British Medical Bulletin

- Oxford Journals
- Medicine
- British Medical Bulletin
- Volume 71, Number 1
- Pp. 115-135

Previous Article

British Medical Bulletin 2005 71(1):115-135; doi:10.1093/bmb/ldh034

Published online 22 February 2005

Xenon: elemental anaesthesia in clinical practice

Robert D. Sanders[*,‡], Daqing Ma[*] and Mervyn Maze[*,†,‡]

[*] Department of Anaesthetics and Intensive Care, Faculty of Medicine, Imperial College London, UK, [†] Biophysics Section, Department of Biological Sciences, Imperial College London, UK and [‡] Magill Department of Anaesthesia, Intensive Care and Pain Management, Chelsea and Westminster Hospital, Chelsea and Westminster Healthcare NHS Trust, London, UK

Correspondence to: Professor Mervyn Maze, Department of Anaesthetics and Intensive Care, Faculty of Medicine, Imperial College London, UK. E-mail: m.maze@ic.ac.uk

Abstract

The ‘noble’ gases have been known to have anaesthetic properties for 50 years yet only recently has their application become a clinical reality. In this review we describe the preclinical and clinical studies that have led to a resurgence of interest in the use of the element xenon as an anaesthetic. Furthermore, we highlight specific areas where xenon demonstrates advantages over other anaesthetics, including safety, beneficial pharmacokinetics, cardiovascular

stability, analgesia and neuroprotection.

Introduction

The ‘noble’ gas xenon possesses numerous salubrious qualities which are currently underutilized in the world of clinical medicine; most notably in the field of anaesthesia. Xenon exists naturally as nine isotopes, of which ^{132}Xe, with a mean atomic weight of 131.293, is the most abundant. However, the gas is extremely rare, representing no more than 8.75×10^{-6}% of atmospheric gases, and hence derives its name from the Greek for ‘stranger’. Discovered in 1898 by Travers and Ramsay, xenon is now manufactured by fractional distillation of air and is used commercially for lasers, high-intensity lamps, flash bulbs, fuel for ion thrusters in the aerospace industry, X-ray tubes and in medicine. Xenon has been used in clinical radiological[1] and anaesthetic practice[2] for 50 years, and in this article we discuss its potential application in clinical anaesthetic practice, highlighting areas in which its unique properties can be exploited.

Anaesthetic mechanism of action

Currently anaesthetics are thought to produce anaesthesia via interaction with receptor targets, most commonly $GABA_A$ receptors and possibly other receptors such as the *N*-methyl-D-aspartate (NMDA) subtype of the glutamate receptor[3] which potentiate inhibitory neurotransmission and inhibit excitatory neurotransmission, respectively. Xenon is thought to exert anaesthetic action by potent non-competitive inhibition of NMDA receptors,[4,5] with little effect on $GABA_A$ receptors or non-NMDA glutamatergic receptors.[4–6] Franks and colleagues[4,5] demonstrated that 80% xenon reduced NMDA-activated currents by approximately 60% (Fig. 1), grouping xenon with nitrous oxide,[7] cyclopropane[8] and ketamine[9] in a class of anaesthetics with effects on NMDA receptors but not on $GABA_A$ receptors.

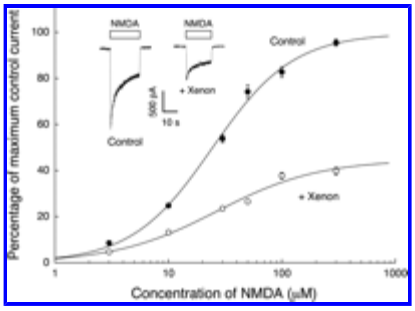
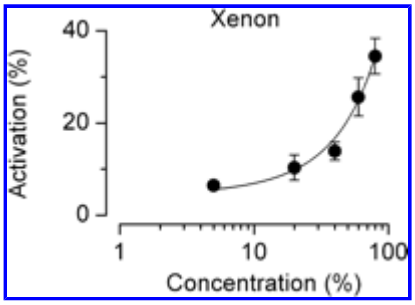


Fig. 1 Xenon inhibits NMDA receptors in cultured rat hippocampal neurons. NMDA activates an inward current (in neurons clamped at –60 mV) with an EC_{50} concentration of 24 ± 2 μM NMDA and a Hill coefficient of 1.2 ± 0.1. Xenon (80%) inhibited the current by approximately 60%, but did not significantly change either the EC_{50} or the Hill coefficient. Each data point represents the mean peak current from at least six cells. The inset shows typical current traces (at 100 μM NMDA) in the presence and absence of xenon.

View larger version (17K):
[in this window]
[in a new window]

Reproduced with permission from Franks *et al.*, *Nature*, **396**, 324, 1998.

Recent studies have implicated neuronal background potassium channels (two-pore-domain potassium channels such as TREK and TASK), which modulate neuronal excitability, as potential targets of anaesthetic action,[10–12] and xenon, nitrous oxide and cyclopropane have been shown to activate TREK-1 but not TASK-3 channels.[13] Xenon (80%) activated TREK-1 channels by 35 ± 2% (Fig. 2) but had little effect on TASK-3 channels, unlike the known GABAergic anaesthetic halothane which activates both.[13] Activation of TREK channels leads to neuronal hyperpolarization which reduces cellular excitability; in addition, this effect is likely enhance NMDA receptor blockade due to the voltage-gated kinetics of this channel. As TREK channel activation is a consistent effect of the anaesthetics tested so far[10–13] it may become a common mechanism of action for all anaesthetics.



View larger version (12K):
[in this window]
[in a new window]

Fig. 2 Xenon concentration–response curve for the activation of TREK-1 channels expressed in HEK 293 cells. Data are mean ± SEM (n = 7–14 cells). Reproduced with permission from Gruss *et al.*, *Mol. Pharmacol.*, **65**, 443–52, 2004.

It is still not known how anaesthetics produce anaesthesia, but significant progress has been made in this field over the last two decades. Study of how an ‘inert’ element such as xenon can produce anaesthesia will be an important probe in furthering inquiry into anaesthetic mechanisms. Currently, antagonism of the NMDA receptor is thought to be xenon’s prime site for anaesthetic action and recent work has also highlighted the role of TREK-1 channels; although their relative contributions are hard to estimate, both sites of action are likely to be involved. It is possible that further targets contributing to the anaesthetic state produced by xenon will be isolated in the future.

Clinical features

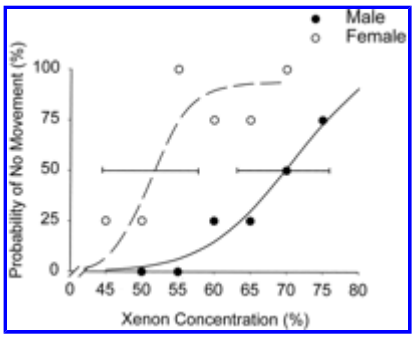
Recently, a large multicentre randomized control trial was conducted across Europe to assess the efficacy and safety profile of xenon

Top
Abstract
Introduction
Anaesthetic mechanism of action

anaesthesia.[14] This study of 224 patients (ASA I–III; 218 patients completed the protocol) demonstrated that xenon (60 ± 5%) was not only safe but also had a faster post-anaesthesia recovery time than isoflurane (end-tidal concentration 0.5%) combined with nitrous oxide (60%). As we will discuss below, xenon was found to be cardiovascularly stable ('cardiostability'), with a tendency to an increased analgesic effect. Furthermore, xenon's cardiovascular, analgesic and safety profile has been evaluated with success in the field of critical care medicine.[15] Clinical application in the field of cardioprotection and neuroprotection will also be discussed.

