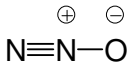
Nitrous oxide Refrigerated Liquid Gas Medicinial

NAME OF THE DRUG

Nitrous oxide

Chemical structure

Nitrous oxide, N_2O
A linear but unsymmetrical molecule of the form 

DESCRIPTION

Pharmaceutical form

Low temperature liquid medical gas (for medicinal use only) supplied in insulated pressure vessels. Liquid is withdrawn and vapourised or gas is withdrawn and warmed to ambient temperature for distribution via pipe networks to usage points.

Specification

Complies with the requirements of the current European Pharmacopoeia monograph for Nitrous oxide.
Nitrous oxide, N_2O, CAS number 10024-97-2

Nitrous oxide	98.0% v/v minimum
Carbon dioxide	300 ppm v/v maximum
Carbon monoxide	5 ppm v/v maximum
Oxides of nitrogen (NO/NO_2)	2 ppm v/v maximum
Water (vapour)	67 ppm v/v maximum

Physical data

Molecular weight	44.01
Physical state in the tank	Refrigerated liquefied gas at approximately -20ºC and 1800kPa
Density of the gas at 15ºC and 101.3 kPa	1.877 kg/m^3
Combustion characteristics	Non flammable, strongly supports combustion
Boiling point	- 88.6ºC (at 101.3 kPa)
Critical temperature	36.4ºC

Sweet smelling colourless non-irritating gas
Nitrous oxide is not very soluble in water and has a low solubility in blood and tissues.

Chemical characteristics

Nitrous oxide is an oxidising substance which will support combustion of materials which may not normally burn in air. The molecule is stable and comparatively unreactive at ordinary temperatures and pressures. At elevated temperatures it decomposes to nitrogen and oxygen. Nitrous oxide will react with powerful reducing agents such as phosphine, stannous chloride and hydrogen. Rust and other impurities especially oil and grease may cause ignitions.

PHARMACOLOGY

Nitrous oxide is an inhalational anaesthetic. The MAC (Minimum Alveolar Concentration) in oxygen is greater than 100%.

Nitrous oxide has analgesic and weak anaesthetic properties. It has no dose related muscle relaxant effect. Onset and recovery from its effects are relatively rapid. Pain reduction may be achieved at a concentration of around 25% whilst a concentration of about 70% is usually needed to produce unconsciousness.

Nitrous oxide alone may increase pulse rate and have depressant effects on respiration.

Pharmacokinetics

Nitrous oxide is rapidly absorbed via inhalation.

The alveolar concentration of N_2O rises rapidly due to its low blood:gas partition coefficient. Likewise, its elimination is very rapid.

The blood:gas partition coefficient of nitrous oxide at 37ºC is 0.47 compared with that of nitrogen of 0.015, causing nitrous oxide to expand into internal gas spaces.

The metabolism of nitrous oxide is minimal.

Nitrous oxide is eliminated from the body mostly by the lungs.

INDICATIONS

Nitrous oxide is indicated in adults and children for:

1. General anaesthesia, usually as an adjuvant to other volatile or intravenous anaesthetics.
2. Analgesia (with oxygen) e.g. dentistry and obstetrics.

CONTRAINDICATIONS

Nitrous oxide should not be administered without the required level of oxygen (at least 30%).

Hypersensitivity to nitrous oxide or any other component in the gas is a contraindication.

Nitrous oxide should not be used with any condition where air is entrapped within a body and where its expansion might be dangerous, such as: the presence of intracranial air; artificial, traumatic or spontaneous pneumothorax; air embolism; decompression sickness; following a recent dive; severe bullous emphysema; during myringoplasty; occluded middle ear; cysts; gross abdominal distension; maxillofacial injuries and following cardiopulmonary bypass or air encephalography and after intraocular gas injection in ophthalmic surgery, for example with sulphur hexafluoride (SF_6) or perfluoropropane (C_3F_8) until the intraocular gas has been completely absorbed.

Nitrous oxide should not be used on intoxicated patients.

After inhaling nitrous oxide for 5-7 days, leucopenia and megaloblastic anaemia have been described, in some cases fatal. A poyneuritic type of neuropathy and spinal cord sclerosis can appear during chronic administration of high concentrations of nitrous oxide. Where there is prolonged exposure, monitoring of peripheral blood for features of megaloblastic anaemia and leucopenia is recommended

PRECAUTIONS

General

A simple asphyxiant in the absence of oxygen. Classified as hazardous according to the criteria of Worksafe Australia.

