Inhaled anesthetics: an historical overview

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Inhalational agents have played a pivotal role in anesthesia history. The first publicly demonstrated anesthetic of the modern era, diethyl ether, was an inhalational anesthetic. The attributes of a good agent, ability to rapidly induce anesthesia, with limited side effects has lead research efforts for over a hundred and fifty years. The explosion hazard was largely conquered with the development of the halogenated agents in the 1950s. Rapid emergence, with limited nausea and vomiting continue to drive discovery efforts, yet the 'modern' agents continue to improve upon those in the past. The future holds promise, but perhaps the most interesting contrast over time is the ability to rapidly introduce new agents into practice. From James Young Simpson’s dinner table one evening to the operating suite the next day, modern agents take decades from first synthesis to clinical introduction.

Key words: history; inhalation agents; anesthetics.

The discovery of surgical anesthetics is the story of inhaled anesthetics. From the ‘dark ages’ where diethyl ether was first synthesized, to the modern operating room, inhalational anesthetics have played a tremendous role in anesthesia. These compounds are the ‘backbone’ of modern anesthetic practice. Indeed, it can be argued that without the inhalational agents there would be no surgical anesthesia. The history of inhalational agents is also the quest for safety as many different agents have been tried. The quest for the perfect agent, one that rapidly induces anesthesia, smells pleasant and is free of side effects continues.

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IN THE BEGINNING

Diethyl ether had been known for centuries. Jabir ibn Hayyam, an 8th-century Arabian philosopher, may have been the first to compounded ether. Alternatively, Raymond Lully, a 13th-century European alchemist may also have created the compound. Diethyl ether was certainly known in the 16th century to Valerius Cordus and Paracelsus who observed that chickens went to sleep and then awakened, seemingly unharmed. Similar observations were made by Robert Boyle, Isaac Newton and Michael Faraday, although none made the conceptual leap to surgical anesthesia.

On March 30, 1842, however, Crawford Williamson Long made the intellectual connection and administered ether with a towel for surgical anesthesia in Jefferson, Georgia. The operation was simple; remove two small tumors on the neck of James M. Venable. He refused to have the tumors excised because he feared the pain that accompanied surgery. Long assured his friend that ether would alleviate pain and gained his patient’s consent to proceed. After inhaling ether from a towel Venable became unconscious. With the procedure successfully completed, Venable reported that he was unaware of the surgical procedure.\(^1\) Long, in determining the first fee for anesthesia and surgery, settled on a charge of $2.00.\(^2\)

William Thomas Green Morton after becoming aware of the phenomenon that ether dropped on the skin provided analgesia, began experimenting with inhaled ether. Liquid ether was easily transported in bottles, and the drug’s volatility and odor permitted effective inhalation. The concentrations required for surgical anesthesia were low enough that hypoxia was not a concern when breathing ether vaporized in air. Ether additionally had a unique property among all inhaled anesthetics: at levels of surgical anesthesia there was no respiratory depression. These properties when combined with ether’s slow uptake provided a significant margin of safety in the hands of relatively unskilled anesthetists.\(^3\)

After anesthetizing a variety of animals, Morton became confident of his skills with ether and anesthetized patients in his office for dental procedures. Encouraged by this success, Morton worked to gain an invitation to give a public demonstration in the Bullfinch amphitheater of the Massachusetts General Hospital. The details of October 16, 1846, and the demonstration of surgical anesthesia, are well known. Morton agreed to provide an anesthetic to Edward Gilbert Abbott, a patient of surgeon John Collins Warren for the removal of a jaw tumor. Morton’s arrival in the amphitheater had been delayed because he was obliged to wait for an instrument-maker to complete a new inhaler. It consisted of a large glass bulb inside of which was a sponge soaked with colored ether and a spout that was placed in the patient’s mouth. An opening on the opposite side from the patient on the bulb allowed air to enter and be drawn over the ether-soaked sponge with each breath.\(^4\) Gilbert Abbott later reported that he was aware of the surgery but had experienced no pain.\(^5\)

America’s greatest contribution to 19th-century, and perhaps all of medicine had been realized. Morton, wishing to capitalize on his ‘discovery’ refused to divulge the contents the inhaler. Several weeks passed before Morton admitted that the active component of the ‘Letheon,’ the colored fluid was diethyl ether. The information concerning Morton’s demonstration went round the world by train, stagecoach, and ship. Even though anesthesia made ‘painless’ surgery possible, the frequency of operations did not rise rapidly, and years would pass before anesthesia was universally recommended.
CHLOROFORM AND OBSTETRICS

James Young Simpson, a successful obstetrician in Edinburgh, Scotland, was among the first to use ether for the relief of labor pain. He rapidly became dissatisfied with ether and sought a more pleasant, rapid-acting anesthetic. David Waldie suggested chloroform, which had first been prepared in 1831. To test this agent, Simpson and his friends inhaled it after dinner at a party in Simpson’s home on the evening of November 4, 1847. They promptly fell unconscious and, when they awoke, were delighted with their success. Within 2 weeks, Simpson submitted his first account of chloroform’s use to *The Lancet*.

