

REVIEW ARTICLE

Xenon: recent developments

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Xenon is the Greek word for stranger. The gas was discovered by Ramsay and Travers in 1898 in the residue left after evaporating liquid air components. It was originally labelled, with others, an inert gas but after discovery of some compounds this group was renamed the noble gases in 1962. It is the heaviest stable gas in this group and the only one which is anaesthetic under normobaric conditions [1].

Xenon constitutes 0.0000087% of the atmosphere, which is estimated to contain around 400 million tonnes. An average room contains about 4 ml. Based on the assumption that the relative distribution of all elements on all planets in the solar system is roughly the same, the earth's atmosphere contains about 2000 times less than expected. It is manufactured by fractional distillation of air, costing around 2000 times as much as nitrous oxide. Where possible it is recycled, e.g. from old computer displays. It is used in lasers, high-intensity lamps, flash bulbs, space applications, X-ray tubes and medicine (imaging, anaesthesia). As an anaesthetic it exhibits many of the features of the ideal agent. Xenon has been used for routine clinical anaesthesia in Russia, Germany, the Netherlands and Sweden. It is considered not to have any occupational and environmental disadvantages and with an MAC of 71% it is more potent than nitrous oxide (N_2O) [2–4]. Xenon has minimal haemodynamic effects and has the lowest blood/gas partition coefficient of any known anaesthetic agent, with very rapid induction and recovery characteristics [5–14].

The realisation in recent years that nitrous oxide is a potent greenhouse gas with potentially toxic biochemical effects in the body has led to continued anaesthetic interest in xenon despite its high cost [15–20]. Research into automated fully closed delivery systems and recovery devices continues in the quest to make xenon anaesthesia economically acceptable [21–32]. Practicable very low

flow and closed breathing systems are now becoming available. All these factors when combined make serious consideration of xenon anaesthesia possible. Much of the work described here is extremely current and in some areas very limited. By necessity the information has been obtained from many different sources. This review concentrates on the technical developments necessary for clinical use, physiological effects and the clinical experience gained so far.

Physical properties

Xenon is a colourless, odourless, tasteless monatomic gas. It has an atomic number of 54 and a molecular weight of 131.3. It has nine stable isotopes and many artificial isotopes [12, 33]. It freezes at -111.9°C and boils at -107.1°C . Xenon is four times as dense as air and 3.4 times as dense as N_2O . It is nonflammable and does not support combustion. Its oil/water solubility coefficient is 20.0 and it has the highest coefficient of any of the noble gases, being the only one with anaesthetic properties at atmospheric pressure. It has an extremely low blood/gas partition coefficient of 0.14, even compared to nitrous oxide (0.47) or sevoflurane (0.65). Xenon diffuses freely through rubber and there can be significant losses of gas by this route during anaesthesia. In one breathing system incorporating silicon rubber tubing, a loss rate of 750 ml.h^{-1} was observed by this route alone [9].

Specific effects on the body

Respiratory

Central

Pittenger *et al.* found that Rhesus monkeys stopped breathing when the partial pressure of xenon slightly exceeded atmospheric pressure [34]. They observed that

the apnoea and muscular relaxation were in excess of what one might expect on the basis of the depth of anaesthesia (as shown on the animals' electroencephalograms) and from experience with other anaesthetic gases. It is very likely that the same central mechanism that causes apnoea at high xenon concentrations is responsible for the marked slowing of respiratory rate observed during 33% xenon inhalation in cerebral blood flow studies [35]. This respiratory slowing is accompanied by a compensatory increase in tidal volume, resulting in little change in minute ventilation. This is unlike other anaesthetic agents which increase respiratory rate and decrease tidal volume and minute ventilation [36, 37].

Lung mechanics

Airway resistance depends not only on airway geometry but also on flow rate, gas density and viscosity [38, 39]. Airway resistance has viscosity-dependent and density-dependent components: it is viscosity-dependent in the presence of laminar flow but is density-dependent with turbulent flow. In peripheral airways, flow is laminar but in more central airways, the resistance changes greatly with flow rate. At a flow of $<1 \text{ l.s}^{-1}$, flow is laminar but above this, turbulent flow is dominant [38]. Xenon has a higher density and viscosity than nitrous oxide (≈ 3 and 1.5 times, respectively). This might be expected to cause an increase in airway resistance during inhalation, especially in patients with obstructive pulmonary disease.

The use of xenon in neuroradiology has an excellent safety record. It has been suggested, however, that patients with reduced pulmonary function may not be suitable for these procedures on safety grounds. In any case the data obtained from cerebral blood flow studies in these patients may be suspect if there is doubt as to whether the end-tidal xenon concentration reflects the arterial value [40].

In experiments by Zhang *et al.* the lungs of intubated dogs were mechanically ventilated with varying ratios of N_2O in oxygen and varying ratios of xenon in oxygen, whilst the pulmonary resistance was measured. This was repeated after bronchoconstriction had been produced by a methacholine infusion. The results suggested that inhalation of a high concentration of xenon increases airway resistance, but only to a modest extent in animals with normal or methacholine treated airways.

