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INTRODUCTION

Compared to other clinically used inhalational anaesthetics xenon has some similar properties to nitrous oxide. Both are gases at atmospheric pressure and different from other volatile or intravenous anaesthetics their respective potencies (MAC xenon: ~70 vol%; MAC nitrous oxide: ~110 vol%) are weak. However, both of them are not only weak anaesthetics but are also good analgesics.

HISTORY

Xenon was discovered in 1898 by Ramsay and Travers after the evaporation of liquid air components, and is thought to be an inert gas because of its unique electron structure. In 1962 it was categorized as a noble gas together with helium, neon, argon, krypton and radon, all of them found in the troposphere in very small amounts. Of these, xenon is the heaviest stable compound with a molecular weight of 131.3. With a relative concentration of 0.0000087 vol% it is rather rare. In 1951 Cullen and Gross first reported the use of xenon as an anaesthetic, they described a rapid loss of consciousness and early recovery using the gas at an 80 vol% concentration.

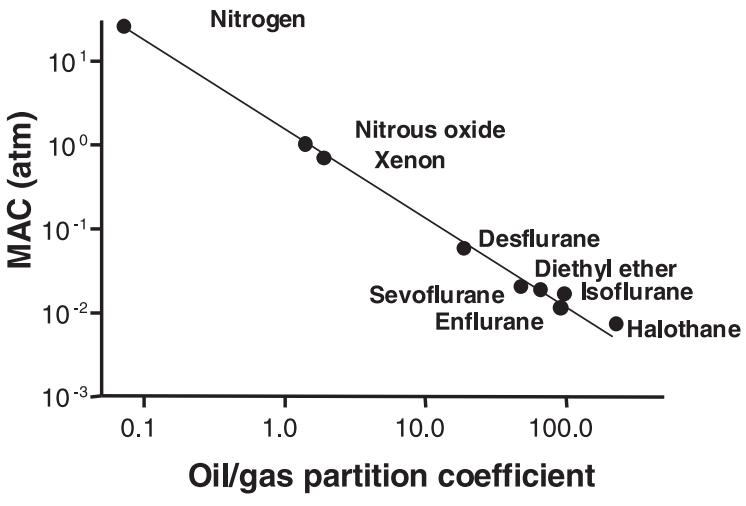
CHEMICAL REACTIVITY

As a noble gas xenon is chemically nearly inert. It is non-explosive, however, under certain conditions it may form chemical compounds with very reactive elements, such as oxygen or fluoride. During anaesthesia it is extremely unlikely that xenon participates in any chemical reaction. Although biotransformation of xenon has not been demonstrated, it is conceivable that xenon is involved in biochemical processes. Similarly there is currently no known pathway for a metabolism of nitrous oxide in the human body.

ACTIONS OF XENON AND NITROUS OXIDE AT SUB-CELLULAR AND CELLULAR LEVELS

Although the analgesic and anaesthetic properties of xenon have been known for more than 5 decades, the exact mechanism of action at the cellular or molecular level is not yet known. A number of studies have been performed to define parameters that are relevant for the action of these compounds.

FIGURE 1. RELATIONSHIP BETWEEN THE OIL/GAS PARTITION COEFFICIENT AND MIMIMUM ALVEOLAR CONCENTRATION (MAC)



