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Neuroprotective Properties of Xenon

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Introduction

Xenon is a colorless, odorless, tasteless, mono-atomic, and inert gas with a relative molecular weight of 131.3, and the empirical formula is Xe. Xenon is an extremely rare gas that represents no more than 0.0875 ppm in the atmosphere; this feature led the discoverers William Ramsay and Morris Travers to name it xenon from the Greek word "ξενοσ" (xenos) for stranger or foreign. Because of xenon's rarity, it is extremely expensive to produce from the residue left from air separation units that are used to produce oxygen; therefore, its commercial applications have been limited to high-priced applications such as the ultimate "clean gas" in the electronics/semi-conductor industry, an ion propellant for space travel, and a bright lighting source, and for medical applications, notably anesthesia, imaging, and neuroprotection following acute ongoing injury.

In this review, the authors trace the development of xenon for medical applications from the physico-chemical properties to the initial preclinical studies, and conclude in randomized clinical trials (RCTs).

Inert but Biologically Active

Because xenon is enshrouded by five filled electron shells, it is incapable of covalent bonding and forming adducts under biological conditions as electrons cannot be donated or accepted. However, because of xenon's relatively high polarizability [1], with a value of 4 compared with 0.2 for helium, it can form dipoles and has an affinity for amino acid residues surrounding preformed hydrophobic cavities thereby changing the functional properties of neighboring proteins by London dispersion forces. In this manner, xenon has been shown to have activity on many proteins, governed mostly by the size and shape of xenon atoms.

Because of its chemical non-reactivity, xenon is not biotransformed, which results in two important features governing its future clinical use. Most xenobiotic drugs are converted into metabolites that may be toxic; as xenon is not metabolized, the dangers posed by toxic metabolites are obviated. Furthermore, xenon in the inspired and expired gases are identical, permitting recirculation of exhaled xenon and thereby limiting the need for a fresh supply of this scarce resource.

Xenon for Anesthesia

Xenon was reported to have anesthetic properties in 1951 [2] and comes closest to exhibiting all of the ideal properties of an inhaled general anesthetic (Table 1). Compared with nitrous oxide, the other non-potent gaseous anesthetic, xenon is 1.5 times more potent; xenon is more suitable than nitrous oxide for anesthesia because of its lower blood/gas solubility and the consequent extremely rapid inflow and washout from the body. Despite this, xenon is infrequently used as an anesthetic even though European market authorization has been in effect for more than a decade; low utilization is attributed to the high cost involved in manufacturing this rare gas from the atmosphere. Therefore, the expense of using xenon as an anesthetic for routine adult surgery appears not to be justified given the available alternatives [3].

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Table 1 Properties of an "ideal" inhalation agent

Obtainable in pure form at a reasonable cost
Inherently stable
Not biotransformable
Lacks organ-specific toxicity
Minimal cardiorespiratory effects
Non-flammable
Low blood-gas partition coefficient for rapid uptake, elimination, and titratability
Sufficiently potent allowing an enriched inspired oxygen concentration
Lacks long-term adverse effects with chronic exposure
Lacks unpleasant smell and irritation to airway
Possesses analgesic and hypnotic properties
Readily reversible central nervous system effects with no stimulation

Drugs produce the anesthetic state via interaction with receptor targets which potentiate inhibitory neurotransmission and/or inhibit excitatory neurotransmission [4]. Xenon is thought to exert anesthetic action by potent non-competitive inhibition of the excitatory NMDA receptors [5] through an action at the binding site of the co-agonist, glycine [6]. Xenon also exerts potent effects on the neuronal background potassium channels including two-pore domain potassium channels such as TREK and TASK, which modulate neuronal excitability [7], and on ATP-sensitive potassium channels [8].

The first reported clinical experience with xenon for anesthesia was published in 1951 by Cullen and Gross, who reported on two patients who underwent surgical procedures (orchiectomy in an 81-year-old man and fallopian tube ligation in a 38-year-old woman who was 24-h postpartum) while receiving a xenon–oxygen (80:20) mixture to achieve the first plane of the third stage of anesthesia [2]. Induction was completed within 5 min and both patients maintained normal blood pressure, pulse rate, and pulse character and had good color throughout the procedures. Within 2 min of discontinuing xenon, both patients were oriented to time, place, and person; several hours later, they were able to recollect information given to them at this time. Since then, numerous clinical studies have investigated the effects of xenon in humans.