In the 19th Century, the relief of obstetrical pain and anesthesia during childbirth had significant social ramifications, making it a controversial subject. The prevailing view held that relieving labor pain was contrary to God’s will. Chloroform gained acceptance after John Snow used it during the deliveries of Queen Victoria. During the monarch’s labor contractions, Snow allowed the Queen to inhale chloroform on a folded handkerchief. She wrote in her journal, ‘Dr. Snow gave that blessed chloroform and the effect was soothing, quieting, and delightful beyond measure.’ By endorsing obstetric anesthesia, the Queen, as head of the Church of England, effectively ended religious debate over the appropriateness of anesthesia for labor and delivery. Four years later, Snow gave a second anesthetic to the Queen, who was again determined to have chloroform, in the same manner.

In 1848, John Snow introduced an inhaler. He realized that successful anesthetics must not only abolish pain but also prevent movement. Using an animal model, he determined the concentration required to prevent movement in response to sharp stimuli. Snow’s work approximated the modern concept of minimum alveolar concentration (MAC) despite the limitations of mid-nineteenth century technology. His studies led him to recognize the relationship between solubility, vapor pressure, and anesthetic potency, concepts that were not fully appreciated until after World War II. Snow published two remarkable books, *On the Inhalation of the Vapour of Ether* (1847) and *On Chloroform and Other Anaesthetics* (1858), which detail his investigations into anesthetic action.

THE SECOND GENERATION OF INHALED ANESTHETICS

Throughout the second half of the 19th century the search continued for the ideal inhaled anesthetic. Unexpected observations led to the discovery of the next inhaled anesthetics to be used routinely, ethyl chloride and ethylene. Ethyl chloride was used as a topical anesthetic and counterirritant. Because ethyl chloride was so volatile, skin transiently ‘froze’ when the agent was sprayed on it. Rediscovery as an inhaled anesthetic came in 1894. A Swedish dentist named Carlson sprayed ethyl chloride into a patient’s mouth to ‘freeze’ a dental abscess, and the patient suddenly lost consciousness.

Ethylene gas had been used to inhibit the opening of carnation buds in Chicago greenhouses, and in 1923, it was speculated that there might be an anesthetic action on humans. Ethylene was not a successful anesthetic because high concentrations were required, it was explosive, and it had an unpleasant odor.

In 1929, another accidental observation led to the discovery of an anesthetic agent. Propylene had demonstrated desirable properties as an anesthetic when freshly
prepared. However, after storage in a steel cylinder, propylene deteriorated into a compound that produced nausea and cardiac irregularities in humans. George Lucas, a chemist, identified cyclopropane among the chemicals the propylene had deteriorated into, and he prepared a sample in low concentration with oxygen. Lucas administered the cyclopropane to two kittens. The animals were quietly anesthetized and quickly recovered unharmed. Lucas understood that cyclopropane was a potent anesthetic. Further animal studies studied its effects and cyclopropane proved to be stable after storage.

Human studies were next. Despite a promising beginning, research was abruptly halted due to several anesthetic deaths in Toronto that had been attributed to ethyl chloride. Concern about Canadian clinical trials of cyclopropane prevented further human studies. Rather than abandon the study, Henderson encouraged an American friend, Ralph Waters, to use cyclopropane at the University of Wisconsin. The Wisconsin group investigated the drug thoroughly and reported their clinical success in 1934.9

While research with cyclopropane was ongoing, Chauncey Leake and MeiYu Chen performed successful laboratory trials of vinethene (divinyl ether) in 1930. They were thwarted in its further development by a professor of surgery in San Francisco who would not allow human studies of the agent. Ironically, Canadian anesthetists who learned of vinethene from Leake and Chen in California, conducted the first human study in 1932 at the University of Alberta, Edmonton. International research collaboration allowed both agents to be developed faster.

All volatile anesthetics of this period were explosive save for chloroform, who’s hepatic and cardiac toxicity limited use in America. Anesthetic explosions remained a rare but devastating complication for both the anesthetist and the patient. To reduce the risk of explosion during World War II, British anaesthetists used trichloroethylene. This nonflammable anesthetic found limited application in America. It decomposed to release phosgene in the presence of soda lime when warmed.

