Xenon anaesthesia

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A volatile anaesthetic agent is liquid at room temperature and atmospheric pressure but vaporizes in an anaesthetic apparatus. The volatile agents in current use include halothane, which was developed in the 1950s, and enflurane and isoflurane, which were introduced clinically in the 1980s. Newer inhalation agents are desflurane and sevoflurane. Nitrous oxide (N_2O) is commonly used in anaesthetic procedures as a gaseous anaesthetic and carrier gas. Nitrous oxide (usually given in an inspired concentration of 70%) increases the effect of the volatile agents and thus reduces their consumption. The concentrations of volatile anaesthetics required for anaesthesia are between 1% and 5% of the patient's inspired air.

In this paper we examine the arguments for a switch to the inert gas xenon. Two of these concern the effects of atmospheric pollution with existing agents. First, because of their effects on the ozone layer, emission of chlorinated hydrocarbons is to be banned by international agreement from the year 2030. As fluorinated hydrocarbons, desflurane and sevoflurane contribute less to the destruction of the ozone layer but their 'greenhouse gas' capacity is ten times that of carbon dioxide; regulations to reduce such emissions were established at the Kyoto Conference of 1997. Nitrous oxide is another gas with ozone-depleting and greenhouse effects on which restrictions were placed at the same conference[1].

Second, there is the question of workplace exposure. Among the discussed effects of chronic workplace exposure to volatile anaesthetic agents are teratogenicity, mutagenicity and an increase in the rate of abortion[1–5]. Data from controlled studies are lacking, but in nearly all countries of the world workplace pollution is seen as undesirable and limits for exposure to anaesthetic gases and vapours have been set[6]. In our opinion, so long as any suspicion of a teratogenic or carcinogenic effect exists, concentrations in the workplace atmosphere should be brought as close as possible to zero.

BACKGROUND

Xenon is an inert or 'noble' gas. It is derived from the atmosphere, which contains xenon in a concentration of 0.00005 ppm (a room of 50 m^3 contains 4 mL of xenon). Knowledge of its anaesthetic properties dates from 1939, when Behnke investigated for the US Navy the reason for 'drunkenness' observed in deep-sea divers. At that time, the diving depth was assessed by professional divers from the mental effects occurring at specific levels below the surface. When Behnke changed the breathing mixtures of the divers they reported by telephone the impressions of being hoisted towards the surface or lowered deeper underwater, though in reality their depth had not changed.

From his experiments Behnke calculated that xenon should have anaesthetic effects even under normobaric pressure, but the gas was too scarce to allow confirmation[7]. In 1941 Lahzarev, in Russia, examined the effects of xenon in man but was unable to publish his results (Burov N, personal communication). It was Lawrence, in 1946, who first published on xenon anaesthesia, in mice[8]. In 1951 Cullen used xenon in two patients (an 81-year-old man for orchiectomy and a 37-year-old woman for tube ligation) and reported only a small requirement for additional anaesthetic substances[9]. Since then, many investigators have noted advantages over nitrous oxide—for example, greater circulatory stability, lower analgesic consumption, lower adrenaline levels, and better regional perfusion of individual organs[10–13]. Xenon's anaesthetic effect is 1.5 times greater than that of nitrous oxide, and its lower blood/gas solubility (0.12 *versus* 0.46) offers possible advantages in terms of rapid inflow and washout[14]. It is non-teratogenic and does not contribute to depletion of the ozone layer[5,15]. The sole disadvantage of xenon is its high price.

NEW INVESTIGATIONS

Technical improvements leading to large reductions of anaesthetic gas expenditure, together with recycling systems for xenon, have led to renewed interest in xenon anaesthesia. Here we focus on some key areas of investigation.

