University Hospitals of Derby and Burton
NHS Foundation Trust

Penthrox (methoxyflurane) - Emergency Department – Clinical Guidelines

Reference No:CG-EMD/3678/23

1 Introduction

Recognition and alleviation of pain in the emergency department should be a priority. As per the RCEM standard, analgesia should be provided to those with moderate to severe pain within 20 minutes of arrival.

Methoxyflurane (Penthrox®) is a fast onset, inhaled, non-opioid analgesic intended for the emergency treatment of pain. It induces muscle relaxation and reduces pain sensitivity by modulating tissue excitability. The risk of abuse with Penthrox is low but caution should be advised.

Penthrox is licensed for the emergency relief of moderate to severe pain in conscious adult patients with trauma and associated pain. **It must not be used for mild pain or any pain associated with causes other than trauma.**

2 Aim & Scope

This policy is to be used by all doctors, nurses, pharmacists, and allied health professionals working in the Emergency Department of UHDB.

This guideline serves to promote the safe and effective use of the Penthrox (methoxyflurane) inhaler in the Emergency Department (ED). It describes the agreed patient groups considered most suitable for the inhaler and precautions and contraindications related to the use.

The guideline suggests appropriate communication between healthcare professionals within ED and those in the Trust but working outside of ED, and ambulance staff, about patients who have received Penthrox.

3 Guidelines Standards and Procedures

1. ED staff should follow the Penthrox user algorithm shown in Appendix A
2. Practical step by step inhaler device instructions are shown in Appendix B
3. Patients may continue to use Penthrox during imaging and transfers within ED, but must remain on a trolley as they may become unsteady.
4. ED staff must complete audit tool found in Appendix C

4 Education and Training

1. Staff are to undergo training for the safe use of the Penthrox inhaler by either a cascade trainer or pharmaceutical company representative, training sessions will be arranged as necessary including updates.
2. Training will include radiographers and fracture clinic staff.
3. A list of all staff trained on the use of Penthrox will be held in both Emergency Departments

5 Indications for Penthrox

Penthrox (methoxyflurane) is licensed for conscious adult patients (18 years and older) with moderate to severe pain (pain score ≥ 4) with traumatic injuries.

It is intended for use as an option for first line analgesia for adult patients with moderate to severe pain from trauma:

- Limb injuries
- Wrist fractures (moderate to severe pain)
- Elbow/shoulder dislocations
- Ankle fractures (moderate to severe pain)
- Dislocated digits
- Open wounds to limbs requiring exploration or washout
- Traumatic abdominal pain
- Pain associated with major trauma
- Chest injuries (pneumothorax is not a contraindication)

6 Contraindications for Penthrox

Penthrox is contraindicated in patients with atraumatic pain and patients with mild pain (pain score <4).

The 'CHECK ALLL' checklist should be used to screen for contraindications

PENTHROX® (methoxyflurane) *Checklist for adm*

IMPORTANT RISK MINIMISATION INFORMATION FOR HEALTHCARE

This checklist is essential to ensure the safe and effective use of m
and appropriate management of important selected risks.
Before using methoxyflurane ...**please CHECK ALLL**.

The patient is not known to have:

C Cardiovascular instability
H Hypersensitivity to methoxyflurane, any fluorinated anaesthetic or to a
E Established or genetically susceptible to malignant hyperthermia or a h
adverse reactions to inhaled anaesthetics in either patient or relatives
C Consciousness reduced (including due to alcohol)
K Kidney impairment

A Age below 18 years
L Lung or respiratory impairment
L Liver impairment
L Last administration of methoxyflurane

If patient has any o
listed here or is tak
drugs listed on the
administer methox

Instruct patient on the correct administration of methoxyflurane.

Reminder: Please read SmPC before administering and give patier
Alert Card. Ensure lowest required dose is administered and maxir
(2 vials) is not exceeded.

