Sevoflurane Anesthesia Following Administration of Atropine-Guaifenesin-Thiopental in Spontaneously Breathing Adult Cattle

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ABSTRACT. The effect of sevoflurane-oxygen anesthesia at surgical depth on clinically important features was evaluated in spontaneously breathing cattle given atropine-guaifenesin-thiopental. The mean end-tidal sevoflurane concentrations ranged from 1.4 to 2.0% for 75 min maintenance. Recovery from anesthesia was extremely rapid and smooth. Heart rate increased and arterial pressure was higher during anesthesia, but respiratory rate did not change significantly. Arrhythmia was not observed. Minute ventilation was low due to decreased tidal volume during anesthesia, and changes in blood gases and pH showed mild respiratory acidosis. There were no marked changes in hematologic or serum biochemical values for 7 days postanesthesia. These findings suggest that sevoflurane is an effective inhalant anesthetic showing rapid recovery from anesthesia.—**KEY WORDS:** cattle, inhalation anesthesia, sevoflurane.

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Sevoflurane is a nonflammable halogenated inhalation anesthetic synthesized by Travenol Laboratories of the United States. This agent has been shown to have some favorable characteristics. For example, sevoflurane has a low blood/gas partition coefficient [18], similar to nitrous oxide, which provides rapid induction of and recovery from anesthesia, and rapid alteration of anesthetic depth [10]. It undergoes limited biotransformation, and has little or no systemic toxicity in rats and dogs [12, 19, 20]. Arrhythmogenic doses of epinephrine for sevoflurane are much higher than those for halothane and enflurane, and similar to those for isoflurane in dogs [8, 9, 20]. Although sevoflurane induces dose-dependent cardiovascular depression in dogs [1, 10], its cardiovascular depression can be controlled rapidly and easily, and it does not have unfavorable effects on coronary circulation and myocardial metabolism [1]. Halothane and isoflurane have been used as effective and safe anesthetic agents in cattle [7, 13, 15–17]. However, to our knowledge, the effects of sevoflurane anesthesia in cattle have not been reported. The purpose of this study was to evaluate the effects of sevoflurane anesthesia following administrations of atropine-guaifenesin-thiopental on selected cardiopulmonary, hematologic, serum biochemical, and clinical features in adult cattle.

Five non-lactating Holstein cows, between 3 and 8 years old (mean, 5.0 years) and 383 and 524 kg in body weight (mean, 462 kg±69 SD), were used. They were given a commercial cattle concentrate, hay and water *ad libitum*. Food and water were withheld 24 hr before anesthesia. The experiments were performed in a large animal operation room controlled at 21 to 24°C.

In standing cows, a polyethylene catheter was inserted into the left carotid artery under local infiltration anesthesia with 5% procaine HCl 1 hr before premedication. Systolic, mean and diastolic arterial pressures (SAP, MAP and DAP, respectively) were measured using a pressure transducer and a strip chart recorder (Minipolygraph RM-6100, Nihon Koden, Japan). A lead-AB electrocardiogram (ECG) was recorded continuously for heart rate (HR) and heart rhythm monitoring during anesthesia. Respiratory rate (RR) was measured by movements of the

thorax or the re-breathing bag. Respiratory tidal volume (TV) was measured using a respirometer (Ohmeda RM 121, Japan) and minute ventilation (MV) was calculated. Arterial blood samples were taken anaerobically from the artery. Arterial oxygen, carbon dioxide pressures (PaO₂ and PaCO₂, respectively) and arterial pH (pHa) were measured using a blood gas analyzer (Blood Gas System 278, Ciba Corning Diagnostic Corp., Japan) at 37°C. Arterial bicarbonate ([HCO₃⁻]a) and base excess (BEa) were also derived. The rectal temperature (RT), HR, RR, arterial pressure (AP), and blood gas values were recorded before premedication, at 15 to 30 min intervals after induction of anesthesia, and at 30 and 60 min after discontinuation of anesthesia. The TV and MV were recorded at 15 min intervals throughout the anesthetic period.

