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Abstract

The direct determination by gas chromatography of blood levels of anesthetic agents has been difficult because of the water content of blood. In the present study, the method of Yokota et al. (1967) was modified by improving the packing materials of the column, the blood sample vaporizer and the flow-path during analysis. As a result, accurate and reproducible determination of halothane, enflurane and isoflurane dissolved in blood was achieved. With this system, blood in which halothane, enflurane and isoflurane had been dissolved could be analyzed without changing the column between samples. Moreover, each sample was prepared in less than 10 min, and more than 100 consecutive determinations could be made with excellent reproducibility. The coefficient of variation was less than 3.8%.

KEYWORDS: determination, halothane, enflurance, isoflurance, gas chromatography

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The direct determination by gas chromatography of blood levels of anesthetic agents has been difficult because of the water content of blood. In the present study, the method of Yokota *et al.* (1967) was modified by improving the packing materials of the column, the blood sample vaporizer and the flow-path during analysis. As a result, accurate and reproducible determination of halothane, enflurane and isoflurane dissolved in blood was achieved. With this system, blood in which halothane, enflurane and isoflurane had been dissolved could be analyzed without changing the column between samples. Moreover, each sample was prepared in less than 10 min, and more than 100 consecutive determinations could be made with excellent reproducibility. The coefficient of variation was less than 3.8%.

Key words : **determination, halothane, enflurane, isoflurane, gas chromatography**

The gas chromatographic determination of the concentration of anesthetic agents dissolved in blood has been performed by various methods: extraction (1, 2), evaporation (3, 4), vacuum extraction (5, 6), passage (7, 8), trapping (9), balance (10, 11), and direct techniques (12, 13). However, apart from direct methods, all of these require complicated pretreatment of the specimen and much time to complete the analysis, so that rapid and accurate quantitative analysis of samples has proven difficult.

In 1967, Yokota *et al.* (14) developed a sample vaporizing apparatus (SVA), and the concentration of halothane dissolved in blood was determined using a column of molecular sieve-5A coated with 0.3% diethylene glycol succinate directly attached to the SVA. However, it was difficult by this method to repeat determinations more than 25 times because water contained in the blood entered the column. Moreover, enflurane and isoflurane could not be determined with the molecular sieve-5A coated with 0.3% diethylene glycol succinate.

The purpose of the present study was to improve Yokota's method and to apply the improved method to the direct determination of the halothane, enflurane or isoflurane dissolved in blood. The aims of the improvements were to reduce the determina-

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tion time to less than 10 min for one test and to allow more than 100 consecutive determinations without changing the column between samples. We improved Yokota's method as follows: The SVA was changed to an aluminium block hollowed out to form a small sample chamber in which the temperature could be controlled. A precolumn (PC) used to remove water from the blood was inserted between the SVA and the main column (MC). The packing material for the MC was changed to molecular sieve-5A with 0.5% thermon-3000.

Materials and Methods

Gas chromatography. The packing materials used were: Porapak® Q (80-100 mesh) with 0.3% silicone GE SE-30 in the PC and resistance column 2 (R2); molecular sieve-5A (60-80 mesh) with 0.5% thermon-3000 in the MC, and Shimalite® Q (100-150 mesh) in resistance column 1 (R1). All these materials were purchased from Shimadzu Seisakusho, Ltd., Kyoto, Japan. We used a Shimadzu GC-6AMPrTF gas chromatograph (Shimadzu Seisakusho, Ltd.) with a thermal conductivity detector (TCD), a flame ionization detector (FID) and a Shimadzu Chromatopac C-R1A data processor.

The improved blood sample vaporizer (IBSV). The IBSV consisted of an aluminium block hollowed out to form a sample chamber, a sampling cock and a heater. The sample chamber had a diameter of 4 mm and a depth of 30 mm (approximately 1/3 of the volume of the SVA sample chamber used by Yokota *et al.*). The heater and a thermosensor connected to a specially constructed temperature controlling apparatus were positioned inside so that the temperature in the sample chamber could be controlled over a range of 50-150°C (Fig. 1 [A]).

