Anesthesiology
63:152–156, 1985

Chemistry of Halothane–Enflurane Mixtures Applied to Anesthesia

B. Korman, B.Sc., M.B.B.S., F.F.A.R.A.C.S., and I. M. Ritchie, Ph.D., F.R.A.C.I.†*

The authors obtained boiling point–composition data and vapor pressure–composition data for the halothane–enflurane system at 20° C and 25° C. This was used to demonstrate the existence of an azeotropic mixture of halothane and enflurane and to predict the output of an enflurane vaporizer contaminated with different amounts of halothane and a halothane vaporizer contaminated with different amounts of enflurane. The study was undertaken because the information allows a comprehensive description of the behavior of a contaminated vaporizer and the required data were not previously available. It was shown that an enflurane vaporizer contaminated with halothane delivers potentially dangerous mixtures of the two agents, whereas an enflurane-contaminated halothane vaporizer does not pose a serious problem. It was concluded that when halothane and enflurane vaporizers are mounted in series, the halothane should be downstream. It is explained why the halothane–enflurane azeotrope is unlikely to be useful clinically. (Key words: Anesthetics, volatile: contamination; enflurane; halothane. Chemistry: azeotrope; boiling point–composition data; vapor pressure–composition data. Physics: boiling point; vapor pressure.)

SEVERAL AZEOTROPIC MIXTURES of anesthetic liquids have been described previously.[1,2]‡ We report the existence of a halothane–enflurane azeotrope and discuss its possible use in anesthesia.

The chemistry of halothane–enflurane mixtures may be used to predict the behavior of a vaporizer, designed for one of the agents but contaminated with the other. Previous discussion of the contamination problem has involved the agents halothane and methoxyflurane.[3,4] The approach was empiric, and rules regarding the order of vaporizers, when these are mounted in series, have been suggested without reference to the underlying chemistry.[5] We believe our approach complements the previous work, allowing the output of the contaminated vaporizer to be predicted over a wide range of working conditions.

Materials and Methods

To demonstrate the existence of the azeotrope, we obtained the temperature–composition (T-x) and vapor pressure–composition (P-x) diagrams for the halothane–enflurane system.

Halothane and enflurane were supplied by I.C.I. and Abbott Laboratories and used without further purification. The halothane contained 0.01% thymol. The enflurane contained no chemical stabilizers.

The apparatus used for obtaining the P-x data is described elsewhere.§ Liquid samples containing different proportions of halothane and enflurane were prepared. Each datum point was obtained by equilibrating, under vacuum, liquid and vapor phases of a prepared sample. The total vapor pressure was measured. Liquid and vapor phases were analyzed with the use of infrared spectroscopy. The temperature of the system was maintained constant at the specified temperature (20 or 25 ± 0.02° C). The pressure and composition were determined to an accuracy of ±0.02 mmHg and ±0.005 mole fraction units, respectively.

The T-x data was obtained with the use of a modified Cottrell boiling point apparatus.¶ Analysis of samples from the liquid and vapor phases was achieved by refractometry. The boiling points and compositions were measured to an accuracy of ±0.1°C and ±0.002 mole fraction units, respectively.

Results

P-x and T-x diagrams have been drawn for the halothane–enflurane system (figs. 1 and 2). They show a vapor pressure maximum (boiling point minimum) azeotrope at a mole fraction of halothane of approximately 0.95.

We compared our measurements of the vapor pressures of the pure components at 20 and 25° C with the values calculated from the Antoine equations given by Rodgers and Hill.[6] Except for one case, the discrepancy of the two sets of numbers did not exceed 0.5%. We

* Clinical Assistant, Department of Anesthetics, Royal Perth Hospital.

† Professor of Chemistry, School of Mathematics and Physical Sciences, Murdoch University.

Received from the Department of Anesthetics, Royal Perth Hospital, Perth, W.A. 6000, Australia, and School of Mathematics and Physical Sciences, Murdoch University, Murdoch, W.A. 6150, Australia. Accepted for publication March 18, 1985. Supported by a research grant from the Royal Perth Hospital.

Address reprint requests to Dr. Ritchie.