Haemodynamic stability

In the first experiments performed by our group, haemodynamic indices, which are affected by all conventional inhaled agents but very little by intravenous agents, were measured under controlled anaesthetic and surgical conditions. In animals, comparison with intravenous

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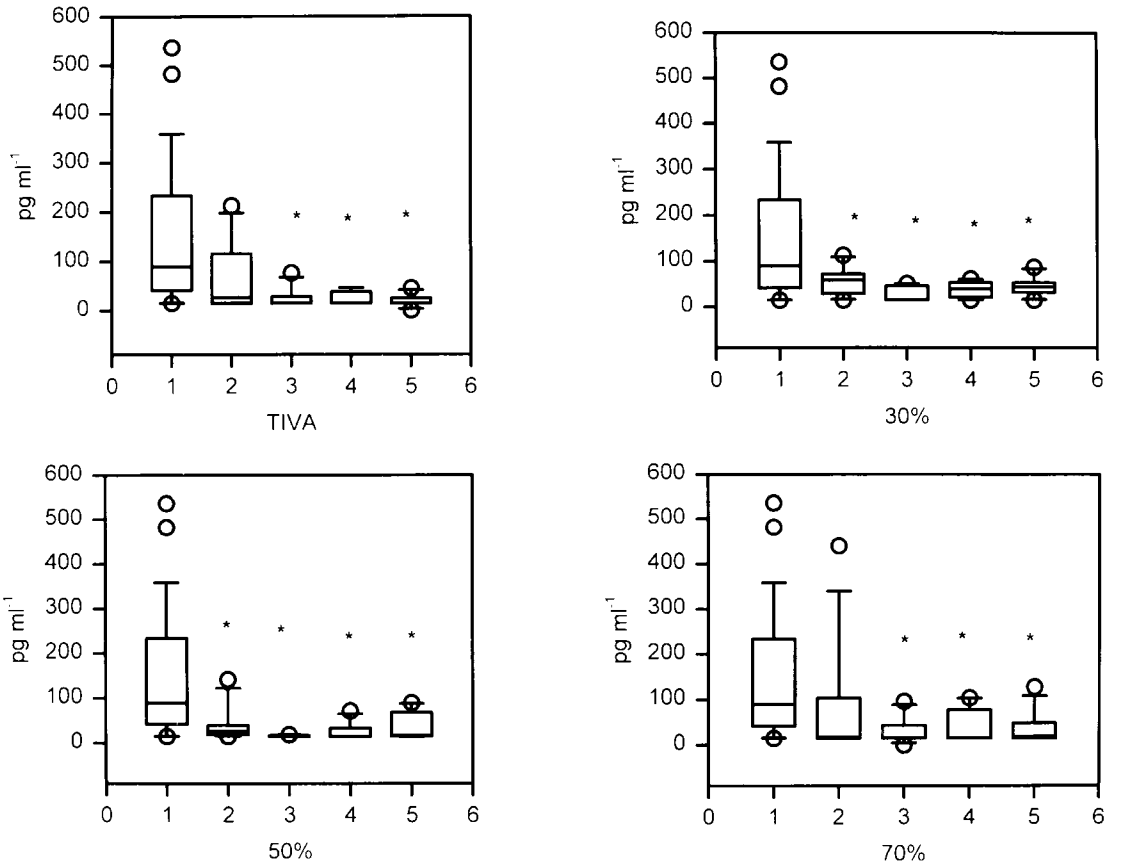

Figure 1 **Plasma adrenaline concentrations during surgery under xenon anaesthesia (30, 50, 70%) compared with total intravenous anaesthesia (TIVA).** Point 1 before surgery; point 2 anaesthesia alone; points 3–5 anaesthesia and surgery

anaesthesia showed no differences in mean arterial pressure, cardiac output, systemic vascular resistance or pulmonary vascular resistance. A major finding was a substantially lower plasma adrenaline concentration during xenon anaesthesia, not only at inspiratory concentrations of about one MAC (minimal alveolar concentration to produce an anaesthetic effect in 50% of patients) but also at subanaesthetic concentrations of half and one-third this amount (Figure 1). In all experiments xenon was sufficient, without additional analgesia, to prevent haemodynamic reactions caused by surgical stimulation. We concluded that xenon has analgesic effects even in concentrations below its MAC[16,17].

This sub-MAC analgesic potency was also found in volunteers. In an investigation by Yagi *et al.*[18] a concentration of 21% xenon raised the pain threshold to about the same extent as 30% nitrous oxide. Goto *et al*[19] reported high cardiovascular stability in patients during xenon anaesthesia; moreover, time to emergence from anaesthesia was shorter than with other techniques and seemed to be independent of operation time—an important difference from conventional inhalation anaesthesia.

