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Vaporization of Mixed Anesthetic Liquids

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The results of erroneous filling of agent-specific anesthetic vaporizers were studied. The fraction of gas flow through the vaporizer was calculated for three vaporizers set to deliver essentially equipotent final concentrations: halothane, 1% (1.25 MAC); enflurane, 2% (1.19 MAC); and isoflurane, 1.5% (1.30 MAC). These fractional flows, at 22° C, were 0.0188 for 1% halothane, 0.0615 for 2% enflurane, and 0.0295 for 1.5% isoflurane. Concentrations were calculated for cases of total filling of a vaporizer with one of the other two agents. In terms of potency of delivered agent, fourfold underdoses or overdoses could result from such errors. Refilling a 25% full vaporizer with the wrong agent then was considered. In order to calculate the concentrations of each agent that would be delivered in such a case, vapor pressures of each were determined in mixtures of two agents. Enflurane and isoflurane could not be separated satisfactorily by gas chromatography. Halothane, when mixed with enflurane or isoflurane, enhanced vaporization of each agent, as well as being somewhat more easily vaporized itself. Halothane, enflurane, and isoflurane do not form ideal solutions when mixed and the resultant vapor concentrations of each of two agents when mixed may be far from those predicted by an assumption of ideality. (Key words: Anesthetics, volatile: enflurane; halothane; isoflurane. Equipment: vaporizers, agent-specific. Physics: vapor pressure; anesthetics, mixed.)

AGENT-SPECIFIC ANESTHETIC VAPORIZERS are in common use and can easily be filled with the wrong anesthetic liquid, despite attempts to design filling systems to avoid such accidents. These vaporizers operate on the principle of diversion of a portion of total gas flow through, and the remainder around, the vapor chamber. The fraction passing through is controlled by the anesthetist, by turning a knob calibrated only for the agent for which the vaporizer was designed. The actual volume of gas flow through the vaporizer per minute is unknown to the operator.

The gas within the vaporizer is saturated with vapor of the liquid contained therein, and the effluent flow is the resultant combination of gas plus vapor. A larger volume leaves the vaporizer than enters it. The per cent vapor delivered to the patient is the vapor volume divided by total flow (total gas plus vapor volumes) times 100. The vapor volume is a function of gas flow through the vaporizer and of the saturated vapor pressure of the liquid in the device. Even if these factors are nearly identical, as when isoflurane is placed in a halothane vaporizer,[1] the potencies of the agents may be different and the anesthetist must know the identity of the anesthetic being given.

Two types of filling error may occur. An empty vaporizer may be filled entirely with the wrong agent, or a vaporizer partly filled with one agent may mistakenly be replenished with another. Results of the first type may be calculated for agents with similar vapor pressures at room temperature, such as halothane, enflurane, and isoflurane. Those of the second type require knowledge of any influence of one agent on the vapor pressure curve of another. Experiments were done to derive such data for the three volatile agents in common use today: halothane, enflurane, and isoflurane.

Methods

Calculations were done for conditions at sea level (760 mmHg) and room temperatures at 20° and 22° C. The data in table 1 were used in calculations.

Flows and concentrations within an agent-specific anesthetic delivery system were calculated from a model shown schematically in figure 1. This model incorporates the following variables: X = total gas flow proximal to vaporizer, ml; Y = gas flow into vaporizer, ml; X − Y

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TABLE 1.

Agent	Vapor Pressure (mmHg)		Vapor Pressure (atm)		MAC (%)
	20°C	22°C	20°C	22°C	
Halothane	243	266	0.320	0.350	0.80
Enflurane	175	189	0.230	0.249	1.68
Isoflurane	238	259	0.313	0.341	1.15

