Xenon as an anaesthetic gas

Although expensive to manufacture, the inert gas xenon has many of the characteristics of the ideal anaesthetic agent. In particular, it confers haemodynamic stability and beneficial effects on organ perfusion. It also has a favourable pharmacokinetic profile allowing rapid induction and emergence. However, widespread clinical application will only be economically feasible if the cost of xenon falls and a low flow delivery system is used.

Xenon is an inert, or noble, gas. Its name is derived from the Greek for 'stranger' because of its rarity – xenon constitutes only 0.0000087% of the earth's atmosphere. The scientists Sir William Ramsay and Morris M Travers discovered it during the study of liquefied air in 1898. Xenon is manufactured by the fractional distillation of air and is highly expensive to produce.

The first recorded use of xenon in humans was in 1951 when Cullen successfully used it to anaesthetize two patients for minor surgery (Cullen and Gross, 1951). In the largest trial so far, 224 patients in six centres were randomly assigned to receive either xenon (60±5%) in oxygen or isoflurane (end-tidal concentration, 0.5%) combined with nitrous oxide (60±5%) and oxygen. The xenon-based anaesthetic gave faster recovery and better cardiovascular stability. The authors concluded that xenon anaesthesia was effective and safe (Rossaint el al, 2003).

Human and animal data suggest that xenon has many highly desirable properties. It causes little cardiovascular depression and may be neuroprotective. Coupled with potent analgesic properties and a low blood/gas partition coefficient that allows rapid onset and offset of action, it is not surprising that many consider it almost the 'ideal' anaesthetic agent.

Physical properties

The physical properties of xenon are shown in *Table 1*.

The minimum alveolar concentration (MAC) of a volatile anaesthetic is the concentration of the anaesthetic agent (measured as a percentage at one atmosphere) that prevents motor response to a standard surgical stimulus in 50% of subjects. Fears of causing hypoxia with high concentrations of xenon in a closed system preclude the direct estimation of MAC but it has been estimated as 63% by studying the MAC-lowering effect of xenon when co-administered with sevoflurane (Nakata et al, 2001).

The blood/gas partition coefficient of xenon (0.12) is much lower than all the other inhalational anaesthetic agents (e.g. desflurane 0.42, isoflurane 1.43, nitrous oxide 0.47), which makes for extremely rapid induction and emergence. Patients given xenon emerge from anaesthesia almost twice as quickly as those given sevoflurane, regardless of the duration of anaesthesia (Goto et al, 1997).

Mechanism of action

Most anaesthetic agents act at $GABA_A$ (gamma aminobutyric acid type-A) receptors, causing neuro-inhibition, but xenon does not. However, it is a potent inhibitor of the excitatory NMDA (N-methyl-D-aspartate) receptor channels (Franks et al, 1998), which may explain its anaesthetic action.

Clinical effects of xenon

Analgesia

Apart from nitrous oxide, xenon is the only currently available anaesthetic gas that is analgesic. Analgesic requirements are less with xenon-based anaesthesia (Lachmann et al, 1990). Yagi et al (1995) examined the effects of xenon and nitrous oxide in equipotent doses (0.3 MAC) on pain threshold and auditory response time in six healthy male volunteers. Both agents increased the pain threshold compared with 100% oxygen inhalation, although the researchers found no significant difference in analgesic effects between them. Pigs undergoing xenon-based anaesthesia had lower plasma catecholamine concentrations than pigs undergoing total intravenous anaesthesia (Marx et al, 1997), which is also supportive of xenon being analgesic.

Table 1. Physical properties of xenon

Colourless, odourless tasteless gas
Atomic number 54
Molelcular weight 131.3
Four times as dense as air and 3.4 times as dense as nitrous oxide
Melting point -111.79°C
Boiling point -108.12°C
Non-flammable and does not support combustion
Oil/water solubility coefficient of 20
Blood/gas partition of coefficient of 0.12

Dr N Baskar *is Staff Anaesthetist and* **Dr JD Hunter** *is Consultant in Anaesthetics and Intensive Care in the Department of Anaesthetics and Intensive Care, Macclesfield District General Hospital, Macclesfield SK10 3BL*

Correspondence to: Dr N Baskar

Cardiovascular system

Xenon anaesthesia confers cardiovascular stability, although not many patients have yet been studied, and most of the studies have been on fit patients, with little important co-morbidity.

Animal experiments suggest that xenon has little effect on the myocardium. Xenon does not depress myocardial function in isolated rat heart (Nakayama et al, 2002), nor does it alter myocardial contractility or the response to inotropic agents in isolated ventricular muscle bundles from guinea pig (Schroth et al, 2002). Preckel et al (2000) saw little negative inotropism when 70% xenon was given to rabbits with chronically compromised left ventricular function.