All animals were premedicated with atropine sulfate (0.05 mg/kg; Wako Pure Chemical, Japan) intramuscularly. After 10 min, anesthesia was induced by intravenous (IV) infusion of a mixture of sodium thiopental (5 g; Rabonal, Tanabe Pharmaceutical, Japan) and guaifenesin (50 g; Fusutojiru, Kyoto Yakuhin, Japan) in 1 l of 5% glucose solution. The endpoint of the infusion was until the animals lay down and could be intubated. The cows were placed in right lateral recumbency on a surgical table, intubated with a cuffed large animal endotracheal tube, and induced to anesthesia with sevoflurane (Sevoflurane, Maruishi Pharma., Co., Japan) over 10 min. Subsequently, they were maintained at a light surgical depth of anesthesia with sevoflurane in oxygen for 75 min under spontaneous ventilation. The depth of anesthesia was judged by ventral rotation of the cow's eye and the lack of response to clamping the coronary ligament of the hoof and to pricking the paralumber fossa and the coronet with an injection needle. Sevoflurane was vaporized in out-of-circuit agent-specific precision vaporizer (Sevotec 3, Ohmeda, England), and delivered by a large animal semi-closed circle CO₂ absorption system (MAA-700, Senko Medical Instrument, Japan). Vaporizer settings were initially 4 to 5% and were gradually reduced during the first 10 min for maintenance concentrations. The oxygen flow rate was initially 4 l/min and then reduced to 2

to 3 l/min. Inspired and end-tidal sevoflurane concentrations of gas specimens drawn from a sampling catheter positioned in the endotracheal tube lumen at near the oral end were measured continuously using an infrared gas analyzer (Capnomac, Datex, Finland) during anesthesia. Gases were sampled at the rate of 200 ml/min. At 75 min after the onset of maintenance anesthesia, the anesthetic circuit was disconnected from the animal. The endotracheal tube was removed immediately after the swallowing motion. The elapsed recovery times from discontinuing the anesthesia to swallowing motion, head-up motion, sternal recumbency, and standing were recorded. Two to 3 hr after anesthesia the animals were returned to their houses and fed as previously.

Jugular venous blood specimens were collected before premedication, at 30 min intervals throughout the anesthetic period, and at 1 hr, 1 day, 3 days, 5 days, and 7 days after discontinuation of anesthesia. Packed cell volume (PCV), red blood cell (RBC), white blood cell (WBC) counts, hemoglobin (Hb), and plasma protein (PP) concentrations were determined. Serum aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP) activities, blood urea nitrogen (BUN), glucose and creatinine concentrations were determined by use of a spectrophotometer (Auto Sipper Photometer U-1080, Hitachi, Japan). Serum sodium, potassium, and chloride ion concentrations were determined by use of a clinical ion meter (CIM-102, Shimadzu, Japan).

Data were analyzed by a two-way analysis of variance comparing time and cow effects. When significant differences were noted, the Tukey's multiple comparison test was used to determine the differences between values

before premedication and values recorded after anesthesia. Differences were considered significant at $p < 0.05$.

All cows lay down promptly and were intubated by IV infusion of a mixture of guaifenesin and thiopental sodium. The mean ($\pm$ SD) duration of infusion was 6.2 ($\pm$ 1.9) min. The mean ($\pm$ SD) induction doses of thiopental sodium and guaifenesin were 6.53 ($\pm$ 2.01) mg/kg and 65.3 ($\pm$ 20.1) mg/kg, respectively. The subsequent maintenance of anesthesia using sevoflurane-oxygen was smooth and easy in each cow. The mean end-tidal sevoflurane concentration ranged from 1.4% at 15 min to 2.0% at 75 min (Table 1). The palpebral and corneal reflexes remained weak. Muscle relaxation of the limbs and jaws was good. A mild amount (200 to 400 ml) of salivation was observed during anesthesia. No serious behavioral side effects were observed.