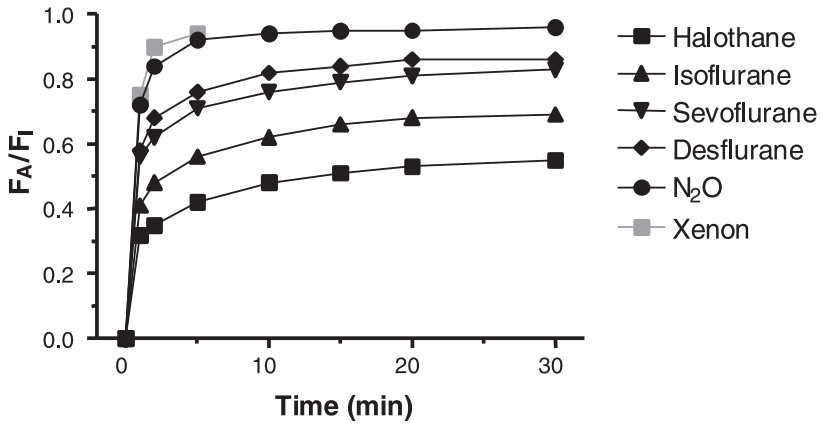
It is known that many anaesthetics exert their actions at a variety of cellular targets. Among these, the super-family of ligand gated ion channels has been demonstrated to be more likely to be influenced in their function at clinical concentrations than other receptors or channel proteins. It has been demonstrated that most anaesthetics, and volatile anaesthetics in particular, act primarily on GABA-A-receptors. However, recently it was shown that xenon potently inhibits NMDA-receptor function [1]. A study compared the effects of nitrous oxide, xenon, isoflurane, and ethanol on nine different recombined ligand-gated ion channels including GABA-A, NMDA, $5HT_3$ and ACh receptors, using a voltage clamp technique. Xenon exerted a stronger effect on NMDA-receptors than on GABA-A-receptors, rendering this anaesthetic distinctly different from isoflurane and ethanol, which had their highest potencies at GABA-A-receptors. Studies looking at the effects of ether, nitrous oxide, and xenon have already hinted that GABA-A-receptors were not affected by xenon. In this respect xenon is markedly different from other volatile anaesthetics.

Another molecular target site that is shared by xenon with other gaseous and volatile anaesthetics is the nAChR. It has been demonstrated that central nervous system nAChR especially those composed of the β2-subunit are inhibited in their function by many anaesthetics at relevant concentrations. Xenon is a potent analgesic at subanaesthetic concentrations. It has been speculated that this antinociceptive effect is due to an action on glutamate receptors, namely the NMDA receptor in a fashion similar to ketamine [2]. A recently discovered target site for xenon is a part of the two pore-domain K-channels. It has been shown that xenon as well as nitrous oxide and cyclopropane activate the TREK-1 channel at clinical concentrations. In contrast the TASK-3 channel that is very sensitive to volatile anaesthetics such as halothane is not as sensitive to xenon.

Anaesthesia and MAC

Xenon has been reported to exert minimal effects on cardiovascular function in either healthy or sick subjects. The rapid induction and emergence when using xenon, make it a nearly ideal anaesthetic gas.

Figure 2. The effect of inspired concentration (F_I) on the rate of rise of alveolar anaesthetic concentration(F_A)



However, the anaesthetic potency of xenon is too weak for it to be used as a single anaesthetic agent. One cannot deliver more than 1 MAC of xenon at a F_iO_2 of 0.3, which is the standard setting for most healthy patients. At a concentration of one MAC however, it is impossible to safely perform a surgical operation. The MAC of volatile anaesthetics has been reported to be decreased when xenon is co-administered. Sevoflurane used as the sole anaesthetic agent has been shown to fail to attenuate the cardiovascular response. However, in combination with either nitrous oxide or xenon the cardiovascular response to skin incision is completely blocked. A follow-up study examined if there was a difference between the effect of nitrous oxide or xenon, in combination with sevoflurane. 43 patients undergoing elective surgery were studied and the MAC was determined according to the up and down method. It showed that the suppression of cardiovascular responses to either xenon or nitrous oxide was identical at 70 vol%, possibly reflecting their nearly identical analgesic properties.

