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Scientific Program

9:00 – 9:05	**Welcome** Ed van der Veen *Amsterdam, The Netherlands* Stephan A. Loer *Amsterdam, The Netherlands*
9:05 – 9:20	**Introduction: Historical perspectives of medical gases** Jaap J. de Lange *Amsterdam, The Netherlands*
Session I	Armand Girbes *Amsterdam, The Netherlands* Kai Zacharowski *Bristol, U.K.*
9:20 – 10:00	**iNO – label or branding?** Claes Frostell *Stockholm, Sweden*
10:00 – 10:40	**Inhaled carbon monoxide (CO) –poison or therapy?** Stephan Stephan A. Loer *Amsterdam, The Netherlands*
10:40 – 11:00	Coffee break
Session II	Victor W.M. van Hinsbergh *Amsterdam, The Netherlands* Piet E. Postmus *Amsterdam, The Netherlands*
11:00 – 11:40	**What can O_2 really do?** Andrea Kurz *Bern, Switzerland*
11:40 – 12:20	**Helium/Oxygen – the discovery of the known?** Peter Germann *Vienna, Austria*
12:20 – 12:50	Lunch break

Session III	Cor J. Kalkman *Utrecht, The Netherlands* Jan Rauwerda *Amsterdam, The Netherlands*
12:50 – 13:30	**Nitrous oxide – old friend, new fellow?** Jörg Weimann *Amsterdam, The Netherlands*
13:30 – 14:10	**Xenon – a neuroprotectant for the future?** Mervyn Maze *London, U.K.*
14:10 – 14:20	**Closing remarks** Jörg Weimann *Amsterdam, The Netherlands*

Nitric oxide inhalation – label or branding?

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Background

Inhalation of nitric oxide (iNO) has been tried clinically in many ICUs since 1992 when first case reports were discussed. The initial main aims were to improve gas exchange and/or selectively reduce lung vascular constriction (1-3). These acute pharmacodynamic effects are caused by vasodilatation of pulmonary vessels, mainly in lung regions open to ventilation. The observed rapid improvement in oxygenation is a result of reduced extrapulmonary shunting, intrapulmonary shunting, or the combination of both. Subsequent studies have indicated that in addition other more discrete extrapulmonary pharmacodynamic effects may be seen as a result of administration of iNO. Among them are modification of renal function in piglets (4) and man (5), modification of expression of nitric oxide synthase in the liver and kidney in rats (6) or modification of tissue injury in the myocardium (7), interaction with the steroid receptor outside the lung (8), and probably more.

Clincal use in paediatric medicine

Clinical use of iNO is at present approved in the USA and European Union only for severe hypoxaemic respiratory failure in the term or near-term newborn (9). This approval is based upon a demonstrated rationale of acutely reduced lung vascular constriction as a result of exposure to iNO, in turn causing reduced extrapulmonary and intrapulmonary shunting. In addition long-term follow-up studies have confirmed a favourable safety profile, with minor or no increase in adverse events in neonates exposed to iNO (10). The two multi-centre studies which serve as a base for these conclusions, were conducted in North America in centers with access to ECMO. The primary endpoint included a reduction in the need for ECMO in the intervention arm, giving evidence that iNO indeed improved oxygenation (11). However reduced mortality was not demonstrated. A recent Cochrane review has examined these studies and did end up with a similar conclusion (12).

iNO has also been extensively studied as an adjunct to therapy of prematurely born babies, with the aims to improve oxygenation and

minimize the development of CLD (chronic lung disease). Recently two American multicentre studies on the use of iNO in premature babies were published, yielding interesting data on the endpoint of reducing the incidence of CLD (13, 14). One of them demonstrated a slightly reduced incidence of CLD. The other failed on that main endpoint, but found indications of other benefits to a subgroup of infants. This again demonstrated how complex the clinical condition of premature babies is and how difficult it is to come to a more definite conclusion in relation to use of iNO. At present it can be stated that there is still not rational to administer iNO to premature babies outside the scope of further clinical trials.

