HALOTHANE-DIETHYL ETHER RATIOS DURING HALOTHANE-DIETHYL ETHER AZEOTROPE ANAESTHESIA

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HALOTHANE AND DIETHYL ETHER form an azeotrope which has been in use as an inhalation anaesthetic since it was reported in 1958.¹ An azeotrope may be simply defined as a constant-boiling-point mixture. Azeotropes are stable to fractional distillation but can be separated by extractive distillation† and gas chromatography. The type of bonding of halothane and diethyl ether is probably of low energy and is either by dipole moments or hydrogen bonds.² The stability of the azeotrope in the body has been questioned, since studies using infrared spectrometry showed changing halothane-diethyl ether ratios in breath during anaesthesia with the azeotrope, suggesting that biological mechanisms may be involved in the breakdown of the azeotrope.³ Changing halothane-diethyl ether ratios may imply changing flammability conditions if "free" diethyl ether is present.

Using three volumes per cent inspired concentration, blood concentrations of each component of the azeotrope have been predicted,¹ and based on the predicted blood levels of diethyl ether, it has been suggested that anaesthesia with the azeotrope offers an advantage over anaesthesia with halothane alone.

The present study is concerned with the determination of halothane-diethyl ether ratios during laboratory and clinical situations and the measurement of blood halothane and diethyl ether concentrations during azeotrope anaesthesia using gas chromatography.

METHOD

Calibration studies

The chromatographic conditions consisted of an F & M model 700 chromatograph with a flame ionization detector, a 6 foot $\times$ 1/8 inch o.d. copper column packed with Porapak Q 50/80 mesh, and a 1 millivolt Moseley recorder. The injection port temperature was 170° C, oven temperature 130° C, detector temperature 200° C, and helium carrier gas flow rate was 50 ml per minute. Quantitation of the area under the halothane and diethyl ether peaks was done by a disc integrator. Sample injections of 400 microlitres of azeotrope vapour were used. All samples were done in duplicate except in the clinical study on respired gas. The azeotrope was made using 66 parts halothane and 34 parts diethyl ether vol/vol.⁴ Repeatability studies were done on azeotrope vapour emerging

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†Extractive distillation is defined as distillation in the presence of a solvent which is relatively non-volatile compared to the components to be separated, and which is selected to enhance the relative volatility of the components.

from a Fluotec vaporizer with a carrier gas flow of three litres of oxygen and three litres of nitrous oxide per minute. The halothane-diethyl ether ratios were determined in five lots of azeotrope made on five different days and over a storage period of 25 days at room temperature.

Laboratory studies

Circle absorber study. To determine the effect of soda lime, carbon dioxide, and water vapour on azeotrope, the following study was done in quadruplicate. Azeotrope vapour from a Fluotec vaporizer was introduced into a closed circle with the absorber off, using equal parts oxygen and nitrous oxide and an additional reservoir bag at the face piece end until both reservoir bags were nearly full. The gas was circulated by alternate squeezing of the reservoir bags. After ten minutes, 400 microlitres of gas from the inspiratory side were sampled and injected into the chromatograph. A Boyle Mark III absorber canister containing fresh soda lime was added to the circuit, and the gas was circulated for ten minutes and again sampled. One hundred per cent carbon dioxide was introduced into the circle continuously for three to five minutes and circulated until the absorber became warm. The system was again sampled. The experiment was repeated with 250 ml of water added to the soda lime canister, and the carbon dioxide, soda lime, and water vapour from the canister introduced simultaneously.

In vitro blood and water study. Samples of 10 ml heparinized whole blood were added to 36.5 ml capacity vials sealed with a rubber stopper and weighed. Azeotrope was injected through the stopper and the vial reweighed and mixed. After equilibration in a water bath at 20° C, 25° C, and 37° C $\pm$ 1.5° C the halothane-diethyl ether ratio was determined by sampling 400 microlitres of the gas phase and injecting them into the chromatograph. This was repeated using 10 ml samples of water equilibrated at 21° C, 25° C, and 37° C.