‡ Howat DDC, Walsh RS: An azeotrope mixture of halothane and methyl n-propyl ether. Proceedings of the First European Congress of Anaesthesiology, 147(a):1, 1962.

§ Korman B, Ritchie IM: The vapour-pressure composition diagram for halothane–methoxyflurane and its relevance to cross-contamination. Aust J Chem 35:1769–1774, 1982.

¶ Rodgers JW, Knight JW, Choppin AR: An improved apparatus for determining vapor–liquid equilibrium. J Chem Ed 24:491–493, 1947.

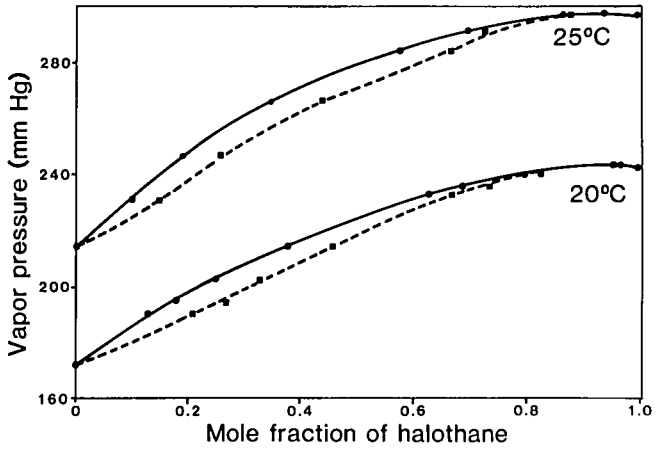

FIG. 1. Vapor pressure–composition diagram for halothane–enflurane at 20.0° C and 25.0° C: liquid composition ●, solid line; vapor composition ■, broken line. In each case, the upper curve shows the total vapor pressure as a function of liquid composition, while the lower curve shows the total vapor pressure as a function of vapor composition. A horizontal line cuts the upper and lower curves at points corresponding to the composition of liquid and vapor in equilibrium at that total vapor pressure. Compositions are expressed as mole fractions of halothane, pressures as mmHg.

also compared our boiling points with those given by the same authors. The agreement was always within 0.1° C.

Discussion

Given the different molecular structures of halothane and enflurane, it is not surprising that mixtures of the two agents are associated with deviations from Raoult's law and azeotrope formation.[7] The composition of the azeotrope is such as to make it unlikely that the properties of halothane and enflurane would be satisfactorily combined. Even if it consisted of a more balanced mixture of the two agents, the azeotrope would not be useful clinically. The reason for this is as follows. An azeotrope is not a chemical compound. Its composition varies with ambient pressure and temperature. During use, small changes in these variables occur within the vaporizer, resulting in the liquid mixture in the vaporizing chamber no longer having a composition corresponding to that of the azeotrope. Under these circumstances, the liquid and vapor compositions will not remain constant but will change in the manner illustrated by figure 3. This diagram is based on the P-x diagram for carbon disulfide and acetone and is typical of azeotropes with a vapor pressure maximum.[8]

On the other hand, an azeotrope associated with a vapor pressure minimum is stable. Small changes in composition of the liquid produce changes in the output of the vaporizer, which move the liquid composition

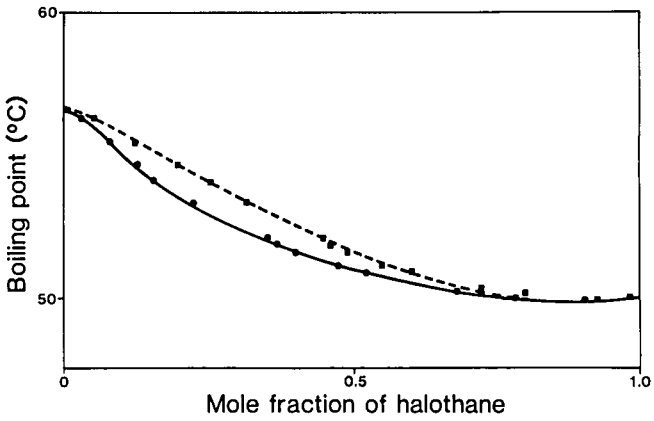

FIG. 2. Boiling point–composition diagram for halothane–enflurane at 1 atm pressure: liquid composition ●, solid line; vapor composition ■, broken line. The upper curve shows the boiling point as a function of vapor composition; the lower curve shows the boiling point as a function of liquid composition. Compositions are expressed as mole fractions of halothane, boiling points in °C.

