

ANALGESIA

Nitrous oxide in emergency medicine

Í O' Sullivan, J Bengner

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Safe and predictable analgesia is required for the potentially painful or uncomfortable procedures often undertaken in an emergency department. The characteristics of an ideal analgesic agent are safety, predictability, non-invasive delivery, freedom from side effects, simplicity of use, and a rapid onset and offset. Newer approaches have threatened the widespread use of nitrous oxide, but despite its long history this simple gas still has much to offer.

"I am sure the air in heaven must be this wonder-working gas of delight".

Robert Southey, Poet (1774 to 1843)

HISTORY

Nitrous oxide (N₂O) is the oldest known anaesthetic agent. Joseph Priestly first discovered "dephlogisticated" or "factitious" air in 1772. Humphrey Davy noted its analgesic and anaesthetic properties in 1800, but it remained a recreational drug ("laughing gas") until 1884, when Horrace Wells used it as an anaesthetic agent during dental extractions. In 1881 Stanislav used N₂O for the treatment of angina pectoris, and in 1969 Ruben completed a study citing more than three million N₂O-oxygen sedations without mishap.¹ Since then N₂O has gained widespread acceptance and is the most frequently used inhalational anaesthetic agent, usually in conjunction with a volatile gas. It is still the agent of choice in dental practice, and a standard analgesic used in prehospital care and obstetrics.

PHYSICAL PROPERTIES

N₂O is a tasteless, colourless gas. It is rapidly absorbed via the pulmonary vasculature directly into the bloodstream and does not combine with haemoglobin or any of the body tissues. This extremely low solubility in blood produces its rapid onset and offset. N₂O displaces nitrogen and increase the volume of gas in body cavities such as the middle ear, sinuses, pleural space, and gastrointestinal tract. N₂O has remarkably few side effects. No incompatibility with other drugs has ever been demonstrated.

ANALGESIC/ANAESTHETIC PROPERTIES

In 1967 Parbrook described the four levels of nitrous oxide analgesia.² Different levels can be reached rapidly, as arterial tension at the brain will be 90% of that inhaled within minutes.³ Parbrook emphasised that clinical signs, rather than the absolute percentage of inhaled N₂O, should

identify these zones as there is considerable variation between people. He also emphasised the importance of the patient's pre-existing beliefs. If volunteers expect to fall asleep while inhaling 30% N₂O then a high proportion do so. An appropriate physical and psychological environment increases the actions of N₂O and may allow lower doses to be more effective. Unlike many other anaesthetic agents, N₂O exhibits an acute tolerance effect, whereby its potency is greater at induction than after a period of "accommodation".

MECHANISM OF ACTION

Some writers have suggested that N₂O, like volatile anaesthetics, causes non-specific central nervous system depression. Others, such as Gillman,⁴ propose that N₂O acts specifically by interacting with the endogenous opioid system. N₂O is known to act preferentially on areas of the brain and spinal cord that are rich in morphine sensitive cells,⁵ and naloxone has been shown to block N₂O analgesia in a stereospecific manner.⁶ In vitro studies have suggested that N₂O has a partial agonist effect at mu, kappa, and possibly other opioid receptors, while positron emission tomography confirms a concentration of N₂O activity in the medial thalamic area.⁷

Several studies have demonstrated a distinction between the awareness and perception of pain. Concentrations of 15%–45% N₂O produces quantifiable and meaningful increases in the threshold for both sensation and tolerance of pain. At concentrations below 50%, the analgesic effect of N₂O follows a linear dose response pattern,⁸ although this is influenced by cognitive and other psychological factors.