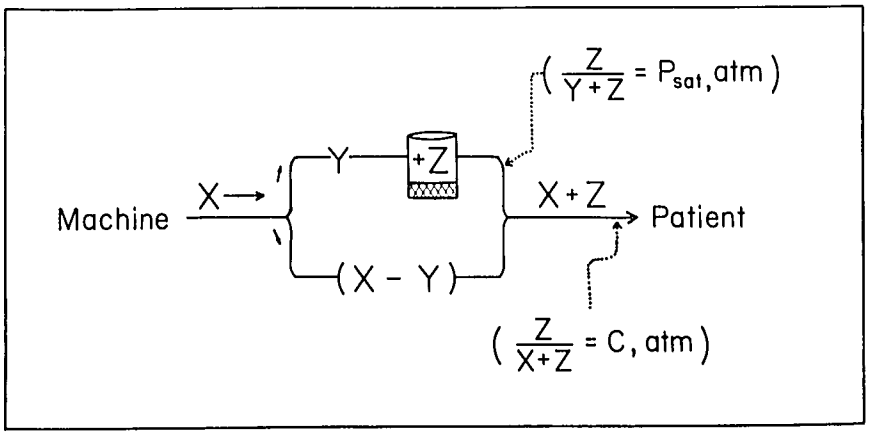

FIG. 1. Schematic representation of anesthetic delivery system. Total gas flow from machine (X) is divided into a vaporizer fraction (Y) and bypass fraction (X − Y). Gas Y equilibrates with vapor Z of the agent in the vapor chamber so that the gas plus vapor leaving the chamber is saturated with Z according to the equation, $\frac{Z}{Y+Z} = P_{sat}$, where P_{sat} is the saturated vapor concentration of the contained liquid. The concentration (C) of Z delivered to the patient is the result of its combination with the total flow, X, so that $C = \frac{Z}{X+Z}$.

= gas flow bypassing vaporizer, ml; Z = vapor volume added to Y, ml;

$$\frac{Z}{Y+Z} = P \text{ (saturated vapor concentration of Z, atm)} \quad (1)$$

$$\frac{Z}{X+Z} = C \text{ (final, delivered concentration of Z, atm)} \quad (2)$$

Using such a system, the operator controls the total gas flow, X, and sets the vaporizer control to deliver the final concentration, C. The vaporizer mechanism determines the portion, Y, of the total flow that is passed through the chamber where Z ml of vapor is added to it. The actual volume of Z depends upon the flow Y and the saturated vapor concentration of the agent, P. At sea level, saturated vapor pressure and saturated vapor concentration are identical when expressed as a fraction of an atmosphere. The symbol, P, therefore will be used to designate both, although P will be called concentration when used in equations defining concentrations. The value of P is also temperature-dependent and most vaporizers employ temperature compensation to adjust the magnitude of Y to correspond to changes in P. An exception to this rule is the Drager vaporizer, which does not adjust Y but, rather, requires the operator to read concentration from a line on the control corresponding to the room temperature. For purposes of the calculations used in this paper, it is assumed that flow Y is altered according to room temperature changes. Values of P used are either those given by the manufacturer of the agent, or calculated by the Clausius-Clapeyron equation from those given at a temperature other than 20 or 22° C.

THEORETICAL

For an agent of given saturated vapor concentration, P, values of X, Y, and Z may be derived from equations (1) and (2).

$$X = \frac{Z(1-C)}{C} \quad (3)$$

$$Y = \frac{Z(1-P)}{P} \quad (4)$$

$$Z = \frac{CX}{1-C} \quad (5)$$

Finally, the fraction of total flow, Y/X, passed through a vaporizer constructed to deliver known concentrations of a given agent, can be derived from equations (3) and (4).

$$\frac{Y}{X} = \frac{C(1-P)}{P(1-C)} \quad (6)$$

Thus, for an agent of known P in a vaporizer that adjusts Y to correspond to changes in temperature, the fractional flow (Y/X) may be calculated independently of the actual value of X. For example:

Halothane,

C = 2% (0.02), T = 22° C, and P = 0.35 atm

$$\frac{Y}{X} = \frac{0.02(1.00-0.35)}{0.35(1.00-0.02)} = 0.0379$$

Flow Y will be 0.0379X. If X = 5,000 ml/min, Y = 190 ml/min. Using these equations, flow fractions were calculated for each of three agent-specific vaporizers.