Clinical use in adult medicine.

In the 1990s a massive exposure of patients with ARDS and ALI took place in many ICUs in the developed countries, often using unapproved industrial quality gas. This clinical use was based on enthusiasm over rapid partial improvement of gas exchange in a majority of patients exposed to iNO during mechanical ventilation (1). When data from more controlled larger studies became available, failing to identify any long-term benefits with iNO (15, 16), this use has gradually tapered off. However iNO has remained in use in some ICUs as a last desperate resort in situations characterized by high pulmonary artery pressures and severe hypoxaemia. There is also a rather large use of iNO during and after cardio-thoracic surgery in some centers, claiming as rationale a better control in states with postoperative hypertensive reactions. However there has so far not been possible to create evidence-based support for clinical uses of iNO on these indications. At a recent European consensus meeting formally endorsed by the European Society of Intensive Care Medicine and the European Association of Cardiothoracic Anaesthesiologists, it was concluded that such use of iNO should only be justified in extreme emergencies outside the scope of clinical trials (17). To summarize, at present there are no approved indications for clinical use of iNO in adult intensive care medicine.

The overall conclusion is that there is evidence for continued limited clinical use of iNO in hypoxaemic term newborns. All other clinical uses of iNO remain experimental and should be performed within clinical trials.

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Inhaled carbon monoxide (CO) –poison or therapy?

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CO toxicity

Carbon monoxide (CO) is a colourless, odourless, tasteless and non-irritating gas which arises during incomplete combustion of organic material. Common sources of toxic concentrations include car exhaust fumes, gas powered engines, heaters and smoke from fire. CO is readily incorporated into the circulation via the lungs, displaces oxygen from haemoglobin and may, in a dose dependent manner, lead to symptoms of intoxication or even death. While accurate epidemiologic data are lacking, CO is suspected to be responsible for more fatalities worldwide than any other toxic substance (1).

Oxygen and CO bind to identical sites of the haemoglobin molecule (2). With an affinity of about 200 times greater than oxygen (3,4), carbon monoxide displaces oxygen forming carboxyhaemoglobin. In addition, binding of CO causes a change in conformation of the haemoglobin molecule resulting in an increased affinity for oxygen at remaining binding sites, and thus shifts the oxygen-haemoglobin dissociation curve to the left (5). At the same time, CO inhibits mitochondrial cytochrome oxidase (6,7). Therefore, CO does not only substantially reduce the oxygen transport capacity of the blood but also impairs oxygen release as well as cellular respiration, readily leading to tissue hypoxia. Moreover, CO also binds to myocardial myoglobin which may cause cardiac decompensation further aggravating tissue hypoxia (8).

A wide variety of other cellular and molecular mechanisms of carbon monoxide toxiticity have been suggested which are beyond the scope of this abstract. These include formation of reactive oxygen and nitrogen species, interference with intracellular enzymes, effects on dopaminergic and serotonergic neural function, and release of excitatory amino acids.

The symptoms and severity of CO intoxication depend on the duration of exposure as well as on the concentration inhaled. Clinical signs of acute intoxication only correlate roughly with carboxyhaemoglobin (COHb) levels measured at hospital admission (1). Patients with COHb levels less than 10% are usually asymptomatic, while mild and unspecific symptoms such as headache, fatigue and dizziness may be observed with concentrations

between 10 and 20%. Higher concentrations can be associated with nausea, vomiting and impaired neurological function. Tachycardia and tachypnea may be present as a compensatory mechanism for tissue hypoxia. Occurrence of seizures, coma, hypotension and bradycardia can be expected with COHb concentrations above 50% while concentrations of more than 70 to 80% are usually fatal (8,9). Survivors of acute CO intoxication are, even after apparent recovery, at risk to develop delayed neuropsychiatric syndroms such as personality changes, psychosis, dementia or parkinsonism (10).

