

# Xenon as an Anesthetic Agent

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*Discovered in 1898 by British chemists, xenon is a rare gas belonging to the noble gases of the periodic table. Xenon is used in many different ways, from high-intensity lamps to jet propellant, and in 1939, its anesthetic properties were discovered. Xenon exerts its anesthetic properties, in part, through the noncompetitive inhibition of N-methyl-D-aspartate receptors.*

*Currently, xenon is being used primarily throughout Europe; however, the high price of manufacturing and*

*scavenging the noble gas has discouraged more widespread use. As technology in anesthetic delivery improves, xenon is being investigated further as a possible replacement for nitrous oxide as an inhalational agent.*

*This article reviews the anesthetic properties of xenon and current and potential research about the gas.*

**Keywords:** General anesthesia, inhalational agent, nitrous oxide, noble gas, xenon.

The search for the ideal anesthetic agent has been ongoing since the inception of anesthesia. The ideal anesthetic agent should be one that not only provides amnesia, analgesia, and muscle relaxation but also does so rapidly and with minimal side effects. Many agents exist, inhalational and intravenous, that fit only part of the profile of the ideal anesthetic agent. In fact, a polypharmacy approach is often employed in which multiple agents are used to induce and maintain anesthesia.

Inhalational agents have been used in the practice of anesthesia for centuries. From diethyl ether and nitrous oxide to sevoflurane and desflurane, inhalational anesthetics have been studied and compared extensively. Xenon has surfaced and resurfaced throughout the years, being studied for its anesthetic properties. The fact that it is odorless, nonpungent, nontoxic, nonexplosive, environmentally friendly, and unlikely to undergo biotransformation has fueled more studies for the use of xenon.<sup>1</sup> Xenon has been used in many ways since its initial discovery. A thorough understanding of xenon's properties, advantages, and disadvantages is essential to the discussion of its use as an anesthetic agent.

## Anesthetic Agents

For centuries, different medications and gases have been used in the practice of anesthesia. The goal of these agents has been to aid in the induction or maintenance of anesthesia. The ideal anesthetic agent is one that provides rapid induction, adequate analgesia and amnesia, depression of the autonomic nervous system, muscle relaxation, rapid emergence, and avoidance of undesirable side effects.<sup>2</sup>

## Pharmacokinetics and Pharmacodynamics

A discussion of the pharmacodynamic properties of volatile agents must include not only the minimum alveolar concentration (MAC) but also how and where these

agents act. The MAC, an important property of inhaled agents to understand, is defined as the concentration, in percentage, of the anesthetic that produces immobility in 50% of patients subjected to a noxious stimulus, such as surgical incision.<sup>3</sup> Anesthetics, in general, are thought to produce anesthesia by interaction with specific receptors in the central nervous system, namely, gamma-aminobutyric acid receptors and, possibly, N-methyl-D-aspartate (NMDA) receptors.<sup>4</sup> Although there is not one specific site of action shared by all inhalation agents, these sites include the reticular activating system, the cerebral cortex, the cuneate nucleus, the olfactory cortex, and the hippocampus.<sup>4,5</sup> The spinal cord, particularly the dorsal horn, has also been shown to be depressed by anesthetic agents.<sup>6</sup> Inhaled anesthetics act primarily on the spinal cord to produce immobility.<sup>6</sup>

Another pharmacodynamic property of inhaled anesthetics is explained by the Meyer-Overton rule. This rule states that the action of general anesthetics is proportional to their partition coefficient in lipid membranes.<sup>7</sup> In other words, the potency of a specific agent correlates closely with the affinity of that agent for the lipid phase, such that as the oil-gas partition coefficient increases, MAC decreases.<sup>8</sup> Although MAC values are simply averages, and individual patient results can vary, it is a useful measure because it mirrors brain partial pressure and it allows a comparison of potency between agents.<sup>8</sup> The MAC of a particular agent is altered by many factors, including temperature, electrolyte concentration, drugs, and age; in fact, MAC has been found to decrease by 6% with each decade increase in age.<sup>9</sup> Minimum alveolar concentration is unaffected by gender, species, or duration of anesthesia.<sup>8</sup> The MAC values and other properties of various inhaled agents are compared in Table 1.<sup>10</sup>

