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METABOLISM OF HALOTHANE DURING AND AFTER ANAESTHESIA IN MAN

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SUMMARY

The metabolism of halothane during and after anaesthesia was studied in eight patients of different age and body weight by estimating the concentration of halothane and one of its metabolites (bromide) in the blood. A gas chromatograph with an electron capture detector was used to estimate halothane, while blood bromide levels were measured by neutron activation analysis. There was an initial burst of bromide production during 20 minutes of halothane administration. Bromide levels then fell, but not to control levels, and remained so until the recovery of the patient from anaesthesia. In the postanaesthetic period, bromide production took place on a larger scale than before.

It is now generally accepted that halothane is metabolized, both in animals (Van Dyke, Chenoweth and Van Poznak, 1964; Cohen, 1969; Cohen and Hood, 1969) and in man (Cascorbi, Blake and Helrich, 1970). "In-vivo" studies have confirmed that dehalogenation takes place and that non-volatile ^{14}C metabolites are excreted in the urine.

Metabolic studies of halothane in humans have been concentrated on measuring excretion products in urine or other excreta. Since the intermediates of halothane metabolism are not known, it is difficult to plot the time course of metabolism during anaesthesia. As each halothane molecule contains one atom of bromine, the blood bromide level should give a guide to the time and extent of halothane breakdown since debromination is known to occur (Rehder et al., 1967).

The present report correlates blood levels of bromide with the simultaneous determination of blood levels of halothane during and after halothane anaesthesia.

METHOD

Clinical studies.

A preliminary study was carried out in a male patient aged 72 years given halothane anaesthesia for 2½ hr for plastic surgery to the hand. Induction was achieved with thiopentone 250 mg and anaesthesia maintained using nitrous oxide (5 l./min), oxygen (2 l./min) and halothane 1½% for 30 min. During the remaining 2 hr 1% halothane was used. A preoperative blood sample was taken for bromide estimation. During anaesthesia venous blood samples were then taken at 10, 30, 60 and 150 min from the start of anaesthesia. In the postoperative period samples of blood were taken at 4 and 7½ hr as calculated from the beginning of anaesthesia.

Following analysis of these samples further studies were carried out on eight patients of different age and body weight. These patients were undergoing minor gynaecological operations and all received thiopentone, nitrous oxide, oxygen and 1½% halothane for 20 min. A preoperative blood sample was taken for the estimation of blood bromide. A further blood sample was taken when the halothane was turned off at the end of the 20-min period of anaesthesia. Respiration was spontaneous in all cases. A sample of blood was taken on recovery of consciousness as determined by response to commands. Further blood samples were taken at 1, 3, 7, 20 and 44 hr, as calculated from the beginning of anaesthesia. The samples were assayed for halothane and whole blood bromide content.

The respiratory efficiency of each patient was assessed by performing two pulmonary function tests. The forced expiratory volume (FEV_1) and the forced vital capacity (FVC). Table I shows the age, body weight, and respiratory efficiency of the eight female patients.

Volunteer studies.

Sodium bromide was administered by intravenous injection in conscious volunteers to study the rate of disappearance of bromide from the blood. In two volunteers 100 mg of bromide was slowly injected over a period of 20 min. In two further volunteers 200 mg of bromide in isotonic glucose was infused

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TABLE I. *Age, body weight and respiratory efficiency of female patients.*

	Patients							
	C	D	E	F	G	H	I	J
Age (yr)	56	25	38	21	39	24	41	36
Body weight (kg)	66.7	38.1	60.3	50.8	65.3	53.6	73.6	71
Respiratory efficiency	within normal limits	78% of normal values	within normal values	within normal values	FEV_1 83% of normal values	91% of normal values	83% of normal values	76% of normal values

by intravenous drip over a period of 1 hr. Blood samples were taken from the opposite arm before, during and after administration to determine blood bromide concentrations.

Laboratory methods.

