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Will Xenon Be a Stranger or a Friend?

The Cost, Benefit, and Future of Xenon Anesthesia

Xenon is both an old and a new anesthetic. Although its anesthetic properties have been known for more than 50 yr, it was largely forgotten until 1990,[1] mainly because of its high cost. Aside from this problem, xenon possesses many of the characteristics of an ideal anesthetic. For example, its blood–gas partition coefficient is extremely small (0.115),[2] yielding rapid emergence from anesthesia[3] regardless of the duration of anesthesia.[4] It lacks teratogenicity,[5] and it produces analgesia,[6] thereby suppressing hemodynamic and catecholamine responses to surgical stimulation.[7,8] It is also a potent hypnotic.[9,10] Unlike many conventional anesthetics, xenon does not produce hemodynamic depression in healthy humans[11] and in dogs with normal hearts and with cardiomyopathy,[12] at least in part because it has no actions on some important cardiac ion channels.[13,14] The characteristics of xenon have been reviewed more extensively elsewhere.[15,16]

Essentially all previous studies of xenon, even in humans, have been relatively small. This issue of ANESTHESIOLOGY contains the first large-scale clinical evaluation of xenon anesthesia.[17] The study, conducted by Roissant *et al.*,[17] demonstrates that xenon and nitrous oxide–isoflurane are at least equivalent in efficacy and safety. This study is undoubtedly a necessary step toward wide application of xenon. However, the real question is whether there is a true future for xenon. In light of the work by Roissant *et al.*,[17] it is reasonable to ask this question now. During the last decade, we have accumulated considerable knowledge about the actions of xenon. However, the answer to this question is not obvious.

The Cost

Xenon currently costs approximately US $10.00 per liter. If one uses a closed breathing circuit, xenon anesthesia is not as expensive as one might expect from the price of the gas, because the amount of xenon absorbed by the tissues is small as a result of its extremely low solubility. In our simulation, based on Japanese prices,[18] anesthetizing a 70-kg adult with 1 minimum alveolar concentration of xenon (71%) for 240 min using a closed circuit requires approximately 16 l of xenon and costs US $167.00 (including the costs for oxygen, muscle relaxants, and the soda lime). This may actually be an underestimate, since the closed-circuit technique requires that the breathing system occasionally be flushed and refilled to wash out nitrogen released from the patients' body tissues. In contrast, the costs of nitrous oxide and isoflurane are US $30.00 and $74.00, respectively, if a closed-circuit technique or a total fresh gas flow rate of 3 l/min (*i.e.*, nitrous oxide, 2 l/min, and oxygen, 1 l/min) are used.

Obviously, this cost analysis depends on the price of xenon, which has fluctuated a great deal over the last 20 yr due to the changing balance between supply and demand within a dynamic market. The price was US $4.00 in the late 1980s, increased to US $18.00 in 1998, and then decreased to the current value of approximately US $10.00. It is difficult to predict the future cost. However, even if the price of xenon is prohibitively high at this time, technologic innovations in xenon production (and a growing market) may lead to lower costs. For example, xenon does not have to be produced *de novo* but can be retrieved from the waste anesthetic gas (*i.e.*, recycling). Because the waste gas contains much higher concentrations of xenon (*e.g.*, 50 to approximately 60%) than does the air (0.087 ppm), its retrieval should be much less costly. The profit incentive may also promote international trade of xenon. Russia, for example, is a promising supplier, because the price of xenon is currently US $5.00 or less in that country.

Can't the Cost of Xenon Be Justified?

Xenon enthusiasts argue that the gas has two advantages: environmental and medical. The environmental advantage is that xenon is not a greenhouse gas and, hence, does not lead to global warming. It is also unreactive and, thus, should not affect the ozone layer, as do nitrous oxide and volatile anesthetics. However, the issue is not this simple. First, simply adopting a low-flow or closed-circuit technique can considerably reduce the negative impacts of conventional anesthetics. Second, xenon is not perfectly environmentally friendly. Producing 1 l of xenon gas requires 220 watt-hours of energy, a million times more than that for nitrous oxide, because xenon is purified by fractional distillation of the liquefied air, which involves multiple heating, cooling, and pressurization processes.[19] This large energy consumption, and the resultant emission of carbon dioxide, certainly

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diminishes the environmental advantage of xenon. Even if xenon has measurable environmental advantages, it is very difficult to incorporate these in a cost-benefit analysis because the value of the environment differs considerably among different countries and societies. Furthermore, environmental protection is considered a "public good" in an economic sense and, thus, cannot be assigned to any individual economic entity.[20]

Does xenon have medical advantages that justify the cost? The investigations over the past decade have revealed many of its advantageous characteristics, but none of these appears sufficient to justify the cost by itself. Xenon provides faster emergence, but the difference is only a matter of minutes, and the time to ward readiness is not affected.[17] A lack of cardiac depression is certainly useful, but whether this represents a real clinical benefit is unclear, particularly since we are already doing a pretty good job anesthetizing millions of patients with fragile hearts. What we really need is evidence that xenon improves outcome (*i.e.*, results in less morbidity and mortality). Such evidence is scarce, even for conventional anesthetics or anesthetic techniques, but xenon needs to be tested against this idealistic criterion because its cost is so high. Because the current anesthetics are so safe, it is unrealistic to expect that xenon will produce measurable improvements in the outcomes of ordinary patients. Therefore, the target population will be high-risk patients. In fact, the kinds of patients excluded from the multicenter trial conducted by Rossaint *et al.*[17] are exactly the ones who might benefit from xenon. For example, pregnant or breast-feeding patients may benefit because xenon is low in teratogenicity and toxicity and because xenon quickly leaves the body after anesthesia. Patients with disturbed liver function and/or renal function may also benefit because of low toxicity and a lack of hemodynamic depression leading to preserved organ perfusion.[21] Those with congestive heart failure may also fare better because of xenon's lack of cardiac depression. However, these patients represent only a small fraction of the total number of people requiring general anesthesia, and the reduced numbers may also have an impact on economics.