When two agents are present in the vaporizer, at vapor pressures P_1 and P_2, respectively, their vapor volumes Z_1 and Z_2 at vaporizer flow Y will be determined by the following equations:

$$\frac{Z_1}{Y+Z_1+Z_2} = P_1; \quad \frac{Z_2}{Y+Z_1+Z_2} = P_2$$

From these it follows that

$$Z_1 = \frac{P_1}{P_2} Z_2 \quad (7)$$

TABLE 2. Fractional Flow into Vaporizer (Y/X)

Vaporizer	Temperature (°C)	Setting	Y/X
Halothane	20	1.0%	0.0215
	22	1.0%	0.0188
Enflurane	20	2.0%	0.0683
	22	2.0%	0.0615
Isoflurane	20	1.5%	0.0334
	22	1.5%	0.0295

If P_1 and P_2 are known, X is determined by the operator, and Y is known from the setting (C) for the given vaporizer at the chosen value of X, Z_1 and Z_2 values can be derived and the final concentrations of each, C_1 and C_2, can be calculated. For example, a halothane vaporizer set to deliver 2% halothane from a flow rate (X) of 5,000 ml/min at 22° C will have a vaporizer flow (Y) of 190 ml/min. If this vaporizer contains agents with vapor pressures of 0.25 atm (P_1) and 0.07 atm (P_2), then

$$\frac{P_1}{P_2} = 3.57 \quad \text{and} \quad Z_1 = 3.57Z_2.$$

Substituting,

$$P_1 = \frac{3.57\ Z_2}{190\ \text{ml} + 3.57Z_2 + Z_2} = 0.25.$$

From this equation, Z_2 = 19.6 ml. Since $Z_1 = 3.57Z_2$, it equals 70 ml. Concentrations C_1 and C_2 are given by:

$$C_1 = \frac{Z_1}{X + Z_1 + Z_2} \quad \text{and} \quad C_2 = \frac{Z_2}{X + Z_1 + Z_2}.$$

Since X is known to be 5,000 ml and Z_1 and Z_2 have been derived, these concentrations are simply calculated.

EXPERIMENTAL

The values, P_1 and P_2, for a mixture of two volatile liquids, will be proportional to the relative molar proportions of the liquids if they behave as an ideal solution. However, solution behavior was unknown for the anesthetics tested. Mixtures of liquid anesthetics were made at 22° C by combining known liquid volumes of two agents in 50-ml glass syringes fitted with 3-way stopcocks. The liquids were mixed thoroughly, then allowed to equilibrate with a 40-ml portion of air overlying it within the sealed syringe. Samples of this air were taken via the stopcock and analyzed by gas chromatography for vapor content of each agent. Standards were from air overlying aliquots of each pure agent. Triplicate samples were measured at each mixture point. Gas-vapor samples were separated on a 4-foot Poropak® P column at 130° C using helium as the carrier gas. Peaks were detected by thermal conductivity. The median values and standard deviations were determined by the procedure of Dean and Dixon.[2] The results were plotted as a function of volume proportions of the two agents, and an "ideal" curve was computed for these mixtures by calculating the molar fractions of each agent at seven different volume fractions. Volumes of each agent were converted to moles by multiplying by its density and dividing this product by the agent's molecular weight.

A Fluotec® vaporizer was drained, then refilled to points where the fluid level indicator suggested it was almost empty (11 ml), at a point where it would probably be refilled (40 ml) and where the liquid meniscus was at the "full" line (111 ml). From these volumes, it was calculated that the first fluid would be between 13 and 36% of the total if the vaporizer were refilled to the "full" line with a second, incorrect liquid. An average figure of 25% was chosen to represent the likely proportion of one liquid anesthetic in the presence of another, in order to interpret the graphic data derived from the sealed syringe experiments described.

