FULL PAPER *Surgery*

Performance of a new carbon dioxide absorbent, Yabashi lime® as compared to conventional carbon dioxide absorbent during sevoflurane anesthesia in dogs

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ABSTRACT. In the present study, we compare a new carbon dioxide (CO_2) absorbent, Yabashi lime® with a conventional CO_2 absorbent, Sodasorb® as a control CO_2 absorbent for Compound A (CA) and Carbon monoxide (CO) productions. Four dogs were anesthetized with sevoflurane. Each dog was anesthetized with four preparations, Yabashi lime® with high or low-flow rate of oxygen and control CO_2 absorbent with high or low-flow rate. CA and CO concentrations in the anesthetic circuit, canister temperature and carbooxyhemoglobin (COHb) concentration in the blood were measured. Yabashi lime® did not produce CA. Control CO_2 absorbent generated CA, and its concentration was significantly higher in low-flow rate than a high-flow rate. CO was generated only in low-flow rate groups, but there was no significance between Yabashi lime® groups and control CO_2 absorbent groups. However, the CO concentration in the circuit could not be detected (≤5ppm), and no change was found in COHb level. Canister temperature was significantly higher in low-flow rate groups than high-flow rate groups. Furthermore, in low-flow rate groups, the lower layer of canister temperature in control CO_2 absorbent group was significantly higher than Yabashi lime® group. CA and CO productions are thought to be related to the composition of CO_2 absorbent, flow rate and canister temperature. Though CO concentration is equal, it might be safer to use Yabashi lime® with sevoflurane anesthesia in dogs than conventional CO_2 absorbent at the point of CA production.

KEY WORDS: canine, compound A, sevoflurane, Yabashi lime®

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Sevoflurane is the most unstable modern volatile anesthetic molecule, which can be degraded in dry carbon dioxide (CO_2) absorbent to compound A (CA) (Fluoro-methyl1-2, 2-difluoro-1-(trifluolimethyl)) [19]. CA has been proven to be nephrotoxic in rats after exposures that have varied in duration from 1 to 3 hr [8, 11, 16] and could create a transient dysfunction in the human nephron [27]. In addition, the possibility of hepatic lesion has been suggested [17, 27]. It is preferable that a CO_2 absorbent with less reactivity to sevoflurane is used for clinical purpose.

Carbon monoxide (CO) is also produced from sevoflurane in combination with CO_2 absorbent [6, 10, 12]. CO production from volatile anesthetic degradation has a safety issue that has necessitated changes in clinical practice and product labeling. Severe CO poisoning resulting from intraoperative volatile anesthetics degradation has been reported [5], with neurologic injury and carbooxyhemoglobin (COHb) concentrations approaching toxic levels.

Following factors may lead to increased CA and CO concentrations during sevoflurane anesthesia; CO_2 absorbent containing strong alkali like NaOH or KOH [7, 14, 21, 24, 25], low fresh gas flow rate [3, 4] and high temperature of the canister [6, 7, 22]. Yabashi lime® (Yabashi product, Gifu, Japan) is recently introduced as CO_2 absorbent and does not contain NaOH or KOH. However, no clinical study has measured the production of CA and CO in a circuit with Yabashi lime® during sevoflurane anesthesia in dogs. The aim of this study is to prove the hypothesis that Yabashi lime® without KOH and NaOH does not increase the concentration of CA and CO and not raise HbCO, compared with a conventional CO_2 absorbent Sodasorb® (Grace, Epernon, France) in sevoflurane anesthetized dogs. And, because the production of CA and CO was related to canister temperature and fresh gas flow rate, we measured the canister temperature and concentration of CA and CO under low or high fresh gas flow rate.

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MATERIALS AND METHODS

Animal model: Four healthy adult dogs (3 females and 1 male beagle), weighing 10–13 kg, were used. Four anesthetic protocols were repeated in each animal with at least one week interval; Yabashi lime® with high-flow rate of oxygen (Group I), Sodasorb® as control CO_2 absorbent with high-flow rate of oxygen (Group II), Yabashi lime® with low-flow rate of oxygen (Group III) and control CO_2 absorbent with low-flow rate of oxygen (Group IV) (Table1). These dogs were treated in accordance with the guideline approved by the Animal Use Committee of Gifu University.

