How I Do It: Penthrox in Urology

Roseanne Ferreira, MD,[1] Kevin C. Zorn, MD,[2] Naeem Bhojani, MD,[2] Bilal Chughtai, MD,[3] Dean S. Elterman, MD[4]

[1]Department of Health Research Methods, Evidence and Impact, McMaster University, Hamilton, Ontario, Canada
[2]University of Montreal Hospital Center, Universite de Montreal, Montreal, Quebec, Canada
[3]Department of Urology, Weill Cornell Medical College, New York Presbyterian, New York, New York, USA
[4]Division of Urology, University Health Network, University of Toronto, Toronto, Ontario, Canada

FERREIRA R, ZORN KC, BHOJANI N, CHUGHTAI B, ELTERMAN DS. How I Do It: Penthrox in Urology. *Can J Urol* 2023;30(1):11448-11452.

Penthrox is a portable handheld inhaler that delivers a low dose of methoxyflurane - an anesthetic with analgesic effects, rapid onset of action, and a favorable side-effect profile. It has been widely used for acute pain management in Australia for the past 40 years. Currently, it is approved for use in over 55 countries, including Canada. Prospective randomized studies highlight Penthrox analgesic effectiveness and safety profile for emergency, prehospital and outpatient settings. In addition, the use of multimodal analgesia, specifically Penthrox, can play an important role in the analgesic management of urological procedures, such as prostatic biopsies and office-based minimally invasive surgical therapies. Herein readers will familiarize themselves with Penthrox, significant studies, and technique used for outpatient urological procedures.

Key Words: Penthrox, methoxyflurane, urology, analgesia, MIST

Introduction

Overview of procedure/technology

Methoxyflurane belongs to a fluorinated hydrocarbon group and was first used as a general anesthetic agent in the 1960s.[1,2] Despite initially being widely used, concerns about hepatotoxicity and irreversible dose-dependent nephrotoxicity led it to fall out of favor and be discontinued from the market in the 1970s. However, at low doses, methoxyflurane has well-documented analgesic properties with a favorable side-effect profile and no evidence of nephrotoxicity.[2,3] Therefore, it was reintroduced as Penthrox, a self-administrated, hand-held inhaler for short term relief of moderate to severe acute pain. Penthrox is currently distributed in Canada at Paladin Labs (Montreal, QC, Canada). Penthrox has been approved for use in over 55 countries, including Canada since 2018.[4] Moreover, it has been extensively used as an analgesic for acute pain in prehospital settings (ambulance), emergency and procedural pain in Australia for over 40 years.[1]

Accepted for publication January 2023

Address correspondence to Dr. Dean S. Elterman, Division of Urology, Department of Surgery, University of Toronto, 399 Bathurst Street, MP-8-317, Toronto, ON M5T 2S8 Canada

Penthrox is an asset in multimodal analgesia. The unique characteristics of this agent, such as non-invasive administration, rapid onset of action, short half-life and portability make it an attractive option for acute pain management in different medical settings and in certain populations.[2] The agent is self-administered by the patient, under supervision, allowing the patient to remain alert and responsive throughout the procedure.[1] Rapid recovery to full psychomotor activities and early return to normal activities makes Penthrox a very suitable non-opioid alternative for a variety of short outpatient surgical procedures such as transrectal ultrasound (TRUS)-guided prostate biopsies, bone marrow biopsy, and colonoscopy.[5-8]

Significant historical studies

Acute pain management

The efficacy, safety, and role of Penthrox in analgesia were extensively studied in the literature.[1,2] The STOP! was a randomized, double-blind, multicenter, placebo-controlled trial that evaluated the efficacy of methoxyflurane for treating acute pain in patients over 12 years of age presenting to the emergency department.[9] Three hundred patients were randomized to receive placebo or up to 6 mL of methoxyflurane. Overall, the intervention significantly reduced pain severity when compared to placebo at all time points (-15.1 mm, $p < 0.0001$). The greatest estimated treatment effect of Penthrox was observed at 15 minutes with a mean difference in Visual Analog Scale (VAS) of -18.5 mm, (95% CI -23.4 to -13.5) adjusted for baseline pain and age group. At the 14 day follow up, there was no laboratory evidence of nephrotoxicity and hepatotoxicity.

