Review

Exposure to methoxyflurane: Low-dose analgesia and occupational exposure

Serah J Allison BSc, BHSc, PGCert, is an Intensive Care Paramedic^{1,2}; Paul D Docherty BE(Hons), PhD is Associate Professor²; Dirk Pons BSc, MSc, MLead, PhD, CPEng, MENZ is Associate Professor²; J Geoffrey Chase BSc, MSc, PhD, FENZ, FASME is Distinguished Professor²

Affiliation:

¹Wellington Free Ambulance, New Zealand

²Department of Mechanical Engineering, University of Canterbury, New Zealand

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Abstract

Introduction

Evidence of nephrotoxicity led to abandonment of methoxyflurane anaesthesia. In lower doses via the Pentrox[®] inhaler, methoxyflurane is used for analgesia. We aim to review the literature to identify the relevance of methoxyflurane as an effective analgesic agent, identify whether there are any patient safety concerns in modern use, and determine occupational risk to healthcare personnel due to environmental methoxyflurane exposure.

Methods

Articles were located via PubMed, ScienceDirect, Google Scholar, Anaesthesiology and the Cochrane Library.

Results

Single low-dose exposure to methoxyflurane may elevate blood fluoride levels below the toxic range, and appears relatively safe for patients. There is limited literature of occupational methoxyflurane exposure within modern parameters. Risks could include nephrotoxicity or hepatotoxicity.

Conclusion

The safety of occupational methoxyflurane exposure is yet to be proved. Further independent studies quantifying occupational exposure and monitoring the health of personnel exposed to methoxyflurane need to be undertaken to ensure safety.

Keywords:

paramedic; emergency medical services; professionalism

Corresponding Author: Paul Docherty, paul.docherty@canterbury.ac.nz

Introduction

Methoxyflurane is a volatile organic liquid (1), or fluorinated hydrocarbon, used as an anaesthetic agent from 1958 (2). It is colourless and has a characteristic odour (3,4). It is non-explosive and vaporises readily (5). A decade after discovery, methoxyflurane was frequently used, making up 10% of annual purchases of inhaled anaesthetics in the United States (2). Sedation and analgesia were described (6,7), which prompted an extension of its use outside of the operating room. However, in the early 1970s researchers determined methoxyflurane caused post-anaesthesia renal failure in some patients. Over two decades of use in anaesthesia, methoxyflurane is estimated to have been responsible for clinical nephrotoxicity in approximately 100 patients worldwide, with related death in approximately 20 cases (8). As a result, methoxyflurane administration was discontinued in the US in 1974 (9) and in the United Kingdom at a similar time (10).

In 1978, Medical Developments International (then Medical Developments Australia) began manufacture of the methoxyflurane delivery device Pentrox® specifically for analgesic use (9). Pentrox® is currently the only widely commercially available methoxyflurane administration device. The Pentrox® inhaler is a tube containing the methoxyflurane drug soaked into a gauze, with a whistle-like mouthpiece for the patient to inhale through (11). It features a 'dilution hole' which allows the patient to control the concentration delivered: 0.2% to 0.4% with the dilution hole open, and 0.5% to 0.7% with the hole closed (12).

Methoxyflurane via the Pentrox® device has been available for administration of pre-hospital analgesia in Australia for decades (13-15), and more recently in New Zealand (16,17). Methoxyflurane is also seeing a re-emergence in hospitals for short procedures, such as dressing changes (18). Methoxyflurane is newly approved in the United Kingdom, the Republic of Ireland, France and Belgium (19,20), so any safety considerations will affect a significant population. In considering approval for methoxyflurane sale and use, relevant authorities typically consider the safety of the patient using information provided by the manufacturer (19,21). However, independent assessment of patient safety is also warranted. The safety of healthcare personnel who may be exposed to methoxyflurane vapour in their occupational environment should also be considered. In this paper, 'healthcare personnel' is an inclusive term for doctors, nurses, hospital support personnel, ambulance personnel, defence force medics, and anyone near the patient care environment during treatment with methoxyflurane. These persons may repeatedly be in the presence of methoxyflurane vapour, and thus may be subject to similar health risks as patients to whom the medication is administered.

We conducted a systematic literature review to identify potential health effects of low-dose analgesia for the patient,

and potential risk associated with occupational methoxyflurane exposure. We used computational analysis techniques to synthesise results for metanalysis.

Methods

We searched PubMed (including MEDLINE), ScienceDirect, Google Scholar, *Anaesthesiology* and the Cochrane Library, using the search term 'methoxyflurane'. Articles were filtered by review of abstract and article content for English language studies relevant to methoxyflurane pharmacodynamics and kinetics, efficacy and safety. Study selection was not limited by publication date, as significant foundation work regarding methoxyflurane was conducted during 1960 to 1980s. The references of each article were searched manually to further expand the papers included for review. Service guidelines for use were identified non-systematically via repeated Google searches using terms such as 'methoxyflurane protocol', or 'methoxyflurane safety manual'. These various levels of search were implemented to maximise the literature considered and to ensure no relevant data was omitted.

