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ENTONOX®

The essential guide

BOC: Living healthcare

Index

Introduction

ENTONOX® is the 50:50 mixture of nitrous oxide (N_2O) and oxygen (O_2). It is a very effective analgesic agent with rapid onset and offset characteristics. Extensive use of ENTONOX and nitrous oxide has shown that its effects are predictable and reliable and it has proved to be a very safe agent with minimal side-effects.

Nitrous oxide was discovered and purified by Priestley, Mayow and Hales in the mid 1700's. The American dentist Horace Wells first used it medically in 1844 to reduce the pain of tooth extraction. During the late 1800's the use of nitrous oxide became popular in the USA and was introduced into Europe, in 1867, by Quincy Coulton[1].

Interestingly, until the late 1800's nitrous oxide was used alone and without any supplemental air or oxygen, therefore some of the sedative and analgesic effects of the gas could have been due to hypoxia.

In 1881 nitrous oxide was introduced for pain relief in childbirth and in 1911 Guedel described an analgesic technique (possibly the first patient controlled analgesia) in which patients self-administered a mixture of air and nitrous oxide during childbirth and minor surgery[2].

BOC Healthcare studied the nitrous oxide/oxygen system after a suggestion from Tunstall in 1961. It was found that it was possible to store a pressurised homogeneous gas mixture containing nitrous oxide at ambient temperature. This led to the BOC pre-mixed gas patent and to the ENTONOX product.

Since the introduction of ENTONOX into obstetric practice by Tunstall in 1961[3] and into the ambulance service by Baskett in 1970[4], ENTONOX has become the mainstay of analgesia for childbirth and pain relief in acute situations.

Today nitrous oxide is an essential ingredient in anaesthesia. As ENTONOX it is a vital part of analgesia for childbirth and is uniquely placed as an ideal agent for the treatment of short-term pain due to almost any cause.

Pharmacology of analgesic action

ENTONOX is a gaseous analgesic agent that is composed of nitrous oxide and oxygen in equal proportions. It is supplied in cylinders that have a white and blue shoulder. The gas is contained at a pressure of either 137bar or 217bar and is delivered to the patient by connecting the cylinder to a demand valve via an integral or external pressure regulator. The patient will self-administer the gas, under the supervision of an appropriate healthcare professional, by using a mouthpiece or facemask attached to a demand valve.

How ENTONOX works

ENTONOX is widely used as an analgesic agent but its mechanism of action has not yet been fully explained. It is known that the effects of ENTONOX take place within the pain centres of the brain and spinal cord and are related to the release of endogenous neurotransmitters such as opioid peptides[5] and serotonin[6,7] and the activation of certain opioid receptors[8,9]. Also, Jevtovic-Todorovic et al.[10] found that N-methyl-D-aspartate (NMDA) receptor currents were inhibited by nitrous oxide and it is known that the NMDA receptor is involved in many CNS pathways, that control sensations, such as pain and euphoria. Whilst many of the anaesthetic effects of nitrous oxide remain unknown, there is increasing clarity as to the analgesic affects of this gas.

A hypothesis by Maze et. al.,[11] suggests that ENTONOX has its analgesic effects by the activation of descending noradrenergic pathways due to the release of opioid peptides in the peri-aqueductal grey area of the midbrain. These descending pathways are thought to modulate pain through the activation of alpha-2 adrenoceptors in the dorsal horn of the spinal cord.

Due to the physical properties of nitrous oxide (namely its blood/gas solubility) ENTONOX works very quickly and analgesia is maximal within 2-3 minutes of inhaling the gas but its effects are apparent within a matter of breaths.

Rapid recovery

Recovery from the effects of ENTONOX are very rapid[12]. Once inhalation of ENTONOX has stopped, there is a fall of 35% in the arterial concentration within 30 seconds[13]. Studies have shown psychomotor recovery, after 30 minutes of exposure. This was shown in a clinical trial undertaken at the HPRU medical research centre using 50% nitrous oxide.[14] In a study by Zacny et. al., there was a subjective feeling of complete recovery, within 5 minutes[15], in individuals who breathed 40% nitrous oxide for 30 minutes.

A study by Martin et al.[16], used a technique shown to be the most sensitive test for detecting impairment of driving ability due to drugs to assess the effect of ENTONOX on simulated driving ability following its use during screening flexible sigmoidoscopy. The group concluded that ENTONOX did not impair driving ability when used for this application.

