Methoxyflurane (Penthrox) for emergency relief of moderate to severe pain

LAY SUMMARY

Acute pain is a type of pain that typically does not last longer than 6 months and stops when its underlying cause has been treated or has healed. It is commonly associated with broken bones, burns, pain after surgery or medical conditions such as heart attacks.

Methoxyflurane is a new drug for the emergency treatment of acute pain. It is inhaled (breathed in) by the patient using a special inhaler. Some studies have suggested that methoxyflurane may be helpful for conscious patients with moderate to severe acute pain following accidents, burns, operation or other trauma.

Methoxyflurane (as Penthrox) is already licensed for use in the UK; it could be an alternative treatment option for patients requiring emergency pain relief.

NIHR HSRIC ID: 11830
TARGET GROUP

- Acute pain: moderate to severe; in conscious patients with trauma and associated pain – emergency analgesia.

TECHNOLOGY

DESCRIPTION

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. It does this by decreasing the extent of gap junction mediated cell-cell coupling and altering the activity of the channels that underlie the action potential. Methoxyflurane (as Penthrox) is self-administered at 3mL (99.9% methoxyflurane) vaporised in a Penthrox inhaler, with a maximum dose of 6mL in a single administration.\(^1\)

Methoxyflurane (as Penthrox) is already licensed in the United Kingdom for this indication in adult patients. Common (≥1% to <10%) reported adverse events include amnesia, anxiety, depression, dizziness, dysarthria, dysgeusia, euphoria, headache, sensory neuropathy, somnolence, hypotension, coughing, dry mouth, nausea, and sweating.\(^1\)

INNOVATION and/or ADVANTAGES

Methoxyflurane offers an additional fast-acting and self-administered treatment option for the emergency relief of pain in conscious patients with trauma or associated pain.

DEVELOPER

Galen Limited.

AVAILABILITY, LAUNCH OR MARKETING

The company received Marketing Authorisation from the MHRA for the emergency relief of moderate to severe pain in conscious adult patients with trauma and associated pain in October 2015. Methoxyflurane (as Penthrox) was launched in the UK in January 2016.

PATIENT GROUP

BACKGROUND

Pain is defined by the International Association for the Study of Pain (IASP 2015) as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage”. Acute pain is commonly associated with surgery, trauma, non-surgical interventions and some medical conditions, for example myocardial infarction, acute pancreatitis and ureteric colic. It is an individual, multifactorial experience influenced, among other things, by culture, previous experience, belief, mood and ability to cope. Effective treatment of acute pain is a fundamental component of quality patient care, due to the adverse physiological and psychological effects which may result from unrelieved severe
Acute pain is of limited duration and usually ceases when the wound heals or the medical condition improves. However, it is important to anticipate and treat acute pain effectively to prevent the development of chronic pain syndromes.

**NHS or GOVERNMENT PRIORITY AREA**


**CLINICAL NEED and BURDEN OF DISEASE**

Inadequately managed acute pain can have psychological, physiological and socioeconomic consequences that can worsen patient suffering, clinical outcome, and increase the financial costs of healthcare. In 2013, it was estimated that approximately two-thirds of inpatients experience acute pain during their stay in hospital. This pain is often poorly relieved, with up to 20% of all inpatients suffering moderate to severe pain at any given time.

Within primary care, approximately £305 million was spent in 2014 on opioid analgesics (£495 million on all analgesics), with almost 23 million prescriptions dispensed in England. However, it is likely that an unknown but large proportion of these items were for chronic rather than acute pain conditions.

In 2014-15, there were 19.6 million Accident and Emergency attendances recorded in England. Approximately 25% of these patients received treatment due to sports injury, road traffic accident, assault, deliberate self-harm, firework injury or other accident. In the same year, approximately 6.5 million patients received treatment from ambulance personnel, of which 63% required transportation to an Accident and Emergency department. In 2014-15, there were 660,338 hospital admissions in England due to external injuries and burns, equating to 3,737,171 bed days and 801,240 finished consultant episodes.

The company states that the primary use of methoxyflurane (as Penthrox) will be in secondary care, specifically hospital emergency departments and pre-hospital applications such as ambulances.

The population likely to be eligible to receive methoxyflurane could not be estimated from available published sources.

**PATIENT PATHWAY**

**RELEVANT GUIDANCE**

**NICE Guidance**


**Other Guidance**

• Faculty of Pain Medicine: The Royal College of Anaesthetists. Core Standards for Pain Management Services in the UK. 2015.
• The Royal College of Anaesthetists. Guidelines for the Provision of Anaesthetic Services for Acute Pain Management. 2014.

**CURRENT TREATMENT OPTIONS**

The assessment and measurement of pain are fundamental to the process of diagnosing the cause of the pain, selecting an appropriate analgesic therapy and evaluating and modifying that therapy according to the response. Pain is recognised as the fifth vital sign and standardised assessment tools are used to measure the intensity of pain that an individual is suffering. Regular and repeated measurements of pain are made to assess ongoing adequacy of analgesic therapy. Treatment of acute pain is tailored to the assessment and requirements of an individual patient.