Results

Methoxyflurane for light sedation and analgesia

Many anaesthetic agents do not provide analgesia (22). However, emergence from methoxyflurane anaesthesia was characterised by analgesia (6) which lasted 30 or more minutes after emergence (23), suggesting utility as an analgesic agent (7,24,25). Methoxyflurane is now considered an effective and fast-acting agent for moderate trauma-related pain. Analgesia appears related to changes in cell membrane thickness, which affects neuronal sodium and potassium channels, and GABAA and glycine receptor activity (26). Quantification of analgesic efficacy during patient care shows average self-reported pain falling from 8.7 to 4.5/10 after 1 minute (27), median analgesia onset time of 4 minutes and median reduction in pain up to 35.0/100 (up to 18.5/100 more than placebo) (28), reduction in pain score by 2.0/10 after 5 minutes and 2.5/10 by arrival at hospital (29), reduction from mean pain score 8.2/10 to 3.7/10 during labour (30). There were 89% of oncology patients undergoing various procedures that rated methoxyflurane as 'moderately' or 'highly' effective at managing pain (31), while 78% using methoxyflurane in an emergency department rated pain management as 'good' or 'very good'. Local anaesthesia alone was more effective than methoxyflurane alone for pain in men undergoing transrectal ultrasound-guided prostate biopsy (32). There were 80% of shoulder dislocations that could be successfully reduced when methoxyflurane was given compared with 98% of dislocations successfully reduced when propofol and an opiate were given, however, the difference was not statistically significant (33). Paediatric studies show achievement of effective analgesia with methoxyflurane in 78.3% of cases (34), and that methoxyflurane performs slightly better than placebo (35). One study found that effective

analgesia was more likely when intravenous morphine or intranasal fentanyl were used instead (36), while another study found that methoxyflurane was more likely to reduce pain score by at least 2 points on a 0 to 10 scale than intranasal or intravenous fentanyl or intravenous morphine (37).

A pilot study found methoxyflurane provided comparable analgesia to a ketamine/midazolam regimen (38). When compared to midazolam/fentanyl during colonoscopy, methoxyflurane produced comparable analgesia, patient anxiety and procedure completion rates, with less time to return to full alertness and time until ready for discharge (39). Methoxyflurane compared favourably with 'standard' emergency department analgesic treatment as judged by the treating clinician, although some analgesic options are unlikely to have had an effect within the 20 minute window of the primary endpoint (40). Another study compared methoxyflurane against 'standard' care including intravenous morphine (0.1 mg/kg). The mean pain in the methoxyflurane group was 6 mm lower on a 100 mm visual analogue scale (VAS) scale than in the intravenous treatment group. Intravenous treatments were infused over 10 minutes, and by study design, would only have been partially efficacious at the 10-minute endpoint (41). Nonetheless, these studies demonstrate that methoxyflurane is an effective rapid-acting analgesic agent. Methoxyflurane has been used successfully in combination with longer acting slower onset oral analgesia (42), or with local anaesthesia (43).

Sedative effects were prolonged in 10% of healthy volunteers in one study who used methoxyflurane through hand-held inhaler devices delivering 0.4–0.6% concentration to achieve light sedation, exhibiting impaired coordination an hour after discontinuation (24). Inhaled concentrations and durations in that study are similar to use of the Pentrox® device with the dilution hole closed (3,12). However, another study showed that healthy volunteers had a return to baseline hand-eye coordination and digit symbol substitution tests at 30 minutes, and auditory reaction time at 60 minutes after 15 minutes of methoxyflurane use (44). Hence, it is feasible that occupational exposure to methoxyflurane vapour could potentially result in performance degradation for the care provider.

Overall, there is good evidence of the effectiveness of methoxyflurane as an analgesic agent, and therefore as a viable option for healthcare personnel aiming to manage the pain of patients in their care. However, some aspects of the recent literature raise concerns. One study reported patients undergoing third molar removal with lignocaine local anaesthesia (localised pain relief) and either methoxyflurane or nitrous oxide sedation, when asked identified a statistically significant preference for methoxyflurane over nitrous oxide. However, an exact binomial test using patient preference data found $p=0.26$, which would not usually meet the criterion for statistical significance (45).

Two other studies compared methoxyflurane with placebo

(28,46). In the first study, patients undergoing bone marrow biopsy reported a reduction in pain of 1.64 on a scale from 0 to 10 with methoxyflurane (46). Whereas no conflict of interest was declared, three of the five authors including the lead author of this study were patent holders for the Pentrox® inhaler (31). The patent application acknowledges bone marrow biopsy is a painful procedure, and although this trial gained ethical approval, subjecting the 48 patients in the placebo group to bone marrow biopsy without analgesia seems an extreme approach. A total of 35% of patients in this study rated their pain as severe, and 30% of eligible people declined to participate (46). In a subsequent study (28) for which two further subgroup analyses have also been published (35,47), 150 patients presented to an emergency department with a mean pain level of 64 mm on a 100 mm VAS but received placebo for 20 minutes (28). While this study also gained ethical approval, given the previously described availability of literature demonstrating methoxyflurane analgesic efficacy it does not seem to conform to the Declaration of Helsinki on the use of placebo control (48).