Recovery from anesthesia was extremely rapid and smooth. Mean ($\pm$ SD) elapsed time to swallowing reflex, head-up motion, sternal recumbency, and standing position was 3.9 ($\pm$ 1.9), 5.0 ($\pm$ 2.0), 11.3 ($\pm$ 1.9), and 16.3 ($\pm$ 3.4) min, respectively. No notable muscle tremor or ataxia was observed after the cows were standing-up.

Table 1 shows the cardiopulmonary findings. The HR increased significantly from the value before premedication during anesthesia. No abnormal ECG alterations were observed throughout the anesthesia period in all cows. The RR, SAP, DAP, and MAP did not significantly change throughout the anesthesia period. The MV was low due to decreased TV during anesthesia. The pHa decreased significantly during anesthesia, and PaCO₂ and PaO₂ increased significantly during anesthesia when compared with those values before premedication. The [HCO₃⁻]a increased slightly at 60 and 75 min of mainte-

Table 1. Cardiopulmonary values (mean $\pm$ SD) of 5 cows anesthetized with sevoflurane and oxygen following administration of atropine-guaifenesin-thiopental

Variable	Before premedication	Time during sevoflurane anesthesia (min)					Time after anesthesia (min)	
		15	30	45	60	75	30	60
HR (beats/min)	60 $\pm$ 17	101 $\pm$ 9 ^{b)}	94 $\pm$ 9 ^{b)}	92 $\pm$ 16 ^{b)}	90 $\pm$ 19 ^{b)}	87 $\pm$ 14 ^{b)}	95 $\pm$ 21 ^{b)}	89 $\pm$ 17 ^{b)}
SAP (mmHg)	173 $\pm$ 29	175 $\pm$ 15	167 $\pm$ 18	164 $\pm$ 23	167 $\pm$ 19	168 $\pm$ 16	ND	176 $\pm$ 16
DAP (mmHg)	122 $\pm$ 39	143 $\pm$ 16	135 $\pm$ 14	133 $\pm$ 19	133 $\pm$ 18	135 $\pm$ 14	ND	135 $\pm$ 15
MAP (mmHg)	145 $\pm$ 28	158 $\pm$ 16	148 $\pm$ 17	145 $\pm$ 19	147 $\pm$ 17	151 $\pm$ 17	ND	153 $\pm$ 16
RR (breaths/min)	13.6 $\pm$ 2.7	17.4 $\pm$ 3.5	17.2 $\pm$ 2.4	17.2 $\pm$ 1.3	16.8 $\pm$ 1.3	17.2 $\pm$ 4.3	14.8 $\pm$ 7.7	12.2 $\pm$ 4.7
TV (l)	ND	1.72 $\pm$ 0.76	1.84 $\pm$ 0.64	1.92 $\pm$ 0.65	1.91 $\pm$ 0.72	2.04 $\pm$ 0.78	ND	ND
MV (l/min)	ND	29.3 $\pm$ 14.0	31.9 $\pm$ 10.2	32.7 $\pm$ 10.8	31.6 $\pm$ 12.2	35.2 $\pm$ 6.5	ND	ND
pHa (units)	7.44 $\pm$ 0.02	ND	7.32 $\pm$ 0.01 ^{b)}	ND	7.32 $\pm$ 0.03 ^{b)}	7.33 $\pm$ 0.03 ^{b)}	7.33 $\pm$ 0.03	7.44 $\pm$ 0.01
PaCO ₂ (mmHg)	39.4 $\pm$ 2.9	ND	58.6 $\pm$ 3.4 ^{b)}	ND	59.4 $\pm$ 5.0 ^{b)}	58.2 $\pm$ 5.1 ^{b)}	42.5 $\pm$ 3.9	40.7 $\pm$ 4.1
PaO ₂ (mmHg)	85 $\pm$ 2	ND	278 $\pm$ 124 ^{b)}	ND	277 $\pm$ 105 ^{b)}	273 $\pm$ 92 ^{b)}	84 $\pm$ 12	80 $\pm$ 10
[HCO ₃ ⁻]a (mEq/l)	26.7 $\pm$ 2.5	ND	29.6 $\pm$ 2.1	ND	30.3 $\pm$ 2.3 ^{a)}	31.5 $\pm$ 3.1 ^{a)}	26.7 $\pm$ 1.5	26.9 $\pm$ 2.2
Base excess (mEq/l)	3.0 $\pm$ 2.3	ND	2.3 $\pm$ 1.7	ND	2.9 $\pm$ 2.2	2.7 $\pm$ 2.3	2.2 $\pm$ 1.3	3.0 $\pm$ 1.7
RT (°C)	38.3 $\pm$ 0.2	38.1 $\pm$ 0.7	37.9 $\pm$ 0.6	37.9 $\pm$ 0.6	37.8 $\pm$ 0.7	37.7 $\pm$ 0.7	38.0 $\pm$ 0.8	38.3 $\pm$ 0.6
Sevoflurane								
Inspired (%)	ND	1.6 $\pm$ 0.4	1.8 $\pm$ 0.7	1.9 $\pm$ 0.5	2.0 $\pm$ 0.5	2.1 $\pm$ 0.4	ND	ND
End-tidal (%)	ND	1.4 $\pm$ 0.4	1.7 $\pm$ 0.7	1.8 $\pm$ 0.4	1.9 $\pm$ 0.5	2.0 $\pm$ 0.4	ND	ND