Anaesthetic potency and depth

Cullen *et al.*[16] originally estimated a minimum alveolar concentration (MAC) value for xenon of 71% of an atmosphere (71% atm); more recently, Nakata *et al.*[17] have estimated it to be somewhat lower, at 63% atm (in a middle-aged population). The same group also noted a gender-dependent difference in MAC values in the elderly (≥65 years), with females having a significantly lower MAC than men (51% atm vs. 69% atm)[18] (Fig. 3). This is especially interesting as volatile anaesthetic agents only show gender-dependent differences in MAC during pregnancy,[19] and the observations of Goto *et al.*[18] may represent a class effect for all NMDA antagonists.



View larger version (20K):
[in this window]
[in a new window]

Fig. 3 The probability of no patient movement in response to skin incision is plotted against the concentration of xenon for patients aged ≥65 years. The continuous and broken curves represent the logistic regression curves for men and women, respectively. By definition, the concentration associated with a 50% probability of no movement (the intersection between the horizontal bar and the regression curve) is the MAC for xenon for each sex. The horizontal bars represent the 95% confidence intervals of the MACs. Reproduced with permission from Goto *et al.*, *Anesthesiology*, **97**, 1129–32, 2002.

The MAC-awake value for xenon was determined in 90 female patients to be 33% atm or 0.46 times its MAC.[20] Therefore xenon is ranked between nitrous oxide (MAC-awake of 0.61 MAC), and isoflurane and sevoflurane (MAC-awake of 0.35 MAC for both). Furthermore, xenon interacts additively with isoflurane and sevoflurane on MAC-awake, unlike nitrous oxide which is infra-additive with either agent.

While there is no effective method for measuring anaesthetic depth, two methods currently being evaluated are mid-latency auditory evoked potentials (MLAEPs), which predict responsiveness to verbal

command,[21,22] and bispectral index (BIS) monitoring, which is an electroencephalographic-derived univariate scale thought to reflect the level of hypnosis in anaesthetized patients.[23] Goto *et al*.[24] found that, unlike isoflurane, BIS monitoring did not correlate with hypnotic depth on emergence from xenon anaesthesia. Later, they found that MLAEPs correlated more closely with depth of hypnosis and concluded that this was a more appropriate form of monitoring xenon anaesthesia.[25] Recently, work from Russia has suggested that BIS is particularly inaccurate on induction and emergence from anaesthesia with xenon but may provide adequate assurance of established anaesthetic depth.[26] Two conclusions can be drawn from these investigations: MLAEPs correlate more closely with the xenon hypnotic state than BIS monitoring, and there is insufficient information available to assure us that either method is completely effective for assessing depth of anaesthesia.

Induction and emergence

Xenon possesses a favourable pharmacokinetic profile with fast induction and emergence[14,27–29] which is independent of the duration of anaesthesia.[15,28] This effect is attributable to its low blood–gas partition coefficient of 0.115,[30] which is significantly lower than those for other inhalational anaesthetics (nitrous oxide, 0.47; sevoflurane, 0.65; desflurane, 0.42). Xenon has been shown to induce anaesthesia faster than sevoflurane (71 ± 21 s vs. 147 ± 59 s),[27] though xenon induction may be associated with agitation, particularly in men.[18] The Xenon Study Group[14] demonstrated the rapid emergence from xenon anaesthesia, showing that xenon exhibited significantly faster recovery than equi-MAC nitrous oxide–isoflurane. Emergence from xenon anaesthesia proved to be two or three times faster than emergence from equi-MAC concentrations of nitrous oxide–isoflurane or nitrous oxide–sevoflurane anaesthesia.[28] Xenon also demonstrated significantly quicker recovery time than an equivalent depth of propofol anaesthesia after coronary artery bypass grafting in 10 male patients in a randomized cross-over study (mean values 3 min 11 s vs. 25 min 23 s).[29]

Rapid emergence times following anaesthesia may be advantageous in a broad spectrum of applications including ‘day-surgery’ out-patient settings, critical care medicine (to afford clinical examination[15]) and cardiac surgery, where both ‘fast tracking’[30] and cardiovascular stability are desirable features.

Cardiovascular system

Xenon is regarded as a cardiostable anaesthetic; inotropic preservation and only a clinically insignificant decrease in heart rate are consistently reported.[14,29,31–34] This effect may be due to less stress-induced sympathetic stimulation,[32] a theory supported by the observation of stable epinephrine levels during xenon anaesthesia.[33] Perioperative plasma cortisol and epinephrine did not rise in the xenon group unlike the rise observed in the nitrous oxide group, despite the fact that more fentanyl was used during nitrous oxide anaesthesia.[33] However, Bedi *et al*.[15] recently showed that there was no difference in plasma catecholamine levels compared with propofol to account for xenon’s cardiostability. Xenon is also considered to suppress both sympathetic and parasympathetic transmission,[35] and therefore xenon’s cardiostability is likely be a consequence of a combination of autonomic direct myocardial and indirect catecholaminergic actions.

Assessment of xenon's effects on compromised myocardium may be more relevant when determining whether xenon will be efficacious in the clinical arena. Dingley *et al.*[29] have directly compared the cardiovascular effects of post-cardiac surgical patients sedated with either propofol or xenon, noting that xenon caused no change in heart rate or mean arterial pressure, and that higher filling pressures and systemic vascular resistance were seen than were evident in propofol-sedated patients. Indeed, ventricular function, as assessed by trans-oesophageal echocardiography, is unchanged during xenon anaesthesia.[34] In a study of 20 patients scheduled for elective coronary artery bypass grafting, xenon decreased indices of cardiac function significantly less than nitrous oxide.[36] In a critical care setting, xenon maintained blood pressure better than propofol throughout an 8 h period, and the authors concluded that xenon's cardiostable properties may have a niche application in states of sepsis or shock where other sedative agents may induce myocardial depression.[15] Animal models of cardiac dysfunction (left ventricular compromise[37] and cardiomyopathy[38]) have also been used to demonstrate xenon's cardiostablity. Furthermore, inhaled xenon (70%) was shown to be cardioprotective during early reperfusion following coronary artery occlusion, reducing infarct size after regional ischaemia in rabbit heart *in vivo*.[39] This would not only be of great advantage to patients who experience ischaemic events under anaesthesia, but is also of great potential for the application of xenon following myocardial infarction.

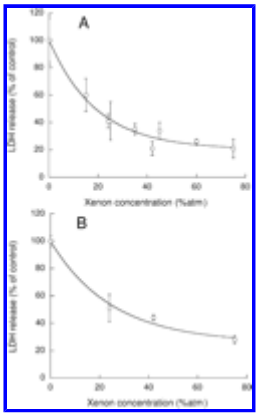
Xenon's cardiostable effect has been investigated *in vitro* where it was found to exert little effect on major cation currents, including those for sodium (I_{Na}), calcium ($I_{Ca,L}$) and potassium ($I_{K,ir}$), in guinea pig myocytes.[40] Xenon exerts no effects on L-type calcium channels in human atrial myocytes, even in the presence of the ß-adrenergic agonist isoproterenol, unlike the known myocardial depressant halothane.[41] In contrast with volatile anaesthetics,[42] xenon showed no deleterious effects on cardiac function in preparations of isolated guinea pig ventricular muscle bundles.[40] Thus xenon appears to be relatively 'inert' in *in vitro* models of cardiac function.

