Review Article

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Xenon: The Future Anaesthetic Agent

Mukesh Somvanshi[1], Archana Tripathi[2], Anupama Gupta[3], Firoz Satpathy[4]

[1,2] Professor [3]Assistant Professor [4]Senior Resident, Department of Anaesthesiology and Critical Care, Govt. Medical College and AG Hospitals, Kota, Rajasthan 324010, India.

Abstract

After the discovery of xenon in 1898, xenon anaesthesia has been studied for decades. The search for an inert gas to replace N_2O led to introduction of xenon in anaesthesia practice. Xenon's anaesthetic properties were discovered in 1939. Since then, a number of studies of xenon anaesthesia have been conducted. The anaesthetic properties of xenon is mainly conferred by the inhibition of *N*-methyl-D-aspartate receptors in the central nervous system. Xenon is an inert gas and, theoretically, is not metabolized to toxic metabolites, does not react with absorbent, and does not deplete vitamin B_{12}, as opposed to other inhaled agents. Xenon is described as having many of the characteristics of an ideal inhalational anaesthetic agent, including rapid induction and emergence, analgesic properties, cardiovascular stability, and neuroprotective qualities. It is non-flammable, non-explosive, non-toxic, devoid of teratogenic effects and does not contribute to the greenhouse effect. Clinically, there are certain disadvantages to xenon anaesthesia. Because of its high density, xenon was found to increase airway resistance and work of breathing in an animal study. Nevertheless, it may be a good choice for high-risk patients with unstable haemodynamics, cardiovascular diseases, expected prolonged recovery from anaesthesia, or advanced age. Moreover, the high cost of xenon associated with its production has discouraged more widespread use. This article reviews the benefits and drawbacks of xenon anaesthesia, and discusses future perspectives.

Keywords: Anaesthesia; Inhalational Agent; Inert Gas; Xenon.

The quest for the ideal anaesthetic agent has been continuous since the begining of anaesthesia. Inhalational anaesthetic agents have been used in the practice of anaesthesia for centuries. The first report of the use of inhalational anaesthetic agents such as ether (1846), chloroform (1847) and nitrous oxide (1844) began to emerge in 1840s. The inhalational anaesthetic agents used in modern practice include the fluorinated ethers isoflurane, sevoflurane and desflurane and gas nitrous oxide (N_2O) and these agents, from diethyl ether and N_2O to sevoflurane and desflurane, have been studied and compared extensively.

The search for an inert gas to replace N_2O led to introduction of xenon in anaesthesia practice. Recently there has been renewed interest in the use of xenon as an anaesthetic agent, as researchers have tried to find a safe and effective substitute for N_2O, which has caused environmental concerns because of its ozone depleting properties [1]. Several advantages of xenon, compared with other inahalational agents, have been demonstrated in various studies which include:

1. Rapid onset and offset of its action due to its low blood gas solubility coefficient.
2. Less CVS depression
3. Neuroprotection and
4. Profound analgesia.

Corresponding Author: Mukesh Somvanshi, Professor, Department of Anaesthesiology and Critical Care, Govt. Medical College and AG Hospitals, Kota, Rajasthan 324010, India.
E-mail: mukeshsomvanshi81@gmail.com

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Xenon is a naturally occurring gaseous element. Xenon derives its name from the Greek word for "stranger" because of its rarity, as it represents 0.0000086% or 0.87 parts per million of air [2]. Xenon exists naturally as 9 isotopes, the most abundant of which is Xe132 [3]. It is discovered in 1898 by British chemists Sir William Ramsay and Morris W. Trave. It is manufactured by fractional distillation of air and is used commercially for lasers, high intensity of lamps, flash bulbs, jet propellants, x-ray tubes and in medicine. As xenon is naturally occurring element, it is not a pollutant or an occupationally hazardous gas, nor does it contribute to global warming or the greenhouse effect[2]. In contrast N_2O is 230 times more potent as a greenhouse gas than is CO_2, taking 120 years to break down. Xenon has many properties of an ideal anaesthetic agents, including the fact that it is odourless, nonpungent, nontoxic, nonexplosive, environmental friendly and unlikely to go biotransformation due to its stability [4]. Although xenon was discovered in the 1898, its anaesthetic properties were not discovered until 1939 by Behnke and Yarbourough [5,6]. In 1946, Lawrence JH reported its narcotic properties in mice [7]. Later in 1951, Cullen and Gross used xenon as an anaesthetic agent in human volunteers and concluded that xenon was capable of producing of complete anaesthesia [8]. It was until 1965, Eager and associates actually established the MAC of xenon at 0.71 or 71% indicating a greater potency [9].