Removing the patient as quickly as possible from CO exposure is crucial. Breathing of pure oxygen to improve oxygenation and to displace CO from haemoglobin, further accelerating pulmonary elimination of CO, is considered the cornerstone of therapy (10,11). Whether hyperbaric oxygen treatment (HBO) is beneficial in severe CO intoxication is further under debate. (12-14). A recent meta-analysis concluded that HBO cannot be routinely recommended (15).

CO as a therapy?

In 1963 Coburn et al. discovered that carbon monoxide is produced in the body as a by-product of haeme-degradation (1). Haeme oxygenase (HO) is the rate limiting enzyme in the breakdown of haeme to free iron, biliverdin, and CO. So far, two HO isoforms have been described: the constitutively expressed HO-2 and the inducible HO-1. HO-1 is mainly induced by cellular stress, including hypoxia, lipopolysaccharide, and reactive oxygen species (2). In recent years, there is growing evidence for a cytoprotective role of the HO/CO pathway (3). This also includes administration of low concentrations of CO (0,005 – 0,05 vol%) via inhalation as a novel therapeutic intervention. Beneficial effects of CO inhalation have been shown in various animal models for various diseases such as hemorrhagic and endotoxic shock (4,5), acute lung injury induced by mechanical ventilation, hyperoxia, or bleomycine (6-8), and ischemia-reperfusion injury of liver, lung, heart, kidney, and bowel (9-13). However, these effects were not equivocal (14,15). In a first randomized, double-blind, placebo-controlled cross-over study in 13 volunteers receiving an intravenous injection of LPS Meyer et al. could not show any effect of inhalation of 500 ppm CO over one hour on vital parameters or inflammatory markers, i.e. plasma levels or expression of IL-6, IL-8, IL-10, TNF-α, CRP (16). The authors commented that the differences between their study and results obtained in animal models may be attributable to species differences (i.e.

differences in haemoglobin affinity for CO) and to the fact that they only studied male volunteers.

In conclusion, there is an increasing literature suggesting not only a role of endogenous CO to have anti-inflammatory, anti-proliferative, and anti-apoptotic properties but also that exogenous (inhaled) CO may be beneficial in certain diseases and may thus offer a novel therapeutic approach.

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32. What can O_2 really do?

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Introduction

In the perioperative period oxygenation might be impaired due to the anesthetics administered, the surgical procedure itself, as well as postoperative pain. Thus at least some oxygen is administered per routine to all surgical patients. Perioperative oxygen is easy to provide and inexpensive. In Europe most patients are given 30% oxygen during surgery. In the United States, the concentrations administered vary widely, ranging from 30% to 100%. Until today there exists no common agreement or general accepted guideline about an optimal inspiratory oxygen fraction and clinicians are well aware about potential risks of long-term supplemental oxygen administration. However, recent studies have shown that supplemental oxygen –for example, 80% oxygen- provides substantial benefit without any risks. The purpose of this review is to provide an overview about benefits and risk of supplemental oxygen administration in the perioperative period.

Recent findings

Supplemental oxygen improves immune function. Thus oxygen significantly increases the expression of all inflammatory cytokines such as IL-1β, IL-8, IFN-β, and TNF. Administration of 100% oxygen does not prevent the perioperative decrease in phagocytosis or bacterial killing; however it diminishes the decrease in each of these functions. As a consequence, phagocytosis and killing are better maintained in patients given 100% oxygen than in those given 30% oxygen.(1) Furthermore 80% inspired oxygen fraction almost doubles subcutaneous tissue oxygen tension and halves the rate of postoperative wound infections. (2)

Supplemental oxygen decreases the rate of postoperative nausea and vomiting after laparoscopic and open abdominal surgical procedures.(3) On the other hand, recently two more studies were not able to identify a positive effect of oxygen. 80 % oxygen did not decrease the incidence of PONV in patients undergoing thyroid surgery. (4) Thus the usage of supplemental oxygen to prevent PONV still remains unclear.

