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## Comparison of the arterial blood gas, arterial oxyhaemoglobin saturation and end-tidal carbon dioxide tension during sevoflurane or isoflurane anaesthesia in rabbits

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The effects of sevoflurane or isoflurane on arterial blood gas, arterial oxyhaemoglobin saturation and end-tidal CO<sub>2</sub> tension were monitored during induction and maintenance of anaesthesia in 10 premedicated New Zealand White (NZW) rabbits.

For induction, the anaesthetic agents were delivered via a face-mask. After induction was completed, an endotracheal tube was introduced for maintenance of anaesthesia for a period of 90 minutes. Changes in heart rate, respiratory rate, arterial blood gas, arterial oxyhaemoglobin saturation, blood pH and end-tidal CO<sub>2</sub> tension were recorded. Although sevoflurane and isoflurane produce similar cardiopulmonary effects in premedicated rabbits, sevoflurane provides a smoother and faster induction because of its lower blood/gas partition coefficient. Thus sevoflurane is probably a more suitable agent than isoflurane for mask induction and maintenance. Its lower blood solubility also makes sevoflurane more satisfactory than isoflurane for maintenance of anaesthesia because it allows the anaesthetist to change the depth of anaesthesia more rapidly.

Irish Veterinary Journal  
Volume 59 (5) 278-281 2006

**Keywords:** Rabbit, Anaesthesia, Inhalation, Sevoflurane, Isoflurane

### Introduction

Sevoflurane is a rapid-acting, inhaled anaesthetic used frequently in human beings and increasingly in animal patients in clinical practice. It has emerged as the most promising agent for inhalation induction in human patients (Smith *et al.*, 1992; Ebert *et al.*, 1998). Due to its low blood solubility (its blood/gas partition coefficient is 0.68), induction and emergence are rapid (Strum and Eger, 1987; Young and Apfelbaum, 1995; Ebert *et al.*, 1998; Flecknell *et al.*, 1999). Sevoflurane has a pleasant, non-pungent odour which permits a smooth and rapid induction by inhalation; it has made mask induction more attractive (Smith *et al.*, 1992; Ebert *et al.*, 1998).

Continuous monitoring of end-tidal CO<sub>2</sub> (ETCO<sub>2</sub>) tension and arterial oxyhaemoglobin saturation by pulse oximetry (SpO<sub>2</sub>) has been considered the minimal standard of care during anaesthesia. The technology to objectively and non-invasively assess gas exchange in anaesthetised animals has recently become readily available. Because of the potential problems associated with hypoventilation, it is important to closely monitor the ventilation status of animals during inhalation

anaesthesia by assessing PaCO<sub>2</sub> (Mutoh *et al.*, 1995). Capnography and pulse oximetry allow for continuous and non-invasive monitoring of ventilation and oxygenation, respectively, in anaesthetised animals (Grosenbaugh and Muir, 1998). Arterial blood gas analysis is an invasive monitoring procedure. However, analysis of carbon dioxide and oxygen in an arterial blood sample defines sufficiency of gaseous exchange.

The cardiovascular effects of sevoflurane appear to be comparable to those of isoflurane. However, the effects of this agent on blood gas, arterial oxyhaemoglobin saturation and end-tidal CO<sub>2</sub> tension in rabbits have not been well studied.

The purposes of this study were to determine the effects of sevoflurane on arterial blood gas, arterial oxyhaemoglobin saturation, end-tidal CO<sub>2</sub> tension and physiological parameters in rabbits and to compare these effects with those induced by isoflurane.

### Materials and methods

Twenty (10 male, 10 female) young New Zealand White rabbits, aged six to 12 months and weighing 4.2±0.6 kg (mean ± 1 SD) were obtained from a research centre for breeding test animals in Uludag University (Turkey) and were free from recognised respiratory pathogens (*Pasteurella* and *Bordetella* spp). The rabbits were floor-housed in groups, on dust-free shavings and autoclaved hay. They were fed a commercial pelleted diet (Ankara Feedstuff Industry, Turkey) and water *ad libitum*. No animal was used more than once.