Experimental set-up: Forty-five min before inhalation anesthesia, all dogs were premedicated with atropine 0.04 mg/kg (i.v.). Fifteen min after the premedication, 0.2 mg/kg of butorphanol and 150 μg/kg of midazolam were injected (i.v.) for sedation. General anesthesia was induced by 7 mg/kg of propofol (i.v.). We used semi-closed circle anesthetic apparatus (Compact 15; KIMURA medical instrument CO., LTD., Tokyo, Japan) with a vaporizer (PPVΣ, Penlon, Oxford, U.K.) throughout the study. Immediately before induction of anesthesia, 1 kg of fresh absorbent was placed in the anesthetic canister. The absorbent was discarded after each case. After tracheal intubation, the animals were positioned in left recumbency and administered 100% oxygen at a flow rate of 3 *l*/min (Groups I and II) or 0.5 *l*/min (Groups III and IV) with 3 mg/kg/hr continuous infusion of propofol for induction of sevoflurane until starting of inhalation anesthesia. Before induction of inhalation anesthesia, 24 G catheter was inserted into a femoral artery, and 1.5 m*l* of arterial blood sample was collected. Gas samples for measurment of CA and CO, and arterial blood samples were collected just before starting of inhalation anesthesia and thereafter 1, 2 and 3 hr, and temperature of the canister was recorded just before starting of inhalation and thereafter every 10 min. After every setting and sampling were finished, the dogs were subjected to inhalation anesthesia and were maintained with 3.0–3.5% sevoflurane concentration according to the individual status and were breathing spontaneously. The anesthesia was continued with sevoflurane for 3 hr. Heart rate (HR), respiratory rate (RR), inspired CO_2 (CO_2), end tidal CO_2 ($ETCO_2$), sevoflurane concentrations, blood pressure, body temperature of animals and oxygen saturation (SpO_2) were monitored continuously as usually every 10 min throughout the experiment (BIO-SCOPE AM120, FUKUDA ME, Tokyo, Japan). In addition, arterial oxygen partial pressure (PaO_2) and arterial carbon dioxide partial pressure ($PaCO_2$) were measured every 1 hr throughout the experiment (i-stat, Fuso Pharmaceutical Industries, Osaka, Japan). The experiments were performed all procedures at room temperature of 25°C.

CA measurement: Sample gas for CA measurement was collected from the inspiratory limb of the circuit just before starting of sevoflurane anesthesia and every hr thereafter. A glass syringe (100 m*l*) was used for sampling, and a silicon grease (Non-absorbing Grease to Hydro Carbons, GL Sciences, Tokyo, Japan) was used to ensure an airtight seal. Immediately, 100 m*l* of the gas was transferred to a bottle that was kept under pressure −80 ± MPa. The sample bottles were stored in the icebox, and the samples were analyzed within a week. The concentrations of CA were measured by employing a gas chromatograph (model GC-7AG; Shimazu, Kyoto, Japan) [4]. The gas chromatograph column was 5 m in length and 3.0 mm in internal diameter, and it was filled with 20% dioctyl phthalate and Chromsorb WAW (GL Sciences) with 80/100 mesh. The injection temperature was 130°C, and the column temperature was 110°C. The carrier gas was nitrogen, and the carrier gas flow rate was 42 m*l*/min. The gas chromatograph was calibrated with standard calibration gas prepared from stock solutions of CA (Maruishi Pharmaceutical Co., Ltd., Osaka, Japan) [4].

Table 1. Animal grouping (n=4)

	High flow late (3 *l*/min)	Low flow rate (0.5 *l*/min)
Yabashi lime®	Group I	Group III
Control lime (Sodasorb®)	Group II	Group IV

CO measurement: For CO measurement, 100 m*l* of gas sample was aspirated from the inspiratory limb of the circuit to a CO detector tube (1LC, GASTEC, Ayase, Japan). The changing color was developed over 4 min. CO concentration was measured just before starting anesthesia and every hr thereafter.

HbCO measurment: 1.5 m*l* of arterial blood was collected from the catheter just before beginning of inhalation anesthesia and every hr thereafter. HbCO concentration was examined by using CO-oximeter (OML3; Radiometer, Copenhagen, Denmark).

Measurement of canister temperature: The carbon dioxide absorbent container of the circuit system was equipped with temperature probes in the upper and lower layers of the container, as described in the previous study [15]. Temperature data were continuously recorded every 10 min.

