Why is xenon not more widely used for anaesthesia?

Many authors write favourably about the use of xenon as an anaesthetic, but the clinical use of xenon is still limited to a small number of patients.

Xenon is a colourless, odourless, tasteless, inert gas, which was discovered by Ramsay and Travers in 1898. It is not toxic – in rats, chronic exposure to a mixture of 80% xenon and 20% oxygen for 2.5 hours per day for 2 weeks did not lead to significant alterations in main organs (Natale et al, 1998). Xenon has several physical differences to the familiar anaesthetics: it has the lowest blood/gas partition coefficient (0.115, Goto et al, 1998) and a remarkably high density of 3.95 g/litre.

The anaesthetic mechanism of xenon is different from other anaesthetics. It has no effect on gamma-aminobutric acid $(GABA)_A$ receptors but inhibits the N-methyl-D-aspartate (NMDA) receptor (Franks et al, 1998). Goto and colleagues measured the midlatency auditory evoked potentials (MLAEP) in humans. They found that xenon, even at low concentration, suppresses MLAEP, as do other volatile anaesthetics, and concluded that it is a good hypnotic (Goto et al, 2001).

WHAT IS KNOWN ABOUT THE USE OF XENON IN HUMANS?

The first serious study was performed by Lachmann and colleagues, who found that a concentration of 70% xenon results in satisfactory anaesthesia for surgical procedures (Lachmann et al, 1990). Compared with a nitrous oxide group, the requirement for fentanyl was reduced by 80% in those anaesthetized with xenon. Awakening was uneventful in both groups but faster in the xenon group. Xenon provided a stable haemodynamic situation with less sympathetic stimulation; adrenaline levels did not rise during the operation (Boomsma et al, 1990).

In a transoesophageal echocardiography study, the fractional area change remained at 65% and did not change in the first 15 minutes of xenon anaesthesia (Luttropp et al, 1993). The same authors noted an increase in the mean cerebral artery flow velocity after 15 and 30 minutes of xenon anaesthesia, although this increase is compared with the flow after propofol induction because they did not measure the flow in the awake patient.

Results of the largest study group of 62 patients (which included the American Society of Anesthesiologists (ASA) classification score 3–4 patients) also emphasize the haemodynamic and pulmonary stability of xenon (Tenbrinck et al, 2001). The total number of patients treated with xenon is still very low compared with other anaesthetic agents, and positive experience in ASA 3–4 patients will largely depend on individual cases.

In a patient with Eisenmenger syndrome scheduled for cholecystectomy (Hofland et al, 2001), xenon provided a relative bradycardia while maintaining good cardiac contractility. This was measured with transoesophageal echocardiography.

The pulmonary effects of xenon are often discussed, as the high density might cause problems in severe pulmonary-compromised patients. Lachmann and colleagues (1990) found a stabilizing effect of xenon on the lungs proven by a lower number of sighs needed to restore thorax–lung compliance. Five severe pulmonary-compromised patients were treated with xenon (Tenbrinck et al, 2001). Intraoperative stabilization of the airways provided good blood gases without extreme ventilatory settings, followed by a rapid and uneventful awakening. Xenon patients often need no supplementary oxygen as proven by blood gases.

Xenon also diffuses to air-filled spaces (bowel, pneumothorax), as does nitrous oxide, but to a lesser extent, and the measured intra-luminal bowel pressure does not differ from controls, as shown in a study undertaken in pigs (Reinelt et al, 2001).

From the few completed clinical studies, it can be concluded that xenon can be a safe anaesthetic, also in ASA 3–4 patients (Dingley et al, 2001; Tenbrinck et al, 2001), provided it is used in a balanced anaesthesia concept. The concentration needed for adequate anaesthesia might be lower than the defined minimal alveolar concentration (MAC) value of 70%, but it is still unknown how much lower (Goto et al, 1998; Tenbrinck et al, 2001). It is important to wait for the definite results of the ongoing multicentre studies simply because they increase the number of patients investigated.

Xenon has recently gained a new use as an anaesthetic in intensive care (Dingley et al, 2001). Dingley and colleagues found the haemodynamic stability of xenon to be beneficial, as well as the rapid, uneventful recovery, as noted in earlier anaesthesia studies (Lachmann et al, 1990; Goto et al, 1997; Tenbrinck et al, 2001).

WHY IS XENON NOT YET IN CLINICAL USE?

The currently used volatile anaesthetics, e.g. nitrous oxide, and intravenous agents, such as propofol, have an influence on environmental pollution (Marx et al, 2001). Toxic effects of these agents on workers in the operating theatre are also suspected, and minimizing exposure is an aim for the coming decade. The introduction of xenon might help to fulfil this aim (Marx et al, 2001).

So why is the use of this noble gas not further propagated in anaesthesia when it is really as good as it seems? Many authors mention, almost without exception, two main disadvantages in using xenon: the price (now around 12 Euro per litre) and the necessity of

using closed circuit anaesthesia systems adapted for xenon administration.

The availability of xenon is limited; this raises the price. The production of xenon is expensive because it is a by-product of the commercial purification of air into its main components, nitrogen and oxygen. Since an average room of 50 m^3 contains only 4 ml xenon, it is clear that huge quantities of nitrogen and oxygen have to be sold to produce 1 litre of xenon. The idea suggested by Marx et al (2001) to collect, clean and reuse most of the xenon out of a closed system will certainly improve the availability, but the influence on price will be minimal. The legislation concerning drug production and administration demands high standards of purity during production to prevent contamination, so it will only be pharmaceutical companies which can clean the used gas for reuse.

Nevertheless, xenon can bring some extra quality in anaesthesia for a higher cost. It is very likely that this higher cost will be paid for patients in whom the advantages seem clear: ASA 3–4 for major surgery or long (>8 hours) and delicate operations, such as free-flap surgery.

Another reason for the limited use of xenon is that its administration requires preferably a closed anaesthesia system. The only currently commercially available system is the Physioflex® system (Drager, Best, Holland) (Tenbrinck et al, 2001). The closed bag-in-bottle Penlon system developed by Dingley will also be introduced to the market, but the few remaining systems used in other xenon studies will probably never be available commercially. Without adequate anaesthesia machines, it will remain difficult to show the benefits of xenon anaesthesia on a larger scale. HM

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KEY POINTS

- Xenon is one of the noble gases.
- Use of a closed circuit anaesthesia system will increase the availability of xenon.
- Xenon provides a stable haemodynamic situation.
- Xenon has the lowest blood/gas partition coefficient of all volatile anaesthetics.
- Xenon can bring extra quality and safety in anaesthesia.