Penthrox: a breath of PHEC air for the military?

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ABSTRACT

Prehospital analgesia is vital to good clinical care and inhaled methoxyflurane (Penthrox) would be a valuable addition to the armed forces medical armoury. Penthrox would provide strong, fast-acting, self-administered and safe analgesia to patients with moderate to severe injuries. In addition, it would provide an option for strong analgesia which would not be subject to the regulations that govern controlled or accountable drugs which gives it a unique position as the military moves its focus from large enduring operations to small short-term training teams supported by lone combat medics in remote locations across the globe.

INTRODUCTION

Effective and safe analgesia is vital to good clinical care. However, there can be supply difficulties for deployed military personnel on both exercises and operations. This can be contributable to the logistical challenges of supplying medication. The modern military is changing and with this there is likely to be more short-term training teams (STTT). These are small groups of soldiers, being deployed in isolation; often in remote countries. They are likely to have lone medic support; or limited healthcare support, often without immediate access to a doctor. These deployments, as well as larger scale exercises, all have a lower risk of significant major trauma, such as gunshots and blasts, compared with the operations that the military has been involved with such as Op HERRICK and Op TELIC. The risk of road traffic incidents remains significant. At present the published trauma data are limited from STTT deployments making risk quantification more difficult.

At present, we rely on an opioid-based analgesic agent, which is a controlled drug (CD). It is necessary to reflect the requirements to comply with UK laws for CDs in order to safely manage them.[1] This can be disadvantageous as the documentation can inhibit the ability to deploy with the required medications. In some countries, our paperwork is not accepted or recognised and there is also the risk medications might be confiscated.

Penthrox inhalers for battlefield analgesia have been discussed before[2] and were not thought to be an appropriate replacement for morphine autoinjectors. With the change to the oral transmucosal fentanyl lozenges (OTFL), and the change to operational methods of healthcare deployment, it is important to revisit this question as Penthrox does have advantages over this type of battlefield analgesia even if a complete replacement is not appropriate. There will always be a need for effective analgesia to be administered by medical professionals and this article will outline the Penthrox inhaler as a possible addition to our military medical armoury.

HISTORY OF METHOXYFLURANE

The active agent methoxyflurane was initially used as an inhaled anaesthetic in the early 1960s due to its improved cardiac stability compared with other fluoridated hydrocarbons. However, within a few years concerns were raised about the nephrotoxicity of this agent. The mechanisms of the renal tubular dysfunction were never established but it fell from favour and its use declined.[3 4] Despite this, in the 1970s the Australian emergency services started using a reduced dose of methoxyflurane as an inhaled analgesic for trauma pain relief. This was on a background of emerging good evidence of both its effectiveness for acute trauma pain relief and also of its renal and hepatic safety.[4–6] More than 5 million doses have been administered with no significant adverse events and studies have confirmed its cardiac and respiratory stability.[3] As well as being used for trauma pain, methoxyflurane is also being increasingly used for both visceral pain and procedures that would otherwise have required intravenous analgesia and sedation.[4]

WHAT IS PENTHROX?

Penthrox is a handheld inhaler which can administer 3 mL of methoxyflurane to a patient providing effective pain relief within 6–10 inhalations and in studies has been shown to have an analgesia effect by within 5 min.[5 7] It reaches peak effectiveness by 15 min. Patients are able to assess their own level of pain and titrate their analgesia to reflect this. Continuous inhalation provides up to 30 min of pain relief per 3 mL of methoxyflurane and intermittent inhalation can provide longer durations. The maximum dose is two 3 mL inhalations per day with a maximum weekly dose of 15 mL. However, it should not be used on consecutive days.[8 9]

The inhaler (figure 1) has an activated charcoal (AC) chamber which absorbs exhaled methoxyflurane and reduces the risk of exposure of active drug to the supervising healthcare practitioner.[8 10 11]

DANGERS

There is a risk of methoxyflurane exposure to healthcare professionals supervising its administration and literature suggests that 19%–35% of methoxyflurane is exhaled unchanged.[12] However, with the addition of the AC chamber this reduces the concentrations to almost zero.[12] Additionally, the Penthrox material safety data sheet reiterates that it only be used in well-ventilated areas which would further negate this risk.[8 13 14] Therefore, use in a prehospital environment such as in the field use would pose a very minimal risk of occupational exposure.

It should be noted that administration of Penthrox in an enclosed ambulance setting could represent a higher risk of exposing healthcare professionals to the active drug. However, this risk also extends to any vaporised or gaseous medications such as Entonox which could have similar issues.[15] There is a concern that the side effects such as nausea, headaches and vomiting could be experienced by the healthcare providers or even by other personnel such as drivers, pilots or force protection elements if used in vehicles which would be a serious concern.[2] However, these reports were prior to the introduction of the AC chamber which is mandatory in the UK and a recent literature review published in the *Journal of Paramedic Practice* also concluded that there is enough evidence and experience of Penthrox for it to be used by the UK Search and Rescue Cadre safely.[16]