Malignant hyperthermia

Malignant hyperthermia (MH) is a genetic anomaly of the ryanodine receptor, leading to an uncontrolled and potentially lethal discharge of calcium ions into the skeletal muscle cell cytosol with a consequent extreme increase of energy consumption[20]. The prevalence of this abnormality is between 1 in 20 000 and 1 in 200 000, and it can be triggered by all known inhalation anaesthetics and depolarizing muscle relaxants. Is xenon likewise a trigger for this? We investigated the question in Pietrain pigs, which are genetic homozygotes for the MH-gene-defect. Whereas all 12 animals developed MH on exposure to halothane and suxamethonium (succinylcholine), none of the animals showed MH when under xenon anaesthesia (Figure 2). Therefore we concluded that xenon is not a triggering substance for MH[21].

Organ distribution

Two hours after xenon administration, the gas is still detectable in the breath, so we investigated whether xenon is stored in specific organs after anaesthesia. Inert xenon

was spiked with ^{133}Xe and xenon anaesthesia was administered under a gamma camera. 10 pigs were anaesthetized for four hours, followed by a two-hour washout period. After two hours, 22% of the xenon was still present in the body, the main storage tissues being fatty tissue and the bowels. No other organ system showed significant storage of xenon.

Bowels

The results of the above study prompted investigation of the influence of xenon on bowel function. With nitrous oxide, diffusion into the bowels causes a progressive decrease in tissue perfusion; hence N_2O is contraindicated for use in ileus and relatively contraindicated for bowel surgery[22]. Xenon has a lower blood/gas partition coefficient than nitrous oxide, so a greater tendency to diffuse into air-filled cavities is to be expected. However, the amount of diffused gas depends also on the diffusion coefficient, which is not known for xenon and organic tissues. We compared xenon diffusion into obstructed bowel segments under xenon anaesthesia, nitrous oxide anaesthesia and nitrogen/oxygen ventilation. The mean increase of gas volume with nitrous oxide was four times that observed with xenon. No increase in intraluminal pressure was observed in the xenon group or the control group. In the nitrous oxide group a significant pressure increase was first observed after 30 minutes of anaesthesia and this rose to a 200% pressure increase after four hours of anaesthesia. According to these results, xenon should not be troublesome in bowel surgery[23].

Cerebral perfusion

Inhalation agents and some intravenous agents increase cerebral blood flow (CBF) and disrupt cerebral autoregulation. Therefore in syndromes with increased CBF, these anaesthetic agents are contraindicated. The influence of xenon on CBF autoregulation is still under vigorous debate. Information comes from computed tomography measurements and studies with ^{133}Xe as tracer. Xenon in concentrations of 33–80% increased CBF in some animals[24,25], but not in monkeys[26]. In patients with cerebral injury xenon in a concentration of 32% did not increase the intracranial pressure[27]. Fink *et al.*[28] recently reported a tightly controlled experiment in pigs in which CBF was unchanged by inhalation of 70% xenon and autoregulation remained constant. In our own investigation, two groups of pigs were exposed either to xenon anaesthesia or to halothane anaesthesia. CBF rose in both groups, but cerebral autoregulation was unaffected by xenon and was reduced by halothane. The differences between Fink's findings and ours are perhaps explained by experimental design or co-medication.

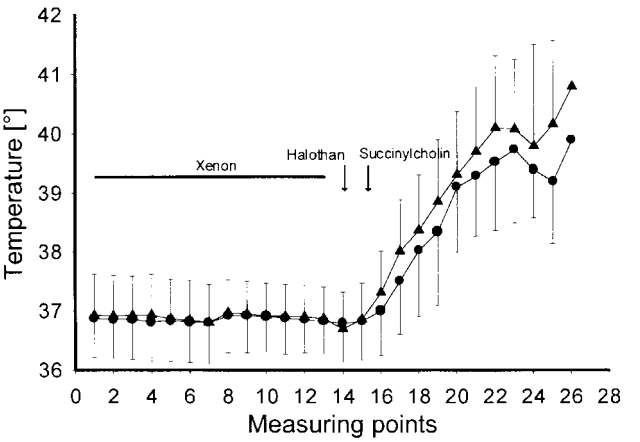

Figure 2 **Body temperature during application of xenon and after triggering with halothane and suxamethonium (succinylcholine).** ●Rectal temperature; ▲Central temperature

COST (Figure 3)

The price of xenon fell from 100 DM per litre in 1982 to 10 DM per litre in 1998. During the past two years the price has increased again, to 20 DM, because of the demands of a telecommunication satellite project scheduled to end in 2004. Thereafter, amounts available for anaesthesia are likely to increase[29]. Nevertheless, without optimal retrieval systems xenon anaesthesia is still thought too expensive by some anaesthetists.

