

## THE HALOTHANE/ETHER AZEOTROPE - A RECONSIDERATION

Dr G. A. Busato, Gorizia, Italy, and Professor G. Bashein, University of Washington, Seattle, USA

Halothane and diethyl ether, the two anaesthetics most commonly used in developing countries, have the unusual property that they form an azeotrope when mixed in the ratio of about 2 parts halothane to 1 part ether. An azeotrope is, according to the Encyclopaedia Britannica, "... a mixture of liquids that has a constant boiling point because the vapour has the same composition as the liquid mixture... The components of the solution cannot be separated by simple distillation." Thus, when the halothane ether azeotrope (**HE**) is placed in an anaesthetic vaporizer, the proportion of halothane and ether that emerges will remain 2:1 for all dial settings and all rates of carrier gas flow. In effect, the azeotrope behaves physically as though it were a single compound.

The nature of the chemical bond between the two substances has not been determined with certainty. However, the facts that the volume of the mixture is slightly less than the sum of the volumes of its constituents, that there is a slight exothermic reaction when the components are mixed, and that the boiling point of the mixture is higher than either of its components all support the proposition that chemical bonding does occur.

The first report of **HE** for anaesthesia was by Hudon<sup>1</sup> in 1958. Notable studies favorable to **HE** include those by Dobkin et al.,<sup>2,3</sup> Wyant et al.,<sup>4,5</sup> Bengtsson et al.,<sup>6</sup> and Kalman, et al.<sup>7-9</sup> The most comprehensive available review of **HE** is in the medical thesis of Kalman (Studies on the halothane-diethyl-ether Azeotrope. Linköping University medical dissertation No. 417, Linköping, Sweden, 1994). Despite favorable reports, **HE** has fallen into disuse in developed countries, probably because of the lack of any commercial marketing, (unjustified) concerns over flammability, and because halothane itself became unpopular.

Pharmacologically, **HE** shares the properties of its component parts. Its organ system effects are described briefly below:

### Circulation

Patients under **HE** anaesthesia exhibit exceptional hemodynamic stability, probably because the ether moiety stimulates sympatho-adrenal activity and decreases vagal tone, which together tend to offset the direct myocardial depression of ether and halothane. Blood pressure tends to be stable, unless the level of anaesthesia is very deep or the patient is severely hypovolemic. Cardiac rate is well maintained, and arrhythmias are rare.<sup>5</sup> Crossover experiments in dogs at 2% concentration of halothane found that cardiac output, blood pressure, and heart rate were better preserved when the dogs also received ether from the azeotrope.<sup>3</sup>

Based upon a clinical series of over 6000 administrations, Wyant<sup>4</sup> suggested that **HE** offers a wider margin of safety than halothane alone that "makes the azeotrope a more desirable agent in the hands of those less skilled than the specialist anesthesiologist." This was confirmed in ventilated pigs, where the median ratio of

the lethal concentration to the effective anaesthetic concentration (MAC) was 3.0.8

### Respiration

The respiratory stimulating effect of the ether component of **HE** tends to offset the depressant effect of the halothane component, so that spontaneous respiration is well maintained at clinical levels of anaesthesia,<sup>6,9</sup> with rather increased respiratory frequency. In our experience the use of a moderate dose of an opioid (e.g., pethidine 1mg/kg) slows-down the frequency, somewhat improving respiration. Any tendency for hypoxia due to reduced alveolar ventilation can easily be overcome with a small amount of supplement of oxygen. Spontaneous ventilation under **HE** without supplemental oxygen cannot be recommended. Furthermore, it is important to note that **HE**, like other volatile anaesthetics, abolishes the ventilatory response to hypoxia<sup>9</sup> and can cause intrapulmonary shunt if atelectasis is present.

**HE** gas induction is faster and more pleasant than with ether, behaving much like halothane alone. It is not irritating to the airway, and it relaxes bronchial muscles, as do its parent substances. Bronchial secretion is not increased. However, salivation is increased, but not as much as with ether or ketamine.

From the point of view of respiration, recovery from **HE** anaesthesia may be safer than with modern anaesthetics. The azeotrope appears to break down in the body, and halothane, having lower blood solubility than ether, is excreted more rapidly during the early phase of recovery.<sup>7</sup> The remaining ether tends to preserve respiratory drive and give analgesia into the early postoperative period, eliminating the need for opioids and their concomitant respiratory depression.

### Hepatic function

No change in liver function has been observed in the early postoperative period after **HE**.<sup>10</sup>

### Anaesthetic Potency

The minimum alveolar concentration (MAC) for **HE** in man was found to be 0.71 vol.% (which has about 0.47% halothane), versus 0.65 % for halothane alone, suggesting that the ether component acts synergistically with halothane.<sup>7</sup> Thus, at a given MAC fraction, **HE** is less expensive to use than halothane.