Clinical application of xenon is likely to succeed in arenas where cardiovascular compromise can be predicted, such as high-risk, cardiac and emergency surgery, and potentially also in situations of shock and sepsis. In addition, patients with cardiac disease may benefit from the cardioprotective nature of xenon anaesthesia.

Neuroprotection

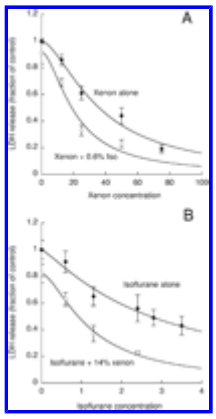
Xenon's capability to act as a neuroprotective agent has also been investigated. As NMDA receptors appear to be crucial to the initiation of neuronal injury and progression to cell death as a result of a variety of insults,[43–45] xenon has been evaluated in various paradigms of neuronal injury. *In vitro* xenon reduced mouse cortical co-culture neuronal injury, quantified by the amount of lactate dehydrogenase (LDH) released into the culture medium, induced by NMDA, glutamate or oxygen–glucose deprivation (OGD). LDH release was significantly reduced at all concentrations of xenon tested (Fig. 4) with xenon IC_{50} concentrations for neuroprotection being 19 ± 6% atm and 28 ± 8% atm for NMDA- and glutamate-induced injury, respectively. Xenon was also effective in protecting against the injury caused by depriving the cell cultures of oxygen and glucose for 90 min with an IC_{50} concentration of 10 ± 4%

atm.[46] Further *in vitro* work on rat cortical cultures showed that xenon (50%) could attenuate hypoxia-induced LDH release,[47] accompanied by a 60% reduction in glutamate release; this effect could be partially antagonized by intracellular calcium chelation. Recent observations have suggested that some calcium signalling in the neuropathological situation is protective,[45,48] dissociating calcium load and neuronal death;[44] in the case of xenon, preliminary evidence suggests that preservation of some calcium signalling is necessary for neuroprotection. In clinical practice xenon is likely to be administered in combination with other anaesthetic agents, and therefore we investigated whether co-administration of isoflurane, a $GABA_A$ agonist,[5] which is also neuroprotective,[49] would enhance xenon neuroprotection. The combination proved to be synergistic[50] (Fig. 5), with the IC_{50} (mean ± SEM) for xenon neuroprotection significantly decreasing from the predicted value of 28 ± 2.0% atm (assuming additivity) to 18.9 ± 2.5% atm in the presence of 0.6% isoflurane.



View larger version (12K):
[in this window]
[in a new window]

Fig. 4 Dose-dependent effect of xenon vs. injury produced by (A) NMDA or (B) glutamate *in vitro*. Co-cultures of mouse neuronal–glial cells were treated with (A) NMDA 250 mM or (B) glutamate 100 mM for 10 min during exposure to oxygen–carbon dioxide–xenon–nitrogen. The xenon and nitrogen concentrations were changed reciprocally such that their aggregate was 75% atm. After 6 h the culture medium was harvested and assayed for LDH. Data are expressed as the percentage mean ± SEM (n = 3) of LDH released into the medium over the 6 h period normalized to LDH release when no xenon is present. Reproduced with permission from Wilhelm *et al.*, *Anesthesiology*, **96**, 1485–91, 2002.

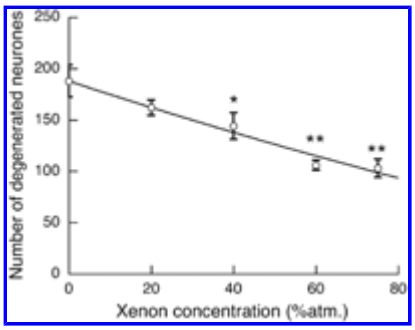


View larger version (14K):
[in this window]

Fig. 5 Xenon and isoflurane alone and in combination inhibited LDH release, expressed as a fraction of maximum LDH release in the absence of agents (mean ± SEM, n = 3 or 4) induced by oxygen–glucose deprivation for 75 min. (A) Closed circles, xenon alone, IC_{50} = 35.9 ± 2.2% atm; open circles, xenon in the presence of 0.6% isoflurane, IC_{50} = 18.9 ± 2.5% atm. (B) Closed circles, isoflurane alone, IC_{50} = 2.72 ± 0.35%; open circles, isoflurane in the presence of 14% xenon, IC_{50} 0.92 ± 0.13% atm. Reproduced with permission from Ma *et al.*, *Anesthesiology*, **99**, 748–51, 2003.

[in a new window]

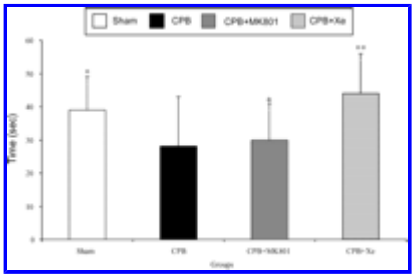
In vivo xenon attenuated neuronal injury induced by administration of *N*-methyl-L-aspartate (NMA) to rats (Fig. 6).[46] Furthermore, we demonstrated the neuroprotective effect of xenon in a focal ischaemia model by administering 70% xenon during transient middle cerebral artery occlusion in mice and found a significant reduction in total, cortical and subcortical infarct size compared with nitrous oxide.[51] This difference in efficacy may be attributable to a differing potency of antagonism of the NMDA receptor (and its subtypes).



View larger version (18K):
[in this window]
[in a new window]

Fig. 6 Dose-dependent neuroprotective effect of xenon *in vivo* on NMA-induced neuronal injury. Rats were injected with NMA 100 mg/kg subcutaneously and humanely killed 4 h later after exposure to air ($n = 7$) or xenon ($n = 5–8$). The arcuate nucleus was sectioned and stained with cresyl violet and the number of degenerated neurons (pyknotic nuclei surrounded by vacuolated cytoplasm) were counted (mean ± SD). *$P < 0.05$, **$P < 0.01$ compared with control. Reproduced with permission from Wilhelm *et al.*, *Anesthesiology*, **96**, 1485–91, 2002.

In order to provide functional correlates (i.e. a cognitive parallel) of this histological effect[46] we studied the effect of xenon in a model of neurological injury induced by cardiopulmonary bypass (CPB).[52] In this model, neuromotor skills, visuospatial memory and spatial memory were assessed for up to 12 days after rats were subjected to CPB in the presence of either xenon or nitrogen (65% atm). Xenon attenuated the neurocognitive dysfunction caused by CPB; this effect was superior to that seen with MK801 (dizolcipine), another NMDA antagonist (Fig. 7).[52] Furthermore, in our focal ischaemia model in mice, xenon provided superior neurocognitive protection to that provided by nitrous oxide, as evidenced in two out of three cognitive tests conducted 24 h after ischaemia.[51]



View larger version (12K):

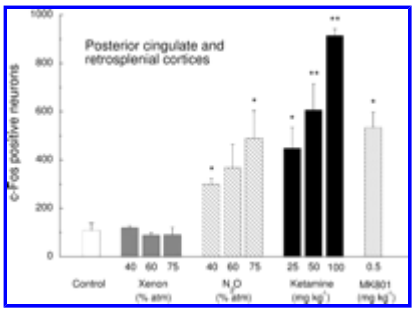
Fig. 7 Spatial memory following CPB. After CPB animals were subjected to 10 consecutive days of Morris water maze testing where they had to locate a submerged platform in one of four quadrants of a pool of water. Twelve days after CPB, animals were subjected to a probe trial, in which there was no platform present, for 60 s. The percentage of time spent in the quadrant of the former platform position was obtained as a measure of spatial bias. Animals in the Sham and CPB+Xe groups spent a longer period in the quadrant of the former

[in this window]
[in a new window]

platform, which indicates that they have a better spatial memory function than the other groups. The results are mean ± SD (n = 10). *P < 0.05, **P < 0.01 compared with the CPB group. †P < 0.05 compared with the CPB + Xe group. Reproduced with permission from Ma *et al*., *Anesthesiology*, **98**, 690–8, 2003.