### FLUORINATED ANESTHETICS

The lightest and most reactive halogen, fluorine, forms exceptionally stable bonds. Although sometimes created with explosive force, these bonds resist separation by chemical or thermal means. Many early attempts to fluorinate hydrocarbons in a controlled manner were frustrated by the marked chemical activity of fluorine. Freon, the first commercial application of fluorine chemistry came in 1930. The first attempt to prepare a fluorinated anesthetic by Harold Booth and E. May Bixby occurred shortly thereafter in 1932. Although their drug, monochlorodifluoromethane and other fluorinated compounds studied during the 30s, had no anesthetic action, their report predicted future developments. ‘A survey of the properties of 166 known gases’ predicted that the best possibility of finding a noncombustible anesthetic agent was in the field of organic fluoride compounds. Additionally they observed that Fluorine substitution for other halogens lowered the boiling point, increased stability, and generally decreased toxicity.10

Help with the problems of halogen chemistry in anesthetic agents came from an unlikely source. The demands of the Manhattan Project for refined uranium-235 drove a better understanding of fluorine chemistry. Researchers learned that uranium could be refined through the creation of an intermediate compound, uranium hexafluoride.
Earl McBee of Purdue University, who had a long-standing interest in the fluoridation of hydrocarbons, directed this part of this project. Simultaneously, McBee had a grant from the Mallinckrodt Chemical Works, a major manufacturer of ether and cyclopropane, to prepare new fluorinated compounds for anesthesia testing. By 1945, McBee’s team had created small amounts of 46 fluorinated ethanes, propanes, butanes, and an ether.

Mallinckrodt had also provided financial support for research in pharmacology at Vanderbilt University where the anesthetic value of these chemicals was appreciated. The chair, Benjamin Robbins, a pharmacologist, was better able to assess the new drugs than most anesthesiologists of the period. While none of the initial compounds was a successful volatile anesthetic, Robbins’ conclusions on the effects of fluorination, bromination, and chlorination in his landmark report of 1946 encouraged later successful studies.11

Another team, at the University of Maryland under Professor of Pharmacology John C. Krantz, Jr., investigated the anesthetic properties of dozens of hydrocarbons over several years. Only one, ethyl vinyl ether, entered clinical use in 1947. The agent was flammable, and Krantz requested that it be fluorinated. In response, Julius Shukys prepared several fluorinated analogs. One of these, trifluoroethyl vinyl ether, or fluroxene, became the first fluorinated anesthetic, and was marketed from 1954 until 1974. It was withdrawn when a delayed discovery showed a metabolite to be toxic in animals. Fluroxene is important, not only because it was first fluorinated volatile anesthetic but because it also underscores the need for continual surveillance of anesthetic drug actions and adverse effects.12

In 1951, Charles Suckling, a British chemist was asked to create a new anesthetic. After two years of research and testing, halothane was created. Suckling made accurate predictions about the concentrations required to induce anesthesia. Halothane was offered to Michael Johnstone, a respected anesthetist of Manchester, England. To his credit, Johnstone recognized halothane’s great advantages over other anesthetics available in 1956. After Johnstone’s endorsement, halothane quickly spread across the world.13

In 1960, methoxyflurane followed halothane and remained popular for a decade. However, following protracted methoxyflurane anesthesia a dose-related nephrotoxicity was caused by inorganic fluoride. Similarly, persistent concern that cases of hepatitis following anesthesia might be due to halothane, focused the search for newer inhaled anesthetics on the resistance to metabolic degradation.

The ongoing search for the perfect volatile anesthetic, with an emphasis on metabolic stability, resulted in two fluorinated liquid anesthetics, enflurane and its isomer isoflurane. Theses two compounds were among 700 synthesized by Ross Terrell in the 1960s. Because enflurane, first synthesized in 1963, was easier to create, it preceded isoflurane. Enflurane use was restricted after it was shown to be a marked cardiovascular depressant and to have convulsant properties. Isoflurane, first synthesized in 1965, was nearly abandoned because of difficulties in purification. After this problem was overcome by Louise Speers, several successful trials were published in 1971. The release of isoflurane for clinical use was delayed a second time when there calls for repeated testing in lower animals, due to concerns that the drug might be carcinogenic. As a consequence, isoflurane was the most investigated drug heretofore used in anesthesia.