More recently, the MEDITA study compared the pain relief and safety of methoxyflurane vs. standard therapy (intravenous morphine for severe pain and intravenous paracetamol or ketoprofen for moderate pain) in the emergency setting.[10] This randomized, active-controlled multicenter trial showed pain control for patients with moderate pain was superior in the methoxyflurane group at 3, 5, and 10 minutes observations. In patients with severe pain, it was non-inferior at 3 minutes and superior at 5 and 10 minutes. There was a significant treatment difference in favor of methoxyflurane measured on a 0-100 mm VAS at 15 min (−5.27 mm, $p = 0.020$), 20 min (−5.89 mm, $p = 0.015$), and 25 min (− 5.04 mm, $p = 0.046$), but not at 30 min (− 5.01 mm, $p = 0.056$). The overall median onset of pain relief was 9 min for the intervention vs. 15 min for the standard therapy group.

Penthrox for outpatient procedures

The 06/61 study, a double-blinded, multicenter, placebo-controlled randomized trial, evaluated methoxyflurane's effectiveness in addition to local anesthesia for procedural pain during bone marrow biopsy (BMB).[6] Patients in the intervention group ($n = 49$) reported less pain during the more painful aspiration part of BMB measured on a 0-10 VAS (3.3 vs. 5.0, $p < 0.001$). In addition, half of the patients in the intervention group rated the medication as "very good" or "excellent", compared to 16.5% in the placebo group ($p = 0.005$). Side effects were rare, and no renal or hepatic toxicity was identified at 30 days follow up. This study found methoxyflurane to effectively reduce overall pain during BMB (VAS 4.9 vs. 6.0, $p = 0.011$), suggesting it to be an effective and safe option for procedural pain management for bone marrow biopsies and aspirations.

Penthrox was also evaluated as a feasible and effective alternative for intravenous sedation for colonoscopy. A total of 251 patients in a multicenter controlled trial were randomized to receive either Penthrox or intravenous sedation with midazolam and fentanyl.[8] There was no difference between groups in VAS pain scores before, during, or immediately after colonoscopy. The rates of hypotension, tachycardia, procedural time, or polypectomy were also not different between groups. Additionally, patients in the Penthrox group awoke at an earlier time (3 ± 0 vs. 19 ± 1 minutes, $p < 0.001$) and were ready for discharge earlier (37 ± 1 vs. 66 ± 2 minutes, $p < 0.001$).

Penthrox in urology

In urology, Penthrox has been studied as an adjuvant analgesic modality for TRUS biopsy. An Australian single-arm cohort of 42 patients undergoing TRUS assessed the role of Penthrox as the sole analgesic agent during the procedure.[5] The overall median VAS pain score (on a 0-10 scale) was 3 (interquartile range (IQR) 2-5), and pain intensity had no correlation to the number of biopsied cores. All patients reported they would be happy to undergo the procedure again if clinically indicated. Side effects - most lightheadedness and sickly-sweet taste - were rare, minor, and transient. Soon after, a cohort compared the outcomes of 72 patients undergoing Penthrox alone or associated with 5 mL periprostatic infiltration of local analgesia (PILA) using 2% lidocaine.[11] The median procedural pain score was lower in the combined analgesia group compared to Penthrox alone, with median VAS of 2 (IQR 1-3) and 3 (2-5), respectively ($p = 0.014$). However, both groups reported they would be happy to receive their respective analgesic technique for repeated procedures in the future.

Recently, Hayne et al evaluated the analgesic value of Penthrox with PILA in a phase 3 double-blinded, placebo-controlled randomized trial with 393 patients.[7] There was no evidence that adding Penthrox improved pain at 15 min post-procedure nor significant difference between Patient's Experience of TRUS Biopsy (PETB) scores between groups (PETB difference 0.31, 95%CI -0.75 to 0.14). However, adding Penthrox improved patient-reported discomfort, overall experience, and willingness to undergo repeat biopsies (odds ratio 1.67, 95% CI 1.12–2.49). After 7-35 days post-biopsy, there was no difference in pain recollection between groups. Finally, side effects were rare and transient. The intervention group reported more dizziness (51% vs. 30%, $p < 0.001$) and no difference in nausea, headache, or presyncope between groups.

