# Nitrous oxide

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Joseph Priestley, a chemist and Presbyterian minister, discovered nitrous oxide in 1772.[1] Its analgesic action was subsequently described in 1800 by Humphrey Davy. Towards the end of the nineteenth century, its anaesthetic properties were recorded under hyperbaric conditions by Paul Bert. Applications for the use of nitrous oxide have developed greatly since that time. It has widespread use in anaesthesia but has many other uses; examples include its use as an aerosol propellant in whipped cream dispensers and for enhancement of engine performance in drag-racing.

## Production and storage

Nitrous oxide is produced commercially by heating ammonium nitrate to 240°C. Water vapour and impurities, including higher oxides of nitrogen, ammonia and nitric acid, are subsequently removed by passage through a series of washers and scrubbers.

Nitrous oxide is stored in French-blue cylinders (pin-index 3, 5) pressurized to ~4400 kPa at room temperature. Nitrous oxide is usually stored below its critical temperature, and thus exists simultaneously in liquid and vapour phases. The cylinders have a filling ratio of 0.75 in temperate countries and 0.67 in tropical countries. Unlike cylinders containing pressurized gas, the cylinder pressure remains effectively constant until all the liquid nitrous oxide vaporizes. A slight fall in pressure may occur during continued venting from a cylinder, and ice may form on the outside of cylinders owing to the cooling consequent upon nitrous oxide's latent heat of vaporization. Large institutions often use pipeline supply of nitrous oxide. This is achieved through a large central bank of cylinders, including reserve banks. The physical properties of nitrous oxide are shown in Table 1.

**Table 1** The physical properties of nitrous oxide

| |
|---|
| Sweet-smelling and colourless |
| Molecular weight 44 |
| Boiling point –88.5°C |
| Critical temperature 36.5°C |
| Blood/gas partition coefficient 0.47 |
| Oil/gas partition coefficient 1.4 |
| MAC 105% |
| Non-flammable, but supports combustion |

## Pharmacokinetics

Inhaled nitrous oxide may produce the second-gas effect.[1 2] This is a consequence of the large fraction of inspired gas that nitrous oxide constitutes and the fact that nitrous oxide diffuses more rapidly across alveolar basement membranes than does nitrogen (because it is 30 times more water soluble). The rapid exit of nitrous oxide from the alveoli causes remaining alveolar gases to be concentrated, thus accelerating the uptake of volatile agent into the blood and speeding the onset of anaesthesia. Additionally, the large net movement of gas from alveoli to blood during the rapid absorption of nitrous oxide causes fresh gas to be drawn into gas-exchanging regions of the lung (i.e. alveoli and respiratory bronchioles), further accelerating uptake of companion gases.

The reverse may occur at the end of anaesthesia, when the administration of nitrous oxide ceases. Nitrous oxide enters the alveoli far more rapidly than nitrogen leaves, causing dilution of the gaseous contents of the alveolus. This results in the dilution of oxygen within the alveoli of patients breathing air and may cause 'diffusion hypoxia'. The dilution of the alveolar contents by the egress of nitrous oxide form the blood may also dilute the concentration of volatile agents, enhancing their elimination, and speeding wakening.

Nitrous oxide is eliminated unchanged from the body, almost entirely via the lungs, although a small amount diffuses through the skin. There is a very small contribution made to elimination through reductive metabolism by anaerobic bacteria in the gut.

Nitrous oxide appears to have activity at several different types of receptor.[3] It has an inhibitory action at *N*-methyl-D-aspartate (NMDA) glutamate receptors, while it has stimulatory activity at dopaminergic, $\alpha_1^-$ and $\alpha_2^-$ adrenergic and opioid receptors.

### Key points

Nitrous oxide is more soluble than nitrogen, and its use in large concentrations is associated with the second-gas effect, diffusion hypoxia and the expansion of air-filled spaces in the body.

It has analgesic effects, probably through central opioid receptor stimulation and spinal cord $\alpha_2$ stimulation.

It is non-flammable, but does support combustion.

It has minimal effects on most organ systems in the acute setting.

Repeated use of nitrous oxide, particularly during lengthy procedures, may precipitate megaloblastic anaemia and spinal cord degeneration.

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## Pharmacodynamics

Nitrous oxide has effects on many physiological systems.[1 4]

### Respiratory

Nitrous oxide causes a decrease in tidal volume and an increase in respiratory rate. The increase in respiratory rate is a consequence of central nervous system activation and possibly activation of pulmonary stretch receptors. Usually, minute ventilation is maintained. It also leads to a reduction in the ventilatory response to hypoxia and hypercapnia. Inhalation of nitrous oxide depresses tracheal mucociliary flow and neutrophil chemotaxis. This may increase the incidence of post-operative respiratory complications.

At low concentrations nitrous oxide has a negligible effect on hypoxic pulmonary vasoconstriction; however, at higher concentrations it may be impaired.

