THE NORTHERN HOSPITAL

METHOXYFLURANE

Introduction

Methoxyflurane (trade name in Australia, **Penthrox**), belongs to the halogenated (or more specifically fluorinated in this case) hydrocarbon group of volatile anaesthetic agents.

It is used as a volatile liquid intended for vaporization and patient self-administration by inhalation using a **specialized inhaler device.**

At **low concentrations** the inhaled vapour is used to provide **analgesia** in **stable and conscious** patients.

The indications for methoxyflurane are:

1. Emergency relief of pain by self administration in conscious hemodynamically stable patients under the supervision of personnel trained in its use.

2. For the relief of pain in monitored conscious patients who require analgesia for short painful procedures.

Due to its **rapid action, portability** and **ease of administration** it is especially useful in the "field" and is favoured particularly by:

- **Paramedics**
- **The Armed Services**
- **Sports medicine physicians.**

History

Methoxyflurane was first synthesized in the late 1940s by William T. Miller and his team of chemists who were at the time working on the Manhattan Project.

The development of organo-fluorine chemistry was actually a spin-off from the Manhattan Project itself, which required fluorine to be produced on the industrial scale for the first time.

Fluorine was need to help separate the fissile U 235 isotope from naturally occurring uranium which consists overwhelmingly of the non-fissile isotope U 238. Naturally occurring uranium consists of less than 1 % of the U 335 isotope.

Methoxyflurane was used as a potent anesthetic agent (typically in doses of 40 60 mL) in the 1960s and 1970s, but in the late 1970s it was abandoned as a general anesthetic due to concerns about its nephrotoxicity and hepatotoxicity.

Classification

The **fluorinated hydrocarbon** group of **volatil**e anaesthetic agents include:

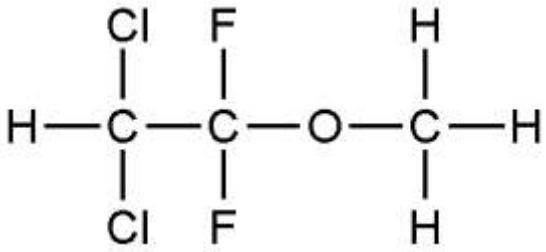
- Desflurane
- Isoflurane
- Sevoflurane
- Methoxyflurane

Chemistry

Methoxyflurane belongs to the **fluorinated hydrocarbon** group of volatile anaesthetic agents.

Its chemical name is 2, 2 - dichloro-1, 1- difluoroethyl methyl ether.

The molecular formula is $C_3H_4Cl_2F_2O$



The chemical structure of methoxyflurane

Physical Properties

Methoxyflurane is a volatile anaesthetic agent with the following physical properties:

1. Colorless liquid at room temperature:

    - All the volatile anaesthetic agents including methoxyflurane are liquids at room temperature.

      Nitrous oxide is a gas at room temperature.

2. Has a characteristic mildly pungent odour

3. It is flammable in air:

    - The **flash point** in air is 62.8 ° C. In a closed system oxygen environment it is 32.8° C.

      A certain concentration of vapour in the air is necessary to sustain combustion, and that concentration is different for each flammable liquid.

      The **flash point** of a flammable liquid is the lowest temperature at which there will be enough flammable vapour to ignite when an **ignition source** is applied.

      The **concentration** required to reach flash point however is usually not achieved under normal therapeutic circumstances.

    - The lower limit of **flammability of vapour concentration** is 7 % in air. In oxygen it is 5.4 %.

      The vapour concentration of methoxyflurane is limited by its vapour pressure at room temperature to a maximum of about 3.5 % at 23° C.

      In practice, this concentration is not reached due to the cooling effect of vaporization.

Methoxyflurane therefore is not flammable except at vapour concentrations well above those recommended for its use. Recommended concentrations are non-flammable and non-explosive in air and oxygen at ordinary room temperatures.

4. Melting point at 760 mmHg (i.e 1 atmosphere) is - 35° C

5. Boiling Point at 760 mmHg (i.e 1 atmosphere) is 104.97 ° C.

Mechanism of Action

The volatile anaesthetic agents are in general terms thought to enhance inhibitory ion channel activity and inhibit excitatory activity in the brain to induce hypnosis and amnesia, and in the spinal cord to cause immobility in response to painful stimuli.

Preparation

Methoxyflurane liquid is stored in **3 ml** glass bottles, which are **airtight** and **amber** to protect the agent from light.

Each bottle contains a solution of 99.9 % methoxyflurane and 0.01 % butylated hydroxytoluene (BHT)

Bottles should be stored at a temperature not exceeding 40° C.

The inhaler is a disposable single-use devise.

An activated charcoal (scavenging) canister s also provided and can be attached to the inhaler

Pharmacokinetics

Absorption:

- Methoxyflurane is a volatile liquid intended for vaporization and administration by inhalation.

Distribution:

- Methoxyflurane is highly lipid soluble.

Metabolism and excretion:

- Up to 30% of the inhaled dose is re-excreted via the lungs.
- Up to 70 % of the absorbed dose is metabolized to:
  - ♥ Free fluoride
  - ♥ Oxalic acid
  - ♥ Difluoro-methoxy-acetic acid
  - ♥ Dichloroacetic acid.
- Methoxyflurane is more susceptible to metabolism than other halogenated methyl ethyl ethers and has greater propensity to diffuse into **fatty tissues.**

  Hence methoxyflurane is released slowly from this reservoir and can be available for biotransformation for many days.

Pharmacodynamics

Methoxyflurane is a highly potent anesthetic agent.

At **low concentrations** the inhaled vapour is used to provide **analgesia** in **stable and conscious** patients.