Additionally, Elterman et al evaluated the safety and efficacy of Penthrox in a pilot study for office-based analgesia for Rezūm, a minimally invasive surgical therapy (MIST) for lower urinary tract symptoms (LUTS) due to benign prostatic hyperplasia (BPH).[12] All patients received protocol analgesia of oral Lorazepam, oral Percocet (oxycodone + acetaminophen), Penthrox, and local lidocaine gel. Patients had a median (range) prostate volume of 53.4 mL (24-158 mL) and received 10.5 (5-21) injections during a median time of 4 minutes 39 seconds (1 min 32s - 7 min 35s). Patients rated their pain intensity on a 0-10 VAS of mean ± standard deviation of 1.4 ± 2.4 after insertion of the Rezūm delivery device, 1.3 ± 2.1 immediately after Rezūm treatment, and 0.9 ± 1.8 at discharge. No side effects were reported, and patients were very satisfied with the convenience, side-effect profile, and global satisfaction of the procedure.

Method and technique

Patient assessment

Patients are evaluated using standard methods as per urological societal guidelines, including medical history, physical examination, and disease-specific diagnostic tests.

We evaluate the patient's fitness for Penthrox use by focusing initially on indications and contraindications as per product monograph.[4] We recommend against using Penthrox for patients with:

1. Ongoing use of analgesic agents for chronic pain.
2. Concomitant use of nephrotoxic agents.
3. INR > 4 or clinical hemodynamic instability.
4. Use of Penthrox within the previous 3 months.
5. Known personal or familial hypersensitivity to Penthrox or other halogenated anesthetics.
6. Clinically significant respiratory depression, cardiovascular instability, renal or hepatic impairment.
7. Altered level of consciousness due to any cause, including head injury, drugs, or alcohol.
8. Known or genetically susceptibility to malignant hyperthermia or a history of severe reactions in either patients or relatives.
9. History of liver dysfunction after previous Penthrox or other halogenated anesthetics use.

Although Penthrox is used in adults older than 65, we monitor them closer as this population has a higher risk for hypotension and bradycardia due to Penthrox's possible reduction in blood pressure.[2]

Penthrox preparation and administration

There are three main components at the Penthrox kit: The Penthrox inhaler (mouthpiece or "the green whistle"), the activated carbon (AC) chamber, and a 99.9% methoxyflurane 3 mL bottle, Figure 1.[4] To prepare and administer this medication we use the following steps:

1. First, insert the AC chamber into the dilutor hole located on the top of Penthrox inhaler.
2. Remove the cap of the methoxyflurane bottle and tilt the inhaler to a 45-degree angle. Pour the bottle's contents into the base of the inhaler while rotating it to ensure the wick is adequately saturated with methoxyflurane.
3. Ensure the patient is in a comfortable position, either sitting or lying down. Place wrist loop over the patient's wrist and instruct them to inhale and exhale through the mouthpiece. This allows the patient to obtain analgesia during inhalation and the AC chamber to adsorb any exhaled methoxyflurane.

Figure 1. Penthrox inhaler, activated charcoal chamber and 99.9% methoxyflurane bottle. Penthrox is a trademark of Medical Developments International Limited, used under license by Paladin Labs.

4. Patient can inhale intermittently or continuously to titrate and tailor their pain management. During use, the patient can cover the hole on top of the AC chamber with their finger if a more concentrated analgesia dosage is required. Minimum dose of analgesia is encouraged.
5. To dispose of Penthrox, place the used inhaler and bottle in a sealed plastic bag and dispose through normal waste.

Analgesic dose and onset

After inhalation, the drug is absorbed into the bloodstream and later diffused to adipose tissue. The onset of pain relief is typically within a median of 4 minutes (95% CI 2-5 minutes) or 6-10 inhalations.[1,3,9] The concentration of vaporized methoxyflurane is 0.2%-0.4% when the dilutor hole is uncovered; this increases to 0.5%-0.7% when the patient covers the hole with a finger.[1] One 3 mL methoxyflurane vial provides 25 to 30 minutes of analgesia on continuous inhalation or 50-55 minutes with intermittent use.[2] If longer analgesia is required, another 3 mL methoxyflurane vial can be used. The maximum recommended dose should not exceed 6 mL in a single administration nor be given on consecutive days.[2,4] The maximum weekly dose of Penthrox is currently 15 mL.[4] Lastly, methoxyflurane's effects are quickly reversed within 3 to 20 minutes after inhalation stops.[4]

Safety

Penthrox has a well-established safety profile.[1] Adverse events are brief and self-limiting. The most commonly reported side effects are nausea, dizziness, somnolence and headache. Patients are monitored for signs of pallor, muscle relaxation, and drowsiness following Penthrox administration. Serious adverse events with Penthrox are considered to be rare.[1,2] To date, we have not experienced any adverse events in our cohort of patients treated with Penthrox.