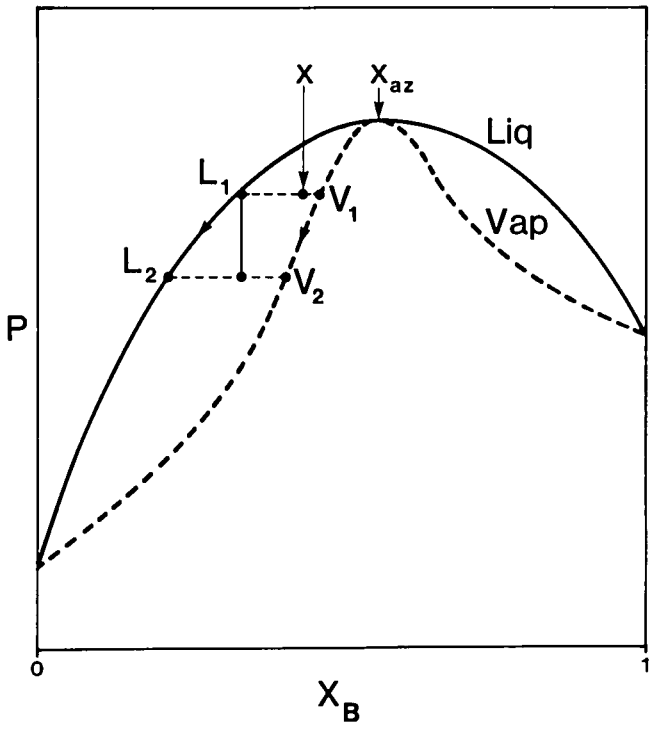

FIG. 3. Pressure–composition diagram for an azeotropic system with a vapor pressure maximum. The upper curve is a plot of the total pressure *versus* composition of the liquid; the lower curve is a plot of the total pressure *versus* composition of the vapor. Suppose the liquid in the vaporizer has a composition x, which is marginally less than the azeotropic composition x_{az}. On vaporization, this produces a liquid and vapor represented by the points L_1 and V_1. The vapor is carried to the patient, and the liquid left in the vaporizer has become enriched in component A. This liquid, in turn, separates into liquid and vapor represented by the points L_2 and V_2. It can be seen that the vapor composition is moving progressively away from x_{az}.