## The Noble Gases

Approximately 117 elements exist today, 94 of which

occur naturally on earth. These elements are divided into groups based on their electron configurations. Group VIII, or group O, of the periodic table is composed of helium, neon, argon, krypton, xenon, and radon.<sup>11</sup> Known collectively as the noble gases, or inert gases, these elements are stable due to a fully occupied outer shell of electrons, which means they are mostly nonreactive, or inert, to forming bonds with other elements.<sup>11</sup> Of particular interest in the field of medicine is the element xenon (Table 2).<sup>12</sup>

### The Chemical Properties of Xenon

Before the anesthetic properties of xenon can be explored, a discussion of its chemical properties is warranted. Xenon was first discovered in 1898 by British chemists Sir William Ramsay and Morris W. Trave.<sup>1</sup> Its discovery was made by the repeated fractional distillation of the noble gas krypton.<sup>1</sup> Xenon is a naturally occurring element that comprises 0.0000086%, or 0.05 parts per million, of air.<sup>2</sup> Indeed, the rarity of this element is the basis for its name. Xenon derives its name from the Greek word for “stranger”<sup>13</sup> and exists naturally as 9 isotopes, the most abundant of which is Xe 132.<sup>14</sup> It can be manufactured by the fractional distillation of liquefied air.<sup>1,2</sup> Commercially, xenon is used in many ways, including in lasers, high-intensity lamps, flash bulbs, x-ray tubes, and medicine.<sup>13,14</sup> Because xenon is a naturally occurring element, it is not a pollutant or an occupationally hazardous gas, nor does it contribute to global warming or the greenhouse gas effect.<sup>2</sup> In contrast, nitrous oxide is 230 times more potent as a greenhouse gas than is carbon dioxide, taking 120 years to break down.<sup>14</sup> These properties define xenon and contribute to its anesthetic profile.

### Xenon in Anesthesia

As discussed previously, xenon has many of the properties of an ideal inhalational agent, including the fact that it is odorless, nonpungent, nontoxic, nonexplosive, environmentally friendly, and unlikely to undergo biotransformation due to its stability.<sup>1</sup> In addition to these characteristics, as will be shown, xenon has a rapid onset of action, analgesic properties, a lack of arrhythmogenicity,

the ability to maintain cerebral autoregulatory mechanisms and cardiovascular stability, and a quick emergence profile.<sup>2</sup> The following sections provide a brief discussion of xenon’s early history, a discussion of its properties, and a comparison of xenon with other anesthetic agents.

### Early Experiments With Xenon

Although xenon was discovered in the late 19th century, its anesthetic properties were not discovered until the late 1940s by J. H. Lawrence, who determined, in mice, that xenon had narcotic properties.<sup>1</sup> A few years later, Cullen and Gross used xenon as an anesthetic agent on human volunteers.<sup>2</sup> After denitrogenation with 100% oxygen, an 81-year-old man and a 38-year-old woman were given xenon and oxygen in an 80:20 mixture; loss of consciousness required 5 minutes in the woman and only 3 minutes in the man.<sup>15</sup> Also noteworthy from this study is the fact that in both patients, “normal” vital signs were maintained throughout their respective procedures.<sup>15</sup> Cullen and Gross<sup>15</sup> concluded that xenon was capable of producing complete anesthesia.

It was not until 1965 that Eger and associates<sup>16</sup> actu-

Property	Result
Symbol	Xe
Atomic number	54
Atomic weight	131.293(6)
Electron configuration	[Kr] 4d <sup>10</sup> 5s <sup>2</sup> 5p <sup>6</sup>
Ground level	<sup>1</sup> S <sub>0</sub>
Ionization potential	12.1298 eV
Physical form	Colorless gas
Melting point	-111.74°C
Boiling point	-108.09°C
Critical temperature	16.62°C
Density	5.366 g/L
Specific heat	0.158 J/g•K

**Table 1.** Physiochemical Properties of Xenon<sup>10</sup>

Agent	MAC (%)	Blood/gas	Brain/blood	Muscle/blood	Oil/gas
Xenon	71	0.115	0.23	0.10	1.9
Nitrous oxide	104	0.47	1.1	1.2	1.4
Desflurane	6.0	0.42	1.3	2.0	18.
Sevoflurane	2.0	0.69	1.7	3.1	53.4
Isoflurane	1.2	1.4	2.6	4.0	90