Safety and tolerability information regarding xenon for inhalation stem mostly from published literature describing clinical studies investigating the anesthetic properties of xenon gas, and the publications contain only summary information. In aggregate, the literature suggests that administration of xenon, as a general anesthetic, to patients both with and without cardiovascular disease is associated with hemodynamic stability that is unparalleled in critical care settings. Side effects identified in the literature that are frequently associated with the use of xenon gas for inhalation as a general anesthetic include raised intracranial pressure [9], bradycardia [3], and nausea and vomiting [10]. Although bradycardia is a safety concern identified for xenon anesthesia, if heart rate slows to the point that systemic blood pressure decreases, then standard positive chronotropic agents such as anti-muscarinic agents (e.g., glycopyrrolate or atropine) and β_1 adrenergic agonists (e.g., isoproterenol) can be administered to reverse it. Xenon is not known to interfere with oxygenation, but in an oxygen and xenon mixture, the greater the percentage of inhaled xenon administered to a subject, the lower the fraction of inspired oxygen that can be administered. Under circumstances in which lung oxygenation is compromised (e.g., from pulmonary edema), a higher fraction of inspired oxygen may be required to prevent arterial hypoxemia.

Xenon has a favorable pharmacokinetic (PK) profile for anesthesia with fast induction and emergence, which is independent of the duration of exposure. This PK effect is attributable to its low blood-gas partition coefficient of 0.115 [11], which is significantly lower than those of other inhalational anesthetics (nitrous oxide, 0.47; sevoflurane, 0.65; desflurane, 0.42). As xenon is excreted by the lungs with no biotransformation by the renal or hepatic systems, it may prove to be the anesthetic of choice in certain circumstances when liver or kidney function decrements.

Xenon has an oil/water solubility coefficient of 20, which is the highest coefficient of all noble gases, and it is the only noble gas with anesthetic properties at atmospheric pressures. The physico-chemical properties of xenon are detailed in Table 2.

Cardiovascular Effects of Xenon in Patients Without Cardiac Diseases

In 1990, Lachmann and associates published a randomized double-blind trial comparing the efficacy and potency of xenon with those of nitrous oxide, with special focus on the cardiovascular and respiratory systems [12]. The authors

Table 2 Physico-chemical properties: Ostwald solubility coefficients of xenon at 37 °C

Ostwald solubility coefficients (mL gas/mL liquid) at 37 °C	
Water/gas	0.075
Oil/gas	1.8
Blood/gas	0.115
Oil/water	20
Muscle/liver/kidney	0.10
Adipose tissue	1.3
Brain, gray substance	0.13
Brain, white substance	0.23

concluded that xenon is a more potent anesthetic than nitrous oxide in suppressing response to surgical stimuli and maintaining hemodynamic stability. Lachmann's group also compared the effect of xenon and nitrous oxide on the neurohumoral response and hemodynamics of 32 ASA class I–II patients, with the same protocol as described above [13]. The investigators concluded that xenon has more favorable hemodynamic, neurohumoral, and antinociceptive properties than nitrous oxide. Luttropp and associates investigated the effects of xenon on in vivo cardiac function using transesophageal echocardiography and hemodynamic measurements [14]. The fractional area in a short-axis view of the left ventricle at the level of the papillary muscles remained unchanged, suggesting that xenon anesthesia had no adverse effect on myocardial function as well as hemodynamics. The first multicenter randomized control trial, involving 224 patients in six centers, compared xenon/oxygen with isoflurane/nitrous oxide anesthesia and concluded that xenon anesthesia is as safe and effective as the isoflurane/nitrous oxide regimen, with the advantage that xenon exhibited more rapid recovery [15]. Also, significantly fewer xenon-anesthetized patients required inotropic support than the isoflurane group. In a single center study involving 160 patients, the hemodynamic effects were compared between those randomized to receive either xenon or propofol [16]. While systolic blood pressure was well maintained after induction with xenon at near baseline levels, propofol caused a significant post-induction decline in pressure that persisted throughout maintenance of general anesthesia. Heart rates were significantly lower in the patients who received xenon. In a multicenter study involving 252 patients scheduled for elective non-cardiovascular surgery, hemodynamic stability, including transesophageal echocardiography, was compared between patients randomized to receive either xenon or isoflurane [17]. While isoflurane decreased the myocardial contractile index, no such change was noted in the xenon-anesthetized patients, leading the authors to opine that xenon enables cardiovascular stability.