Improved flow-path for analysis of blood for halogenated anesthetic agents. Fig. 1 shows the improved flow diagram used in this study. The anesthetic agents, water and other organic materials in a blood sample were first vaporized, and then sent to the PC for separation of the

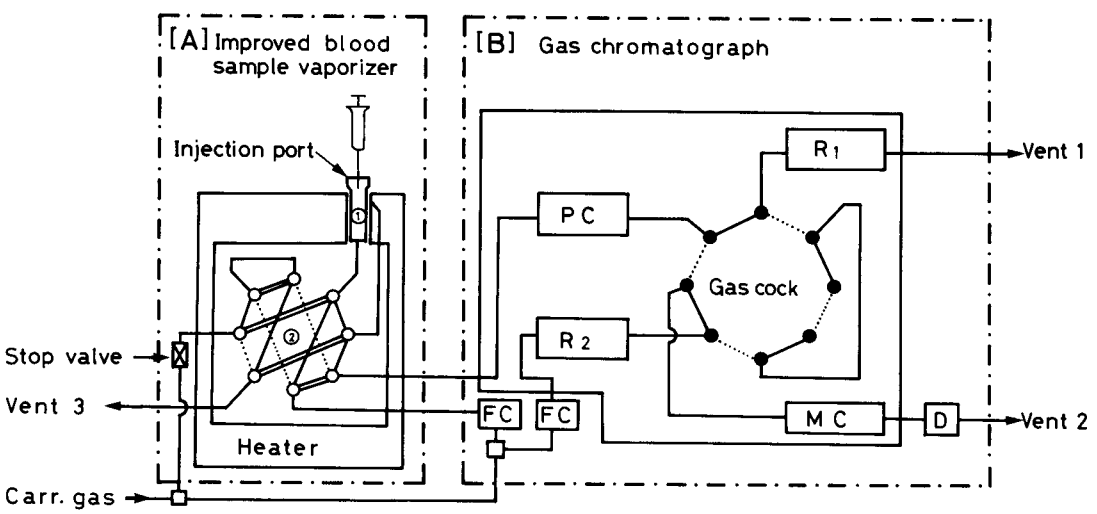

Fig. 1 Flow diagram for gas chromatographic (GC) determination of blood containing halogenated anesthetic agents. The sample is injected into the sample chamber by setting the sampling cock of the improved blood sample vaporizer [A] to "SAMPLE" (○·····○). The water and anesthetic agents in the injected sample are vaporized and sent into the precolumn (PC) of the gas chromatograph [B] by switching the sampling cock to "CARRIER" (●——●). The water is separated from the anesthetic agents in the PC. This water moves faster than the anesthetic agents and is removed via R1 (Flow 1, ●——●). The anesthetic agents are led into the main column (MC) by switching the gas cock to Flow 2 (●——●) and measured quantitatively. ①, sampling chamber; ②, sampling cock; FC, flow controller; D, detector. See Fig. 2 and Table 3 for further explanations.

anesthetic agents. Fig. 2 shows the flow-path of the carrier gas within the GC in Fig. 1 [B]. After the water removed by the PC was led to the resistance column (R1) using the gas cock, the flow-path of the carrier gas was switched from flow 1 to flow 2. The anesthetic agents remaining in the PC were then led into the main column (MC). As shown in Fig. 3, the water was sent in the direction of R1 until the peak of the anesthetic agents began to appear (T1 ; initial retention time). Ten seconds before T1, the gas cock was used to switch the flow of carrier gas, and as shown on the right in Fig. 3, the anesthetic agents contained in the tailing water peak were led into the MC. The concentrations of anesthetic agents were calculated by connecting the signal from the FID to a Chromatopac C-R1A data processor. The standard samples were made by dissolving the anesthetic agent in 100 ml of blood while weighing on a balance scale. Five-μl aliquots of each standard sample were determined 5 times by GC. The concentration of anesthetic agents was indicated by the average of the peak areas of the 5 determinations. The concentration of anesthetic agents in 5-μl aliquots of unknown samples was calculated from the average peak