Refrigerated liquid contact with eyes and skin may cause cold burns. Contact with exposed cold pipework may also cause cold burns.

Addiction and abuse of nitrous oxide have been reported. Delirium has been reported upon withdrawal.

Care should be taken with long term usage of nitrous oxide. Chronic exposure to nitrous oxide, such as in abuse, can inactivate vitamin B_{12} and may result in polyneuropathy, megaloblastic anaemia, bone marrow depression and reproductive effects (see Adverse Reactions). A full blood examination should be performed in abusers, professionals chronically exposed and patients receiving ongoing therapy for evidence of megaloblastic change in red blood cells and hypersegmentation of neutrophils.

Scavenging of waste nitrous oxide gas should be used to reduce operating theatre and equivalent treatment room levels to a level below 25 ppm exposure limit of nitrous oxide (Worksafe exposure standard TLV TWA). Rescue personnel are advised to monitor nitrous oxide concentration before entering confined spaces and poorly ventilated areas which have been contaminated by a nitrous oxide leak. Chronic occupational exposure to nitrous oxide may lead to bone marrow or neurological impairment (see Use in Pregnancy).

When nitrous oxide is used in conjunction with other volatile or intravenous anaesthetic agents, the MAC of those agents may be reduced by up to 50%.

At the end of nitrous oxide/oxygen anaesthesia, ventilation with air may lead to *diffusion hypoxia* due to the ongoing elimination of nitrous oxide in the alveoli lowering the oxygen partial pressure. Diffusion hypoxia may be minimised by washing out the nitrous oxide with oxygen at the conclusion of the anaesthetic and providing oxygen via facemask for at least 20 minutes while the patient is recovering.

Nitrous oxide should never be given with less than 21% oxygen. At high altitude or in the presence of disorders affecting oxygenation, the amount of nitrous oxide required will vary.

Nitrous oxide passes into gas containing spaces in the body faster than nitrogen passes out. Prolonged anaesthesia may result in bowel distension and expansion of other non-vented gas containing cavities.

Nitrous oxide should be used with caution in patients with severe hypotension or those at risk of vitamin B_{12} deficiency.

Nitrous oxide has not been known to trigger malignant hyperthermia (see Adverse Reactions).

Check the following before use

Nitrous oxide is non-flammable but strongly supports combustion (including some materials which do not normally burn in air). It is highly dangerous when nitrous oxide comes into contact with oils, greases and tarry substances due to the risk of spontaneous combustion.

Operability of oxygen mixing apparatus and availability of oxygen.

Tanks of refrigerated liquid nitrous oxide are usually connected to reticulation systems around the usage area.

Refrigerated liquid nitrous oxide tanks are provided with liquid level indicating gauges.

Use of refrigerated liquid tanks

Tanks should be kept in a segregated and secure area with access to approved personnel only.

Refrigerated liquid nitrous oxide storage tanks are installed by the supplier in accordance with Commonwealth, State and Territory Dangerous Goods legislation. The area around them must be kept clean and clear of any combustible materials. They must be installed on suitable foundations and be in a well ventilated area with adequate access for deliveries and maintenance. Only suitably trained persons should operate the storage tank.

Additional information is contained in the Material Safety Data Sheet for the product from the sponsor.

Occupational exposure standard

Worksafe exposure standard TLV TWA is 25 ppm.

Cold burns

Burns should not occur if the product is administered correctly (see Accidental Contact under Overdosage).

Carcinogenicity and mutagenicity

Nitrous oxide was tested for carcinogenic potential in rats and mice. No carcinogenic effect was seen in mice exposed to nitrous oxide (40%, 4 hours per day) or rats exposed to low concentrations of halothane-nitrous oxide (10 ppm:500 ppm, 7 hours per day).

Nitrous oxide gave mixed results in limited assays for genotoxicity. In assays for gene mutations nitrous oxide was negative in the Ames test and sex-linked recessive lethal assay in *Drosophilia melanogaster*, but was positive in Chinese hamster lung cells. The potential to cause chromosomal damage has not been investigated. An increased frequency of chromosomal aberrations was observed in bone marrow cells and spermatogonia of rats treated with a mixture of nitrous oxide and halothane. Nitrous oxide also caused an increased incidence of sister chromatid exchanges (SCE) in human lymphocytes *in vitro.*

Clinical studies have suggested that nitrous oxide may be associated with genotoxic events. DNA strand breaks were reported in surgical patients treated with isoflurane-nitrous oxide-oxygen, 1 day after surgery. An increased frequency of SCE, but not micronuclei, was found in the lymphocytes of operating room personnel exposed to nitrous oxide and isoflurane. An increase in SCE was also found in operating room personnel exposed to halothane and nitrous oxide.