Table 1. Physicochemical properties of xenon and nitrous oxide (from various sources)

	Xenon	Nitrous oxide
Molecular weight	131.1	44.0
Molecular diameter (Å)	4.0055	3.879
Blood/gas partition coefficient	0.47	0.14
Oil/gas partition coefficient	1.4	1.9
MAC (in humans)	1.05	0.71
Greenhouse effect	-	+
Molecular weight	44.02	131.29
Freezing point	-90.0°C	-111.9°C
Boiling point	-88.5°C	-108.2°C
Density (g/l)	5.40	1.81
Viscosity (micropoises)	226	145
Thermal conductivity (mW*cm-1*K-1)	0.057	0.173
Thermal capacity (cal*K-1*mol-1)	4.97	9.19

Effects on the cardiovascular system

Xenon has been reported to possess a remarkably safe hemodynamic profile. In pigs it has been demonstrated that haemodynamic parameters as well as plasma catecholamine levels remained within normal limits during xenon anaesthesia. Even at sub-anaesthetic concentrations of xenon a significant decrease in plasma levels of adrenaline were observed possibly reflecting the high analgesic potency of xenon[3].

In a study looking at the haemodynamic effects of xenon vs. nitrous oxide, 32 adult patients undergoing gynaecological, plastic or orthopaedic surgery were studied. In each group anaesthesia was maintained using either 70 vol% nitrous oxide or 70 vol% xenon and fentanyl was added when blood pressure increased by more than 20% from baseline. The anaesthetist was unaware of the gas used. In this setting it was found that incremental fentanyl was necessary in all patients receiving nitrous oxide and only in 50% of the patients receiving xenon, while awareness did not occur in either group. No differences in blood pressure, heart rate or the changes during surgery were observed between the groups. The study also looked at the levels of adrenaline in the two groups before, during and after surgery. The xenon group showed adrenaline levels less than baseline levels throughout the operation, and only returned to control values at the end of surgery. The nitrous oxide group showed a continuous increase in plasma adrenaline concentrations with a significant difference at the end of the operation. In addition, the nitrous oxide group showed increased adrenaline values immediately postoperatively, not returning to baseline for six hours. There was no apparent difference in recovery time or the quality of recovery and the attending anaesthetists were not able to tell which gas was used [4].

A subsequent study examining otherwise healthy ASA 1 patients undergoing open cholecystectomy or hysterectomy the effect of xenon on the myocardium was studied using echocardiography. No alteration in the mean fractional area change was observed during induction with xenon.

A large multicenter trial of xenon vs. isoflurane, for elective surgery on 224 patients has shown that xenon maintained stable respiratory and circulatory conditions. In comparison to the isoflurane group the hemodynamic parameters of the xenon group appeared superior [5].

Effect on cerebral circulation

The effect of xenon on cerebral blood flow seems to vary according to the model used and the species studied. In radiology, radioactive xenon isotopes have been in use for a long time for the determination of cerebral blood flow. In volunteers, the administration of 33 vol% xenon leads to a significant increase in cerebral perfusion. Increases in perfusion have also noted in patients with traumatic brain injury. Thus some authors have recommended the prophylactic use of hyperventilation in patients receiving xenon for diagnostic purposes.

In an experimental setting involving swine it was demonstrated that xenon left cerebral autoregulation intact under different conditions [6]. Studies using transcranial Doppler ultrasonography have found differing results; increases as well as non-significant changes in cerebral blood flow velocities have been reported [7-9].

Effects on the gastrointestinal tract

Xenon has a low blood-gas-partition coefficient of 0.12-0.14. An observational study using 21 pigs was performed to compare the effects of xenon and nitrous oxide upon the bowel [10]. Three groups of animals were studied, one receiving 75 vol% xenon, one 75 vol% nitrous oxide and one 75 vol% nitrogen for 240 minutes, anaesthesia was induced and maintained intravenously. After a laparotomy was performed, segments of bowel 15 cm in length were isolated in a gas tight manner, filled with 30 ml of air, and the intraluminal pressure measured through an inserted catheter. Both in the nitrous oxide and in the xenon group the volume of the bowel increased compared to the nitrogen control group (88 vs. 39 vs. 21 mls). Intraluminal pressure in the xenon group was similar to that of the control nitrogen group, as opposed to the significant pressure rise in the nitrous oxide group.