Determination of bromide in blood. A method of neutron activation analysis originally described by Bowen (1959) and Belkas and Souliotis (1966) was used in this study. Blood samples and a standard concentration of bromide (control) were irradiated and subjected with a known weight of bromide (carrier) to chemical separation and precipitated as silver bromide. Radioactivity in these precipitates was counted and the concentrations of bromide in the samples calculated by comparing the counts of the samples with those of the control. In duplicate samples of blood at varying concentrations of bromide the mean difference was 4.5% ± 1.95 and the mean of the SD of twelve duplicate estimations was ± 0.87. The 95% confidence limits of a single estimation was ± 1.6% (Atallah and Geddes, 1973).

Quantitative estimation of halothane in blood. This technique has already been described in full (Atallah and Geddes, 1972). A Perkin Elmer F11 gas chromatograph with an electron capture detector was used. Halothane was extracted from blood samples by n-heptane, as originally described by Butler and Hill (1961). One μl of this extract was placed on a column containing 15% silicon fluid MS550 as stationary phase on Universal B.60–80 mesh. The mean recovery of halothane from blood, in the range 7.10–36.13 mg/100 ml, was 96.98% ± 2.27. The mean of the standard deviations of duplicate extractions was ± 0.87. With low blood halothane concentrations, 112.54–323.00 μg/100 ml, the mean per cent recovery was 107.41 ± 5.18 and the mean of the standard deviations of duplicate extractions was ± 2.89.

RESULTS

Pilot study.

In the patient studied while receiving the 2½-hr halothane anaesthetic the blood bromide concentrations rose from the preoperative value of 8.3 μg/ml to a maximum of 11.7 μg/ml at 60 min (fig. 1, table II). No further rise occurred until the end of the 2½-hr anaesthetic. Samples taken 4 and 7½ hr after induction of anaesthesia showed evidence of a further rise in circulating bromide levels. These findings suggested that debromination took place early in anaesthesia and again following recovery from anaesthesia. No data concerning blood halothane levels were obtained.

Studies in eight patients.

Blood bromide. The administration of halothane 1½% for 20 min was associated with a definite rise in blood bromide (table III, fig. 2). In the follow-

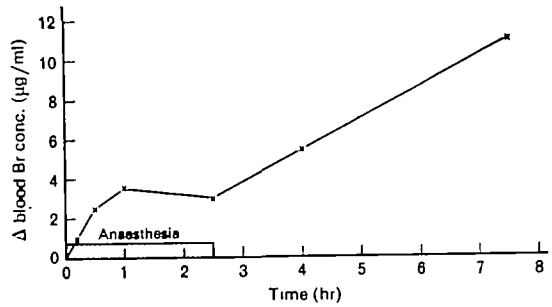


FIG. 1. The blood bromide concentrations (μg/ml) above the preoperative level, in a 72-year-old male patient anaesthetized with halothane, nitrous oxide and oxygen for 2½ hr.

TABLE II. *Blood levels of bromide in a 72-year-old before, during and after anaesthesia with halothane, nitrous oxide and oxygen for 2½ hr.*

Time of samples (min) from the beginning of anaesthesia	Blood bromide concentrations (μg/ml)	Increase above preoperative level (μg/ml)
Preoperative	8.3	
10	9.2	0.9
30	10.9	2.6
60	11.7	3.4
150	11.4	3.1
240	13.9	5.6
450	19.4	11.1

TABLE III. *Blood bromide concentration (μg/ml) in female patients before, during and after, anaesthesia with halothane lasting 20 min.*

Time from induction	Patients							
	C	D	E	F	G	H	I	J
Preoperative	7.2	6.1	6.0	5.1	4.0	7.3	6.6	8.1
20 min	11.6	10.4	9.3	7.7	8.0	12.7	10.4	10.7
30 min	9.1	6.2	6.4	5.2	6.7	8.8	—	10.8
1 hr	9.4	8.4	7.6	8.4	6.8	9.4	7.6	10.6
3 hr	18.0	11.9	12.9	10.5	12.3	15.0	12.7	20.2
7 hr	28.5*	13.6	16.4	13.7	16.1	18.9	14.6	28.7
20 hr	30.6	15.1	24.1	14.4	23.2	20.6	21.0	28.5
44 hr	32.8	15.0	19.9	—	23.5†	23.4	19.3	26.5