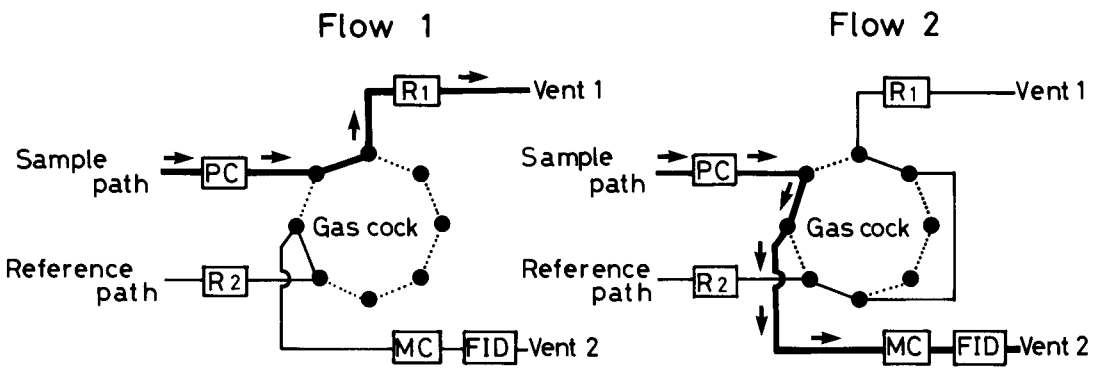

Fig. 2 Changes in the flow-path of carrier gas within the gas chromatograph due to switching of the gas cock. After the water separated by the PC is led to the resistance column R1 (left side of the diagram), the flow-path of the carrier gas is switched from flow 1 to flow 2. Anesthetic agents remaining in the PC are then led into the MC and determined.

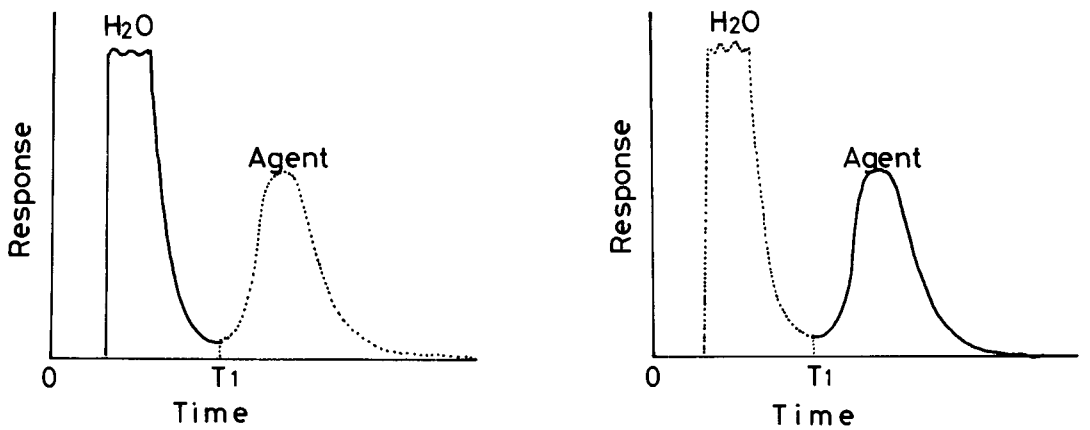

Fig. 3 Switching time for the carrier gas flow-path. The left chromatogram illustrates the passage of water through the resistance column 1 (R1) when the peak for the anesthetic agent first begins to appear (T1 : initial retention time). Ten seconds before T1, the gas cock is switched to the position shown on the right, and the anesthetic agent contained in the tailing water peak is led into the main column and determined.