Physiochemical properties

Atomic number	54
Atomic weight	131.293(6)
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

Physical form Colorless nonflammable gas and does not support combustion.

Table 1: A Comparison of Xenon with Other Currently Used Inhalational Agents

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

MAC - minimum alveolar concentration.

Table 1 compares Xenon's MAC and partition coefficients with that of other inhalational agents. It has lowest blood gas partition coefficient of any inhalational agent. Its favourable pharmacokinetics makes it suitable for faster induction and emergence [10,11]. Induction of anaesthesia with xenon is faster than with sevoflurane 71±21 vs 147±59 sec [12]. Emergence from xenon anaesthesia is 2-3 times faster than that from equi-MAC concentration of N_2O/isoflurane or N_2O/sevoflurane anaesthesia [13]. Xenon is found to be three times more efficacious than sevoflurane at blocking cardiovascular response to incision at equi-MAC concentration. It is additive with isoflurane and sevoflurane at MAC awake [14]. Xenon can diffuse freely through rubber, with significant losses of gas by this route during anaesthesia, thereby increasing the cost of xenon anaesthesia.

Xenon is a noble gas, but under special condition it is capable to form certain compounds with very low reactivity like clathrates, fluorides, chlorides, oxides, oxyfluorides, peroxynates and complex salts. However, it is unlikely that xenon is involved in any biochemical reactions when used in anaesthetic concentrations [15]. As xenon is Inert gas hence not metabolized. There is no renal or hepatic clearance. Xenon is mainly eliminated through lungs; approximately 95% of inhaled xenon is removed in first pass after discontinuation [2].

Mechanism of Action

Most inhalational anaesthetic agents act by increasing the activity of the GABA system. Xenon works by inhibiting excitatory N-methyl- D-aspartate (NMDA) receptors in the CNS with insignificant effect on GABA receptors or non-NMDA glutaminergic receptors [16,17]. The analgesic effects of xenon are also explained by its inhibition of NMDA receptors in the CNS as well as in the dorsal horn of spinal cord [3,18]. Similar to other volatile anaesthetic agents, it reduces the whole brain metabolism of glucose [19] or inhibits neurotransmission system in glycine receptors [20].

Pharmacodynamics

Cardiovascular

It is well known that inhalational agents disrupts haemodynamic stability and can have ionotropic effects. This can be dangerous for patient with high cardiovascular risk. Xenon anaesthesia is associated with cardiovascular stability with no significant changes in myocardial contractility, cardiac index, blood pressure or systemic vascular resistance. The haemodynamic stability was a result of less stress induced sympathetic stimulation, a theory supported by stable epinephrine levels during xenon anaesthesia. Compared with N_2O anaesthesia, much less fentanyl was required to maintain cardiovascular stability during xenon anaesthesia [1,21]. Xenon was found to depress both sympathetic and parasympathetic transmission [22]. The mechanism of autonomic action of xenon has yet to be explained. Xenon also attenuates myocardial depressant effect of isoflurane [23]. Ventricular functions, as assessed by transesophageal echocardiography, are unchanged during xenon anaesthesia [24,25]. Even in presence of compromised myocardium, xenon anaesthesia is remarkably stable [26].

CNS and Neuroprotection

As xenon is an NMDA receptor antagonist, it exhibit unique neuroprotective action without coexisting neurotoxicity. As activation of the NMDA receptors appear to be crucial to the initiation of neuronal injury and death from a variety of insults [27], its neuroprotective effects have been examined in a series of in vitro and in vivo studies. Xenon also attenuates cardiopulmonary bypass–induced neurocognitive dysfunction [28]. Xenon may therefore be a useful agent when protection against neurological injury required.

