S (3.0 ± 0.3%). The plasma fentanyl concentrations (6.12 ± 0.88 to 7.78 ± 1.12 ng/ml) in 7 out of 9 horses in Group SF were stable and did not change significantly throughout the operation. The mean dobutamine infusion rate required for maintaining a mean arterial blood pressure between 60 and 80 mmHg during the operation in Group SF (0.56 ± 0.30 μg/kg/min) was significantly lower than in Group S (0.90 ± 0.16 μg/kg/min). The qualities of the recoveries were clinically acceptable, and serious complications were not observed in either group. In conclusion, continuous IV fentanyl administration reduced the sevoflurane requirement by 13% in thoroughbred racehorses undergoing orthopedic surgery; however, fentanyl was considered to be less effective in horses compared with other species.

Key words: analgesia, fentanyl, racehorse, sevoflurane.

Perioperative pain management is important in equine practice, since the adverse physiological effects of pain may worsen the outcome of the treatment. Nonsteroidal anti-inflammatory drugs (NSAIDs), such as flunixin meglumine and phenylbutazone, are commonly used to relieve inflammation and provide analgesia for horses with mild to moderate pain. However, the use of NSAIDs alone can be insufficient to adequately alleviate severe pain in conditions such as orthopedic diseases. On the other hand, fentanyl is a synthetic μ-opioid receptor agonist of the 4-anilinopiperidine series that is commonly used as an analgesic for moderate to severe pain in a number of species [17]. In humans and small animals, balanced anesthesia with fentanyl provides perioperative analgesia and improves hemodynamics by minimizing the necessary inhalation concentration of anesthetic agents for general anesthesia [11, 12, 23].

Although the pharmacokinetics of IV administered fentanyl in horses have been described, the clinical efficacies of fentanyl in horses have not been well investigated. Therefore, there are varying opinions concerning clinical usage of fentanyl in horses among researchers [16, 20]. The purpose of this study was to assess the clinical efficacy of IV fentanyl administration in racehorses undergoing orthopedic surgery. To evaluate the effects of IV fentanyl administration on the end-tidal sevoflurane concentration (ETSEVO) in thoroughbred racehorses, the ETSEVO required for internal fixation of longitudinal fractures was compared between horses anesthetized with sevoflurane-fentanyl and those anesthetized with sevoflurane alone.

MATERIALS AND METHODS

Horses: Eighteen thoroughbred racehorses with longitudinal fractures of the proximal phalanx (P1), the third metacarpus (Mc3) or the third metatarsal (M3) underwent internal fixation under general anesthesia. Fracture characteristics were incomplete and nondisplaced, and articular fragments were not observed in any of the cases. Nine horses (2 females and 7 males, 3.8 ± 2.0 years old) with fractures of the front P1 (4 horses), hind P1 (1 horses) and Mc3 (4 horses) weighing 400 to 516 kg (476 ± 38 kg) were anesthetized with sevoflurane alone (Group S), and nine horses (9 males, 3.0 ± 0.4 years old) with fractures of the front P1 (3 horses), hind P1 (3 horses), Mc3 (3 horses) and Mt3 (2 horses) weighing 428 to 508 kg (485 ± 26 kg) were anesthetized with a sevoflurane and fentanyl combination (Group SF). No abnormality was found in any of the horses in the results of preanesthetic blood examination and electrocardiography. Food was withheld from horses overnight before the operation, but water was freely accessible.

Anesthesia and instrumentation: Three 14-G catheters were placed in external jugular veins, two on the same side for fentanyl and other drug administration and one on the opposite side for collecting blood to measure the fentanyl concentration in Group SF. All horses were premedicated with xylazine (1.0 mg/kg; Celactar, Bayer, Tokyo, Japan), and anesthesia was induced by a rapid injection of 5% guaifenesin (1,000 ml/head; 5% Guaifenesin, Shinyo Pure
To assess the effect of fentanyl on the quality of recovery from anesthesia, all horses in Group SF were allowed to recover without assistance and given no additional drugs. The times taken from the end of anesthesia to appearance of spontaneous respiration, extubation, first movement, first attempt to stand and standing were recorded. The behavior and clinical response during the course of recovery were scored according to Muma’s report [8] as follows: G5 (excellent, single coordinated effort to stand with minimal to no ataxia), G4 (fair, single attempt to stand with some ataxia), G3 (good, quiet recovery with more than one attempt to stand), G2 (marginal, uncoordinated attempts to stand with or without minor injury) and G1 (poor, multiple, uncoordinated attempts resulting in major or life-threatening injury). All horses in Group S were assisted, and xylazine (100 mg/head) was administered when necessary.

