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REVIEW ARTICLES

Xenon: no stranger to anaesthesia

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Xenon derives its name from the Greek for 'stranger' because of its rarity, representing no more than $8.75 \times 10^{-6}\%$ of the atmosphere or 0.0875 ppm. Discovered in 1898, it is manufactured by fractional distillation of air and is used commercially for lasers, high intensity lamps, flash bulbs, jet propellant in the aerospace industry, X-ray tubes, and in medicine. The total amount of xenon in the atmosphere would occupy around 10^{14} litres at atmospheric pressure, which is more than 10 million times the amount currently produced each year. Xenon has been used experimentally in clinical anaesthetic practice for more than 50 yrs.[8] Over this period of time, reports of clinical studies reveal that several hundred surgical patients have successfully received this noble gas as part of their anaesthetic regimen. Xenon's safety and efficacy profile in this setting appears to be unequalled and only its relatively high cost has precluded its more widespread clinical use. Concerns over cost are now being mitigated by technological developments in the delivery and recycling of xenon that will permit much less total gas to be expended for each anaesthetic administration.

Over the last decade there has been renewed interest in the use of xenon as an anaesthetic, as investigators have sought to find a safe and effective substitute for nitrous oxide, which has caused environmental concerns because of its ozone-depleting properties.[33] Since then, studies have demonstrated several advantages of using xenon when compared with not only nitrous oxide, but most other potent inhalation agents. These include:

1. A pharmacokinetic benefit as a result of its extremely low blood/gas partition coefficient,[24] which results in a rapid onset and offset of its action.[23 46]

2. Less cardiovascular depression.[4 10 33 35]
3. Neuroprotection.[37 64]
4. Profound analgesia.[33 48]

This review will deal with some of the benefits of xenon anaesthesia, with a view to identifying those areas where it may be used to clinical advantage.

Mechanisms of action

Xenon potently inhibits *N*-methyl-D-aspartate (NMDA) receptors non-competitively, with little effect on $GABA_A$ receptors or non-NMDA glutamatergic receptors.[9 12] Franks and colleagues[9 12] (Fig. 1), demonstrated that 80% xenon reduced NMDA-activated currents by approximately 60%. These results further showed that the pre-synaptic effects of xenon must be minimal, consistent with the observation that several voltage-gated ion channels in cardiac tissue are unaffected by clinically relevant concentrations of xenon.[58] Nitrous oxide has also been shown to be effective at inhibiting the NMDA receptor.[30]

Yamakura and Harris,[67] subsequently found that both xenon and nitrous oxide can also inhibit nicotinic acetylcholine receptors (nAChR) comprising the $\alpha_4\beta_2$ subunits. It is unlikely that the analgesic action of these gases is a result
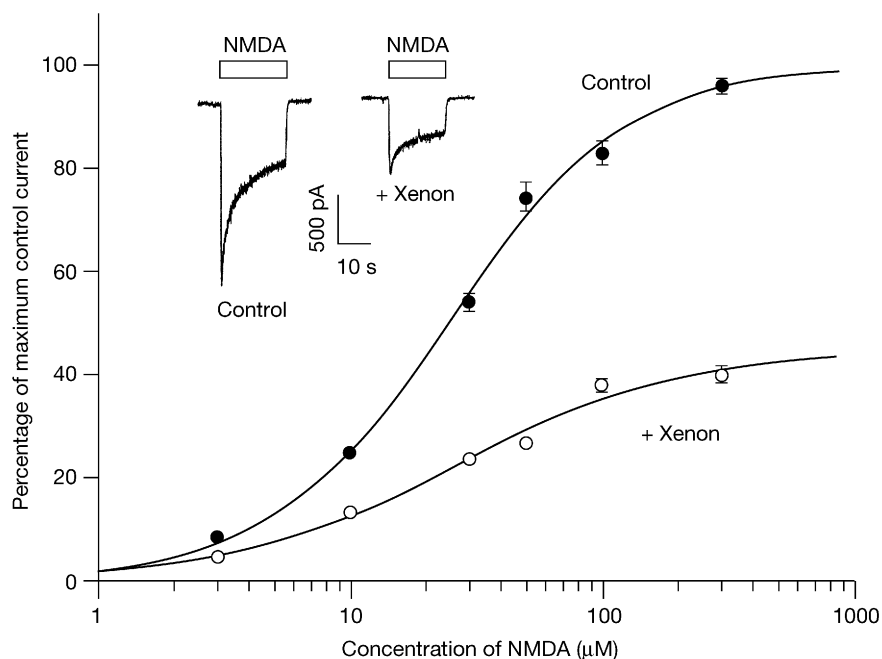
Fig 1 Xenon inhibits NMDA receptors in cultured rat hippocampal neurones. NMDA activates an inward current (in neurones clamped at −60 mV) with an EC_{50} concentration of 24 ($\pm$2) μM NMDA and a Hill coefficient of 1.2 ($\pm$0.1). Xenon inhibited the current by approximately 60%, but did not significantly change either the EC_{50} or 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. Reproduced with permission from *Nature* 396: 324 copyright 1998, Macmillan Publishers Ltd.[12]