The P_{aO_2} , P_{aCO_2} and peak airway pressures were unaffected by xenon inhalation with both normal and constricted airways. They concluded that xenon may be a safe anaesthetic gas as far as lung mechanics are concerned [41]. Similar work has been carried out in ventilated pigs in which inspiratory resistance, peak and mean airway pressures were measured with various gas mixtures, with and without methacholine-induced bronchoconstriction [42]. A significant increase ($p < 0.05$) in inspiratory airway

resistance, with and without bronchoconstriction, was seen with a 70% xenon/30% oxygen mixture when compared with a 70% nitrogen/30% oxygen mixture used as a control. This effect was not observed when the study was repeated with a 70% N_2O /30% oxygen mixture. Nonsignificant increases in peak and mean airway pressures were seen with both xenon and N_2O .

Lachmann *et al.* compared the effects of 70% xenon/30% O_2 and 70% N_2O /30% O_2 on lung mechanics. These workers demonstrated that expiratory lung resistance was higher in both the xenon and N_2O groups compared with baseline, but there was no significant difference between the two groups [43]. Oxygen saturation decreased below 92% in eight patients in the N_2O group but not in any patient in the xenon group. They concluded that there was only slight deterioration in lung mechanics during xenon anaesthesia, and suggested that it can be used safely in older patients and those with chronic lung diseases.

Diffusion hypoxia (Fink effect)

If a patient who has been breathing a gas mixture rich in N_2O then abruptly switches to room air, a reduction in arterial oxygen partial pressure is seen, known as diffusion hypoxia or the Fink effect. As the alveolar N_2O tension diminishes, rapid equilibration with mixed pulmonary capillary blood releases N_2O into the alveoli, whilst nitrogen diffuses only slowly in the opposite direction. The expired volume can exceed the inspired volume as the alveoli are flooded with N_2O and the alveolar concentration of oxygen is reduced, causing a decline in arterial oxygen saturation. A similar phenomenon with xenon may also occur. This has been anecdotally suggested in Russian work where 100% oxygen had not been administered at the end of the period of xenon anaesthesia; some volunteers experienced periods of reduced levels of consciousness during recovery [6].

The arterial partial pressure of oxygen has, however, recently been studied in pigs during the elimination phases of both xenon and N_2O [44]. It was found to decrease less with xenon than with N_2O and the authors concluded that diffusion hypoxia with xenon was unlikely to occur. An explanation may be that where diffusion of gas across a blood or water film occurs, the main factor determining the diffusion rate is the solubility of the gas in the liquid. Since the blood/gas partition coefficient of xenon is much lower than that of nitrous oxide, then xenon may diffuse into alveoli more slowly than N_2O in a potential diffusion hypoxia situation.

Cardiovascular

In studies on human volunteers during clinical anaesthesia xenon appears to produce cardiovascular stability with no significant changes in myocardial contractility as assessed

by echocardiography, cardiac index, blood pressure or systemic vascular resistance [5–8, 10]. Examples of such studies include one in which 70% xenon in oxygen was compared with 70% N₂O in oxygen. The xenon mixture resulted in cardiostable anaesthesia with much reduced requirements for fentanyl during gynaecological, plastic and orthopaedic surgery [5]. In another study, there were no observed haemodynamic changes during different inhaled concentrations of xenon of 30, 50 and 70% in acutely instrumented laboratory animals [10]. In many studies the heart rate has been reported to have a tendency to decrease with increased variability of the cardiac rhythm as this slowing occurs [7–9]. This phenomenon has also been noted by Marx *et al.*, although their findings were not statistically significant [10]. These minimal cardiovascular effects of xenon in oxygen are in contrast to current volatile agents which can all produce a decrease in arterial blood pressure; halothane and enflurane also decrease cardiac output [45, 46].

The mechanism of heart rate reduction in humans is not yet known and in a recent report it has been suggested that xenon actually attenuates the myocardiodepressant effect of isoflurane [11]. In animal models, all current routinely used anaesthetic agents depress ion currents in isolated ventricular myocytes. In contrast, when tested at a concentration of 80%, xenon was found to have no inhibitory effect on cardiac ion channels for calcium, sodium and inward potassium flow [47].

Cerebral blood flow (CBF) during xenon anaesthesia has been well investigated in connection with its applications in neuroradiology. However, there seems to have been very little research on the effects of xenon on blood flow to other regions of the body. Though somewhat limited, a study by Lachmann *et al.* is the only work in this area known to us [48]. They examined the effects of three different anaesthetics on the cardiac output and the blood flow through the brain, liver, kidneys and small intestine in pigs. Each animal received three types of anaesthetic in random order: (a) 66% N₂O in oxygen supplemented with 1% halothane; (b) 70% xenon in oxygen with no opioid or volatile agent supplementation; and (c) a combination of thiopentone and fentanyl, the doses of which were not given. The xenon was noted to produce the highest regional blood flow in all these organ groups when compared with the other anaesthetic regimens. Interestingly, the largest percentage increase was seen in cerebral blood flow.

