Clinical, cardiopulmonary, hematological and serum biochemical effects of sevoflurane and isoflurane anesthesia in oxygen under spontaneous breathing in sheep

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Accepted 14 September 1999

Abstract

Effects of sevoflurane and isoflurane anesthesia in oxygen on clinical, cardiopulmonary, hematological, and serum biochemical findings were compared in sheep breathing spontaneously undergoing minor surgical operations during short-term (60–80 min) or long-term (3–4 h) anesthesia. All sheep were premedicated with atropine sulfate (0.1 mg/kg) intramuscularly, and 10 min later, induced to anesthesia by intravenous infusion of sodium thiopental (mean 14.1 ± 3.4 S.D. mg/kg). After intubation, they were anesthetized with either isoflurane or sevoflurane in oxygen at a total gas flow rate of 1.5 l/min. The results revealed that recovery time with sevoflurane was more rapid than with isoflurane. Respiration rates, tidal volume, minute ventilation and heart rates during sevoflurane anesthesia were similar to those during isoflurane anesthesia. The degree of respiratory acidosis during sevoflurane anesthesia was also similar to that during isoflurane anesthesia. There were no significant differences between sevoflurane and isoflurane anesthesia in hematological and serum biochemical values.

Keywords: Sevoflurane; Isoflurane; Sheep; Inhalation anesthesia; Cardiopulmonary

1. Introduction

A new halogenated inhalant, sevoflurane, has a low blood/gas partition coefficient similar to nitrous oxide (Strum and Eger, 1987), and produces rapid induction of and recovery from anesthesia and rapid alteration of anesthetic depth (Kazama and Ikeda, 1985; Eger and Johnson, 1987; Hikasa et al., 1996a, 1997b). The arrhythmogenic dose of adrenaline for sevoflurane is higher than that for halothane and enflurane, and similar to that for isoflurane in dogs (Hayashi et al., 1988) and cats (Hikasa et al., 1996b) Sevoflurane appears to be a new anesthetic showing promise. The anesthetic potency and cardiopulmonary effects of isoflurane have been well described in lambs...
Sevoflurane has been used as an effective anesthetic producing a rapid recovery in adult cattle (Hikasa et al., 1994a) and horses (Hikasa et al., 1994b). The effects of sevoflurane anesthesia on right ventricular function and oxygenation for one-lung ventilation with positive end-expiratory pressure to the dependent lung have been studied using open-chest sheep (Fujita et al., 1993). However, there is no information available on clinical anesthesia with sevoflurane in small ruminants. The purpose of this study was to compare the clinical, cardiopulmonary, hematological, and serum biochemical effects of sevoflurane-oxygen with those of isoflurane-oxygen anesthesia, at a surgical depth of anesthesia in spontaneously ventilating sheep undergoing some surgical operations.

2. Materials and methods

2.1. Animals

Twenty-nine healthy sheep (Suffolk or Corriedale) of either sex (6 months to 5 years of age), weighing from 33–62 kg bodyweight (mean 46.4 ± 9.9 S.D. kg), were used in this investigation. Health status was evaluated on the base of history, physical examinations, complete blood counts, serum biochemical profiles, and electrocardiograms using standard methods. They were given a commercial ruminant concentrate, hay and water ad libitum. All sheep were fasted for 24 h before anesthesia. Anesthesia and selected operations were carried out in a room at 21–24°C. Intra- or post-operative analgesics were not given in any sheep. A broad-spectrum antibiotic, ampicillin (10 mg/kg) was administered intramuscularly twice a day for 3 days post-operatively in all sheep.