The patient can drive home just 30 minutes after ENTONOX administration, provided a healthcare professional has judged them competent and the patient agrees that they feel able to drive.

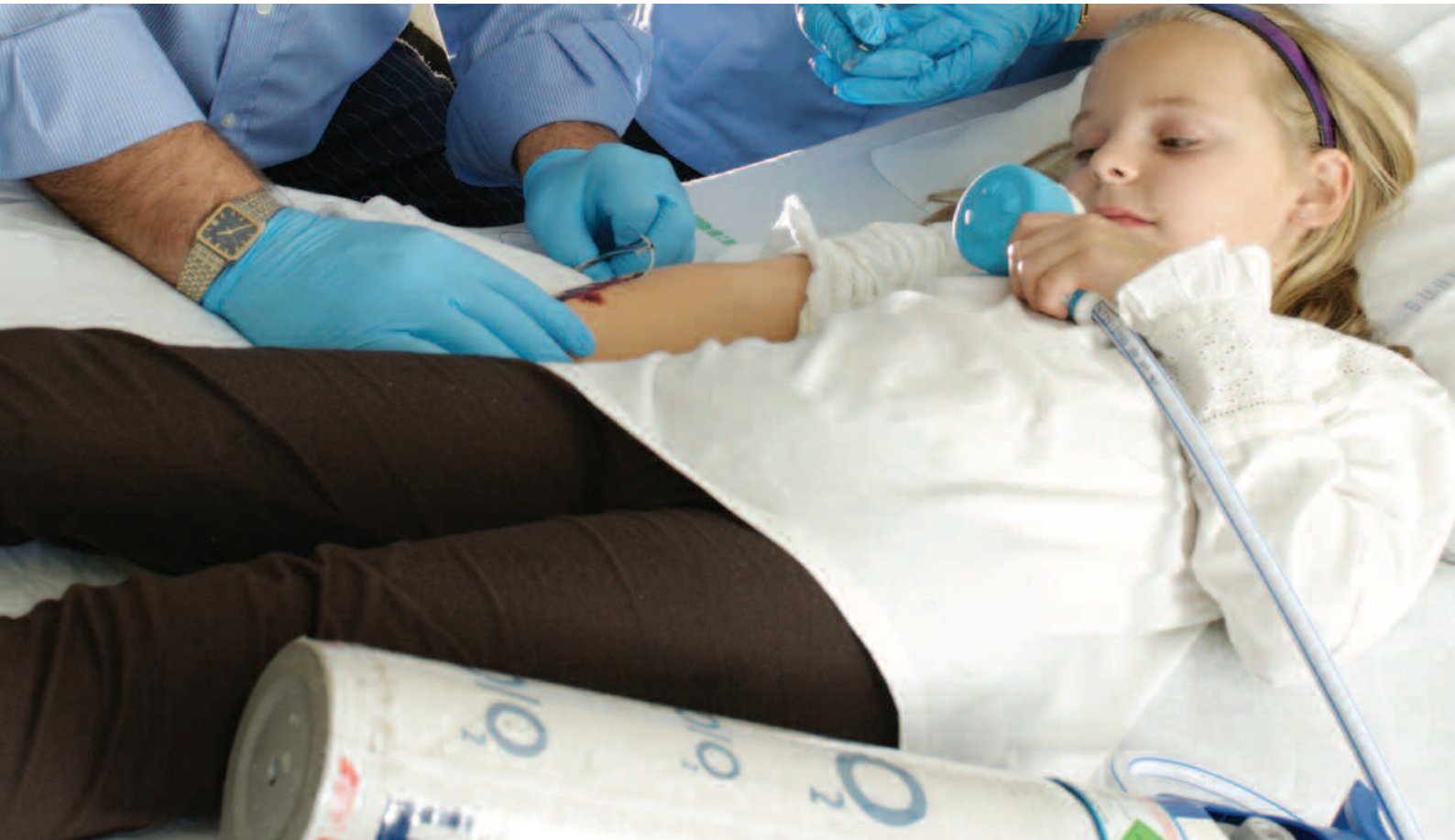
Additional care is needed when ENTONOX is administered to a patient who has been given concomitant medication.