TABLE 3. Examples of Vaporizer Inflow (Y) at 5,000 ml Total Flow (X)

Vaporizer	Setting	Vaporizer Flow (Y) (ml/min) 20°C	22°C
Halothane	1.0%	108	94
Enflurane	2.0%	342	308
Isoflurane	1.5%	167	147

TABLE 4. Output in Per Cent and MAC in O_2 of Erroneously Filled Vaporizers at 22°C

Vaporizer	Liquid	Setting (%)	Output (%)	Output, MAC
Halothane	Halothane	1.0	1.00	1.25
	Enflurane	1.0	0.62	0.37
	Isoflurane	1.0	0.96	0.84
Enflurane	Enflurane	2.0	2.00	1.19
	Isoflurane	2.0	3.09	2.69
	Halothane	2.0	3.21	4.01
Isoflurane	Isoflurane	1.5	1.50	1.30
	Halothane	1.5	1.56	1.95
	Enflurane	1.5	0.97	0.57

Results

Calculations were made for the agent-specific vaporizer filled entirely with the wrong liquid agent. The following concentrations were chosen: halothane, 1% (1.25 MAC); enflurane, 2% (1.19 MAC); and isoflurane, 1.5% (1.30 MAC). For these vaporizers, at these settings, the fractions of total flows (Y/X) into the vaporizers are shown in table 2. Next, a total flow rate from the machine (X) of 5,000 ml/min was assumed, and multiplied by these fractions to derive the actual vaporizer flows shown in table 3. Further calculations were made only for a room temperature of 22° C. At this temperature, the vaporizer flows in table 3 would become saturated with vapor at

the vapor pressure of that agent. The vapor volumes so added to a total flow of 5,000 ml/min were calculated for correctly and incorrectly filled vaporizers. The results are given in table 4. Depending on which agent is contained in a given vaporizer, fourfold overdoses or underdoses are possible when the vaporizer is mistakenly believed to contain the proper agent and is turned to a setting appropriate for that agent, between 1.2 and 1.3 MAC.

The vapor concentration curves for two anesthetic agents mixed in varying proportions are shown in figures 2 and 3. In those figures, the curves representing vapor concentrations that would overlie ideal solutions are given for reference. No data are given for enflurane–isoflurane mixtures since we could not separate them sufficiently well by gas chromatography to quantitate their vapor concentrations when mixed together. Deviations from ideality were greatest for enflurane and least for halothane. These curves give values of P_1 and P_2 of two agents in a given mixture. From these values, actual concentrations, C_1 and C_2, can be calculated when two agents are mixed, as when a vaporizer three-quarters empty is refilled with a different agent. Reading the P_1 and P_2 values from the figure for these two agents, at the abscissa point of 25% one agent and 75% the other, such calculations were made and are shown in table 5.