Conclusions

The investigations over the past decade and the current multicenter trial by Rossaint *et al.*[17] have set the stage for us to embark on the crucial step of testing whether xenon improves outcomes in high-risk patients. Several hypotheses appear worthy of investigation. For example, does xenon better preserve the function of vital organs such as the liver and kidneys in patients who have preexisting dysfunction in these organs? Does xenon facilitate recovery of trauma patients in the shock state by its lack of hemodynamic depression, leading to better perfusion of vital organs? Does xenon improve outcome in patients undergoing major surgery by providing more optimal hemodynamics?§ Before answering these questions, we cannot make a convincing conclusion as to whether xenon is a stranger (after which the gas is named) or a friend to anesthesiologists.

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The Alveolar Epithelium

Suspect or Innocent Bystander?

THE alveolar epithelium is often viewed as a passive bystander in respiratory function, functioning primarily as a barrier. Through the work of Pan *et al.*[1] and others,[2–4] we have learned that it plays an active role in maintaining homeostasis in the alveolar space through production of key proteins, such as surfactants, surfactant apoproteins, and cytokines, and through the clearance of excess alveolar liquid *via* the activity of basolateral sodium–potassium ATPases. These synthetic and homeostatic functions become particularly important in the setting of acute lung injury, in which failure of the alveolar epithelium is associated with increased mortality.[5,6]

Studying the alveolar epithelium is complex; *in vivo* studies are complicated by the participation of a number of active cell types, including alveolar type I and type II cells and alveolar macrophages. To determine the contributions of each cell type is impossible. Alternatively, *in vitro* studies are complicated by the fact that, thus far, it has proved impossible to culture pure alveolar type I cells, the cell type that provides the majority of cells forming the alveolar barrier. Nevertheless, *in vitro* studies have provided crucial information about the metabolic and synthetic activity of the alveolar epithelial barrier.

In this issue of ANESTHESIOLOGY, Giraud *et al.*[7] report an elegant series of experiments describing the effects of inhaled anesthetics on the ability of alveolar type II cells to produce inflammatory cytokines. Using recombinant murine interleukin (IL) 1β–primed alveolar type II cells, Giraud *et al.*[7] showed reversible inhibition of IL-6, macrophage inflammatory protein 2, and monocyte chemoattractant protein 1 secretion using clinically relevant concentrations of inhaled anesthetics. The reduced secretion was not a result of toxicity, as the investigators controlled for cell viability by measuring lactate dehydrogenase release, which was not increased. It is interesting to note that the inhibitory effect was identical in all three anesthetics tested, suggesting a common mechanism. The effect of the anesthetics appeared to be at the transcriptional level, as macrophage inflammatory protein 2 mRNA concentrations were decreased in a similar manner to the protein. It is intriguing to speculate what might have happened to the mRNA concentrations of a "housekeeping" gene such as B-actin, which might have suggested an effect of differential gene expression, perhaps mediated by the transcription factor nuclear factor κB, as opposed to global suppression of transcriptional activity caused by the anesthetics.

What are the implications of the findings of Giraud *et al.*[7]? First, there is increasing evidence that anesthetics affect alveolar type II cellular function *in vitro*[8,9] and in animals,[10,11] so they likely have similar effects in humans. The complex interactions between the cellular components of the alveolar space likely are responsible for the diversity of responses seen with common injuries such as pneumonia or aspiration of gastric contents. Could inhaled anesthetics be used as a therapy in most patients with acute lung injury? This seems unlikely, as the same authors have shown that prolonged exposure to anesthetics may induce cytotoxicity. In addition, Molliex *et al.*[8] demonstrated halothane-induced inhibition of sodium–potassium ATPase activity in alveolar type II cells, which would be expected to worsen or inhibit alveolar liquid clearance in the setting of acute lung injury. Caution should be exercised in assuming that less inflammation in the lung is good: inflammation may be beneficial, as it plays a key role in bacterial killing. Perhaps more interesting is to speculate what effects inhaled anesthetics may have in a patient who suffers an intraoperative infectious insult to the lung, either through the bloodstream (bacteremia) or airspaces (gastric aspiration). Should these patients be transitioned to an intravenous anesthetic in an effort to spare the alveolar epithelium any adverse effects? The answer to this question will require careful *in vivo* analysis, but we now have the ability to measure the response of a number of systems simultaneously using modern molecular genetic techniques such as gene chip analysis. Until then, a change in clinical practice is not justified; however, the innovative studies of Giraud *et al.*[7] suggest that manipulation of the alveolar epithelium may be a strategy that we eventually can employ to decrease the effects of acute lung injury.

◆ This Editorial View accompanies the following article: Giraud O, Molliex S, Rolland C, Leçon-Malas V, Desmonts J-M, Aubier M, Dehoux, M: Halogenated anesthetics reduce interleukin-1β–induced cytokine secretion by rat alveolar type II cells in primary culture. ANESTHESIOLOGY 2003; 98:74–81.

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