Safety and efficacy

The level of analgesia has been compared with the effects of opiates. Chapman et al.[17] found that 20-30% nitrous oxide had a comparable pain relieving effect to 15mg of subcutaneous morphine and Dundee and Moore[18] showed that 50% nitrous oxide (ENTONOX) was equivalent to approximately 100mg pethidine.

Due to the low fat solubility of nitrous oxide, it does not accumulate to any great extent within the body. In addition, nitrous oxide is not metabolised by the body and will be eliminated completely by the lungs.

The pharmacological profile of ENTONOX offers rapid onset of potent analgesia with speedy reversal of effects when required. This fast offset of action offers a clear advantage over all other analgesic agents, and if used in combination for pain relief allows a reduction in the doses of the other agents used (e.g. morphine, pethidine), thus reducing the often serious side-effects associated with them.



ENTONOX and clinical therapy

The reduction and elimination of pain and anxiety is extremely important to healthcare professionals and patients alike. ENTONOX has proved to be a useful analgesic and sedative agent that is fast, safe and easy to handle.

ENTONOX is widely used in many clinical areas in hospitals and in the ambulance service. The benefits of ENTONOX for the relief of acute pain and discomfort due to short procedures in accident and emergency departments, hospital wards and clinics are now increasingly recognised by healthcare professionals. This reflects the enthusiasm and eagerness shown by many hospital staff in their use of ENTONOX for the benefit of providing pain relief for patients.

Obstetrics

During childbirth, ENTONOX analgesia can help to relieve the pain experienced by women as they undergo labour. It does not completely eliminate the sensation associated with contractions, but reduces the level of pain and anxiety to make them more manageable.

It is used during early labour to help mothers cope with the pain during contractions and, if required, for uncomfortable vaginal examinations and suturing. It is generally used towards the end of the first stage of labour. The gas mixture allows, as near as possible, the mother to experience the sensation of a natural birth.

It is an effective method of pain relief for mothers who want to remain in control during labour[19]. ENTONOX is self-administered under the supervision of midwives, allowing mothers to adjust their intake to suit their own individual pain thresholds and comfort levels.

ENTONOX is known to cross the placenta but has no known negative effects on the baby during childbirth. In fact, the oxygen component will increase the levels of oxygen in the bloodstream, which ultimately will pass via the placenta to the baby. This is good for the baby, especially during labour contractions[19].

ENTONOX and emergency care

In 1970 Baskett first used ENTONOX as part of the immediate care given by the ambulance service. Since then many studies have reported on the beneficial effects of ENTONOX. Donan et al.[20] showed, in 240 patients with traumatic chest, abdominal or back pain, over 90% experienced relief of their pain and apart from drowsiness, no side-effects were reported.

Stewart et al.[21] showed the safety of ENTONOX in pre-hospital care in a 1983 study of over 1,000 patients. They found no serious complications, but reported the following minor side-effects:

- 10.3% dizziness - 3.7% excitation
- 5.7% nausea - 0.3% numbness
- 7.6% became drowsy or fell into a light sleep but all could be readily roused by verbal command, all could cough and swallow on request and no cardiovascular side-effects were noted.

Today ENTONOX forms an integral part of the immediate care offered by ambulance staff and first responders. ENTONOX has the benefit of a non-invasive mechanism of delivery, few side-effects or contraindications and is simple to use. These properties make ENTONOX an ideal analgesic for treating patients in the pre-hospital setting as well as accident and emergency departments.

ENTONOX for painful procedures

ENTONOX has been used widely in the treatment of pain due to injury and also pain caused by medical intervention, investigation and treatment.

Colonoscopy

ENTONOX is used during colonoscopy because of its benefits over intravenous, intramuscular and oral sedation. Saunders et al.[22] showed effective sedation with ENTONOX compared with pethidine and midazolam. They reported fewer episodes of arterial desaturation as well as faster recovery and reduced time to discharge in the ENTONOX group.

In another study by Lindblom et al.[23], recovery time after colonoscopy was reduced by 37 minutes in the ENTONOX group compared with the intravenous ketobemidone and midazolam group, with similar levels of relief from discomfort in both groups.

Notini-Gudmarsson et al.[24] found similar results when comparing ENTONOX with intravenous pethidine for routine colonoscopy.