All experiments were conducted in accordance with the Animal Research Ethics Committee at the Uludag University of Turkey.

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### Apparatus

A small plastic face-mask (Kruuse [Veterinary Equipment] Ltd, Marslev, Denmark) and a Jackson-Rees modification of the Ayre's T-piece were used for induction. Isoflurane was delivered from an Isoflurane A-3 vaporiser (Kimura Medical Co., Tokyo, Japan) and sevoflurane from a temperature and flow compensated vaporiser (Blease, Genuine Part, England). Both agents were delivered in 100% oxygen at 4L/minute. Electrodes were placed on the rabbit's skin, on the medial aspects of the upper forelegs and of the upper left hindleg, and the electrocardiogram was recorded by connecting the electrodes to an electronic monitoring apparatus (Burdick Medic-5, Burdick Inc., USA). Pulse oximetry ( $SpO_2$ ) readings and pulse rate were obtained with a pulse oximeter (Vet/OXTM 4403, SDI, USA) with the probe placed on the tongue. End-tidal  $CO_2$  ( $ETCO_2$ ) tension and respiratory rate were monitored continuously with a sidestream-sampling capnograph (Normocap 200, Datex-Ohmeda). During the induction period, the sampling adapter (AMS  $CO_2$  absorber for veterinary purpose, AMS Company, Ankara, Turkey) was connected between the face-mask and the Jackson-Rees modification of the Ayre's T-piece. During the maintenance period, the sampling adapter was connected between the endotracheal tube and the Jackson-Rees modification of the Ayre's T-piece in a similar manner. A catheter (22g, IV cannula, Transplastics, Germany) was inserted into the ear artery for blood gas analysis. Arterial blood samples were collected in heparinised capillary tubes, and blood pH,  $PaO_2$  and  $PaCO_2$  were measured by blood gas analyser (RapidLab 248, Chiron Diagnostic Ltd, Halstead, Essex, UK). Lactated Ringer's solution (10 ml/kg per hour) was administered into the other ear vein.

### Experimental protocol

The animals were prepared as described above. After a five to 10 minute period, baseline measurements were recorded. Xylazine (3mg/kg: Rompun®, Bayer, Turkey) was injected intramuscularly, for premedication. The animals were restrained manually by gently positioning the operator's arms on either side of the animal's body. After placement of the face-mask, 100% oxygen was provided for two to three minutes at a fresh gas flow rate of 4L/minute. Any struggling was noted by an observer, and this was used to assess the quality of induction. After this initial period, sevoflurane (Sevorane®, Abbott, UK) at a vaporiser setting of 6%, or isoflurane (Forane®, Abbott, UK) at a vaporiser setting of 4%, was delivered in the oxygen stream in a similar manner. The anaesthetic gas concentration was maintained at this level until induction was completed. When induction was complete, an endotracheal tube was inserted using a premature baby laryngoscope and the non-rebreathing system was attached to it. The anaesthetic vaporiser was then turned to a setting of 3% (sevoflurane) or 2% (isoflurane) for maintenance of anaesthesia for a 90 minute period.

Cardiopulmonary responses (heart rate, respiratory rate, rectal temperature, arterial oxyhaemoglobin saturation and end-tidal  $CO_2$  tension) and blood gas values were recorded every 15 minutes from the time of induction to the beginning of recovery. After anaesthesia, all rabbits were extubated and observed in the post-anaesthesia care unit for a further hour.

### Data analysis

All data were expressed as mean  $\pm$  1 SD. The cardiopulmonary variables and values for time to event were compared between groups using one-way analysis of variance (ANOVA) for repeated measures. If statistically significant effects were found, Tukey's *post hoc* test was applied to the differences between groups. The changes within each anaesthetic group were compared using one-way ANOVA for repeated measures, followed by Tukey's *post hoc* test when appropriate. Values of  $P < 0.05$  were considered statistically significant.