**Table 2.** A Comparison of Xenon With Other Currently Used Inhalational Agents in Terms of MAC and Partition Coefficients<sup>2,8,12</sup>

MAC indicates minimum alveolar concentration.

ally established the MAC of xenon at 0.71, or 71%, indicating a greater potency than the widely used nitrous oxide, which has a MAC of 1.04, or 104%. Xenon is therefore 1.5 times more effective than nitrous oxide in depressing gross purposeful movement to noxious stimuli, such as skin incision.<sup>17</sup> Clinical trials of xenon continued throughout the late 20th century, with no observation of detrimental effects; however, the major consistently reported hindrance to the use of xenon was its high cost,<sup>2</sup> which is a recurring issue today.

### Pharmacokinetic and Pharmacodynamic Profile

The most important pharmacokinetic property of xenon is its blood-gas coefficient and how that relates to its induction and emergence times. In 1973, Steward and colleagues<sup>18</sup> reported that the blood-gas partition coefficient of xenon is generally accepted to be 0.14. However, through a series of experiments in the late 1990s, Goto et al<sup>19</sup> determined the blood-gas coefficient of xenon to actually be closer to 0.115. As stated previously, the blood-gas partition coefficient of an agent indicates its speed of onset. The significance of this finding is that in comparison with other inhalational agents, xenon has much faster onset and emergence times. Of the inhalational agents in use today, only nitrous oxide and desflurane, with blood-gas coefficients of 0.47 and 0.42, respectively, even come close to xenon in terms of speed of onset. The same is true for the emergence profile of xenon. In the studies by Cullen and Gross,<sup>15</sup> both patients who received xenon anesthetics were oriented to time, place, and person within 2 minutes of discontinuation of the gas. Because of the inert properties of xenon, once it is turned off, it washes out quickly; about 95% of it is exhaled in the first pass by the lungs.<sup>20</sup> Table 2 compares xenon's blood-gas partition coefficient with that of other inhalational agents.

Most general anesthetics exert their anesthetic action through potentiation of inhibitory synaptic receptors, mainly gamma-aminobutyric acid receptors.<sup>21</sup> Xenon, however, seems to have no effect on gamma-aminobutyric acid receptors; rather, it exerts its anesthetic action by blocking excitatory NMDA receptors in the central nervous system.<sup>21</sup> Other NMDA receptor antagonists with similar actions include nitrous oxide<sup>22</sup> and ketamine.<sup>23</sup> The analgesic effects of xenon are also explained by its inhibition of NMDA receptors in the central nervous system and by inhibition of NMDA receptors in the dorsal horn of the spinal cord.<sup>14,24</sup>

As mentioned previously, the MAC for xenon was thought to be 71%. More recent estimates of the MAC value for xenon have estimated it to be around 63%.<sup>25</sup> This makes it more potent than nitrous oxide, with a MAC value of 104%, which is clinically unobtainable without hyperbaric conditions. Another value often

measured and compared is MAC-awake, which is the concentration at which a patient opens the eyes to verbal command.<sup>1</sup> The MAC-awake for xenon is 33%, or 0.46 MAC, whereas the MAC-awake for nitrous oxide is 63%, or 0.61 MAC.<sup>26</sup>

### Advantages and Disadvantages of Xenon

Xenon as an anesthetic agent has many distinct advantages and one glaring disadvantage. As discussed, xenon has rapid induction and emergence times based on its low blood-gas partition coefficient. Goto and colleagues<sup>27</sup> found that induction of anesthesia with xenon was faster than with sevoflurane. In comparison with nitrous oxide, Goto and colleagues<sup>27</sup> found that emergence from xenon anesthesia is 2 or 3 times faster than that from comparable MACs of nitrous oxide/isoflurane and nitrous oxide/sevoflurane anesthesia. Furthermore, xenon compares favorably with other anesthetic agents. In 2001, Dingley and colleagues<sup>28</sup> found that xenon had a significantly quicker recovery time compared with an equivalent depth of propofol anesthesia. Other advantages of xenon include its analgesic properties, its cardiovascular stability, and its neuroprotective qualities. Finally, a discussion of xenon's disadvantages must include its costs.