Clinical study. Six premedicated patients undergoing elective minor urologic or plastic surgical procedures were induced with intravenous thiopental or diazepam and given halothane-diethyl ether azeotrope from the same Fluotec vaporizer. Three patients were anaesthetized using a Fluotec vaporizer outside a circle absorber system with the vaporizer set up to 2.5 during induction and 0.75 to 1.5 for maintenance and with carrier gases of 3 litres of oxygen and 3 litres of nitrous oxide per minute. Respirations were spontaneous. Gas samples were taken at intervals for chromatographic analysis from the inspiratory and expiratory sides of the corrugated tubing. After inhalation anaesthesia had been established for 13 to 15 minutes, simultaneously 10 ml heparinized radial artery and peripheral venous blood samples were taken anaerobically for determination of halothane and diethyl ether concentrations. Arterial and venous blood samples were taken from an additional patient anaesthetized with azeotrope for 38 minutes. End expiratory gas samples were taken three to five minutes following cessation of anaesthesia.

Three patients were anaesthetized with azeotrope using a non-rebreathing circuit with a flow of 4 litres of oxygen and 4 litres of nitrous oxide per minute. End expiratory breath samples were taken at intervals during anaesthesia, with

spontaneous respiration and following cessation of anaesthesia for chromatographic analysis.

In three patients end expired halothane and diethyl ether were quantitated during recovery from azeotrope anaesthesia. It was assumed that at a Fluotec setting of 1.0 and 8 litres of gas passing through the vaporizer, two-thirds volume per cent halothane and one-third volume per cent diethyl ether emerged.⁴ The integrated areas of the halothane and diethyl ether chromatographic peaks from this Fluotec setting were used to determine the expired breath concentrations.

Blood halothane and diethyl ether concentrations were determined by blood-air equilibration.⁵ A calibration curve for halothane and diethyl ether was made by placing 10 ml samples of heparinized whole blood into three 36.5 ml rubber stoppered vials, weighing, injecting three different halothane and diethyl ether concentrations, and reweighing. The vials were mixed and equilibrated in a water bath at 22° C for thirty minutes. Four hundred microlitre samples of the gas phase in the vials were injected into the chromatograph and the calibration curve constructed. Blood samples from the anaesthetized patients were similarly equilibrated at 22° C, and the blood concentration determined from the calibration curve.

OBSERVATIONS AND DISCUSSION

Calibration

Figure 1 is a sample chromatogram of halothane-diethyl ether azeotrope. Elution times were eighteen seconds for water vapour, 100 seconds for diethyl ether, and 155 seconds for halothane. The mean halothane-diethyl ether vapour ratio of five lots of azeotrope was found to be 1.65 ± 0.03 (SE) and the ratio was unaltered throughout all Fluotec settings of 0.5 to 4.0. The halothane-diethyl ether ratio of azeotrope changed little when determined on ten different days over a period of twenty-five days with a mean ratio of 1.60 ± 0.01 (SE). Injection repeatability of ten consecutive gas samples of azeotrope at a 1 per cent Fluotec setting with 3 litres of oxygen and 3 litres of nitrous oxide per minute resulted in a mean integrated area of $1,610 \pm 11$ (SE) for diethyl ether and $2,753 \pm 38$ (SE) for halothane.

Laboratory studies

Figure 2 shows the results of the circle absorber experiment. The mean halothane-diethyl ether ratios following contact with soda lime, soda lime and carbon dioxide, and soda lime, carbon dioxide, and water vapour are statistically significantly different ($p < 0.01$) from that of azeotrope. The mean ratios after contact with carbon dioxide and carbon dioxide with water vapour were not statistically different from the ratio after contact with soda lime alone ($p > 0.05$). Thus, soda lime can break down the azeotrope. Since the ratio increased, halothane is present in a proportionately greater quantity in the gas phase. Soda lime is known to adsorb inhalation anaesthetics, and the results suggest that diethyl ether is adsorbed onto soda lime in proportionately greater quantity than halothane.