Patient is not taking:
CYP-450 enzyme inducers (e.g. alcohol, isoniazid, phenobarbital, r
carbamazepine, efavirenz or nevirapine). Antibiotics with known n
(e.g. tetracycline, gentamicin, colistin, polymyxin B or amphoterici
Concomitant use of methoxyflurane with CNS depressants may pr
depressant effects and patients should be observed closely.

Healthcare professionals are asked to report any suspected adverse
the MHRA via the Yellow Card Scheme online at www.mhra.gov.uk/
search for MHRA Yellow Card in the Google Play or Apple App Store
Any suspected adverse reactions should also be reported to Galen I
028 3833 4974 and select the customer services option, or e-mail
customer.services@galen-pharma.com.

MAT-PEN-UK-000389. Date of Preparation: August 2021 Approved by M

7 Special Warnings

Nephrotoxicity

Methoxyflurane causes nephrotoxicity at high doses due to inorganic fluoride ions, a metabolic breakdown product. Nephrotoxicity is associated with serum levels greater than 40 umol/l, following a single dose 3ml dose of methoxyflurane levels are below 10 umol/l.

Despite this significant safety margin, the lowest dose of methoxyflurane should be used especially in the elderly and patients at risk of renal disease.

Concomitant use of methoxyflurane with medications which are known to have nephrotoxic effects should be avoided, as there is potential for an additive nephrotoxic effect.

Hepatotoxicity

Methoxyflurane is metabolised in the liver. Patients with hepatic impairments and at risk of hepatic impairment, including patients receiving CYP450 enzyme inducers, should not receive Penthrox.

Elderly Patients

Potential effects on blood pressure and heart rate are not significant at analgesic doses but elderly patients may be at increased risk and caution should be exercised in the elderly.

Administration prior to orthopaedic intervention

There have been no studies into levels of fluoride ions at analgesic Penthrox doses and there have been no reported adverse nephrotoxic effects following extensive use in Australasia for 30 years. Trust advice is therefore to avoid Penthrox if the patient would require operative intervention within 6 hours.

Occupational/staff exposure

Penthrox contains the excipient, butylated hydroxytoluene (E321), a stabiliser. Butylated hydroxytoluene may cause local skin reactions (e.g. contact dermatitis), or irritation to the eyes and mucous membranes.

To reduce occupational exposure to methoxyflurane, the Penthrox Inhaler should always be used with the Activated Carbon (AC) Chamber which adsorbs exhaled methoxyflurane. Multiple use of Penthrox Inhaler without the AC Chamber creates additional risk.

- After loading the Penthrox Inhaler, replace cap onto Penthrox bottle
- After use, place used Penthrox Inhaler and used bottle in plastic bag provided, seal and dispose of responsibly.

Any clinical staff concerned that they are suffering from symptoms related to using Penthrox to inform medical staff working in the ED immediately.

To reduce the risk of occupational exposure to methoxyflurane**,** it is recommended that staff should not routinely be administering more than 2 doses per shift. The room should be adequately ventilated.

Pregnancy and Breast Feeding

Caution with the use of Penthrox in pregnancy, especially in the first trimester, and in breast feeding.

Anaesthetics following Penthorx

Caution using Sevoflurane after Penthrox use.

Interacting Medications

Methoxyflurane's metabolism is mediated by CYP450 (particularly CYP 2E1, CYP 2B6, and to some extent CYP 2A6) enzymes and therefore mediations that are enzyme inducers (such as alcohol, isoniazid, phenobarbital, rifampicin, carbamazepine, efavirenz, rifampicin or nevirapine) will increase the rate of metabolism and might increase its potential toxicity and should be avoided when given concomitantly.

Concomitant use of PENTHROX with CNS depressants

If CNS depressants such as opioids, sedatives or hypnotics, general anaesthetics, phenothiazines, tranquilisers, skeletal muscle relaxants, sedating antihistamine and alcohol can add to these depressant effects. If opioids are given concomitantly with PENTHROX, the patient should be observed closely.