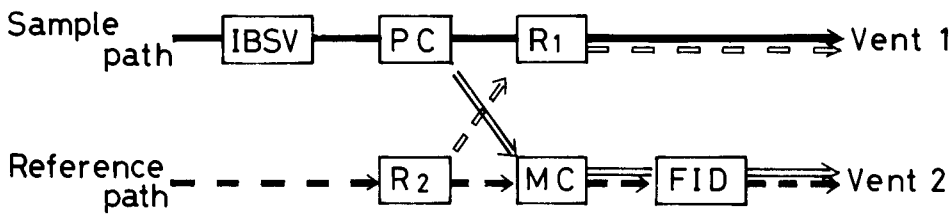

Fig. 4 Gas chromatographic (GC) flow-path in order to evalute the main column (MC) packing material. In order to evalute the MC packing material, the GC flow-path was connected to a flame ionization detector (FID). The temperature of the GC column and the time to switch the carrier gas flow were as determined in Fig. 3. Closed arrow: flow 1, open arrow: flow 2.

areas of the standard samples.

The optimal conditions for the improved method.

Selection of packing materials for the PC. In order to evaluate the PC packing material, the column of the GC was connected to a TCD so that the water content could be monitored. The GC conditions were set as follows: The carrier gas was helium at a flow rate of 150 ml/min. The TCD bridge current was set at 150 mA with a range of 1 mV. The temperature of the IBSV was 100°C, and the column temperature was 115°C. The separation of halothane and water by PC was examined using Porapak® Q, Porapak® Q with 0.3% silicone GE SE-30 and Porapak® Q with 0.5% silicone GE SE-30. The sample used in this analysis was prepared by putting 2 ml of pure water and 50 μl of halothane into an air-tight syringe. After the mixture was shaken well with the aid of a stainless steel pellet, 5-μl aliquots of the mixture were analyzed.

Determination of the optimal column temperature and the time (T1 of Fig. 3) to change the flow-path. The PC used was Porapak® Q coated with 0.3% silicone GE SE-30. The temperature of the GC column was raised in increments of 5°C from 105°C to 125°C, and the effect of the column temperature on the separation of water from anesthetic agents was studied. The sample solutions containing halothane, enflurane or isoflurane were prepared as mentioned above and used in this experiment.

Selection of the packing materials for the MC. In order to select the MC packing material, the GC flow-path was connected to an FID as shown in Fig. 4. The conditions for the GC were set as follows: The flow rate of nitrogen gas as the carrier was 150 ml/min. Those of H_2 and air were 65 ml/min and 1000 ml/min, respectively. The sensitivity was 1000 MΩ with a range of 80 mV. The temperature of the GC column and the time to switch the carrier gas flow were determined as mentioned above. The MC was packed with molecular sieve-5A, either non-coated, or coated with 0.5% or 1.0% thermon-3000. The samples were prepared by dissolving 19.0 mg of halothane, 18.0 mg of enflurane or 16.0 mg of isoflurane in 100 ml of heparinized blood. Analysis were made on 5-μl aliquots of each sample.

Determination of the optimal temperature for the IBSV and the optimal time for vaporization. In order to investigate the optimal temperature for the IBSV and the optimal time for vaporization, samples consisting of blood and anesthetic agents prepared as above were used under the optimal column conditions determined as above. The temperature of the IBSV was raised in 5°C increments from 60°C to 140°C. The time required to vaporize anesthetic agents was investigated at each IBSV temperature every 30 sec starting from 0 to 120 sec. Each sample was analyzed 5 times, and the reproducibility was examined.

The recovery rate of the improved method. The recovery rate was defined as the ratio between the determined values of the same amount of each anesthetic agent in the blood and in the air.

Results

The results of evaluating the packing materials for the PC are shown in Table 1. T1 is the time when the water content has

Table 1 Column temperature and the gas chromatographic pattern of anesthetic agents[a]

