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Biodegradation of Isoflurane in Dogs

Takayuki SAKAI, Nobuo MATSUMOTO, Hitoshi YOSHIDA and Masuhiko TAKAORI

Department of Anesthesiology,
Kawasaki Medical School, Kurashiki 701-01, Japan

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ABSTRACT. The uptake, elimination and biodegradation of isoflurane were studied in 12 mongrel dogs. The amount of isoflurane taken up by the body during three hours of either 1.5% or 0.5% isoflurane anesthesia was measured and the subsequent elimination of isoflurane in the expired gas was measured for five hours. The excess urinary excretion of fluoride were measured during 72 postanesthetic hours. It was revealed that 94.3% of the isoflurane taken up by the body was exhaled in an unaltered form after isoflurane anesthesia. No excess urinary excretion of fluoride was detected at either of the inspired concentrations of isoflurane for the 72 hour period after isoflurane anesthesia.

Key words : biodegradation — isoflurane — inorganic fluoride

Isoflurane is the most stable of all the volatile anesthetic agents in clinical use. The biodegradation rate of isoflurane in man has been estimated as below 0.2%.[1] The major degradated product of isoflurane excreted in urine is non-ionic fluoride in man and ionic fluoride in Fischer 344 rats.[2] This is due to species differences. However, neither qualitative nor quantitative studies of the biodegradation of isoflurane in dogs have been reported. This study was carried out to investigate not only the uptake, elimination and biodegradation of isoflurane in dogs but also to determine the influence of different inspired concentrations of isoflurane.

MATERIALS AND METHODS

Twelve mongrel dogs weighing 12.1±1.7 kg (11.9±2.1 kg in H group and 12.4±1.1 kg in L group) were anesthetized with 25 mg/kg of pentobarbital sodium intravenously. After a lower median laparotomy, a balloon catheter (14 Fr, JMS®) was inserted into the urinary bladder for continuous collection of urine and then the abdominal cavity was closed. Polyethylene catheters (8 Fr, length 105 cm) were inserted into the carotid artery and into the right atrium via the jugular vein for blood sampling. These catheters were filled with heparinized saline to prevent coagulation and the animals were plastered to protect the catheters.

Three days later the dogs were anesthetized again with pentobarbital sodium and their tracheas were intubated with a cuffed endotracheal tube. Ventilation was maintained by a piston type non-rebreathing respirator. The tidal volume and respiratory rate were fixed at 15 ml/kg, and 12/min,

酒井資之，松本信夫，吉田　仁，高折益彦

respectively. The inspiratory gas was 40% oxygen balanced with nitrogen. The animals were divided randomly into two groups. Seven (H group) inspired 1.5% isoflurane for three hours, while the other five (L group) inspired 0.5% isoflurane for the same length of time. All the expired gas was collected into resin bags for up to five hours after the end of anesthesia. 20 ml of the inspired gas was sampled every 30 minutes during anesthesia. Arterial blood was collected every 30 minutes during anesthesia in order to measure the concentration of isoflurane. Venous blood was collected for the measurement of the serum inorganic fluoride level before anesthesia and at 3, 5, 8 hours and seven days after anesthesia.

The concentration of isoflurane in the inspired and expired gas was measured by gas chromatography using a Yanaco®, G-180 equipped with an FID and a 200 cm long stainless column packed with Silicon DC-550. Helium was used as the carrier gas, and the oven temperature was set at 180°C.

The volume of expired gas was measured by a wet gas meter (Shinagawa Seisakusho). The total amount of isoflurane taken up by the experimental animal during the 3 hours of anesthesia was calculated from the difference in the amount of isoflurane in the inspired and expired gas. Subsequently, the amount of isoflurane eliminated from the body in 5 hours was calculated directly from the amount of isoflurane in the expired gas. The amount of isoflurane eliminated was plotted against time on semilogarithmic graph paper, and a single exponential equation was derived as the last phase of the elimination curve. The amount of isoflurane expired from 5 hours to infinity was calculated by integration of the equation.

The level of isoflurane in the arterial blood was also measured by the gas chromatograph used together with a carburetor in which the blood was equilibrated with air.[3] The level of isoflurane in arterial blood was expressed as the ratio (%) to the partial pressure of isoflurane of the inspiratory gas during the anesthesia (blood-inspiratory ratio). The inorganic fluoride concentrations in blood and urine were measured by a fluoride electrode (Orion®, Model 96-09) and an ion meter (Orion®, Ion Analyzer Model 407A). The total amount of urinary fluoride (the sum of organic and inorganic fluoride) was measured in the same fashion after conversion of the organic fluoride to an inorganic form by the combustion method. Since small amounts of fluoride compounds are excreted normally in urine, any increased excretion of fluoride after isoflurane anesthesia was defined as the "excess excretion value"; i. e., the difference between the average value of urinary fluoride in the three day period before isoflurane anesthesia and subsequent values. Since Fiserova-Bergerova[4] demonstrated that inorganic fluoride released from fluoride compounds by biodegradation is deposited in bone and excreted in urine to the same extent, the sum of the amount of excess excretion of total urinary fluoride and that of excess excretion of inorganic fluoride was regarded as the total amount of fluoride produced in the body by the biodegradation of isoflurane. The biodegradation rate of isoflurane was obtained by dividing the estimated value of the total amount of fluoride produced in the body by the amount of the isoflurane taken up by the body, which was converted into the amount of fluoride.