of inhibition of nAChR because activation of these receptors elicits antinociception.[40] Xenon (and nitrous oxide) has been reported to competitively inhibit $5HT_{3A}$ receptors expressed in *Xenopus* oocytes,[60] but this has yet to be confirmed in mammalian cells. It is notable that these receptors have been implicated in postoperative nausea and vomiting, and in peripheral and central nociception.

It is not possible to state categorically which of these effects on ligand-gated and receptor-gated ion channels are causally linked to the anaesthetic action of xenon. As with nitrous oxide and cyclopropane, xenon distinguishes itself from all other volatile and gaseous anaesthetic agents by exerting no action at the $GABA_A$ receptor. On balance, it is likely that antagonism of the NMDA receptor is responsible, at least in part, for its anaesthetic action.

Measuring the xenon anaesthetic state

Several surrogate measures have been advocated as indicating the depth of the anaesthetic state and the effect of xenon on these is now considered. EEG changes are similar during anaesthesia with either xenon or nitrous oxide, exhibiting attenuation of α waves at lower concentrations, with the appearance of θ and δ wave activity at higher concentrations.[31] The bispectral index (BIS), an electro-encephalographic-derived univariate scale, is thought to reflect the level of hypnosis in anaesthetized patients.[56] As the BIS algorithm was empirically developed from EEG recordings from 'GABAergic anaesthetics' (e.g. propofol),

it has not fared as well in relation to general anaesthetics with NMDA antagonistic properties such as ketamine.[43 59] Goto and colleagues[22] investigated the suitability of BIS to monitor the emergence from xenon anaesthesia compared with isoflurane anaesthesia. A BIS value lower than 50 (a value normally associated with deep hypnosis[57]) did not guarantee adequate hypnosis during xenon anaesthesia, a property shared by other 'non-GABAergic' anaesthetics (e.g. ketamine, nitrous oxide,[2] and α_2 adrenergic agonists[68]). Mid-latency auditory evoked potentials (MLAEPs) may predict wakefulness during anaesthesia, defined as the presence of a response to verbal command.[17 49 61] Goto and colleagues,[21] randomly assigned 60 patients to receive xenon, isoflurane, sevoflurane, or nitrous oxide supplemented with epidural anaesthesia. They found that the MLAEP is closely associated with responsiveness to verbal command during emergence from anaesthesia with xenon, isoflurane, and sevoflurane but not with nitrous oxide. The close correlation of MLAEPs to the hypnotic state during xenon anaesthesia, suggests that this may be a more appropriate form of monitoring than BIS monitoring and highlights a further difference between xenon and nitrous oxide (for which neither system appears effective).

Minimum alveolar concentration

In the first assessment of the MAC for xenon, Cullen and colleagues estimated a value of 71% of an atmosphere;[7] subsequently it has been estimated to be somewhat lower at

63%.[45] It is important to note that both these MAC values were determined in studies in which another inhalation anaesthetic (halothane or sevoflurane) was co-administered and thus the MAC value for xenon was extrapolated by the lowering of the MAC of the inhalation agent in the presence of xenon.[45] While it is preferable that MAC studies be done in the absence of other anaesthetic compounds, the risk of hypoxia in a closed-circuit system with xenon at concentrations greater than 70% makes such a study unfeasible.

The MAC-awake value for xenon was determined in 90 female patients to be 33% or 0.46 times its MAC.[20] In terms of the MAC-fraction, this is smaller than that for nitrous oxide (0.61 MAC), but greater than those for isoflurane and sevoflurane (both 0.35 MAC). The same study found that unlike nitrous oxide, xenon interacts additively with isoflurane and sevoflurane on MAC-awake.