### Results

Cardiopulmonary data recorded during mask induction and maintenance of anaesthesia with sevoflurane and isoflurane are summarised in **Table 1**. Pre-induction values for each variable in conscious and premedicated animals were not significantly different between the sevoflurane group and the isoflurane group. Intramuscular administration of xylazine induced moderate sedation in both groups. Placement of the face-mask and administration of oxygen did not cause any change in respiratory rate. Exposure to sevoflurane caused very little aversion and relatively few bouts of struggling behaviour. In contrast, isoflurane induced excessive struggling in all animals, necessitating very firm restraint, in spite of sedation.

Times to loss of the palpebral reflex and to successful tracheal intubation were significantly shorter with sevoflurane (126 seconds  $\pm$  36) than with isoflurane (150 seconds  $\pm$  31). None of the rabbits given sevoflurane had episodes of induction-related complications (struggling, ataxia or excitement).

Cardiopulmonary effects of sevoflurane and isoflurane, during the induction and maintenance periods, were similar with the exception of a slightly decreased heart rate in the sevoflurane group. The heart rate values during anaesthesia with isoflurane were slightly higher than pre-induction rates, although they were still within the physiological reference range.

A decrease in respiratory rate compared with the pre-induction rate was observed during induction and maintenance with both agents. An associated respiratory acidosis, characterised by an increase in  $PaCO_2$ , was observed in both groups. The respiratory depressant effects, characterised by increased  $PaCO_2$  and decreased blood pH values, were associated with decreases in respiratory rate. Arterial  $PaCO_2$  rose from 30.5mmHg ( $\pm$  7.0) to a peak of 50.6mmHg ( $\pm$  10.2) in the sevoflurane group and from 33.6mmHg ( $\pm$  5.4) to a peak of 51.5mmHg ( $\pm$  11.7) in the isoflurane group. Blood pH values were normal in all animals prior to induction and fell to  $7.25 \pm 0.11$  during sevoflurane anaesthesia and to  $7.16 \pm 0.09$  during isoflurane anaesthesia. These changes were significant ( $P < 0.05$ ). Time to recovery of righting reflex also differed significantly between treatment groups: 219 seconds ( $\pm$  103) in the sevoflurane group versus 615 seconds ( $\pm$  326) in the isoflurane group. The recovery was smooth and uneventful in all rabbits.

### Discussion

This study was designed to monitor arterial blood gas, arterial oxyhaemoglobin saturation and end-tidal  $CO_2$  tension in rabbits during mask induction and maintenance of anaesthesia with sevoflurane and isoflurane. The adverse effects of halogenated volatile anaesthetics associated with mask induction, as experienced clinically

Table 1.

Cardiorespiratory parameters (heart rate, respiratory rate, arterial oxyhaemoglobin saturation and end-tidal CO<sub>2</sub>), blood gas values and rectal temperatures of rabbits anaesthetised with sevoflurane (SEVO) and isoflurane (ISO).