Cardiac complications during the perioperative period are common and may be associated with hypoxemia and tachycardia. Postoperative oxygen therapy has shown a possible beneficial effect on arterial oxygen saturation and heart rate not only in high-risk patients, but also in an unselected general patient population.(5)

Preconditioning with oxygen might improve organ function after liver transplantation, cardiac surgery and might furthermore improve outcome after spinal ischemic insults.

Supplemental perioperative oxygen administration is not associated with clinically important side effects. The best known and described oxygen side effect are atelectasis.(6) However, supplemental oxygen does not increase postoperative atelectasis in patients undergoing colon surgery

Experimental as well as clinical data suggest, that hyperoxic paO_2 (500-700 mmHg) leads to myocardial reperfusion damage; maintaining a more physiologic paO_2 during reperfusion following ischemia may attenuate injury. Hyperoxic reperfusion exacerbates renal dysfunction after 30 minutes of complete normothermic ischemia in rabbits. In contrast eubaric hyperoxemia improved neurological and neuropathological outcome after transient cerebral ischemia in rats. Continuous oxygen therapy offered the greatest benefit, while increased oxygen tension beyond 200 mmHg were of no further advantage.(7) The mechanism of benefit of hyperoxemia might involve the vascular component, with impaired autoregulation in the area of ischemia. Vasoconstriction due to a high paO_2 allows shunting of blood into the infarct from adjacent normal brain.

In humans, prolonged high oxygen exposure is reported to induce cough, shortness of breath, decrease vital capacity and increase alveolo-capillary permeability, finally leading to pulmonary intestinal edema and pulmonary fibrosis. Oxygen free radicals seem to play a key role in the pathophysiology of oxygen toxicity. However, the administration of 80% oxygen for less than 24 hours is considered safe; 100% oxygen at one atmosphere leads to irreversible damage after 6 days. However, these time ranges are far beyond oxygen treatment durations in anesthesia and surgery. Consequently direct oxygen toxicity only plays a negligible role in regards to perioperative oxygen administration.

Summary

Supplemental perioperative oxygen administration might be a simple, inexpensive and safe treatment option to improve patient outcome. The optimal inspired oxygen concentration still needs to be evaluated.

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Helium/Oxygen – the discovery of the known?

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History (1)

COOK registered in 1923 a helium/oxygen mixture called heliox with the US Patent Office. Alvan Barach first used it for medical purposes in 1934 and confirmed the biological inertness of helium by exposing mice to 79% helium and 21% oxygen for 2 months without deleterious effects. He reported the successful usage of helium-oxygen mixtures in four cases of asthma in adults and two cases of upper airway obstruction in infants. Of interest, the patients were relieved of their dyspnoea in 6 to 10 breaths, and when the helium was removed the dyspnoea came back in 3 or 4 breaths. Barach was the first to use helium to improve air flow in patients with airways obstruction, but it was soon cast aside for other treatment modalities. After the explosion of the dirigible Hindenburg in 1937, Congress regulated the sale of helium, and its availability was further reduced during World War II. Since then, it has been relegated mainly to use in upper airway obstruction or to diagnostic studies. Safety and efficacy have been described for both spontaneously breathing patients and for intubated patients receiving mechanical ventilation, but its therapeutic potential has not been fully explored. After the war, with the advent of pharmacologic bronchodilators with improving side-effect profiles, helium was cast aside as a treatment for asthma. There were a few reports of its respiratory usage showing the lack of significant improvement in asthmatic patients and in patients with emphysema. Helium-oxygen was described to be an effective treatment of upper airway obstruction in 1976 and there were scattered reports for this usage until 1986. In the 1980s medicinal oxygen/helium resurfaced due to the rise of death by asthma, evidence of beneficial action is conflicting despite the fact that clinical trials and case reports showed benefit in selected patients. In 1987, the use of helium-oxygen in the treatment of patients with asthma resurfaced in Hartford, CT, and in France, and it became known as heliox.