Anesthetics	Pattern	Column temperature (°C)				
		105	110	115	120	125
Halothane	T_1	8 : 15	6 : 40	6 : 20	4 : 40	3 : 35
	T_2	10 : 25	8 : 25	7 : 50	5 : 40	4 : 50
	T_3	15 : 00	11 : 30	10 : 00	8 : 00	7 : 00
	H	8	12	18	19	25
Enflurane	T_1	6 : 15	4 : 50	4 : 08		
	T_2	7 : 55	6 : 20	5 : 10		
	T_3	11 : 00	10 : 00	7 : 00		
	H	12	16	23		
Isoflurane	T_1	5 : 10	4 : 15	3 : 40		
	T_2	6 : 30	5 : 25	4 : 20		
	T_3	10 : 00	7 : 30	6 : 30		
	H	16	23	26		

a: T_1, initial retention time of the agent; T_2, retention time of the peak; T_3, total analysis time. Time is shown as min : sec. H, the height in mm from the base line at time T_1 to the tailing line of the water peak under the present conditions. See the text for details.

finished leaving the PC and the anesthetic agent has begun to appear. When only Porapak® Q was used, T1 was 10 min. With Porapak® Q coated with 0.3% silicone GE SE-30, T1 was 6 min 20 sec, and with Porapak® Q coated with 0.5% silicone GE SE-30, T1 was 5 min.

Table 1 shows the patterns of separation of water and anesthetic agents according to the column temperature. T1 is the time from the beginning of the analysis to the beginning of the peak of the anesthetic agent. H is the height from the base line at time T1 to the tailing line of the water content peak. T2 is the retention time for the anesthetic agent peak. T3 is the time of completion of the analysis. For completion of one analysis within 10 min, Table 1 shows that good separation of water and anesthetic agents occurred when the column temperature and T1 were, 115℃ and 6 min 20 sec for halothane, 110℃ and 4 min 50 sec for enflurane and 105℃ and 5 min 10 sec for isoflurane (underlined in Table 1).

Most of the water content was first allowed to flow out from the PC via R1, then the flow of the carrier gas was switched 10 sec before the peak of the anesthetic agent began to appear from the PC column (T1). In other words, from the beginning of analysis, it takes 6 min 10 sec for halothane, 4 min 40 sec for enflurane and 5 min for isoflurane.

The molecular sieve-5A reacted with halothane only, and not with enflurane or isoflurane. All three anesthetic agents, halothane, enflurane and isoflurane, reacted with molecular sieve-5A coated with thermon-3000 (either 0.5% or 1.0%). However, molecular sieve-5A coated with 1.0% thermon-3000 could not be used over 25 consecutive times.

Table 2 shows the results of the investigation of the IBSV temperature and the optimal time for vaporizing the sample in the IBSV sample chamber. For all three anesthetic agents, the variability in results was the least and the highest concentrations were obtained when the IBSV temperature was between 100℃ and 120℃, and the time

Table 2 Correlation between the temperature of the apparatus for heat vaporization of the sample and the time when the sample was held in the vaporization chamber[a]

Anesthetics	Temperature (°C)	Vaporization time (sec)			
		0	30	60	120
Halothane	60	18.39±0.61	18.06±0.44	17.95±0.55	16.98±0.61
	80	18.52±0.50	18.69±0.39	18.40±0.45	17.05±0.60
	100	18.62±0.41	18.80±0.30	18.53±0.44	17.02±0.58
	120	18.62±0.51	18.81±0.35	18.62±0.47	17.05±0.61
	140	18.55±0.77	18.75±0.42	18.03±0.61	16.77±0.75
Enflurane	60	17.62±0.29	17.75±0.28	17.75±0.21	16.39±0.25
	80	17.88±0.27	17.87±0.14	17.76±0.12	16.32±0.17
	100	17.93±0.15	17.90±0.11	17.81±0.13	16.49±0.16
	120	17.92±0.15	17.89±0.13	17.80±0.11	16.50±0.18
	140	17.86±0.22	17.89±0.15	17.85±0.16	16.31±0.21
Isoflurane	60	15.31±0.80	15.35±0.85	14.80±0.82	13.58±0.91
	80	15.44±0.82	15.43±0.50	14.85±0.55	13.62±1.01
	100	15.46±0.85	15.49±0.55	15.05±0.41	13.58±0.72
	120	15.48±0.90	15.41±0.60	14.88±0.45	13.36±0.82
	140	15.30±0.72	15.05±0.91	14.78±0.72	13.24±0.95

a: Each value represents the mean± S. D. for samples of halothane (19 mg/dl blood), enflurane (18 mg/dl blood) and isoflurane (16 mg/dl blood) dissolved in blood. Five determinations were made under each set of conditions.