The low partition-coefficient of xenon predicts a lower transport capacity in the blood and a low rate of diffusion of xenon into gas filled volumes. However, the ability of various substances to diffuse into an adjacent space is also influenced by their respective molecular diameters (xenon 4.0055 Å; see table 1) and their diffusion coefficients, which may be modified by a number of factors such as the polarity of the substance. Inhalation of xenon in swine did not alter mesenteric metabolic balance compared to intravenous anaesthesia [11]. Another study in swine showed that xenon does not alter mesenteric blood flow and this may be of advantage for abdominal surgery. It may be concluded that xenon can be used in abdominal surgery when factors such as haemodynamic control are of concern.

Xenon and respiratory mechanics

The physical parameters of xenon render this gas distinctly different from the other gases used in anaesthesia. The high density and viscosity of xenon alter the physical properties of a gas mixture used for anaesthesia when a high fraction of xenon is used. There are two implications arising from this that have to be dealt with by the anaesthesiologist: 1) The behaviour of monitoring devices for respiratory monitoring may be influenced, 2) respiratory mechanics of the patient may be altered, especially in the case of patients whose lung function is compromised.

In particular, flow meters may be affected by the different physical properties of xenon. Although most flow meters are designed to correct their readings according to the composition of the gas used, most of them were not designed for the use with xenon and may thus show false reading without compensating for possible errors. In a study looking at the practicality of using standard flow meters for xenon anaesthesia it has been demonstrated that only those utilising rotating vanes give sufficiently accurate readings when xenon is used, whereas three other types of flow meters did not.

Both, the density of xenon and its viscosity are higher than those of other clinically used gases, an effect that pressured a producer of anaesthetic apparatuses to redesign one of their machines for the administration of xenon because its ventilator did break after only short periods of use.

In addition, in patients with lung disease, the physical properties of a gas may affect respiratory mechanics. The effect of xenon on respiratory mechanics was studied in comparison to nitrous oxide in pigs. Two groups of eight pigs were ventilated either with 70 vol% nitrous oxide or 70 vol% xenon and airway pressure as well as resistance was measured. Both groups of animals were then subjected to a metacholine infusion to induce bronchocospasm and measurements were repeated. Both under normal conditions and throughout bronchoconstriction the airway resistance was significantly higher in the xenon group compared to the nitrous oxide group. Airway pressures did not differ during normal airway conditions, however, during bronchoconstriction there was a significant increase in airway pressure in the xenon group compared to the nitrous oxide group (P_{peak} xenon 33.2 ± 5.5; P_{peak} nitrous oxide 28.4 ± 5.7 cm H_2O).

Another animal study looked at the effect of xenon on respiratory mechanics both under normal conditions and during bronchospasm [12]. In contrast to the previously cited study, the authors did not administer 70 vol% xenon throughout the study but instead used 50 vol% xenon during bronchoconstriction. This change in experimental conditions possibly lead to the finding that there was no difference in airway resistance between normal ventilation and ventilation during bronchoconstriction [12]. In addition, airway resistance in dogs is different from that in pigs and conditions are also different if airway resistance is measured when the chest is open.

The main factor responsible for the change in airway resistances if one switches from nitrous oxide to xenon appears to be the change in the viscosity and density of the gas [13]. However, gas exchange was not affected during ventilation with xenon. The authors of the first study conclude that although there is a change in respiratory mechanics during xenon anaesthesia that these changes are not of clinical relevance for the following reasons : 1) During general anaesthesia the ventilator and not the patient has to overcome increases in airway resistance, 2) the increase in airway resistance is small under healthy conditions and only moderate during bronchoconstriction and finally, 3) gas exchange does not deteriorate during xenon anaesthesia [14].

A study in healthy swine concluded that xenon did not alter diameter of the airways, however, different physical parameters have to be taken into account when airway resistance is determined [15].