Cardiovascular Effects of Xenon in Patients With Cardiovascular Diseases

Ten patients after coronary artery bypass graft surgery (performed on cardiopulmonary bypass) were randomized to receive either propofol or xenon for sedation while being ventilated in the ICU [18]. The patients were crossed over to the alternative sedative after some hours. Compared with propofol sedation, xenon sedation did not change the heart rate or blood pressure; left ventricular stroke work index was similar.

Effects of xenon on hemodynamics in patients scheduled for coronary artery bypass graft surgery have also been assessed [19]. Statistically significant differences were found between the two groups' mean arterial pressure (MAP), fractional area change of the left ventricle, and end-diastolic area of the left ventricle. Xenon decreased the MAP and fractional area change significantly less and increased end-diastolic area significantly more than nitrous oxide. In a safety and feasibility study involving 20 patients undergoing coronary artery bypass surgery, xenon, at varying concentrations (0%, 20%, 35%, and 50% v/v), was administered while on cardiopulmonary bypass [20]. Despite theoretical concerns about expansion of gas bubbles, the cerebral embolic load, measured by middle cerebral artery Doppler, was no higher in patients who received xenon. Troponin levels tended to be lower 24 h after surgery in patients who received xenon. Twenty-six patients scheduled for implantation of an internal cardioverter-defibrillator were randomized to receive either xenon or propofol (both with remifentanil) for maintenance of general anesthesia [21]. Most of these patients had heart failure from ischemic heart disease or dilated cardiomyopathy. In contrast to propofol, surgical patients maintained on xenon had no changes in either the MAP or the left ventricular ejection fraction.

Central Nervous System Effects of Xenon

Volunteers ($n = 12$) were randomized to receive general anesthesia with xenon or propofol and the cerebral metabolic rate was assessed with the positron emission tomography (PET) ligand ^{18}F-fluorodeoxyglucose [22]. The xenon-exposed volunteers had cerebral metabolic rates globally reduced by 26% compared with those exposed to propofol alone. In another study, using ^{15}O-labeled water, the regional cerebral blood flow was monitored by PET scanning during xenon anesthesia in nine volunteers [23]. Xenon statistically significantly decreased the regional cerebral blood flow in several of the gray matter areas studied while regional cerebral blood flow increased by 22.1% (± 13.6%) in the white matter. A follow-up PET study, involving five healthy subjects, assessed regional cerebral blood flow and regional cerebral glucose metabolism using ^{15}O-labeled water and ^{18}F-labeled fluorodeoxyglucose, respectively [24]. In general, the regional reduction in cerebral metabolism was greater than the regional decrement in cerebral blood flow. Luttrop et al. [14] investigated the effects of inhalation of 65% xenon on cerebral blood flow velocities, using Doppler sonography in 17 ASA class I patients undergoing abdominal surgery; they found that cerebral blood flow velocity was unchanged during the first 5 min of xenon anesthesia, but was significantly increased in the left and right, middle, and the right anterior cerebral arteries after 15 and 30 min. In addition, Giller et al. [25] noted that administration of 25%, 30%, or 35% of xenon for 5 min to normal volunteers resulted in an increase in cerebral blood flow, measured by Doppler velocity, in 85% of subjects and a decrease in cerebral blood flow in 15% of subjects. These findings are in contrast to the findings of the PET studies described in the preceding paragraph. Reasons for these discrepancies could

be differences in the patient populations (i.e., healthy volunteers versus patients undergoing surgery), differences in the duration of xenon administration, and differences in the methodology used to assess blood flow. In a trial involving supplementation of therapeutic hypothermia with administration of xenon to neonates suffering from hypoxic ischemic encephalopathy, Azzopardi and colleagues reported a significant reduction in seizure activity in patients randomized to receive 30% xenon [26].