* at 8 hours † at 27 hours

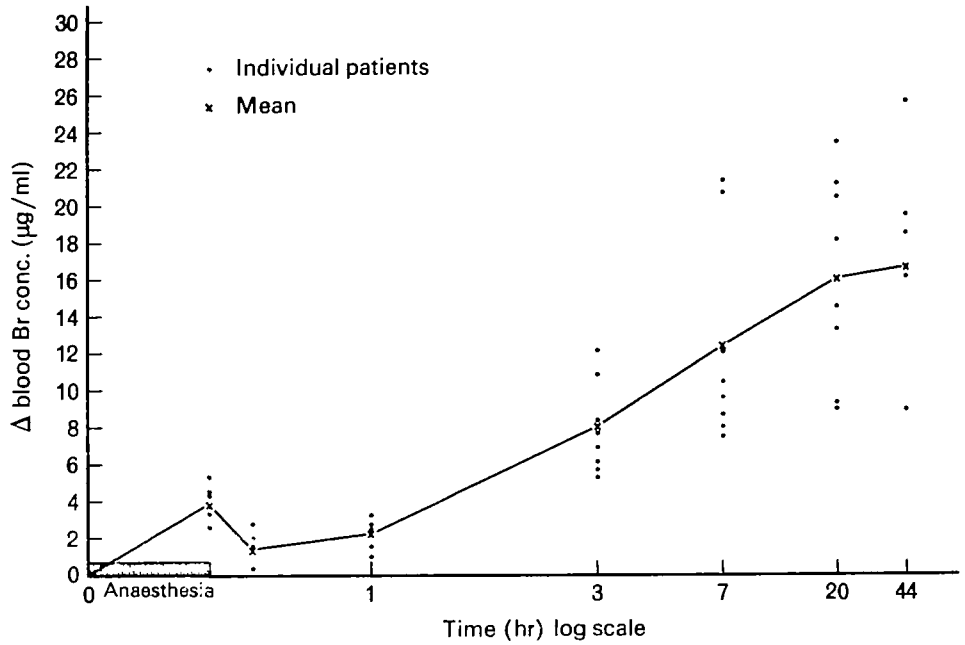


FIG. 2. Increase in blood bromide concentrations (μg/ml) in eight female patients during and after halothane anaesthesia lasting 20 min.

ing 10 min the blood bromide level fell in all but one patient examined at this time. At 1 hr after induction of anaesthesia four patients showed a rise of blood bromide above the level observed at 30 min. By 3 hr in all patients there was a further elevation of blood bromide suggesting that there was now active debromination of halothane taking place. This rise continued to a greater or lesser degree at 7 and 20 hr in all patients. By 44 hr little further rise in blood bromide was observed.

Blood halothane. The venous halothane concentrations at the end of 20 min of halothane anaesthesia were in the range 7600–10,650 μg/100 ml (table IV). At the time of recovery from anaesthesia there was less variation in the blood halothane concentration between patients (2200–3000 μg/100 ml). Halothane in trace amounts could still be identified in venous blood 44 hr after induction of anaesthesia.

Volunteer studies.

The rate of disappearance of bromide from the blood of two volunteers, following intravenous administration of 100 mg of bromide given during 20 min is shown in figure 3 and table V. There was an increase in the blood bromide above the pre-administration level. A rapid fall took place in the first 10 min after completion of infusion and this then slowly decreased over the observed period. The

TABLE IV. *Blood halothane concentrations (μg 100 ml) in eight female patients during and after halothane anaesthesia lasting 20 min compared with the increase of bromide (μg/ml) above the preanaesthesia level.*