**Plasma fentanyl analysis:** Blood samples were collected at 0, 30 and 60 min after initiation of the surgical procedure (after completing the fentanyl loading dose), at the end of anesthesia and immediately after standing from 7 out of 9 horses in Group SF. All blood samples were immediately placed on ice, and then the plasma was separated from the blood and frozen at −20°C. Fentanyl in plasma was extracted using diethyl ether under alkaline conditions. The extract was analyzed by a high-performance liquid chromatography-mass spectrometry system (HPLC/MS, Shimadzu Co., Tokyo, Japan). The minimum quantifiable concentration of fentanyl in the plasma was 0.16 ng/ml.

**Statistical analysis:** Two-way repeated-measures ANOVA tests were applied to compare cardiovascular and blood gas data between two groups. A one-way repeated-measures ANOVA test was applied to compare plasma fentanyl concentrations in Group SF. Dunnett tests (multiple pairwise comparisons vs baseline values) were applied when significant differences were identified. Age, body weight, mean ETSEVO, mean dobutamine infusion rate and total anesthesia time were compared between the two groups using Mann-Whitney’s U tests. Values are given as means ± SD, and statistical significance was set at \( P<0.05 \).

**RESULTS**

There were no significant differences in age and body weight between the two groups. The mean ETSEVO in Group SF (2.6 ± 0.2%) was significantly lower \( (P=0.009) \) than that of Group S (3.0 ± 0.3%). The plasma fentanyl concentrations during the operation and after standing in Group SF are shown in Fig. 1. The plasma fentanyl concentrations were stable and did not change significantly throughout the oper-
The HR, SAP, DAP and MAP values during the operation in both groups are shown in Table 1. HR significantly increased with duration of operation in both groups; however, there were no significant differences between the groups. The MAP values were maintained within the target values throughout the operation in both groups, and there were no significant differences between the groups. The mean dobutamine infusion rate required for maintaining MAP within the target values in Group SF (0.56 ± 0.30 μg/kg/min) was significantly lower ($P=0.019$) than that of Group S (0.90 ± 0.16 μg/kg/min). The results of blood gas analysis are shown in Table 2. The PaCO$_2$ values were maintained within the target values throughout the operation in both groups.

The total anesthesia time was 118 ± 6 min in Group SF and 109 ± 11 min in Group S, and there were no significant differences between the two groups. The mean times taken from the end of anesthesia to appearance of spontaneous

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**Table 1.** Mean values (± SD) of heart rate (HR) and systolic (SAP), diastolic (DAP) and mean (MAP) arterial blood pressures during the surgical procedure in the horses of Group S and Group SF

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>HR (bpm)</th>
<th>SAP (mmHg)</th>
<th>DAP (mmHg)</th>
<th>MAP (mmHg)</th>
<th>HR (bpm)</th>
<th>SAP (mmHg)</th>
<th>DAP (mmHg)</th>
<th>MAP (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>31 ± 3</td>
<td>96 ± 7</td>
<td>52 ± 3</td>
<td>66 ± 4</td>
<td>29 ± 5</td>
<td>96 ± 6</td>
<td>55 ± 7</td>
<td>68 ± 8</td>
</tr>
<tr>
<td>10</td>
<td>31 ± 4</td>
<td>96 ± 6</td>
<td>53 ± 4</td>
<td>65 ± 7</td>
<td>30 ± 5</td>
<td>97 ± 7</td>
<td>56 ± 6</td>
<td>67 ± 7</td>
</tr>
<tr>
<td>20</td>
<td>33 ± 4</td>
<td>98 ± 7</td>
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<td>66 ± 3</td>
<td>30 ± 5</td>
<td>96 ± 7</td>
<td>54 ± 5</td>
<td>69 ± 8</td>
</tr>
<tr>
<td>30</td>
<td>35 ± 5</td>
<td>99 ± 8</td>
<td>54 ± 5</td>
<td>67 ± 4</td>
<td>31 ± 5</td>
<td>98 ± 7</td>
<td>56 ± 4</td>
<td>68 ± 8</td>
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<td>40</td>
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<td>99 ± 6</td>
<td>56 ± 5</td>
<td>70 ± 6</td>
<td>32 ± 5</td>
<td>98 ± 5</td>
<td>56 ± 4</td>
<td>69 ± 7</td>
</tr>
<tr>
<td>50</td>
<td>37 ± 6*</td>
<td>100 ± 7</td>
<td>53 ± 5</td>
<td>70 ± 7</td>
<td>33 ± 6</td>
<td>97 ± 6</td>
<td>57 ± 4</td>
<td>69 ± 6</td>
</tr>
<tr>
<td>60</td>
<td>38 ± 7*</td>
<td>100 ± 5</td>
<td>56 ± 4</td>
<td>71 ± 4</td>
<td>34 ± 6*</td>
<td>98 ± 6</td>
<td>59 ± 6</td>
<td>69 ± 4</td>
</tr>
</tbody>
</table>