Use of the Pentrox® device

The Pentrox® manufacturer currently recommends the device be used to deliver analgesic doses up to 6 mL per day and up to 15 mL per week (4). A 6 mL dose represents 0.59 MAC-hours exposure according to one report, although it is unclear how this value was determined (45). This is similar to what might be interpolated from data in other research, where 6 mL would represent 0.68 MAC-hours (49). Total administration time of 6 mL is reportedly up to 80 minutes (15). This is significantly longer than the 29.4 to 51.8 minutes that can be calculated for the administration of 6 mL doses from simulation data (49). This difference is possibly due to patients needing to inhale more frequently in the early phase of administration, while inhaling less frequently once a therapeutic level of methoxyflurane in the body is achieved. Regardless, environmental contamination with methoxyflurane vapour may occur for a prolonged period with a patient using the Pentrox® inhaler. Ambulance patients utilised the Pentrox® inhaler for a mean duration of 29 minutes (50). A retrospective database review of 97,705 cases where a patient received analgesia from ambulance personnel showed methoxyflurane was the sole analgesic agent in 55% of cases. When an analgesic agent was given, methoxyflurane was administered in 60% of cases overall (51). These studies demonstrate methoxyflurane can be a frequently used analgesic option. Thus, there are numerous occasions where ambulance personnel may be exposed to environmental methoxyflurane vapour for half an hour or more.

Nephrotoxicity

Serum fluoride was significantly increased in those who received methoxyflurane analgesia compared with placebo (46). Although no values were reported, a secondary report of this study indicates mean serum fluoride was 4.7 $\mu\text{mol/L}$, with a maximum of 10 $\mu\text{mol/L}$. It appears that no renal function tests were conducted (19), although this is well below the previously

suggested toxic threshold of 40 $\mu\text{mol/L}$ (3). Patients presenting to an emergency department with acute pain received one 3 mL dose of methoxyflurane via Pentrox[®] inhaler (28). The authors of that study stated there were no nephrotoxicity markers on blood tests at the time or 14 days subsequently (28,47). Patients who received methoxyflurane for colonoscopy showed no renal dysfunction in blood tests at 1 month follow up (57).

Methoxyflurane was administered on several occasions to healthy volunteers: two to three episodes of inhalation each, with 4–6 days between each episode, to determine whether repeated exposure affected either liver or kidney function. The authors reported no changes in any measure, although no data are reported to allow independent confirmation. The authors concede the small sample size (six subjects) also limits drawing any conclusions regarding safety (24). Another paper presented two case reports of elderly women receiving methoxyflurane analgesia during dressing changes. In the first case, 60 mL methoxyflurane was administered over 14 days. Renal failure with oliguria initially responsive to peritoneal dialysis ensued, and the patient died from an infective complication four months later. In the second case, 60 mL methoxyflurane was administered over 16 days. Serum fluoride was 495 $\mu\text{mol/L}$, renal failure occurred that was initially responsive to haemodialysis. However, the patient died due to renal failure six months later (58). Note that the patients in these case reports received significantly higher weekly doses than the current weekly recommended maximum of 15 mL (4).

An ambulance patient record review was sponsored by the Pentrox[®] manufacturer, but was designed, undertaken, interpreted and written without input from the company. The review linked patient care records with hospital morbidity records, emergency department records, and the death register (59). That researcher included all patients transported by ambulance between 1990 and 2000 (135,770 patients), with follow up until 2004, meaning patient outcome was measured between 4 and 14 years. Patients who received methoxyflurane (17,629 patients) were compared with those who received none. No increased risk of occurrence of any renal disease diagnosis was observed. However, this was not a controlled trial (59), so the cohort receiving methoxyflurane may not have been matched with the cohort that did not

receive methoxyflurane and thus, increased risk could not be confirmed.

A recent review determined methoxyflurane was not associated with nephrotoxicity in analgesic doses (26). Another systematic review of studies of patients receiving methoxyflurane analgesia for up to 60 minutes reportedly found no reports of renal dysfunction or of serum fluoride levels above 20 $\mu\text{mol/L}$ (11), which the authors noted was well below the threshold for toxicity (3). A table of the 'general relationship between MAC-hours, serum fluoride and blood methoxyflurane levels in humans reported in the literature' was provided (11). That review concluded that analgesic doses from the Pentrox[®] inhaler will result in significantly lower metabolite formation than anaesthetic doses, and therefore analgesia probably will not produce renal toxicity (11). We compared the reported serum fluoride values (11) with those found elsewhere in the literature. We located only one study which measured both dose in MAC-hours and also serum fluoride for each patient (60). The anaesthesia regimen described by Churchill et al in 1976 (61) approximates mean 0.7 MAC-hours exposure with reported mean serum fluoride of 34 $\mu\text{mol/L}$. Patient dose from Yoshimura et al in 1976 (62) can be converted from grams to MAC-hours by using 3 mL methoxyflurane as equivalent to 0.34 MAC-hours (49). Peak serum fluoride values can be estimated from these studies by least squares first and second order interpolation and extrapolation. Results of our analysis are provided in Table 1. Our analysis shows previously reported figures (11) approximate the values determined from one study (60) but are approximately half of the values determined from another study. Hence, the relationship between methoxyflurane exposure and resultant serum fluoride has not been clearly resolved. Furthermore, this analysis does not consider repeated low-dose exposure.