2.2. Anesthetic procedures

The sheep were randomly assigned into four groups of 6–9 animals. Two groups of sheep were anesthetized with sevoflurane or isoflurane for short-term of 60–80 min, and underwent a surgery for subcutaneous relocation of the left carotid artery for collection of arterial blood samples in the future. Another two groups were anesthetized with sevoflurane or isoflurane for long-term of 3–4 h, and underwent operations for attachments of ruminal fistula, duodenal cannula and several electrodes into the duodenal muscles through the paracostal approach of laparotomy during anesthesia. All of the surgical procedures just mentioned were done on each of the animals. All sheep were premedicated intramuscularly with atropine sulfate (0.1 mg/kg; Tanabe, Japan). After 10 min, anesthesia was induced by intravenous infusion of sodium thiopental (mean 14.1 ± 3.4 S.D. mg/kg; Rabonal, Tanabe, Japan). The end-point of the infusion was until the animals lay down and could be intubated. The animals were placed in lateral recumbency on a surgical table, intubated with auffed endotracheal tube, and anesthetized with either isoflurane (Forane, Dinabott, Tokyo, Japan) in oxygen (O1) or sevoflurane (Sevofrane, Maruishi Pharma, Osaka, Japan) in oxygen (OS) at a total gas flow rate of 1.5 l/min delivered to anesthetic system (Beaver 20, Kimura Medicals, Tokyo, Japan). They were maintained at a surgical plane of anesthesia while breathing spontaneously. The depth of anesthesia was judged by the lack of painful response to surgeries. In addition, the lack of painful response to clamping the interdigital web of pads with Kocher’s forceps and palpebral response were monitored at 15–30 min intervals during anesthesia. A positive response to painful stimuli was defined as gross purposeful muscular movement of the head or extremities. If an animal showed a positive response to the stimuli, the end-tidal concentration was increased by 10–20% and, after approximately 5 min, the stimuli were repeated. The palpebral response showed a slight or no reflex during anesthesia.

Agent-specific precision vaporizer was used for sevoflurane (Mark II, Acoma Medicals, Tokyo, Japan). Isoflurane was vaporized from a halothane vaporizer (Honey Matic M-3, Kimura Medicals, Tokyo, Japan). The Inspired and end-tidal concentrations of the anesthetic gases in specimens drawn from a sampling catheter positioned in the connection at the oral end of the endotracheal tube were measured continuously using an infrared gas analyzer (Capnomac Ultima, Datex, Helsinki, Finland). Airway gas was continuously sampled at the rate of 200 ml/min and the gas was not returned to the circuit. Immediately after the surgical operations were completed, the
anesthetic circuit was disconnected from the animal. The endotracheal tube was removed immediately after return of swallowing movements. The elapsed times from discontinuing anesthesia to first lift of the head, standing and walking were recorded. Although this study was not double blinded in the recovery time evaluation, recovery evaluation by the observer was consistent among all of the sheep and between anesthetics.

2.3. Cardiopulmonary measurements

A lead Apex-Base electrocardiogram (ECG) was recorded continuously to monitor heart rate (HR) and heart rhythm throughout the anesthetic period. Respiration rate (RR), respiratory tidal volume (TV) and minute ventilation (MV) were measured according to the methods described previously (Hikasa et al., 1994a, b). Arterial blood samples were collected from a polyethylene 22-gauge catheter inserted into the auricular artery prepared previously. Arterial oxygen and carbon dioxide partial pressures (PaO₂ and PaCO₂), arterial pH (pHₐ), arterial bicarbonate ([HCO₃⁻]ₐ), and base excess (BEa) were measured according to the procedures reported previously (Hikasa et al., 1996a, 1997b). The TV and MV were measured at 15–30-min intervals during anesthesia. The HR, RR and arterial blood gases were measured before atropine was injected (baseline), at 15- or 30-min intervals during anesthesia, and at 30 and 60 min postanesthesia.

2.4. Hematological and serum biochemical measurements

Jugular blood samples were collected before atropine was injected (base-line), at 30–60 min intervals throughout the anaesthetic period, and at 1 h, 1 or 3 days after discontinuing anesthesia. Packed cell volume (PCV), red blood cell (RBC) counts, plasma protein (PP) concentrations, serum aspartate transaminase (AST), alanine transaminase (ALT) and alkaline phosphatase (ALP) activities, blood urea nitrogen (BUN), creatinine, glucose, sodium, potassium, and chloride concentrations were determined according to the procedures described previously (Hikasa et al., 1997b, 1998).