On the whole, the studies have shown effective sedation and analgesia using ENTONOX, with more rapid recovery times and no serious side-effects being noted. Some studies have found less effective analgesia with ENTONOX, compared to alternative analgesics, but have found good patient acceptability and faster recovery[25].

For more information see “Effect of ENTONOX on other systems”.

Paediatrics

ENTONOX and other nitrous oxide/oxygen mixtures have been extensively studied in paediatric practice with encouraging results. Griffin et al.[26] reported the reduced apprehension and the positive view taken by the patients, parents and staff in approximately 3,000 painful procedures performed under ENTONOX analgesia.

Many reports have shown the benefits of nitrous oxide mixtures in a variety of conditions and procedures in paediatric practice.

- Effective analgesia and anxiolysis during venous cannulation with the use of ENTONOX [27].
- Better anxiolysis and analgesia with nitrous oxide/oxygen mixture compared with EMLA cream for venous cannulation[28].
- Significant decrease in measures of anxiety during laceration repair with the use of ENTONOX [29].
- Reduced procedure time and effective analgesia for outpatient fracture reduction compared with intravenous regional anaesthesia[30].
- Effective and safe analgesia for fracture reduction with self-administered ENTONOX and haematoma block[31].
- Comparison of ENTONOX vs. intra-muscular sedation for the reduction of fractures in children in which the ENTONOX was, at least, as effective as meperidine + promethazine and had far quicker onset time and time to discharge[32].
- ENTONOX provides effective and painless analgesia in a paediatric emergency department [33,34].

All these studies have shown the benefits of ENTONOX in paediatric practice. They highlight the benefits of ENTONOX analgesia such as faster onset time, rapid recovery, the non-invasive nature of administration and a very low incidence of side-effects.

ENTONOX for painful procedures continued...

As in the case of paediatric use, the benefits of ENTONOX in the adult population as a treatment for painful procedures and conditions are obvious.

From the work done in the ambulance and obstetric/midwifery fields, ENTONOX is known to be a safe and effective treatment for moderate to severe pain, either alone or in combination therapy. In addition to this large body of evidence, there is further work pointing to its benefits in specific areas.

- Effective, safe and relatively inexpensive analgesia with ENTONOX for the removal of nasal packs[35].
- Nitrous oxide/oxygen mixtures as effective analgesia for vascular and interventional procedures[36].
- Benefits of nitrous oxide/oxygen mixture for outpatient surgery (intra-ocular implants)[37].
    - Accepted as a non-toxic conscious sedation modality with simple equipment that allows safe, easy administration.
    - The drug is particularly desirable in the elderly who may have respiratory or cardio-vascular disease, and seems ideally suited to ambulatory surgi-centres[37].
- Effective analgesia with ENTONOX in acute myocardial ischemia, without significant side effects [38].

ENTONOX is ideal for the treatment of acute pain in accident and emergency departments. It also offers a safe and effective alternative to the commonly used analgesic agents (e.g. morphine, Oramorph, pethidine and NSAID's) in the control of pain due to short procedures. For example:

- fracture manipulation
- dermatological procedures
- endoscopy
- wound dressing changes
- suturing of lacerations
- burns dressing
- venepuncture
- orthopaedic joint manipulation
- vascular procedures
- patient mobilisation
- radiological procedures
- wound drain removal.

As well as having a proven pain relieving effect on its own, when used in combination with other analgesic agents, the use of ENTONOX may allow for a dose reduction of these drugs thus reducing the (usually more serious) side-effects associated with them.

Dentistry

Since Horace Wells started using nitrous oxide for analgesia during dentistry in the 1840's, the use of nitrous oxide in air or oxygen has spread all over the world. Its safety in the pain relief of patients undergoing dental treatment has been well documented or demonstrated. In 1972 Ruben[39] estimated that more than 3,000,000 patients had been given nitrous oxide with no serious side-effects being reported. Today in modern dentistry in the UK, a variable mixture of nitrous oxide and oxygen is used to control pain relief and levels of sedation.