Statistical analysis: Results are presented by means and SD. All measurements, including CA, CO and HbCO concentrations, and increased temperature of the canister were compared by repeated-measures ANOVA. Significance was assigned at $P<0.05$.

RESULTS

No significant differences were found between the four groups of consecutive monitoring of HR, RR, inspired CO_2, $ETCO_2$, sevoflurane concentrations, blood pressure, body temperature of animals, SpO_2, PaO_2 and $PaCO_2$.

CA measurement: Yabashi lime® was totally lacking CA production throughout the experiment. CA production was significantly higher in control CO_2 absorbent groups (Groups II and IV) ($P<0.05$) at each measurment point (Fig. 1). Moreover, CA production was significantly higher in low-flow rate (Group IV) than in high-flow rate (Group II) in control CO_2 absorbent groups.

CO measurement: There were significant differences of CO production between high-flow rate groups (Groups

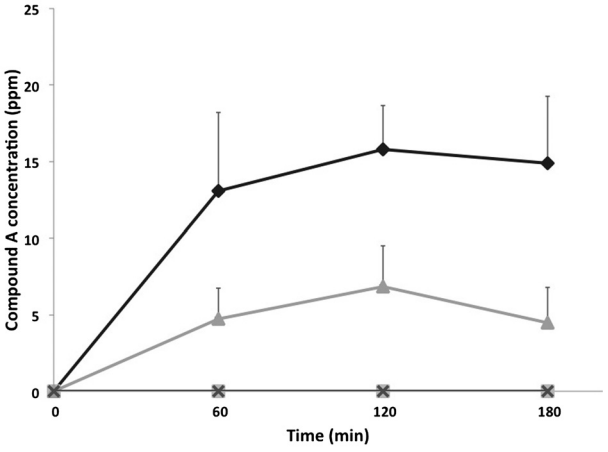

Fig. 1. Comparison of compound A (CA) concentrations in an anesthesia circuit after Sevoflurane with Yabashi lime® and Sodasorb®. × Group I, ▲ Group II, ■ Group III and ◆ Group IV. There are significant differences between Group IV vs Groups I, II, III and Group II vs Groups I, II at each measurement point (repeated-analysis of variance $P<0.05$). Values are means ± SD (n=4).

I and II) and low-flow rate groups (Groups III and IV) at each measurment point ($P<0.05$) (Fig. 2). High-flow rate groups (Groups I and II) were totally lacking CO production throughout the experiment. CO production was significantly affected by flow rate, but was not affected by the type of absorbent.

HbCO measurment: No significant differences were found between the four groups in consecutive monitoring of the HbCO (Fig. 3).

Measurement of canister temperature: In the upper layer of canister temperature, it isn't shown remarkable changes in the temperature. However, in the lower layer of canister temperature, there were significant differences between high-flow rate groups (Groups I and II) and low-flow rate groups (Groups III and IV) ($P<0.05$). In addition, between low-flow rate groups (Groups III and IV), there was a significantly higher temperature in control CO_2 absorbent than Yabashi lime® ($P<0.05$) (Fig. 4).

DISCUSSION

The main finding of our study is that CA was not detected with Yabashi lime® by using semi-closed circle anesthetic apparatus even with low-flow rate (Group III) sevoflurane. On the other hand, CA was produced by Sodasorb®. CA is formed by the elimination of hydrogen fluoride from sevoflurane, which is initiated by proton abstraction [9]. The presence of strong bases, such as NaOH and KOH, in the CO_2 absorbent may be a factor in the dehalogenation of sevoflurane to CA [25]. Sodasorb® is mainly made of $Ca(OH)_2$, but contains a small amount of KOH and NaOH. On the other hand, Yabashi lime® mostly consists of $Ca(OH)_2$ and does not contain any NaOH and KOH. Yabashi lime® therefore does not generate CA (Table 2). Other researchers also sug-