FIGURE 1. Chromatogram of diethyl ether (1) and halothane (2).

In vitro blood and water study. Table I lists the altered halothane–diethyl ether ratio of azeotrope after the addition of different concentrations to blood and water, and the effect of temperature on the ratio. Since the ratio increased, proportionately more halothane is present in the gas phase. The change in ratio with temperature and concentration of azeotrope in both blood and water is compatible with the fact that halothane and diethyl ether have different slopes of their blood/gas and water/gas partition coefficients at different temperatures. There is a marked difference in halothane–diethyl ether ratios in blood compared to water, with more halothane being present in the gas phase above water. This is explainable by the fact that the blood/gas partition coefficient for halothane at 37° C is 2.3 and the water/gas coefficient 0.74, signifying that halothane is more soluble in blood than in water. In contrast, at 37° C diethyl ether has a blood/gas partition coefficient of 12.1 and a water/gas coefficient of 13.1, signifying greater solubility in water than in blood. It is postulated that the change in halothane and diethyl ether ratio in blood and water occurs by extractive distillation. The solvent in this case has a boiling point 50 to 100° C higher than the azeotrope.⁶

FIGURE 2. Mean halothane-diethyl ether ratios in the circle absorber study (see text). The bars indicate the standard error of the mean.

Therefore, water probably acts as the solvent for the extractive distillation of halothane-diethyl ether azeotrope.

Clinical studies. The changes in halothane-diethyl ether ratios in the respired gases of patients anaesthetized with azeotrope are shown in Figure 3 where the circle absorber system was used and Figure 4 where a non-rebreathing system was used. The results show that the body breaks down halothane-diethyl ether azeotrope.

Since the ratio changes are greater in end expired breath of the non-rebreathing system, it is probable that soda lime played little role in azeotrope breakdown in the circle system; this is especially likely when one considers the continued inflow of fresh azeotrope, nitrous oxide, and oxygen to the circle system to "dilute" the expired ratio change. The results are in general agreement with those

TABLE I
HALOTHANE-DIETHYL ETHER RATIOS IN BLOOD AND WATER

Azeotrope added (mg %)	Temperature (°C)			
	20	21	25	37
Blood				
5.0	6.95		5.73	3.52
12.9	5.99		5.22	3.52
23.9	5.33		4.51	2.87
Water				
6.6		16.40	12.64	7.18
15.6		10.10	8.29	4.56

FIGURE 3. Mean halothane-diethyl ether ratios in the inspired and expired sides of a circle system in patients anaesthetized with azeotrope and following cessation of anaesthesia. The bars indicate the range of ratio change.

reported except that it is postulated that the breakdown of halothane-diethyl ether azeotrope is by the physio-chemical method of extractive distillation and not by biological mechanisms.³ There was a predominance of halothane in the expired breath during the period of study. This implies that proportionately more diethyl ether was being taken up by the body. End expired samples taken in four of the six patients during recovery from anaesthesia showed a halothane-diethyl ether ratio lower than that of the azeotrope and therefore a greater quantity of diethyl ether present than in the azeotrope. In the three patients in whom end expired gases were quantitated, the patient who showed the lowest ratio had 0.04 volumes per cent halothane and 0.03 volumes per cent diethyl ether present. The azeotrope re-forms in expired breath,¹ and this would leave little free diethyl ether — well below the minimum flammability of 2 volumes per cent.⁷