Table 3 Optimal analytic conditions for gas chromatography of halogenated anesthetic agents dissolved in blood[a]

Precolumn : Resistance column 2 (R_2)	Porapak® Q (Silicone GE SE-30, 0.3% coating), 80～100 mesh, packed in stainless column (length 1 m, internal diameter 3 mm)
Main column	Molecular sieve-5A(thermon-3000, 0.5% coating), 60～80 mesh, packed in stainless column (length 1 m, internal diameter 3 mm)
Resistance column 1 (R_1)	Shimalite® Q, 100～180 mesh
Carrier gas	N_2, Flow 1 and 2, 150 ml/min
Temperature	Blood sample vaporizer : 100°C Column for Halothane : 115°C Enflurane : 110°C Isoflurane : 105°C Detector : 130°C
Time for switching the flow from precolumn to main column for	Halothane : 6 min 10 sec Enflurane : 4 min 40 sec Isoflurane : 5 min 00 sec
Flame ionization detector	H_2 flow rate : 65 ml/min Air flow rate : 1000 ml/min Sensitivity : 10^3 MΩ Range : 0.08 V
Time for vaporization of the sample	30 sec

a: The gas chromatograph used was a Shimadzu Model GC-6AMPrTF.

used to vaporize the sample was 30 sec. With an IBSV temperature of 100℃ and vaporizing time of 30 sec, the concentrations of halothane, enflurane and isoflurane were determined to be 18.8±0.30 mg/dl, 17.9±0.11 mg/dl and 15.49±0.55 mg/dl, respectively.

The determined concentrations began to decrease at a vaporization time of 60 sec, and by 120 sec, those of halothane, enflurane and isoflurane had decreased by 8%, 10% and 15%, respectively, in comparison with the control values. The discrepancy between repeated analyses also increased. There were no differences in the times needed to analyze anesthetic agents due to differences in the temperature of the IBSV. The optimal conditions for the IBSV for analysis of blood in which anesthetic agents were dissolved were a temperature of 100℃ and a vaporization time of 30 sec in the sample chamber.

The best conditions for the determination of each of the anesthetic agents are summarized in Table 3. Using the conditions shown in Table 3, the results from an analysis of a sample blood containing 19.0 mg/dl of halothane, 15.0 mg/dl of enflurane and 15.5 mg/dl of isoflurane are shown in Figs. 5 and 6. Fig. 5 shows actual chromatographic patterns of halothane dissolved in blood, from the left: 10-μl, 5-μl, 3-μl and 1-μl blood samples containing 19.0 mg/dl of halothane. The halothane amounts obtained by determination were 1906.69 ng/10 μl, 956.05 ng/5 μl, 573.29 ng/3 μl and 181.51 ng/1 μl, respectively. As seen in Fig. 6, the determined values correlated well with the amounts of each anesthetic agent in each blood sample. The curves obtained by analyzing blood of various volumes were linear between 185 and 1900 ng, 148 and 1500 ng, and 150 and 1550 ng for halothane, enflurane, and isoflurane, respectively. The curves passed through the origin extraporated. There was little variability in the data, the coefficient of variation being less than 3.8%. When determinations of 5-μl samples were repeated more than 100 times, the determined values all