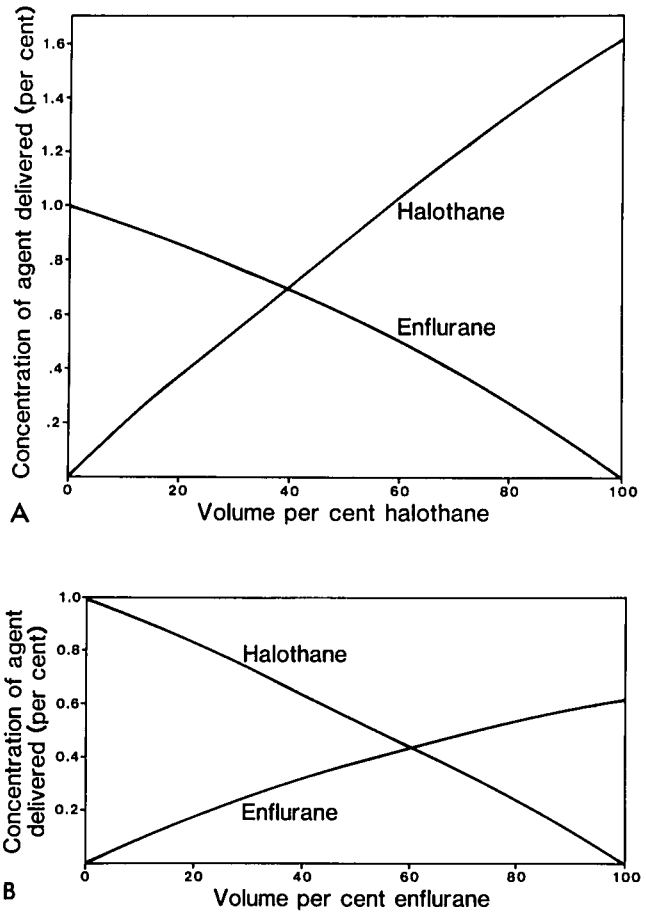

FIG. 4. Output of vaporizer-specific agent and contaminant as a function of contaminant concentration for (*A*) an enflurane vaporizer contaminated with halothane, (*B*) a halothane vaporizer contaminated with enflurane. In each case the vaporizer has been set to deliver 1%. The composition of the liquid in the vaporizer is expressed as the vol% of the contaminant. Curves have been drawn for 20° C. The diagram for 25° C is not appreciably different.

toward that of the azeotrope. This applies to the azeotropes of halothane with diethyl ether[9] and methyl n-propyl ether.[10]

P-x diagrams also may be applied to the situation where a vaporizer intended for use with one agent has been contaminated with another agent. Such contamination could occur due to accidental filling or to cross-contamination between in-series vaporizers.

We have previously shown that liquid mixtures of halothane and methoxyflurane obey Raoult's law.** The vapor above such mixtures is therefore significantly enriched in halothane. In methoxyflurane vaporizers of the variable-bypass type, a large proportion of the incoming gas is diverted through the vaporizing chamber. These two facts explain why a methoxyflurane vaporizer, contaminated with halothane, delivers dangerous concentrations of the more volatile agent.[3,4]

In the case of halothane and enflurane, the liquid and vapor curves on the P-x diagram almost coincide, particularly at high concentrations of halothane. This means that when halothane is contaminated with small amounts of enflurane (<5% on the mole fraction scale), there is no enrichment of the vapor with enflurane. On the other hand, when liquid enflurane is contaminated with halothane, the vapor undergoes slight enrichment in halothane.

Using the P-x data, it is possible to predict the output of a contaminated vaporizer of the variable-bypass temperature-compensated type (see Appendix 1). The output of the contaminant depends on the amount present in the liquid and the dial setting selected. It varies almost linearly with the dial setting. Figure 4*A* shows the predicted output of an enflurane vaporizer set at 1% and contaminated with varying amounts of halothane. Figure 4*B* shows the output of a halothane vaporizer, also set at 1% and contaminated with varying amounts of enflurane. The enflurane vaporizer contaminated with halothane is potentially dangerous. It is possible to express the output of such a vaporizer in terms of an equivalent concentration of enflurane (see Appendix 2). The results are shown in figure 5. (The figure also shows the equivalent halothane output when a halothane vaporizer is contaminated with enflurane.)

Most enflurane vaporizers may be set to deliver up to 5% enflurane. The equivalent concentration of en-

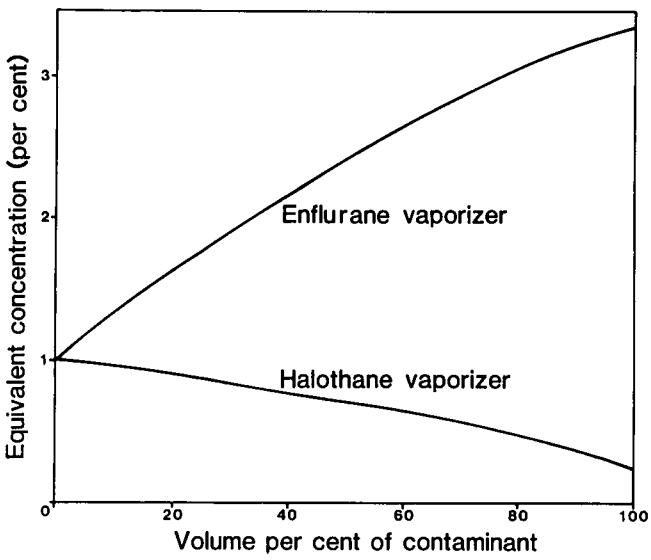

FIG. 5. Output of a contaminated vaporizer at 20° C and set at 1%, expressed as the equivalent output of the agent specific to the vaporizer. *Upper curve:* enflurane vaporizer contaminated with halothane. *Lower curve:* halothane vaporizer contaminated with enflurane. The diagram for 25° C is not appreciably different.