Women in labour who received methoxyflurane analgesia demonstrated a correlation between methoxyflurane dose and urine fluoride concentration. Newborns of those women demonstrated a similar correlation (63). Biochemical markers of renal failure were not measured in that study, which was an acknowledged limitation. Another study observed women using the Cardiff Penthrane Inhaler delivering 0.35% methoxyflurane for analgesia during childbirth for a mean duration of 73 minutes. That study found no significant difference in blood or

Table 1. Comparison of figures quoted in Dayan (11) with values found in other research with human subjects

Study	Best-fit model	Serum fluoride ($\mu\text{mol/L}$) by MAC-hours exposure									
		≤ 0.5	1	1.5	2	2.5	3	3.5	4	4.5	≥ 5
Dayan (2016) (11)	-	10-13	20		40	>50					>90
Cousins (1973) (60)	First order	8.6	17.2	25.8	34.4	43.0	51.6	60.2	68.8	77.4	85.8
	Second order	11.9	23.3	34.1	44.3	54.1	63.2	71.8	79.9	87.4	94.2
Churchill (1976) (61)	-	34									
Yoshimura (1976) (62)	First order	17.8	35.6	53.4	71.2	88.8	106.6	124.3	142.1	159.9	177.7

urine measures of kidney function between those receiving methoxyflurane or those receiving nitrous oxide. There was also no relationship between duration of using methoxyflurane and kidney function (64). Women in a third study who received methoxyflurane during labour had a mean peak serum fluoride level of 18.75 $\mu\text{mol/L}$, which typically occurred 2 hours postpartum (65). Serum fluoride decreased over the next 48 hours but had not returned to baseline by that time. Mean umbilical cord fluoride was highest immediately following delivery, at 11.95 $\mu\text{mol/L}$, and approximately halved to 5.79 $\mu\text{mol/L}$ by 48 hours postpartum. At day one after birth the child's mean urine fluoride was 39.05 $\mu\text{mol/L}$. These findings suggest newborns receive maternal fluoride and/or metabolise methoxyflurane to fluoride themselves. At day one, mean urine volume was within normal limits (66), suggesting no significant fetal renal effect. The researchers noted 'no maternal or neonatal problems were encountered' but did not measure biochemical markers of renal function in mothers or newborns, nor urine volume in mothers (65). Therefore, subclinical signs of nephrotoxicity would not have been identified if they were present. These studies reinforce the potential for the fetuses of exposed pregnant healthcare personnel to accumulate fluoride. No studies linked methoxyflurane with reproductive health effects.

Hepatotoxicity

One study reported no changes in any liver function tests after subjects were repeatedly exposed to methoxyflurane (24), although no test results were reported to confirm this claim. No increased risk was identified by linked database review of patients who received pre-hospital analgesia (59). No indications of hepatotoxicity were found after 3 mL methoxyflurane analgesia (28,47). Patients who received methoxyflurane for colonoscopy showed no liver dysfunction on blood tests at 1 month follow up (57).

Conversely, there have been reports of hepatitis after single methoxyflurane administrations (67-69). Three such cases are of women receiving methoxyflurane analgesia during labour. In the first case, a woman developed hepatitis with subacute hepatic necrosis following delivery, which improved after 23 days (67). Another woman evidenced hepatitis 6 days after delivery, recovering after an unstated period (67). The third case developed hepatitis 4-6 days after each of two pregnancies where she used methoxyflurane analgesia during the second stage of labour (69). These case reports did not describe the total delivered methoxyflurane dose. A middle-aged man who had been using methoxyflurane 2-4 mL almost every day for approximately 6 weeks for insomnia developed hepatitis, with resolution of clinical and biochemical abnormalities 52 days after methoxyflurane discontinuation (68). However, these anecdotal cases cannot confirm if methoxyflurane caused the hepatitis or distinguish between the effects of dose or repetition, and can thus not be used to infer the potential risks of patients or healthcare personnel.

Cardiac and other effects

The manufacturer of Pentrox® report the effect of 12 mL methoxyflurane, twice the recommended maximum daily dose (4), on cardiac and vital sign parameters of healthy volunteers (25). 'QTc' is a measured interval of electrical activity on a patient's electrocardiogram (ECG), and a prolonged QTc is associated with increased risk of sudden cardiac death (70). Subjects demonstrated a mean change in QTc of 5 ms, with a one-sided upper 95% confidence interval (confidence interval) of 10 ms (direction not stated, presumed to be positive). This value is a small but not insignificant increase, and extrapolation (70) indicates that the upper 95% CI increase of 10 ms equates to an adjusted hazard ratio of sudden cardiac death of 1.38 for women and 1.24 for men compared with those with mean QTc. The authors stated there was no evidence of any effect on heart rate, on the other measures of ECG activity or on ECG morphology but did not report any statistics on other ECG parameters (25).

The linked database review calculated the risk of any ischaemic heart disease, any diabetes, or any cancer diagnoses in those who received methoxyflurane versus those who did not. No increased risk was identified in any of those categories (59). Adverse effects, most commonly headache and dizziness, were significantly more likely with methoxyflurane compared with placebo (28). In one study, 42% of adult patients receiving methoxyflurane were judged by the investigator to experience treatment-related adverse events, although no patients discontinued use due to these effects (47). In another study, 13 adverse events occurred over 173 procedures where methoxyflurane was used, including hypotension, desaturation, cough and nausea (38). In patients undergoing colonoscopy, there were significant decreases in procedure time, incidences of hypotension and incidences of respiratory desaturation in patients receiving methoxyflurane compared with anaesthesia-assisted deep sedation using agents selected by the treating anaesthesiologist (57).