Neuroprotection

Xenon is thought to exert neuroprotective action by acting as an antagonist at NMDA receptors. Excessive entry of calcium, mediated by NMDA receptors, triggers biochemical cascades that ultimately lead to neuronal cell death. NMDA-induced neurotoxicity is through "excitotoxicity" from overactivation of NMDA receptors that underlies the acute neuronal injury observed following insults such as stroke, cardiac arrest, and traumatic brain injury. NMDA receptor antagonists are neuroprotective in in vitro and in vivo brain injury models [27]. Following the discovery that xenon inhibits NMDA receptors [5], it was shown that xenon could protect neuronal cell cultures against injury induced by NMDA, glutamate, or oxygen-glucose deprivation [28]. The same study showed xenon to be neuroprotective in vivo against neuronal injury caused by subcutaneous injection of *N*-methyl (D, L)-aspartate in rats. Subsequently, this finding was corroborated by Petzelt et al., in an in vitro model of hypoxia [29] and in an in vivo model of stroke [30]. Other NMDA receptor antagonists such as nitrous oxide, ketamine, and dizocilpine (MK-801) have intrinsic neurotoxicity, but xenon not only appears to be devoid of these neurotoxic effects but also ameliorates the injury produced by other NMDA antagonists [31]. Furthermore, xenon upregulates the transcription factor hypoxia inducible factor 1 alpha (HIF 1α) and its downstream cytoprotective effectors including erythropoietin [32, 33]. Xenon has now been shown to afford neuroprotection in a variety of mammalian in vitro and in vivo models and meets the Stroke Treatment Academic Industry Roundtable recommendation for proceeding to clinical trials [34].

Phase II Clinical Trial in Out-of-Hospital Cardiac Arrest Patients

Based upon successful animal studies investigating the effects of xenon in the setting of cardiac arrest [35, 36] and because of the synergistic interaction between xenon and therapeutic hypothermia [37, 38], the Xe-Hypotheca trial (NCT 00879892; May 2009–September 2014) was initiated at a single academic site (University of Turku Hospital, Finland) to determine the feasibility and cardiac safety of inhaled xenon when added to therapeutic hypothermia for successfully resuscitated out-of-hospital cardiac arrest (OHCA) patients [39]. Feasibility was established after the first 36 patients were randomized to receive either therapeutic hypothermia alone ($n = 18$) or therapeutic hypothermia in combination with xenon by inhalation ($n = 18$), with a target concentration of at least 40% xenon for 24 h. In the xenon group, the median end-tidal xenon concentration was 47% and duration of xenon inhalation was 25.5 h. Xenon did not induce significant conduction, repolarization, or rhythm abnormalities. Median dose of norepinephrine during hypothermia was 2.95 mg in xenon-treated patients and 5.30 mg in patients treated with therapeutic hypothermia alone ($p = 0.06$). Heart rate was statistically significantly lower in xenon-treated patients than that in patients treated with therapeutic hypothermia alone ($p = 0.04$). From the initial results of this trial, the investigators concluded that xenon treatment in combination with hypothermia is feasible and has favorable cardiac features in OHCA patients. The Xe-Hypotheca trial was extended to a second site in 2013 (University of Helsinki Hospital, Finland) with an expanded cohort; the effect of xenon on ischemic white matter damage was assessed by fractional anisotropy from diffusion tensor magnetic resonance imaging (MRI) [40]. Neurological outcome and mortality at 6 months were also assessed. A total of 224 patients were screened for eligibility. One hundred and ten OHCA patients, aged 24–76 years, were randomized to receive either hypothermia treatment alone for 24 h (control group, $n = 55$) or inhaled xenon, administered to achieve an end-tidal xenon concentration of at least 40%, combined with hypothermia (33 °C) for 24 h (xenon group, $n = 55$). The primary endpoint was severity of ischemic white matter brain injury as evaluated by fractional anisotropy from diffusion tensor MRI; MRIs were scheduled within 16 h after rewarming of a patient (ranging between 36 and 52 h after OHCA). Secondary endpoints were neurological outcome, assessed with cerebral performance category score (from 1 = conscious, alert, able to work, might have mild cognitive deficit, to 5 = death) and modified Rankin Scale (score from 0 = no symptoms at all to 6 = death), mortality at 6 months, and complication rate within 7 days of post-CA. However, the trial was not powered to detect statistically significant differences in clinical efficacy (i.e., mortality at 6 months and neurological outcome) between groups. The primary endpoint was assessed in the complete case population. Survival at 6 months and complication rate were analyzed in the intention-to-treat population. Kaplan–Meier survival curves and a Cox proportional hazards model were used to compare mortality at 6 months between groups.

