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Review Article

REVIEW ARTICLE

A review of the safety and efficacy of inhaled methoxyflurane as an analgesic for outpatient procedures

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Abstract

Methoxyflurane delivered via a hand-held inhaler is a proven analgesic which has been used in Australasia for emergency relief of trauma associated pain since the 1970s. The agent is self-administered by the patient under the supervision of trained personnel. More than 5 million patients have received inhaled methoxyflurane without significant side effects. Methoxyflurane is also licensed in Australasia for the relief of pain in monitored conscious patients requiring analgesia for minor surgical procedures. Recent clinical studies undertaken in a variety of outpatient settings, including colonoscopy, prostate biopsy, dental procedures, bone marrow biopsy, and the management of burns dressings, indicate that inhaled methoxyflurane has significant analgesic activity, without producing deep sedation or respiratory depression. Return to full psychomotor activity is rapid. Thus, methoxyflurane may be a suitable and well-tolerated alternative to traditional i.v. sedative agents for outpatient medical and surgical procedures. There are direct advantages to the patient in terms of rapid recovery and an early return to normal activities, and significant benefits for outpatient departments in terms of cost saving and rate of throughput. Further randomised controlled trials comparing the efficacy, safety, and cost-effectiveness of inhaled methoxyflurane against traditional i.v. sedative techniques are currently in progress.

Keywords: analgesics; colonoscopy; methoxyflurane; minor surgical procedures; hypnotics and sedatives

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Editor's key-points

- Small-scale studies have demonstrated that methoxyflurane can provide satisfactory analgesia for various procedures, avoiding the risks of deep sedation.
- Administration brings psychomotor impairment, which resolves rapidly on stopping inhalation, with rapid return to full fitness.
- Further studies, including large randomised controlled trials, are required. The authors suggest that these are likely to add to the evidence supporting the widespread use of this agent.

Historical perspective: methoxyflurane as an anaesthetic agent

Interest in fluorinated hydrocarbons and ethers as anaesthetic agents began in the 1940s.[1] Extensive testing by the pharmaceutical industry on several potential agents led to the introduction of halothane (Ayerst Laboratories, New York, USA) and methoxyflurane (Abbott Laboratories, Montreal, Canada) as volatile anaesthetics for general anaesthesia in 1960. Artusio and colleagues,[2] Van Poznak and colleagues,[3] and Millar and Morris[4] investigated the anaesthetic and physiological properties of methoxyflurane. This agent was found to have significant benefits over other volatile anaesthetics available at the time. In particular, cardiovascular stability was maintained under methoxyflurane anaesthesia and the dysrhythmias commonly noted with halothane were absent. This was a particular benefit in operations where adrenaline was required to be used as part of an infiltration local anaesthesic (LA) technique, or in sick patients who already exhibited high levels of catecholamine secretion secondary to the stress response.[4,5] Of specific relevance to this review, the profound analgesic properties of methoxyflurane, which extended well into the postoperative period, were recognised early on.[6,7]

Many clinical studies conducted during the early 1960s suggested improved safety of methoxyflurane over halothane in a wide variety of clinical anaesthetic settings, and thousands of general anaesthetics were performed using this agent.[5,8] However, in the mid-1960s, concerns over the renal toxicity of methoxyflurane began to emerge.[9] Two significant case series described an unusual form of high output acute renal failure correlated with the intraoperative use of methoxyflurane as a general anaesthetic.[10,11] The clinical manifestations included excessive diuresis, thirst, and severe hypernatraemia resistant to vasopressin administration, indicating impaired renal tubular concentrating ability.[9] The vast majority of these patients recovered full renal function within a relatively short space of time, with most recorded deaths being related to complications of the primary surgical pathology.[9] Nevertheless, the need to manage fluid balance in the presence of high output renal failure led to prolonged hospital admission and the patients' stay in hospital was a significant contributing factor to poor long-term outcome in some cases.[9]

The exact cause of the renal tubular dysfunction has never been established. Although methoxyflurane is a fluorinated ether, other volatile agents inducing higher serum concentrations of inorganic fluoride do not produce high output renal failure.[12] A metabolic pathway unique to methoxyflurane, resulting in the production of other potentially nephrotoxic agents acting in tandem with inorganic fluoride to inhibit tubular reabsorption, has been postulated, but never directly proven.[9,13] Postoperative renal tubular dysfunction has only been observed in a retrospective setting where long duration inhalational anaesthesia resulted in high cumulative doses of methoxyflurane.[14–16] Nevertheless, methoxyflurane was withdrawn from North American clinical anaesthetic practice in the late 1970s, and fell into gradual disuse globally as an anaesthetic agent over the next 10 years, as newer volatile agents with more rapid onset and offset became available.

Low-dose inhaled methoxyflurane as a potent short-term analgesic for emergency trauma pain

Although methoxyflurane has been withdrawn for use as an anaesthetic agent, low-dose methoxyflurane delivered via a hand-held inhaler has been used by the Australian emergency services for the short-term relief of acute trauma pain since the early 1970s. Clinical trials have confirmed that this agent provides effective pain relief in acute trauma with no evidence of either renal or hepatic toxicity.[17,18] The portability, safety profile, and rapid onset of analgesia means that this formulation of methoxyflurane is a very common type of pain relief given by Australian paramedics,[19,20] and more than 5 million doses of inhaled methoxyflurane have been used in trauma patients with no significant adverse events reported.[21] Recent studies have confirmed the cardiovascular and respiratory stability of this agent in the pre-hospital setting, not only for trauma pain, but also for acute visceral pain.[22]

In the last few years, attention has focussed on whether methoxyflurane delivered via a hand-held inhaler can provide high quality, well-tolerated analgesia for a variety of outpatient procedures which would otherwise require i.v. sedation and analgesic techniques.[23] In addition, recent clinical studies have suggested that methoxyflurane has an anxiolytic effect,[23,24] and these combined properties of potent analgesia and reduced anxiety may make methoxyflurane a suitable and well-tolerated alternative to i.v. sedative agents.

Dosage and administration of inhaled methoxyflurane

The physical and chemical properties of methoxyflurane are central to its efficacy as an analgesic for short medical and surgical outpatient procedures. It is a highly lipid soluble volatile liquid with a high blood:gas partition coefficient.[21] The minimum alveolar concentration of 0.2% suggests potent anaesthetic activity. However, in practice, the high lipid solubility and low vapour pressure of methoxyflurane means that the onset of sedation is very slow and thus, inhalation of small doses over a short period limits the sedative effect of this agent.[25]

Methoxyflurane is currently presented in liquid form in a 3 ml vial, which is poured into a hand-held inhaler (Penthrox® inhaler or 'green whistle', Medical Developments International, Victoria, Australia). The liquid is absorbed onto a wick and the patient inhales vaporised methoxyflurane via a mouthpiece. The inhaler has a dilutor hole which entrains air during inhalation, so that the concentration of agent delivered is either 0.2–0.4% when the dilutor hole is uncovered or 0.5–0.7% when the patient closes the dilutor hole with a finger. Analgesia is usually felt within a few breaths. The maximum recommended dose of methoxyflurane in a 24-h period is 6 ml (two vials).[5] Either one or two vials of methoxyflurane are