Summary: methoxyflurane for light sedation and analgesia

Methoxyflurane produces analgesic and light sedative effects, and has been used for analgesia on numerous occasions. Nephrotoxicity may occur in large or repeated analgesic doses. Methoxyflurane appears not to produce patient nephrotoxicity in single doses up to the Pentrox® manufacturer's currently recommended limit of 6 mL, which represents ~0.59 to 0.68 MAC-hours of methoxyflurane exposure for that patient. This exposure is significantly lower than the level of exposure identified as associated with nephrotoxicity. Methoxyflurane use by a woman who is pregnant but not in labour has not been explicitly studied. Women who receive methoxyflurane during labour may deliver newborns with elevated serum fluoride, but no harmful effects of this have been identified. There are some isolated reports linking methoxyflurane with hepatotoxicity, and one study found that methoxyflurane moderately increased QTc suggesting moderately increased risk of sudden cardiac death.

However, a large retrospective study found no association between methoxyflurane and increased occurrence of hepatic, heart disease, diabetes or cancer problems. Prospective studies have often had small sample sizes and inconsistent reporting of methoxyflurane dose and measures of effect. Limitations of study design, sample size or reporting indicate the need for further research to confirm patient safety.

Analysis of potential bias in methoxyflurane studies

Financial relationships between individual researchers and the pharmaceutical industry (71) and pharmaceutical industry sponsorship of research (72) are potential sources of bias in the publication of medical research. All studies of methoxyflurane use in human subjects since 2007 have used the Pentrox® inhaler as this device is the only easily available method of administering methoxyflurane. We conducted an analysis of this research to determine the potential for bias.

Studies investigating patient preference, reduction in patient pain and occurrence of harmful effects were included for analysis of bias. We categorised such studies as:

- Having a high risk of bias (studies conducted by the Pentrox® manufacturer or patent holders, or whose authors received funding from the Pentrox® manufacturer), or possible bias (no conflict of interest statement provided); or
- Unlikely bias (no bias identified, and authors declared no conflict of interest).

The studies were also categorised as:

- Positive outcome (significant decrease in reported pain, positive comparison with alternative analgesia, or lack of significant adverse effects); or
- Marginal/negative outcome (not significant decrease in reported pain, or equal or less effective than alternative analgesia).

Note that a 'significant decrease in reported pain' was defined as a reduction in pain severity of $\geq 30\%$ (36), and not based on the language used by each study to describe their results.

Note that a 'significant decrease in reported pain' was defined as a reduction in pain severity of $\geq 30\%$ (36), and not based on the language used by each study to describe their results. A positive outcome was reported in two studies published by the manufacturer of Pentrox® (25,31), and by seven publications that received financial assistance or equipment from the Pentrox® manufacturer (28,30,35,40-42,59). The risk of bias is potentially problematic in these studies. Positive outcomes were also reported by six other studies that did not provide a conflict of interest statement (27,34,37,43,45,47). Four studies reported positive outcomes and explicitly declared no competing interests (33,44,50,57).

One study received funding from the manufacturer of Pentrox®, three of the five study authors were patent holders, and reported a marginal/negative outcome (46). One further study reported a marginal/negative outcome and did not declare any competing interests (32). A further four studies

reporting marginal/negative outcomes declared no competing interests (29,36,38,39).

Table 2 summarises the potential for bias against our categorised outcomes. Barnard's unconditional test is an accurate method for determining statistical significance in 2x2 tables (73). A two-sided Barnard's unconditional test with pooled variance on this data yields $p=0.0453$ for this categorisation. Thus, it is unlikely the apparent association between potential bias and positive study finding is simply due to chance. This result serves to highlight the need for further investigation by independent researchers.

Table 2. Counts of positivity of outcome and potential for bias in studies using Pentrox® inhaler

Counts of potential bias vs. positive findings		
	Positive outcome	Marginal/negative outcome
High risk of bias, or possible bias	15	2
Unlikely bias	4	4

Occupational exposure to methoxyflurane

Overview of occupational risk and mitigation approaches

Methoxyflurane has been widely used for analgesia across Australia and New Zealand (13,14,16-18,52-55), and is beginning to be used in the UK (56). Most available organisation guidelines for use of methoxyflurane include instructions on limiting occupational exposure. Some give specific instruction regarding use in confined spaces, such as: disallowing (13) or cautioning against (16,17) administration in confined spaces; limiting administration inside the ambulance to a single 3 mL dose per patient (14,52); limiting the number of doses an ambulance officer can administer in the ambulance to two per day (14); or advising that the ambulance be ventilated (16,17,54). Use of the activated carbon filters are explicitly recommended in five service guidelines (16-18,54,56). Two guidelines do not have any special instructions on use of the carbon filters (53, 55), although it is possible those providers have policy statements regarding methoxyflurane in other documents. It is beyond the scope of this review to investigate the frequency of use of methoxyflurane within each individual organisation, or whether guidelines for occupational safety within each organisation have changed over time.