8 Prescribing

1. Penthrox® should be prescribed on the current approved prescribing system for the area.
2. Starting dose one bottle of 3ml Penthrox given via inhalation route only.
    - Onset of pain relief is rapid and should occur within 6-10 inhalations or 4-5 minutes. Continuous inhalation provides analgesia for 25-30 minutes. Intermittent inhalation provides analgesia for one hour.
    - Patients should be encouraged to assess their own level of pain and titrate the amount of Penthrox inhaled for adequate pain control.
3. A second dose may be prescribed after senior ED clinician review.
4. No more than 6ml of Penthrox® can be administered in a single day.
5. Administration on consecutive days is not recommended. The total dose to a patient in a week should not exceed 15ml.

Example of Penthrox prescription

Date	Medicine	Dose	Route	Administration Instructions/Indication	Time require
12/4/2018	Methoxyflurane (Penthrox)	3ml	Inhaled	Inhale dose when required for pain relief. Patient controlled analgesia.	XX:XX

9 Administration

Appendix B gives guidance on how a patient can safely administer Penthrox.

1. Penthrox should be self-administered under supervision of a person trained in its administration, using the handheld Penthrox inhaler.

2. A copy of the patient information leaflet (PIL) and alert card should be provided to all patients receiving Penthrox (available in each pack of Penthrox®).

    a. The date and time of administration to the patient and number of vials administered should be recorded on the Patient Alert card by the member of staff in A&E who delivered the inhaler to the patient.

3. Patients must be advised to inhale and exhale through the custom-built Penthrox inhaler to avoid unnecessary exposure of staff to any methoxyflurane gas.

4. Any staff member supervising administration of Penthrox® must be trained appropriately in the use of the inhaler before undertaking supply.

5. The patient can continue to inhale the Penthrox® handheld device en-route to and inside the radiology department if imaging is required.

10 Patient Monitoring

1 Common side effects include dizziness, nausea, coughing, drowsiness, euphoria, dysarthria, amnesia, anxiety, taste disturbance, blurred vision, altered level of consciousness, headache, nausea, paraesthesia hypotension, cough and sweating. These side effects tend to be short-lived.
2 Routine patient monitoring is not required for the sole use of methoxyflurane although it does not obviate the requirement for monitoring of other agents if they are used in conjunction.
3 Patients should be advised not to drive or operate machinery if they develop side effects and should only do so, when they are symptom-free.
4 Patient to be discharged with patient alert card.

11 Disposal of Medicines

1 Inhalers are for single patient use only

2 After use, the Penthrox® device must be disposed of in a sealed plastic bag (provided in pack) which should then be placed in a yellow clinical waste bin.
3 A record of who performed the disposal should be recorded in Meditech or the ED cascard.

12 Monitoring Compliance

1. The use of Penthrox® will be audited within 12 months to ensure compliance with this guideline.
2. Adherence to this guideline will be audited at least once in every three year period. The results of the audit will be presented in governance meetings and to the Trust Drugs & Therapeutic meeting. If deficiencies in care are identified, an action plan will be agreed upon and be implemented in time for the next audit cycle.

13 Supporting References.

1. Royal College of Emergency Medicine. Best Practice Guidelines. Management of Pain in adults. June 2021. RCEM_BPC_Management_of_Pain_in_Adults_300621.pdf (cloudinary.com)

2. Summary of Product Characteristics (SPC) for the Penthrox 3mL inhalation vapour, liquid. Galen Limited. Electronic Medicines Compendium (EMC). Last updated 27/3/2023
PENTHROX 99.9%, 3 ml inhalation vapour, liquid - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)

3. Penthrox administration check list for HCP use, August 2021.
http://www.medicines.org.uk/emc/RMM.395.pdf

4. Summary of Product Characteristics (SPC) for gentamicin 40mg/ml injection. Hospira UK Ltd. Electronic Medicines Compendium (EMC). Last updated 05/2018.
http://www.medicines.org.uk/emc/medicine/21665

5. Analgesic use of methoxyflurane. Dayan A.D. Human and Experimental Toxicology; Jan 2016; vol. 35 (no. 1); p. 91-100

6. The role of methoxyflurane in acute pain management. Porter KM, Dayan AD, Dickerson S, Middleton PM Open Access Emerg Med. 2018 Oct 18;10:149-164.