The ‘analgesic ladder’ introduced for treatment of cancer pain by the World Health Organization (WHO) has been adapted for the treatment of acute pain. It is made up of the following three steps:

**Step one**
- Non-opioid +/- adjunct; e.g. paracetamol, aspirin or non-steroidal anti-inflammatory drugs +/- nitrous oxide, gabapentinoids, ketamine, lignocaine and clonidine.

**Step two**
- Weak opioid +/- non-opioid +/- adjunct; e.g. codeine or tramadol +/- paracetamol, aspirin or non-steroidal anti-inflammatory drugs +/- nitrous oxide, gabapentinoids, ketamine, lignocaine or clonidine.

**Step three**
- Strong opioid +/- non-opioid +/- adjunct; e.g. oxycodone, diacurphine, fentanyl, or alfentanil +/- paracetamol, aspirin or non-steroidal anti-inflammatory drugs +/- nitrous oxide, gabapentinoids, ketamine, lignocaine or clonidine.

Drugs should be initiated at the step in the analgesic ladder appropriate to the level of pain, as dictated by the pain scale.

The provision of effective acute pain management can be optimised by collaboration with other healthcare professionals such as physiotherapists, pharmacists and clinical psychologists.
Expert opinion states that the main second line treatment of acute pain is paracetamol, used orally or intravenously (IV), in combination with morphine. Paracetamol is considered a very effective base-line medication but morphine has variable effect and patients may suffer from nausea with this medication. Furthermore, expert opinion states that modalities already exist for effective control of acute pain, such as IV ketamine titrated for analgesia, but they are under-used most likely due to training requirements and lack of familiarity by clinicians.

**EFFICACY and SAFETY**

<table>
<thead>
<tr>
<th>Trial</th>
<th>NCT01420159, MEOF-001; methoxyflurane vs placebo; phase III.</th>
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<tbody>
<tr>
<td>Sponsor</td>
<td>Medical Developments International Limited.</td>
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<tr>
<td>Status</td>
<td>Complete and published.</td>
</tr>
<tr>
<td>Source of information</td>
<td>Publication[15], trial registry[16].</td>
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<tr>
<td>Location</td>
<td>United Kingdom.</td>
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<tr>
<td>Design</td>
<td>Randomised, placebo-controlled.</td>
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<tr>
<td>Participants</td>
<td>n=300; aged 12 years and older; minor trauma; pain score ≥4 to ≤7 as measured using Numerical Rating Scale at the time of admission; no life-threatening condition requiring immediate admission to operating room or intensive care unit; no known pregnancy or lactation; no presence of any other clinical conditions that may impact on the patient’s ability to participate in the study; no acute intoxication with drugs or alcohol; no current use of analgesics for chronic pain; no known personal or familial hypersensitivity to fluorinated anaesthetics; no known personal or familial history of malignant hyperthermia; no clinically significant respiratory depression; no use of methoxyflurane in the previous 4 weeks; no clinically significant cardiovascular instability.</td>
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<td>Schedule</td>
<td>Randomised to methoxyflurane as two 3mL inhalers self-administered; or placebo as two 5mL inhalers self-administered.</td>
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<td>Follow-up</td>
<td>Follow-up 16 days.</td>
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<td>Primary outcome</td>
<td>Visual analogue scale (VAS) pain score.</td>
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<tr>
<td>Secondary outcome/s</td>
<td>Use of rescue medication; time to pain relief; number of responders; safety analysis.</td>
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<td>Key results</td>
<td>For methoxyflurane vs placebo groups, respectively: mean change in VAS pain score from baseline to 5 minutes, -23.1 vs -11.3mm; from baseline to 10 minutes, -28.9 vs -14.8mm; from baseline to 15 minutes, -34.0 vs -15.5mm; from baseline to 20 minutes, -35.0 vs -19.0mm; median time to first pain relief, 4 vs 10 minutes; use of rescue medication, 2 vs 25 patients.</td>
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<td>Adverse effects (AEs)</td>
<td>Treatment-emergent AEs were experienced by 59.1% and 40.9% of methoxyflurane and placebo groups, respectively; 1.3% of methoxyflurane-treated patients and 2% of placebo-treated patients withdrew due to treatment-emergent AEs.</td>
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**ESTIMATED COST and IMPACT**

**COST**

Methoxyflurane (as Penthrox) is already marketed in the UK; 3mL dose vaporised in a Penthrox inhaler costs £17.89.

* Expert personal communication.
## IMPACT - SPECULATIVE

### Impact on Patients and Carers

- Reduced mortality/increased length of survival
- Reduced symptoms or disability
- Other: *expert opinion states that the self-administration of pain relief is beneficial as it gives the patient control over their pain, which is an advantage psychologically*. 
- No impact identified

### Impact on Health and Social Care Services

- Increased use of existing services
- Decreased use of existing services
- Re-organisation of existing services
- Need for new services
- Other
- None identified

### Impact on Costs and Other Resource Use

- Increased drug treatment costs
- Reduced drug treatment costs
- Other increase in costs.
- Other reduction in costs.
- Other
- None identified

### Other Issues

- Clinical uncertainty or other research question identified: *expert opinion states that the principal area of clinical uncertainty with this medication is the potential for risk of abuse should methoxyflurane cause euphoria. However, this could be avoided by use as a prescription only medication, or use as a controlled substance*. 
- None identified

## REFERENCES


* Expert personal communication.
Horizon Scanning Research & Intelligence Centre