The manufacturer of Pentrox® estimates the inhaler has been used to provide over 5 million doses of methoxyflurane analgesia (11). This represents many opportunities for healthcare personnel to be occupationally exposed to methoxyflurane vapour. The Australian Therapeutic Goods Administration (TGA) collate reported cases of adverse effects from a range of stimuli (74). There were no reported cases of adverse effects caused by occupational exposure to methoxyflurane, thus suggesting occupational safety. However, while reassuring, this report lacks the scientific rigor to determine safe occupational exposure parameters. The TGA

warns health professionals of the potential risk of repeated occupational exposure and suggests they take steps to mitigate that risk. They recommend considering use of the activated charcoal filter and awareness of the risk of use in enclosed or poorly ventilated environments (74). Early reviews of methoxyflurane noted high blood gas solubility (2,75). This means patients exhale a significantly lower proportion of methoxyflurane into the local environment than they would other inhaled agents (76). This has positive implications for occupational safety of methoxyflurane compared with other inhaled agents. However, patients continued to exhale methoxyflurane for at least 12 days after being anaesthetised (77). This result suggests that patients administered methoxyflurane while outside of an ambulance would exhale methoxyflurane vapour into the much smaller ambulance environment and, subsequently, hospital rooms. Hence, occupational exposure is greater than the period of administration alone.

We found no research of the effects of methoxyflurane on the fertility of occupationally-exposed personnel of childbearing age, nor on the fetuses of occupationally-exposed pregnant personnel.

Occupational exposure from anaesthesia

Anaesthetists' work environment was contaminated with between 1.3 ppm methoxyflurane when delivering 0.2% methoxyflurane to the patient, and 9.8 ppm when delivering 1.0% methoxyflurane to the patient. By installing a local exhaust system, environmental concentrations were reduced to between 0.015 and 0.095 ppm. Before use of that exhaust system, methoxyflurane concentration on the anaesthetist's expired breath was measured following exposure. The period methoxyflurane was detectable on breath was related to the duration of exposure (77). A simple least-squares fitted second-order spline model of environmental contamination versus administered concentration yielded the end-of-exposure to cessation of expiration of methoxyflurane times shown in Table 3. The modern Pentrox® inhaler is significantly different from the anaesthetic system used in this study. However, this data provides an indication as to how long methoxyflurane would likely be present in the body for a given exposure.

Table 3. Our calculation of MAC-hours exposure and time until methoxyflurane undetectable on breath, using data from Corbett and Ball (77)

Anaesthetist exposure	Duration of exposure (minutes)	MAC-hours of exposure	Time until methoxyflurane undetectable on breath (hours)
A	130	0.0046	10.6
B	300	0.0097	28.6
C	360	0.0115	30.4

Occupational exposure from doses higher than used contemporarily

The Penthrane Analgizer was historically used as analgesia for women during labour. The analgizer is similar to the modern Pentrox® inhaler, although a larger (15 mL) dose was used in the analgizer. Methoxyflurane concentration in the air of delivery rooms without a local exhaust system was 0.5 to 0.8 ppm, whereas with a local exhaust system the concentration was 0.1 to 0.3 ppm (78). Mean urine fluoride of delivery suite personnel exposed to 0.5 to 0.8 ppm methoxyflurane was 0.707 ppm, whereas unexposed controls had mean urine fluoride 0.352 ppm (79). Further study of personnel in a delivery suite with methoxyflurane air concentration 0.3–0.8 ppm found renal and hepatic biomarkers (blood urea nitrogen, uric acid, aspartate aminotransferase, alanine aminotransferase) were elevated compared with non-exposed controls (80). This demonstrates that occupational exposure to methoxyflurane has potential to affect health.

Occupational exposure in contemporary use

The only studies of modern ambulance officer occupational exposure to methoxyflurane (81-83) do not appear to be published, and discussion is based on results as cited in two secondary sources (3,29). One of those secondary sources (3) describes potentially contestable room ventilation conditions (discussed later in this review), suggesting those authors' summaries of unpublished studies must be viewed with great caution. Treating ambulance officer 8-hour time-weighted average (TWA) airborne methoxyflurane concentration is reported as 0.06 ppm (81). It appears this study measured exposure during one patient contact and then divided that figure by 8 hours. Therefore, this result should be viewed as the occupational exposure if the ambulance officer were to only treat a single patient per day with methoxyflurane, which may not reflect actual practice. Elsewhere, ambulance officer exposure remained below 2 ppm over an hour and 0.5 ppm averaged over a work shift, provided oxygen was not administered through the inhaler (83). It is not current practice to administer oxygen through the inhaler (4). When methoxyflurane was administered using the Pentrox® inhaler, ambulance personnel were exposed to 0.2–7 ppm per treatment (82). These values are in the order of anaesthetist exposures previously reported (77). The wide range of exposure concentrations likely represents a range of environments in which methoxyflurane was administered, including outdoors, indoors and administration inside the ambulance. It is unknown whether the activated charcoal filter was used. Mean ambulance attendant 8-hour TWA was 0.23 ppm (maximum 1.5 ppm) (82). This value is ~4 to 25 times higher than elsewhere reported ambulance officer TWA exposure (81). This difference may represent differences in utilisation of methoxyflurane by personnel of different organisations, and differences in ambulance configuration.