HR=heart rate; SAP=systolic arterial pressure; DAP=diastolic arterial pressure; MAP=mean arterial pressure; RR=respiratory rate; TV=tidal volume; MV=minute ventilation; RT=rectal temperature; and ND=not determined. a) Significant difference from values before premedication ($p < 0.05$). b) Significant difference from values before premedication ($p < 0.01$).

Table 2. Hematologic and serum biochemical values (mean±SD) of 5 cows anesthetized with sevoflurane and oxygen following administration of atropine-guaifenesin-thiopental

Variable	Before premedication	Time during sevoflurane anesthesia		Time after anesthesia				
		30 min	60 min	1 hr	1 day	3 days	5 days	7 days
PCV (%)	31.1±5.0	29.6±3.8	29.3±4.3	29.9±4.0	31.4±4.0	28.6±3.2	28.7±3.0	28.0±3.2
Hb (g/dl)	9.2±1.7	8.7±1.1	8.6±1.3	8.8±1.7	9.4±1.6	8.7±1.3	8.4±1.2	8.4±1.5
RBC ($\times 10^4$ cells/ μ l)	540±81	507±16	501±36	503±38	547±49	503±47	537±81	541±104
WBC ($\times 10^3$ cells/ μ l)	9.0±5.6	7.3±2.3	7.9±2.5	11.1±5.1	8.4±4.2	8.3±3.7	7.4±2.1	8.5±1.6
PP (g/dl)	8.6±0.6	8.3±0.7	8.2±0.7	8.3±0.5	8.3±0.5	8.2±0.7	8.2±0.5	8.2±0.4
AST (IU/l)	21.6±3.6	21.6±4.0	21.1±3.8	22.9±4.0	29.2±3.9 ^a	23.1±3.0	20.7±1.4	21.2±1.7
ALT (IU/l)	5.7±2.8	5.5±2.9	5.3±2.7	5.4±2.9	6.5±3.2	5.3±1.5	5.4±1.1	5.8±1.1
ALP (IU/l)	51.2±35.2	43.2±31.3	45.0±34.1	48.7±30.2	48.8±29.2	45.1±24.8	48.1±28.4	55.6±37.0
Glucose (mg/dl)	67.1±9.5	83.5±6.4	79.9±5.4	95.6±14.7 ^a	58.1±17.3	71.5±5.8	67.6±1.6	68.0±1.9
BUN (mg/dl)	14.0±0.9	12.3±1.1	12.5±1.5	12.4±1.0	12.0±1.9	11.5±2.0	13.9±0.9	15.1±2.8
Creatinine (mg/dl)	1.0±0.2	0.9±0.2	0.9±0.2	1.1±0.2	1.1±0.2	0.9±0.2	0.8±0.1	0.9±0.2
Sodium (mEq/l)	141±4.3	140±4.9	141±4.0	140±3.9	144±3.6	141±2.0	137±9.9	143±4.7
Potassium (mEq/l)	3.9±0.3	3.8±0.5	3.9±0.4	3.7±0.3	4.3±0.4	4.3±0.4	4.0±0.5	4.0±0.4
Chloride (mEq/l)	105±2.8	105±5.7	101±4.2	102±3.5	107±1.7	103±5.7	99±14.3	105±3.7