Development of Guideline	Meg Reynolds – Specialist pharmacists Acute Medicine
In consultation with	Emergency Department
Approved by	Acute Medicine – Dec 2023 Medicine Division -
Review date	Dec 2026
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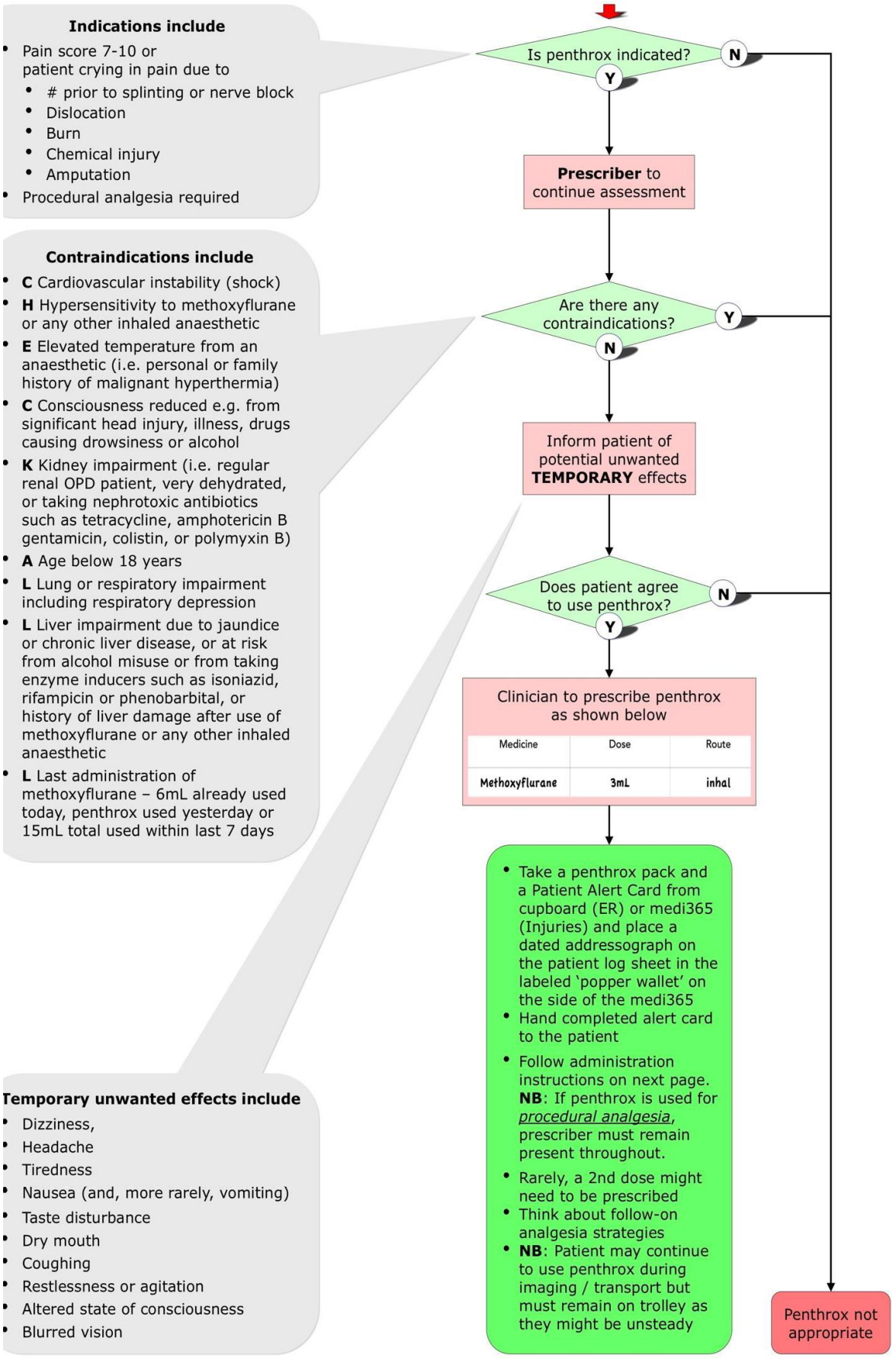
Appendix A – Indication Flowchart