Although Penthrox is a volatile anesthetic that has the potential to trigger malignant hyperthermia, this side effect is very rare, with one case reported in over 40 years of use in Australia.[1] Moreover, a low dose of Penthrox does not affect myocardial contractility, and no clinically significant effect on vital signs has been reported. Additionally, despite renal toxicity being extremely rare, with no evidence in the literature of low dose methoxyflurane-induced renal dysfunction, this drug is contraindicated in patients with renal impairment. Nephrotoxicity previously reported on high-anesthetic doses is not appreciated with low analgesic doses.[2]

There has been no evidence of adverse events to occupational exposure. Levels of methoxyflurane in areas where the analgesic inhaler is frequently administered are generally very low, suggesting minimal risk to staff in the procedure room.[1]

Monitoring the pain

We measure pain intensity using a 10-point validated Visual Analog Scale at 4 time points: baseline - before any analgesia is given; after the cystoscope insertion and before treatment or stimulation is applied; immediately after the procedure; and at discharge. We found that collecting further information using a scale that measures global medication performance, such as the Treatment Satisfaction Questionnaire for Medication (TSQM 1.4), aids us in understanding how our standard of care aligns with patients' standards of comfort and overall procedural experience.[13]

Post-procedural pain management

Once procedure is completed, the Penthrox device is disposed of. We do not offer Penthrox for post-procedural pain management. We recommend discharging patients home with stepwise ample analgesics appropriate to procedure performed and at the physician's discretion. Post MIST, all patients should consider acetaminophen and NSAID as per label, not exceeding the maximal dose. An opioid such as codeine 30 mg orally as needed, max 3 times a day. Lastly, hydromorphone or oral dose of steroids should be considered in case of breakthrough pain.

Our experience

Our experience with Penthrox is as a tool for multimodal analgesia during office-based MISTs. Our analgesia approach starts 1-hour before patient positioning and prep with 1 to 2 mg oral Lorazepam and 5 mg/325 mg oral Percocet (oxycodone + acetaminophen), followed by intra-urethral application of lidocaine gel 30 minutes prior procedure. Lastly, the patient is instructed to start using Penthrox 5 minutes before the procedure. Since our MISTs duration is rarely longer than 10 minutes, we never used more than one vial per patient. During Penthrox use, we monitor vital signs (heart rate, blood pressure, oxygen saturation, and respiratory rate) at 5, 10, 15, 20, and 30 minutes after the beginning of Penthrox inhalation and every 30 minutes until discharge.

Lastly, despite severe adverse events, such as malignant hyperthermia, being extremely rare, urologists should be equipped with dantrolene and oxygen at their clinic.

Discussion and conclusions

Penthrox is a self-administrated inhalational anesthetic with analgesic effects. Potential advantages highlight the use of methoxyflurane via Penthrox as a convenient option for analgesia, including rapid onset of action and short recovery, high patient satisfaction, minimal cardiovascular effects, and user-friendliness. It is a promising "minimally invasive" pain management option for urological procedures.

The use of this technology in multimodal anesthesia can potentially expand the use of new MISTs in office-based settings, with the possibility of reducing the healthcare burden of BPH-related management. Penthrox was found to be an effective, feasible, and low-cost pain management strategy for Rezūm.[12] The patient-reported pain intensity for the Penthrox pilot study was smaller than the ones reported at the Rezūm II trial, where 68.9% of patients received oral sedation, 20.9% had a prostatic block, and 10.2% received conscious intravenous sedation.[12,14] Larger cohort studies are required to evaluate the role of Penthrox as standalone analgesic management of urological office-based procedures and its cost-effectiveness. Furthermore, seamless adoption of new technology can be influenced by ease of use, reproducibility, and short learning curve. We hope our example of the use of Penthrox on Rezūm and standardized technique can be the catalyst for urologists interested in expanding their office-based MISTs and TMISTs without worrying about shortcomings of additional anesthesia personnel and access to additional equipment.