Time from start of anaesthesia		Patients							
		C	D	E	F	G	H	I	J
20 min	Hal.	7600	10650	9360	10100	9050	9050	5350	5050
	ΔBr	4.4	4.3	3.3	2.6	4.0	5.4	3.8	2.6
30 min	Hal.	2500	2200	2300	2450	3000	2200	—	2500
	ΔBr	1.9	0.1	0.4	0.1	2.7	1.5	—	2.7
1 hr	Hal.	1488	1050	1100	600	1275	988	613	1340
	ΔBr	2.2	2.3	1.6	3.3	2.8	2.1	1.0	2.5
3 hr	Hal.	438	120	253	238	320	156	313	238
	ΔBr	10.8	5.8	6.9	5.4	8.3	7.7	6.1	12.1
7 hr	Hal.	168	31	93	88	75	44	66	91
	ΔBr	21.3*	7.4	10.4	8.6	12.1	9.6	8.0	20.6
20 hr	Hal.	44	7	19	18	26	8	16	61
	ΔBr	23.4	9.0	18.1	9.3	19.2	13.3	14.4	20.4
44 hr	Hal.	16	3	5	—	20	3	12	20
	ΔBr	25.6	8.9	13.9		19.5†	16.1	12.7	18.4

* at 8 hours † at 27 hours

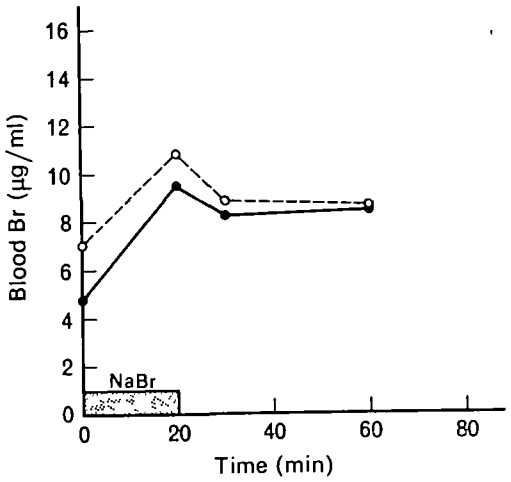


FIG. 3. The blood bromide concentrations (μg/ml) in two volunteers before during and after intravenous infusion of sodium bromide 100 mg over a period of 20 min.

TABLE V. *The blood bromide concentrations in two volunteers before and after slow intravenous injections of 100 mg of sodium bromide over a period of 20 min.*

Time calculated from the beginning of injection (min)	Blood bromide concentration (μg/ml)	
	1	2
Preinjection	4.4	6.7
20	9.6	11.0
30	8.4	8.9
60	8.4	8.7
120	8.0	8.0

blood bromide concentrations in the other two volunteers following the infusion of 200 mg bromide solution over 1 hr are shown in figure 4 and table VI. There was a rise in the blood bromide concentration

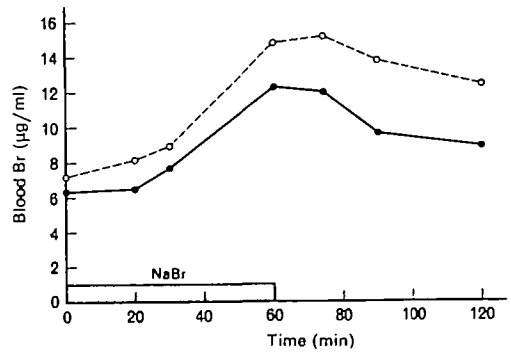


FIG. 4. The blood bromide concentrations (μg/ml) in two volunteers before, during and after intravenous infusion of 200 mg bromide solution over a period of 60 min.

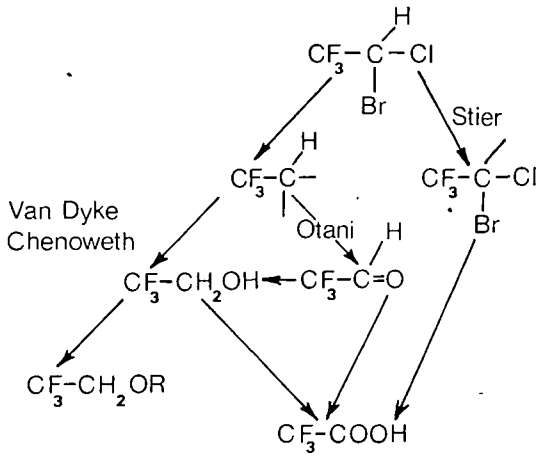
TABLE VI. *The blood bromide concentrations in two volunteers before, during and after slow intravenous infusion of 200 mg sodium bromide solution over a period of 60 min.*