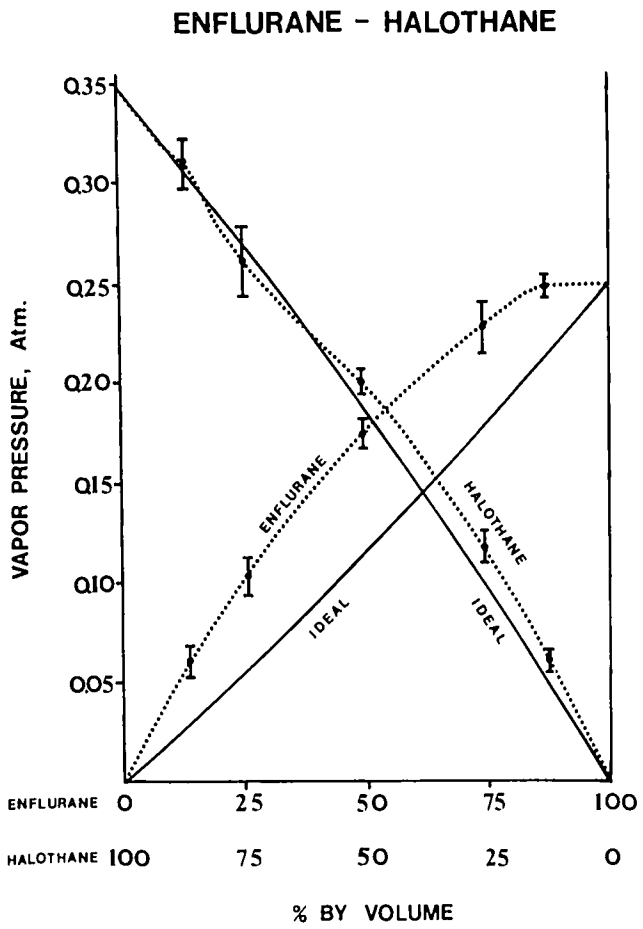

FIG. 2. Experimentally determined (dotted lines) and calculated ideal (solid lines) vapor pressures of halothane and enflurane when combined at 760 mmHg and 22° C. Ordinate: vapor pressure (concentration) in atmospheres; Abscissa: % enflurane or halothane, by liquid volume, in the mixture. Ideal curves calculated from molar fractions of each agent.

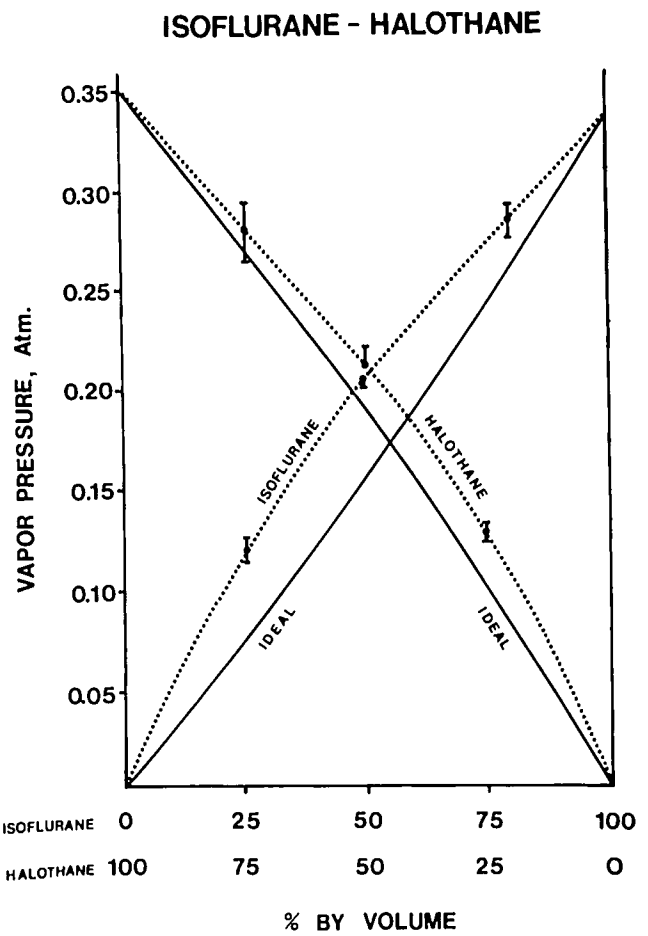

FIG. 3. Experimentally determined (dotted lines) and calculated ideal (solid lines) vapor pressures of halothane and isoflurane when combined at 760 mmHg and 22° C. Ordinate: vapor pressure (concentration) in atmospheres; Abscissa: % isoflurane or halothane, by liquid volume, in the mixture. Ideal curves calculated from molar fractions of each agent.

Discussion

Anesthetic vaporizers may be either non-agent-specific or agent-specific. The former is typified by the Copper Kettle®, or the Vernitrol®, in which a volatile liquid is placed and through which a known amount of oxygen is passed. The anesthetist must know the vapor pressure of the contained liquid at the ambient temperature, and be able to calculate vapor volume delivered and, in turn, final concentration after this vapor and its carrier oxygen is mixed into the bypass gas flow. These vaporizers have the advantage of flexibility, in allowing any liquid to be used in them, but are disadvantageous in requiring the

TABLE 5. Vaporizer Output after Incorrectly Refilling from 25% Full to 100% Full

Vaporizer	Setting (%)	Refill Liquid	Vaporizer Outputs						Total MAC
			Halothane		Enflurane		Isoflurane		
			%	MAC	%	MAC	%	MAC	
Halothane	1.0	Enflurane	0.33	0.41	0.64	0.38	—	—	0.79
	1.0	Isoflurane	0.41	0.51	—	—	0.90	0.78	1.29
Enflurane	2.0	Halothane	2.43	3.03	0.96	0.57	—	—	3.60
Isoflurane	1.5	Halothane	1.28	1.60	—	—	0.57	0.50	2.10

calculations described. This has resulted in increasing use of agent-specific devices.