Animal studies have established MAC values for dogs (1.19 atm[11]), rats (1.61 atm[32]), rabbits (0.85 atm[16]), and rhesus monkeys (0.98 atm[63]).

Clinical features

Induction and emergence

Xenon has a blood:gas partition coefficient of only 0.115,[24] which is significantly lower than those for other inhalation anaesthetics (nitrous oxide 0.47, sevoflurane 0.65, and desflurane 0.42). Consequently, several studies have revealed extremely short induction and emergence times for xenon anaesthesia. Induction of anaesthesia with xenon is faster than with sevoflurane (71 (21) *vs* 147 (59) s).[46] Emergence from xenon anaesthesia is two or three times faster than that from equi-MAC concentrations of nitrous oxide/isoflurane or nitrous oxide/sevoflurane anaesthesia.[23] Furthermore, prolonged xenon anaesthesia does not lengthen the emergence time. Dingley and colleagues,[10] reported a significantly quicker recovery time when compared with an equivalent depth of propofol anaesthesia (3 min 11 s compared with 25 min 23 s). The extremely rapid emergence times after xenon anaesthesia may be used to advantage not only in outpatient settings but also in cardiac surgery, where both 'fast tracking' and cardiovascular stability are desirable features (see below).[6]

Cardiovascular system

Xenon anaesthesia is associated with remarkable cardiovascular stability, with only a clinically insignificant decrease in heart rate being reported.[4 10 33 35] Lachmann[33] suggested that the haemodynamic stability was a result of less stress-induced sympathetic stimulation, a theory supported by the observation of stable epinephrine levels during xenon anaesthesia.[4] Compared with nitrous oxide anaesthesia, much less fentanyl was required to maintain cardiovascular stability during xenon anaesthesia.[4 33] Perioperatively, plasma cortisol and epinephrine increased

in the nitrous oxide group but did not change in the xenon group, despite the fact that more fentanyl was used during nitrous oxide anaesthesia.[4] When Dingley and colleagues directly compared the cardiovascular effects of post-cardiac surgical patients sedated with either propofol or xenon,[10] they noted that xenon caused no change in heart rate or MAP, and higher filling pressures and systemic vascular resistance were seen than were evident in propofol-sedated patients. Xenon anaesthesia compared favourably with total i.v. anaesthesia (pentobarbital and buprenorphine), with respect to haemodynamic variables in the pig.[41]

The autonomic nervous system effects of xenon anaesthesia were compared with those caused by either isoflurane or nitrous oxide/isoflurane in 39 patients (ASA I–II); xenon was found to depress both sympathetic and parasympathetic transmission more than isoflurane at 0.8 MAC.[29] The mechanism behind the autonomic actions of xenon has yet to be elaborated.
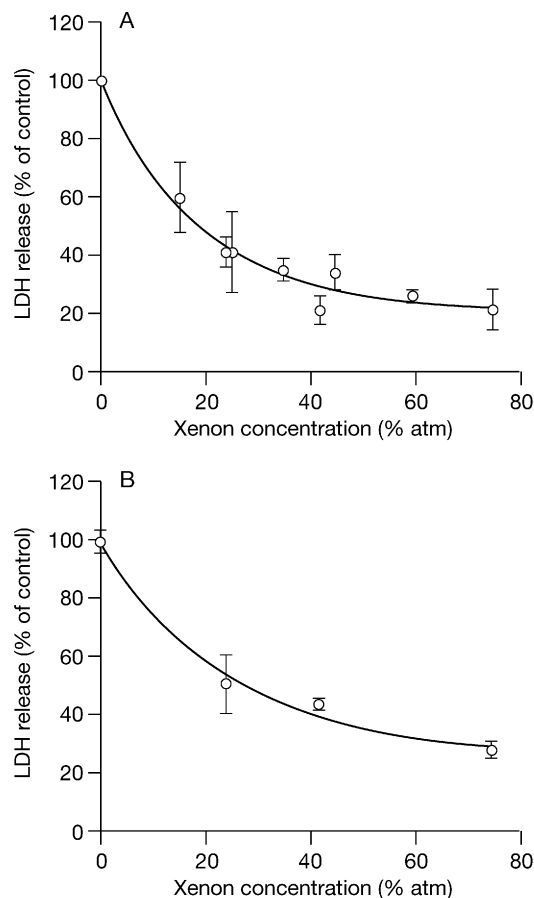
Ventricular function, as assessed by transoesophageal echocardiography, is unchanged during xenon anaesthesia.[35 44] The lack of effect of xenon on cardiac contractility was confirmed in preparations of isolated guinea pig ventricular muscle bundles; in comparison, in the same study, isoflurane was found to decrease myocardial force development by 30%.[58] Xenon induced no obvious electrical, mechanical, or metabolic cardiac effects, or nitric oxide-dependent flow response in isolated guinea pig hearts. These 'inert' cardiac properties of this noble gas probably have their basis in the fact that xenon has little effect on major cation currents including those for sodium [I_{Na}], calcium [$I_{Ca, L}$], or potassium [I_{Kir}]) in guinea pig myocytes.[58]