Cerebral blood flow and intracranial pressure

Inhaled stable xenon can be used to enhance computerised tomography (CT) images and the radioactive isotope ¹³³Xe can be used to measure cerebral blood flow. Despite its clinical utility, the safety and accuracy of xenon-enhanced

scanning has been questioned because there have been inconsistent reports of its effect on cerebral blood flow. In awake monkeys, stable xenon (33% inhaled concentration) reduced CBF by 12% and cerebral oxygen consumption by 16% but had no effect on either parameter when the animals were anaesthetised with fentanyl [49]. In another study, however, xenon (80% inhaled concentration) produced anaesthesia and a 50% increase in CBF [50]. In experimental freeze-induced intracranial hypertension, xenon 33% did not increase intracranial pressure [51].

Investigations carried out on human volunteers using xenon (33% inhaled) have demonstrated an increase in CBF [52]. In acute head injury patients, an increase in ICP and reduction of cerebral perfusion pressure has been reported during inhalation of 33% xenon although no cerebral oligoemia or ischaemia resulted from this. The authors concluded that xenon-enhanced CT scanning was safe as long as hyperventilation was employed to protect against any rise in intracranial pressure [53]. Inhalation protocols are being developed to shorten the period of xenon inhalation for enhanced CT scanning because of the possibility of increased CBF [54].

A transcranial Doppler study in humans has also registered regional increases in blood velocities of some cerebral arteries during 65% xenon in oxygen anaesthesia for abdominal surgery [8]. Xenon cannot be recommended as a suitable anaesthetic for neurosurgical procedures on the basis of current knowledge.

The discrepancy between the results in primates and humans may be explained by interspecies variation in the sensitivity to xenon. Indeed, the MAC of xenon in Rhesus monkeys is reported to be 98% whilst in humans it is 71% [55, 56]. Since MAC values for other anaesthetic agents seem to be similar between species, this discrepancy is unusual. It may reflect the fact that previous MAC studies have used relatively small sample sizes due to the extreme cost of using xenon in nonbreathing circuits. The MAC value for monkeys for example is derived from the study of just seven animals. We are aware that larger MAC studies are in progress in the United Kingdom to clarify the value in humans with a greater degree of confidence. Russian experience suggests that a 60% xenon concentration produces clinical anaesthesia in humans under conditions of minor surgical stimulus [6].

Renal

We are not aware of any studies concerning specific renal effects apart from that of Lachmann *et al.* suggesting increased renal blood flow [48].

Endocrine/neurohumoral

In a Russian study, 38 surgical patients received anaesthesia with either N₂O or xenon in oxygen with supplementary

doses of fentanyl as required according to a protocol. Patients' lungs were ventilated using a muscle relaxant to facilitate tracheal intubation and mechanical ventilation. Plasma concentrations of ACTH, cortisol and prolactin were measured using radio-immunological methods. There was a higher fentanyl requirement in the N₂O group and the concentrations of all these hormones were increased in both groups. The authors concluded that xenon does not impair the stress response to surgery [57].

Boomsma *et al.* in a similar experiment compared the cardiovascular stability of xenon anaesthesia with N₂O in humans [5]. Incremental doses of fentanyl were given during anaesthesia if the arterial blood pressure rose by more than 20% above the pre-anaesthetic value, with more being required in the N₂O group. Several different surgical procedures were performed and plasma concentrations of dopamine, adrenaline, noradrenaline, cortisol, prolactin and growth hormone were measured on up to 11 occasions before, during and after anaesthesia. Perioperatively, plasma noradrenaline and prolactin increased in both groups. In contrast, adrenaline and cortisol increased in the N₂O group but remained unchanged in the xenon group. Growth hormone reduced to less than control values in the xenon group but not in the N₂O group; dopamine was unchanged in both. Postoperatively, concentrations of noradrenaline, adrenaline, cortisol and prolactin were increased in both groups and dopamine was raised in the N₂O group. All values returned to normal over a 220-min postoperative measurement period.

To control for the differences in surgical stimuli in such experiments, Marx *et al.* recently investigated plasma dopamine, adrenaline and noradrenaline concentrations in pigs mechanically ventilated with varying concentrations of xenon and subjected to a standard surgical stress [10]. These were compared to a control group receiving total intravenous anaesthesia with pentobarbitone and an identical surgical stimulus. Both groups received a single dose of buprenorphine analgesia. Depth of anaesthesia was held as constant as possible by assessment of spectral edge frequency. Whilst dopamine and noradrenaline concentrations remained within normal limits, it was noted that adrenaline concentrations were significantly reduced in all the xenon groups. This included those receiving concentrations of less than 1 MAC (50% and 30%) [10].

In volunteers, nitrous oxide and halothane have been reported to increase sympathetic nerve activity and increase plasma noradrenaline concentrations [58]. Similar effects are seen with isoflurane and desflurane [59]. Dramatic sympathetic activation can be observed when there is a rapid increase in the inspired desflurane concentration [60]. It has been suggested that this might be an effect

due to the pungency of the agent or to the rapid wash-in characteristics of desflurane. Xenon has a three-fold lower blood/gas solubility than desflurane with extremely rapid wash-in characteristics. A rapid change from 0 to 70% xenon concentration in the work by Marx *et al.* failed to produce any such sympathetic reaction however, suggesting that the rapidity of wash-in alone does not account for this phenomenon [10].