2.5. Statistical analyses

Data were analyzed by one-way analysis of variance for repeated measures to compare time-related variables within each anaesthetic group and Tukey’s multiple comparison test was used to identify differences between means. For unpaired comparisons between sevoflurane and isoflurane groups the data underwent an analysis of variance. When the F-value was not significant, a Student’s t-test was used to determine the significance of differences. When a significant F-value was found, a Wilcoxon–Mann–Whitney test was used for the statistical evaluation. The significance level of all tests was set at P < 0.05.

3. Results

3.1. Maintenance anesthesia and recovery from anesthesia

The duration (mean ± S.D.) of anesthesia with isoflurane and sevoflurane was 69 ± 7 and 67 ± 4 min for short-term anesthesia, and 190 ± 17 and 201 ± 20 min for long-term anesthesia, respectively. Mean end-tidal concentrations of isoflurane and sevoflurane during maintenance anesthesia were 0.8–1.0% and 1.1–1.3% and 1.5–2.1% for short-term, and 1.2–1.4% and 1.1–1.3% and 1.5–2.1% for long-term, respectively (Table 1).

Mild salivation was observed during maintenance anesthesia in all groups. The amount (mean ± S.D.) of salivation fluids during OI and OS anesthesia were 29 ± 10 and 26 ± 14 ml/h in short-term anesthesia, and 33 ± 24 and 26 ± 9 ml/h in long-term anesthesia, respectively. There was no significant difference in the amount of fluids between OI and OS groups.

As shown in Table 2, mean elapsed times to first lift of the head and standing–walking following OS anesthesia were significantly shorter than those following OI anesthesia in both short and long-term.

3.2. Cardiopulmonary findings

In all groups, RR during maintenance anesthesia decreased significantly when compared with base-line value (value before atropine injection). The HR in all groups increased significantly from base-line during maintenance anesthesia. There were no significant
differences between OI and OS groups in both HR and RR (Fig. 1). However, HR in OI group during long-term anesthesia tended to be higher than that during OS group. Both TV and MV in OS groups did not significantly differ from those in OI groups (Fig. 2). In both OI and OS groups, TV in long-term anesthesia tended to be higher than that in short-term anesthesia, but not significantly (Fig. 2). In all groups, no abnormal ECG alterations were observed throughout anesthesia.

As shown in Fig. 3, the pH\textsubscript{a} in all groups decreased significantly during maintenance anesthesia when compared with base-line value. The PaCO\textsubscript{2} and PaO\textsubscript{2} in all groups increased significantly during maintenance anesthesia. The [HCO\textsubscript{3}–]\textsubscript{a} in all groups increased slightly during anesthesia and at 30–60 min postanesthesia when compared with base-line value. The BE\textsubscript{a} increased slightly at 30–60 min postanesthesia. The degrees of acidosis and hypercapnia in OS group did not significantly differ from those in OI group during either short or long-term of anesthesia, although both acidosis and hypercapnia tended to be greater in OI group than OS group during long-term anesthesia. There were no significant differences in blood gases and acid–base values between OI and OS groups at any time.

### 3.3. Hematological and serum biochemical findings

The PCV, PP and RBC values decreased significantly from base-line values during anesthesia in all groups (Table 3). There were no significant differences between OI and OS groups in PCV, PP and RBC at any time (Table 3).

Serum AST, ALT, ALP, glucose, BUN, creatinine, sodium, potassium and chloride did not significantly change from base-line values at any time after anesthesia in any group, except that potassium in both OI and OS groups decreased slightly from base-line values at 60 min of anesthesia. There were no significant differences between OI and OS groups in serum biochemical values at any time.

