Xenon: Anesthesia for the 21st century

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Xenon is a naturally occurring, gaseous element that comprises 0.000008% of air, or 0.05 parts per million. It was discovered by Ramsey and Travers in 1898. Xenon is found on the Periodic Table in group 0, which is the group commonly referred to as the noble or inert gases. It is obtained by fractionally distilling liquefied air. Xenon has been studied sporadically within the discipline of anesthesia as a replacement for nitrous oxide. Because it is a naturally occurring element, xenon is not a pollutant. It is not an occupationally hazardous gas. It is neither teratogenic nor fetotoxic, as is nitrous oxide; it does not contribute to the depletion of stratospheric ozone, as do chlorofluorocarbons and nitrous oxide. Xenon does not contribute to global warming and the greenhouse effect, as does nitrous oxide. Xenon provides excellent anesthesia and analgesia at its minimum alveolar concentration, 71%, as well as excellent analgesia at "subanesthetic" concentrations. Xenon also provides excellent cardiovascular and hemodynamic stability and offers both rapid induction and emergence. Because of the relatively high cost of xenon, a low-flow, closed-system technique is needed to be most cost effective.

Key words: Anesthesia, inhalation, nitrous oxide, xenon.

Introduction
The perfect anesthetic would seem to be one that offers rapid induction, adequate analgesia, reflex ablation, autonomic nervous system depression, amnesia, and rapid emergence with minimal to no untoward effects. In the past, both the patient and the anesthetist were at risk because of the explosive properties associated with inhaled anesthetics, most notably with cyclopropane and diethyl ether. Patients continue to experience prolonged nausea and/or vomiting from the modern anesthetic arsenal, whether intravenous or inhalational. Additionally, growing awareness of environmental concerns, both microenvironmental and global, have placed more scrutiny on contributions to stratospheric ozone depletion, global warming/greenhouse effects, and the occupational hazards surrounding the medical gases and volatile chlorofluorocarbons used in anesthesia.

Xenon is a naturally occurring element in the earth’s atmosphere. Table 1 shows the composition of atmospheric gases. Xenon is obtained by fractionally distilling liquefied air. It was discovered in 1898, by Sir William Ramsey and Morris W. Travers. On the Periodic Table, xenon is found in group 0, which is commonly referred to as the noble or inert gases because of the original belief that these elements did not participate in chemical reactions and did not form any compounds with any other atoms or molecules. However, in 1962, Bartlett reported the production of xenon platinum fluoride [Xe+(PtF₆)]; subsequently, additional xenon compounds have been synthesized. Table 2 lists the physical properties of xenon.

Historical perspective
In the 1930s, various gaseous admixtures were tested for use in breathing apparatuses for deep-sea diving. During the process of testing the
various admixtures, the narcotic-like effects of nitrogen under hyperbaric conditions were first observed.\textsuperscript{3,4} Subsequent admixtures, some of which incorporated krypton or xenon, were tested in an effort to eliminate the nitrogen narcosis that was observed. During the testing of the admixtures containing krypton or xenon, narcotic-like effects similar to those generated by nitrogen were observed during the hyperbaric conditions of diving. When tested under normobaric conditions, krypton provided no observable signs of analgesia but did cause dizziness and an alteration in the tonal quality of vocalizations.\textsuperscript{5,6} However, even under normobaric conditions, xenon demonstrated very good to excellent analgesia and a relatively rapid loss of consciousness.\textsuperscript{5,7}

Xenon was first used as an anesthetic in human volunteers in 1951.\textsuperscript{7} The volunteers in this crossover study initially breathed either 50% nitrous oxide or 50% xenon in oxygen through a closed system. The volunteers then verbally reported their subjective comparison of the 2 gases. All volunteers reported more dizziness and greater alteration of consciousness when breathing 50% xenon.\textsuperscript{7} From these initial observations and reports, Cullen and Gross\textsuperscript{7} proceeded to use xenon as the sole anesthetic for an 81-year-old man, who presented for inguinal hernia repair, with excellent results. A second patient, a 38-year-old woman undergoing surgery for fallopian tubal ligation, was anesthetized with 80% xenon/20% oxygen. In contrast to the first patient, this patient reacted to the skin incision by groaning and having a partial laryngospasm indicative of inadequate anesthesia. She was given an intravenous dose of 50 mg of meperidine, and the surgery was accomplished without further incident. From their observations during this trial, Cullen and Gross\textsuperscript{7} concluded that xenon was capable of producing satisfactory anesthesia.