Of the randomized patients, six patients in the control group and seven patients in the xenon group were missing MRI data and were excluded from the complete case population. The mean (±SD) global fractional anisotropy value of all voxels in the xenon group (0.433 [± 0.028]) was significantly different than that in the control group (0.419 [± 0.033]) ($p = 0.03$). The age-, gender-, and site-adjusted mean global

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fractional anisotropy values were 3.8% higher in the xenon group than those in the control group (adjusted mean difference 0.016 [95% CI, 0.005 to 0.027]; $p = 0.006$). The severity of observed widespread injury was demonstrated; on average, 41.7% of the white matter tracts, including major commissural, associative, and projection fibers, were significantly more severely injured in the control group than in the xenon group. These fibers are involved in multiple important cognitive functions such as attention, memory, language, emotions, auditory, visual and executive processing, and motor functions of the body.

At 6 months, 75 patients (68.2%) were alive and able to provide follow-up data. In ordinal analysis of modified Rankin Scale, median (interquartile range) value was 1 (0 to 6) in the xenon group and 1 (0 to 6) in the control group (median difference = 0 [95% CI, 0 to 0]; $p = 0.68$). The Kaplan–Meier survival estimate (panel A) after 6 months was 27.7% (15/55 patients) in the xenon group and 34.5% (19/55 patients) in the control group (adjusted hazard ratio = 0.49 [95% CI, 0.23 to 1.01]; $p = 0.053$) (Fig. 1).

It was concluded that among comatose survivors of OHCA, treatment with inhaled xenon combined with hypothermia resulted in less white matter damage, as measured by fractional anisotropy of diffusion tensor MRI, than treatment with hypothermia alone. In contrast, there was no statistically significant difference between groups in neurological outcomes or mortality at 6 months. However, the study was underpowered to detect a statistically significant difference in clinical outcome due to the rarity of severe neurological impairment in long-term survivors after CA; about 90% of CA patients who are alive at the 6-month follow-up have experienced a good neurological outcome (cerebral performance category 1–2). While there was no statistically significant difference in neurological outcomes or mortality at 6 months, unpublished data demonstrates that there was a trend to a survival benefit.

A predefined secondary objective was to assess the effect of inhaled xenon on myocardial ischemic damage [41]. Troponin-T levels were measured at hospital admission, and at 24 h, 48 h, and 72 h post-CA. Among comatose OHCA patients, inhaled xenon combined with hypothermia resulted in less severe myocardial injury than with hypothermia alone, as demonstrated by the significantly reduced release of troponin-T.

Rates of serious adverse events (SAEs) in the xenon group were not significantly different from the rates of SAEs in the standard of care group [40]. SAEs seen in both the xenon and standard of care groups include status epilepticus, acute kidney injury (in the "risk," "injury," or "failure," RIFLE categories), pulmonary edema, ventricular fibrillation, ventricular tachycardia, atrial fibrillation, coronary stent thrombosis,