Another point to discuss is xenon's effect on cerebral blood flow when it used as neuroprotectant. Frietsch T et al reported that in the first 5 min of exposure, xenon increases cerebral blood flow; thereafter, xenon's effect on the cerebral blood flow appears to reverse [29]. In human beings xenon produced increased regional blood flow in all organs, largest percentage increase in the cerebral blood flow [1]. The global increase in cerebral blood flow may in turn increase the intracranial pressure (ICP), but preserves autoregulation, probably due to redistribution of blood from corticocerebeller to white matter [30]. Inhalation of 33% xenon, for 20 minutes in 13 patients, 3 days after severe head injury showed clinically significant increase in ICP and cerebral perfusion pressure [31]. Despite of these changes, there were no arteriovenous oxygen difference values which would be indicative of cerebral oligaemia or ischaemia. However, in monkeys, 33% xenon reported to reduce cerebral blood flow by 12% and cerebral oxygen consumption by 16% [32].

Analgesia

Xenon produced analgesia by inhibiting NMDA receptors. It also acts at the level of spinal cord, particularly in the dorsal horn. It manifests more potent analgesic action than N_2O, the only other anaesthetic gas with true analgesic efficacy. Various researchers compared xenon and N_2O. Peterson-Felix et al found that xenon has an analgesic potency 1.5 times that of N_2O [33]. Fentanyl requirement was lower in a xenon based anaesthesia compared with that of N_2O (fentanyl 0.05 vs 0.24mg) and fewer patients required fentanyl (35 vs 95%) [1]. Further studies have found that during xenon anaesthesia lower doses of propofol required to prevent movement than with N_2O [34]. The difference in analgesic potency between xenon and N_2O is more difficult to define when tested in volunteers with experimental pain. When heat stimulation was used to provoke pain, xenon and N_2O were equivalent analgesic [35]. When electrical stimulation is used to provoke pain, xenon is more potent than N_2O [33]. Xenon produces minimal stress response to painful stimuli. Xenon attenuates haemodynamic reactions caused by surgical stimulus and requires only one-fifth of fentanyl required by N_2O group [36]. Because of its potent analgesic properties, xenon is used for the treatment of angina pectoris and for change of painful dressings [37].

The mechanism of analgesic action for xenon differs from N_2O although both gases are NDMA antagonists [15,16,38]. N_2O produces analgesia by release of endogenous ligands for opiate receptors in the periaqueductal grey region, which indirectly activates inhibitory neurons in the spinal cord. Xenon acts at spinal cord dorsal horn and suppresses the effect of both pinch and touch on the firing of wide dynamic range movements [17, 39]. Furthermore, nitrous oxide induced analgesia can be antagonised by naloxone [40]. 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 opiate receptors [35].

Respiratory System

Xenon cause slowing of respiration secondary to central respiratory depression; but it maintains the

minute ventilation by compensatory increase in tidal volume. Lachman B et al demonstrated that peak airway pressure, PaO_2 and $PaCO_2$ remained unaffected during xenon anaesthesia but they suggested that xenon although safe, should be used cautiously in older patients with chronic lung disease [1].

Xenon is unlikely to cause diffusion hypoxia, as its blood/gas partition coefficient is much lower than that of N_2O and it diffuse in to the alveoli more slowly than N_2O.

Xenon has a density of approximately three times and its viscosity is twice that of N_2O. It can, therefore, be expected that xenon anaesthesia in high concentration will lead to an increase in airway resistance and need higher driving pressure for ventilation. Various animal studies have shown either a moderate increase in airway resistance with high xenon concentration or no change to airway resistance during xenon anaesthesia. However, some studies on humans have observed no significant increase in airway resistance under xenon anaesthesia [42].

Organ Perfusion

It has been shown that compared to other anaesthetic regimens, xenon anaesthesia produces the highest regional blood flow in brain, liver, kidney and intestine. All volatile anaesthetics currently used, cause a reduction in the regional blood flow which carries the potential danger of tissue hypoxia. Xenon, therefore, appears to be interesting alternative for anaesthetic in the transplant surgery.

Toxicity

As xenon is excreted through the lungs without any change by hepatic or renal system, it can be safely used for anaesthesia in patients with hepatic and renal dysfunction. Xenon exerts no effects on coagulation, platelet function or immune system [3]. In vivo and in vitro studies suggest that xenon does not trigger malignant hyperthermia in MH-susceptible swine [42,43].

Embryotoxic or teratogenic changes were not observed in pregnant Wistar rats, nor was xenon found to be allergenic [44]. Xenon has proven to increase pulmonary resistance due to its greater density [50]. This can increase work of breathing with increase the risk in patients with COPD, morbid obesity and in premature infants [2].