Spontaneous neuronal injury, such as occurs with stroke and perinatal brain injury, cannot necessarily be approached in a prospective manner, i.e. application of the agent before the injury. Therefore investigation of whether an agent is effective with post-injury administration is important for clinical application in these scenarios. In a model of transient global ischaemia (temporary middle cerebral artery occlusion in adult rats for 90 min), application of 50% xenon for 3 h, starting 15 min after the insult, significantly reduced neuronal damage in the cortex and striatum; interestingly, 70% xenon was ineffective.[53] As a large degree of neuronal damage post-insult occurs in the penumbral region of infarct, xenon appears to preserve this region. Theoretically, retrospective treatment with xenon could be applied to neurological conditions such as stroke; however, it will be prudent to establish a ‘window’ of effective retrospective treatment in animals before extrapolating this treatment to human trials.

The MAC of xenon is estimated to be 63–71% atm;[16,17] therefore the concentrations required for neuroprotection are significantly sub-anaesthetic. Thus, in contrast with other anaesthetics that require anaesthetic or supra-anaesthetic doses to act as a neuroprotectant,[49,54,55] xenon maybe effective at more clinically acceptable concentrations or where anaesthesia is not required or may even be detrimental (e.g. in patients with cardiovascular compromise). It should be noted that other NMDA receptor antagonists have faired poorly in clinical trials so far despite showing promise in preclinical experiments. In some instances, this is because of unfavourable pharmacological properties which prevent rapid transfer of the NMDA antagonist across the blood–brain barrier. Almost all NMDA antagonists tested so far exhibit psychomimetic behavioural changes;[56,57] pyramidal neuronal damage in the posterior cingulate and retrosplenial (PC/RS) cortices[7,58,59] are considered to be morphological correlates of the behavioural changes. We showed that ketamine and nitrous oxide increased c-Fos expression in PC/RS cortices dose dependently, a neurotoxic feature not caused by xenon (Fig. 8).[60] In addition, xenon,[61] like haloperidol[60] and eliprodil,[62] can ameliorate the neurotoxic effects of other NMDA antagonists.



View larger version (26K):

Fig. 8 Concentration or dose–response effects of xenon, nitrous oxide and ketamine on the number of c-Fos positive neurons in the posterior cingulate and retrosplenial cortices. Rats were exposed to increasing doses or concentrations of three anaesthetics which antagonize the NMDA receptor. The rats were killed and the brains harvested and prepared for c-Fos immunostaining. MK 801 is included as a known positive control for the production of a c-Fos immunohistochemical lesion in the posterior cingulate and retrosplenial cortices. Results are shown as mean ± SEM. *P < 0.05, **P < 0.01 vs.

[in this window]
[in a new window]

control. Reproduced with permission from Ma *et al*., *Br. J. Anaesth.*, **89**, 739–46, 2002.

Recent *in vitro* research has suggested that xenon acts not only on NMDA channels but also on TREK-1 channels (discussed above). TREK-1 channels are also activated by the neuroprotective agents riluzole,[63] a therapeutic agent used to treat amyotrophic lateral sclerosis, and polyunsaturated fatty acids.[64] Consequently, it has been postulated that these channels contribute to neuroprotection. As TREK-1 channels are activated by intracellular acidosis and reduce neuronal excitability, this is certainly feasible.

Xenon is not 'inert' with respect to cerebral haemodynamics; increased cerebral blood flow (CBF)[65–67] with preserved cerebral autoregulation[66–68] is thought to occur acutely with xenon administration. This is an area of crucial importance to the clinical application of xenon, as any neuroprotective or anaesthetic agent that may be used in a situation where raised intracranial pressure (ICP) is likely (e.g. neurosurgery) must have a predictable and safe effect on CBF. Indeed, a theoretical concern that increasing CBF may worsen ICP is an important consideration with an agent of this class. There have been no reports of an increase in ICP with xenon administration in animal models, despite reported vasodilatation.[69] In humans, xenon has been used without compromise in radiology; in one study of head trauma sufferers, xenon appeared to increase intracranial and cerebral perfusion pressure but without any evidence of cerebral oligaemia or ischaemia.[70] Further information is required to define whether xenon may be used safely in situations of raised ICP.

Analgesia

Consistent with its ability to inhibit the NMDA receptor, xenon provides analgesic effects. In clinical studies xenon consistently provides a significantly greater analgesic effect than nitrous oxide.[32–34,71,72] However, Rossaint *et al*.[14] found only a tendency to increased analgesic effect compared with 1 MAC isoflurane–nitrous oxide, although this effect may have been underestimated as xenon was only administered at 0.9 MAC. Indeed, recent work in critical care, where a long duration of sedation is required, has suggested that xenon possesses very potent analgesic action, with only one of 21 patients requiring any more than minimal alfentanil during an 8 h period.[15] Many comparisons have been made between xenon and nitrous oxide; however, not only do they have different potencies, but they also exhibit different analgesic profiles. Nitrous oxide's mechanism of antinociception has been clarified recently,[73] showing a dependence on opiate and adrenergic signalling that xenon does not share.[74] In addition, xenon is active at the level of spinal cord, whereas nitrous oxide is not,[75] which may indicate differing potencies in the inhibition of the NMDA receptors in the dorsal horn of the spinal cord. Opposing effects have been further demonstrated, as nitrous oxide does not exert any antinociceptive effect in the formalin test in the neonatal rat[76] whereas xenon does.[77] Extrapolation of these results to humans suggests not only that xenon may provide analgesia in the paediatric population but also that the use of nitrous oxide for analgesia may be imprudent. We await clinical studies to address these issues. Xenon may be of particular utility in neonatal anaesthesia as the neonatal myocardium is very sensitive

to the depressant effects of volatile anaesthetics;[78] whether xenon exerts a salubrious cardiostable effect in the neonate is currently not known.

Organ effects

Xenon appears to exert no deleterious effects on other organ systems. Prolonged xenon exposure in the critical care setting was not associated with any further deterioration in haematological and biochemical variables.[15] These data are consistent with previous reports suggesting that xenon exerts no effects on coagulation[79] or platelet function *in vitro*[80] or on the immune system.[81] Xenon does not impair hepatic or renal function[15,82] and has been used safely in hepatic surgery.[83] Indeed, as xenon is excreted in the lungs with no modification by the renal or hepatic systems, it may prove to be the anaesthetic of choice in surgery or critical care when these systems are impaired.

Concerns over increased airway pressure during xenon ventilation led to hypotheses centred upon an increased airway resistance induced by this gas.[84,85] However, recent work has suggested that the increase is attributable to the physical properties of the gas and that bronchoconstriction is not a contributing factor.[86] Calzia *et al.*[87] have evaluated the effect of xenon on diffusion hypoxia and concluded that this phenomenon is unlikely to occur with the administration of xenon.

