Isoflurane as a general anesthetic: Will it displace all other volatile anesthetics?

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The author details the history of isoflurane usage in the United States, focusing on its physical/chemical properties, its effects on the various systems of the body, and its contraindications.

History
The discovery of the anesthetic properties of nitrous oxide, ether and chloroform satisfied the original need to relieve the pain of surgery. No significant additional inhalational anesthetics were introduced in the ensuing 80 years.

The interplay between pharmacology and anesthesiology may be seen with the introduction of several new agents from 1925-1945. Waters discovered cyclopropane, which became the most important anesthetic agent to be developed and introduced into clinical practice. All of the anesthetic agents available by 1950 possessed at least one of two defects: they were explosive when given with oxygen or they were toxic. The development of the atom bomb provided the needed economy in fluorine chemical technology and led to the synthesis of fluoroxyene, halothane, methoxyflurane, enfurane and finally isoflurane. Apart from halothane, all were ethers. The ether linkage provided a stability of cardiac rhythm which was not present with alkanes such as halothane.1

Terrell of Ohio Medical Products discovered enfurane in 1963 and isoflurane in 1965. Exhaustive testing in animals and humans suggested that isoflurane was an excellent anesthetic without any significant toxicity. It was ready to be released into clinical practice in 1975. However, a pilot study in mice by Corbett in 1976 suggested that isoflurane might be a hepatocarcinogen.2 Further studies did not confirm Corbett's finding, given that the mice used in the original study were contaminated with polybrominated biphenyls, which are potential mutagenic carcinogens.3

Isoflurane was approved by the Food and Drug Administration (FDA) and released in the United States in December, 1979. The availability of isoflurane for clinical use was targeted for the spring of 1981 following its introduction in Canadian and United States teaching centers.

Physical/chemical properties
Isoflurane is nonflammable at all anesthetizing concentrations. It is stable without the addition of a preservative. No degradation was detectable during five years of storage. It resisted breakdown by sunlight or strong alkali.4 The low blood/gas partition coefficient of isoflurane allows rapid induction and recovery from anesthesia. Its rapid elimination and minimal metabolism result in a low potential for viscerotoxicity. Its vapor pressure 31.9 kPa (240 mmHg) at 20°C is nearly identical to that of halothane 32.5 kPa (244 mmHg).
Like enflurane and methoxyflurane, isoflurane is a methyl ethyl ether. The three ethers differ from halothane which is an alkyl halide. All four modern anesthetics are halogenated. All are flurinized and chlorinated and in addition halothane is brominated. Interchange of anesthetics, however, is not recommended because of the potential for misidentification and vaporizer contamination.

Minimum alveolar concentration (MAC)

The minimum alveolar concentration of isoflurane which prevents movement in response to surgical incision in 50% of patients is 1.15% in the 30 to 55 year-old age group and reaching 1.05% in patients over the age of 55 years. If nitrous oxide is used, the isoflurane requirement decreases by slightly less than 1% of MAC for each percent of nitrous oxide used.

If 70% nitrous oxide is used, the average inspired concentration of isoflurane may be reduced to 1.3-1.4% to provide optimum concentration of isoflurane during maintenance of anesthesia. The requirement of isoflurane is decreased in older age groups; when there is a decreasing body temperature; in pregnancy; and when sedative-narcotic drugs, catecholamine-depleting agents (alpha methyl dopa) or lidocaine are administered. Chronic alcohol ingestion increases isoflurane MAC.

Uptake and distribution

The blood/gas partition coefficient of 1.4 for isoflurane is lower than any other available potent anesthetic agent (enflurane 1.9, halothane 2.3). This allows a rapid induction of anesthesia. An alveolar concentration equal to 50% of the inspired concentration is reached after four minutes with isoflurane, five minutes with enflurane and 30 minutes with halothane.

Recovery is rapid with isoflurane as alveolar ventilation rapidly decreases the arterial partial pressure of the agent. Almost all isoflurane taken up is eliminated unchanged via the lungs. Isoflurane is only modestly soluble in rubber (0.62 rubber/gas coefficient at 23°C) and consequently its loss into the anesthetic circuit is small.

Effects on the respiratory system

Like halothane and enflurane, isoflurane is a potent respiratory depressant. In a study of unstimulated human volunteers, the arterial PCO$_2$ during spontaneous ventilation was found to be 6.6 kPa (50 mmHg) at 1 MAC and 8.6 kPa (65 mmHg) at 1.5 MAC. Surgical stimulation decreased PCO$_2$ by 0.6-1.7 kPa (5-13 mmHg), a sufficient reduction to cause PCO$_2$ values to be less than 6.6 kPa (50 mmHg) even at deep levels of isoflurane anesthesia (Figure 1).

In humans, isoflurane, halothane and enflurane each decrease the ventilatory response to hypoxia even though PCO$_2$ is held constant. Thiopental appears to be less depressant. Like halothane, isoflurane can depress the bronchoconstrictive response to antigen injections in sensitized animals. Isoflurane can be used for the asthmatic patient.

Figure 1.
Arterial P$_{CO_2}$ during spontaneous ventilation in unstimulated healthy volunteers awake and during anesthesia. (Data from Eger with permission.)