### Cardiovascular

Nitrous oxide causes direct myocardial depression, but increases central sympathetic outflow. In general, arterial pressure is little affected by nitrous oxide. Pulmonary vascular resistance is increased due to constriction of the pulmonary vascular smooth muscle. This may lead to an increase in right atrial pressure. Consequently, nitrous oxide is probably best avoided in those with known pulmonary hypertension. Other vascular beds are also altered; there is a decrease in renal and hepatic blood flow due to an increase in vascular resistance of these beds.

### Central nervous system

Nitrous oxide increases cerebral blood flow, cerebral metabolism and intracranial pressure.[5] The increase in cerebral metabolism probably accounts for the increase in cerebral blood flow, rather than a direct vasodilatory effect. These changes are particularly marked when there is disruption of normal cerebral autoregulation and may result in a significant (and potentially detrimental) decrease in cerebral perfusion. These effects are of obvious importance in patients undergoing neurosurgical procedures, but must also be considered in those with cerebral or cerebrovascular pathology (e.g. head injury or cerebrovascular disease) for extracranial surgery.

### Neuromuscular

Most volatile anaesthetic agents depress the neuromuscular junction and augment the effects of non-depolarizing neuromuscular blockers. In contrast, nitrous oxide has the potential to increase skeletal muscle activity and has less depressant activity at the neuromuscular junction than other currently used inhalational anaesthetic agents. It does not appear to potentiate the action of non-depolarizing neuromuscular blocking agents.

### Analgesic actions

Nitrous oxide has analgesic actions thought to be mediated by activation of opioid receptors in the periaqueductal grey of the midbrain.[3] This leads to modulation of nociceptive pathways through the release of norepinephrine and activation of $\alpha_2^-$ adrenoceptors in the dorsal horn of the spinal cord. This may explain acute to tolerance to nitrous oxide that may be seen as a consequence of depletion of central opioid peptides.

## Clinical applications

### General anaesthesia

Although nitrous oxide has anaesthetic properties, it is not suitable as a sole anaesthetic agent under standard atmospheric conditions. Its minimum alveolar concentration (MAC) is 105% at 1 atmosphere pressure. However, it is used extensively in combination with other volatile anaesthetic agents. This reduces the required dose of volatile agent and hence reduces the cardiovascular depression that occurs with most volatile agents. The low cost of nitrous oxide also encourages its use in combination with other (more expensive) modern volatiles.

### Obstetrics

Nitrous oxide was first used as an analgesic during labour in 1881 by Stanislaw Klikovich, who administered pre-mixed nitrous oxide 80% in oxygen. Although not a potent analgesic during labour, it appears safe for pregnant women, their babies and healthcare workers who are in attendance. For many women, it provides adequate labour analgesia but co-ordination of administration with contractions can be difficult. Maternal side-effects include nausea, dizziness, paraesthesia and dry mouth. In the UK, it is administered as pre-mixed nitrous oxide 50% and oxygen 50% via a demand valve.

### Pain management

Nitrous oxide can provide excellent analgesia for acutely painful procedures such as fracture reduction and changes of burns dressings. In the emergency department setting, it may also have a role in the management of the pain of ureteric colic and sickle cell crises and positioning for radiological procedures.[6] However, repeated or long-term use is discouraged because of the risks described below. It can also be useful in the theatre setting for supplementation of regional techniques.

## Adverse effects of nitrous oxide

### Postoperative nausea and vomiting

Postoperative nausea and vomiting (PONV) is a major cause of anaesthetic morbidity and nitrous oxide has been implicated in its aetiology. The mechanism for the emetogenic potential of nitrous oxide is not fully understood but changes in middle ear pressure, bowel distension and activation of dopaminergic neurones may all be involved. Meta-analyses of published work have found that omission of nitrous oxide reduces the risk of

**Table 2** Clinical situations where the use of nitrous oxide may have serious deleterious consequences

| Clinical situation | Adverse effect |
|---|---|
| Intestinal obstruction | Difficult closure of the abdomen<br>Increased intra-abdominal pressure<br>Intestinal rupture |
| Intraocular gas (e.g. $SF_6$, $C_3F_8$) | Loss of sight<br>Pain |
| Middle ear surgery | Disruption of grafts<br>Disruption of ossicular chain |
| Pneumothorax/pulmonary bullae | Rapid increase in size<br>Ventilatory and cardiovascular effects |
| Air embolism | Rapid increase in size and effects |
| Pneumocephalus | Raised intracranial pressure<br>Cerebral damage |
| Decompression sickness | Rapid increase in symptoms<br>Distal organ damage |

PONV by nearly 30% and that the maximal effect of nitrous oxide omission is seen in female patients.[7] When considering the potential benefits of nitrous oxide omission, the incidence of adverse outcomes (such as awareness) must also be considered.

## Air-filled spaces

The relative solubilities of nitrous oxide and nitrogen cause rapid expansion of nitrogen-containing spaces when nitrous oxide is commenced. Pressure or volume changes may result or, more frequently, a combination of the two occurs, depending upon the nature of the space (e.g. pneumothorax, bowel, middle ear).[1] These changes can have deleterious consequences. There are several clinical situations where nitrous oxide should be avoided owing to the potentially dangerous effects of space expansion (Table 2).