Even in the presence of compromised myocardium, xenon anaesthesia is remarkably stable. In a study of 20 patients undergoing elective coronary artery bypass grafting, xenon decreased indices of cardiac function significantly less than nitrous oxide. Heart rate did not change significantly although it tended to decrease, and the cardiac output and sympathetic tone were maintained in these patients with limited cardiovascular reserve.[28]

In animal models of cardiac disease, the beneficial properties of xenon are further revealed. Rabbits with chronically compromised left ventricular function (through coronary artery ligation), exhibit no cardiac deterioration,[55] and the echocardiographic changes were insignificant with 70% xenon. Furthermore, inhaled xenon (70%) during early reperfusion after coronary artery occlusion reduced infarct size after regional ischaemia in the rabbit heart *in vivo*.[54] In dogs with pacing-induced cardiomyopathy, the addition of xenon produced minimal cardiovascular effects.[27]
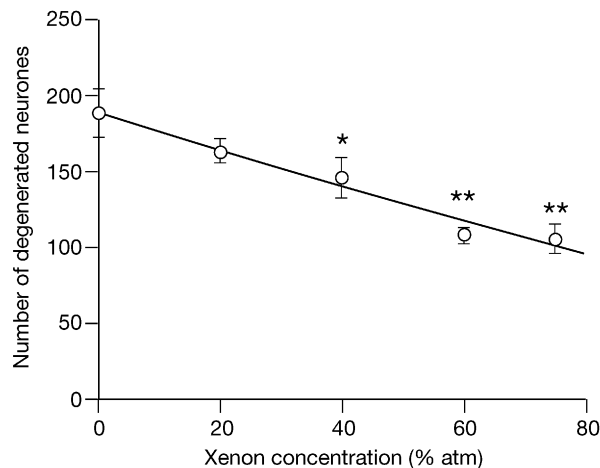
Neuroprotection

As stated above, xenon is an inhibitor of glutamatergic NMDA receptors. As activation of the NMDA receptor appears to be crucial to the initiation of neuronal injury

Fig 3 Dose-dependent neuroprotective effect of xenon *in vivo* on NMA-induced neuronal injury. Rats were injected with NMA 100 mg kg^{-1} s and destroyed 4 h later after exposure to air (NMA; *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 *Anesthesiology*.[64]

Fig 2 Dose-dependent effect of xenon *vs* injury produced by either NMDA (A), or glutamate (B), *in vitro*. Co-cultures of mouse neuronal-glial cells were treated with either NMDA, 250 mM (A) or glutamate, 100 mM (B) for 10 min during exposure to $O_2/CO_2/Xenon/N_2$. The xenon and N_2 concentrations were changed reciprocally such that their aggregate was 75% of 1 atm. After 6 h, the culture medium was harvested and assayed for LDH. Data are expressed as % 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 *Anesthesiology*.[64]

depriving the cell cultures of oxygen for 90 mins with an IC_{50} concentration of 10 (4)% atm.[64] As the MAC of xenon has most recently been estimated as 63%, the concentrations required for neuroprotection are significantly sub-anaesthetic. Thus, in contrast to other anaesthetics that require anaesthetic or supra-anaesthetic doses to act as a neuroprotectant,[64 66] xenon may be effective at more clinically acceptable concentrations.