Studies on toxicity

Haematological

It is now well known that nitrous oxide has haematological, fetotoxic and neurological effects with prolonged exposure due to its interaction with vitamin B₁₂ [16–20]. There are few such studies on xenon, although due to its low reactivity such effects are unlikely. In a Russian experiment, dogs inhaled a mixture of 80% xenon and 20% oxygen for 2 h every 3 days for a period of 2 weeks. The authors stated that there were no toxic effects on the basis of their functional, biochemical, haematological and morphological findings [61]. One study investigating mechanisms of anaesthesia has shown that aggregation of platelets is inhibited by nitrous oxide but potentiated by xenon. These effects, however, only become statistically significant at greater than two atmospheres of pressure so these effects may only be of importance to deep-sea divers breathing specialist gas mixtures [62].

Fetotoxicity

In one study, four groups of pregnant rats were subjected to mixtures of oxygen, oxygen and nitrogen, oxygen and xenon and oxygen and N₂O for 24 h. Twenty days later, the fetuses were examined and in the first three groups the incidence of microscopic organ abnormalities such as hydrocephalus and gastroschisis was 1–3%. In the nitrous oxide group, however, the incidence was very significantly higher at 15%, with an incidence of skeletal abnormalities of 37% [63]. Nitrous oxide may be teratogenic because of metabolite formation, an effect on blood flow through the uterus or its well known effects on vitamin B₁₂ biosynthesis. Since xenon is at least as potent as nitrous oxide, the mechanism for teratogenicity of nitrous oxide is not related to the intrinsic mechanism of anaesthesia.

Other

Rabbits exposed to 50–70% xenon for 48 h show no microscopic changes in any organs [64]. Biochemical investigation of patients before and after xenon anaesthesia has shown no pathological changes [65].

Malignant hyperthermia

There is evidence emerging to suggest that xenon does not trigger malignant hyperthermia. Muscle specimens from

16 patients susceptible to malignant hyperthermia have been exposed to xenon. Such samples typically show lower contracture thresholds to agents such as caffeine and halothane. When exposed to xenon, none of these samples demonstrated any similar effects and no evidence was obtained to suggest that xenon triggers malignant hyperthermia in humans [66].

N₂O, by comparison, may be a weak triggering agent although it is considered by some to be safe for use in susceptible patients. There has been at least one reported case of nitrous oxide triggering the condition [67].

Diffusion into enclosed spaces

It is well known that N₂O can diffuse into and enlarge closed spaces such as the bowel, pneumothoraces, the middle ear and tracheal tube cuffs. An enclosed space containing air can enlarge in the presence of an inhaled N₂O/oxygen (i.e. nitrogen-free) mixture because it will diffuse into the space about 25 times faster than the nitrogen present can diffuse out. The theoretical maximum increase in volume of the gas within the gut when breathing a 66% N₂O/33% oxygen mixture is 200%. Xenon accumulation in the bowel has been demonstrated in pigs during anaesthesia [68]. Differences in gas density have only small effects on the rate of diffusion but where gas transfer across blood or water films is concerned, the major factor determining diffusion rate is the solubility of the gas in the liquid. The blood/gas partition coefficient of N₂O is 0.47 but the value for xenon is only 0.14, so it is likely that this phenomenon will be observed with xenon but to a lesser degree than is currently seen with N₂O.

Metabolism/elimination

Xenon is a noble gas and under special conditions it is capable of forming compounds with very reactive elements. Known compounds include clathrates, fluorides, chloride fluorides, chlorides, oxides, oxyfluorides, xenates, fluoroxenates, perxenates and complex salts. Enzymic reactions have also been observed. It is extremely unlikely that xenon is involved in any biochemical reactions when used as an anaesthetic, although the possibility cannot be ruled out completely [69].

Elimination of xenon is mainly through the lungs and this aspect has been studied by Luttrupp *et al.* in animals ventilated with 100% oxygen after a period of 2 h of 70% xenon anaesthesia. In pigs of 37–39 kg, it was estimated that it took 5–10 min to recover 1 litre of xenon in expired air, 15–20 min to recover another litre and 30 min to recover a third litre. In the pig in whom xenon washout was studied the longest, about 4.4 l had been recovered after 4 h of oxygen breathing [21].

Nonanaesthetic medical uses of xenon

For more than 30 years xenon has been used for investigation of cerebral blood flow as a whole or for mapping the different vascular regions of the brain [70, 71]. Xenon has been applied in two forms — as a stable radiodense molecule for xenon-enhanced computed tomography (Xe/CT) or as the radioactive isotope ¹³³Xe for extracranial detection of its clearance. It can be given by intracarotid injection, intravenous injection or by inhalation [71–73]. The estimation of the cerebral blood flow by xenon clearance is based on the principle that the uptake and clearance of an inert diffusible gas is proportional to the blood flow in the tissue.

Xenon also has potential as a contrast agent in magnetic resonance imaging (MRI) since it can be 'hyperpolarised' by laser light to give off strong MRI signals [74]. When dissolved in suitable fluids and injected, the image quality is similar to that currently obtained with radioisotopes.