The few human studies that have been done also suggest that xenon anaesthesia confers notable haemodynamic stability. Luttropp and colleagues (1993) did not see any adverse effects on myocardial contractility using transoesophageal echocardiography in healthy adults. Mean arterial pressure remained higher throughout surgery when xenon was compared with isoflurane-nitrous oxide anaesthesia (Rossaint et al, 2003), and systolic blood pressure remained higher when compared with propofol anaesthesia (Coburn et al, 2005) (*Figure 1*). There was also a slight reduction in heart rate (*Figure 2*) which had been reported previously.

Xenon has been compared with propofol for postoperative sedation in patients who had undergone coronary revascularization (Dingley et al, 2001). With xenon, mean arterial pressure was higher, vascular tone was better maintained, and myocardial contractility, as determined by left ventricular stroke work index, was not affected.

Xenon may be cardioprotective. Preckel and colleagues (2002) occluded a major coronary artery in rabbits. During reperfusion, the rabbits inhaled either oxygen-enriched air (30% oxygen) or a mixture of 70% xenon and 30% oxygen, which apparently reduced the infarct size.

Cerebral effects

Animal and in-vitro studies suggest that xenon may be neuroprotective. Giving 60% xenon via a membrane oxygenator to rats undergoing cardiopulmonary bypass was associated with less postoperative neurological and neurocognitive dysfunction than in control animals given oxygen-enriched air (Ma et al, 2002). This is possibly related to inhibition of NMDA receptors, activation of which is thought to be important in neuronal injury. However, we do not have enough information from human observation to know if this matters clinically.

All volatile agents impair autoregulation of cerebral blood flow; xenon is no exception. It seems to cause an initial increase in flow. Breathing 35% xenon in oxygen increases mean regional cerebral blood flow in 20 normal volunteers (Hartmann et al, 2002). An increase has also been shown by Doppler sonography (Luttropp et al, 1993). Plougmann and colleagues (1994) studied the effects of xenon inhalation in patients with severe brain trauma. There was a rapid increase in intracranial pressure and a decrease in cerebral perfusion pressure, although there was no apparent further damage from cerebral ischaemia. Xenon should not yet be used in patients with head injury.

Respiratory effects

Unlike other anaesthetic agents, which increase respiratory rate and decrease tidal volume, high concentrations of inspired xenon decrease respiratory rate with a presumably compensatory increase in tidal volume (Dingley et al, 1999). Short periods of apnoea have been reported during computed tomography cerebral blood flow examinations with 32% inhaled stable xenon (Latchaw et al, 1987).

Figure 1. Xenon anaesthesia is associated with maintenance of systolic blood pressure. Systolic blood pressure is shown as mean (standard deviation), *P<0.05. Induction was at time 0. From Coburn et al (2005).

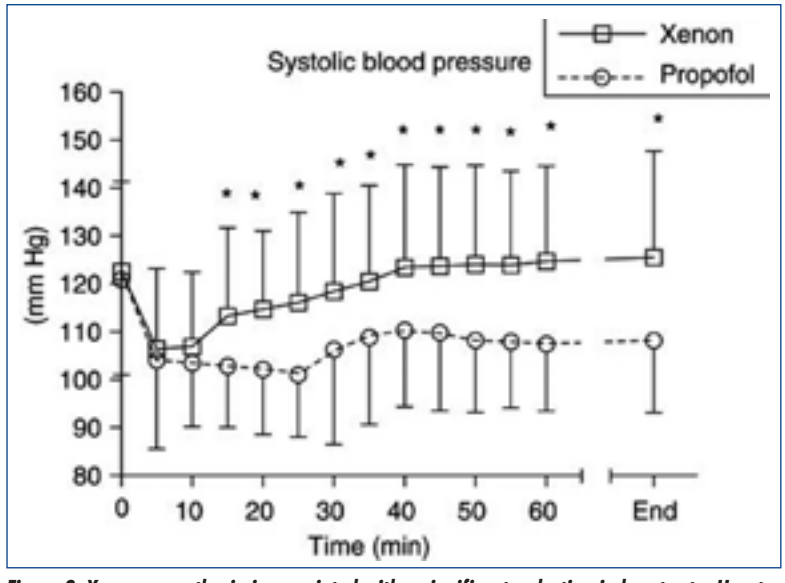
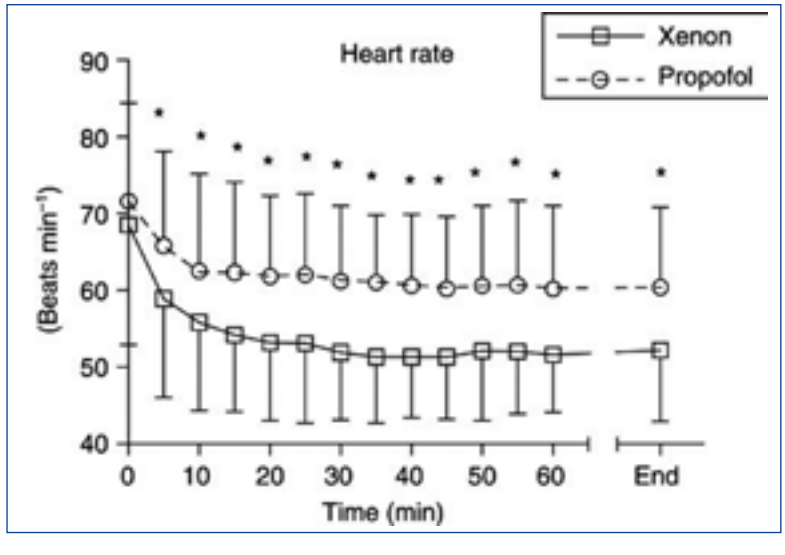