Environmental Effects

The major volatile anaesthetic agents used today are chlorofuorocarbon based and are known to deplete the ozone layer [46] and as such their emission is being banned by international agreement from 2030.

The montreal summit of 2007 accelerated this date for developed countries to 2020. As said earlier, N_2O is 230 times more potent as a greenhouse gas than CO_2, taken 120 years to breakdown and the amount released as an anaesthetic contributes 0.1% of greenhouse effect [47]. In contrast, xenon appears to be environmentally safe, nonreactive and has no deleterious ecological effects. Thus xenon has certain environmental and legal advantages.

Pharmacoeconomics

The major disadvantage of the xenon anaesthesia is its high cost. In UK, the cost of 2 hour of xenon anaesthesia using 20 L xenon is about £300 compared to £10 with volatile anaesthetic agents and £20 with propofol anaesthesia [48].

As xenon is an expensive gas, therefore, closed circuit delivery must be used. Methods to reduce the cost of xenon anaesthesia include decreasing consumption, recycling of used xenon and reducing manufacturing cost. The major cost is due to the priming and flushing of the delivery circuit; if the delivery system could be refined to avoid the need for priming and flushing [49] than xenon anaesthesia would cost more affordable, assuming the closed circuit delivery.

Another mean to improve the cost effectiveness of xenon anaesthesia are xenon recycling system [46]. The major disadvantage of this system is that anaesthesia would have to be maintained with another agent while xenon was recovered, thereby negating the beneficial emergence property of xenon [3]. Dingley and Masson recently developed a cryogenic device to recover xenon from waste anaesthesia gas [50].

An interesting note is that Nakata et al pointed out that xenon anaesthesia is financially viable with longer duration of anaesthesia [51]. After 4 hrs of xenon administration in a completely closed circuit, xenon becomes comparable in cost to other anaesthetics. This gives a closer edge in cardiac and neurological surgeries in which prolonged anaesthesia is required and rapid recovery is beneficial [3]. Unfortunately, even if the cost of xenon anaesthesia can be reasonable reduced, it is still unlikely to gain widespread use due to its limited availability [49].

Induction and Emergence with Xenon

Reports suggests that xenon anaesthesia being used routinely during general surgery, gynaecological surgery and orthopaedic surgery in Russia, Europe [52,53]. Burov NE et al [37] described four stages of anaesthesia with 70% xenon and 30% O_2

Stage 1 - Stage of paraesthesia and hypoalgesia with pins and needle sensation all over the body.

Stage 2 - Stage of euphoria with increased pshycomotor activity where patient struggles to remove facemask, does not obey commands but has full recollection of commands.

Stage 3 - Stage of analgesia and partial amnesia noted by 3^{rd}-4^{th} min.

Stage 4 - Stage of surgical stimulus shows a degree of muscle relaxation with pronounced diaphragmatic breathing.

Because of high cost and limited availability, xenon should be conserve during anaesthesia. The patient lungs should be denitrogenated with 100% O_2 for 5 min before xenon inhalation. The amount of xenon necessary for primary equilibrium is about 0.1 L/kg body weight and xenon expenditure of 50-70 mL/min during steady state anaesthesia, depending on diffusion loss via the circuits and tubings permeability [54]. As xenon possess rapid onset, consciousness lost within 3 min. Xenon has no effect on nondepolarising muscle relaxants. Xenon concentration should never be below 40% as the MAC awake of xenon is about 30% volume which is below the desired concentration for anaesthesia [8].

Recovery from xenon is rapid and found to be 2-3 times faster with equi-MAC concentration of N_2O-sevoflurane/isoflurane anaesthesia [13] and 8-10 times faster recovery with equivalent depth of propofol anaesthesia [55]. Burov et al observed that patients woke up in 2 min and were fully conscious in 4 min after xenon anaesthesia [37]. Because of these recovery properties, xenon anaesthesia is now recommended during day care surgical procedures, in ICU and during cardiac surgery where cardiovascular stability will improve the surgical outcome [56].

Replacing the N_2O and volatile anaesthetic agents by an inert gas, xenon, can reduce the pollution and environmental hazards. Despite the high cost and limited availability, xenon is a potent inhalational anaesthetic with many salubrious qualities. With a favourable phrmacodynamic and pharmacokinetic properties: quick onset and rapid emergence, cardiac, neuroprotective, analgesic properties and environment protective qualities, xenon could very well be the future anaesthetic agent.

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