PCV=packed cell volume; Hb = hemoglobin; RBC = red blood cell; WBC = white blood cell; PP = plasma protein; AST = serum aspartate transaminase; ALT = alanine transaminase; ALP = alkaline phosphatase; and BUN = blood urea nitrogen. a) Significant difference from values before premedication ($p < 0.05$).

nance anesthesia. There were no significant changes in BEa at any time. The mean RT decreased slightly during anesthesia, but not significantly.

Table 2 shows the hematologic and serum biochemical findings. There were no significant changes in PCV, Hb, RBC, WBC, or PP values at any time after anesthesia. The mean AST increased slightly 1 day after discontinuation of anesthesia. The mean blood glucose increased significantly at 1 hr after discontinuation of anesthesia. The ALT, ALP, BUN, creatinine, sodium, potassium, and chloride ion values did not significantly change at any time after anesthesia.

The minimal alveolar concentration (MAC) of sevoflurane in cattle was not determined. However, the ratio of MAC values for any pair of halothane, enflurane, isoflurane, and sevoflurane has been reported to be constant with the species [4]. The MAC ratios of sevoflurane/halothane in humans, cats and dogs are 2.22 (1.71%/0.77%), 2.17 (2.58%/1.19%) and 2.71 (2.36%/0.87%), respectively [4]. In calves, the MAC of halothane is 0.83% [17]. The MAC of sevoflurane in cattle is expected to be approximately 1.8 to 2.2%. Therefore, the surgical anesthesia in the current study might have been maintained on approximately 1 MAC or concentrations less than 1 MAC of sevoflurane in adult cows given atropine-guaifenesin-thiopental.

The blood/gas partition coefficient for sevoflurane (0.69) in human blood has been shown to be much lower than that for halothane (2.3), enflurane (1.9) and isoflurane (1.4) [11, 18], indicating that anesthetic induction and recovery with sevoflurane would be expected to be more rapid than that with the other three inhalants. The current results showed that recovery from sevoflurane anesthesia was extremely rapid and smooth. Recovery times to head-up motion and standing posture in the

current study seemed to be shorter than those following halothane- or isoflurane-oxygen anesthesia in steers that were given guaifenesin-thiamylal [7].

Sevoflurane produces dose-dependent circulatory depression such as a decrease in AP, cardiac output, and systemic vascular resistance in dogs [1, 10]. The HR has been reported to be unchanged or slightly decreased with the increase in sevoflurane concentration in dogs [1, 10]. In the current study, the HR increased significantly during anesthesia. This may be the result of atropine premedication. In this respect, atropine premedication may not be necessary for sevoflurane anesthesia in cattle given guaifenesin-thiopental. However, abnormal ECG alterations were not observed, showing that cardiac rhythm is stable during sevoflurane anesthesia in cattle. On the other hand, the AP did not significantly change from values before premedication and MAP remained constant between the mean of 145 and 158 mmHg during anesthesia. However, all cows in this study were hypertensive before premedication and during sevoflurane anesthesia. Hypertension has been defined as SAP greater than 160 mmHg or DAP greater than 95 mmHg in humans [14]. In nonanesthetized-standing cows, higher carotid AP, which was measured with the transducer placed at heart level, has been reported when the animals were restrained or when people were in the immediate environment of the animal [5]. These factors might be responsible for the higher AP before premedication observed in the current study. Hypertension has also been shown in adult cattle anesthetized with guaifenesin-thiopental-halothane [15] or xylazine-halothane [13]. This hypertension was associated with a decrease in cardiac output and increase in HR and total vascular resistance [15]. Such higher AP has not been recorded in calves anesthetized with 1 to 1.5 MAC halothane alone [17] and thiopental-halothane [16], and in