In an *in vivo* model of brain injury in rats, xenon, in a concentration-dependent manner, reduced neuronal degeneration provoked by *N*-methyl DL-aspartate (NMA) administration in the arcuate nucleus of the hypothalamus (Fig. 3).[64]

Functional outcome studies using a rat cardiopulmonary bypass (CPB) model of neurological injury, confirmed the neuroprotective effect of xenon first established biochemically and morphologically.[64] 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. Neurocognitive dysfunction after CPB was attenuated by xenon, which proved to be superior to that seen with another NMDA antagonist, MK801 (dizolcipine) (Figs 4–6).[38]

Previously, several NMDA receptor antagonists have shown remarkable efficacy against neurological injury in pre-clinical models of cerebral injury, but have failed to live up to their promise when subsequently investigated in clinical settings. In some instances, this is because of unfavourable pharmacological properties preventing rapid transfer of the NMDA antagonist across the blood–brain barrier. Almost all NMDA antagonists tested thus far exhibit psychomimetic behavioural changes;[39] pyramidal neuronal

and death from a variety of insults,[34] xenon's putative neuroprotective effects have been examined in a series of *in vitro* and *in vivo* studies.

In a primary culture of neuronal and glial cells from the cerebral cortex of neonatal mice, predictable injury (reflected by the amount of LDH released into the culture medium) can be produced with either NMDA, glutamate, or oxygen deprivation. In order to assess the possible neuroprotective effects of xenon, LDH assays were performed 6 h after brief exposures to either NMDA or glutamate, in the presence of increasing concentrations of xenon. LDH release was significantly reduced at all concentrations tested (Fig. 2) with xenon IC_{50} concentrations for neuroprotection being 19 (6) and 28 (8)% atm for NMDA and glutamate-induced injury, respectively. Xenon was also effective in protecting against the injury caused by
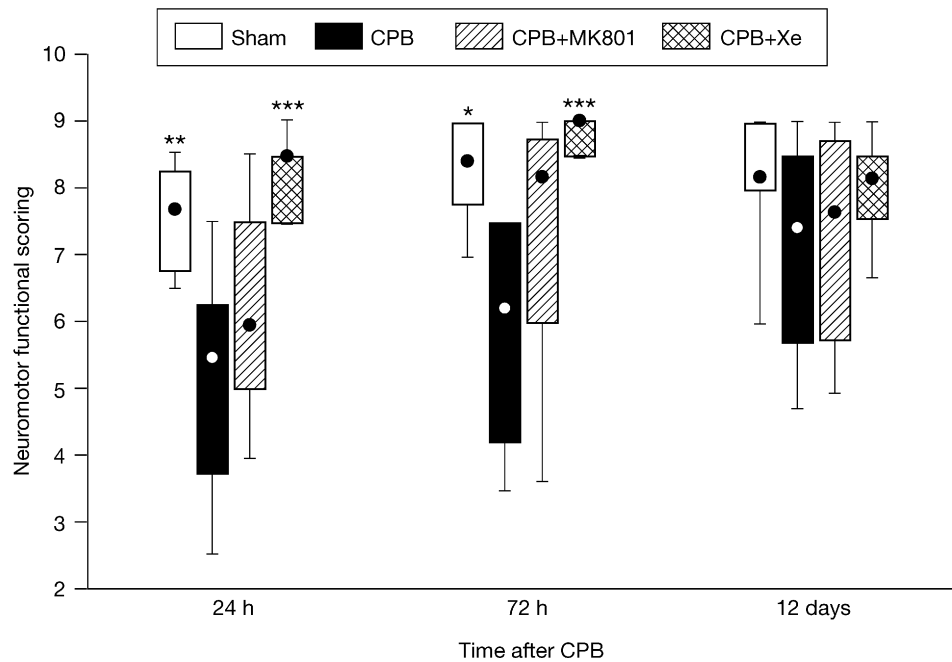
Fig 4 Neuromotor function after CPB. One, three, and twelve days after CPB, neuromotor function was assessed in rats using (i) rotating screen, (ii) a balance beam, and (iii) prehensile traction. A maximum score of 3 in each testing paradigm indicates normal performance so that aggregate normal performance will score '9'. Values are mean (SD), n=10. *P<0.05, **P<0.01, ***P<0.001 compared with CPB group at the same time point. Reproduced with permission from *Anesthesiology*.[38]
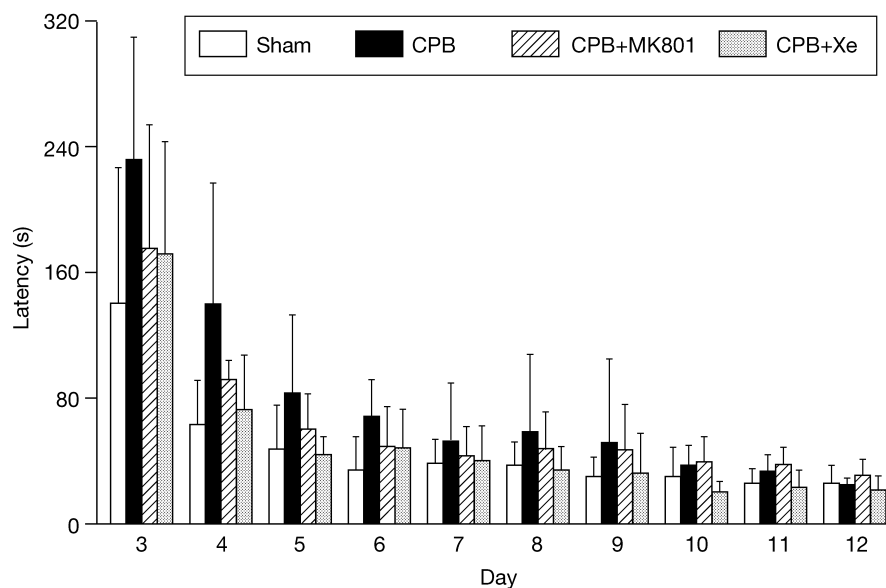