The use of xenon in neuroradiology has been an important tool in studying regional variations in cerebral blood flow in occlusive cerebrovascular disease, dementia and psychiatric disorders. Xenon has also been used to monitor changes in CBF in patients with severe head injuries [75] and to study cerebral perfusion during anaesthesia [76].

Anaesthetic use: clinical experience

In 1951, Cullen used xenon on an 81-year-old having an orchidectomy [77]. After 10 min pre-oxygenation, the xenon was then administered at 80% concentration and the patient lost consciousness in 3 min. Surgery began 10 min after the anaesthetic started. At the end of the anaesthetic the patient was conscious after 2 min and fully orientated within 5 min.

During radiological investigations it has been noticed that xenon in concentrations of more than 50% can lead to euphoria which can progress to respiratory depression and loss of consciousness. A common observation in such investigations with ≈ 33% xenon is that the respiratory rate slows and the tidal volume tends to rise, partially compensating for this [36]. Owing to its very low blood/gas solubility coefficient, one would expect the onset of anaesthesia to be very rapid. In one study, 24 patients were premedicated with 0.05 mg.kg⁻¹ of midazolam and asked to take vital capacity breaths of 1 MAC xenon or sevoflurane in oxygen until they lost consciousness [13]. The patients breathing xenon lost consciousness more rapidly than those receiving sevoflurane, mean (SD) induction times being 71 (21) s and 147 (59) s, respectively. In this study, the respiratory rate and tidal volume were reduced in both groups but this was less apparent in the xenon group [13].

Four stages of xenon anaesthesia have been described from observations on 12 patients in a Russian study in which 70% xenon/30% oxygen was administered [6]. The first is a stage of paraesthesia and hypoalgesia with a 'pins and needles' sensation all over the body. The second stage is euphoria, with increased psychomotor activity as if the subjects were trying to share their feelings with observers. At this stage subjects tried to remove the mask and did not follow commands although they had full recollection of the commands that were given. The third stage is described as analgesia and partial amnesia and this occurs by the third or fourth minute. The fourth stage is the stage of surgical anaesthesia; a degree of muscle relaxation is seen with pronounced diaphragmatic breathing. In this study all the patients woke up within 2 min and were fully conscious within 4 min. As they first started to regain consciousness the patients were initially disorientated and reported feeling that they were in an unknown environment where all the observers appeared as manikins. The pain threshold took longer to return than did full consciousness, being back to normal by 10–12 min after cessation of xenon administration [6].

In a recent Japanese study, recovery times were recorded in humans after approximately 2 h of anaesthesia with three different anaesthetic regimens: 60% xenon, 60% N₂O + 0.5% isoflurane, 60% N₂O + 0.7% sevoflurane. The mean (SD) times taken until the patients could count backwards from 10 to 1 in less than 15 s were; 6 (1.6), 14.3 (2.8) and 10.5 (2.5) min, respectively [14].

It has also been suggested that fast emergence from xenon anaesthesia is seen regardless of the duration of the anaesthetic and this is consistent with its low blood/gas partition coefficient [78].

Xenon has been used in anaesthesia for many different types of surgery, including general, gynaecological and orthopaedic operations. It has also been used for at least one Caesarean section without any reported problems [65, 79].

Analgesic effects

A comparison of the anaesthetic efficacy and potency of a 70% xenon/30% oxygen mixture in comparison to a 70% N₂O/30% oxygen mixture was performed by Lachmann *et al.* [43]. In this study, the xenon group required only one-fifth of the amount of fentanyl required by the N₂O group in order to attain predetermined haemodynamic stability targets. It must be noted in this study, however, that equi-MAC concentrations of the agents were not compared. Luttropp *et al.* found that the mean dose of fentanyl needed to supplement xenon anaesthesia was rather low, and supports the previous findings of Boomsma *et al.* who also concluded that xenon is a potent analgesic [5, 9].

Experiments have also been carried out to investigate the analgesic properties of xenon at subanaesthetic concentrations. A Japanese study examined the effect of 0.3 MAC of either xenon or nitrous oxide on pain threshold and auditory response time. There was no difference in analgesic effect between the two groups. When compared to 100% oxygen, the response time to auditory stimuli was prolonged with xenon but not with nitrous oxide. The analgesic effects of neither gas were reversible with naloxone [80]. A Russian report describes the use of xenon for the treatment of angina pain and for analgesia during painful changing of dressings [6].