Figure 2. Xenon anaesthesia is associated with a significant reduction in heart rate. Heart rate is shown as mean (standard deviation), *P<0.05. Induction was at time 0. From Coburn et al (2005).



Xenon has a higher density and viscosity than oxygen, air or nitrous oxide, so it would be expected to increase airway resistance, and this has been confirmed in animals (Zhang et al, 1995). Studies in humans by Lachmann et al (1990) suggested that there was only a slight reduction in lung compliance during xenon anaesthesia, and that xenon can be used safely in those with chronic lung disease.

Toxicity

From the few studies done in humans and animals, prolonged administration of xenon, unlike nitrous oxide, seems safe. It is also safe to use in patients susceptible to malignant hyperthermia. Froeba and colleagues (1999) exposed malignant hyperthermia-sensitive pigs to 70% xenon in oxygen for 2 hours and were unable to show any changes in metabolic or haemodynamic variables, or any increases in plasma catecholamine concentrations, which would have been suggestive of malignant hyperthermia.

Bowels

Nitrous oxide diffuses into air-filled spaces faster than nitrogen diffuses out, which increases pressure in a fixed volume. Hence, nitrous oxide is relatively contraindicated in bowel obstruction. Although xenon has a lower blood/gas partition coefficient than nitrous oxide, and the same would be expected, experiments in which obstructed segments of bowel were examined during xenon/oxygen anaesthesia failed to show any rise in intra-luminal pressure. This is most likely because of the different diffusion constants of nitrous oxide and xenon (Marx et al, 2000).

Cost

Xenon is a rare gas and difficult to manufacture in large volumes. This is reflected in its high cost (approximately US $10.00 per litre), which has limited its widespread use. Anaesthetizing a 70 kg adult with 1 MAC of xenon for 4 hours using a closed circuit would cost approximately US $167.00 (£100) (Goto et al, 2003). Even using very low flow systems, the cost of xenon-based anaesthesia is significantly higher than currently used anaesthetic regimens. For instance, the typical costs for a 45–60-minute procedure using low flow sevoflurane anaesthesia is approximately £5.00 ($8.70) (Thwaites et al, 1997).

KEY POINTS

- Xenon is a noble gas which possesses many of the properties of the ideal anaesthetic agent.
- Its rarity in the atmosphere makes production highly expensive.
- It causes minimal cardiovascular depression and may have neuroprotective properties.
- It is a potent analgesic.
- It has rapid onset and offset of action because of an extremely low blood/gas partition coefficient.
- It remains to be seen whether xenon anaesthesia will ever be economically viable.

Monitoring

Xenon cannot be monitored with conventional anaesthetic gas analysers. As its cost-effective use demands low flow anaesthesia, delivery of gas to the patient must be monitored accurately. Mass spectroscopy, thermal conductivity and ultrasound have been used experimentally. Mass spectrometry is accurate, but its bulk and cost make it clinical unfeasible. Perhaps the most promising method is ultrasound, which works on the principle that xenon is a dense gas that conducts sound faster than any of the other gases present (King et al, 2005).

Conclusions

Xenon has many highly desirable properties. It is a potent analgesic and provides excellent cardiovascular stability. It has no known toxicity in humans, and experimental evidence is emerging to suggest that it may be neuroprotective. Its pharmacokinetic profile is also favourable, allowing rapid induction and emergence from anaesthesia. However, it is extremely expensive to manufacture and difficult to monitor accurately clinically. There are also no human studies showing an improved clinical outcome from xenon-based anaesthesia. As modern anaesthetic agents already are extremely safe, it is difficult to envisage the widespread use of xenon-based anaesthesia until prices fall substantially. BJHM

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Conflict of interest: none.

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