Xenon does not does not trigger malignant hyperthermia in susceptible swine.[88,89] Burov *et al.*[90] found no evidence of toxicity in several *in vitro* and *in vivo* paradigms involving two species given xenon either acutely (Balb/c mice and Wistar rats) or subchronically (Wistar rats and mongrel dogs).[90] Studies of microorganisms and mice showed that xenon has no mutagenic or carcinogenic properties.[91] No embryotoxic or teratogenic changes were found in pregnant Wistar rats, nor was xenon found to be allergenic.[90]

Delivery and recycling systems technology

A major limiting factor in the development of routine xenon anaesthesia is the expense of recovering the gas from the atmosphere; the current cost of 1 litre of xenon with a purity of 99.99% is approximately $10. Therefore closed-circuit delivery appears to be an economic necessity for the application of xenon anaesthesia.[91] The Xenon Study Group recently used a total of 24.6 ± 10.2 litres of xenon for 211 ± 102 min of closed-circuit anaesthesia;[14] we estimate the costs of this to be approximately $70 per hour. A cost analysis for a 40-year-old ASA I adult male weighing 70 kg undergoing simulated elective surgery found that 240 min of closed-circuit xenon anaesthesia would cost $356 (approximately $90 per hour).[92] Most of this cost can be attributed to priming and flushing the delivery circuit. The reduction in priming costs by denitrogenation of the delivery circuit could be achieved by breathing pure oxygen for 20 min pre-anaesthesia. However, this may not be acceptable for routine theatre activity, and so Rossaint *et al.*[15] periodically flushed the circuit with a fresh oxygen–xenon mixture. If xenon

anaesthesia is to be employed routinely, an economic necessity may be complete denitrogenation pre-anaesthesia.

Dingley and colleagues have been at the forefront of developing xenon closed-circuit anaesthesia, and their experience with a long duration of anaesthesia in critical care suggested that inhalational sedation with xenon was economically viable.[15] They have pointed out that xenon anaesthesia becomes more financially viable with longer duration of administration; after 4 h of administration xenon becomes comparable in cost to other anaesthetics.[92] Thus xenon may yet prove to be the anaesthetic of choice in settings such as critical care or cardiac surgery, where prolonged administration of anaesthesia is necessary and fast emergence is beneficial.

Measurement of xenon concentration is not accurate with traditional anaesthetic machines, and mass spectrometers and thermal conductivity sensors have been utilized to circumvent this problem. Mass spectrometers are the 'gold standard' but are costly, and thermal conductivity, as used by the Xenon Study Group,[14] appears to be a more clinically acceptable method. Thermal conductivity is effective because xenon conducts heat better than other gases found within the anaesthetic circuit. Comparison of the accuracies of mass spectrometry and thermal conductivity suggests that there is no clinically significant difference between the two technologies during xenon anaesthesia.[93]

Advances in recycling system technology will allow further improvement in the cost efficiency of xenon anaesthesia. Recycling systems which can reclaim xenon to a purity of >99% are available;[90] however, for the efficient use of the recycling system, anaesthesia would have to be maintained with another agent while xenon was recovered, negating xenon's beneficial emergence pharmacokinetics. Therefore development of recycling or refining technology may have to occur before the full clinical benefit of xenon anaesthesia can be discovered.

Environmental effects

The major volatile anaesthetics are based on chlorofluorocarbons (CFCs) and are known to deplete the ozone layer; in addition, nitrous oxide is 230 times more potent as a greenhouse gas than carbon dioxide, taking 120 years to break down. The amount of nitrous oxide released as an anaesthetic contributes 0.1% of the greenhouse effect.[94] In contrast, xenon is a naturally occurring constituent of the environment and has no detrimental ecological effect. However, xenon's ecological superiority must be balanced against the energy consumed in its recovery by the fractional distillation of liquid air.

Conclusions

The attention that the Xenon Study Group has recently given to

xenon anaesthesia is deserved; we have further highlighted its potential clinical applications and exemplary safety record. Xenon has notable pharmacokinetic, cardiostable, neuroprotective and analgesic advantages over other anaesthetics, and further clinical trials are warranted to evaluate its effectiveness in the operating theatre and critical care unit. As delivery technology develops, xenon will become a more viable option in the anaesthetic armamentarium.

- Abstract
- Introduction
- Anaesthetic mechanism of action
- Clinical features
- Delivery and recycling systems...
- Environmental effects
- Conclusions
- Declaration of interest
- References

Declaration of interest

Professor Maze is a board member of an Imperial College spin-out company (Protexeon Ltd) that is interested in developing clinical applications for medical gases, including xenon. Professor Maze is a paid consultant in this activity. In addition, Air Products has funded, and continues to fund, work in the author's laboratory that bears on the actions of xenon as an anaesthetic and neuroprotectant, and Air Products has a financial stake in Protexeon Ltd.

- Top
- Abstract
- Introduction
- Anaesthetic mechanism of action
- Clinical features
- Delivery and recycling systems...
- Environmental effects
- Conclusions
- Declaration of interest
- References

References

- Top
- Abstract
- Introduction
- Anaesthetic mechanism of action
- Clinical features
- Delivery and recycling systems...
- Environmental effects
- Conclusions
- Declaration of interest
- References

1. Ball WC Jr, Stewart PB, Newsham LG, Bates DV (1962) Regional pulmonary function studied with xenon 133. *J. Clin. Invest.*, **41**, 519–31.[ISI][Medline]
2. Cullen, SC, Gross EG (1951) The anaesthetic properties of xenon in animals and human beings, with additional observations on krypton. |t *Science*, **113**, 580–2. [Free Full Text]
3. Franks NP, Lieb WR (1994) Molecular and cellular mechanisms of general anaesthesia. *Nature*, **367**, 607–14.[CrossRef][Medline]
4. Franks NP, Dickinson R, de Sousa SL, Hall AC, Lieb WR (1998) How does xenon produce anaesthesia? *Nature*, **396**, 324.[CrossRef][Medline]
5. De Sousa SL, Dickinson R, Lieb WR, Franks NP (2000) Contrasting synaptic actions of the inhalational general anesthetics isoflurane and xenon. *Anesthesiology*, **92**, 1055–66.[CrossRef][ISI][Medline]
6. Plested AJ, Wildman SS, Lieb WR, Franks NP (2004) Determinants of the sensitivity of AMPA receptors to xenon. *Anesthesiology*, **100**, 347–58.[CrossRef][ISI][Medline]
7. Jevtovic-Todorovic V, Todorovic SM, Mennerick S *et al.* (1998) Nitrous oxide (laughing gas) is an NMDA antagonist, neuroprotectant and neurotoxin. *Nat Med.*, **4**, 460–3.[CrossRef][ISI][Medline]
8. Raines DE, Claycomb RJ, Scheller M, Forman SA (2001) Nonhalogenated alkane anesthetics fail to potentiate agonist actions on two ligand-gated ion channels. *Anesthesiology*, **95**, 470–7. [CrossRef][ISI][Medline]
9. Anis NA, Berry SC, Burton NR, Lodge D (1983) The dissociative anaesthetics, ketamine and phencyclidine, selectively reduce excitation of central mammalian neurones by *N*-methyl-

aspartate. *Br J. Pharmacol.*, **79**, 565–75.[ISI][Medline]