- *Analgesic Properties of Xenon.* As previously mentioned, the analgesic properties of xenon are consistent with its ability to inhibit NMDA receptors. Also, xenon seems to be active at the level of the spinal cord, particularly in the dorsal horn. Many comparisons have been made between xenon and nitrous oxide, the only other anesthetic gas with true analgesic efficacy.<sup>13</sup> In 1998, Petersen-Felix et al<sup>17</sup> performed a series of experiments on human volunteers comparing the analgesic properties of xenon and nitrous oxide. These experiments included the nociceptive reflex to repeated stimuli, pain tolerance to ischemia, electrical stimulation, mechanical pressure, and cold.<sup>17</sup> The results of the study suggested that xenon has an analgesic potency 1.5 times that of nitrous oxide.<sup>17</sup> Although xenon and nitrous oxide are NMDA receptor antagonists, their mechanism of action is different. The antinociceptive effects of nitrous oxide are dependent on opioid receptors, particularly in the periaqueductal gray area of the brain.<sup>29</sup> Furthermore, nitrous oxide-induced analgesia can be antagonized by naloxone.<sup>29</sup> As for xenon, it was found that naloxone has no effect on the rise in pain threshold, suggesting that the analgesic effects are not mediated by opioid receptors.<sup>30</sup> Further studies have found that anesthesia with xenon has led to lower intraoperative opioid requirements<sup>31</sup> and to lower doses of propofol needed to prevent movement than with nitrous oxide.<sup>32</sup>

- *Cardiovascular Stability With Xenon.* Although a majority of the studies conducted on xenon are related to the mechanism of its anesthetic action, data on the cardiovascular effects of xenon have accumulated during the

past decade.<sup>33</sup> Lachmann and associates<sup>31</sup> reported a randomized, double-blind comparison of the efficacy and potency of xenon versus nitrous oxide and their effects on the circulatory and respiratory systems in relatively healthy patients (ASA physical status I and II). The researchers measured heart rate, noninvasive blood pressure, arterial oxygen saturation, end-tidal carbon dioxide, and lung mechanics.<sup>31</sup> They reported that the average amount of fentanyl required was about 5 times greater in the nitrous oxide group than in the xenon group and that changes in systolic blood pressure throughout the procedures were significantly smaller in the xenon group ( $P < .01$ ).<sup>31</sup> They concluded that xenon is more effective than nitrous oxide at maintaining hemodynamics.<sup>31</sup> In a similar study of patients classified as ASA physical status class I and II, Boomsma and associates<sup>34</sup> reported increased fentanyl requirements with nitrous oxide and that blood concentrations of epinephrine and cortisol increased significantly in the nitrous oxide group but did not change in the xenon group, indicating that xenon has more favorable hemodynamic, neurohumoral, and anti-nociceptive properties than does nitrous oxide.

Little is known about the cardiovascular effects of xenon in the diseased heart; in fact, most of the studies published are animal studies. However, in one study, a patient with cardiac tamponade undergoing bilateral femoral-popliteal bypass surgery received xenon for maintenance of anesthesia with no significant alteration in blood pressure, heart rate, cardiac output, systemic vascular resistance, pulmonary artery resistance, or central venous pressure.<sup>33</sup> Ishiguro<sup>33</sup> also reported unpublished data of the effects of xenon on hemodynamics in 20 patients undergoing coronary artery bypass graft surgery. Xenon was found to decrease mean arterial pressure, cardiac output, and systemic vascular resistance less than nitrous oxide.<sup>33</sup>

One interesting animal study measured the direct effect of xenon on the isolated heart, particularly the cardiomyocytes, to investigate the effect of xenon on major cation channels.<sup>35</sup> In this study, isolated guinea pig cardiomyocytes were used. The study determined that xenon did not alter any measured electrical, mechanical, or metabolic factors, nor did it alter major cation currents, including sodium channels, L-type calcium channels, and inward-rectifier potassium channels.<sup>35</sup> Another animal study by Hettrick et al<sup>36</sup> on dogs with induced cardiomyopathy found that xenon produced minimal cardiovascular effects. Finally, a study by Marx et al<sup>37</sup> measured the cardiovascular effects of xenon in varying concentrations versus total intravenous anesthesia on pigs. Investigators found that during xenon anesthesia, plasma adrenaline concentrations were reduced not only at concentrations of 1 MAC but also at subanesthetic concentrations.<sup>37</sup> This may have occurred due to the analgesic effects of xenon.<sup>37</sup> The authors' overall conclu-

sion was that xenon was an inhalational agent with little influence on the cardiovascular system.<sup>37</sup>