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<th>PaCO$_2$ (torr)</th>
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Figure 2.
Arterial blood pressure with controlled ventilation in unstimulated human volunteers during anesthesia. (Data from Eger with permission.)
patient or for those suffering from chronic obstructive pulmonary disease (COPD).

Effects on cardiovascular system

Although all modern inhalation anesthetics can cause myocardial depression, there appears to be quantitative differences between isoflurane and enflurane or halothane. Unlike enflurane or halothane, 1-2 MAC isoflurane does not decrease myocardial function or cardiac output (provided PCO$_2$ is maintained at a normal level).

Animal studies suggest a greater margin of safety for isoflurane. In rats, myocardial concentration of isoflurane (which produces cardiovascular collapse) is 5.7 times higher than the myocardial concentration present at a minimum level of anesthesia. This difference is significantly smaller for enflurane (3.3), halothane (3.0) and methoxyflu- rane (3.7), suggesting a greater margin of safety for isoflurane.

All modern, potent inhalation anesthetics (including isoflurane) lower systemic arterial blood pressure in a dose-related fashion (Figure 2). A dose-related depression of ventricular function in the intact dog has also been demonstrated. Though isoflurane does not alter cardiac output, there is decrease of total peripheral resistance. Isoflurane produces vasodilation of cutaneous, splanchnic and cerebral vascular beds.

Heart rate is modestly increased at the highest level of isoflurane anesthesia in man. Deepening anesthesia does not cause a further increase in heart rate. This is in contrast to enflurane, which causes a dose-related increase in rate, and to halothane which causes no increase in rate.

Unlike anesthetics containing ether linkage (isoflurane, enfurane, and the like), halothane increases the sensitivity of the heart to the arrhythmogenic effects of epinephrine. In humans given 1.25 MAC isoflurane, the dose of epinephrine which produces three or more ventricular extra-systoles when injected submucosally is 6.7 mcg/kg, while for halothane the dose is 2.1 mcg/kg. These data imply a greater margin of safety to the use of isoflurane in the presence of increased levels of epinephrine (Figure 3).

Effects on the central nervous system

All inhaled anesthetics produce dose-related depression of the brain which is reflected in alterations in the EEG (gradual progression to burst suppression to an isoelectric state). It was presumed that isoflurane like its isomer enflurane possessed excitatory properties. Several studies have shown that isoflurane anesthesia is not associated with convulsive activity even with or without hypocapnia.

Recently Newberg and Michenfelder have shown that isoflurane is unique among the volatile anesthetics in that an isoelectric electroencephalogram (EEG) can be produced in man with a clinically relevant end-expired concentration (2.4%) without marked systemic hemodynamic effects. Furthermore, it was shown that concentrations of isoflurane necessary to abolish cortical activity

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**Figure 3.**
Incidence of ventricular arrhythmia following epinephrine injection during anesthesia and surgery. (Data from Johnston, et al, with permission.)

**Figure 4.**
Cerebral blood flow awake and during anesthesia in human volunteers during eucapnia. (Data from Eger with permission.)
have no direct toxic effect on cerebral metabolic pathways. Assuming that cerebral metabolic depression without toxicity relates to brain protection, a potential clinical use of isoflurane is that of cerebral protection in circumstances correctly cited as appropriate for barbiturate therapy. Whether this relates to the lower solubility of isoflurane (hence rapid elimination) or to its lesser catabolism or to some other factor is not known.

Like other inhaled anesthetics, isoflurane decreases cerebrovascular resistance and increases cerebral blood flow (Figure 4). At a deeper level, all three agents produce significant increases in cerebral blood flow (hence increases in intracranial pressure). In man, increases in intracranial pressure are prevented by passive hyperventilation even in the presence of space-occupying lesions. This is in contrast with halothane in which hyperventilation must be applied before administration of the agent.

**Neuromuscular effects**

All modern anesthetics can inhibit neuromuscular impulse transmission and may decrease the strength of muscle contraction. The ethers appear to be more effective in this regard than halothane. In this respect, isoflurane is equal to enflurane, but is roughly two to three times more potent than halothane (Figure 5). Potentiation implies not only that less relaxant is required to achieve a given level of relaxation, but also that the relaxant effect can be reversed by elimination of the anesthetic.

**Obstetrical anesthesia**

Isoflurane, enfurane and halothane produce significant dose-related depression of contractility of human uterine muscle. Clinical experience with isoflurane in obstetrics (both vaginal and cesarean section) is thus far limited.

**Malignant hyperthermia**

Britt et al. found that halothane is more likely to trigger malignant hyperthermia and that isoflurane and enfurane possess the same properties. Like any modern potent inhaled agent, isoflurane should not be administered to patients suspected of being susceptible to malignant hyperthermia.

**Metabolism and viscerotoxicity**

As noted above, isoflurane and enfurane are the most stable of the modern anesthetics. This stability affects their vulnerability to biodegradation. Of all the anesthetics, isoflurane is the least metabolized in humans and animals. Only 0.17% of isoflurane can be recovered as metabolites, compared to ten times this for enfurane and 100 times this for halothane. This relatively low biotransformation suggests that isoflurane should have little or no potential viscerotoxicity. If there is one principle that has been learned over the last few years, it is that the anesthetics with low biotransformation rates have less potential for renal and hepatic damage. This asset is by all means sufficient to justify isoflurane's existence.

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