Cuff pressures of endotracheal tubes and laryngeal masks can increase significantly during prolonged administration of nitrous oxide. This may lead to local ischaemia and mucosal damage. Regular checks of cuff pressure should be made using a pressure gauge during prolonged surgery. Inflation of the cuff with a gas mixture that has the same composition as the inhaled gas mixture can prevent excessive changes in cuff pressures.

## Blood and nervous system

Prolonged administration of nitrous oxide causes inhibition of methionine synthetase, which results in interference with DNA synthesis in both leukocytes and erythrocytes.[3] Vitamin $B_{12}$ is required as a coenzyme for methionine synthetase. However, vitamin $B_{12}$ is oxidized by nitrous oxide and so is unable to interact with methionine synthetase. In addition, nitrous oxide reduces the motility and chemotactic response of leucocytes.

Nitrous oxide associated bone marrow suppression was first seen in the 1950s after long term sedation with nitrous oxide. Oxidation of the cobalt atom in $B_{12}$ by nitrous oxide can precipitate megaloblastic changes in the bone marrow and a neuropathy in experimental animals. Such changes may also be observed in humans and are of particular concern where there is clinical or subclinical $B_{12}$ or folate deficiency. Mild megaloblastic changes are seen in healthy people after 12 h of anaesthesia and these changes become marked after 24 h. The neurological alteration can range from transient mild paraesthesia through to a picture that resembles subacute combined degeneration of the cord. High dose $B_{12}$ and folate can help to prevent these unwanted actions.

## Potential administration of a hypoxic mixture

It is possible to deliver a hypoxic mixture of gases to a patient from anaesthetic machines where no hypoxic guard is fitted. This can have catastrophic consequences and, in order to prevent it, the Medical Device Agency [SN2001(15)] has stated that all anaesthetic machines in use must be fitted with either a hypoxic-guard or an oxygen analyser.

## Occupational exposure

In the pre-scavenging era, there were concerns that nitrous oxide might contribute to the increased relative risk of miscarriage and reduced fertility seen in female theatre workers.[8] However, providing that anaesthetic gases are scavenged and the levels of ambient nitrous oxide are maintained below 100 p.p.m., it appears that the safety of those who have long-term occupational exposure is not compromised.

## Recreational use

Nitrous oxide has been a drug of abuse since the early days of its development; it was particularly popular in the 1970s. It can produce an intense 'high' and feelings of flying, diving and floating when inhaled in high concentrations. However, its use has many associated risks, including hypoxic injury (as it is rarely used with oxygen), subacute combined degeneration of the cord and frostbite. Frostbite of the vocal cords has been recorded after direct inhalation from nitrous oxide canisters.

## Teratogenicity

There is good evidence from mammalian models that prolonged exposure to nitrous oxide is teratogenic. In rats, nitrous oxide can cause skeletal anomalies, encephalocoele, gastroschisis and microphthalmia. The mechanism of the teratogenicity is thought to be multifactorial and not simply a consequence of impaired DNA synthesis. Stimulation of $\alpha_1^-$ adrenergic neurones may play a partial role in nitrous oxide induced teratogenicity. Indeed in animal models, $\alpha_1$-adrenoceptor antagonists have partially prevented nitrous oxide teratogenesis. It is hypothesized that activation of adrenergic neurones leads to decreased ciliary activity, which may cause disordered organogenesis and explain why *situs inversus* has been observed.[3] The evidence is less established in humans but there is a good argument for nitrous oxide-free anaesthesia during at least the first trimester of pregnancy.

### Environmental concerns

Nitrous oxide, like carbon dioxide, methane and perflurocarbons, is a greenhouse gas. Most environmental nitrous oxide is produced via the use of nitrogen-based fertilizers in agriculture, burning of fossil fuels and sewage management programmes. It is 200–300 times more effective at trapping heat than is carbon dioxide, and contributes to global warming. However, nitrous oxide only constitutes 5% of greenhouse gases. Concerns about the environmental impact of anaesthetic use of nitrous oxide are probably unfounded; anaesthesia accounts for <1% of total nitrous oxide emissions.[8] The contribution of anaesthetic gases may be even lower with the increasing use of low-flow systems.

## The future of nitrous oxide

Nitrous oxide has played a vital role during the development of anaesthesia as a speciality. However, there are many who would argue that there is no place for nitrous oxide in modern anaesthetic practice.[8] Thus, its future appears far from certain and there may come a time when it is no longer regularly used in general anaesthesia. However, presently, there is no gaseous alternative to nitrous oxide. I.V. drugs, such as remifentanil, have been suggested as replacements.[5] However, they have potential problems. Any alternative needs to be well validated and have a safety record comparable with, or exceeding that of, nitrous oxide. A major advantage of the use of inhaled nitrous oxide (compared with an i.v. drug) is that the exhaled concentration may be measured, providing an indication of *in vivo* partial pressures.

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**See multiple choice questions 106–110**