In a study commissioned by the New South Wales ambulance service it was determined that methoxyflurane is unlikely to pose a significant risk to ambulance officers but it was recommended that no more than two patients should be administered Penthrox in one shift by a sole practitioner.[17] If this medication was incorporated into military practice then by limiting the number of inhalers per module this guidance could be used to protect military practitioners although

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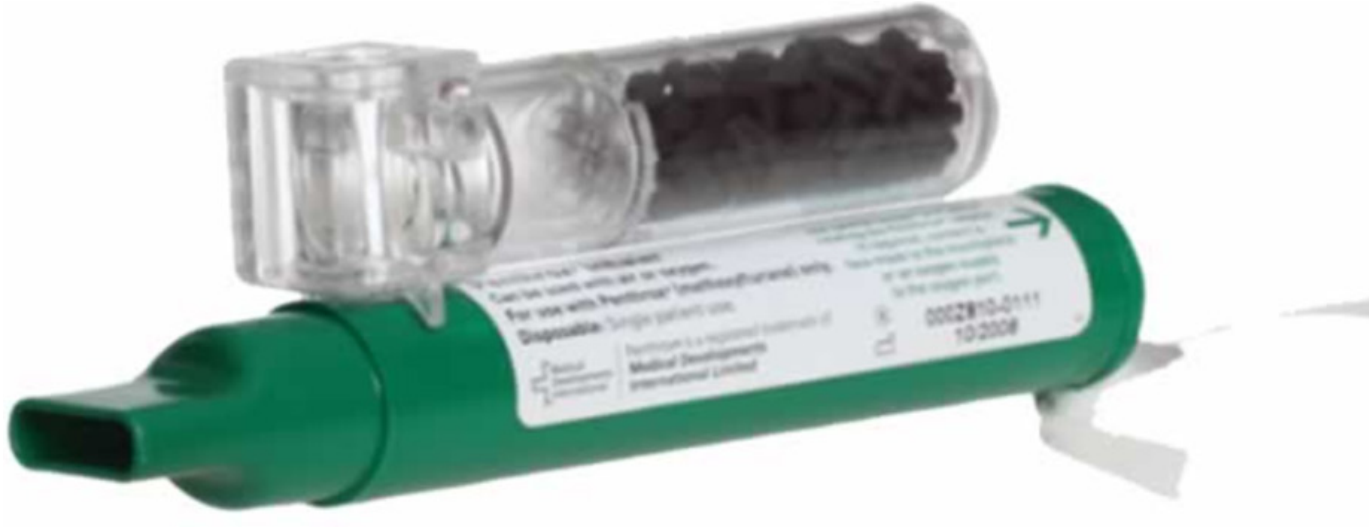

Figure 1 Photograph of Penthrox device.[28] Image used with kind permission from EMed. Penthrox—'Green whistle'. 2018. Available: http://www.emed.ie/Analgesia/Methoxyflurane.php

it should be noted that this advice was based on using the inhaler without the AC chamber.

Penthrox is at risk of abuse and its manufacturer has a total of six reported incidents on record. Half of these cases were by '*Army medics*' who abused it while on a 6-month tour in Afghanistan and the three remaining cases involved ambulance staff in Australia.[14] In response to a freedom of information (FOI) request, the UK Ministry of Defence (MOD) stated that they either do not hold the information about morphine autoinjector or OTFL abuse or that collating it would exceed the appropriate cost limit of FOI requests. It is therefore difficult to stratify this risk of abuse in comparison to the risk regarding current analgesia options.

If adopted by the military then it will likely impose some accountable status on Penthrox in order to limit the potential for abuse. It would not be classed as a CD under 1971 Misuse of Drugs Act; however, the MOD identifies other products as accountable drugs which it chooses to manage the same as CDs.[1] It is possible the MOD will choose to manage Penthrox similarly but we believe it is important that these restrictions do not inhibit the flexibility and relief from the complex CDs paperwork that Penthrox represents.

Minor side effects which include sedation, vomiting, hallucinations, confusion, dizziness, cough and headache have been reported, but the most common was drowsiness which was prevalent in 11% of adults.[8] The spectre of renal toxicity will always haunt Penthrox use,[17] however it has been calculated that for an adult patient a dose of at least 20 g of methoxyflurane is required to produce subclinical nephrotoxicity. It should be noted that this is 13 times the recommended daily dose delivered by 2×3 mL Penthrox inhalers.[6 17]

The main concern and potential limitation for Penthrox is the possible interaction with sevoflurane. Sevoflurane is an inhalational anaesthetic agent. It is commonly used for induction and maintenance of general anaesthesia. Sevoflurane is metabolised by cytochrome P450 2E1 to hexafluoroisopropanolol and this releases inorganic fluoride and CO_2.[18] Preclinical data suggest that the defluorination of sevoflurane by hepatic enzymes may be increased by certain agents. These include alcohol, isoniazid and barbiturates. This leads to production of fluoride. Other factors influencing the fluoride production include concentration of sevoflurane given, duration of anaesthesia and obesity. It has been reported that following administration of methoxyflurane, the development of vasopressin-resistant, polyuric renal failure correlates with serum inorganic fluoride concentrations >50 µM.[18] However, the data based on animal and human studies suggest that due to sevoflurane's rapid pulmonary administration, the methoxyflurane-derived threshold does not appear valid and at present inadequate data exist to elevate the nephrotoxicity of elevated fluoride concentrations.