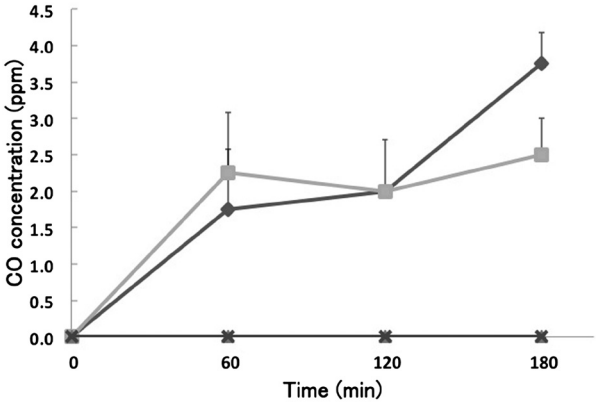

Fig. 2. Comparison of carbon monoxide (CO) concentrations in an anesthesia circuit after Sevoflurane with Yabashi lime® and Sodasorb®. × Group I, ▲ Group II, ■ Group III and ◆ Group IV. There are significant differences between Group IV vs Groups I, II and Group III vs Groups I, II at each measurement point (repeated-analysis of variance $P<0.05$). Values are means ± SD (n=4).

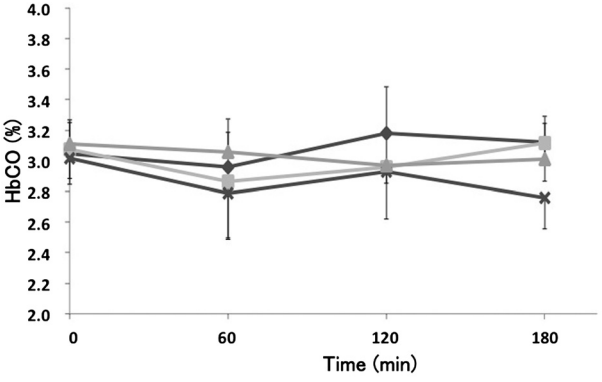

Fig. 3. Carboxyhemoglobin (HbCO) concentrations in the arterial blood. × Group I, ▲ Group II, ■ Group III and ◆ Group IV. No significant differences were found between the four groups of consecutive monitoring of the COHb (repeated-analysis of variance $P>0.05$). Values are mean ± SD (n=4).

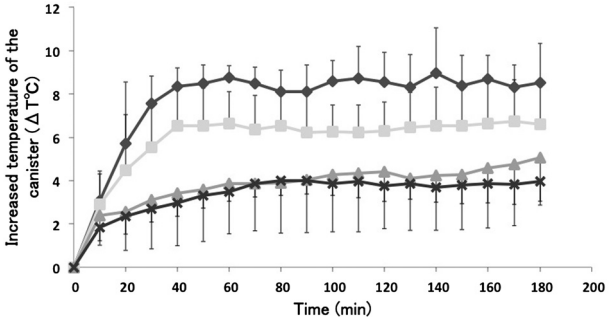

Fig. 4. Increased temperature in the lower layer of the canister. × Group I, ▲ Group II, ■ Group III and ◆ Group IV. There were significant differences between Group IV vs Groups I, II, III and Group III vs Groups I, II on 20 min later after the start of the experiment. Values are means ± SD (n=4).

Table 2. Chemical composition of the carbon dioxide (CO_2) absorbents* (weight%)

CO_2 absorbent	$Ca(OH)_2$	KOH	NaOH	H_2O
Sodasorb®	89	3	2.68	12–19
Yabashi lime®	84	–	–	16

*Values were provided by the respective manufacturers. Sodasorb® (Grace, Epemon, France), Yabashi lime® (Yabashi product, Gifu, Japan). $Ca(OH)_2$=calcium hydroxide, KOH=potassium hydroxide, NaOH=sodium hydroxide.

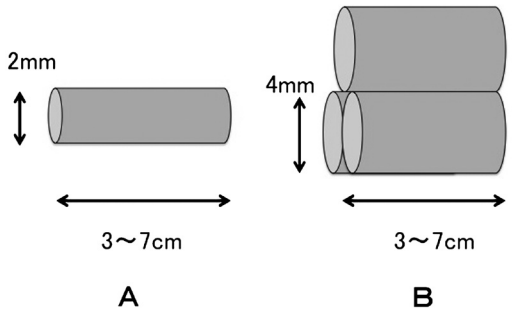

Fig. 5. The illustration shape of control CO_2 absorbent (Sodasorb®) (A) and Yabashi lime® (B). The shape of Sodasorb® is single cylinder. On the contrary, the shape of Yabashi lime® is triplet cylinder. Adhesion areas between units in the canister are smaller in Yabashi lime® than Sodasorb®, so the surface area of Yabashi lime® in the canister is larger than Sodasorb®.

gested that the presence of strong bases, such as NaOH and KOH, may accelerate CA production [21, 24–26].