Potential ways to make xenon anaesthesia economically acceptable

Reduce manufacturing cost

The low concentration of xenon in air means that xenon recovery is only practicable where there are large air separation plants producing over 1000 tonnes of oxygen per day. Russia extracts 25–30% of the world's xenon. It is noteworthy that although all their oxygen plants have the facility to extract xenon this process only takes place in about half of them. A 1000 tonne per day oxygen plant will only produce around 4 cubic metres of xenon per day, obtained as a concentrate in combination with krypton. Owing to the small volumes involved at this point in the process, the final separation from krypton is currently done on a laboratory scale. The current cost of manufacture is US\$10 per litre and £10 per litre in the UK. World production is around 6 million litres a year. By 2001 this value is predicted to rise to 9.5 million litres, and all manufacturers have announced an increase in manufacturing capacity. Three million litres of this, however, will be for aerospace use in the near future. Ionised xenon will be used to produce thrust to manoeuvre satellites, and also to counteract static electricity build up on the international space station. Most of the gas used in these ways will be lost from the atmosphere forever. In the medium term the cost may therefore not fall despite increased production, and in the extreme long-term xenon could become even scarcer. Increasing production rate of a commodity can often lead to a decrease in unit cost; however, the prospects for making xenon affordable for anaesthesia in this way are by no means certain. Approaches based on very efficient breathing systems and/or recovery devices will also be required.

Use of semiclosed systems

Studies have been conducted in Russia with 70% xenon/30% oxygen anaesthesia in spontaneously breathing patients via face mask and laryngeal mask airway, using a xenon fresh gas flow of 2 l.min⁻¹. Whilst effective as an anaesthetic technique, this equates to a cost in the UK of

£1200 per hour and was abandoned as being uneconomic [15]. Several patents exist for similar mask-based systems with suggested uses including dental anaesthesia and inhalation analgesia. One interestingly describes the use of a xenon/oxygen/helium mixture for inhalation analgesia [27]. The helium is suggested as a way of compensating for the high density of xenon and although good in theory is likely to be prohibitively expensive in practice. This is unfortunate as xenon might otherwise be an ideal inhalation analgesic in childbirth and dentistry.

Use of very low flow systems

Due to the high cost of using a xenon fresh gas flow of $21 \text{ l} \cdot \text{min}^{-1}$, the same Russian team then conducted studies at lower fresh gas flows. Patients were anaesthetised intravenously, given a muscle relaxant and had a tracheal tube placed. Their lungs were mechanically ventilated through a fully closed circle system and bellows which had been previously primed with a 70% xenon and 30% oxygen mixture. The volume of gas in the circle at this point was ≈ 1.3 times the vital capacity of the lungs of the patient with the bellows inflated. The patients were ventilated for 2 min from this system before any more fresh gas was added. The purpose of this priming manoeuvre was to allow a rapid increase in inspired xenon concentration to around 1 MAC without wastage of gas. If the patient had been connected to the circle before the xenon was added, it would have been necessary to flush the circle with xenon to achieve a 70% xenon concentration rapidly which would have necessitated wastage of xenon via the spill valve. After 2 min, the system was then operated as a low-flow circle, with a fresh gas flow of $0.31 \text{ l} \cdot \text{min}^{-1}$ oxygen and $\approx 0.31 \text{ l} \cdot \text{min}^{-1}$ xenon being used, representing a xenon use of $16\text{--}18 \text{ l} \cdot \text{h}^{-1}$. This equates to a cost in the UK of £160–£180 per hour and probably represents the lowest cost xenon anaesthetic achievable with near-conventional anaesthetic equipment and techniques [15]. It is, however, still uneconomic when compared with the cost of current anaesthetic regimens.

Use of fully closed systems

A standard circle system can be used fully closed if the fresh gas supply is constantly adjusted to exactly match uptake by the patient. In practice this is time consuming and a degree of automation of this process might be desirable. Three fully closed breathing systems have been described suitable for xenon anaesthesia with varying degrees of automation of the delivery process.

Gas piston

This arrangement consisted of an anaesthesia circle system with carbon dioxide absorber and one-way valves, a ventilator supplying oxygen as the driving gas to the

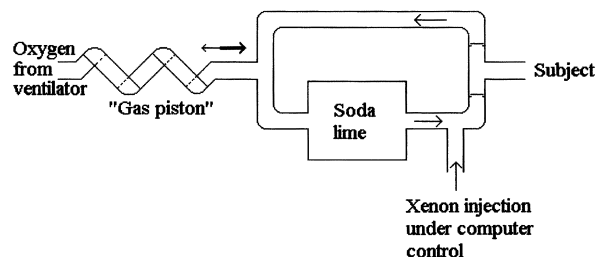


Figure 1 Gas piston or exchanger based system: a conventional circle system with carbon dioxide absorbent and one-way valves is connected to a ventilator by a long hose or 'gas piston', through which oxygen enters the circle to match uptake. This net flow opposes the tendency of the circle contents to diffuse back towards the ventilator, so rendering the system functionally closed. Xenon is added under computer control.

circle and a large dead space (gas piston) in the form of a long tube between ventilator and circle (Fig. 1) [9, 21]. As oxygen is consumed from the circle by the patient, there is an overall net flow of oxygen along the gas piston from the ventilator towards the circle. This offsets the tendency of any other gas or volatile agent in the circle to diffuse back up the gas piston towards the ventilator expiratory outlet. If designed correctly therefore the system becomes functionally, though not physically, closed. Aliquots of xenon have been injected into such an arrangement under computer control to successfully create an automatic fully closed xenon administration system, which has been used in both animals and humans. The mean (SD) volume of xenon used in humans of mean weight 72.4 kg was 6.5 (1.0) litres in the first 15 min, 8.9 (1.6) litres for the first hour and 9.6 (0.5) litres over 2 h. It was considered that these figures might be further improved upon, as there may have been a small loss of xenon through the gas piston and by diffusion through the circuit. The cost therefore is less than that when using a semiclosed circle. It should be noted that the xenon requirement is very high in the first 15 min and then settles to a much lower value.