A study by Ruff et al measured occupational exposure in a 50 m² procedure room with room ventilation 3.5 ACH during methoxyflurane use for procedural sedation for bone marrow biopsy (84). The study authors noted that the Pentrox[®] device had an incorporated charcoal filter, but no information is provided regarding whether patients were compliant in exhaling through the filter. Nurses who prepared the delivery device and stood adjacent to the patient had median (IQR) exposures of 0.92 ppm (0.33–1.27 ppm) with maximum exposure of 2.88 ppm. Haematology trainees who stood behind the patient had median (IQR) exposures of 0.20 ppm (0.1–0.39 ppm) with maximum exposure of 0.61 ppm (84). These values are below the safety limit of 15 ppm over 8 hours previously proposed (3). These values imply safety for occupational single dose exposure.

Analyses

Table 4 collates the conditions and calculated exposure with extrapolated duration of exhalation of methoxyflurane by affected ambulance personnel. These calculations yield a wide range of predicted exhalation period outcomes which in one case exceeds the durations of anaesthetist methoxyflurane exhalation following occupational exposure shown in Table 3 (77).

Historic serum fluoride versus methoxyflurane data from anaesthetised patients (60) was extrapolated to conclude that ambulance officer occupational exposure would not produce nephrotoxicity (3). We previously investigated the range of possible regression lines that could result from such extrapolation, finding a wide range of possible serum fluoride values could result from ambulance personnel

occupational exposure with up to a 4.3% likelihood of exceeding a safety threshold of 40 µmol/L depending on the model used (85). Extrapolation over several orders of magnitude does not provide assurance of occupational safety. The same anaesthetised patient dataset was used to determine a recommended maximum exposure level (MEL) 8-hour TWA of 15 ppm. The authors stated the odour threshold for methoxyflurane is 0.13–0.19 ppm and concluded methoxyflurane can be detected by smell at safe concentrations (3). Therefore, the authors conclude that smell is not a reliable indicator of toxic concentration of methoxyflurane.

Treatment environment contamination and healthcare worker 8-hour TWA methoxyflurane exposure has been modelled (3). Exposure in a health facility treatment room was determined to be a maximum 3.86 ppm 8-hour TWA, while exposure in an ambulance was determined to be a maximum 8-hour TWA 0.77 ppm. The lower ambulance environment ventilation rate of 26 air changes per hour used in the model is only achieved when cab and rear air conditioning systems are operating, while the ventilation rate for an ambulance without any airflow systems activated is only 2.9 ACH (86). This suggests that ambulance environmental contamination may be higher than determined by this model. Additionally, the model assumes the carbon filter will reduce occupational exposure by 85%, a figure obtained directly from the Pentrox[®] manufacturer. It may be assumed this rate was determined in experimental settings with the patient exhaling exclusively through the carbon filter. Non-compliance, such as with agitated or conversational patients, is expected to significantly reduce the contribution of the carbon filter. Although the activated charcoal scavenging chamber is mentioned by some reviewers, we have not identified primary publication of the effect of the filter on environmental contamination and consequent occupational exposure.

Table 4. Predicted exposures and durations of methoxyflurane being detectable on breath

Study	Parameters		Exposure (MAC-hours) ×10 ⁻³	Predicted time exhaling methoxyflurane (hours)
Dahlgren (1979) (78)	Low exposure	Local exhaust 0.1 ppm room conc. Half hour exposure	0.031	0.1
	High exposure	No local exhaust 0.8 ppm room conc. 8-hour exposure	4.000	10.2
Hibbs (2000) (81)	TWA	0.06 ppm avg. conc. 8-hour average	0.300	0.7
Flynn (2000) (83)	Did not exceed	0.5 ppm avg. conc. 12-hour average	3.800	9.6
Coffey (2011) (82)	Low exposure	0.2 ppm Half hour exposure	0.063	0.2
	High exposure	7 ppm 8-hour exposure	35.000	120.3
	TWA	0.23 avg. conc. 8-hour average	1.200	2.9

Summary of occupational exposure

Healthcare personnel may be exposed to a wide range of environmental methoxyflurane concentrations, likely dependent on frequency and duration of patient contact, use of contamination mitigation equipment, and the work environment itself. Further research should be published regarding frequency and magnitude of occupational exposure to methoxyflurane in typical environments. All reported environmental concentrations are below the calculated MEL 8-hour TWA of 15 ppm, yet alteration in renal function has been demonstrated in delivery suite personnel below that level. Methoxyflurane equilibrates between lung (breath) and body tissue, and prolonged detection of methoxyflurane on breath demonstrates that occupationally inspired methoxyflurane will remain in the healthcare worker's body for a significant period. These findings also suggest that methoxyflurane could possibly accumulate if not completely eliminated before re-exposure. Finally, fluoride and other metabolites remain present long after the period of methoxyflurane elimination (77,87).

Occupational exposure standards

Neither Australia (88), New Zealand (89), South Africa (90), the UK (91) or the US (92,93) appear to have enforceable legal standards for methoxyflurane exposure. Canada has provincial legal standards. Two Canadian provinces were investigated and prescribe a TWA limit of exposure of 2 ppm, either averaged over 8 hours (94) or a working day or week (95). British Columbia additionally sets a limit for any 30-minute period at 6 ppm, and a moment-to-moment exposure limit of 10 ppm (94). WorkSafeBC clarify that the guiding principle with regard to exposure should be minimisation of exposure regardless of legal limit (94). In the US, the National Institute for Occupational Safety and Health recommend an exposure limit of 2 ppm for any 60-minute period, although this is not a legal standard (91). Older Australian Material Safety Data Sheets indicate the Australian National Occupational Health and Safety Commission (ANOHSC, now Safe Work Australia) historically suggested application of a TWA exposure standard of 0.5 ppm (96). Newer Australian Material Safety Data Sheets (MSDS) refer to the determination (3) of a MEL of 15 ppm (97). In New Zealand, neither workplace (89) nor pharmaceutical (4) guidelines provide any recommendations of safe exposure limits for methoxyflurane.