10. Patel AJ, Honore E, Lesage F, Fink M, Romey G, Lazdunski M (1999) Inhalational anesthetics activate two-pore-domain background K^+ channels. *Nat. Neurosci.*, **2**, 422–6.[CrossRef][ISI][Medline]
11. Patel AJ, Honore E (2001) Properties and modulation of mammalian 2P domain K+ channels. *Trends Neurosci.*, **24**, 339–46.[CrossRef][ISI][Medline]
12. Patel AJ, Honore E (2001) Anesthetic-sensitive 2P domain K^+ channels. *Anesthesiology*, **95**, 1013–21.[CrossRef][ISI][Medline]
13. Gruss M, Bushell TJ, Bright DP, Lieb WR, Mathie A, Franks NP (2004) Two-pore-domain K^+ channels are a novel target for the anesthetic gases xenon, nitrous oxide, and cyclopropane. *Mol. Pharmacol.*, **65**, 443–52.[Abstract/Free Full Text]
14. Rossaint R, Reyle-Hahn M, Schulte AM *et al.*: Xenon Study Group (2003) Multicenter randomized comparison of the efficacy and safety of xenon and isoflurane in patients undergoing elective surgery. *Anesthesiology*, **98**, 6–13.[CrossRef][ISI][Medline]
15. Bedi A, Murray JM, Dingley J, Stevenson MA, Fee JP (2003) Use of xenon as a sedative for patients receiving critical care. *Crit. Care Med.*, **31**, 2470–7.[CrossRef][ISI][Medline]
16. Cullen SC, Eger EI, Cullen BF, Gregory P (1969) Observations on the anesthetic effect of the combination of xenon and halothane. *Anesthesiology*, **31**, 305–9[ISI][Medline]
17. Nakata Y, Goto T, Ishiguro Y *et al.* (2001) Minimum alveolar concentration (MAC) of xenon with sevoflurane in humans. *Anesthesiology*, **94**, 611–14.[CrossRef][ISI][Medline]
18. Goto T, Nakata Y, Morita S (2002) The minimum alveolar concentration of xenon in the elderly is sex-dependent. *Anesthesiology*, **97**, 1129–32.[CrossRef][ISI][Medline]
19. Stanski DR (2000) Monitoring depth of anesthesia. In Miller RD (ed.) *Anesthesia*. Philadelphia, PA: Churchill Livingstone, 1087–116.
20. Goto T, Nakata Y, Ishiguro Y, Niimi Y, Suwa K, Morita S (2000) Minimum alveolar concentration-awake of xenon alone and in combination with isoflurane or sevoflurane. *Anesthesiology*, **93**, 1188–93.[CrossRef][ISI][Medline]
21. Thornton C, Barrowcliffe MP, Konieczko KM *et al.* (1989)The auditory evoked response as an indicator of awareness. *Br. J. Anaesth.*, **63**, 113–15.[Abstract/Free Full Text]
22. Newton DE, Thornton C, Konieczko KM *et al.* (1992) Auditory evoked response and awareness: a study in volunteers at sub-MAC concentrations of isoflurane. *Br. J. Anaesth.*, **69**, 122–9. [Abstract/Free Full Text]
23. Rampil IJ (1998) A primer for EEG signal processing in anesthesia. *Anesthesiology*, **89**, 980–1002.[CrossRef][ISI][Medline]
24. Goto T, Nakata Y, Saito H *et al.* (2000) Bispectral analysis of the electroencephalogram does not predict responsiveness to verbal command in patients emerging from xenon anaesthesia. *Br. J. Anaesth.*, **85**, 359–63.[Abstract/Free Full Text]
25. Goto T, Nakata Y, Saito H, Ishiguro Y, Niimi Y, Morita S (2001) The midlatency auditory evoked potentials predict responsiveness to verbal commands in patients emerging from anesthesia with xenon, isoflurane, and sevoflurane but not with nitrous oxide. *Anesthesiology*, **94**, 782–9. [CrossRef][ISI][Medline]
26. Sal'nikov PS, Burov NE. (2003) Electrophysiological features of xenon anesthesia. *Anesteziol. Reanimatol.*, **1**, 12–17 (in Russian).[Medline]
27. Nakata Y, Goto T, Morita S (1997) Comparison of inhalation inductions with xenon and sevoflurane. *Acta Anaesthesiol. Scand.*, **41**, 1157–61.[ISI][Medline]
28. Goto T, Saito H, Shinkai M, Nakata Y, Ichinose F, Morita S (1997) Xenon provides faster emergence from anesthesia than does nitrous oxide-sevoflurane or nitrous oxide-isoflurane. *Anesthesiology*, **86**, 1273–8.[CrossRef][ISI][Medline]
29. Dingley J, King R, Hughes L *et al.* (2001) Exploration of xenon as a potential cardiostable sedative: a comparison with propofol after cardiac surgery. *Anaesthesia*, **56**, 829–35.[CrossRef]

[ISI][Medline]
30. Goto T, Suwa K, Uezono S, Ichinose F, Uchiyama M, Morita S. (1998) The blood-gas partition coefficient of xenon may be lower than generally accepted. *Br. J. Anaesth.*, **80**, 255–6. [Abstract/Free Full Text]
31. Cheng DC, Karski J, Peniston C *et al.* (1996) Early tracheal extubation after coronary artery bypass graft surgery reduces costs and improves resource use. A prospective, randomized, controlled trial. *Anesthesiology*, **85**, 1300–10.[CrossRef][ISI][Medline]
32. Lachmann B, Armbruster S, Schairer W *et al.* (1990) Safety and efficacy of xenon in routine use as an inhalational anaesthetic. *Lancet*, **335**, 1413–15.[CrossRef][ISI][Medline]
33. Boomsma F, Rupreht J, Man in 't Veld AJ, de Jong FH, Dzoljic M, Lachmann B (1990) Haemodynamic and neurohumoral effects of xenon anaesthesia. A comparison with nitrous oxide. *Anaesthesia*, **45**, 273–8.[ISI][Medline]
34. Luttropp HH, Romner B, Perhag L, Eskilsson J, Fredriksen S, Werner O (1993) Left ventricular performance and cerebral haemodynamics during xenon anaesthesia. A transoesophageal echocardiography and transcranial Doppler sonography study. *Anaesthesia*, **48**, 1045–9.[ISI][Medline]
35. Ishiguro Y, Goto T, Nakata Y, Terui K, Niimi Y, Morita S (2000) Effect of xenon on autonomic cardiovascular control—comparison with isoflurane and nitrous oxide. *J. Clin. Anesth.*, **12**, 196–201.[CrossRef][ISI][Medline]
36. Ishiguro, Y (2001) Cardiovascular effects of xenon. *Int. Anesthesiol. Clin.*, **39**, 77–84.[CrossRef][Medline]
37. Preckel B, Schlack W, Heibel T, Rutten H (2002) Xenon produces minimal haemodynamic effects in rabbits with chronically compromised left ventricular function. *Br. J. Anaesth.*, **88**, 264–9. [Abstract/Free Full Text]
38. Hettrick DA, Pagel PS, Kersten JR *et al.* (1998) Cardiovascular effects of xenon in isoflurane-anesthetized dogs with dilated cardiomyopathy. *Anesthesiology*, **89**, 1166–73.[CrossRef][ISI][Medline]
39. Preckel B, Mullenheim J, Moloschavij A, Thamer V, Schlack W (2000) Xenon administration during early reperfusion reduces infarct size after regional ischemia in the rabbit heart *in vivo*. *Anesth. Analg.*, **91**, 1327–32.[Abstract/Free Full Text]
40. Stowe DF, Rehmert GC, Kwok WM, Weigt HU, Georgieff M, Bosnjak ZJ (2000) Xenon does not alter cardiac function or major cation currents in isolated guinea pig hearts or myocytes. *Anesthesiology*, **92**, 516–22.[CrossRef][ISI][Medline]
41. Fassl J, Halaszovich CR, Huneke R, Jungling E, Rossaint R, Luckhoff A (2003) Effects of inhalational anesthetics on L-type Ca2+ currents in human atrial cardiomyocytes during beta-adrenergic stimulation. *Anesthesiology*, **99**, 90–6.[CrossRef][ISI][Medline]
42. Stowe DF, Monroe SM, Marijic J, Bosnjak ZJ, Kampine JP (1991) Comparison of halothane, enflurane, and isoflurane with nitrous oxide on contractility and oxygen supply and demand in isolated hearts. *Anesthesiology*, **75**, 1062–7.[ISI][Medline]
43. Lipton SA, Rosenberg PA (1994) Excitatory amino acids as a final common pathway for neurologic disorders. *N. Engl. J. Med.*, **330**, 613–22.[Free Full Text]
44. Sattler R, Tymianski M (2000) Molecular mechanisms of calcium-dependent excitotoxicity. *J. Mol. Med.*, **78**, 3–13.[CrossRef][ISI][Medline]
45. Hardingham GE, Bading H (2003) The yin and yang of NMDA receptor signalling. *Trends Neurosci.*, **26**, 81–9.[CrossRef][ISI][Medline]
46. Wilhelm S, Ma D, Maze M, Franks NP (2002) Effects of xenon on *in vitro* and i*n vivo* models of neuronal injury. *Anesthesiology*, **96**, 1485–91.[CrossRef][ISI][Medline]
47. Petzelt C, Blom P, Schmehl W, Muller J, Kox WJ (2003) Prevention of neurotoxicity in hypoxic cortical neurons by the noble gas xenon. *Life Sci.*, **72**, 1909–18.[CrossRef][ISI][Medline]
48. Hardingham GE, Fukunaga Y, Bading H (2002) Extrasynaptic NMDARs oppose synaptic NMDARs by triggering CREB shut-off and cell death pathways. *Nat. Neurosci.*, **5**, 405–14.[ISI]