Effect of ENTONOX on other systems

Respiratory system

The effects of ENTONOX on respiration are minimal. There is a small decrease in tidal volume that is compensated for by a small increase in respiratory rate. The combined effect of these changes is often a slight increase in minute ventilation without a change in blood carbon dioxide (CO_2) levels. Diffusion hypoxia is a phenomenon that can occur after inhaling nitrous oxide in anaesthesia. It is due to nitrous oxide diffusing out of the body faster than nitrogen can diffuse in, thus resulting in dilution of the oxygen contained within the lungs and a reduction in arterial oxygen levels and saturation. Wilkins et al.[40] and Einarsson et al.[41] showed that the use of ENTONOX did not result in arterial desaturation unless hyperventilation took place (hyperventilation with the resulting decrease in arterial CO_2 and reduced ventilatory drive).

Gastro-intestinal system

The safety of ENTONOX in gastro-intestinal procedures has been shown. There were no significant alterations in bowel function reported when ENTONOX was used as analgesia for colonoscopy in the papers covered. Krogh et al.[42] showed that the use of nitrous oxide in major colonic surgery did not worsen bowel distension, did not increase post-operative nausea and vomiting, did not affect post operative ileus and did not increase anastomosis break-down rate. Two further randomised trials did not show any effect of nitrous oxide on operating conditions during or bowel function after abdominal surgery[43,44].

The effects of ENTONOX and nitrous oxide on the bowel have been argued. It has been accepted as safe for use, as sedation, during colonoscopy and endoscopy.


Entonox

Considerations for use of ENTONOX

Contraindications

ENTONOX should not be used in any condition where gas is entrapped within a body and where its expansion might be dangerous, such as:

- artificial, traumatic or spontaneous pneumothorax
- air embolism
- decompression sickness
- following a recent dive
- following air encephelography
- severe bullous emphysema
- use during myringoplasty
- gross abdominal distension
- in patients having received recent intraocular injection of gas (such as SF_6).

Enclosed gas spaces

The use of ENTONOX is contraindicated in all cases where there is trapped gas space within the body because nitrous oxide will, rapidly, diffuse into the space, thus increasing its size.

Side-effects

Most side-effects associated with the correct use of ENTONOX for short-term use are minimal and wear off quickly.

Effects on vitamin synthesis

The nitrous oxide part of ENTONOX can affect vitamin B_{12} synthesis by inhibiting the enzyme methionine synthetase. This effect is of importance if the therapeutic exposure to ENTONOX exceeds a total of 24 hours, or more frequently than every 4 days. In these circumstances close clinical supervision and haematological monitoring is required. Nitrous oxide can also interfere with folate metabolism and DNA synthesis, which can impair bone marrow function. Nunn et al.[45] reported that evidence of actual harm to patients is lacking unless in extreme circumstances and stressed that the effects on vitamin B_{12} and folate require prolonged exposure.

Mild nausea

There is very little evidence to suggest ENTONOX has an emetic effect and all studies reviewed display very low levels of nausea and vomiting during its use.

Dizziness, euphoria and mild nausea are sometimes experienced but rapidly subside following withdrawal of the gas.

Safety and the environment

Occupational exposure

Long term occupational exposure to significant levels of nitrous oxide can result in myeloneuropathy - a condition similar to sub-acute combined degeneration of the spinal cord in which there is peripheral sensory and motor impairment.

This condition has been reported in individuals addicted to the inhalation of ENTONOX and nitrous oxide. There has also been concern that nitrous oxide exposure can lead to fertility problems as a result of a study on pregnant rats that were exposed to high levels of nitrous oxide for prolonged periods[46]. There has been very little evidence that similar effects occur in humans but a questionnaire by Rowland et al.[47] suggested a slightly higher risk of abortion in dental nurses working in rooms without scavenging.

Alternatively, a study involving almost 4,000 midwives[48] stated that the use of nitrous oxide is not associated with an increased risk of abortion. In order to reduce the risks to staff, the UK H&SE has set an occupational exposure limit of 100ppm over an 8-hour time weighted average (TWA). This is a fifth of the dose at which no effects were seen in animal studies and represents a level at which there is no evidence that human health would be affected. A study by Henderson et al.[49] in 1999 showed that over a 14 month period, in the anaesthetic rooms, operating theatres and recovery rooms of 8 hospitals within Wales, the time weighted average levels all fell within the occupational exposure limit.

A study commissioned by EIGA on the toxicological effects of nitrous oxide in humans suggested that there was no causal relationship between fertility and nitrous oxide exposure[50]. This was providing that the correct controls (scavenging, air exchange systems) were used to maintain the recommended air quality (100ppm for the UK).