*: Significantly different from the 0 min value ($P<0.05$).

**Table 2.** Mean values (± SD) of pH, PaO$_2$ and PaCO$_2$ during the surgical procedure in the horses of Group S and Group SF

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>pH</th>
<th>PaO$_2$ (mmHg)</th>
<th>PaCO$_2$ (mmHg)</th>
<th>pH</th>
<th>PaO$_2$ (mmHg)</th>
<th>PaCO$_2$ (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>7.33 ± 0.03</td>
<td>374 ± 102</td>
<td>52 ± 3</td>
<td>7.36 ± 0.03</td>
<td>449 ± 65</td>
<td>52 ± 3</td>
</tr>
<tr>
<td>15</td>
<td>7.33 ± 0.02</td>
<td>404 ± 75</td>
<td>54 ± 1</td>
<td>7.35 ± 0.03</td>
<td>460 ± 71</td>
<td>51 ± 2</td>
</tr>
<tr>
<td>30</td>
<td>7.34 ± 0.02</td>
<td>383 ± 84</td>
<td>53 ± 2</td>
<td>7.35 ± 0.03</td>
<td>464 ± 72</td>
<td>50 ± 3</td>
</tr>
<tr>
<td>45</td>
<td>7.35 ± 0.03</td>
<td>425 ± 61</td>
<td>52 ± 3</td>
<td>7.36 ± 0.03</td>
<td>472 ± 68</td>
<td>51 ± 2</td>
</tr>
<tr>
<td>60</td>
<td>7.34 ± 0.02</td>
<td>407 ± 84</td>
<td>52 ± 3</td>
<td>7.36 ± 0.03</td>
<td>466 ± 71</td>
<td>51 ± 2</td>
</tr>
</tbody>
</table>
respiration, extubation, first movement, first attempt to stand and standing in Group SF were 12 ± 6, 20 ± 7, 28 ± 12, 50 ± 20 and 58 ± 20 min, respectively. The scores for recovery in Group SF were G5 for 3 horses, G4 for 4 horses and G3 for 2 horses. No apparent complications were observed after anesthesia in any of the cases.

DISCUSSION

A reduction in the minimum alveolar concentration (MAC) of inhalant agents after administration of various drugs is often used as a measure of analgesia in both humans and animals [11, 14, 18]. In this study, a reduction of about 13% in the sevoflurane requirement was observed in horses administered fentanyl as part of the anesthetic regimen. All horses utilized in this study had the same fracture characteristics and underwent the same surgical procedure, and so the surgical invasions were considered to be to a similar extent in both groups. Therefore, plasma fentanyl concentrations of 6.12 ± 0.88 to 7.78 ± 1.12 ng/ml appeared to produce a certain degree of analgesic for serve pain in horses, and this effect might have lead to reduction of the sevoflurane requirement. The minimum effective analgesic concentrations of fentanyl have been reported to be 0.63 ± 0.25 ng/ml or between 1 and 1.5 ng/ml for humans [2, 7] and 0.95 ng/ml for dogs [15]. However, the response to opioids varies among species which may be related to different opioid receptor types and distributions. It was reported that the distribution, density, and subtype of opioids in the central nervous system showed marked differences between dogs and horses [4]. Therefore, it is inadequate to apply the data obtained from other species directly to horses. Although the plasma concentrations of fentanyl required to provide analgesia in horses have not been determined, there are some reports about the clinical usability of fentanyl in horses. Thomasy et al. [21] reported that transdermal fentanyl with a peak serum concentration of 2.2 ± 1.1 ng/ml significantly decreased pain scores, but did not change lameness scores. Sanchez et al. [16] reported that fentanyl administration did not produce a significant antinociceptive effect except in the highest fentanyl group, with a corresponding mean serum fentanyl concentration of 7.82 ± 2.10 ng/ml, among fentanyl groups administered 4 different doses. Thomasy et al. [22] demonstrated a significant (18%) reduction in the MAC of isoflurane after fentanyl administration, correlating to a mean plasma concentration of 13.31 ng/ml. Thus, plasma fentanyl concentrations of 6.12 ± 0.88 to 7.78 ± 1.12 ng/ml appeared to be the minimum values required to reduce the sevoflurane requirement for orthopedic surgery in racehorses. Fentanyl at approximately 6 to 10 ng/ml decreases the MAC of isoflurane by 53% in dogs [5], and fentanyl at 10 ng/ml decreases the MAC of isoflurane by 82% in humans [11]. The 13% reduction in sevoflurane requirement in this study was small in comparison to the other species, and so fentanyl was considered to be less effective in horses compared with the other species.