yearling steers anesthetized with atropine-guaifenesin-thiamylal-halothane or-isoflurane [7]. The higher AP during sevoflurane anesthesia observed in the current study might have been characteristic for adult cattle.

Sevoflurane induces a dose-dependent respiratory depression in dogs [3]. The present findings showed that the RR did not significantly change during sevoflurane anesthesia, whereas the TV was lower than the normal value in adult Holstein cows [6] and the MV was low due to a decreased TV. The changes in blood gases and pH_a showed mild respiratory acidosis during sevoflurane anesthesia, and were similar to the values reported in adult cattle anesthetized with xylazine-halothane [13] and less than those seen in adult cattle anesthetized with guaifenesin-thiamylal-halothane at 1.5 MAC [2] or in steers anesthetized with guaifenesin-thiamylal-halothane or-isoflurane [7]. In the current study, the low oxygen flow rates (2 to 3 l/min) were used successfully during maintenance anesthesia by using a multi-gas monitor. If the monitoring of inspired oxygen in the anesthetic breathing circuit indicates a warning of the delivery of hypoxic gas mixtures to the animal, the oxygen flow rates should be increased to those that are greater than the minute oxygen consumption.

Sevoflurane is metabolized to hexafluoroisopropanol and inorganic fluoride in dogs [12]. Inorganic fluoride, which is a common metabolite of halogenated anesthetic agents, is known to be associated with nephrotoxicity. However, serum fluoride concentrations never exceeded the level inducing nephrotoxicity in dogs and rats anesthetized with 2–4% sevoflurane for 2–4 hr [12]. On the other hand, sevoflurane is unstable on exposure to soda lime and the decomposition of sevoflurane by soda lime produces some toxic products [20]. However, only a few % of sevoflurane has been reported to decompose in 3 hr [20]. Hepatic injury in rats with sevoflurane varies inversely with the oxygen concentration administered during anesthesia, and the extent of hepatic injury produced by sevoflurane does not differ from that produced by isoflurane both anesthetics being less toxic than halothane [19]. In the present study, no marked changes in serum AST, ALT, ALP, BUN, or creatinine values were observed for 7 days post-anesthesia, suggesting that hepatic and renal injuries are not induced following sevoflurane-oxygen anesthesia for 75 min in healthy adult cattle. Also, no significant changes in PCV, Hb, RBC, WBC, PP, serum sodium, potassium, or chloride ion values were observed, showing that these hematologic variables and serum electrolyte balance are maintained in good condition during and after sevoflurane anesthesia. Blood glucose values increased at 1 hr after anesthesia, which may be due mainly to the muscle activity and sympathetic stimulation caused by recovery from anesthesia.

Complications such as regurgitation, ruminal tympany and salivation occur frequently during halothane anesthe-

sia of cattle [21]. In the current study, 2 cows regurgitated a small amount (approximately 100 ml) of ruminal fluid during maintenance anesthesia. Severe tympany was not observed in all cows. The amount of salivation observed in this study was similar to that observed during halothane anesthesia of atropinized cattle reported previously [21].

The present findings suggest that sevoflurane is an effective inhalant anesthetic showing rapid recovery from anesthesia and minimal adverse effects except for hypertension in healthy adult cattle given atropine, guaifenesin and thiopental. However, this agent is relatively expensive.

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