Time calculated from the start of infusion (min)	Blood bromide concentration (μg/ml)	
	3	4
Preinfusion	6.2	7.1
20	6.4	8.6
30	7.6	9.2
60	12.4	14.6
75	12.0	15.0
90	9.6	13.6
120	8.8	12.4

over the period of administration and the blood bromide level slowly decreased during the period of blood sampling.

DISCUSSION

The possible pathways of metabolism of halothane are given in figure 5. Trifluoroacetic acid is a known metabolite excreted in the urine (Stier, 1964; Stier and Alter, 1966). This end-product of halothane metabolism has been supposed to be formed either through trifluoroethanol (Van Dyke and Chenoweth, 1965b), through a labile ionized intermediate compound (Stier, 1968) or through trifluoroacetaldehyde by the oxidation reduction systems of the body as has been suggested by Otani (Airaksinen, 1968). These intermediate metabolites have not as yet been identified. Dehalogenation is, however, a necessary step to obtain trifluoroacetic acid.



Possible routes of metabolism of halothane molecule

FIG. 5. Possible routes of metabolism of halothane molecule.

The bond energies of the atoms of halothane are given in table VII. The highest bond energy is between fluorine and carbon. This explains why the trifluoride part of the molecule is not affected by metabolism (Van Dyke, Chenoweth and Larsen, 1964; Van Dyke and Chenoweth, 1965a). Bromine and chlorine are less tightly bound and are more readily removed. For each molecule of halothane metabolized one bromine atom is produced (Stier, 1968).

TABLE VII. *Bond energies of the halothane molecule.*

Atomic bond	Energy in K cal/mole
C–Br	54.0
C–Cl	66.5
C–H	87.3
C–F	107.0

Distribution of bromide in the body.

Bromide has been found to have a partition in the body similar to that of chloride. The rate of passage of bromides through capillary walls is nearly equal to that of chloride (Hahn and Hevesy, 1940). Following injection, bromide passes rapidly into the tissues, and mainly into the extracellular fluid, but only slowly into the brain and cerebrospinal fluid (Söremark, 1960a). Excretion of bromide is slow and mainly renal (Ucko, 1936). Bodansky and Modell (1941) in dogs, injected a large dose of bromide intravenously and found that 0.6% was excreted in the urine in the first hour. Söremark, (1960b), using ^{82}Br reported that the biological half-life of bromide ions in human blood was 12 days.

In the human volunteers the blood bromide level rose during the period of administration of sodium bromide. At the end of either 20 min or the 1-hr infusion, the blood bromide level began to fall. There was an initial rapid fall suggesting a phase of early redistribution followed by a slower rate of fall indicating saturation of a body compartment. In all the anaesthetized patients, there was an initial rise of blood bromide similar to that seen when bromide was administered by intravenous infusion. This suggested that active metabolism of halothane was taking place with liberation of bromide. At the end of administration of halothane there was a fall in the level of circulating blood bromide presumably due to a discrepancy between the rate of production of bromide and the factors responsible for its disappearance from the blood.

In the volunteers who received 100 mg of bromide in 20 min the blood bromide level fell in a manner similar to the mean concentration of bromide seen in the eight patients after 20 min of halothane anaesthesia (fig. 2). In these patients little or no production of bromide took place immediately after halothane administration but bromide release continued for some 44 hours.

Blood halothane concentrations.

An attempt was made to relate the blood halothane level with the presence or absence of the production of bromide. In table IV the blood bromide increase above the preanaesthetic level is tabulated with the

blood halothane concentration. In samples taken 1 hr after anaesthesia there was a slight increase in the bromide concentration above that observed at 30 min in four patients (D, E, F, and H), while in the remaining three patients (C, G, and J) there was no appreciable increase in the blood bromide. In the latter three patients the blood halothane concentration was higher than in the previous four patients. When the halothane concentration fell in these three patients a small rise in the blood bromide level was then observed.