Physioflex device

This is a fully closed circle anaesthetic machine (Fig. 2) [22]. In place of the traditional bellows, it has a series of moving diaphragms, which allow an integral computer to be aware of the volume of the system as well as control mechanical ventilation. The volume of the system is less than 4 l and into this the computer delivers aliquots of oxygen, air, N_2O and volatile agent as required after analysis of the constituents of the circle. The fresh gas flow is equal to the patient uptake. A fan propels gas around this circle at $70 \text{ l} \cdot \text{min}^{-1}$ rendering the usual one-way valves unnecessary and to promote even gas mixing. The anaesthetist merely has to set the desired end-tidal

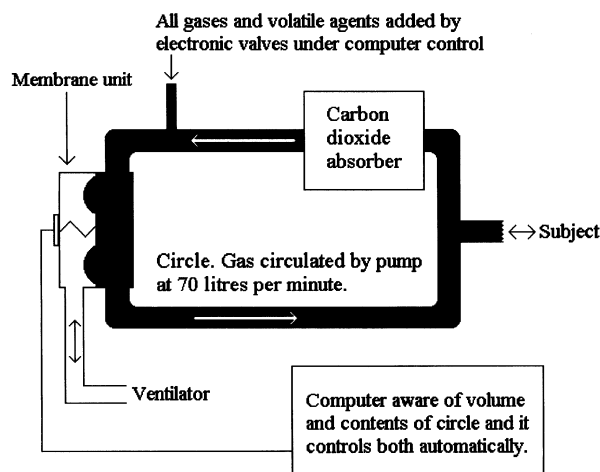


Figure 2 Physioflex device (basic principle). Gas is circulated by a pump around a circle system containing a carbon dioxide absorber at $70 \text{ l} \cdot \text{min}^{-1}$, rendering one-way valves unnecessary. A ventilator drives the circle through a series of flexible diaphragms. A computer monitors the volume and contents of the circle and modifies both by injection of appropriate volumes of gas or volatile agent.

concentrations of all constituents within the circle on the computer. Several machines have been modified by fitting an additional electronic valve to deliver aliquots of xenon. To rapidly achieve a high inspired xenon concentration, however, xenon has to be flushed into the system causing initial wastage before running fully closed for maintenance of anaesthesia.

Balanced circle system

Another suitable fully closed breathing system has been described (Fig. 3) [31]. This consists of a closed breathing system of low volume with a carbon dioxide absorber. Connected to this is a bellows within bottle arrangement, which is actuated by a mechanical ventilator using oxygen as the driving gas delivered to the bottle. When running fully closed, oxygen is consumed from the breathing system by the patient via the lungs, which causes the bellows to slowly empty with time. A valve arrangement is fitted to the bellows in bottle such that at each end-inspiration a small aliquot of oxygen, typically 20 ml, is added via a visible flow indicator into the closed part of the system. For use with xenon, a computer-controlled feedback system similar to that described by Luttrupp *et al.* could be used [21]. The device has some similarities to the gas piston arrangement but is mechanically closed rather than functionally so. It has a moving bellows, which is reassuring to the anaesthetist, and the addition of oxygen is visible rather than assumed. An advantage of the bellows is that it can be primed with xenon at the start of an anaesthetic, as has been described by the Russian workers,

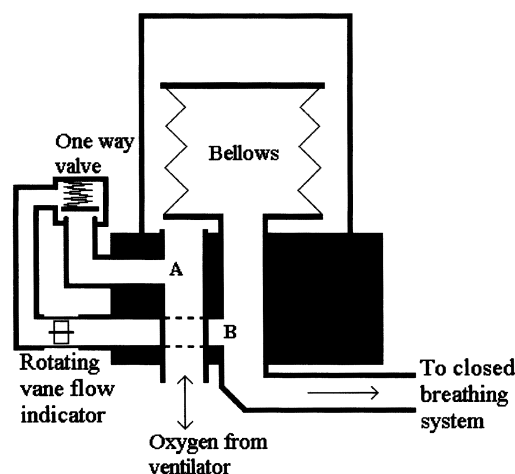


Figure 3 Balanced circle. A bag in bottle arrangement is connected to a closed breathing system with carbon dioxide absorber (not shown), and driven with oxygen from a ventilator. The pressure at A is equal to the pressure at B unless the bellows empties fully. Once balanced, this occurs at each end-expiration whereupon pressure $A > B$ and aliquots of oxygen are added to the closed system through a one-way valve, matching uptake from it. Gases such as xenon added to the breathing system under computer control cannot escape, however, as it is fully closed.

producing a rapid initial rise in xenon concentration whilst the system remains closed. This is in contrast to the Physioflex which requires a flush of xenon, or the gas piston in which this may be difficult to achieve without xenon spillage.