### Flammability

Flammability of a vapor is not simply a physical property of the material, but rather is dependent upon the source of ignition used, the carrier gas(es), the geometric configuration of the test chamber, temperature, and other factors. Boivin<sup>11</sup> used an electric filament and reported that **HE** was nonexplosive in concentrations of 10.7% or less in oxygen. Later, Brown<sup>12</sup> used a higher-energy electric spark in a recognized standard test apparatus. He

concluded that **HE** is nonflammable in air for all practical purposes, and that its lower limit of flammability in oxygen is 7.25%. Raventos, using a similar apparatus found a lower limit of 8.0% in oxygen.<sup>13</sup> The fact that ether alone has a lower limit of flammability of in oxygen of 2.1% suggests that the presence of halothane in the mixture does little to moderate the flammability of the ether moiety (e.g., 7.25% **HE** contains about 2.4% ether).

The flammability tests indicate that the OMV<sup>6</sup> and plenum-type vaporizers should not produce flammable concentrations of the mixture at any dial setting. However, caution should be used with non-calibrated vaporizers, they have not been formally tested as to the output concentration obtained at maximal settings. Like other anaesthetics, **HE** is more flammable in nitrous oxide mixtures than in oxygen/air mixtures<sup>13</sup>

Comparative properties of the azeotrope and its components are summarized in the table below.

#### Tips for use of **HE**

The only additional equipment required is a graduated measuring cup or cylinder. Although the azeotrope is nonflammable in air, the ether component is flammable, so the azeotrope should be prepared in a well-ventilated area, away from sources of ignition. A large quantity can be prepared in advance, because the azeotrope is stable for at least 4 months when kept out of bright light.<sup>11</sup> It can be administered with the OMV,<sup>6</sup> any plenum-type vaporizer designed for halothane, or a non-calibrated Boyle's

Bottle-type of vaporizer. Because the OMV lacks temperature compensation, the concentration emerging from it at any given dial setting will diminish by about half over two hours.<sup>6</sup> **HE** should not be placed in an EMO ether vaporizer, as the thymol from the halothane will ruin it.

Inhalation induction with **HE** is neither unpleasant nor unduly long and is similar to that of halothane. With any calibrated vaporizer, the dial setting should be increased progressively to a dial setting of 4-5 and kept there for some minutes after loss of consciousness, carefully attempting from time to time to insert the laryngoscope if intubation is to be done without a muscle relaxant. Surgery can commence after 5-10 minutes.

The typical dial setting for maintenance is 1 to 2 (corresponding roughly to 0.9 to 1.5% or 1.3 to 2 MAC). However, owing to the wide margin of safety, higher concentrations can be used, when necessary.

Muscle relaxation is fairly good, probably due to the relaxing properties of ether. Nondepolarizing muscle relaxants are potentiated, and can be used sparingly for abdominal surgery and not at all for extra-abdominal interventions. The azeotrope, like its component parts, will relax uterine muscle and should be used only in low concentrations during Caesarean section.

In the absence of opioids, muscular tone, blood pressure, pupil size, eyelid reflex, spontaneous respiration depth and rate (if allowed) all help in assessing the depth of anaesthesia.

Table 1

	Halothane	Diethyl Ether	Azeotropic Mixture
Molecular weight	197.4	74.1	158 (calculated)
Boiling point @ 760 mmHg or 100 kPa (°C)	50.2	34.6	52
Vapor pressure @ 20°C (kPa [mmHg])	32.1 [243]	49.1 [373]	28.4 [216]
Liquid density	1.86	0.72	1.48
MAC (% v/v)	0.65 - 0.75	2.0	0.71
Working concentration (% v/v)	0.85 - 1.5	3 - 7	1.0 - 1.5
Flammability	No	2% to 80% in O <sub>2</sub> 2% to 36% in Air	7% to 67 % in O <sub>2</sub> not in Air
Mask induction	Acceptable, quick	Unpleasant	Acceptable, not long
Clinical signs of depth	No	Yes	Similar to ether
Induction/recovery time	Short	Long	Short
Awake analgesia	+/-	+++	++
Muscular tone	—	Decreased	Decreased
Cardiovascular function	Decreased	Stimulated	Stimulated
Respiratory function	Decreased	Maintained	Maintained

Awakening time, even after a long procedure, is about 10-15 minutes.<sup>6</sup> Postoperative nausea and vomiting are said to occur in about 10% of patients.<sup>4</sup>

### Conclusion

The azeotrope of halothane and ether appears to share many of the virtues of its constituent parts, while ameliorating their undesirable properties. It is less expensive than halothane alone and may be a safer in the hands of less experienced anaesthetists. It should be considered for routine use in developing countries.

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