Box 1 Indications for use of nitrous oxide in the emergency department

- Relief of pain from musculoskeletal injuries
- Reduction of joint dislocations
- Adjunct to other analgesia in forearm fracture manipulation
- Adjunct to lignocaine (lidocaine) in laceration repair
- Adjunct to other analgesia in wound care and abscess drainage
- Adjunct or single agent for analgesia during childbirth
- Prehospital analgesia
- Positioning for radiological or endoscopic examinations
- Sickle pain
- Ureteric colic
- Myocardial chest pain
- Migraine

See end of article for authors' affiliations

Correspondence to:
Dr Í O' Sullivan, Bristol and Weston Emergency Departments, Bristol Royal Infirmary, Marlborough Street, Bristol BS2 8HW, UK; lomhar.O'Sullivan@ubht.swest.nhs.uk

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CLINICAL STUDIES

Clinical studies focusing on the analgesic properties of N₂O have shown varying degrees of pain relief. In the following section we have graded published evidence according to the widely recognised criteria described by Sackett *et al.*⁹

In 1964, Parbrook found that inhalation of 20%–25% N₂O produced a similar analgesic potency to 10 mg–15 mg of intramuscular morphine.¹⁰ [level of evidence 2b]

In adults, N₂O has been used for the reduction of fractures and joint dislocations.^{11, 12} [level 2b]. It has also been used for the relief of pain from musculoskeletal injuries, wound care, suture removal, ureteric colic, acute abdominal pain,¹³ [level 2b] and some uncomfortable diagnostic procedures.

N₂O has also been successfully used for the relief of myocardial pain,¹⁴ [level 4] while Trinier's small study of the use of N₂O in migraine showed that 80% of patients achieved symptomatic relief, and did not require rescue medication at one hour.¹⁵ [level 4]

In children, many of the published studies are poorly designed and include only small numbers. Nevertheless, a consistent pattern of moderate to good pain relief is seen. Both 50% and 30% N₂O:O₂ mixtures have been shown to be effective adjuncts to lignocaine (lidocaine) in the repair of lacerations,^{16, 17} [level 2b] while one more recent and better designed study demonstrated that 50% N₂O was superior to oral midazolam for this purpose, with a combination of the two agents increasing side effects without additional benefit.¹⁸ [level 1b] 50% N₂O also compared favourably with intramuscular morphine and sedation in paediatric forearm fracture manipulation.¹⁹ [level 2b] Gregory reported that N₂O produced similar levels of analgesia to lignocaine Bier's block in paediatric forearm fracture manipulation,²⁰ [level 2b] but Hennrikus demonstrated less impressive results when comparing 50% nitrous oxide and haematoma block with 50% nitrous oxide alone.^{21, 22} [level 4]

Entonox analgesia has been successfully and safely used in the prehospital setting and in the ambulance service for many years.^{23–29} It is also very useful as a sole agent or adjunct in delivery suites because it is devoid of effects on the baby.³⁰

SIDE EFFECTS

Vitamin B12

N₂O oxidises cobalamin and thereby inactivates vitamin B12, a cofactor of methionine synthetase. The resulting decrease in DNA production can be detected by an abnormal deoxyuridine (dU) suppression test. Abnormal dU tests have been recorded in patients with exposures lasting only two to four hours. Megaloblastosis and other bone marrow findings similar to those of pernicious anaemia are seen after prolonged N₂O exposure. Prolonged exposure to N₂O can also cause a myeloneuropathy similar to subacute combined degeneration of the cord.³¹ Acute exposure may precipitate a similar clinical syndrome in patients with pre-existing subclinical vitamin B12 deficiency,³² and depression of white cell formation may also occur.³³ Addiction to N₂O has occasionally been reported,³⁴ and misuse should be considered in those presenting with suspicious neurological symptoms or signs.

Cardiovascular effects

N₂O has been shown to produce a fall in cardiac output, stroke volume, P_{aco}₂ and mean arterial pressure with a rise in peripheral resistance,^{35–37} but these changes are similar to those seen when subjects inhale 100% oxygen.³⁵ Some papers have cited a direct myocardial depressant effect of N₂O, which is most marked in patients with reduced cardiac reserve. It has also been shown to cause mild increases in pulmonary vascular resistance in normal subjects, but a more marked response in those with pre-existing pulmonary hypertension. N₂O should therefore be avoided in pulmonary oedema or patients with pulmonary hypertension, particularly mitral stenosis.

Box 2 Contraindications to the use of nitrous oxide in the emergency department

- Pressure effects
 - Intracranial air, bowel obstruction, middle ear disease, decompression sickness, ascitic bullous lung disease, air embolism
- Impaired conscious level
- Early pregnancy
- B12 or folate deficiency
- Immunosuppression
- Significant cardiac failure

Respiratory system

N₂O in sub-anaesthetic doses has no direct respiratory effects. In common with other inhalational anaesthetics, tidal volume decreases as the inspired concentration rises. However, this effect is offset by an increase in respiratory rate. Stewart's experiments on healthy volunteers breathing Entonox demonstrated that the net effect is a rise in arterial oxygen saturation and a slight fall in P_{aco}₂.³⁸ N₂O profoundly depresses the ventilatory stimulation produced by both hypoxia and hypercarbia, and this can potentiate the apnoea caused by the concomitant administration of any respiratory depressant.

Gastrointestinal

Opinion is polarised as to whether or not N₂O causes nausea and vomiting.^{39, 40} It can certainly increase intestinal and middle ear volumes, which may in turn lead to nausea. Although vomiting has not been reported in trials where exposure is comparatively limited a recent meta-analysis of 10 studies has confirmed an association between postoperative emesis and N₂O.⁴¹

EQUIPMENT

In the emergency department N₂O is usually supplied by one of two different systems:

"Entonox" is a pre-prepared 50:50 mixture of N₂O and oxygen. This is supplied in blue cylinders with blue and white quarters on the neck. The cylinder of mixed gases is pressurised to approximately 13 700 kPa (1980 psi). Cylinders of Entonox are attached to a patient delivery system that incorporates a two stage valve. The first stage acts as a pressure reducing valve, while the second is a "demand valve", that only allows gas to flow when the pressure is below atmospheric (that is, the patient supplies a negative pressure through inhalation). The patient either holds a tight fitting mask to their face or applies the necessary suction via a mouthpiece. This demand system makes overdose almost impossible, because as the patient's conscious level falls the mask or mouthpiece will no longer be retained in position, causing room air to be inhaled.

The second method of providing N₂O is via a piped wall supply or directly from cylinders of nitrous oxide, which have a blue body and neck and are filled to a pressure of 4400 kPa (638 psi). In this situation the N₂O is mixed with oxygen using a machine designed for the purpose (for example, an anaesthetic "Boyle's" machine or the Ohmeda "Quantiflex" system). This permits high gas flows and a wide range of N₂O concentrations, but runs the risk of inadvertently delivering a hypoxic mixture. Therefore where such systems are used specific safety measures must be in place (see below).

SAFETY

The greatest risk in administering N₂O is that a hypoxic mixture will be delivered. While Entonox delivery has the inbuilt safety mechanism described above, and the "pin index" system ensures that only the correct cylinder can be attached

to anaesthetic equipment, there is a theoretical risk that if an Entonox cylinder falls below a certain temperature (termed the "pseudo-critical temperature") the N₂O will separate out as a liquid.⁴² This will cause gas delivered from such a cylinder to be initially very rich in oxygen, falling to hypoxic levels as the cylinder is emptied. However, as the "pseudo-critical temperature" is -5.5°C this is rarely a risk in practice. On the other hand, when N₂O is delivered by other means the risk of hypoxia is very real. This was starkly emphasised by the recent tragic death of a 3 year old girl, who was inadvertently given N₂O instead of oxygen in an emergency department resuscitation room. A subsequent document from the Royal College of Anaesthetists, supported by a position statement by the Faculty of Accident and Emergency Medicine,⁴³ indicates that machines used to deliver N₂O must be properly checked, incorporate an anti-hypoxia linkage, and also possess a functioning oxygen analyser with a low concentration alarm in the common gas outflow or breathing system. Virtually all modern equipment will meet these criteria, but as emergency departments are often the last destination of antiquated anaesthetic machines (and that involved in this tragedy was 17 years old), it is essential that all departments conform to these standards, and that N₂O is only administered by appropriately trained clinicians.