In addition, there is a positive correlation between the increased canister temperature and CA generation [25]. In the present study, the lower layer of canister temperature with low-flow rate of oxygen was significantly lower in Yabashi lime® (Group III) than control CO_2 absorbent (Group IV). Better CO_2 absorbent shape is less prone to channeling, which is inequality of the air flow [13, 20]. This might be related to Yabashi lime® pellet original shape which makes lower density in the canister, and larger surface area than Sodasorb® as control CO_2 absorbent in this study (Fig. 5) [26]. It may be easy to discharge heat of canister for its peculiar shape. When we used control CO_2 absorbent with low-flow rate of oxygen (Group IV), increased temperature of the lower layer of the canister and concentration of CA is higher than other groups. However, there were no remarkable changes in the upper layer of the canister construction of anesthesia apparatus. It may be because of aspirated air from the animal flow bottom to top, and it touches with a lower layer of the absorbent in first in anesthetic circuit that we used in this experiment. Therefore, the more CO_2 molecule is absorbed by the lower layer of the absorbent than the upper. Furthermore, when we used high-flow rate of oxygen (Groups I and II), there were no differences even between groups of the lower layer of the canister. We suggest that in the case of high-flow rate of oxygen, the accumulated CO_2 molecules are diluted or exhausted as excess gas by carrier gas, so concentrations of CO_2 in the circuit are declined [23]. Similar reason is thought for CA and may be the major reason why CA concentration with low-flow rate of oxygen in using control CO_2 absorbent (Group IV) is higher than high-flow rate of oxygen (Group II).

CO is produced by the reaction between CO_2 absorbent and the inhaled anesthetic [14]. Factors accelerating CO generation are similar to those that accelerate CA generation [13, 14]. We found that the CO concentration in the circuit is not affected by the component of absorbent, but by the flow rate. However, no differences were found in COHb between any groups of this experiment. As we mentioned above, CO molecules may also be diluted or exhausted as excess gas by carrier gas like CO_2 or CA with high-flow rate of oxygen [22]. In other words, CO molecules are likely to accumulate with a low-flow rate of oxygen, so CO concentration is increased. In addition, it may be related to the increased temperature of the canister and CO concentration. In this study, we found that CO concentration and increased temperature of the canister were significantly higher in use of a low-flow rate of oxygen than a high-flow rate. Other researchers suggest that CO production increases in high temperature of the canister [6]. There were no obvious findings that Yabashi lime® is superior to control CO_2 absorbent in the point of CO concentration. However, concentrations of CO in 4 groups were extremely low and not up to the level that affects HbCO level.

In the present study, CA and CO were diluted or exhausted as excess gas by carrier gas, because we used semi-closed circuit. CO concentrations are not up to affecting HbCO levels in any groups. However, it is said that sevoflurane generates less CO than isoflurane and desflurane [1, 6]. It is possible that CO concentrations are up to higher levels and affect the HbCO level by using isoflurane and desflurane. We need more studies by using other anesthetic circuits or other inhalation anesthetics.

The toxicity of CA remains controversial. Data from animal and human studies regarding the safety of CA during low-flow sevoflurane anesthesia are insufficient to prove safety [13]. Therefore, the application of absorbents that minimally or not degrade sevoflurane to CA would eliminate any potential hazard from this toxic compound [2]. Our results suggest that Yabashi lime® is safer than conventional CO_2 absorbent in the point of not generating CA. More studies about the safety of CO_2 absorbent products in dogs undergoing sevoflurane anesthesia are needed.

A limitation of this study was 3 hr setting experiment for measuring of CA generation after sevoflurane anesthesia. In other studies, the experimental setting for measuring CA production was 4 or 5 hr after sevoflurane anesthesia [9, 14]. In fact, the practical cases are forced for prolonged periods of anesthesia. Moreover, the toxicity of CA is defined by the product concentration and time [18]. Therefore, further studies should examine the CA production after a prolonged period of anesthesia.

In conclusion, though the CO concentration is equal, it is safer to use Yabashi lime® with semi-closed anesthetic circuit and sevoflurane than conventional CO_2 absorbent that

contains strong alkali like NaOH or KOH in the point of CA concentration.

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