Rationale (2)

The rationale in heliox administration is that gas of a lesser density can more easily bypass an obstruction and therefore be inspired further with

less effort and resistance. Helium is a colourless tasteless, non-combustible, non-explosive gas that is seven times lighter than air. One of its most important properties is that it is biologically inert and insoluble in human tissues having no bronchodilator anti-inflammatory effect. Its key benefit seems to be as a temporising agent working while conventional treatments have time to act. Helium has the lowest specific gravity of any gas with the exception of hydrogen, which is highly combustible.

Low specific gravity is usually associated with low density, and this is proportional to the flow rate of the gas, the lower the density, the higher the rate of flow. Combining helium and oxygen gas (Heliox) results in a gas with a similar viscosity to air but with at substantially lower density.

To understand how heliox may be of benefit in various disorders of the airways, it is necessary to be familiar with a few concepts of physics. Gas flow in airways may be laminar, turbulent, or a combination of the two (transitional). Due to flow rate and airway resistance in obstructions in most cases it is turbulent. Laminar flow is the most efficient way in which oxygen is delivered to the more distal parts of the bronchial tree. The type of flow occurring at any given point is determined by the Reynolds number of the gas. This is a unitless quantity that is proportional to the product of the airway diameter and the velocity and density of the gas, divided by its viscosity. When the Reynolds number is high (greater than 3790) flow is predominantly turbulent. The effective cross sectional area of the airways increases with each division of the airways from the trachea to bronchi—as this happens the flow rate of inspired gas falls. As the flow rate drops, the Reynolds number falls and flow becomes more laminar than turbulent. Within the substance of the lungs, there will be a transitional region where turbulent flow becomes laminar. Exercise or any other disease that increases ventilatory requirements will shift this transitional area distally causing a greater predominance of turbulent flow.

Medicinal oxygen/ helium acts by lowering the resistance to gas flow within the airways and permitting an increase in ventilation. This it does for two main reasons. Firstly, and most importantly, breathing medicinal oxygen/ helium leads to a reduction in the Reynolds number, converting turbulent flow efficiently into laminar flow. Secondly, because of its low density, medicinal oxygen/ helium decreases the pressure gradient needed to achieve a given level of turbulent flow and this in theory reduces the work of breathing. The use of medicinal oxygen/ helium in asthma and upper airways obstruction has not been for the treatment of the underlying disease, but has been used to reduce airways resistance and respiratory muscle work until definitive treatments act.

Clinical Indications

In upper airways obstruction, heliox appears to be of reasonable effect in severe respiratory distress that results from upper airways obstruction (3). The gas mixture allows the intensivist to "buy time" while aggressive bronchodilator treatment aimed at alleviating the obstruction may take effect. The benefits of medicinal oxygen/ helium in COPD are less clearly reported, although there is ongoing research into its use in place of oxygen in acute exacerbations. Some studies show that medical oxygen/ helium consistently improves both inspiratory and exspiratory flow producing a reduction in dynamic hyperinflation with a consequent improvement in gas exchange (4). Reduction in hyperinflation improves mechanical advantage by increasing respiratory muscle efficiency and decreasing the work of breathing. Decreased work of breathing will reduce the volume of carbon dioxide produced. The major problem is in most cases not just oxygen transport to the alveoli but the inability to exhale carbon dioxide properly. In summary current evidence is insufficient to support the use of helium-oxygen mixtures in the standard treatment of acute exacerbations of COPD, but state that future randomised trial would be of value. Several randomized protocols support that the use of heliox in severe asthma results in a more rapid decrease in pulsus paradoxus and in airflow obstruction.

Current "practical clinical" policy is that in acute severe asthma in spontaneously breathing patients, heliox can be given after failure of the initial bronchodilatator therapy (5). Its main advantage is that intubation can frequently be avoided. Besides an improvement in blood gases use of heliox results in a reduction in inflation pressure and adds to hemodynamic stability. Lee et al (6) observed improved hemodynamical stability in patients with severe chronic obstructive pulmonary disease during acute respiratory failure in presence of persistent intrinsic positive end-expiratory pressure-induced hemodynamic changes despite ventilator management. Our own workgroup presently explores the hemodynamic effects of heliox in patients with biventricular failure and superimposed severe chronic obstructive pulmonary disease; preliminary results identically suggest an improvement in cardiac performance due to reduction of intrinsic peep.