The pharmacokinetics of fentanyl in horses that are awake and under isoflurane anesthesia have been reported [10, 16, 20, 21]. The loading dose (5.0 µg/kg) and maintenance dose (0.1 µg/kg/min) of fentanyl administered in this study were determined in reference to these previous studies. In a previous study, a loading fentanyl dose of 3.03 µg/kg followed by a maintenance dose of 0.059 µg/kg/min resulted in a plasma fentanyl concentration of 8.43 ng/ml, and a loading fentanyl dose of 4.69 µg/kg followed by a maintenance dose of 0.113 µg/kg/min resulted in a plasma fentanyl concentration of 13.31 ng/ml under isoflurane anesthesia [22]. In the present study, the target fentanyl concentration was set above 10 ng/ml; however, the actual plasma fentanyl concentrations were between 6.12 ± 0.88 and 7.78 ± 1.12 ng/ml, and these values were somewhat lower than those we had predicted. Pharmacokinetics, including drug distribution, metabolism and excretion, can be influenced by various factors, such as age, breed, physical condition and other administered drugs. The ages and breeds of horses used in the previous studies varied, whereas all the horses used in the present study were relatively young thoroughbred racehorses. The horses used in the present study had continued to display signs of moderate to severe pain associated with fractures, which might have altered blood flow due to production of inflammatory mediators and corticosteroids. Moreover, the effects of inhalation anesthetic agents on fentanyl clearance were considered to be different between isoflurane and sevoflurane. Although, the actual plasma fentanyl concentrations in the present study were lower than the target values, they were stable in individuals over time during the course of anesthesia, and interindividual variability was comparatively small. Therefore, the loading dose and the maintenance dose of fentanyl administered in the present study were considered to be adequate for clinical use in thoroughbred racehorses under sevoflurane anesthesia.

Sevoflurane induces a dose-dependent decrease in hemodynamic variables in horses, and so reduction of the dose of sevoflurane may promote cardiovascular stability and improve perianesthetic care [1, 3, 19]. On the other hand, opioids have been reported to produce minimal effects on cardiovascular function. In the present study, the reduction of the sevoflurane concentration induced by fentanyl administration may have contributed to the significant decrease in the requirement of dobutamine for maintenance of MAP within the target values. However, the improvement level of the cardiovascular depression was small, and so inotropic agents were necessary even though fentanyl was administered.

All horses in both groups recovered from anesthesia without any complications. Recovery from anesthesia is a potentially dangerous period for horses. Therefore, all horses in Group S were assisted and xylazine was administered when necessary to minimize the risk of complications during the recovery phase. For this reason, recovery data in Group S were excluded in the present study. On the other hand, all horses in Group SF were allowed to recover without assistance and given no additional drugs in order to
assess the effect of fentanyl on the quality of recovery from anesthesia. Opioids have been reported to induce central nervous system excitation and subsequent locomotor activity [6]. In another study, the behavioral characteristics of a horse recovering from general anesthesia after administration of a high dose of morphine were clearly not desirable [18]. In the present study, such adverse effects were not observed in Group SF, and the qualities of the recoveries were clinically acceptable. However, adverse effects or toxicosis may appear if higher doses of fentanyl are administered. In any case, if the horses in Group SF were assisted and appropriate agents were administered, the qualities of the recoveries would be improved and become similar to those previously described for horses recovering from sevoflurane anesthesia [9, 13].

In conclusion, continuous IV fentanyl administration reduced the sevoflurane requirement by 13% in thoroughbred racehorses undergoing orthopedic surgery; however, fentanyl was considered to be less effective in horses compared with other species.

REFERENCES