The specific vaporizers automatically shunt a portion of gas flow through the vaporizing chamber. The size of this portion is unknown to the anesthetist, so if the contained agent is other than the one for which the vaporizer was designed, the concentration of the new agent cannot be deduced since necessary data are lacking. One purpose of the present study was to make the calculations needed to derive these data. Should one elect to fill an empty vaporizer with a different agent, the settings to deliver a desired anesthetic concentration can be calculated. On the other hand, if a vaporizer is filled erroneously, large errors in delivered anesthetic concentration (in terms of MAC to represent potency) will occur. This is particularly important in this era of waste gas scavenging, removing vapor odor as a means of error detection, and widespread use of muscle relaxants and mechanical ventilation, unfortunately making close clinical observation less likely. Either gross overdoses or underdoses can cause serious complications.

The refilling of a partially filled vaporizer with the wrong agent occasionally occurs, and is always unintentional. Although halothane, enflurane and isoflurane do not react chemically or form azeotropes, they evidently influence the extent of each other's ease of vaporization. They do not form ideal solutions, in which there are neither special forces of attraction nor of repulsion between dissimilar molecules and in which there are no changes in internal energy upon mixing. The partial vapor pressure of each component of an ideal solution is directly proportional to its molar fraction in the solution, that is, to the ratio of the number of moles of it to the total moles in the solution. Since they are so similar, it is likely that enflurane and isoflurane form an ideal solution and that their partial vapor pressures would be proportional to their molar fractions. In non-ideal solutions, the attraction between dissimilar molecules may be greater or less than that between similar molecules. This will cause a decrease or increase in the ease with which molecules can leave the liquid phase and thus contribute to the partial vapor pressure over the solution. It appears that halothane facilitates vaporization of both enflurane and isoflurane by this means, and in the process is itself somewhat more likely to vaporize. Thus, when a refilling error is made, more of each agent is delivered than would be the case with an ideal solution.

The clinical consequences depend upon the potencies of each agent, as well as the delivered vapor concentrations. For example, halothane and isoflurane have nearly identical vapor pressures but differ significantly in potency. If a halothane vaporizer 25% full is refilled with isoflurane, the delivered potency presumed to be 1.25 MAC will have changed insignificantly, to 1.29 MAC. The reason for such a small difference is that the low potency of isoflurane is compensated by the considerable increase in its vapor pressure over such a mixture. In the converse situation, an isoflurane vaporizer set to deliver 1.5% (1.30 MAC), the increased vaporization of the more potent halothane causes delivery of a combined potency of 2.10 MAC. Thus, in no instance should it be assumed that agents can be mixed, even if their vapor pressures are the same.

There have been efforts, over the years, to devise systems of anesthetic vaporizer filling that will preclude errors. More than a decade ago, Munson encouraged use of an indexed pin safety system,[3] and a technologically sophisticated delivery system prototype a few years later[4] included a canister system for volatile agents that would, in the words of the authors, minimize "opportunities for mix-ups." The problem still exists, however, and the present study suggests that such efforts should be renewed.

References

1. Steffey EP: Isoflurane concentrations delivered by isoflurane and halothane specific vaporizers. ANESTHESIOLOGY 53:S19, 1980
2. Dean RB, Dixon WJ: Simplified statistics for small numbers of observations. Anal Chem 23:636–638, 1951
3. Munson ES: Hazards of agent-specific vaporizers. ANESTHESIOLOGY 34:393, 1971
4. Cooper JB, Newbower RS, Moore JW, Trautman ED: A new anesthesia delivery system. ANESTHESIOLOGY 49:310–318, 1978