- *Neuroprotective Qualities of Xenon.* N-methyl-D-aspartate receptor agonism is necessary for brain function; however, excessive NMDA agonism and antagonism can cause neurotoxic effects and neuronal cell death.<sup>38</sup> Excessive stimulation of NMDA receptors leads to excess calcium entry into cells, which triggers a biochemical cascade resulting in cell death.<sup>39</sup> In certain types of neuronal injuries such as strokes, trauma, and seizures, this is the primary mechanism for neuronal injury.<sup>38</sup> On the other hand, neuronal cell death is also associated with NMDA antagonism and has been noted with other NMDA antagonists such as ketamine and nitrous oxide.<sup>38</sup>

It is interesting that xenon seems unique in that it has the ability to protect against NMDA agonism-induced neuronal injury in a dose-dependent manner without associated NMDA antagonism-induced neurotoxic effects.<sup>39</sup> Xenon has been shown to reduce the size of cerebral infarction in rats<sup>40</sup> and to reduce c-fos expression in vivo.<sup>41</sup> It also reduces cardiopulmonary bypass-induced cognitive dysfunction in rats.<sup>40</sup> Studies of xenon compared with nitrous oxide and ketamine found that while all 3 agents had neuroprotective qualities related to their antagonism of NMDA receptors, nitrous oxide and ketamine could also lead to neurotoxic effects related to dopaminergic metabolic changes, which xenon lacks.<sup>39,41</sup> Furthermore, xenon has been shown to counteract the neurotoxic effects of ketamine, which suggests that xenon, in addition to its ability to antagonize NMDA receptors, is likely to have additional targets.<sup>39</sup> Further studies by Rex and associates<sup>42,43</sup> demonstrated that general anesthesia with 1 MAC of xenon induces a global decrease in cerebral metabolism, unlike other NMDA antagonists such as nitrous oxide and ketamine. This finding suggests that NMDA antagonism is not the primary mechanism of anesthetic action for xenon in the human brain.<sup>42</sup>

Another important topic related to the discussion of neurological protection is that of cerebral blood flow (CBF). Cerebral blood flow can have an impact on intracranial pressure. One study by Laitio and associates<sup>44</sup> quantified the effects of 1 MAC of xenon anesthesia on CBF. Although most studies on CBF and xenon were animal studies, this particular study assessed human volunteers and used only xenon as the sole inhalational agent.<sup>44</sup> The results of this study indicated that xenon decreased CBF, especially in the cerebellum, thalamus, and cortical areas, whereas it increased CBF in the white matter and in parts of the precentral and postcentral gyrus.<sup>44</sup> In short, although its exact mechanism of action is unknown, it has been demonstrated that xenon is neuroprotective in certain situations.

- *The Cost of Xenon Anesthesia.* Although other disadvantages exist, the major disadvantage of xenon anesthe-

sia is the high cost associated with its production.<sup>45</sup> Studies demonstrating the cost-effectiveness of xenon take into consideration its pharmacokinetic and pharmacokinetic properties, not its cost of production. Xenon is a rare element, and although it is environmentally friendly, manufacturing of this noble gas consumes an enormous amount of energy.<sup>1</sup> Associated costs with the introduction of any new anesthetic agent are multifactorial and involve the purchase of new equipment such as vaporizers, monitors, and anesthesia machines.<sup>1</sup> According to Hanne et al,<sup>12</sup> a reduction of these costs in the near future is unlikely. Although the price has declined drastically in the past 2 decades, 1 L of xenon costs approximately \$20 today, compared with pennies per liter for nitrous oxide.<sup>10</sup> One study by Nakata and associates<sup>46</sup> found that the cost of xenon anesthesia in a 40-year-old, ASA physical status I man weighing 70 kg costs \$356 for 240 minutes of closed-circuit anesthesia. In comparison, closed-circuit anesthesia with nitrous oxide and isoflurane costs only \$52.<sup>46</sup> The majority of the cost of xenon anesthesia was due to the inability to reuse scavenged gas and priming the anesthesia machine proximal to the breathing system. This was a notable factor at the beginning of the anesthetic before complete rebreathing had been established.<sup>46</sup>