Recycling

To reduce the cost, we constructed a recycling device based on a thermodynamic procedure. The purification process is

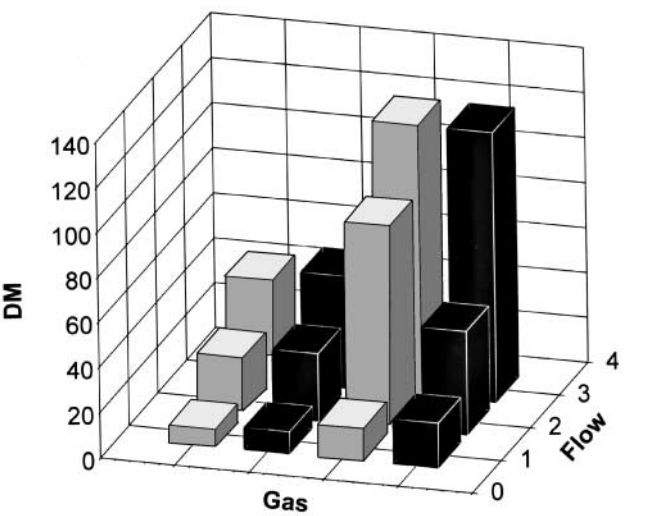

Figure 3 **Cost of anaesthesia (two hours) with (from left) enflurane, isoflurane, desflurane and xenon at fresh gas flows of 3, 2 and 1 L/min.** Right column, from back to front, shows costs of xenon with closed system anaesthesia, closed system anaesthesia with priming of ventilator and closed system anaesthesia with priming and recycling

based on liquefaction of a 70% xenon mixture at a pressure of >60 bar and a temperature of -20°C. Oxygen and nitrogen stay gaseous during this process whereas xenon gas is liquefied and can be stored in the reservoir, either for reuse in the anaesthesia device or for despatch to the supplier for further purification. Our first experiments gave a recycling rate of 70% with a purity of higher than 90%. The device is now being refined and is expected to reach a recycling efficiency of higher than 90% with 99% gas purity[30,31]. Different recycling concepts, based on molecular sieving or simple collection of gas mixtures for industrial purification, have been developed and patented in Italy and Russia[30,32].

Closed system anaesthesia

A further decrease in xenon usage, amounting to 4.5 L per anaesthetic procedure, can be achieved by priming anaesthetic ventilators with the anaesthetic gas mixture before use and careful denitrogenation of the patient. With that technique, our animal experiments suggested a saving equivalent to 6.7 L in a 70 kg patient in four hours of anaesthesia[33].

Undiscovered sources

Another aspect, probably influencing availability and price in the far future, is 'missing xenon'. The earth's atmosphere contains two thousand times less xenon than we would expect from other planets in our solar system, and one view is that it was lost during formation of the primary atmosphere[34]. Another view, however, is that this xenon is still present on our planet[8]. Calculations and experiments by Berkeley laboratories in California did not encourage the idea that xenon–iron complexes are present in the Earth's core[35], but the critical parameters used in our recycling process lead us to suspect that xenon, like methane, may form gas hydrates in the deep sea. The ice shell of the Antarctic is now being tested[36].

CONCLUSION

Replacement of nitrous oxide and the volatile anaesthetic gases by the rare gas xenon, which is inert in the workplace and the environment, would simultaneously reduce workplace and environmental hazards. Its favourable haemodynamic characteristics point to clinical advantages. Steps towards routine use of xenon must include improvements in closed-system anaesthesia and better methods of recycling. At present its high cost is an obstacle to widespread clinical use.

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