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IS METHOXYFLURANE A SUITABLE BATTLEFIELD ANALGESIC?

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Abstract

Anecdotal reports of mechanical failure of morphine autojets have triggered a review of possible alternatives. Methoxyflurane is one such alternative already widely used by the Australian and New Zealand Defence Forces. The potential benefits and likely significant drawbacks of methoxyflurane are reviewed with the aim of stimulating discussion.

Introduction

The ideal pre-hospital analgesic should be easily portable, have no serious adverse effects on either patient or provider, have no potential for abuse and should not be a controlled substance, be stable in all climatic conditions with no requirement for specific storage or transport, work within a few minutes of first dose, last for sufficient time for the casualty to reach additional aid, and have no contraindications to its use. This is a tall order for any analgesic.

Morphine autojets are currently the only method of analgesia available on the battlefield unless medical personnel take additional analgesia in to the field. Although intramuscular (IM) morphine is a recognised gold standard for pain relief, morphine is a controlled drug with all the problems that this involves. It also has the potential to cause respiratory depression, nausea and vomiting and can be slow to take effect particularly in the shocked patient. Anecdotal reports of mechanical failure of morphine autojets (Hodgetts TJ, Personal Communication) have triggered consideration of alternatives in pre-hospital analgesia. This review focuses on one specific alternative.

Methoxyflurane is a volatile anaesthetic agent with significant analgesic properties at sub-anaesthetic concentrations. It is available as a single use, hand-held, self-administering device currently in use with ambulance services in Australia, the Australian Defence Force and the New Zealand Defence Force (1) as the Penthrox inhaler, giving inspired concentrations of 0.2%-0.4% from the 3ml bottle providing up to 25 minutes of analgesia (1). A maximum dose of 6ml/day and 15ml/week can be used. A scavenging system is available which reduces environmental pollution while the patient is breathing through the device, although methoxyflurane will be expired by the patient when they are not breathing on the inhaler (1).

This paper aims to review the safety and efficacy of methoxyflurane and assess whether it could be used to replace morphine as the primary analgesic in the pre-hospital environment.

Saftey of Methoxyflurane

Initially used as an inhaled anaesthetic, methoxyflurane was found to produce nephrotoxicity secondary to inorganic fluoride, a metabolite of methoxyflurane (2). Despite falling out of favour as an anaesthetic it has continued to be used at lower doses as an inhaled analgesic. Initially it was used in labour and delivery and during burns dressing changes, while additional studies were performed to ascertain its safety at these lower doses (2-6) . These studies are all small, of poor quality and show contradictory results. One paper investigating the effects of methoxyflurane on renal function in 150 women during childbirth (6), they found that there was a significant difference in serum creatinine, serum uric acid and glutamic oxaloacetic transaminases between the control group using nitrous oxide and the treatment group who used a maximum dose of 5ml of methoxyflurane suggesting some effect on renal function even at this low dose in this particular population. The clinical significance is unknown.

There are 2 case reports of 3 women who developed hepatitis following methoxyflurane analgesia during labour, one on 2 separate occasions. Epidemiological circumstances and negative serological studies suggested drug toxicity (7, 8). Both authors postulated that a hypersensitivity reaction was responsible. If methoxyflurane is used it may result in idiosyncratic hepatitis although exact rates are not known. As with many inhaled anaesthetic agents there is also a small but unquantified risk of malignant hyperpyrexia, which has been reported to the Australian Therapeutic Goods Administration only once in over 2 million uses since 1975 - similarly only one case of cholestatic hepatitis has been so reported (9), although the probability of under-reporting is acknowledged (10,11).

Two studies have examined the effects of exposure of medical staff to methoxyflurane at work. The first found highly significant differences in urinary fluoride levels despite exposure levels of only 0.5 – 0.8 ppm of methoxyflurane (12). The second showed significant changes in the levels of blood urea nitrogen, serum glutamic transaminases, and serum glutamic oxaloacetic transaminases in exposed personnel (13). The long term effects of this exposure are not known.