Appendix B- Administration of Penthrox

1	Ensure the Activated Carbon (AC) Chamber is inserted into the dilutor hole on the top of the PENTHROX Inhaler.	
2	Remove the cap of the bottle by hand. Alternatively, use the base of the PENTHROX Inhaler to loosen the cap with a ½ turn. Separate the Inhaler from the bottle and remove the cap by hand.	
3	Tilt the PENTHROX Inhaler to a 45° angle and pour the total contents of one PENTHROX bottle into the base of the Inhaler whilst rotating.	
4	Place wrist loop over patient's wrist. Patient inhales and exhales PENTHROX through the mouthpiece to obtain analgesia. First few breaths should be gentle and then breathe normally through Inhaler.	
5	Patient exhales into the PENTHROX Inhaler. The exhaled vapour passes through the AC Chamber to adsorb any exhaled methoxyflurane.	
6	If stronger analgesia is required, patient can cover dilutor hole on the AC chamber with finger during use.	
7	If further pain relief is required, after the first bottle has been used use a second bottle if available. Alternatively use a second bottle from a new combination pack. Use in the same way as the first bottle in step 2 and 3. No need to remove the AC Chamber. Put used bottle into the plastic bag provided.	
8	Patient should be instructed to inhale intermittently to achieve adequate analgesia. Continuous inhalation will reduce duration of use. Minimum dose to achieve analgesia should be administered.	
9	Replace cap onto PENTHROX bottle. Place used PENTHROX Inhaler and used bottle in sealed plastic bag and dispose of responsibly (see section 6.6).	

Appendix C – Penthrox Audit Tool

Penthrox Audit Tool

Attached patient addressograph sticker

Details of trauma injury/ injuries:

Type of injury	
Limb injuries	
Wrist fractures (moderate to severe pain)	
Elbow/shoulder dislocations	
Ankle fractures (moderate to severe pain)	
Dislocated digits	
Open wounds to limbs requiring exploration or washout	
Traumatic abdominal pain	
Pain associated with major trauma	
Chest injuries (pneumothorax is not a contraindication	
Other (please provide details)	

CHECK ALLL list has been reviewed/ Penthrox is appropriate for the patient: Y / N (please circle)

Pain Assessment

Patient pain score prior to administration of analgesia: _____/10

Patient pain score at 15 minute post Penthrox administration: _____/10

Patient pain score during manipulation : _____/10

Patient satisfaction with procedure: ……/10

How many Penthrox inhalers were used? 1 2 (please circle)

Did the patient experience side effects? Y / N (please circle)

If yes, please describe the type and severity (1-10) below: Tick the box and number severity. Spare boxes for other.

Dizziness	Amnesia	Nausea
Drowsiness	Anxiety	Paraesthesia
Euphoria	Sweating	Hypotension
Dysarthria	Taste disturbance	
Cough	Headache	

Did the patient require additional analgesia? Y / N (please circle) If so, what was given and how much?

Did the patient need conscious sedation Y / N (please circle)

Time spent in ED _____

Was discharge delayed for any reason e.g. lack of appropriate staff to discharge patient?

Y / N If yes, please describe reason for delay below:

Clinician comments (regarding Penthrox): Please include your thoughts on patient/staff satisfaction and if any perceived time was saved in the patients journey or for staff.

Treating clinician details

Name of clinician: _____

Professional Registration number: _____

Date: _____

Signature of clinician: _____

For Audit Purposes (no need for clinician to complete):

Time patient arrived:

Time patient discharged:

Time in department:

Pain score reduction: