Inhaled methoxyflurane – an explorable alternative to nitrous oxide?

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Key points

Nitrous oxide has recognised environmental and occupational health risks, with environmental concerns becoming of greater relevance with rising awareness of global warming.

Methoxyflurane has wide evidence base within the field of medicine, showing its analgesic and sedative effects, making it useful in trauma patients and invasive outpatient procedures.

There is limited evidence of the use of methoxyflurane as a sedative drug in dentistry; this evidence base needs to be created to explore viable alternatives to nitrous oxide for inhalation sedation.

Abstract

Nitrous oxide is a widely used and well-established form of inhalation sedation in dentistry. Its properties have a wide margin of safety and allow for anxious, paediatric and adult patients to receive dental treatment with minimal impact upon discharge. Nitrous oxide has drawbacks, however, including its environmental impact and need for specialist equipment. Methoxyflurane is another drug which could prove to be an alternative to nitrous oxide. Methoxyflurane's use has proved popular within emergency medicine in Australia and New Zealand for its potent analgesic effects and recognition of its anxiolytic effect. As a result, its use in invasive outpatient procedures has now become popular. Unfortunately, there is very limited evidence of its use within dentistry as a form of inhalation sedation and analgesic. A wider evidence base should be established, as methoxyflurane could prove to be an effective and environmentally friendly alternative to nitrous oxide.

Discussion

Nitrous oxide (N_2O) is widely used within dentistry, in combination with oxygen, as a form of inhalation sedation. Its properties lend itself well to dental treatment, allowing for rapid onset of sedation at titratable levels and rapid recovery to allow patients to continue normal activities following treatment. As a drug, N_2O has a wide margin of safety, with a generally low potency, reflected by its minimum alveolar concentration of 105%. Its use and evidence base within dentistry to manage anxiety is extensive, proving effective for both adult and paediatric patients alongside appropriate behavioural management techniques.[1,2]

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Sustainability and the environmental impact of dentistry has become a growing topic in recent years.[3] Recognition of the impact we can have has become common knowledge and in turn, practices are slowly changing. Indeed, sustainability is being incorporated into undergraduate curricula to ensure new generations of dental professionals are more environmentally conscious within their clinical practice.[4]

Concerns have been raised regarding the environmental impact of N_2O which is a known anthropogenic greenhouse gas, causing ozone depletion and contributing to climate change.[5] Main sources of N_2O being released into the atmosphere come from agriculture but we must recognise emissions from medical N_2O. In line with current guidance, scavenging is recommended to minimise potential side effects of N_2O on clinical staff through occupational exposure; however, this results in the N_2O being released directly into the atmosphere.[6] New technology, in the form of N_2O destruction units have been developed. These units allow exhaled N_2O to be broken down to regular air which can be safely returned to the atmosphere. However, this equipment is expensive and somewhat cumbersome. With N_2O being a reliable and well-established sedative agent within the dental field, its potential withdrawal from use for environmental or health concerns would be deeply impactful. While its withdrawal is not yet being considered, we must be aware that its use has been suspended in some hospital settings.[7] Indeed, N_2O has now also been classified as a Class C drug, which may bring about regulations regarding storage and access.[8] Therefore, the consideration of alternative drugs and methods of inhalation sedation would be beneficial, with one such alternative being methoxyflurane.

Methoxyflurane was originally an anaesthetic agent used in the 1960s and early 1970s. It is a colourless, volatile liquid with a distinct fruity odour. At low concentrations it is chemically stable and non-flammable at normal room temperature. Supplied as a methoxyflurane inhaler (Pethrox, Galen Limited, Craigavon, Northern Ireland), a 3 ml liquid vial is opened and poured onto a wick within the inhaler. The patient can then inhale the vapour via a mouthpiece. A dilutor valve, to which a chamber of activated carbon is attached, allows for the concentration to be changed,

with 0.2–0.4% inhaled with the dilutor valve uncovered and 0.5–0.7% with the dilutor valve closed by occlusion with a finger. The activated carbon chamber reduces atmospheric release of the drug on exhalation. Figure 1 shows these features. A maximum dose of 6 ml (two vials) can be used within 24 hours. At present, the use of the Penthrox inhaler is not licenced for those under the age of 18. Common side effects as reported by the manufacturer are dizziness, euphoric mood, headaches, somnolence and nausea.[9] Contraindications for the use of methoxyflurane can be seen in Box 1. Regarding occupational exposure, evidence suggests this is minimal; nurses undertaking bone marrow biopsy lists showed exposure levels far below the maximum calculated exposure limit of 15 ppm.[10]

With regard to more concerning side effects, methoxyflurane's use as an anaesthetic agent was suspended due to inducing dose-dependent renal and hepatic toxicity.[11] Despite this, its use has continued at lower doses for its potent analgesic and anxiolytic effects. Methoxyflurane has established itself well mainly within Australia and New Zealand within emergency medicine, mainly in pre-hospital and trauma settings for the above properties. When used at sub-anaesthetic doses, methoxyflurane is able to produce rapid, effective, and importantly, lasting analgesia, owing to its high blood-gas partition co-efficient.[12,13,14] It is also highly soluble in lipids, thus allowing its diffusion into fatty tissue. This may also act as a reservoir, allowing for lasting analgesia.[15] We unfortunately do not know the length of its sedative effects. Following on from this, methoxyflurane has started to be used within outpatient settings to allow for various invasive procedures, for example, in burns dressings, prostate biopsy and colonoscopy.[11] It was proven equally effective for use in outpatient colonoscopies when compared to intravenous sedation.[16] However, in this study, a small number of patients did require additional intravenous sedation on top of the Penthrox inhaler to complete the procedure. With an evidence base established for its analgesic properties, there is recognition of its sedative effects too. However, there are limited studies within the literature specifically assessing the drugs anxiolytic effects.

Other aspects of the drug can also present drawbacks when considering its use within dentistry. Methoxyflurane is not licenced for those aged under 18 in the UK, thus preventing its use in a large part of the patient population. N_2O is arguably one of the biggest tools in the treatment of paediatric patients. Being unable to use Penthrox inhalers with children will clearly be a large barrier for finding alternatives to N_2O. Encouragingly, it is licenced for use in paediatric patients in Australia and proven effective in management of analgesia.[17] This gives precedent for its use in paediatric patients in the UK.

Additionally, there are no guidelines for its safe use in out-patient settings. If this drug were to be introduced in dental practice, would an escort be needed? Would the patient be able to drive home following the appointment? These questions can only be answered with more research and agreement among the profession. From the evidence available, it does seem minimal recovery time would be needed, and patients should be able to return to normal daily activities quickly.[11] Indeed, vital signs monitoring is not needed when using this drug.[10] When consulting the British National Formulary, maximum doses cannot exceed 6 ml per day (two vials), 15 ml per week (five vials), avoiding use on consecutive days. This will require consideration for patients who may need treatment over multiple visits. Lastly, the inhalation of the drug requires putting the inhaler to the mouth; this would naturally stop dental treatment. More issues may be created where restorative treatment is taking place, such as maintaining moisture control or using rubber dam.

With the above data, it can be appreciated how methoxyflurane could lend itself well within the dental field to aid with analgesia and anxiety management, with some disadvantages. Unfortunately, there is limited evidence regarding its use within dentistry specifically, with only one recent study comparing its use in third molar extractions to N_2O. In this study, methoxyflurane was shown to be as effective as N_2O for inhalation sedation.[18] The use of inhaled methoxyflurane in dentistry in certain countries still prevails, however, despite the lack of a well-rounded evidence base.[19]

From the available data and information regarding methoxyflurane, we can see it acts as a potent analgesic drug with recognised anxiolytic/sedative properties. It is rapidly acting, with a relatively quick recovery time as well. It has a

Fig. 1 Penthrox inhaler (a = mouthpiece; b = dilutor valve; c = activated carbon chamber; d = removable cap, where methoxyflurane can be poured onto wick). Image courtesy of Galen

Box 1 Contraindications for use of inhaled methoxyflurane[20,21]

- Use as an anaesthetic agent
- Hypersensitivity to methoxyflurane
- Malignant hyperthermia
- Patients or patients with a known family history of severe adverse reactions after being administered with inhaled anaesthetics
- Patients who have a history of showing signs of liver damage after previous methoxyflurane use or halogenated hydrocarbon anaesthesia
- Clinically significant renal impairment
- Clinically evident cardiovascular instability or respiratory depression
- Interactions with isoniazid, methylphenidate, phenobarbital, primidone, rifampicin, St John's wort

good margin of safety, with doses provided by the Penthrox inhaler being far below those needed to produce any renal or hepatic toxicity, and it is used safely within other health care settings. The inhaler design is simple and would not require adaptation of existing dental clinics for its use. Regarding environmental concerns, the activate carbon chamber should prevent environmental release of the drug. No sedative agent is perfect, however, and the disadvantages discussed here must also be considered. More research needs to be undertaken to establish its efficacy in managing dental pain and anxiety to allow for its use alongside dental treatment. Should it be proven effective, methoxyflurane could be a useful and environmentally friendly alternative to N_2O.

Ethics declaration

The authors declare no conflicts of interest.

Author contributions

Jack Williams and Katherine Wilson both conceived the idea for the opinion paper following reading a published paper regarding methoxyflurane. Jack Williams wrote the paper, with contribution and guidance from Katherine Wilson. Both authors finalised the opinion paper before submission.

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Correction to: First in the world for dental haptics training to transform learning

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