Ironically, the two ‘newest’ inhalation agents, desflurane and sevoflurane were developed in the 1960s. Concerns regarding inhalation agents presently on the market in the 1980s and 1990s (halothane with associated hepatitis; isoflurane with coronary
steal; enflurane with fluorine nephrotoxicity and seizures) as well as pressure on anesthesiologists to improve efficiency, outcomes and safety prompted further development of these drugs.\textsuperscript{14}

Sevoflurane was first synthesized in the 1960s; animal testing led to the belief that its characteristics as an anesthetic were excellent.\textsuperscript{15} The developer, Baxter-Travenol had no interest in inhaled anesthetics. Also, compared to contemporary anesthetics, toxicity was a concern the due to potential fluorine release as well as reaction with soda lime.\textsuperscript{16} It was not developed further until 1983 when Baxter contracted with Maruishi Pharmaceutical Company for further study in Japan; limited human trials took place in the United States with Anaquest in 1985. Again, because of concerns regarding toxicity, these were abandoned in the United States in 1986. Human trials continued in Japan and approval was given for clinical use in 1990. By 1994, 60% of the Japanese market was held by sevoflurane.\textsuperscript{14} In 1993 Maruish and Abbott Laboratories agreed to pursue further testing in the United States and in 1995 the FDA granted approval for the clinical use of sevoflurane.

Concerns regarding sevoflurane included fluorine release and renal failure, although after widespread use on millions of patients, this has not been shown to occur.

Another concern was the interaction of sevoflurane with soda lime; the resultant byproduct was ‘compound A’ (an olefin) that has been found to be lethal to rodents. Production of compound A is facilitated by low flow rates (less than 2 liters per minute), high concentrations of sevoflurane, increased temperature of the carbon dioxide absorbant and dehydration of the soda lime or Baralyme. Avoidance of these factors lessens the chance of toxicity and has been found to be uncommon. There is no (theoretic or real) evidence of hepatic toxicity due to sevoflurane, although there are case reports of liver enzyme elevation postoperatively.\textsuperscript{17} One significant advantage of sevoflurane is a pleasant odor and its lack of being a noxious stimulus to the airways. This broadens the use of sevoflurane as an induction agent for children and adults as well as to maintain anesthesia.

Among the 700 compounds developed by Terrell in the 1960s was desflurane, designated I-653.\textsuperscript{18,19} After its discovery, there was little further development as production involved the use of elemental fluorine, which can be potentially explosive, and the physical property of having a vapor pressure close to 1 atmosphere. It was not until 1988 when the first human trials took place in London.\textsuperscript{18}

Because of its high vapor pressure, clinical use necessitated a different type of vaporizer; thus the Tec 6 was developed. The Tec 6 vaporizer maintains a constant pressure and is electrically heated to maintain a constant temperature as dual circuit gas/vapor blender.\textsuperscript{20} Unfortunately, despite the fact that it was the most technologically advanced vaporizer in use, the manufacturer initiated a medical device recall in July 1994. There were major problems with very high (17–20%) delivered concentration and a gas leak when in the off position.\textsuperscript{21} Since these problems have been remedied, there have been few reports of problems with these specialized vaporizers.

Significant benefits of desflurane include its low solubility allowing rapid induction and awakening from anesthesia, and stability provided by fluorine substitution with almost no metabolism (approximately 0.02%). Unfortunately, it is such a pungent agent that inhalation induction in adults is commonly accompanied by coughing, breath-holding and sympathetic stimulation is thought to be due to airway irritation. In children, the irritant effects are just as significant or greater; thus it is the only anesthetic not approved for induction.

One concern regarding toxicity related to desflurane is the interaction with soda lime or Baralyme to form carbon monoxide (CO). CO formation is facilitated by
dehydration of the CO₂ absorber, with Baralyme greater than soda lime, and a low flow technique. CO levels have been documented to be quite elevated in patients, although there have not been any adverse outcomes documented. Unfortunately, CO toxicity may be confused in the post-operative state with mental irritability; nausea, vomiting, headache, dizziness and motor/visual disturbances making clinical diagnosis difficult.

Despite the fact that these agents have been shown to decrease time to awakening with faster eye opening, response to verbal command, orientation to person, place and time there has not been a clear benefit shown in decreased time to ambulation or discharge from PACU or to home. Whether this is due to no difference between agents, confounding factors such as blood loss, nausea, vomiting, and the like, or the ‘mindset’ of recovery not to discharge patients early regardless of their status, is unclear. These agents are more expensive than isoflurane and halothane; the cost is very dependent upon the flow rate. Because of conflicting information regarding earlier awakening but no difference in time to discharge, there is still controversy regarding cost effectiveness.

CONCLUSIONS

From the ‘dark ages’ until the current time, the search for an anesthetic agent that has a pleasant induction, rapid awakening without significant pain or side effects continues. In many ways, the history of this search is the history of inhalational anesthesia, with a special emphasis on volatile agents. Over the past approximately one hundred and sixty years anesthesiology has come a considerable way to finding such an agent. Yet, even with the newest agents, there are side effects and problems with metabolism that keep it from being the ‘perfect’ anesthetic. As a specialty we are closer, yet the search continues. How different will history of volatile and inhalational anesthesia be in another hundred sixty years?

REFERENCES