		B	I	15	30	45	60	75	90
HR (beats/min)	ISO	218±70	188±43 <sup>ab</sup>	200±31 <sup>ab</sup>	209±25 <sup>b</sup>	201±14 <sup>ab</sup>	196±23 <sup>ab</sup>	209±31 <sup>b</sup>	198±39 <sup>ab</sup>
	SEVO	234±58	54±27 <sup>a</sup>	233±35	244±39	240±42	255±41 <sup>a</sup>	260±42 <sup>a</sup>	266±29 <sup>a</sup>
RR (beats/min)	SEVO	100±30	38±7 <sup>ab</sup>	37±8 <sup>a</sup>	36±5 <sup>a</sup>	34±5 <sup>a</sup>	36±11 <sup>a</sup>	35±9 <sup>a</sup>	34±9 <sup>a</sup>
	ISO	78±24	43±13 <sup>a</sup>	36±12 <sup>a</sup>	34±10 <sup>a</sup>	37±10 <sup>a</sup>	34±10 <sup>a</sup>	32±7 <sup>a</sup>	35±5 <sup>a</sup>
SpO <sub>2</sub> (%)	SEVO	91±5	91±4	91±4	90±4	94±2	94±2	92±4	89±6
	ISO	94±3	94±4	90±4	91±5	93±4	93±3	94±4	94±3
ETCO <sub>2</sub> (mmHg)	SEVO	ND	32±9	36±6	37±6	35±7	36±4	36±6	37±5
	ISO	ND	28±10	29±8	30±6	30±5	33±7	34±7	32±8
pH	SEVO	7.40±0.04	7.25±0.11 <sup>a</sup>	7.32±0.06	7.39±0.08	7.41±0.04	7.38±0.05	7.41±0.05	7.39±0.05
	ISO	7.38±0.05	7.16±0.09 <sup>a</sup>	7.34±0.08	7.40±0.06	7.41±0.04	7.41±0.05	7.41±0.05	7.42±0.05
PaCO <sub>2</sub> (mmHg)	SEVO	30.5±7.0	48.1±11.5 <sup>a</sup>	46.1±6.9 <sup>a</sup>	45.5±9.7 <sup>a</sup>	43.3±9.0 <sup>a</sup>	48.3±8.6 <sup>a</sup>	48.7±8.8 <sup>a</sup>	50.6±10.2 <sup>a</sup>
	ISO	33.6±5.4	56.0±9.6 <sup>a</sup>	52.1±9.7 <sup>a</sup>	47.1±8.6 <sup>a</sup>	8.9±9.2 <sup>a</sup>	51.3±10.0 <sup>a</sup>	52.3±7.2 <sup>a</sup>	51.5±11.7 <sup>a</sup>
PaO <sub>2</sub> (mmHg)	SEVO	67.70±21.37	248.16±177.47 <sup>a</sup>	227.53±181.16 <sup>a</sup>	397.88±166.10 <sup>a</sup>	306.52±172.38 <sup>a</sup>	308.60±107.28 <sup>a</sup>	361.28±137.38 <sup>a</sup>	344.25±126.63 <sup>a</sup>
	ISO	72.89±13.37	240.58±191.60 <sup>a</sup>	302.71±173.45 <sup>a</sup>	300.78±137.90 <sup>a</sup>	295.11±139.80 <sup>a</sup>	317.45±131.76 <sup>a</sup>	370.55±164.92 <sup>a</sup>	373.39±114.11 <sup>a</sup>
RT (°C)	SEVO	39.02±0.35	38.70±0.46	38.42±0.76	38.17±0.94	37.80±1.11	37.50±1.23	37.28±1.35	37.05±1.45
	ISO	38.52±0.68	39.20±0.57	39.09±0.59	38.74±0.70	38.27±0.88	38.00±0.92	37.67±0.95	37.45±1.13

Data are expressed as mean ± 1SD.

**B:** basal values; **I:** induction values; **15, 30, 45, 60, 75, 90:** stage of anaesthesia (expressed in minutes); **HR:** heart rate; **RR:** respiration rate; **SpO<sub>2</sub> (%):** arterial oxyhaemoglobin saturation;

**ETCO<sub>2</sub> (mmHg):** end-tidal CO<sub>2</sub>; **RT (°C):** rectal temperature; **ND:** not done.

Arterial blood gas values: PaCO<sub>2</sub> (mmHg), PaO<sub>2</sub> (mmHg) and pH.

<sup>a</sup>Significantly different from baseline value (P < 0.05); <sup>b</sup>Significantly different from ISO group (P < 0.05).

in animals, are characterised by apnoea, breath-holding, laryngospasm, bronchoconstriction or body movements (Mitsuhata *et al.*, 1994; Mutoh *et al.*, 2001a,b). Some of these induction-related complications (e.g., struggling) also accompany mask induction in rabbits (Flecknell *et al.*, 1995, 1999) and dogs (Mutoh *et al.*, 1995). In this experiment, induction-related complications induced by isoflurane necessitated very firm restraint in spite of sedation whereas these complications were not evident when sevoflurane was used. This was unlike the study reported by Flecknell *et al.* (1999). However, none of their rabbits were premedicated.