Fig 5 Neurocognitive outcome as evaluated daily (from post-experimental days 3–12) after CPB by visual-spatial learning with the Morris water maze. The time for animals to find the platform (based on four trials at each time point) is referred to as the latency (mean (SEM), n=10). Analysis of variance revealed that the Sham, CPB+MK801 or CPB+Xe group were significantly different from the CPB group statistically (CPB *vs* Sham: F=18.2, P<0.0001; CPB *vs* CPB+MK801: F=20.7, P<0.0001; CPB *vs* CPB+Xe: F=21.6, P<0.0001). Repeated measures with Student–Newman–Keuls, followed by analysis of variance, shows a significant difference when compared with the CPB group at the third and fourth postoperative day. Reproduced with permission from *Anesthesiology*.[38]

damage in the posterior cingulate and retrosplenial cortices (PC/RS)[1 30 51] are morphological correlates of the behavioural changes. Ma and colleagues[37] showed that ketamine and nitrous oxide dose-dependently increased c-Fos expression in PC/RS cortices, a neurotoxic feature not caused by xenon (Fig. 7).

Xenon may therefore be a useful agent when protection against acute neurological injury is required. However, it is
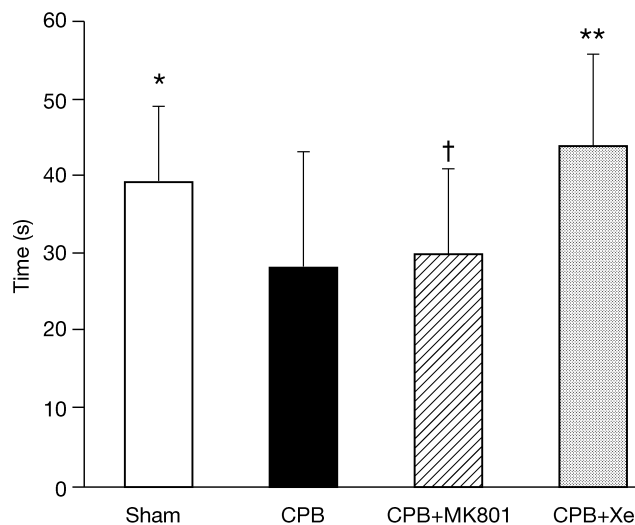
Fig 6 Spatial memory after CPB. Twelve days after CPB, animals were subjected to a probe trial for 60 s, in which there was no platform present. The percentage of time spent in the quadrant of the former platform position was obtained as a measure of spatial bias. Animals in the Sham and CPB+Xe groups spent a longer period in the quadrant of the former platform, which indicates they have better spatial memory function than the other groups. The results are mean (SD) (*n*=10). *P*<0.05, **P*<0.01 compared with CPB group. †*P*<0.05 compared with CPB+Xe group. Reproduced with permission from *Anesthesiology* **302**.[38]

important to consider xenon's effect on cerebral blood flow (CBF) when its use as a neuroprotectant is being contemplated. The most recent study in animals[13] confirms earlier studies[26] that suggest that in the first 5 min of exposure, xenon increases CBF; thereafter, xenon's effects on CBF appear to reverse. It is notable that despite changes in CBF, reactivity to carbon dioxide is maintained and, therefore, changes in blood flow can be reversed with hyperventilation. Another animal study showed that 0.3 and 0.7 MAC xenon administration did not cause an increase in intracranial pressure (ICP), (while dilating pial arterioles by 10 and 18%, respectively and venules by 2 and 4%, respectively), and preserved carbon dioxide reactivity of the brain vessels.[16]