[Medline]
49. Miura Y, Grocott HP, Bart RD, Pearlstein RD, Dexter F, Warner DS (1998) Differential effects of anesthetic agents on outcome from near-complete but not incomplete global ischemia in the rat. *Anesthesiology*, **89**, 391–400.[CrossRef][ISI][Medline]
50. Ma D, Hossain M, Rajakumaraswamy N, Franks NP, Maze M (2003) Combination of xenon and isoflurane produces a synergistic protective effect against oxygen–glucose deprivation injury in a neuronal–glial co-culture model. *Anesthesiology*, **99**, 748–51.[CrossRef][ISI][Medline]
51. Homi HM, Yokoo N, Ma D *et al*. (2003) The neuroprotective effect of xenon administration during transient middle cerebral artery occlusion in mice. *Anesthesiology*, **99**, 876–81.[CrossRef][ISI][Medline]
52. Ma D, Yang H, Lynch J, Franks NP, Maze M, Grocott HP (2003) Xenon attenuates cardiopulmonary bypass-induced neurologic and neurocognitive dysfunction in the rat. *Anesthesiology* **98**, 690–8.[CrossRef][ISI][Medline]
53. David HN, Leveille F, Chazalviel L *et al*. (2003) Reduction of ischemic brain damage by nitrous oxide and xenon. *J. Cereb. Blood Flow Metab.*, **23**, 1168–73.[CrossRef][ISI][Medline]
54. Yamaguchi S, Midorikawa Y, Okuda Y, Kitajima T. (1999) Propofol prevents delayed neuronal death following transient forebrain ischemia in gerbils. *Can. J. Anaesth.*, **46**, 593–8.[Abstract/Free Full Text]
55. Pittman JE, Sheng H, Pearlstein R, Brinkhous A, Dexter F, Warner DS (1997) Comparison of the effects of propofol and pentobarbital on neurologic outcome and cerebral infarct size after temporary focal ischemia in the rat. *Anesthesiology*, **87**, 1139–44.[CrossRef][ISI][Medline]
56. Malhotra AK, Pinals DA, Weingartner H *et al.* (1996) NMDA receptor function and human cognition: the effects of ketamine in healthy volunteers. *Neuropsychopharmacology*, **14**, 301–7.[CrossRef][ISI][Medline]
57. Lees KR (1997) Cerestat and other NMDA antagonists in ischemic stroke. *Neurology*, **49**, S66–9.
58. Olney JW, Labruyere J, Price MT (1989) Pathological changes induced in cerebrocortical neurons by phencyclidine and related drugs. *Science*, **244**, 1360–2.[Abstract/Free Full Text]
59. Allen HL, Iversen LL (1990) Phencyclidine, dizocilpine, and cerebrocortical neurons. *Science*, **247**, 221.
60. Ma D, Wilhelm S, Maze M, Franks NP (2002) Neuroprotective and neurotoxic properties of the 'inert' gas, xenon. *Br. J. Anaesth.*, **89**, 739–46.[Abstract/Free Full Text]
61. Nagata A, Nakao Si S, Nishizawa N *et al.* (2001) Xenon inhibits but N_2O enhances ketamine-induced c-Fos expression in the rat posterior cingulate and retrosplenial cortices. *Anesth. Analg.*, **92**, 362–8.[Abstract/Free Full Text]
62. Wang S, Yang Q, Moller CJ, Sharp FR, Haglid KG (1996) Eliprodil prevents expression of the 70 kDa heat shock protein in MK801-injured neurones. *Pharmacol. Toxicol.*, **79**, 166–8.[ISI][Medline]
63. Duprat F, Lesage F, Patel AJ, Fink M, Romey G, Lazdunski M (2000) The neuroprotective agent riluzole activates the two P domain K(+) channels TREK-1 and TRAAK. *Mol. Pharmacol.*, **57**, 906–12.[Abstract/Free Full Text]
64. Lauritzen I, Blondeau N, Heurteaux C, Widmann C, Romey G, Lazdunski M (2000) Polyunsaturated fatty acids are potent neuroprotectors. *EMBO J.*, **19**, 1784–93.[CrossRef][ISI][Medline]
65. Frietsch T, Bogdanski R, Blobner M, Werner C, Kuschinsky W, Waschke KF (2001) Effects of xenon on cerebral blood flow and cerebral glucose utilization in rats. *Anesthesiology*, **94**, 290–7.[CrossRef][ISI][Medline]
66. Hartmann A, Wassman H, Czernicki Z, Dettmers C, Schumacher HW, Tsuda Y (1987) Effect of stable xenon in room air on regional cerebral blood flow and electroencephalogram in normal baboons. *Stroke*, **18**, 643–8.[Abstract]
67. Schmidt M, Marx T, Kotzerke J *et al.* (2001) Cerebral and regional organ perfusion in pigs during xenon anaesthesia. *Anaesthesia*, **56**, 1154–9.[CrossRef][ISI][Medline]