Other technologies to reduce cost

Reclamation devices

Even if fully closed systems are used, it is likely that occasional flushes of the circle system with xenon will be required, either to permit an initial rapid rise in the circle xenon concentration, or to remove accumulations of gases such as nitrogen, methane and acetone, for example, which can dilute the xenon down to a subanaesthetic concentration. Because of this there are two research groups looking at xenon retrieval technologies to allow recovery of this wasted xenon. The first group is at the University of Ulm, Germany [23, 26]. In this device, waste gases are passed through a filter system consisting of a cooling trap, activated charcoal and molecular sieves to remove all volatile substances. The remaining oxygen/nitrogen/xenon mixture is compressed to 60 atmospheres and cooled to below 16°C such that only the xenon liquefies. The liquid xenon is transferred to another container for re-use. Recent testing in pigs in conjunction with a partially closed rebreathing system allowed 67% of the xenon to be recovered, at a purity of 89%.

The second group is based at the Botkin Hospital,

Moscow, Russia [15, 25]. In this device several containers of adsorbent such as charcoal, each the size of a coffee mug, are cooled in liquid nitrogen and evacuated by a pump. Waste gas is slowly passed through them and all the constituents solidify. The containers are then allowed to warm up very slowly and the xenon boils off first. This passes to an evacuated gas cylinder also cooled in liquid nitrogen. When this cylinder is then allowed to warm to room temperature, the xenon within pressurises the cylinder rendering it ready for reattachment to the anaesthetic machine. It is claimed to produce > 99% purity xenon but the percentage xenon recovered is not known.

Circle priming

A study from Japan has described a technique for priming a circle with xenon before use which minimises the wastage which can occur if a xenon flush is used to achieve this objective with a normal circle [24]. A specially modified circle is filled with oxygen and by use of valves is temporarily functionally arranged as a long tube. Three litres of xenon are injected using a special syringe such that this tube is just filled to its distal end with xenon. By rearrangement of the valves the system is then converted back to an anaesthesia circle ready for use.

Measurement of xenon concentration

Many proposed xenon delivery systems rely on computer control of the xenon concentration. Xenon can be added to dilute down the measured oxygen concentration to a desired value and this has been done successfully [21]. However, it would be desirable in a commercial machine to also measure the xenon concentration. Being a noble gas, conventional methods cannot be used and only methods based on its physical properties can be applied. The Dräger Physioflex device initially used a mass spectrometer. This was effective but far too expensive. Other lower cost devices have included piezoelectric adsorption [21], thermal conductivity and ultrasound [32]. The piezoelectric method depends on adsorption of gas into an oil film on an oscillating quartz crystal, so changing its frequency of oscillation. The thermal conductivity method exploits the fact that xenon conducts heat far better than any other gas likely to be found in the breathing system. The ultrasonic method has been successfully used recently for the first time and exploits the fact that xenon as a very dense gas will conduct sound faster than any other gas likely to be found in the breathing system.

Environmental issues

Nitrous oxide is a so-called 'greenhouse gas' and more than 20 billion litres are used every year in Europe. It constitutes

up to 10% of all the chemical pollutants in the atmosphere. Ten per cent of all nitrous oxide emissions are thought to derive from anaesthesia [15]. Ultraviolet light from the sun causes it to be degraded, forming NO_x radicals which damage the ozone layer. An international agreement on reduction of such emissions was settled in the Kyoto Conference in 1997. The anaesthetic volatile agents halothane, isoflurane and enflurane are H-CFCs and also contribute to depletion of the ozone layer. The annual European production of all volatile agents exceeds 10 000 tonnes or 1.6 billion litres [15]. It was initially thought in the 1980s that anaesthetic H-CFCs played a very minor part in ozone depletion but more recent calculations suggest that they cannot be ignored. H-CFCs were therefore included in international protocols in 1992 [81]. The main protocol of this type, the Montreal protocol, states that by the year 2030 the production of these partly halogenated hydrocarbons should be stopped entirely. One hundred and sixty-five countries representing greater than 80% of world production of these agents have now ratified this protocol.

Politicians are now taking these problems seriously and steps already taken include a ban on fluorocarbons as propellants for aerosol containers. In Germany, research into the use of xenon in anaesthesia is currently being funded by the Federal Foundation for the Protection of the Environment.

Conclusion

Xenon is an inhalational analgesic and anaesthetic agent of sufficient potency to require minimal supplementation. It results in very rapid onset, and recovery from, anaesthesia. It is not subject to biotransformation and appears to be the most cardiostable anaesthetic agent known. It has been used in anaesthesia for many different types of surgery, e.g. general, gynaecological plastic and orthopaedic. It fulfils almost all the criteria of the ideal anaesthetic agent and so, despite its cost, continues to be of considerable anaesthetic interest. Technological advances will soon make economical delivery systems a practical possibility and it may even become possible to recycle this gas. Owing to environmental concerns alone there may turn out to be no alternative but to develop the technology for using this gas even if this incurs a moderate increase in cost. There is a certain attraction in retrieving a gas from the atmosphere for anaesthesia and then allowing it to return there, unchanged in any way.

The process of legal approval for xenon as an anaesthetic agent was started in Europe in 1996.

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