In 1952, 5 patients were anesthetized using xenon. Two received only xenon as the inhalation agent, and 3 received cyclopropane and supplemental meperidine in addition to the xenon.\textsuperscript{8} During this trial, Pittinger et al\textsuperscript{8} compared numerous physiologic indicators before and during xenon anesthesia, including complete blood count, platelets, clotting times, white blood cell differentials, serum chemistry, urinalysis, and urea clearance. They found no changes in any of these indicators that could be attributed to xenon anesthesia. Trials of xenon continued sporadically throughout the 1950s and 1960s with no observation of detrimental or untoward effects.\textsuperscript{9,11} The major hindrance consistently reported by all the early investigators was the cost of xenon when compared to the cost of nitrous oxide.\textsuperscript{7,11}

Environmental issues
Since the early 1970s, awareness and concern have steadily increased regarding the condition of the earth’s atmosphere. In particular, global warming (the so-called greenhouse effect) and the condition of stratospheric ozone have been the primary focus of atmospheric environmental reports. Global warming refers to the steady increase in the average global temperature attributable to the ever-increasing amounts of pollutants released into the atmosphere each year. The reactions of the pollutants with each other and with the elements of air produce the chemical equivalent of a blanket that interferes with radiant cooling of the earth.

Ozone consists of 3 covalently bonded oxygen atoms (O\textsubscript{3}). Near the surface of the earth, ozone is considered a pollutant, a significant contributor to “smog” and an irritant to the eyes and airways.

<table>
<thead>
<tr>
<th>Table 1. Atmospheric gases (composition of air)</th>
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<tr>
<td><strong>Gas</strong></td>
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<tr>
<td>Nitrogen</td>
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<tr>
<td>Oxygen</td>
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<td>Argon</td>
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<td>Carbon dioxide</td>
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<td>Neon</td>
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<td>Helium</td>
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<td>Krypton</td>
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<tr>
<td>Hydrogen</td>
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<td>Xenon</td>
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<table>
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<th>Table 2. Physical properties of xenon</th>
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<tr>
<td><strong>Symbol</strong></td>
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<tr>
<td>Atomic number</td>
</tr>
<tr>
<td>Atomic weight</td>
</tr>
<tr>
<td>Specific gravity (density)</td>
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<tr>
<td>Freezing point</td>
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<tr>
<td>Boiling point</td>
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<td>Valence</td>
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However, ozone is found naturally in the stratosphere, the second layer of the atmosphere nearest the surface. In the uppermost portion of the stratosphere, ozone acts to absorb and/or reflect a great portion of the ultraviolet radiation the earth receives from the sun.

Numerous chemicals contribute to the greenhouse effect, most notably carbon dioxide, chlorofluorocarbons, methane, and nitrous oxide. Nitrous oxide arrives in the stratosphere from several sources. The largest amounts come from microscopic degradation of agricultural fertilizers. Once in the atmosphere, nitrous oxide has a very long lifetime, estimated at about 150 years.\(^2\)

Although the major portion of atmospheric nitrous oxide is the result of the breakdown of agricultural fertilizers, the medical industry makes a significant contribution to the overall total. Modern anesthesia scavenging systems collect waste anesthetic gases, nitrous oxide included, and vent them directly into the atmosphere. In 1988, an estimated 1 billion liters of nitrous oxide were released over the United Kingdom alone.\(^3\) In 1997, an estimated 20 billion liters were released into the atmosphere over Europe.