In mild to moderate paediatric bronchiolitis beneficial effects of heliox were largely witnessed in nonintubated infants whereas application via hood did not appear effective (7). Although the clinical effect has not been statistically significant in the few trials to date, heliox may reduce the need

for intubation and mechanical ventilation in acute bronchiolitis and shorten overall stay.

In addition heliox appears to enhance delivery of inhaled bronchodilators to the lower airways in patients both with and without lower airway obstruction. Delivering aerosols with heliox seems to increase aerosol deposition in obstructed airways due to heliox's lower density (8).

Other so far rather anecdotal uses of heliox include the use in children with bronchopulmonary dysplasia, the use of heliox during bronchoscopy or even as a treatment for pneumothorax and hyperammonaemia.

Conclusion

Heliox seems to exert both pulmonary and hemodynamic beneficial effects in disease states due to airway obstruction. Controversy over its effects is mainly due to the limited number of trials and patients as well as the differing and partly jury-rigged modes of delivery.

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Nitrous oxide – old friend, new fellow?

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Since more than 150 years nitrous oxide (N_2O, laughing gas) is used for anaesthesia and analgesia in daily clinical routine worldwide. Over this long time, hardly any other drug has been used by anaesthesiologists so often and in such a large number of patients.

Nitrous oxide is an inhalational anaesthetic with weak hypnotic and stronger analgesic effects. Having a MAC value of 104% anaesthesia with N_2O alone is only possible – just in theory – under hyperbaric conditions. Thus, during anaesthesia nitrous oxide is used as part of an anaesthetic regimen in inspiratory concentrations of 50-70%. Combining N_2O with other drugs – i.e. intravenous anaesthetics, opiates, or inhalational anaesthetics – may enhance their anaesthetic/analgesic effect as well as reduce side effects of either of the drugs.

Nitrous oxide has the lowest blood-gas partition coefficient (0.47) of all registered inhalational anaesthetics – now with exception of xenon – and thus cerebral concentrations equillibrate with alveolar concentrations extremely fast (1). Since N2O is not metabolised, elemination of nitrous oxide from the body only depends on ventilation (the anaesthist himself during general anaesthesia) and is independent of renal or liver function. As with all inhalational anaesthetics, blood levels of nitrous oxide can be monitored online by measuring the exhaled concentration breath by breath. Due to these properties N_2O is mainly used in ambulatory surgery, for short and less painfull procedures, and in patients in whom side-effects of other analgetics (s.a. respiratory depression by opioids) must be minimal. There is no doubt regarding the effectiveness of N_2O alone to work as an analgesic (2) or of N_20 to augment anaesthesia (3). Especially for induction of anaesthesia by inhalation in children the 'second gas effect' of nitrous oxide (4) in combination with the modern inhalational anaesthetic sevoflurane is a domain for N_2O.

Cardiocirculatory and respiratory side effects of nitrous oxide are minor. While direct negative inotropic effects have been shown in animal studies, clinically this effect is counteracted by a concomitent stimulation of sympathic tone. N_2O dilates intracranial vessels which may result in an increase in intracranial pressure, especially in patients with already impaired cranial compliance. Therefore, patients with known or risk for

increased intracranial pressure (i.e. patients with head trauma) should not receive N_2O. Being a gas nitrous oxide diffuses into gas filled spaces along its concentration gradient. This results in well established contraindications for the use of nitrous oxide: ileus, pneumothorax, pneumoperikardium, ear surgery, air embolism, and cardio- and neurosurgery. Cuff pressure of intratracheal tubes should be monitored carefully and adjusted.