N₂O has been shown to accumulate in inadequately ventilated operating theatres, and levels in excess of the recommended 100 parts per million may occur in the emergency department after only a few minutes use of Entonox.⁴⁴ Wherever possible it should be used in a large, well ventilated area for as short a time as is necessary. When using piped N₂O, an efficient scavenging system should be used, and all equipment must be regularly checked for leaks.

In some animal models N₂O has been proved to be directly teratogenic, because of its inactivation of vitamin B12.⁴⁵ A review of the published data indicates that properly administered N₂O with a scavenger system does not increase the incidence of spontaneous abortions, infertility or teratogenicity in exposed pregnant women.⁴⁶

N₂O should not be given to patients after head injury or to anybody with an impaired mental state. It should also not be given to patients with significant cardiac failure as they often require higher oxygen concentrations, and N₂O may have a negative inotropic effect in patients who are already suffering myocardial decompensation.⁴⁷ N₂O is far more soluble than nitrogen and will diffuse into enclosed pockets of air, expanding their volume. It is thus contraindicated in patients with pneumothoraces or bullous lung disease, decompression sickness, air embolism, otitis media, or those with bowel obstruction or intracranial air collections. Finally, because of its effects on DNA and potential teratogenicity, N₂O use should be restricted in the first two trimesters of pregnancy and in patients with B12 deficiency, folate deficiency, or known immunosuppression.

CONCLUSION

N₂O enjoys a non-invasive mechanism of delivery, very few side effects or contraindications, simplicity of use and a rapid onset and offset, bringing it close to the ideal analgesic agent for use in emergency medicine. "Entonox" is a safe and effective preparation that is well established in prehospital care, delivery suites and emergency departments, and that incorporates mechanisms that virtually guarantee its safety. In general, evidence supporting the use of N₂O in other forms is of a poor quality, and merits further study. In the absence of such evidence it could be argued that the use of other delivery systems, such as a Boyle's machine, entails an unacceptable clinical risk without clear benefit. We, however, believe that in view of its excellent overall safety record¹ it is a better choice than many other agents currently in use, and adherence to the safety measures outlined above will ensure that there is no

repeat of a recent tragedy. Overall, N₂O has a comprehensive record spanning many decades and millions of patients: its versatility and clinical effectiveness continue to commend it as an analgesic agent that is as useful in the 21st century as it was in the 19th century.

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Contributors

Íomhar O'Sullivan initiated and drafted the review. Jonathan Bengier provided additional data and edited the paper. Íomhar O'Sullivan acts as guarantor.

Authors' affiliations

Í O' Sullivan, Bristol and Weston Emergency Departments, Bristol Royal Infirmary, Bristol UK