In addition to the reflective, or greenhouse, nature of nitrous oxide in the atmosphere, it also contributes to the destruction of the ozone layer in the earth’s atmosphere. In the stratosphere, nitrous oxide can undergo photodissociation, which produces nitric oxide.\(^4\) The nitric oxide produced becomes part of a catalytic reaction with ozone to produce nitrogen dioxide and molecular oxygen. In this reaction, a nitric oxide molecule combines with an ozone molecule to produce a molecule of nitrogen dioxide and molecular oxygen. The newly formed molecular oxygen then reacts with 2 molecules of nitrogen dioxide to form 2 molecules of nitric oxide and 2 molecular oxygens. This second reaction returns the nitric oxide, unchanged, as the catalyst for the degradation of ozone.\(^4\) The Figure shows the chemical equation for these reactions. The overall result is that 1 ozone molecule combines with 1 oxygen atom to produce 2 molecular oxygens, which results in ozone depletion.\(^5\)

The effects of nitrous oxide on the global environment are reflected in the concerns about nitrous oxide in a much smaller environment: the operating room. Such concerns were first raised in 1967 in the former Soviet Union. Vaisman\(^6\) also reported what appeared to be a higher than expected number of spontaneous abortions among female anesthesiologists. In the ensuing 30 years since Vaisman’s report, numerous retrospective studies have focused on reproductive outcomes among individuals chronically exposed to anesthetic gases.\(^15\)\(^-\)\(^23\) Studies report increased rates of spontaneous abortions and/or children with congenital anomalies among personnel chronically exposed to trace anesthetic gases. In 1980, Lane et al\(^24\) reported that nitrous oxide is fetotoxic, based on experimental results on pregnant rats exposed to concentrations of nitrous oxide ranging from 70% to 75% on the 9th day of gestation. Further, nitrous oxide has been reported to produce megaloblastic changes in bone marrow upon repeated exposures within 24 hours\(^25\) and can induce myeloneuropathy.\(^26\)

### Xenon’s advantages

As a result of the environmental concerns surrounding the use of nitrous oxide, both microscopically and globally, investigation of the use of xenon as a replacement for nitrous oxide has been renewed. As previously stated, xenon is a naturally occurring element in the earth’s atmosphere. It has a very low reactivity and was believed to be completely nonreactive or inert; it forms only a very few compounds with fluorine and oxygen.\(^2\) As a naturally occurring element, xenon is not considered an atmospheric pollutant. Because of its very low reactivity, it does not result in depletion of stratospheric ozone. It is nontoxic, nonexplosive, and is nonteratogenic.\(^24\)

Xenon has a blood-gas partition coefficient of 0.14\(^27\) and a minimum alveolar concentration
(MAC) of 71%. Table 3 compares the anesthetic properties of xenon with those of nitrous oxide, isoflurane, desflurane, and sevoflurane. Because of the lower blood-gas partition coefficient, xenon provides a more rapid induction, as well as emergence, than nitrous oxide. Cullen and Gross and Pittinger et al demonstrated that xenon provided very good to excellent analgesia. More recent investigations better quantify the analgesia provided by xenon in comparison to nitrous oxide. Patients anesthetized using xenon 70%/oxygen 30% required about 80% less supplemental fentanyl than a similar group anesthetized with nitrous oxide 70%/oxygen 30%. Xenon also has demonstrated good to excellent analgesic properties at subanesthetic concentrations of 30% (0.42 MAC) and 50% (0.70 MAC). In addition to the reduction in required supplemental intravenous opiates, xenon also affords reduction of the amount of hypnotic required to achieve and maintain the desired level of anesthesia. Furthermore, as a result of xenon’s potency, the use of volatile inhalational anesthetics, such as isoflurane, desflurane, and sevoflurane, can be significantly reduced and possibly eliminated, for certain surgical procedures.

Numerous investigators have studied the physiological effects of xenon and have reported similar effects:

1. Unconsciousness is achieved rapidly, and the pain threshold is significantly increased.
2. Vital signs remain quite stable and are virtually unchanged from preoperative measurements.
3. There is a lack of arrhythmogenicity, although it may produce slight bradycardia.
4. Xenon’s use results in suppression of the stress response to painful stimulation.
5. The performance of the left ventricle is not affected during xenon anesthesia.
6. Cerebral autoregulatory mechanisms also appear to remain intact during the use of xenon.
7. Patients anesthetized with xenon awaken more rapidly than those anesthetized with nitrous oxide.