The protocol followed for face-mask induction was identical to that used in the study by Flecknell *et al.* (1999), which had been derived from standard veterinary anaesthetic induction and maintenance

methodology. Because of the occurrence of periods of apnoea in the study by Flecknell *et al.* (1999), inhalation of a gradually rising concentration of anaesthetic was not used here. It was thought that a technique that gives a rapid increase in the concentration of the inhaled agent during mask induction may be more appropriate than a technique that delivers a slowly increasing concentration of the agent. By rapid mask induction, it was possible to avoid long induction periods and violent struggling efforts. Surgical anaesthesia was reached faster with sevoflurane than with isoflurane because of the lower blood/gas partition coefficient.

In this study, xylazine was selected for premedication because it produced light to moderate sedation with small changes in cardiopulmonary functions in rabbits. It was clearly demonstrated that

the use of xylazine improved the speed and quality of mask induction with sevoflurane. This procedure did not appear to distress the rabbits in the sevoflurane group but, as in previous studies (Flecknell *et al.*, 1995, 1999; Hedenqvist *et al.*, 2001), there was considerable evidence that rabbits resent mask induction with isoflurane, as expressed by violent struggling and pawing at their faces to remove the face-mask. Monitoring is essential during anaesthesia. In rabbits, as with other animals, it is possible to use invasive and non-invasive procedures (Mutoh *et al.*, 1995; Grosenbaugh and Muir, 1998). Non-invasive techniques include capnography, pulse oximetry, assessment of heart rate, respiratory rate and rectal temperature. The invasive techniques of blood arterial gas analysis were applied in this study.

Both inhalants had similar cardiopulmonary effects during the induction and the maintenance periods, with the exception of a decreased heart rate in the sevoflurane group. The heart rate values during anaesthesia with isoflurane were higher than preinduction rates, although they were still within the physiological reference range for maintenance under isoflurane anaesthesia. The difference in heart rates between two groups may have been related to more stress in rabbits anaesthetised with isoflurane because it is more irritating than sevoflurane (Mutoh *et al.*, 1995; Flecknell *et al.*, 1999; Hedenqvist *et al.*, 2001). Okamoto *et al.* (1996) reported that inhalation of 1% to 4% isoflurane in anaesthetised rabbits has been shown to increase heart rate as a result of direct sympathetic stimulation, in addition to stimulation of the baroreflex elicited by a decrease in arterial blood pressure.

All volatile anaesthetic agents have been reported to cause a dose-related respiratory depression in rabbits (Flecknell *et al.*, 1995, 1996, 1999; Okamoto *et al.*, 1996; Hedenqvist *et al.*, 2001). In this study, decreased respiratory rates, which were reflected in higher end-tidal CO<sub>2</sub> tensions, were recorded in both anaesthetic groups. The mild respiratory depression was qualitatively similar to those of previous studies in anaesthetised rabbits (Flecknell *et al.*, 1999; Hedenqvist *et al.*, 2001). It is possible that slowing of breathing during induction and maintenance of anaesthesia is caused by both respiratory reflexes and anaesthetic effects of the inhalants.

As in previous studies (Flecknell *et al.*, 1999; Hedenqvist *et al.*, 2001), respiratory depression due to volatile anaesthetic agents produced elevations of arterial PaCO<sub>2</sub> and end-tidal CO<sub>2</sub> tension. However, reduction in arterial PaO<sub>2</sub> and hypoxaemia did not occur. Arterial oxyhaemoglobin saturation was constant during the anaesthetic period with both agents predictable because of the high inspired oxygen fraction.

In conclusion, both sevoflurane and isoflurane produced similar cardiopulmonary effects in premedicated rabbits. However, sevoflurane was considered a more suitable agent for mask induction since it provided a smoother and more rapid induction, due to its lower blood/gas partition coefficient. Its lower blood solubility also makes sevoflurane more desirable for maintenance of anaesthesia than isoflurane because of the facility to change the depth of anaesthesia more rapidly and to hasten recovery.

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