Investigation into the effects of xenon (33%) inhalation for 20 min in 13 patients, 3 days after severe head injury, showed clinically significant increases in ICP and cerebral perfusion pressure.[53] Despite these changes, there was no deterioration in arteriovenous oxygen difference values which would be indicative of cerebral oligaemia or ischaemia.

Xenon's effect on cerebral metabolic rate needs clarification. Frietsch and colleagues[13] found no significant changes in metabolism although cerebral glucose utilization decreased in 18 of 40 brain structures investigated with xenon at 70% atm. Plougmann and colleagues[53] suggested that xenon was not metabolically neutral as they found fluctuations in the arteriovenous oxygen difference. It is also apparent from this study that there is a great deal of

individual variation in the effects of xenon in head-injured patients. More research is required in humans to define the impact of xenon anaesthesia on cerebral metabolic and haemodynamic variables.

Analgesia

Xenon exhibits more potent analgesic action than nitrous oxide, the only other anaesthetic gas with true analgesic efficacy. Supplementation with fentanyl was lower in a xenon-based anaesthetic compared with that of nitrous oxide (fentanyl 0.05 *vs* 0.24 mg), and fewer patients required supplementation (35 *vs* 95%).[33] As changes in haemodynamic variables were used as surrogate markers of the need for further fentanyl, the study may be biased because of the independent effects of each drug on these variables (none with xenon *vs* sympathetic stimulation with nitrous oxide). Analgesic efficacy was investigated using a different approach in which the fentanyl concentrations required to suppress both somatic (Cp50) and haemodynamic (Cp50-BAR) responses were measured in patients at the time of incision.[48] In the presence of 0.7 MAC nitrous oxide, significantly higher concentrations of fentanyl were required (Cp50 of 3.26 ng ml^{-1}; Cp50-BAR 4.17 ng ml^{-1}[18]) compared with patients receiving 0.7 MAC xenon (Cp50 0.72 ng ml^{-1} and Cp50-BAR 0.94 ng ml^{-1}[48]). As both sevoflurane and xenon are relatively haemodynamically stable, cardiovascular variables in response to painful stimuli can be used as surrogates to directly compare the analgesic efficacy of these two drugs. Using this approach, xenon is three times more efficacious at blocking cardiovascular responses to incision than sevoflurane at equi-MAC concentrations.

The difference in analgesic potency between nitrous oxide and xenon is more difficult to define when tested in volunteers with 'experimental pain'. When heat stimulation was used to provoke pain, nitrous oxide and xenon were equivalent analgesics.[65] When electrical stimulation is used to provoke pain, xenon is 1.5 times more potent than nitrous oxide.[52]