Delivery room concentrations of methoxyflurane of 0.1–0.8 ppm (78-80) may exceed the historical ANOHSC standard but would be acceptable by all current standards. Reported and modelled exposure of Australian ambulance personnel (3, 81-83), modelled exposure of treatment facility personnel (3), and observed exposure of procedure room nurses (84) could exceed Canadian and US standards in some circumstances but are also below the MSDS recommended MEL.

Limitations

This review was restricted to English language, searchable

published literature. As such there is a risk some papers have been overlooked. Inclusion of other literature reviews in this review somewhat mitigates this weakness, as this allowed us to compare our analysis with that of other reviewers.

Extrapolation and interpolation used to compare across studies generally used small data sets. Hence, it difficult to draw definitive conclusions. This weakness reinforces the need for further research to measure safety in a range of relevant situations. A case for occupational safety may be assumed but has not been proven.

Conclusions

Methoxyflurane has been demonstrated to be a rapid acting and effective analgesic agent in isolation or in combination with other analgesia, and may be used instead of other analgesic or light sedative agents in some instances. Although patients receiving methoxyflurane frequently experience side effects such as dizziness or headache, patients still frequently indicate satisfaction and do not discontinue use.

Historic high dose anaesthetic use had implicated toxic metabolites causing renal failure. There is evidence of patient safety with the lower analgesic doses used in the modern setting, including a lack of nephrotoxicity identified in database reviews, a low number of significant adverse events reported to Australian authorities, and infrequent case reports of adverse health effects. However, this is evidence for safety of patients receiving one-off or infrequent doses of methoxyflurane.

Occupational exposure levels of methoxyflurane appear to usually be below most recommended limits. However, little is known about long term health effects of occupationally exposed personnel at the levels reported. Hence, there is not enough evidence to draw conclusions regarding safety with occupational exposures to methoxyflurane. It is remarkable that methoxyflurane is approved for use in a number of countries in which there is no occupational exposure standard. Evidence in favour of the occupational safety with methoxyflurane exposure is the long-standing use of methoxyflurane in Australian ambulance services without reported effects. However, this should not be considered conclusive proof. In particular, numerous health effects may go unnoticed, unattributed or unreported.

This review has also identified a number of gaps in the literature regarding occupational exposure.

The first relates to the actual exposure experienced by healthcare personnel, which is poorly established. There is limited publication of the frequency and duration of exposure of healthcare personnel to methoxyflurane vapour in various contemporary settings. Furthermore, there is the complication of the environmental setting. This relates to enclosure size, air change rate, patient-personnel proximity and patient

compliance with exhaling through the filter. For example, the confined space of an ambulance interior may present a different exposure level to a hospital treatment room. There is a need for further studies with control over these environmental variables, so that the exposure in different settings can be determined. This is important for the next two points, but could also have the benefit of identifying where changes to hardware and procedures may help reduce occupational exposure.

The second is whether exposure to methoxyflurane vapour in the working environment affects the cognitive performance of healthcare personnel. Possible areas to investigate are speed and judgement in decision making, and rate or likelihood of human errors. There may also be effects on physical performance. A line of research based on human factors may be appropriate for this.

The third concerns the long-term consequences of occupational exposure. Key questions here are whether or not toxic metabolite accumulation occurs over time in occupationally-exposed healthcare personnel, and how various exposure parameters may contribute to accumulation. There is the further complication that individual healthcare personnel may respond differently, whether from individual differences in susceptibility or as an effect with concomitant medication they may be taking. The risk of exacerbation of comorbidities such as pre-existing renal or hepatic disease has not been satisfactory excluded, and would therefore benefit from further study. Another long-term risk that has not been excluded is harm to the developing fetus of pregnant healthcare personnel. These are challenging questions to address in a research design because of the need for longitudinal studies, compounded by the potentially large number of independent variables. Nonetheless this is worthwhile and potentially useful results might be achieved by longitudinal studies on relatively homogenous samples. It may be useful to measure markers of renal and hepatic function directly, or to observe for suspected toxic metabolite presence in exposed healthcare personnel.

The proportion of papers with links to methoxyflurane manufacturers and undeclared conflicts of interests is of concern, as is the accuracy of some analysis and degree of extrapolation undertaken in some research. There is a need for further independent research, robust representation of occupational exposure, and comprehensive (and completely disclosed) testing protocols.

Pending the results of further research, we recommend that healthcare services utilising methoxyflurane ensure good ventilation of the working environment and use of the activated carbon filter with the delivery device.

Competing interests

The authors declare no competing interests. Each author of this paper has completed the ICMJE conflict of interest statement. SJA is an employee of Wellington Free Ambulance, working frequently in patient contact as an Intensive Care

Paramedic and thus potentially administering and exposed to methoxyflurane vapour

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