The Student t-test and the paired t-test were used for the statistical analyses.

RESULTS

The blood-inspiratory ratio of isoflurane in arterial blood during three hours of anesthesia as well as the blood pressure and heart rate measured simultaneously are shown in Table 1. The ratio was 75.2±8.4% in the H group and 78.1±10.3% in the L group after 30 minutes of anesthesia. It reached 89.7±10.1% and 92.0±10.3% at 180 minutes, respectively ($p<0.01$). Mean systolic blood pressure in the H group decreased from 141 to 112 mmHg after 30 minutes of anesthesia ($0.01<p<0.05$) and remained unchanged for the subsequent 150 minutes. Similarly, in the L group it decreased from 140 to 120 mmHg after 30 minutes ($0.01<p<0.05$) and remained unchanged for the subsequent 150 minutes. The heart rate remained unchanged throughout the anesthetic period in both groups.

The serum inorganic fluoride concentration in the H group was 2.42±0.64 μmole/L before the anesthesia and increased to 3.29±1.13 μmole/L at 3 hours after anesthesia ($0.01<p<0.05$) and to 2.85±1.07 μmole/L at 5 hours ($0.05<p<0.10$). It then returned to the initial level by 8 hours and remained unchanged thereafter. In the L group, it increased from 2.46±0.36 μmole/L to 3.04±0.34 μmole/L at 3 hours after anesthesia ($p<0.01$) and then returned to the preanesthetic level at 5 hours and remained unchanged thereafter. There were no differences in the absolute value of the serum inorganic fluoride level between the H and L groups throughout the period of observation.

As shown in Table 2, the concentration of isoflurane in inspired gas was 1.42±0.15% in the H group and 0.51±0.05% in the L group. The amount of isoflurane taken up by the body during 3 hours of anesthesia was 17.3±3.2 mmole and 7.5±2.2 mmole, respectively. The amount of isoflurane expired in an unaltered form during the postanesthetic period corresponded to 92.7±11.8% and 96.4±11.6% of the amount the anesthetic taken up by the body during the anesthesia, respectively. The half life ($T_{1/2}$) of the last phase of the elimination curve was 2.4±0.8 hours in the H group and 2.6±0.6 hours in the L group.

As the urinary excretion of total fluoride reached its peak on the first day after isoflurane anesthesia and returned to the preanesthetic level on the fourth postoperative day, the excess fluoride excretion during the 72 hours after anesthesia was 43.6±55.6 μmole in the H group, and 2.4±22.7 μmole in the L group. The estimated value of total fluoride product was 60±106 μmole in the H group, and −22±64 μmole in the L group. None of these fluoride values were statistically increased. The degradation rate of isoflurane was 0.07±0.12% in the H group, and −0.08±0.19% in the L group. None of these values was considered changed statistically.

DISCUSSION

Holaday *et al.*[1] reported that 95% of the isoflurane absorbed by the human body was exhaled in an unaltered form. Degradated products which corresponded to 0.2% of the absorbed isoflurane were excreted fully in urine as organic and inorganic fluoride within 3 days of anesthesia. In our study, 94.3±11.3% of the isoflurane absorbed was expired. The half life of the last phase of the elimination curve in our study was presumed to relate to elimination from

TABLE 1. Blood-inspiratory ratio of isoflurane in arterial blood, systolic blood pressure and heart rate during anesthesia

	group	before	30	60	90	120	150	180 min
blood-inspiratory ratio (%)	H	—	75.2± 8.4	82.9± 9.4	85.2± 9.1	87.1± 9.3	88 5± 9.9	89.7±10.1
	L	—	78.1±10.3	84.9±10.1	88.2±10.7	89.9± 9.9	91.1±10.0	29.0±10.3
systolic BP (mmHg)	H	141±29	112±17*	113±20*	113±15*	113±10*	114±10*	112±13
	L	140±30	120±25*	115±30*	118±26*	120±28*	125±30*	128±28
heart rate (b.p.m.)	H	142±28	130±19	128±10	130±12	130±12	126±10	129±11
	L	130±30	120±24	125±20	130±18	135±20	140±22	142±26

H : n=7, L : n=5, mean±SD, * : $0.01<p<0.05$ compared with the value before anesthesia