In pre-clinical studies designed to determine the mechanism of analgesic action, it appears that xenon differs from nitrous oxide although both these gases are NMDA receptor antagonists.[9][12][30] Nitrous oxide provokes release of endogenous ligands for opiate receptors in the periaqueductal grey region, which indirectly activates descending inhibitory neurons in the spinal cord. Here, the released norepinephrine activates adrenergic receptors to mediate the antinociceptive effect.[15] Yet, neither an opiate antagonist nor an α$_2$ adrenergic antagonist attenuated the antinociceptive properties of xenon.[50] Comparison between the effects of nitrous oxide and xenon on spinal cord dorsal horn neurons in spinal cord-transected cats anaesthetized with alpha-chloralose and urethane demonstrated that while xenon suppressed the effects of both pinch and touch on the firing of wide dynamic range neurons, nitrous oxide was
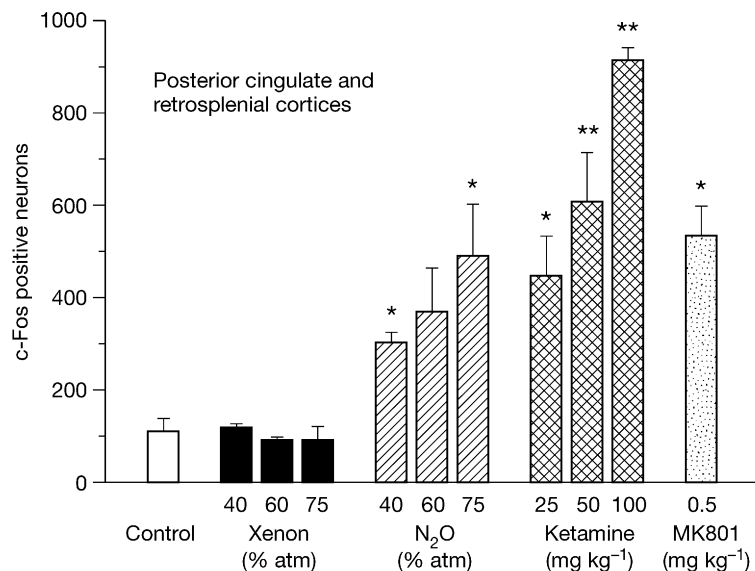
Fig 7 Concentration or dose–response effects of xenon, nitrous oxide and ketamine on the number of c-Fos-positive neurons in the posterior cingulate and retrosplenial cortices. Rats were exposed to increasing doses or concentrations of three anaesthetics, which antagonize the NMDA receptor. Rats were destroyed and brains harvested and prepared for c-Fos immuno-staining. 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 control. Reproduced with permission from the Br J Anaesth.[37]

ineffective.[42] Thus, Adachi and colleagues[42] postulated that the antinociceptive action of xenon was greater at the level of the spinal cord than nitrous oxide, with no role for descending inhibitory systems in its analgesic effect, a finding supported by their earlier work.[62]

Toxicity

In vivo and *in vitro* experiments suggest that xenon does not trigger malignant hyperthermia (MH) in MH-susceptible swine.[3] [14] Burov and colleagues reported no evidence of toxicity in several *in vitro* and *in vivo* paradigms involving two species given xenon either acutely or sub-chronically.[5] Studies of microorganisms and mice showed xenon has no mutagenic or carcinogenic properties.[5] No embryotoxic or teratogenic changes were found in pregnant Wistar rats, nor was xenon found to be allergenic.[5] Xenon was shown to moderately stimulate the immune response and increase the cellularity of lymphoid organs.[5]

Pharmacoeconomics

Xenon is an expensive gas; the current cost of 1 litre of xenon with a purity of 99.99% is approximately $10, but may change depending on 'market forces'. Therefore, closed-circuit delivery appears to be an economic necessity for the application of xenon anaesthesia.[36] An analysis of the cost of a 40-yr-old ASA I, adult male weighing 70 kg undergoing simulated elective surgery, found that 240 min of closed-circuit xenon anaesthesia would cost $356.[47] The bulk of this cost is attributed to the priming and flushing of

the delivery circuit; if the delivery technology could be refined to remove nitrogen without the need for priming and flushing,[25] then xenon anaesthesia would cost a more affordable $108, assuming the availability of the closed-circuit delivery device.

Among the recent technological advances to improve the cost-efficiency of xenon anaesthesia are xenon recycling systems, including one pioneered by Burov and colleagues in Russia, in which xenon can be purified to more than 99%.[5] For the efficient use of the recycling system, anaesthesia would have to be maintained with another agent while xenon was recovered.

Environmental effect

The ecological impact of an anaesthetist's work is increasingly coming under scrutiny. Our major volatile anaesthetics are CFC based and are known to deplete the ozone layer. Nitrous oxide is 230 times more potent as a greenhouse gas than carbon dioxide, takes 120 yr to breakdown, and the amount released as an anaesthetic contributes 0.1% of the greenhouse effect.[19] In comparison, xenon appears to be environmentally safe.

Conclusions

Xenon is a potent inhalation anaesthetic with many salubrious qualities; expense has so far mitigated the development of its use for anaesthesia, but recent research has suggested a niche for xenon, based on its pharmacokinetic, cardiac, neuroprotective, and analgesic properties.

For example, xenon may be the anaesthetic of choice for 'fast-track' cardiac surgery where its rapid emergence, cardiostability, and neuroprotective qualities can come to the fore. Furthermore, settings in which the risk of intraoperative neurological injury is high (e.g. major intracranial vascular surgery) may be another opportunity for the clinical application of xenon. We await the results of clinical trials to investigate whether neurocognitive deficits can be reduced by the administration of xenon in cardiac surgical patients.

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