- *Reducing the Cost of Xenon Anesthesia.* Given xenon's favorable pharmacological profile, the development of any means to offset its high costs is warranted. Methods to reduce costs of xenon include decreasing consumption, recycling used xenon, and reducing manufacturing costs.<sup>12</sup> Although flushing and priming of the system accounts for the major costs, closed-circuit anesthesia seems to be the only economically acceptable technique for xenon delivery.<sup>12</sup> Another means of cost reduction is the development of a xenon recycling system.<sup>13</sup> One such device in Germany is capable of removing accumulated nitrogen, acetone, and methane to obtain pure xenon.<sup>1</sup> The drawback to this recycling system, however, is that for xenon to be recovered, another agent would have to be used to maintain anesthesia, thereby negating the beneficial emergence properties of xenon.<sup>14</sup> Dingley and Mason<sup>47</sup> recently developed a cryogenic scavenging system that shows promise.

An interesting note related to the cost of xenon anesthesia is that according to the study by Nakata and associates,<sup>46</sup> after 4 hours of administration in a completely closed system, xenon becomes comparable in cost to other anesthetics. This gives xenon a clear edge in settings such as cardiac and neurological surgery, in which prolonged administration of anesthesia is required and rapid emergence is beneficial.<sup>14</sup> Unfortunately, even if the cost of xenon anesthesia can be even reasonably reduced, it is still unlikely to gain widespread use due to its limited availability.<sup>12</sup>

- *Other Advantages and Disadvantages of Xenon.* Other advantages of xenon include its environmental effects, its

effects on organ systems, and its lack of toxic effects. The major anesthetic agents used today are chlorofluorocarbon-based and are known to deplete the ozone layer.<sup>13</sup> In comparison with the other inhalational agents, xenon is a naturally occurring constituent of the environment and has no detrimental ecological effects.<sup>14</sup> In addition, xenon seems to have no adverse effects on various organ systems.<sup>14</sup> It does not impair hepatic or renal function<sup>48</sup>; in fact, it may prove to be the anesthetic of choice in surgery when these systems are impaired.<sup>14</sup> Reports also suggest that xenon exerts no effects on coagulation, platelet function, or the immune system.<sup>14</sup> Finally, experiments suggest that xenon does not trigger malignant hyperthermia<sup>49</sup> and that diffusion hypoxia is unlikely during recovery from xenon anesthesia.<sup>12</sup>

In addition to the high cost, xenon has other disadvantages. Although more research is needed, the study on the analgesic properties of xenon by Petersen-Felix et al<sup>17</sup> demonstrated a high incidence of postoperative nausea and vomiting. Another disadvantage of xenon that is similar to that of nitrous oxide is its ability to diffuse into closed spaces. Although the diffusion rate of xenon is slower than that of nitrous oxide due to the lower blood solubility of xenon, it may not be the best choice of anesthetic for patients at risk for gas embolism, pneumothorax, or ileus.<sup>12</sup> Last, xenon has proven to increase pulmonary resistance due to its greater density.<sup>50</sup> This can increase work of breathing, which increases the risk in patients with conditions such as moderate to severe chronic obstructive pulmonary disease, morbid obesity, airway tumors, and in premature infants.<sup>2</sup>

## Summary

Similar to other fields, anesthesia is ever changing. New anesthetic agents are constantly being tested and added to the market. The ability to understand and adapt to these changes is essential to the practice of anesthesia. Inhalational agents are as old as anesthesia itself, and although it has been around for many years, xenon has only recently been extensively studied for use in anesthesia. Despite the disadvantages of xenon, such as high cost and limited availability, its pharmacokinetic and pharmacodynamic properties warrant further consideration. With a quick onset, analgesic properties, cardiovascular and neurological stability, and environment-protective qualities, xenon could very well be the anesthetic of the future.

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