Efficacy

There is ample evidence that methoxyflurane provides useful analgesia (14-17). This has mostly been in burns patients requiring dressing changes, and in labour and delivery. It has comparable analgesic effect to that provided by nitrous oxide 50% in oxygen, although in one trial more patients preferred nitrous oxide(15). The onset of analgesia is rapid with a

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significant rise in the pain threshold within 2 minutes of administration (18). When used as a post-operative analgesic, significantly more analgesia was provided by 10mg of IM morphine than 15ml of methoxyflurane. Aside from the differences in analgesia provided, 12/40 patients either refused or discontinued use of methoxyflurane mostly because of nausea or choking on the vapour (19); no patient refused morphine. Methoxyflurane has been successfully used in children (20, 21) as an analgesic for painful ward procedures or dressing changes. Evidence from the pre-hospital environment is scarce. In a study looking at 105 patients aged 15 months to 17 years receiving methoxyflurane pre hospital, mostly for limb injuries, there was a mean drop in pain score from 8/10 to 4/10 at 2-5 minutes after initiation of treatment and 3/10 at 10 minutes. No serious complications were reported, however one third of those under 5 years of age and 7/88 (8%) of the over 5's were deeply sedated (22).

Military Perspective

A trial comparing 3 different hand held inhalers for methoxyflurane showed that after inhaling methoxyflurane until unable to hold the device, half of the subjects suffered vertigo and were unable to walk in a straight line immediately after inhalation, with the rate falling to a quarter at 30 mins after inhalation - all had returned to normal by 2 hours (23). This would have important implications for patient transport. Ambulance services have found that a proportion of their personnel experience headaches, nausea, vomiting and skin irritation when patients were using methoxyflurane analgesia in the back of the ambulance. Furthermore, 23% of treating officers and 11% of drivers in a test sample experienced exposure to methoxyflurane in excess of safe levels (24). The scavenging system that has since been introduced may alleviate some of these problems although patients will continue to off gas once they have stopped using the inhaler. The extent or relevance of this problem is unknown. Methoxyflurane has not been tested in many of the environments that the military are required to work in: specifically, hot, windy, wet or enclosed spaces and close to military ordnance. Methoxyflurane also has specific handling issues. It is an inhaled anaesthetic and as such may have to travel as Dangerous Air Cargo with associated problems for rapidly deploying troops. The opinion of the RAF would be essential before it's introduction. It also has a flash point of 62.8º C which may be exceeded in certain military environments. Patients with severe facial trauma, agitated patients and those being managed as expectant may all need analgesia but may not be able to manage to use the methoxyflurane inhaler. Similarly, it could not be used with a respirator.

Discussion

Morphine has many drawbacks to its use, including serious side effects and problems with handling due to its controlled status. It can also take a variable time to work when give by the intramuscular route. A drug of comparable or better safety with similar analgesic properties would be welcome. On balance, Methoxyflurane is probably safe for the casualty; although the literature is unable to provide specific evidence of its safety as a pre-hospital analgesic, its safe use in over 2 million cases is reassuring. Its effects on the dehydrated shocked battlefield casualty are however still open to debate.

Issues remain over the safety of providers. Australian ambulance crews have experienced side effects from occupational exposure to the drugs and similar symptoms may be expected in a proportion of military personnel exposed to the drug in an enclosed environment (24). Furthermore, if drivers of ambulances are affected by methoxyflurane vapours this adds an additional risk to an already hazardous environment. Use of methoxyflurane by multiple casualties in an enclosed space may cause a build up of vapours not experienced in a civilian environment despite the scavenging system.

The analgesia provided by methoxyflurane while significant and fast acting is not as great or as long lasting as that provided by IM morphine. Its maximum duration of action of 50 mins on low flow (or presumably 25 mins on high flow) does not allow time for the casualty to be transported from the battlefield. It could however provide useful additional analgesia while morphine was being administered. It could also be used alongside morphine when insufficient analgesia is obtained although no data exist as to its safety or additional efficacy when used in this way. Before methoxyflurane could be recommended for military use, decisions or further assessment would have to be reached on, transportation of the drug by air, the safety of using methoxyflurane in a battlefield in high temperatures with the potential for naked flame, the build up of methoxyflurane in the back of an ambulance with more than one casualty using the drug, and the safety of the drug in dehydrated patients and with concomitant use of opiate analgesia.

Conclusions

A potential alternative primary battlefield analgesic to intramuscular morphine exists in the form of methoxyflurane. It provides rapid relief from pain but carries with it several logistical and safety concerns which the published literature does not really address. A full review of all possible alternatives should be undertaken, including methoxyflurane and debate regarding its potential value is welcomed.

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