### 4. Discussion

The concentration of sevoflurane during maintenance anesthesia in this study was approximately
1.6 times higher than that of isoflurane. The minimal alveolar concentration (MAC) of isoflurane in sheep has been reported to be 1.41–1.53% (Brett et al., 1987; LeDez and Lerman, 1987; Bernards et al., 1996). Although MAC value of sevoflurane in sheep is unknown, it has been reported that the ratio of potencies for any pairing of inhalant anesthetic agents is constant from species to species (Doi et al., 1988) and provides a means for assessing the validity of preexisting or newly determined MAC values (Drummond, 1985). The end-tidal sevoflurane/isoﬂurane concentration ratio (equal to approximately 1.6) during maintenance anesthesia in our study is very similar to the
Table 3
Hematological values during surgical depth of anesthesia with isoflurane and sevoflurane in spontaneously breathing sheep

<table>
<thead>
<tr>
<th>Variable</th>
<th>Period of anesthesia</th>
<th>Anesthetic</th>
<th>No. of sheep</th>
<th>Base-line</th>
<th>Time during maintenance anesthesia (min)</th>
<th>Time after anesthesia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>30</td>
<td>60</td>
<td>90</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Packed cell volume (%)</td>
<td>Short</td>
<td>Isoflurane</td>
<td>8</td>
<td>33</td>
<td>3</td>
<td>26$^b$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sevoflurane</td>
<td>9</td>
<td>34</td>
<td>2</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>Long</td>
<td>Isoflurane</td>
<td>6</td>
<td>34</td>
<td>3</td>
<td>30$^a$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sevoflurane</td>
<td>6</td>
<td>35</td>
<td>4</td>
<td>29$^b$</td>
</tr>
<tr>
<td>Plasma protein (g/dl)</td>
<td>Short</td>
<td>Isoflurane</td>
<td>8</td>
<td>6.3</td>
<td>0.3</td>
<td>5.8$^b$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sevoflurane</td>
<td>9</td>
<td>6.2</td>
<td>0.4</td>
<td>5.8</td>
</tr>
<tr>
<td></td>
<td>Long</td>
<td>Isoflurane</td>
<td>6</td>
<td>6.9</td>
<td>0.5</td>
<td>6.2$^a$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sevoflurane</td>
<td>6</td>
<td>6.8</td>
<td>0.4</td>
<td>6.1$^b$</td>
</tr>
</tbody>
</table>

$^a$ Significantly different from base-line value at $P < 0.05$.

$^b$ Significantly different from base-line value at $P < 0.01$. 
sevoflurane/isoflurane MAC ratio (equal to 1.7) in humans (Scheller et al., 1988).

The blood/gas partition coefficient for sevoflurane in human blood is much lower than that for halothane and isoflurane, and similar to that for nitrous oxide (Strum and Eger, 1987; Steffey, 1994), indicating that recovery from anesthesia with sevoflurane would be more rapid than that with the other two inhalant anesthetics. The current results demonstrated clearly that recovery times following OS anesthesia were significantly shorter than those following OI anesthesia in both short and long-term of anesthesia in sheep. These results are in agreement with those obtained previously in cats (Hikasa et al., 1998).

Sevoflurane induces dose-dependent respiratory depression in cats (Hikasa et al., 1997a), dogs (Doi et al., 1987) and humans (Doi and Ikeda, 1987). The RR in cats at surgical depth of anesthesia with sevoflurane-oxygen is reportedly higher than that with isoflurane-oxygen (Hikasa et al., 1996a). The present findings in sheep revealed that RR, TV and MV during sevoflurane-oxygen anesthesia do not differ from that during isoflurane-oxygen anesthesia. The TV during long-term anesthesia in both OI and OS groups tended to be higher than that during short-term anesthesia, suggesting that this may be due to the difference in the degree of surgical stimulation in the long surgery versus the short surgery. This study also revealed that both anesthetics produced respiratory acidosis (increase in PaCO2 and decrease in pH), and that the degree of respiratory acidosis during sevoflurane anesthesia did not significantly differ from that during isoflurane anesthesia, although respiration acidosis tended to be greater in isoflurane than sevoflurane during long-term anesthesia. Therefore, the present findings indicate that sevoﬂurane, similar to isoflurane, induces respiratory depression at a light-surgical depth of anesthesia in sheep. These findings in sheep are in agreement with those reported in cats (Hikasa et al., 1996a, 1997b, 1998). In the present study, however, the PaCO2 during maintenance anesthesia with either sevoflurane or isoflurane is higher than that reported previously in dogs (Steffey and Howland, 1977; Doi et al., 1987), cats (Hikasa et al., 1996a, 1997b, 1998), and humans (Doi and Ikeda, 1987). In ruminants, distension of the rumen due to increasing ruminal gases impairs the ventilation (Ungerer et al., 1976), and positioning in lateral recumbency is associated with respiratory depression (Fujimoto and Lenehan, 1985). These factors may contribute to the fact that hypercapnia during anesthesia in sheep was greater than that in small animals reported previously. It may be desirable that sheep being anesthetized with either isoflurane or sevoflurane are mechanically ventilated in order to avoid hypercapnia.