Several prospective, double-blinded studies have looked at a possible association of nitrous oxide with bowel distension, but results were conflicting (5-7). Surgeons blinded for group assinement were not able to tell from intraoperative bowel appearance if nitrous oxide was used or not (7,6). With regard to postoperative bowel function Pedersen et al. (5) detected a delay of first postoperative defaecation by 10.3 hours in the N_2O group in patients following hysterectomy. Studying 344 patients scheduled for colon resection Akca et al. (9) reported an increased incidence of 'moderate-to-severe' bowel distension. Of interest, in a subsequent publication by the same group in 408 patients (10) this effect could not be detected, even though the patients of the first study were part of the second study.

Two meta analyses (11,12) revealed a small but significant increase in postoperative nausea and vomiting (PONV) when nitrous oxide is used during anaesthesia. The odds ratio of this effect was 1.3, which is low as compared to the emetic effect of volatile anaesthetics (i.e. sevoflurane 14.5, isoflurane 19.8) or of opiods used postoperatively (2.5)(13). However, in most studies nitrous oxide was combined with other anaesthetics and, thus, did not evaluate the emetic effect of N_2O alone. The recently published 'IMPACT' study (14) evaluating 6 different interventions to reduce the risk for PONV in a total of 5.200 patients demonstrated that omitting nitrous oxide during anaesthesia will reduce the incidence of PONV by 12.1% (from 38% with N_2O to 31% without N_2O). It should well be noticed that the meta-analysis by Tramèr et al. revealed that omitting nitrous oxide during anaesthesia also will increase the risk of intraoperative awareness with a number-needed-to-treat of 46 (12).

Toxicity of nitrous oxide includes its well documented inhibition of vitamin B12 which was first noticed in 1956. This side-effect only becomes clinically important if nitrous oxide is inhaled over longer periods either continuously over days or intermittently over months (15). In its statement „Waste Anesthetic Gases Information for Management in Anesthetizing Areas and the Postanesthesia Care Unit (PACU)" the Committee on Occupational Health of Operating Room Personnel of the American Society of Anesthesiology (ASA) concludes that there is no clinical evidence for

nitrous oxide to have teratogenic, mutagenic, or karzinogic effects (see the ASA website at http://www.ASAhq.org). N_2O, as CO_2 and methane, is one of the known greenhouse gases. However, nitrous oxide waste from medical sources accounts for less than 0.1% of the yearly total greenshouse gas emissions. There is no direct association between nitrous oxide and the occurrence of the 'ozone hole' (16).

Conclusion

Nitrous oxide is one of the best studied anaesthetics used in general anaesthetia practice. It has clear indications and contraindications. To be 'old fashioned' does not seem to be a good enough reason – and also not a very scientific one - to abandon its use. The contrary may be true: the use of an anaesthetic which has been used safely and effectively for more than 150 years may only be stopped in favour of another, if this other anaesthetic has proven its superiority.

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Xenon – a neuroprotactant for the future?

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Xenon, the noble inert gas, has been used safely for anaesthetic and imaging applications in patients of all ages; however, scarcity of this element (present in only 87.5 parts per billion of the atmosphere) precludes full clinical exploitation. Xenon is a potent antagonist of the NMDA subtype of the glutamate receptor, a protein that is pivotal in the propagation of acute nerve injury. In a series of in vitro neuronal culture studies xenon reduced neuronal apoptosis induced by NMDA, glutamate, oxygen-glucose deprivation. We have observed the neuroprotective effects of xenon in rodent models of acute neuronal injury caused by excitotoxicity, cardiopulmonary bypass, middle cerebral artery occlusion, and hypoxia-ischaemia as well as anaesthetic toxicity in neonates. Importantly, xenon lacks the toxicity that characterises other NMDA receptor antagonists. Xenon also can prevent acute neurological injury when administered up to 24 h prior to the provocation ("preconditioning) through a mechanism that requires new protein synthesis. A dose-ranging feasibility and tolerability trial of xenon in cardiac surgical patients demonstrated xenon safety as a prelude to a randomised placebo-controlled safety and efficacy evaluation of xenon for prevention of postoperative neurocognitive dysfunction following cardiac surgery.

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