Environmental pollution

Nitrous oxide has an influence on the green house effect since it reduces heat radiation. However, the energy information administration (USA) states the principal source of nitrous oxide is the breakdown of fertilisers and natural compounds in the soil. Medical nitrous oxide contributes approximately 0.1% of the total release of nitrous oxide into the atmosphere in the USA[51].

Safe working recommendations

According to the American Society of Anesthesiologists' task force on trace anaesthetic gases there is insufficient evidence to recommend any routine medical surveillance of personnel exposed to trace concentrations of waste anaesthetic gases as long as routines are followed that ensure compliance with existing occupational limits[52].

To minimise the potentially negative effects on health from chronic exposure to trace concentrations in the working environment, most authorities have set clear recommendations on ambient air quality. The maximum limits set in the UK and Ireland for the average exposure level, measured over an eight hour period is 100 ppm. This is well below the limits that are likely to have any effect on the midwives and medical personnel working within the hospital or at the patient's home. These levels should be adhered to wherever ENTONOX is used[52].

- ENTONOX should be administered in rooms with proper ventilation and/or air exchange systems set to the proper levels.
- National air quality guidelines should be followed.

Summary

Nitrous oxide and ENTONOX have been used in pain relief, sedation and anaesthesia for more than 40 years. Millions of patients have been treated without any serious side-effects or adverse events having been reported. The effects of ENTONOX are fast. They are felt after only three to four breaths and are maximal after just 2-3 minutes. The effects also disappear rapidly once ENTONOX is removed and even with sensitive psychometric tests, it is difficult to display residual effects after 30 minutes.

The patient may drive home 30 minutes following cessation of administration of ENTONOX, providing a healthcare professional judges them competent and the patient agrees they are able to do so.

Additional care is needed when ENTONOX is administered to a patient who has been given concomitant medication.

Great strides have been made in the pre-hospital, emergency and hospital management of patients, yet the relief of pain and suffering is something that is often forgotten, or provided in a sub-optimal fashion. In addition, it is easy not to appreciate the pain the patient has, or overlook it as it is produced while one is seeking to help.

The optimal analgesic should have rapid onset, short duration, few side-effects and no major adverse reactions. Nitrous oxide, as ENTONOX, known since 1776, is perhaps the drug that comes closest to meeting the ideal[53].

ABBREVIATED PRESCRIBING INFORMATION:

Name of the medicinal product: ENTONOX (oxygen 50.0% +/- 2.0%, nitrous oxide 50.0% +/- 2.0%)
Therapeutic indications: ENTONOX is used exclusively for the relief of pain.
Posology and method of administration: ENTONOX is administered through a facemask or mouthpiece. The facemask or mouthpiece is connected to an ENTONOX supply through a demand valve system which allows the ENTONOX to be self-regulated by the patient. The demand valve is operated by the act of inhalation of the patient and closes down when the patient ceases to inhale. There are no contra-indications to the use of ENTONOX in any age group.
Contra-indications: ENTONOX should not be used in any conditions where air is entrapped within a body and where its expansion might be dangerous.
Special warnings and precautions for use: The nitrous oxide constituent of ENTONOX causes inactivation of vitamin B_{12}, which is a co-factor of methionine synthase. Folate metabolism is consequently interfered with and DNA synthesis is impaired following prolonged administration of ENTONOX. Prolonged or frequent use of ENTONOX may result in megaloblastic marrow changes, myeloneuropathy and sub acute combined degeneration of the spinal cord. ENTONOX should not be used for more than a total of 24 hours, or more frequently than every 4 days, without close clinical supervision and haematological monitoring. Specialist advice should be sought from a haematologist in such cases. Haematological assessment should include an assessment for megaloblastic change in red cells and hypersegmentation of neutrophils. Neurological toxicity can occur without anaemia or macrocytosis and with B_{12} levels in the normal range. In patients with undiagnosed subclinical deficiency of vitamin B_{12}, neurological toxicity has occurred after single exposures to nitrous oxide during general anaesthesia. Reduced fertility in healthcare personnel has been reported where they have been repeatedly exposed to levels of nitrous oxide above the specified occupational exposure limits in inadequately ventilated rooms. In patients taking other centrally acting depressant medicinal products, such as morphine derivatives and/or benzodiazepines, concomitant administration of ENTONOX may result in increased sedation, and consequently have effects on respiration, circulation and protective reflexes. If ENTONOX is to be used in such patients, this should take place under the supervision of appropriately trained personnel (see Interaction with other medicinal products). Thorough ventilation or scavenging of waste gases should reduce operating theatre and equivalent treatment room levels of ambient nitrous oxide to a level below 100ppm. ENTONOX is non flammable but strongly supports combustion and should not be used near sources of ignition. Smoking should be prohibited when using ENTONOX. Under no circumstances should oils or grease be used to lubricate any part of the ENTONOX cylinder or the associated equipment used to deliver the gas to the patient. Where moisturising preparations are required for use with a facemask or in nasal passages, oil based creams should not be used. Check that hands are clean and free from any oils or grease. Where alcohol gels are used to control microbiological cross-contamination ensure that all alcohol has evaporated before handling ENTONOX cylinders or equipment.
Interaction with other medicinal products and other forms of interaction: The nitrous oxide constituent of ENTONOX inactivates vitamin B_{12} and potentiates the effects of methotrexate on folate metabolism. High-dose oxygen may increase the risks of amiodarone-induced postoperative adult respiratory distress syndrome. Pulmonary toxicity can develop in patients treated with bleomycin who are exposed to conventional oxygen concentrations during anaesthesia. High oxygen fraction may potentiate pulmonary toxicity caused by exposure to agents such as paraquat which are toxic to the lung. There is a risk of additive effects when nitrous oxide (contained in ENTONOX) is used in combination with drugs having a central depressant action (e.g. opiates, benzodiazepines and other psychotropics). If concomitant central acting agents are used the risk for pronounced sedation and depression of protecting reflexes should be acknowledged.