Approximately 95% of inhaled xenon is removed in the first pass after discontinuation. In their initial investigation in 1951, Cullen and Gross observed awakening within 2 minutes of discontinuation of xenon and orientation within 5 minutes. In addition, there have been no reports of emetogenic problems associated with xenon anesthesia.

### Disadvantages of xenon

Currently, the predominant use of xenon is in association with computed tomography cerebral blood flow (CBF) studies. Xenon has been reported to increase CBF by 75% to 96% in rats and 28% to 31% in healthy human volunteer patients. Increased CBF can produce an increase in the intracranial pressure, particularly if the increased CBF is accompanied by an increase in the cerebral blood volume. In turn, an increase in intracranial pressure results in a decreased cerebral perfusion pressure. This concern is particularly relevant in patients with acute head injury.

Data from several investigators are contradictory. Therefore, because of a lack of definitive investigative conclusions as to its safety, administering xenon to surgical patients with acute head injury or intracranial pathology seems to be contraindicated.

Xenon has a specific gravity, or density, of 5.887 g/L compared to air, with a density of 1.00 g/L, and nitrous oxide, with a density of 1.53 g/L. When breathing heavy gases, airway resistance for a particular lung volume is proportional to the flow rate of the gas. Due to its greater density, xenon does result in an increase in pulmonary resistance. Increasing the pulmonary resistance results in an increase in the work of breathing. Therefore xenon should be used with caution if administered via traditional mask, laryngeal mask airway, oruffed oropharyngeal airway. Those most at risk using these delivery methods are patients with moderate to severe chronic obstruc-
tive pulmonary disease, the morbidly obese, the premature infant, or patients with airway tumors or mechanical obstruction of the airway; in short, any patient suspected of having limited energy reserves to carry out the work of breathing. Even a slight increase in the work of breathing can quickly deteriorate to exhaustion, hypoventilation, and respiratory failure.

Cost is a disadvantage that has appeared in virtually every investigation of xenon for anesthesia purposes. In 1980, xenon cost approximately $60 per liter. Currently, the price for xenon is approximately $9.50 per liter (this price quote is from a local supplier in North Carolina; prices from other local/regional suppliers will likely vary). In addition, at present no anesthetic delivery system is designed specifically for use of xenon. However, Drägerwerk AG (Lübeck, Germany) is attempting to modify its machine, the Dräger Cicero, to make it capable of administering xenon and to incorporate an integrated xenon-recycling unit, the Cicero-Xe (personal communication: Ian Seppalt, MD, anesthesiologist, Newtown, New South Wales, Australia). Due to the relative high cost of xenon, about $9.50 per liter compared to pennies per liter for nitrous oxide, both low-flow technique and a closed system are required to attempt to limit the cost of administration. A xenon-recycling unit within the anesthesia machine also would help tremendously with cost containment. Estimates of the amount of xenon needed for a single hour of anesthesia are 10 to 13 liters80 at a cost of $95 to $123.50 for the first hour alone. Currently, Tomas Marx, MD, of Ulm, Germany, is working in conjunction with Drägerwerk AG in the development and refinement of an integrated xenon-recycling system.47

Summary

Researchers have been striving to perfect the art and science of anesthesia since its development. The perfect anesthetic would afford a rapid induction; provide adequate analgesia and amnesia, reflex ablation, and autonomic nervous system depression; and afford an equally rapid emergence. Studies have demonstrated a paucity of untoward physiological effects. Presently, the chief hindrances to xenon are the relatively high cost of obtaining it and the need for new equipment in order to administer it effectively. These concerns are being addressed. Over the past 20 years, the cost of obtaining xenon has fallen dramatically and new equipment for its administration is currently being researched and developed in Europe.35

REFERENCES

(7) Cullen SC, Gross EG. The anesthetic properties of xenon in animals and human beings, with additional observations on krypton. Science. 1951;115:580-582.


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