** Korman B, Ritchie IM: The vapour–pressure composition diagram for halothane–methoxyflurane and its relevance to cross-contamination. Aust J Chem 35:1769–1774, 1982.

flurane delivered when such a vaporizer is contaminated with halothane is by no means trivial, even when the degree of contamination is small. For example, an enflurane vaporizer contaminated with 20 vol% halothane will deliver a vapor with a potency 1.5 times that of the dialed concentration of enflurane. When halothane and enflurane vaporizers are mounted in series, the halothane vaporizer therefore should be placed downstream.

Appendix 1

In the following equations, the subscripts e, h, m refer to enflurane, halothane, and methoxyflurane, respectively.

A. Relationship between mole fraction, x, and vol%, V.

The number of moles, N, of a compound is calculated by dividing the mass of the compound by its molecular weight, M.

The mole fraction of halothane, x_h, in a mixture of halothane and enflurane is given by:

$$x_h = N_h/(N_h + N_e) \quad (1)$$

$$= 1/\{1 + (N_e/N_h)\} \quad (2)$$

For a liquid mixture,

$$N_e/N_h = (100 - V_h)D_eM_h/V_hD_hM_e \quad (3)$$

where D_e, D_h are the densities of liquid enflurane and halothane, respectively.[11]

B. Relationship between dial setting and flow-splitting ratio.

If the vaporizer diverts a fraction, f, of the fresh gas flow through the vaporizing chamber of an uncontaminated vaporizer, the volume, K liters, of agent added to each liter of fresh gas flowing through the vaporizer is given by:

$$K/(K + f) = P^*/P_b \quad (4)$$

where P^* and P_b are the saturated vapor pressure of the agent and barometric pressure, respectively. The concentration, G%, of agent delivered by the vaporizer may be determined from:

$$G/100 = K/(1 + K) \quad (5)$$

Eliminating K between equations (4) and (5) and solving for f, we obtain:

$$f = G(P_b - P^*)/P^*(100 - G) \quad (6)$$

C. Output of a contaminated vaporizer.

If the same vaporizer is now contaminated with a mole fraction x of contaminant in the liquid, associated with a mole fraction y of contaminant in the vapor, then each liter of fresh gas will collect an additional L liters of contaminant vapor where:

$$L/(K + L + f) = yP/P_b \quad (7)$$

$$K/(K + L + f) = (1 - y)P/P_b \quad (8)$$

Here P is the total vapor pressure. Solving for K and L we have:

$$L = yPf/(P_b - P) \quad (9)$$

$$K = (1 - y)Pf/(P_b - P) \quad (10)$$

The percentage of the initial agent delivered by the vaporizer is then:

$$100K/(1 + K + L) = 100Pf(1 - y)/(P_b + Pf - P) \quad (11)$$

while the percentage of contaminant delivered is:

$$100L/(1 + K + L) = 100Pfy/(P_b + Pf - P) \quad (12)$$

Points to plot figure 4*A* are obtained as follows. For the case of an enflurane vaporizer contaminated with halothane and operating at 20°C, we first determine f from equation (6). (With G = 1, f = 0.0346.) For each value of V_h, x_h is calculated in equation (2). The value of y_h and *P* associated with this value of x_h are then determined from figure 1. This is done by extending a vertical line upward from the value of x_h on the mole fraction axis until it cuts the upper curve (*i.e.*, the liquid composition curve). A horizontal line drawn at this point cuts the pressure axis at P and the lower curve (*i.e.*, the vapor composition curve) at y_h. These values of f, P, and y are used in equations (11) and (12). Similar calculations allow the other graphs in figures 4*A* and 4*B* to be plotted.