Suppression of halothane metabolism with increasing blood concentrations has been reported by Cascorbi, Blake and Helrich (1970). These authors administered trace doses of ^{14}C-labelled halothane to two volunteers in the absence and presence of anaesthetic concentrations of halothane. They reported that less radioactive urinary metabolites were recovered following halothane anaesthesia. Sawyer and his colleagues (1971), in animal studies using Hormel miniature swine found that the fraction of halothane removed from blood by the liver increased as halothane concentration fell. They attributed this to either microsomal enzyme saturation or possibly complete suppression of metabolism by halothane at anaesthetic concentrations. Brown (1971), studied the influence of halothane in the in-vitro biotransformation of a variety of drugs by hepatic mixed function oxidase enzymes of the rat's liver. He found that halothane diminished the rate of oxidation of hexobarbitone, amylobarbitone and pentobarbitone, and the demethylation of aminopyrine. This inhibition was dose-dependent and reversible. Our findings suggest that halothane at anaesthetic concentrations, also inhibits its own dehalogenation, and that this is reversed as the blood concentration fails.

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METABOLISME D'HALOTHANE DURANT ET APRES L'ANESTHESIE CHEZ L'HOMME

SOMMAIRE

Le métabolisme d'halothane pendant et après l'anesthésie a été étudié chez huit patients d'âge et poids corporel différents, en estimant la concentration de l'halothane et d'un de ses métabolites (bromure) dans le sang. Un appareil de chromatographie gazeuse avec un détecteur de la capture d'électrons a été utilisé pour déterminer l'halothane, tandis que les taux sanguins de bromure étaient mesurés par l'analyse de l'activation des neutrons. Il y eut initialement une forte production de bromure durant 20 minutes de l'administration d'halothane. Les

taux de bromure diminuaient ensuite mais sans atteindre le niveau contrôle, et demeuraient inchangés jusqu'au moment où le malade se réveilla de l'anesthésie. La production de bromure en période post-analgésique était plus grande qu'auparavant.

ÜBER DEN STOFFWECHSEL VON HALOTHAN WÄHREND UND NACH DER NARKOSE BEIM MENSCHEN

ZUSAMMENFASSUNG

An acht Patienten von verschiedenem Alter und Körpergewicht wurde der Stoffwechsel von Halothan während und nach der Anaesthesie untersucht, durch Schätzung der Konzentration von Halothan und von einem seiner Metaboliten (Bromid) im Blut. Ein Gaschromatograph mit einem elektronischen Auffangdetektor wurde zur Schätzung von Halothan verwandt, während der Spiegel der Bromide im Blut mittels der Neutronenaktivation zur Analyse bestimmt wurde. Es fand sich ein initialer Anstieg der Bromid-Produktion während der ersten 20 Minuten der Halothananwendung. Dann sank der Bromidspiegel ab, allerdings nicht bis zum Ausgangswert. Er blieb so bis zum Erwachen des Patienten aus der Narkose. In der postanaesthetischen Periode erfolgte die Bromidproduktion in größerem Ausmaße als vorher.

METABOLISMO DEL HALOTHANE DURANTE Y DESPUES DE LA ANESTESIA EN EL HOMBRE

RESUMEN

Se estudió el metabolismo del halothane durante y después de la anestesia en ocho enfermos de diferente edad y peso, determinando la concentración de halothane y de uno de sus metabolitos (bromuro) en la sangre. Para determinar el halothane se empleó un cromatógrafo de gas con un detector de captación electrónico, mientras que los niveles de bromuro en sangre fueron medidos por análisis de activación de neutrones. Había un aumento inicial de la producción de bromuro durante 20 minutos de la administración de halothane. Los niveles de bromuro caían después, pero no hasta los valores de control, permaneciendo así hasta la recuperación del enfermo de la anestesia. En el período postanestésico, la producción de bromuro tiene lugar en una mayor escala que antes.