J Bengier, Emergency Department, Bristol Royal Infirmary

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REFERENCES

- 1 Ruben H. Nitrous oxide analgesia in dentistry: its use during 15 years in Denmark. *Br Dent J* 1972;**132**:195-6.
- 2 Parbrook GD. The levels of nitrous oxide analgesia *Br J Anaesth* 1967;**39**:974-82.
- 3 Kety SS. Theory and applications of exchange of inert gas at lungs and tissues. *Pharmacol Rev* 1951;**3**:1.
- 4 Gillman MA. Analgesic (sub anaesthetic) nitrous oxide interacts with the endogenous opioid system. *Life Sci* 1986;**39**:1209-11.
- 5 Haugen FP, Melzack R. The effects of nitrous oxide on responses evoked in the brain stem by tooth stimulation. *Anesthesiology* 1957;**18**:183-95.
- 6 Moody EJ, Mattson M, Newman AH, et al. Stereospecific reversal of nitrous oxide analgesia by naloxone. *Life Sci* 1989;**44**:703-9.
- 7 Gyulai FE, Firestone LL, Mintun MA, et al. In vivo imaging of nitrous oxide - induced changes in cerebral activation during noxious heat stimuli. *Anesthesiology* 1997;**86**:538-48.
- 8 Benedetti C, Chapman CR, Colpitts YH, et al. Effects of nitrous oxide concentration on event-related potentials during painful tooth stimulation. *Anesthesiology* 1982;**56**:360-4.
- 9 Sackett DL, Straus SE, Richardson WS, et al. *How to teach and practice EBM*. 2nd edn. London: Churchill Livingstone, 2000:173-7.
- 10 Parbrook GD, Rees GAD, Robertson GS. Relief post-operative pain: comparison of a 25% nitrous and oxygen mixture with morphine. *BMJ* 1964;**2**:480-2.
- 11 Uglow MG. Kocher's painless reduction of anterior dislocation of the shoulder: a prospective randomised trial. *Injury* 1998;**29**:135-7.
- 12 Gleeson AP, Graham CA, Meyer AD. Intra-articular lignocaine versus entonox for reduction of acute anterior shoulder dislocation. *Injury* 1999;**30**:403-5.
- 13 Payne CG, Edbrooke DL, Davies GK. Minor procedures in the accident and emergency department: can entonox help? *Archives of Emergency Medicine* 1991;**8**:24-32.
- 14 Thompson PL, Lown B. Nitrous oxide as an analgesic in acute myocardial infarction. *JAMA* 1976;**235**:924-7.
- 15 Triner WR, Bartfield JM, Birdwell M, Raccio-Robak N. Nitrous oxide for the treatment of acute migraine headache. *Am J Emerg Med* 1999;**17**:252-4.
- 16 Burton J, Auble T, Fuchs S. Effectiveness of 50% nitrous oxide/50% oxygen during laceration repair in children. *Acad Emerg Med* 1998;**5**:112-17.
- 17 Gamis A, Knapp J, Glenski J. Nitrous oxide analgesia in a pediatric emergency department. *Ann Emerg Med* 1989;**18**:177-80.
- 18 Luhmann JD, Kennedy RM, Lang Porter F, et al. A randomised clinical trial of continuous flow nitrous oxide and midazolam for sedation of young children during laceration repair. *Ann Emerg Med* 2001;**37**:20-7.
- 19 Evans JK, Buckley SL, Alexander AH. Analgesia in paediatric orthopaedics: a comparison of nitrous oxide to intramuscular sedation. *Orthop Trans* 1992;**16**:818-22.
- 20 Gregory PR, Sullivan JA. Nitrous oxide compared with intravenous regional anaesthesia in pediatric forearm fracture manipulation. *J Pediatr Orthop* 1996;**16**:187-91.
- 21 Hennrikus W, Shin A, Klingelberger C. Self administered nitrous oxide and a haematoma block for analgesia in the outpatient reduction of fractures in children. *J Bone Joint Surg* 1995;**77-A**:335-9.
- 22 Hennrikus WL, Simpson RB, Klingelberger CE, et al. Self administered nitrous oxide analgesia for pediatric fracture reductions. *J Pediatr Orthop* 1994;**14**:538-42.