68. Lewett W, Williams C, Gupta A, Hummel R, Keenan R (1996) Effect of 70% xenon on cerebral blood flow velocity in anaesthetized patients. *Acta Neurol. Scand.*, **166**, 42–3.
69. Fukuda T, Nakayama H, Yanagi K *et al.* (2001) The effects of 30% and 60% xenon inhalation on pial vessel diameter and intracranial pressure in rabbits. *Anesth. Analg.*, **92**, 1245–50. [Abstract/Free Full Text]
70. Plougmann J, Astrup J, Pedersen J, Gyldensted C (1994) Effect of stable xenon inhalation on intracranial pressure during measurement of cerebral blood flow in head injury. *J. Neurosurg.*, **81**, 822–8[ISI][Medline]
71. Nakata Y, Goto T, Saito H *et al.* (2000) Plasma concentration of fentanyl with xenon to block somatic and hemodynamic responses to surgical incision. *Anesthesiology*, **92**, 1043–8.[CrossRef][ISI][Medline]
72. Yagi M, Mashimo T, Kawaguchi T, Yoshiya I (1995) Analgesic and hypnotic effects of subanaesthetic concentrations of xenon in human volunteers: comparison with nitrous oxide. *Br. J. Anaesth.*, **74**, 670–3.[Abstract/Free Full Text]
73. Fujinaga M, Maze M (2002) Neurobiology of nitrous oxide-induced antinociceptive effects. *Mol. Neurobiol.*, **25**, 167–89.[CrossRef][ISI][Medline]
74. Ohara A, Mashimo T, Zhang P, Inagaki Y, Shibuta S, Yoshiya I (1997) A comparative study of the antinociceptive action of xenon and nitrous oxide in rats. *Anesth. Analg.*, **85**, 931–6.[Abstract]
75. Miyazaki, Y, Adachi T, Utsumi J, Shichino T, Segawa H (1999) Xenon has greater inhibitory effects on spinal dorsal horn neurons than nitrous oxide in spinal cord transected cats. *Anesth. Analg.*, **88**, 893–7.[Abstract/Free Full Text]
76. Ohashi Y, Stowell JM, Nelson LE, Hashimoto T, Maze M, Fujinaga M (2002) Nitrous oxide exerts age-dependent antinociceptive effects in Fischer rats. *Pain*, **100**, 7–18.[CrossRef][ISI][Medline]
77. Ma D, Sanders RD, Halder S, Rajakumaraswamy N, Franks NP, Maze M (2004) Xenon exhibits antinociceptive effect on the formalin test in newborn Fischer rats. *Anesthesiology*, **100**, 1313–18. [CrossRef][ISI][Medline]
78. Baum VC, Palmisano BW (1997) The immature heart and anesthesia. *Anesthesiology*, **87**, 1529–48.[CrossRef][ISI][Medline]
79. Horn NA, Hecker KE, Bongers B, Baumert HJ, Reyle-Hahn SM, Rossaint R (2001) Coagulation assessment in healthy pigs undergoing single xenon anaesthesia and combinations with isoflurane and sevoflurane. *Acta Anaesthesiol. Scand.*, **45**, 634–8.[CrossRef][ISI][Medline]
80. de Rossi LW, Horn NA, Baumert JH, Gutensohn K, Hutschenreuter G, Rossaint R (2001) Xenon does not affect human platelet function *in vitro*. *Anesth. Analg.*, **93**, 635–40. [Abstract/Free Full Text]
81. Bedi A, McBride WT, Armstrong MA, Murray JM, Fee JP (2002) Xenon has no effect on cytokine balance and adhesion molecule expression within an isolated cardiopulmonary bypass system. *Br. J. Anaesth.*, **89**, 546–50.[Abstract/Free Full Text]
82. Reinelt H, Marx T, Kotzerke J *et al.* (2002) Hepatic function during xenon anesthesia in pigs. *Acta Anaesthesiol. Scand.*, **46**, 713–16.[CrossRef][ISI][Medline]
83. Avdeev SV, Pak AV, Strezh VA (2002) Liver blood flow during xenon anesthesia in surgical hepatology. *Anesteziol. Reanimatol.*, **3**, 27–31 (in Russian).[Medline]
84. Calzia E, Stahl W, Handschuh T, Marx T *et al.* (1999) Respiratory mechanics during xenon anesthesia in pigs: comparison with nitrous oxide. *Anesthesiology*, **91**, 1378–86.[CrossRef][ISI][Medline]
85. Zhang P, Ohara A, Mashimo T, Imanaka H, Uchiyama A, Yoshiya I (1995) Pulmonary resistance in dogs: a comparison of xenon with nitrous oxide. *Can. J. Anaesth.*, **42**, 547–53. [Abstract/Free Full Text]
86. Baumert JH, Reyle-Hahn M, Hecker K, Tenbrinck R, Kuhlen R, Rossaint R (2002) Increased airway resistance during xenon anaesthesia in pigs is attributed to physical properties of the gas. *Br. J. Anaesth.*, **88**, 540–5.[Abstract/Free Full Text]

87. Calzia E, Stahl W, Handschuh T *et al.* (1999) Continuous arterial $P(O_2)$ and $P(CO_2)$ measurements in swine during nitrous oxide and xenon elimination: prevention of diffusion hypoxia. *Anesthesiology*, **90**, 829–34.[CrossRef][ISI][Medline]
88. Baur CP, Klingler W, Jurkat-Rott K *et al.* (2000) Xenon does not induce contracture in human malignant hyperthermia muscle. *Br. J. Anaesth.*, **85**, 712–16.[Abstract/Free Full Text]
89. Froeba G, Marx T, Pazhur J *et al.* (1999) Xenon does not trigger malignant hyperthermia in susceptible swine. *Anesthesiology*, **91**, 1047–52.[CrossRef][ISI][Medline]
90. Burov NE, Kornienko LI, Makeev GN, Potapov VN (1999) Clinical and experimental study of xenon anesthesia]. *Anesteziol. Reanimatol.*, 56–60 (in Russian).
91. Lynch C, III, Baum J, Tenbrinck R (2000) Xenon anesthesia. *Anesthesiology*, **92**, 865–8. [CrossRef][ISI][Medline]
92. Nakata Y, Goto T, Niimi Y, Morita S (1999) Cost analysis of xenon anesthesia: a comparison with nitrous oxide-isoflurane and nitrous oxide-sevoflurane anesthesia. *J. Clin. Anesth.*, **11**, 477–81.[CrossRef][ISI][Medline]
93. Luginbuhl M, Lauber R, Feigenwinter P, Zbinden AM (2002) Monitoring xenon in the breathing circuit with a thermal conductivity sensor. Comparison with a mass spectrometer and implications on monitoring other gases. *J. Clin. Monit. Comput.*, **17**, 23–30.[CrossRef][Medline]
94. Goto T. Is there a future for xenon anesthesia?/Le xenon a-t-il un avenir en anesthesie? *Can. J. Anaesth.*, **49**, 335–8.

This article has been cited by other articles:

Online ISSN 1471-8391 - Print ISSN 0007-1420

Oxford Journals *Oxford University Press*

- Site Map
- Privacy Policy
- Frequently Asked Questions

Other Oxford University Press sites:

Oxford University Press GO

- **Similar articles in this journal**
- **Similar articles in PubMed**
- **Alert me to new issues of the journal**
- **Add to My Personal Archive**
- **Download to citation manager**
- **Request Permissions**
- **Disclaimer**

Google Scholar

- **Articles by Sanders, R. D.**
- **Articles by Maze, M.**
- **Search for Related Content**

PubMed

- **PubMed Citation**
- **Articles by Sanders, R. D.**
- **Articles by Maze, M.**

Related Collections

- **Anaesthesia**