Disclosures

Dr. Elterman is a consultant/investigator for Boston Scientific, Procept BioRobotics, Olympus, Urotronic, Prodeon, and Zenflow. Dr. Chughtai is a consultant for Boston Scientific, Olympus, Procept and Prodeon. Dr. Zorn is a consultant/investigator for Boston Scientific and Procept BioRobotics. Dr. Bhojani is a consultant/investigator for Boston Scientific, Procept BioRobotics, and Olympus. Dr. Ferreira reports no relevant conflicts of interest. □

References

1. Jephcott C, Grummet J, Nguyen N, Spruyt O. A review of the safety and efficacy of inhaled methoxyflurane as an analgesic for outpatient procedures. *Br J Anaesth* 2018;120(5):1040-1048.
2. Porter KM, Dayan AD, Dickerson S, Middleton PM. The role of inhaled methoxyflurane in acute pain management. *Open Access Emerg Med* 2018;10:149-164.
3. Dayan AD. Analgesic use of inhaled methoxyflurane: Evaluation of its potential nephrotoxicity. *Hum Exp Toxicol* 2016;35(1):91-100.
4. Government of Canada HCPAC and RB. Penthrox - Drug Product Database Online Query [Internet]. [cited 2023 Jan 10]. Available from: https://health-products.canada.ca/dpd-bdpp/info.do?lang=en&code=96490
5. Grummet J, Huang S, Konstantatos A, Frydenberg M. The "green whistle": a novel method of analgesia for transrectal prostate biopsy. *BJU Int* 2012;110(Suppl 4):85-88.
6. Spruyt O, Westerman D, Milner A, Bressel M, Wein S. A randomised, double-blind, placebo-controlled study to assess the safety and efficacy of methoxyflurane for procedural pain of a bone marrow biopsy. *BMJ Support Palliat Care* 2014;4(4):342-348.
7. Hayne D, Grummet J, Espinoza D et al. "Pain-free TRUS B": a phase 3 double-blind placebo-controlled randomized trial of methoxyflurane with periprostatic local anaesthesia to reduce the discomfort of transrectal ultrasonography-guided prostate biopsy (ANZUP 1501). *BJU Int* 2022;129(5):591-600.
8. Nguyen NQ, Toscano L, Lawrence M et al. Patient-controlled analgesia with inhaled methoxyflurane versus conventional endoscopist-provided sedation for colonoscopy: a randomized multicenter trial. *Gastrointest Endosc* 2013;78(6):892-901.
9. Coffey F, Wright J, Hartshorn S et al. STOP!: a randomised, double-blind, placebo-controlled study of the efficacy and safety of methoxyflurane for the treatment of acute pain. *Emerg Med J* 2014;31(8):613-618.
10. Mercadante S, Voza A, Serra S et al. Analgesic efficacy, practicality and safety of inhaled methoxyflurane versus standard analgesic treatment for acute trauma pain in the emergency setting: a randomised, open-label, active-controlled, multicentre trial in Italy (MEDITA). *Adv Ther* 2019;36(11):3030-3046.
11. Huang S, Pepdjonovic L, Konstantatos A, Frydenberg M, Grummet J. Penthrox alone versus Penthrox plus periprostatic infiltration of local analgesia for analgesia in transrectal ultrasound-guided prostate biopsy. *ANZ J Surg* 2016;86(3):139-142.
12. Elterman DS, Zorn KC, Bhojani N, Chughtai B. Efficacy and safety of methoxyflurane (Penthrox) for pain control during water vapor thermal therapy (Rezum) for benign prostatic enlargement. *Can J Urol* 2022;29(6):11355-11360.
13. Atkinson MJ, Sinha A, Hass SL et al. Validation of a general measure of treatment satisfaction, the Treatment Satisfaction Questionnaire for Medication (TSQM), using a national panel study of chronic disease. *Health Qual Life Outcomes* 2004;2:12.
14. McVary KT, Gange SN, Gittelman MC et al. Minimally invasive prostate convective water vapor energy ablation: a multicenter, randomized, controlled study for the treatment of lower urinary tract symptoms secondary to benign prostatic hyperplasia. *J Urol* 2016;195(5):1529-1538.