MANAGEMENT OF MEDICATION

In the UK and Australia, Penthrox is a prescription-only medicine and is not classed as a CD. Transport is therefore much less restrictive than other opiate analgesia.[9 14 19] Furthermore, it is not a dangerous good or mixture according to the international air transport association and no civil aviation authority approval is required for its transport.[14] This classification has huge advantages over other rapid-acting analgesics as there would be considerably less process required for transporting Penthrox which is a particularly useful advantage for lower risk short-term deployments including overseas exercises as well as for sport and adventurous training expeditions.

EFFECTIVENESS AS AN ANALGESIC AND PORTABILITY

There is a wealth of evidence to support Penthrox as an analgesic for prehospital use and its effect is equivalent to using Entonox (nitrous oxide).[3 5 7 10 11 20]

The double-blinded, multicentre randomised controlled trial conducted by Coffey *et al* provides the highest quality of evidence for its effectiveness as an analgesic but it does lack a direct comparison with any other analgesics.[10]

Blair and Frampton conducted a review of methoxyflurane in trauma pain which recognised Coffey *et al*'s work as high-quality evidence of the effectiveness as an analgesic but also recognised the paucity of direct head-to-head comparisons of methoxyflurane to other analgesic agents. It concludes that it may be broadly comparable to Entonox with predominantly logistical advantages over it.[3]

Porter *et al*'s systematic review specifically compares, although indirectly, methoxyflurane with nitrous oxide and concludes they are both similarly suitable for use in trauma patients and also

recognises the practical advantages of methoxyflurane.[5]

There are clear advantages of having this level of analgesia easily portable for the environments the military operate and although Entonox may be available in military ambulances, Penthrox inhalers could be easily carried in medical bergans. Another documented benefit is that Penthrox can be used for patients with perceived respiratory issues such as a pneumothorax, a scenario when Entonox is contraindicated.[21] Both Entonox and low-dose methoxyflurane provide an equal and well-tolerated analgesia and are suitable for the treatment of pain in trauma patients in emergency care.[5 7 10]

MILITARY USE

In the deployed combat medical technician (CMT) module (*584*) analgesia options are restricted to ibuprofen, paracetamol or OTFL which leaves a gap at the second step of the WHO analgesic ladder.[22] In the deployed Medical Officer module (*587*) the addition of co-codamol, midazolam, morphine sulfate amps and ketamine does rectify this problem although none of the rapid-acting options are as straightforward to administer as Penthrox. Penthrox could act as a bridging agent, particularly for moderate trauma.

Penthrox is very fast acting which does provide a substantial advantage over other preparations including the OTFL. In a placebo-controlled double-blinded trial, OTFL was observed to only start to have a statistically significant improvement in pain over a placebo at 15 min after the start of administration[23] and the product literature also suggests this.[24]

In contrast, Penthrox has been observed to have analgesic action 5 min.[5 7 8] This represents an improvement in onset of analgesia which would be of particular benefit to CMTs as they have a more limited choice of analgesia available in their modules than doctors. Additionally, the mechanism of delivery via the inhaler is easier to administer, compared with a lozenge which required continuous movement '*twirling*'[24] in order to effectively deliver the medication.

The military operate in a variety of challenging environments. Despite the widespread use by the Australian and New Zealand Defence Forces there is very little evidence describing Penthrox being used in adverse climatic conditions. That said, Penthrox has been used extensively with more than 5 million doses recorded as having been administered in Australia over the last 40 years both by its military, including on operations, and within the general public setting by ambulance services and first response teams.[4 5 7 10 25 26] This could demonstrate by proxy some degree of effectiveness in the huge variety of challenging environments that Australia represents. However, if Penthrox was adopted by UK military more research would have to be conducted to demonstrate the effectiveness of this medication in extreme conditions.

Incorporation of Penthrox into UK military use would require a widespread education programme for all healthcare professionals to capture all staff who may use them, which would certainly be logistically challenging. Penthrox has begun to be more widely used in the UK, including being recommended by Joint Royal Colleges Ambulance Liaison Committee as being suitable for adults with moderate to severe trauma for use by our paramedics.[27] As Penthrox becomes more mainstream in the UK, it is important that it is strongly considered for use in the military and we believe it is well positioned to have a positive role in military prehospital emergency care (PHEC).

CONCLUSION AND OUTSTANDING ISSUES

Although there is a plethora of high-quality analgesic agents that are available to UK military doctors while deployed on exercise or operations these are not currently licensed for dispensing by or considered safe for use by CMTs, with the majority being dangerous in inexperienced hands. Penthrox is uniquely positioned as a fast-acting, patient-administered and broadly safe analgesic which could be used safely while being supervised by a CMT. As well as providing a type of rapid pain relief for trauma that would be easily transportable to remote locations with minimal paperwork it would also provide a broader choice of analgesia to patients with moderate to severe injuries.

However, this must be tempered with the requirement for accounting to avoid abuse as well as the need for evidence for Penthrox in extreme environments.

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