Impairment of fertility

The germ cells of mice exposed to nitrous oxide for 14 weeks (50% nitrous oxide, 4 hours/day) showed no evidence of toxic effects due to nitrous oxide.

The fecundity of female dental assistants was reduced by 60% for those women working greater than or equal to 5 hours per week with unscavenged nitrous oxide. Similarly, fecundity was reduced in a Swedish study of midwives in those women assisting at more than 30 deliveries per month.

Use in pregnancy (Category A)

All general anaesthetics carry the potential to produce central nervous system and respiratory depression in the newborn infant. In routine practice this does not appear to be a problem. However, in the compromised fetus, careful consideration should be given to this potential depression and to the selection of particular anaesthetic drugs, doses and techniques.

Inhalation anaesthetics cross the placenta. Treatment of rats with nitrous oxide (75% or 60% for each 24 hour period during organogenesis) resulted increased incidences of resorptions (days 8 and 11 of gestation), visceral abnormalities (day 8, right sided aortic arch and left-sided umbilical artery) and minor skeletal anomalies (days 8 and 9). Increased rates of resorptions, decreased fetal size and skeletal abnormalities have been reported in rats exposed to nitrous oxide concentrations of 0.1% throughout gestation. There were no adverse effects on the fetuses of mice exposed to 50% nitrous oxide during organogenesis.

There was no evidence of teratogenic effects in pregnant women exposed to single, brief anaesthetic exposure to nitrous oxide during pregnancy.

Studies of operating room personnel chronically exposed to low concentrations of inhalation anaesthetics show that pregnancies in female personnel and the wives of male personnel may be subject to increased incidences of spontaneous abortions, stillbirths and possibly birth defects. However, the methods used in obtaining and interpreting the data in these studies have been questioned. Studies on dental staff's exposure to anaesthetic gases had conflicting results. One study showed an increased risk of spontaneous abortion among dental assistants exposed to nitrous oxide. Another showed no increased risk for dental assistants either practising in private clinics or working in dental school services (OR 0.4). Others demonstrated increased risk of spontaneous abortion among dental assistants exposed to nitrous oxide for 3 or more hours weekly in places without scavenging systems. A study of Swedish midwives exposed to nitrous oxide in more than 50% of deliveries showed no increased risk of spontaneous abortion (OR 0.95). The effect of scavenging was excluded because many midwives were unsure about whether such equipment had been present in the delivery rooms. Several animal studies (in which operating room conditions were simulated) have failed to show fetotoxic or teratogenic effects following chronic exposure of male and/or female animals to low concentrations of inhalation anaesthetics prior to and /or during gestation.

Use in lactation

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when nitrous oxide is administered to a nursing woman.

Effects on the ability to drive and to use machines

Nitrous oxide is rapidly eliminated but it is recommended that driving, use of machinery and other psychomotor activities should not be undertaken until 24 hours have elapsed after nitrous oxide anaesthesia. General anaesthetics may cause a slight decrease in intellectual function for two to three days following anaesthesia.

Interactions with other drugs

Nitrous oxide reduces the amount of volatile anaesthetics required for anaesthesia when administered concomitantly.

Nitrous oxide and CNS depressants may lead to increased CNS depression, increased respiratory depression and increased hypotensive effects.

Nitrous oxide and opioids together may lead to further circulatory depression. High dose fentanyl with nitrous oxide may decrease heart rate and cardiac output.

Nitrous oxide potentiates the effects of methotrexate on folate metabolism, leading to stomatitis and myelosuppression.

The uptake of an inhalational anaesthetic from the lungs is accelerated by the uptake of nitrous oxide when administered concomitantly. This is known as the second gas effect.

Effects on Laboratory Tests

There are no known significant effects on laboratory tests, other than those associated with megaloblastic anaemia.

ADVERSE REACTIONS

General
Cold burns (see Accidental Contact under Overdosage)

Cardiovascular
Cardiovascular depression, hypotension, arrhythmia, increased pulmonary vascular resistance

Respiratory
Hypoxia, diffusion hypoxia, asphyxia

Neurological
Headache, dizziness, confusion, CNS excitation and depression, raised intracranial pressure, anxiolytic effects, euphoria, neuropathy, seizures, drowsiness. Exceptionally heavy occupational exposure and addiction have resulted in myeloneuropathy and subacute combined degeneration of the cord.

Gastrointestinal
Nausea, vomiting, bowel distension following prolonged anaesthesia.