Table II lists the arterial and peripheral venous blood concentrations of halothane and diethyl ether after thirteen to fifteen minutes of nitrous oxide and azeotrope anaesthesia. The additional patient studied after 38 minutes of azeotrope anaesthesia had an arterial blood concentration of 2.8 mg per cent diethyl ether and 6.0 mg per cent halothane, and peripheral venous blood concentration of 2.1 per cent diethyl ether and 5.0 mg per cent halothane. The halothane concentrations were consistent with light halothane anaesthesia. The arterial blood diethyl ether concentrations were lower than predicted¹ and well below the 17 to 62 mg per cent reported for ether analgesia.⁷ The diethyl ether arterial blood

FIGURE 4. Mean halothane-diethyl ether ratios in end expired gas in patients anaesthetized with azeotrope using a non-rebreathing system, and following cessation of anaesthesia. The bars indicate the range of ratio change.

concentration range of 17 to 62 mg per cent was achieved after an induction of anaesthesia using high inspired concentrations to Guedel's stage III, plane 1 depth of anaesthesia, and then lightening the patient to Artusio's stage I plane 3 depth, which was maintained with 0.7 to 1.7 volume per cent inspired diethyl ether. The arterial blood diethyl ether concentrations in the present study are consistent with the fact that maximal inspired concentration of diethyl ether during induction was approximately 0.8 volumes per cent (Fluotec set at 2.5) and the maintenance concentrations 0.25 to 0.5 volumes per cent (Fluotec set at 0.75 to 1.5).

TABLE II
BLOOD CONCENTRATIONS (mg %) AFTER 13-15 MINUTES OF AZEOTROPE ANAESTHESIA

Patient	Arterial		Venous	
	diethyl ether	halothane	diethyl ether	halothane
1	2.2	7.6	1.8	5.0
2	1.9	4.8	1.0	3.2
3	1.6	4.7	1.4	3.9
Mean	1.9	5.7	1.4	4.0

SUMMARY

The bond(s) which join halothane-diethyl ether azeotrope can be broken by gas chromatography, soda lime, water, and blood, *in vitro* and in the body.

Soda lime breaks the bonding probably in a manner similar to that in gas chromatography. It is postulated that water, blood, and the body break the bonding by extractive distillation. Halothane-diethyl ether ratios in expired breath during azeotrope anaesthesia increased, indicating a greater proportional uptake of diethyl ether by the body; and the ratio tended to decrease during recovery, indicating a greater proportional elimination of diethyl ether. During recovery from azeotrope anaesthesia, expired diethyl ether concentrations were below the minimum flammability limit even without taking into consideration reformation of azeotrope in expired breath, which in itself would decrease the likelihood of flammability. Arterial and venous blood concentrations of halothane and diethyl ether during light azeotrope anaesthesia were determined. The diethyl ether blood concentrations are well below those reported for diethyl ether analgesia.

RÉSUMÉ

Les liens qui unissent l'halothane-diéthyl éther azéotropique peuvent être brisés par chromatographie gazeuse, par la chaux sodée, l'eau et le sang in vitro et in vivo. La chaux sodée brise la liaison probablement de la même manière que la chromatographie gazeuse. On admet que l'eau, le sang et l'organisme brisent la liaison par distillation d'extraction. Le rapport halothane-diéthyl éther augmentait dans l'air expiré durant l'anesthésie au mélange azéotropique, ce qui indiquait une plus grande absorption de diéthyl éther par l'organisme; par contre le rapport tendait à diminuer durant le réveil, ce qui indiquait une plus grande élimination proportionnelle de diéthyl éther. Durant le réveil de l'anesthésie au mélange azéotropique, les concentrations de diéthyl éther expiré étaient au-dessous de la limite inférieure d'inflammabilité, même sans tenir compte de la reformation, dans l'air expiré, de mélange azéotropique qui en soi diminuerait la possibilité d'inflammabilité. On a déterminé les concentrations dans le sang artériel et dans le sang veineux d'halothane et de diéthyl éther durant l'anaesthésie légère au mélange azéotropique. Les concentrations de diéthyl éther dans le sang sont sensiblement inférieures à celles qu'on rapporte pour l'anesthésie au diéthyl éther.

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