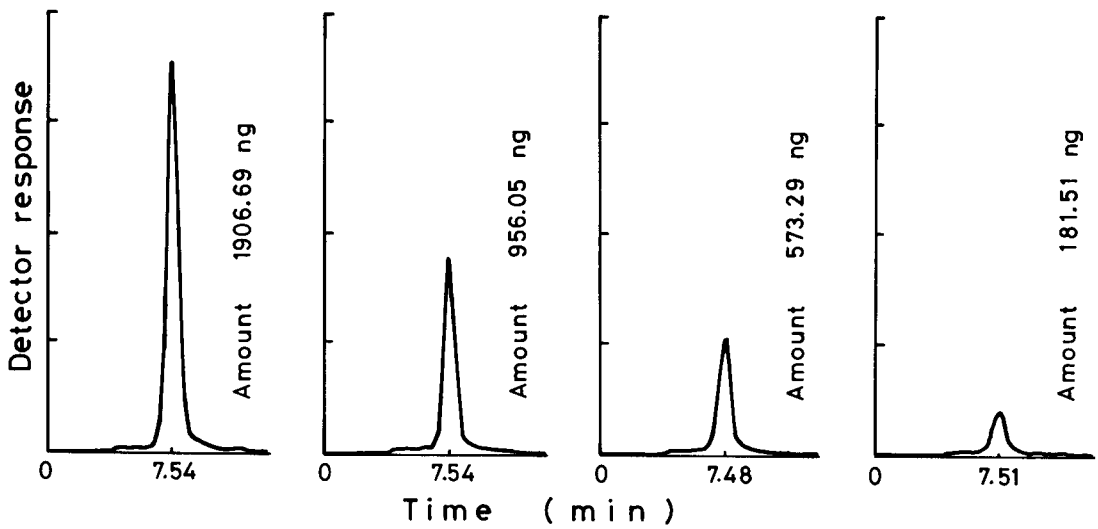

Fig. 5 Chromatographic patterns of halothane dissolved in blood. Chromatograms of 10-μl, 5-μl, 3-μl and 1-μl samples of halothane (19.0 mg/dl, dissolved in blood). The retention time was about 7.5 min. The determined values were very close to the calculated values.

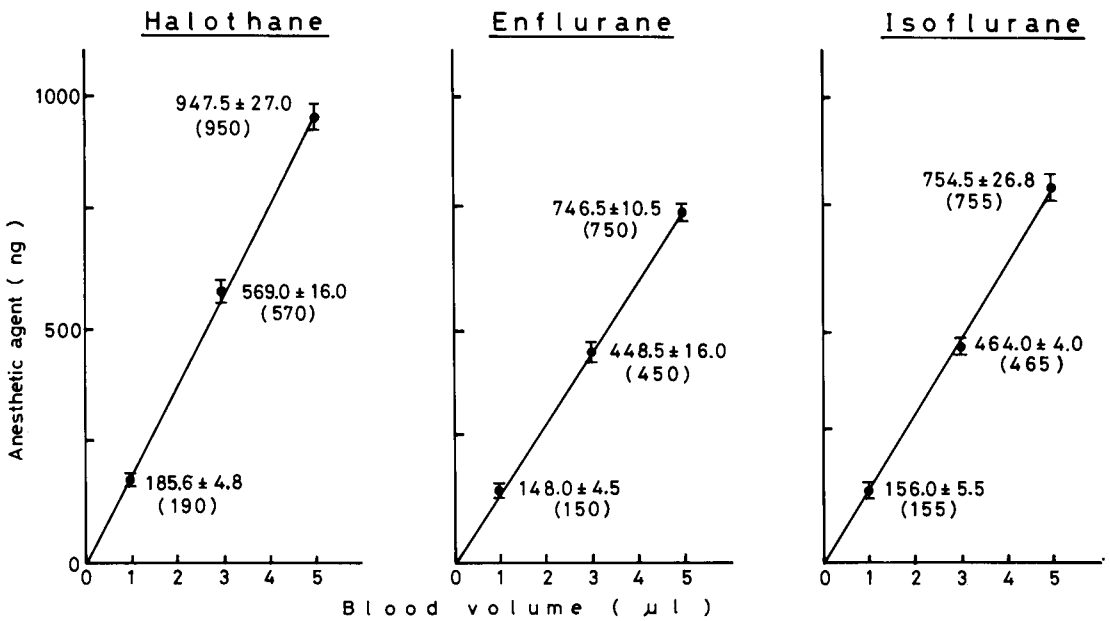

Fig. 6 Correlation between calculated and gas chromatographically obtained values for halothane, enflurane and isoflurane dissolved in blood. The values in the figure show the average and standard deviation for 1-μl, 3-μl and 5-μl samples of halothane (19.0 mg/dl), enflurane (15.0 mg/dl) and isoflurane (15.5 mg/dl) dissolved in blood. Each sample was determined 5 times. The values in parentheses are the amounts of the anesthetic agents applied. The vertical bar shows standard deviation. Numerals in parentheses show the calculated values. The values obtained by the present method were very close to the actual values, and the coefficient of variation was less than 3.8%.