Haematological
Inactivation of vitamin B_{12} (a cofactor in methionine synthesis). Folate metabolism is consequently interfered with and DNA synthesis is impaired following prolonged nitrous oxide administration. This results in symptoms similar to vitamin B_{12} deficiency and megaloblastic bone marrow changes. Bone marrow depression with resultant leukopenia, thrombocytopenia and severe megaloblastic anaemia have been noted.

Pregnancy and Lactation
See Use in Pregnancy and Use in Lactation.
Prolonged occupational exposure to high levels of nitrous oxide may affect a woman's ability to become pregnant.

Addiction and abuse of nitrous oxide have been reported.

DOSAGE AND ADMINISTRATION

Premedication

Premedication should be selected according to the needs of the individual patient and in consideration of the respiratory depressant effect of nitrous oxide.

General Anaesthesia

The use of nitrous oxide in general anaesthesia is mainly as an adjuvant to other volatile inhalational anaesthetics. Its use as the sole anaesthetic agent can lead to hypoxia and inadequate depth of anaesthesia.

In the average adult, nitrous oxide is administered by inhalation through a suitable anaesthetic apparatus in concentrations up to 70% with oxygen as the balance.

The concentration of nitrous oxide administered during maintenance of anaesthesia must be individualised depending upon the condition of the patient and supplemental medications administered.

The concentrations required in children must be individualised.

The inspired concentration of oxygen may need to be increased in elderly patients or those with pulmonary disease.

The efflux of nitrous oxide from the tissues via the lungs at the end of anaesthesia may lead to diffusion hypoxia if supplemental oxygen is not administered.

Analgesia

In the average adult, nitrous oxide is administered by inhalation through a suitable face mask in concentrations up to 50% with oxygen as the balance.

The concentrations required in children must be individualised.

Routes of administration

Nitrous oxide is inhaled through a face mask or tracheal tube by means of an anaesthetic apparatus. The gas is breathed in by the patient and absorbed through the lungs.

Nitrous oxide should only be administered by medical personnel trained in the appropriate techniques.

OVERDOSAGE

Symptoms and signs

Inappropriate or deliberate inhalation of nitrous oxide will ultimately result in unconsciousness, passing through stages of increasing light-headedness and intoxication, and, if the person were to be within a confined space, death from anoxia could result.

Other signs may include: bradycardia, respiratory depression, cardiovascular depression and severe hypotension.

Treatment

There is no specific antidote. Treatment measures include: discontinuation of nitrous oxide, basic life support, assisted or controlled ventilatory support with oxygen and other symptomatic and supportive treatment.

Accidental Contact

Local pain usually warns of freezing, but sometimes no pain is felt or is short lived. Frozen tissues are painless and appear waxy, with a pale yellowish colour. Thawing of the frozen tissue can cause intense pain. Shock may occur if the area is large.

Loosen any clothing that may restrict circulation and seek immediate hospital attention for all but the most superficial injuries. Do not apply direct heat to the affected parts, but if possible place the affected part in lukewarm water. Sterile dry dressings should be used to protect damaged tissues from infection or further injury, but they should not restrict circulation. Alcohol and cigarettes should not be given.

PRESENTATION

Please consult the Material Safety Data Sheet for medical nitrous oxide from the sponsor.

Pharmaceutical form

Low temperature liquid medical gas (for medicinal use only) supplied in insulated pressure vessels. Liquid is withdrawn and vapourised or gas is withdrawn and warmed to ambient temperature for distribution via pipe networks to usage points.

Pallet Tank (PT)	PT700 Nominal Water Capacity 710 litres.
Portable Cryogenic Container (PCC)	PCC Nominal Water Capacity 160-180 litres

Storage

The normal precautions required in the storage and use of refrigerated liquid tanks are applicable. Please refer to Commonwealth, State and Territory Dangerous Goods legislation and the appropriate Australian Standards eg (AS1894). The area around the tanks must be kept clean and clear of any combustible materials. They must be installed on suitable foundations and be in a well ventilated area with adequate access for deliveries and maintenance. Only suitably trained and authorised persons should operate the storage tank. Access by the public should be denied.

NAME AND ADDRESS OF THE SPONSOR

BOC Gases Australia Limited
Riverside Corporate Park
10 Julius Avenue
NORTH RYDE NSW 2113

ABN 95 000 029 729

TGA Approval date: 2 November, 2001
Date of this amendment 9th April 2008
AUST R 34464

[1]Date annotated at request of TGA Office 7th November, 2008.