Diffusion hypoxia

As the inert gas volume moving between capillary blood and alveolar space differs with varying gas solubility, specific gases may concentrate or dilute during uptake or elimination. This is the reason why an outpour of gas occurs at the end of a nitrous oxide based anaesthesia, an effect called diffusion hypoxia. The solubility of nitrous oxide is higher (0.47) than that of nitrogen (0.015), thus the concentration of nitrous oxide rises during wash-out into the alveolar space. The mechanism of hypoxia is twofold: 1) oxygen is displaced by the eluting gas, decreasing the oxygen diffusion gradient and hence uptake is diminished, 2) carbon dioxide may be diluted in the alveoli, thus decreasing respiratory drive and ventilation. Since the solubility of xenon is lower than that of nitrous oxide but higher than that of nitrogen it may be concluded that a similar effect also occurs during xenon anaesthesia but may be less pronounced.

Recently, a study in pigs was performed addressing the question of diffusion hypoxia after nitrous oxide vs. xenon anaesthesia [16]. The lungs of pigs were ventilated either with a mixture of 30 vol% oxygen and either 70% nitrous oxide or 70 vol% xenon for 30 min. At the end of this period all animals were ventilated with 30 vol% oxygen and 70 vol% nitrogen. Arterial oxygen partial pressures were determined during nitrogen wash-in. The change in arterial PaO_2 was much less in the xenon group when compared with those that received nitrous oxide (ΔPaO_2 6mmHg vs. 17mmHg) [16]. This confirmed the consideration that inert gas exchange is mainly determined by the blood-gas partition coefficient. Although the lipid solubility of xenon is greater than that of nitrous oxide, more xenon may be taken up during an anaesthetic than nitrous oxide. However, only the part of the gas that is actually dissolved in the blood and passes through the lungs may diffuse into the alveolar space so that lipid solubility is only of minor importance to these effects.

Organ protection

Recently it has been demonstrated that xenon may exert protective effects on several organ systems. It has been shown to have neuroprotective properties in several models of neuronal injury. In hypoxic neurons it was demonstrated that xenon exerts its action through a calcium dependent mechanism. However, xenon was also reported to have no neurotoxic effect unlike other NMDA antagonists, this has been questioned at least for higher concentrations of xenon [17,18].

Another important organ that appears to be protected by xenon is the heart. In a similar way to volatile anaesthetics which exert a preconditioning effect that is comparable to ischemic preconditioning, xenon has also been shown to protect the myocardium through the same mechanism [19].

Teratogenic effects, toxic effects

In a study comparing the teratogenic effects of nitrous oxide and xenon, pregnant rats were exposed to either 70 vol% nitrous oxide or xenon in 30 vol% oxygen. 20 days after exposure the fetuses were evaluated for anomalies. The rats of the nitrous oxide group showed a high rate of fetal absorption, with skeletal and other macroscopic anomalies such as encephalocele, anophthalmia, microphthalmia, and gastroschisis. In contrast, the xenon group was found to have much less in the way of anomalies (3% vs. 37%). Thus the authors conclude that xenon in direct comparison to nitrous oxide does not exert teratogenic effects [20].

In order to determine possible adverse effects of a long term exposure to xenon, dogs were exposed to 80 vol% xenon in oxygen every third day for two weeks. At the end of the study no side effects relating to the xenon were found, looking at morphological, hematological or biochemical parameters. In contrast to long term exposure to nitrous oxide, after xenon no effects were noted on methionine synthetase and vitamin B12 metabolism.

Economical and ecological aspects

In Germany xenon is currently undergoing phase 3 trials and may thus be clinically available within a few years. However, xenon is relatively expensive. A litre of xenon gas currently costs about €10–15 (in Germany). The xenon requirement for a routine anaesthetic is about 40 litres, so on average xenon anaesthesia will cost about 400–600 €. There are many projects under way to reduce the amount of xenon needed for anaesthesia. The use of closed systems, in anaesthesia machines like the Physioflex allows us to use less than half of the xenon required in standard anaesthesia machines. Recycling systems may allow the reuse of xenon from the anaesthesia system at the end of the procedure and may thus reduce costs even further.

Summary

Xenon shares many clinical as well as physicochemical properties with nitrous oxide, while exerting fewer side effects. However, xenon is not available in abundance. Thus its cost may prohibit the general use of xenon for anaesthesia in the future.

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