Pregnancy and lactation: Pregnancy - There is no published material that shows that nitrous oxide is toxic to the human foetus. Therefore, there is no absolute contra-indication to its use in the first 16 weeks of pregnancy. Lactation - there are no known adverse effects to using ENTONOX during the breast-feeding period.
Effects on ability to drive and use machines: Adverse psychometric effects will normally cease shortly after the administration of ENTONOX has stopped due to the rapid elimination of the nitrous oxide component of the medical gas mixture from the body. When ENTONOX is used as a sole analgesic/sedative agent, driving and use of complex machinery is not recommended until: the healthcare professional has judged that the patient has returned to their normal mental status, the patient feels that they are competent to drive after the relevant procedure is completed, at least 30 minutes has elapsed after the administration of ENTONOX has ceased. Additional care is needed when ENTONOX is administered to a patient who has been given concomitant medication.
Undesirable effects: Events such as euphoria, disorientation, sedation, nausea, vomiting, dizziness and generalised tingling are commonly described. These events are generally minor and rapidly reversible. Prolonged or frequent use of nitrous oxide, including heavy occupational exposure and addiction, may result in megaloblastic anaemia. Agranulocytosis has been reported following prolonged nitrous oxide administration (see 'Special warnings and precautions for use') Myeloneuropathy and sub acute combined degeneration have also been reported following prolonged or frequent use. However in patients with undiagnosed subclinical deficiency of vitamin B_{12}, neurological toxicity has occurred after a single exposure to nitrous oxide for anaesthesia (see 'Special warnings and precautions for use'). Addiction may occur. Nitrous oxide passes into all gas containing spaces in the body faster than nitrogen passes out. Prolonged exposure may result in bowel distension, middle ear damage and rupture of ear drums.
Overdose: When used appropriately, there is no risk of overdose with ENTONOX. Inappropriate, unwitting or deliberate inhalation of ENTONOX will ultimately result in unconsciousness, passing through stages of increasing light headedness and intoxication. The treatment is removal to fresh air, mouth-to mouth resuscitation and, if necessary, the use of an oxygen resuscitator.
Marketing Holder: BOC Limited, The Priestley Centre, 10 Priestley Road, the Surrey Research Park, Guildford, Surrey UK, GU2 7XY.
Marketing Authorisation number: PL 0735/5017R. Pharmacy medicinal product.

Further prescribing information regarding ENTONOX can be found in the full 'Summary of Product Characteristics' available from BOC Healthcare at www.bochealthcare.co.uk.

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