fell on this line. The average recovery rates were 98% for halothane, 97% for enflurane and 98% for isoflurane, respectively. It is clear that the actual values of three anesthetic samples of 5-μl, 3-μl and 1-μl are on a straight line which, if extrapolated, passes through the origin.

Discussion

This study was undertaken to improve the direct GC method of Yokota *et al.* for the determination of halothane, enflurane and isoflurane dissolved in blood.

The sample chamber of the IBSV was made smaller to decrease the variability in the data, to lessen the disruption in the carrier gas flow within the sample chamber resulting from switching the sampling cock on and off, and to allow insertion of the PC between the IBSV and MC.

In the method of Yokota *et al.*, the concentration of halothane is calculated from the height of the peak. However, in the present study, the peak width of the anesthetic agent was wider because the PC was inserted between the IBSV and the MC, so the concentration was calculated from the area of the peak using a data processor. In the method of Yokota *et al.*, all water content of the blood enters the column (packed with molecular sieve-5A coated with 0.3% diethylene glycol succinate), so determinations could not be repeated more than 25 times. In the present study, the concentration of anesthetic agents was determined in the MC after most of the water content of the blood had been removed by the PC; hence it became possible to repeat determi-

nations more than 100 times.

When Porapak® Q is coated with more than 0.5% GE SE-30 silicone, the anesthetic agents are not clearly separated from the tailing part of the water, and a large amount of water enters the MC with the anesthetic agents, so that determinations can not be repeated more than 25 times. When Porapak® Q is coated with 0.3% silicone GE SE-30, the ability to retain the water and anesthetic agents becomes smaller than with Porapak® Q alone, and the time for one determination decreases to 3 min 40 sec. From these results, Porapak® Q coated with 0.3% silicone GE SE-30 was selected as the packing material.

Molecular sieve-5A coated with 0.5% thermon-3000 was selected as the packing material for the MC, because thermon-3000 was sensitive to halothane, though not to enflurane or isoflurane. However, if the thermon-3000 is coated, it also becomes sensitive to enflurane and isoflurane. Moreover, a small amount of water enters the MC at the time of determination, and molecular sieve-5A has the ability to retain this water. A 0.5% coating was used because water retention became less with a coating greater than 0.5%, so that repeated analysis of blood samples became impossible. A coating of less than 0.5% is not sensitive to enflurane or isoflurane. The 0.5% coating enabled determination of halothane, enflurane and isoflurane together.

Shimalite® Q was used as the packing material in R1 to match the resistance with MC and to prevent changes in the resistance as the water passes through after separation from the blood in the PC.

It was thought that problems might occur during the analysis because a small amount of water entered the MC as the anesthetic agent was led into the MC from the PC. However, when only the PC itself was connected to the TCD with a TCD range of 1 mV, and the height of the peak at time T1 (H) was less than 20 mm, more than 100 consecutive determinations could be made. If the column temperature was raised, H became greater than 20 mm and the determination time became faster, but repeated determinations became impossible because a large amount of water entered the MC. If the column temperature was lowered, H became less than 10 mm and the interference due to water disappeared, but the determination required a very long time.

When the flow-path was switched at T1, a small amount of water entered the MC, but it did not interfere with repeated determinations because of the water retention ability of the molecular sieve-5A. Peaks were obtained with all agents.

The linearity of the anesthetic agent determined by the present method was excellent. The coefficient of variation was very small (less than 3.8%) and was smaller than the coefficient (5.1%) obtained by Yokota *et al.* (14). The present direct GC method is, therefore, excellent for determining the concentration of halothane, enflurane and isoflurane dissolved in blood.

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