D. Output of a methoxyflurane vaporizer contaminated with halothane.

In this case, Raoult's law is obeyed. The partial pressures of halothane and methoxyflurane, P_h, P_m, are therefore given by:

$$P_h = x_hP_h^* \quad (13)$$

$$P_m = (1 - x_h)P_m^* \quad (14)$$

y_h and P are then obtained from:

$$P = (P_h + P_m) \quad (15)$$

$$y_h = P_h/P \quad (16)$$

Values obtained using equations (11) and (12) agree well with experiment.††

E. Relationship between vaporizer output and dial setting, G.

Substituting for f from equation (6) into equations (11) and (12),

$$100Pyf/(P_b - P + Pf) = 100Py(P_b - P^*)G/\{100P^*(P_b - P) + P_b(P - P^*)G\} \quad (17)$$

$$100P(1 - y)f/(P_b - P + Pf) = 100P(1 - y) \times (P_b - P^*)G/\{100P^*(P_b - P) + P_b(P - P^*)G\} \quad (18)$$

The second term in the denominator of these expressions is generally small when compared with the first term. Its elimination leads to the following good approximations:

$$100Pyf/(P_b - P + Pf) = 100Py(P_b - P^*)G/100P^*(P_b - P) \quad (19)$$

$$100P(1 - y)f/(P_b - P + Pf) = 100P(1 - y)(P_b - P^*)G/100P^*(P_b - P) \quad (20)$$

†† Korman B, Ritchie IM: The vapour–pressure composition diagram for halothane–methoxyflurane and its relevance to cross-contamination. Aust J Chem 35:1769–1774, 1982.

Hence, the output of the initial agent and the contaminant both vary almost linearly with the dial setting.

Appendix 2

Suppose the enflurane vaporizer delivers concentrations C_e and C_h of enflurane and halothane, respectively. This is equivalent to a concentration C of enflurane where:

$$C = C_e + (C_h MAC_e / MAC_h)$$

Here MAC_e and MAC_h are MAC for enflurane and halothane and it has been assumed that the effects of halothane and enflurane are additive.[12]

For a halothane vaporizer contaminated with enflurane, the equivalent halothane concentration is given by:

$$C = C_h + (C_e MAC_h / MAC_e).$$

The authors gratefully acknowledge the generosity of I.C.I. and Abbott Laboratories in providing the anesthetic agents used for this study. They would also like to thank the Government Chemical Laboratories and the Public Health Department of Western Australia for the loan of a Miran® 1A Infrared Analyser.

References

1. Hudon F, Jacques A, Boivin PA: Fluothane-ether: An azeotropic mixture. Can Anaesth Soc J 5:403–408, 1958
2. Krantz JC, Johnson S, Ling L, Kozler VF: The anaesthetic properties of the azeotropic mixture of trifluoro-ethyl vinyl ether (Fluoromar) and 1,1,2-trifluoro 2,2,1-trichloroethane (Genetron 113). J Pharmacol Exp Ther 130:492–496, 1960
3. Dorsch SE, Dorsch JA: Chemical cross-contamination between vaporizers in series. Anesth Analg 52:176–180, 1973
4. Murray WJ, Zsigmond EK, Fleming P: Contamination of in-series vaporizers with halothane–methoxyflurane. ANESTHESIOLOGY 38:487–490, 1973
5. Dorsch JA, Dorsch SE: Understanding Anesthesia Equipment. Baltimore, The Williams and Wilkins Company, 1975, pp 136–137
6. Rodgers RC, Hill GE: Equations for vapour pressure versus temperature: Derivation and use of the Antoine equation on a hand-held programmable calculator. Br J Anaesth 50:415–424, 1978
7. Glasstone S: Textbook of Physical Chemistry, second edition. London, Macmillan, 1948, pp 709–715
8. Daniels F, Alberty RA: Physical Chemistry, fifth edition. New York, John Wiley and Sons, 1979, p 102
9. Hall KD, Forbes Norris MD, Sidney Downes AB: Physical chemistry of halothane–ether mixtures. ANESTHESIOLOGY 21:522–530, 1960
10. Howat DDC: A new azeotropic mixture. Anaesthesia 18:446–461, 1963
11. Korman B, Ritchie IM: Densities of liquid halothane, methoxyflurane and enflurane between 0 degrees and 35 degrees C. ANESTHESIOLOGY 57:42–43, 1982
12. Quasha AL, Eger EI: MAC, Anesthesia, vol 1. Edited by Miller RD. New York, Churchill Livingstone, 1981, pp 273–274