The HR is unchanged or decreased slightly as sevoflurane concentration increased in dogs (Kazama and Ikeda, 1988) and cats (Hikasa et al., 1997a), however, it is also reported to increase in dogs (Bernard et al., 1990; Frink et al., 1992b). Isoflurane has been reported to induce a slight increase HR in dogs (Bernard et al., 1990; Frink et al., 1992b), but induce a decrease in HR in lambs (Brett et al., 1987, 1989) and in cats (Hikasa et al., 1997b). In the current study, HR during anesthesia in each group increased from baseline, which is presumably due to the influence of atropine premedication. There were no significant differences in HR between the groups, indicating that HR during OS anesthesia does not differ from that during OI anesthesia in sheep. However, HR during OI anesthesia in long-term surgery tended to be higher than that during OS anesthesia, which may result from sympathetic activation due to the high PaCO2 in the long-term OI group. In addition, arrhythmia was not observed in sheep anesthetized with OS or OI. Therefore, sevoflurane-oxygen anesthesia produces a stable HR similar to isoflurane-oxygen anesthesia in sheep premedicated with atropine.

The current study revealed that hemodilution occurs during sevoflurane anesthesia similar to isoflurane anesthesia in sheep. These findings are in agreement with previous results that a surgical depth of anesthesia with OS or OI induces hemodilution in cats (Hikasa et al., 1996a, 1998), which may be caused by sequestration of RBCs in the spleen or by shifts in body fluids associated with the decrease in arterial pressure due to vasodilation and decreased cardiac output during anesthesia.

Renal effects of sevoflurane have been associated with inorganic fluoride production during metabolism, with resulting nephrotoxicity reported in rats, dogs and humans (Martis et al., 1981; Frink et al., 1992a). No such effect was observed in sheep. On the other hand, the extent of hepatic injury with sevoflurane does not differ from that with isoflurane; both anesthetics being less toxic than halothane in rats (Strum et al., 1988).
et al., 1987). In the current study, no significant changes in serum AST, ALT, ALP, glucose, BUN and creatinine values were observed for 3 days post-anesthesia in all groups. These results indicate that hepatic and renal injuries are not produced after 3–4 h anesthesia with sevoflurane as well as isoflurane in healthy sheep. In addition, no marked changes in serum sodium, potassium and chloride ion concentrations were observed in both anesthetic groups, indicating that electrolyte balance during and after anesthesia with sevoflurane is similar to isoflurane in sheep.

In conclusion, this study demonstrated that recovery time from anesthesia with sevoflurane-oxygen was more rapid than with isoflurane-oxygen in healthy sheep that underwent minor surgical procedures. Respiration rates, tidal volume, minute ventilation, heart rates, arterial blood gases and acid-base values during sevoflurane-oxygen anesthesia were similar to that during isoflurane-oxygen anesthesia. There were no significant differences between sevoflurane-oxygen and isoflurane-oxygen anesthesia in hematological and serum biochemical values.

Acknowledgements

The authors thank Maruishi Pharmaceutical Co., Ltd., for the gift of sevoflurane, and Miss K. Kondo and Mrs. T. Kakuta for their technical assistance.

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