TABLE 2. Uptake, elimination and degradation of isoflurane

	No.	weight (kg)	conc. of isoflurane inspired (%)	amount of isoflurane absorbed (mmole)	T½ of the last phase of the elimination curve (hour)	rate of isoflurane expired (%)	excess urinary fluoride excretion (μmole/72 hours) Total	Inorganic	total fluoride product (estimated value) (μmole)	degradation rate of isoflurane (%)
H	1	15.0	1.65	18.0	3.5	100.5	109	95	204	0.23
	2	9.5	1.56	13.7	3.3	113.7	44	−22	22	0.03
	3	10.0	1.19	15.3	2.1	84.8	88	52	140	0.18
	4	13.5	1.33	16.9	1.5	98.2	86	45	131	0.16
	5	13.0	1.39	20.5	2.6	82.9	31	31	62	0.06
	6	12.0	1.44	22.2	2.3	87.1	−39	−39	−78	−0.07
	7	10.0	1.38	14.3	1.4	82.0	−14	−48	−62	−0.09
mean±SD		11.9±2.1	1.42±0.15	17.3±3.2	2.4±0.8	92.7±11.8	43.6±55.3	16.3±53.5	60±106	0.07±0.12
L	1	12.0	0.48	6.4	2.0	85.0	−25	−95	−120	−0.38
	2	11.0	0.46	4.8	2.7	113.0	−8	−8	−16	−0.07
	3	13.0	0.58	10.9	2.7	86.5	35	8	43	0.08
	4	14.0	0.52	7.8	2.1	102.4	13	13	26	0.07
	5	12.0	0.51	7.4	3.6	94.9	−3	−40	−43	−0.12
mean±SD		12.4±1.1	0.51±0.05	7.5±2.2	2.6±0.6	96.4±11.6	2.4±22.7	−24.4±44.6	−22±64	−0.08±0.19

muscle tissue.[1] The true last phase of the elimination curve corresponding to elimination from adipose tissue was not determined since the observation period was too short.

Hitt *et al.*[2] reported that the main degradated products of isoflurane excreted in urine were TFA (trifluoroacetic acid) and inorganic fluoride. They further observed that the composition of the metabolites in man differed from that in rats. Namely, inorganic fluoride made up 60% of the urinary metabolites in Fischer 344 rats, while TFA made up 80% of urinary metabolites in man. In both rats and man, urinary fluoride excretion returned to normal within 3 or 4 days of anesthesia.

In our study, excess excretion of fluoride in the urine after isoflurane anesthesia was not detected. This seems to be because the increase in urinary fluoride caused by the biodegradation of isoflurane was much smaller than the daily change in the physiological urinary fluoride excretion. Although Halsey *et al.*[5] reported on the hepatic clearance of enflurane (14%), halothane (35%), and methoxyflurane (52%), they could not detect any clearance of isoflurane from blood passing through the liver in miniature swine. In our previous study,[6] the biodegradation rates of halothane, enflurane and methoxyflurane in man were 18%, 2.3% and 46%, respectively. As mentioned above, the biodegradation rate of isoflurane in man was reported to be less than 0.2%.[1] Enflurane is more stable in the body than halothane and methoxyflurane. Isoflurane, which is the isomer of enflurane, is considered to be much more stable than enflurane. In dogs, the biodegradation rate of halothane is below 10%,[7] which is just half of that in man.[6] Therefore, it is likely that the biodegradation rate of isoflurane in dogs would also be lower than in man.

In this study, the serum inorganic fluoride level was elevated maximally to a peak at the end of the 3 hours of anesthesia. It was 3.29 μM/L after 3 MAC·hours of anesthesia in the H group dogs and 3.04 μM/L after 1.1 MAC·hours in the L group dogs. In man, the peak serum inorganic fluoride level was reported to be 4.4 ± 0.4 μM/L after 3.1 ± 1.3 MAC·hours of anesthesia.[8] In Fischer 344 rats, it was reported to be 6.5 ± 1.2 μM/L after 4.0 MAC·hours of anesthesia and only 7.3 ± 0.6 μM/L even after 15 MAC·hours of anesthesia.[9] Considering these results, the serum inorganic fluoride level after isoflurane anesthesia should never reach 50 μM/L, which is considered to be the critical level required to produce renal toxicity. Therefore, isoflurane is unlikely to affect the kidney adversely.

As the solubility of isoflurane in either blood or fat is lower than that of enflurane and halothane, the uptake and equilibration of isoflurane into the body is thought to be completed more rapidly than with other volatile anesthetic agents. The rapid increase in the partial pressure of isoflurane in arterial blood during anesthesia shown in this study supports this theory.

In summary, 94.3% of the isoflurane absorbed by the body during 3 hours of anesthesia in dogs was exhaled mostly in an unaltered form after anesthesia and no increase in the urinary excretion of fluoride produced by the biodegradation of isoflurane was detected after anesthesia. The rate of biodegradation of isoflurane in dogs was found to be lower than that in man. The serum inorganic fluoride level increased only minimally after isoflurane anesthesia in dogs in exactly the same manner as it does in man. Therefore, isoflurane may be considered to be a safe anesthetic agent for dogs.

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