- 23 **Baskett PF**. Entonox. *Proc Roy Soc Med* 1972;**65**:7–8
- 24 **Stewart RD**, Paris PM, Stoy WA, *et al*. Patient-controlled inhalational analgesia in prehospital care: a study of side-effects and feasibility. *Crit Care Med* 1983;**11**:851–5.
- 25 **Johnson JC**, Atherton GL. Effectiveness of nitrous oxide in a rural EMS system. *J Emerg Med* 1991;**9**:45–53.
- 26 **McKinnon KDL**. Prehospital analgesia with nitrous oxide/oxygen. *Can Med Assoc J* 1981;**125**:836–40.
- 27 **Amey BD**, Ballinger JA, Harrison EE. Prehospital administration of nitrous oxide for control of pain. *Ann Emerg Med* 1981;**10**:247–51.
- 28 **Donen N**, Tweed WA, White D, *et al*. Pre-hospital analgesia with entonox. *Canadian Anaesthetists Society Journal* 1982;**29**:275–9.
- 29 **Baskett PJF**. Nitrous oxide in pre-hospital care. *Acta Anaesth Scand* 1994;**38**:775–6.
- 30 **Olofsson C**, Irestedt L. Traditional analgesic agents: are parenteral narcotics passe and do inhalational agents still have a place in labour? *Baillieres Clin Obstetr Gynaecol* 1998;**12**:409–21.
- 31 **Lazyer RB**. Myeloneuropathy after prolonged exposure to nitrous oxide. *Lancet* 1978;iii:1227–30.
- 32 **Hadzic A**, Glab K, Sanborn KV, *et al*. Severe neurological deficit after nitrous oxide anaesthesia. *Anaesthesiology* 1995;**83**:863–6.
- 33 **British Medical Association and Royal Pharmaceutical Society of Great Britain**. *British National Formulary*. Number 41. London: British Medical Association and Royal Pharmaceutical Society of Great Britain, March 2001.
- 34 **Sandoval VA**. Nitrous oxide: a serious look at laughing gas. *Texas Dental Journal* 1993;**110**:13–16.
- 35 **Everett GB**, Allen GD. Simultaneous evaluation of cardiorespiratory and analgesic effects of nitrous oxide-oxygen inhalation analgesia. *J Am Dent Assoc* 1971;**83**:129–33.
- 36 **Thornton JA**, Fleming JS, Goldberg AD, *et al*. Cardiovascular effects of 50% nitrous oxide and 50% oxygen mixture. *Anaesthesia* 1973;**28**:484–9.
- 37 **Trieger N**, Loskota WJ, Jacobs AW, *et al*. Nitrous oxide—a study of physiological and psychomotor effects. *J Am Dent Assoc* 1971;**82**:142–50.
- 38 **Stewart RD**, Gorayeb MJ, Pelton GH. Arterial blood gases before, during, and after nitrous oxide:oxygen administration. *Ann Emerg Med* 1986;**15**:1177–80.
- 39 **Watcha MF**, White PF. Postoperative nausea and vomiting. *Anesthesiology* 1992;**77**:162–84.
- 40 **Hartung J**. Nitrous oxide—it's enough to make you vomit. *Anesthesiology* 1993;**78**:403–4.
- 41 **Divatia JV**, Vaidya JS, Badwe RA, *et al*. Omission of nitrous oxide during anesthesia reduces the incidence of postoperative nausea and vomiting. A meta-analysis. *Anesthesiology* 1996;**85**:1055–62.
- 42 **Davis PD**, Parbrook GD, Kenny GNC. *Basic physics and measurement in anaesthesia*. 4th edn. Oxford: Butterworth-Heinemann, 1996.
- 43 **Faculty of Accident and Emergency Medicine**. *Position statement on anaesthetic machines in the A&E resuscitation room*. London: Faculty of Accident and Emergency Medicine, 2001. (<http://www.faem.org.uk/position1.html>)
- 44 **Dula D J**. Nitrous oxide levels in the emergency department. *Ann Emerg Med* 1981;**10**:575–8.
- 45 **Fink BR**, Shepard TH, Blandau RJ. Teratogenic activity of nitrous oxide. *Nature* 1967;**8**:146–8.
- 46 **Clark MS**, Renehan BW, Jeffers BW. Clinical use and potential biohazards of nitrous oxide/oxygen. *Gen Dent* 1997;Sept/Oct:486–91.
- 47 **Jastak JT**, Donaldson D. Nitrous oxide. *Anaesth Prog* 1991;**38**:142–53.