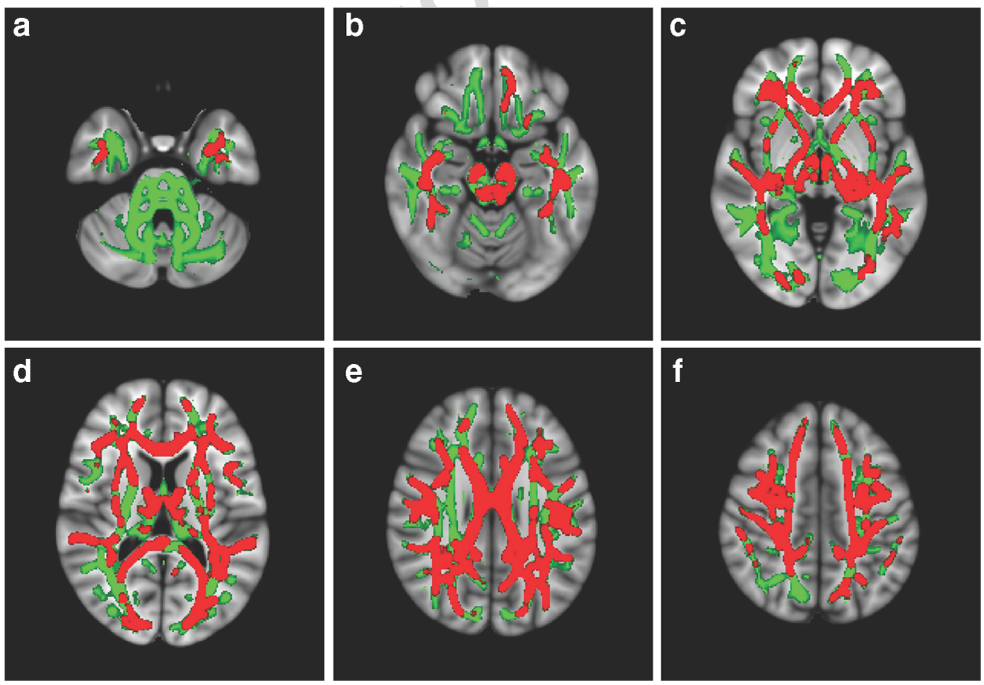

Fig. 1 Whole-brain fiber tractography of fractional anisotropy. Fractional anisotropy (FA) is a scalar value representing directionality of water diffusion. White matter damage leads to a loss of microstructural organization that can be quantified by the loss of directionality in the diffusion of water molecules in the white matter tracts. Using data from a diffusion tensor imaging sequence of an MRI scan performed within 72 h of rewarming, panels **a**–**f** represent sequential ascending horizontal planes of the major tracts in the brain. The visualization presents the results of the voxel-wise tract-based spatial statistics analysis of FA values between the xenon group and the control group. Voxels with significantly ($p < 0.05$, family-wise error corrected for multiple comparisons) higher fractional anisotropy values in the xenon group were identified and are shown in red in the statistical visualization (i.e., 41.7% of all 119,013 analyzed voxels), whereas areas in which there were no significant difference in fractional anisotropy values between the groups are shown in green (modified from reference [40])

sepsis, pneumonia, multi-organ failure, adult respiratory distress syndrome, and subarachnoid hemorrhage SAEs only observed in the xenon group included bradycardia treated with pacemaker ($n = 1$ event) and serious bleeding (gastrointestinal, $n = 1$ event). SAEs only observed in the standard of care group included third-degree atrioventricular block ($n = 1$ event), carotid dissection ($n = 1$ event), carotid thrombosis ($n = 1$ event), and serious bleeding (intracranial, $n = 1$ event).

Conclusion and Potential Future Applications

Xenon exhibits many features of a putative neuroprotective agent with an ideal pharmacokinetic profile for use following acute neurological injury. Studies involving several different acute neurological injury models in a variety of animal species from four laboratories have consistently demonstrated the neuroprotective efficacy of xenon even when administered as long as 6 h following neurological injury. The mechanisms for neuroprotection appear to involve (i) antagonism of the NMDA receptor whose activation is pivotal for the excitotoxic damage that follows neurologic injury, and (ii) upregulation of HIF 1α and the resulting cytoprotection from erythropoietin, a downstream effector of the transcription factor.

A phase 2 RCT (Xe-Hypotheca) demonstrated significantly less white matter brain damage, as reflected by higher global fractional anisotropy values, in subjects randomized to receive xenon by inhalation during the 24-h period of targeted temperature management.

The stage is now set for a pivotal phase 3 RCT, XePOHCAS (NCT03176186), to determine the efficacy (using endpoints of good functional outcome and survival at 30 and 90 days), safety, and cost-effectiveness of xenon, at a dose of 50% of 1 atmosphere, in the management of post-cardiac arrest syndrome patients. The trial is likely to report its outcome in 2021 or before depending on the interim analysis at the halfway point of the 1436-patient trial to be conducted in 7 countries in Europe and North America.

In the event that xenon exhibits neuroprotective efficacy in the XePOHCAS trial, then subsequent trials are likely to be conducted in other acute neurological injury settings including stroke and traumatic brain injury. As with the XePOHCAS trial, the maximal dose of xenon is likely to be restricted to ≤ 50% of 1 atmosphere as these patients may also have lung injury that will require an F_iO_2 of no less than 0.5 to avoid hypoxemia.

A further clinical application may be in pediatric surgical settings to obviate the occurrence of anesthetic-induced developmental neurotoxicity (AIDN). For AIDN, xenon may be particularly effective both by reducing exposure to high concentrations of neurotoxic volatile anesthetics by virtue of xenon's anesthetic properties and because the neurotoxicity may be obviated by xenon's neuroprotective properties.

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