Pain relief is rapid and begins after **6 - 8** inhalations and continues for several minutes after stopping inhalation

The patient then uses the inhaler intermittently during treatment/ transport to hospital.

Each **3 milliliter** dose lasts approximately **30 minutes** on average, but can last somewhat longer,

After use, recovery commonly occurs within 5 - 10 minutes

Clinical Effects

With a minimum alveolar concentration (MAC) of 0.2 %, methoxyflurane was an extremely potent anesthetic agent.

Clinical effects of the inhaler preparation include:

1. Moderate analgesia:
    - Methoxyflurane vapour provides moderate analgesia when inhaled at low concentrations.
    - It has significant analgesic properties at concentrations well below those that are required for general anaesthesia.
2. Mild sedation/ drowsiness:
    - Anesthesia occurs with relatively higher doses than those delivered by the inhaler devices.
    - Unconsciousness should not occur when used within the recommended dose range.
3. Mild amnesic effects.
4. Myocardial sensitization:
    - All the fluorinated hydrocarbon anesthetic agents can cause sensitization of the myocardium to the effects of catecholamines. The myocardium however is only **minimally** sensitized to adrenaline by **methoxyflurane.**
5. In higher/ excessive doses or in those with cardiorespiratory comorbidities or the elderly, CVS effects become more prominent and can include:
    - Bradycardia
    - Depression of myocardial contractility, with reduced cardiac output.
    - Hypotension.

Advantages

The advantages of the delivery system of methoxyflurane include:

1. Can be self administered by patients:

    - This gives the patient a certain degree of control over their analgesia, which in turns reduces anxiety.

    - Self administered oral administration may be more comfortable for some patents compared to the intranasal delivery of fentanyl.

2. Convenient delivery system:

    - It is simple to use, small and compact and easily portable, compared with the large cumbersome systems required to deliver **nitrous oxide.**

      This gives it great utility in the "field" and so is especially favoured by **paramedics** and the **armed services.**

3. Has less respiratory depression than opioids

4. Avoids the use of needles.

5. Useful when IV access for opioid administration is difficult (or impossible) or when intranasal delivery of fentanyl cannot be used (facial trauma).

Disadvantages

1. Lack a closed scavenging system:

    - Off gassing of methoxyflurane from both the delivery device and patient lung exhalation may pose some risk to health workers, **particularly in closed or poorly ventilated environments.** [8]

      Multiple use increases this risk.

      The use of methods to reduce occupational exposure to methoxyflurane, including the attachment of the **activated carbon (AC) chambers** should be considered.

2. Methoxyflurane has relatively more adverse reaction potential than do opioid agents and nitrous oxide, though *careful patient selection* and *appropriate dosing* should circumvent most of these problems.

Indications

Methoxyflurane can be used for adults and children over the age of 5 years

The indications for methoxyflurane are:

1. Emergency relief of pain by self administration in conscious hemodynamically stable patients under the supervision of personnel trained in its use.

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Due to its **rapid action, portability** and **ease of administration** it is especially useful in the "field" and is favoured particularly by:

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Contraindications/ precautions

These include:

1. Use as an anaesthetic agent:

    - Although methoxyflurane is an anesthetic agent, its delivery via the inhaler unit is not designed for the provision of true (surgical) anesthesia

    - Furthermore, because of the potential for nephrotoxic effects methoxyflurane is **not** used as an anaesthetic agent.

      Methoxyflurane impairs renal function in a dose related manner. The risk is related to the **total dose both in terms of time and concentration** as well as the frequency of exposure.

      Nephrotoxicity is greater with methoxyflurane than with other halogenated anaesthetics because of the slower metabolism over several days resulting in prolonged production of fluoride ions and metabolism into other potentially nephrotoxic substances.

      Therefore the lowest effective dose of methoxyflurane should always be administered, especially in aged or obsess patients.

2. Renal impairment/ failure

    - Including diabetic patients who may have an increased likelihood of developing nephropathy if they have preexisting impaired renal function

3. Hypersensitivity to fluorinated anaesthetics

4. Cardiovascular instability:

    - Hypotension/ cardiac failure/ arrhythmias

5. Respiratory depression

6. Head injury / altered conscious state.

7. A history of possible adverse reactions in either patient or relatives

    - e.g. malignant hyperthermia (an absolute contraindication).

8. Liver disease:

    - It is advisable not to administer methoxyflurane to patients who have shown signs of liver damage, especially after previous methoxyflurane or halothane anaesthesia.

9. Obese patients is a relative contraindication:

    - Large fat stores can accumulate methoxyflurane with subsequent increased exposure to its nephrotoxic metabolites.

10. Elderly patients:

    - *Caution* should be exercised in the elderly due to increased susceptibility to adverse CNS and CVS effects.

11. Avoid in:

    - Children under the age of 5 years

    - Older patients who are unable to self-administer.

12. Avoid contact with eyes and skin, the solution can cause irritation.

13. Concurrent use of the antibiotic **tetracycline:**

    - The concurrent use of tetracycline and methoxyflurane for **anaesthesia** has been reported to result in fatal renal toxicity.

      The possibility exists that methoxyflurane may enhance the adverse renal effects of other drugs including certain antibiotics of known nephrotoxic potential such as gentamicin, kanamycin, colistin, polymyxin b, cephaloridine and amphotericin

Pregnancy

All general anaesthetics' cross the placenta and carry the potential to produce central nervous system and respiratory depression in the new born infant.

In routine practice this dose does not appear to be a problem; however in a compromised fetus, careful consideration should be given to this potential depression, and to the selection of anaesthetic drugs, doses and techniques.

In **preeclampsia/ eclampsia** methoxyflurane should be avoided due to the possibility of existing renal impairment.

Breast feeding

Considered safe when used appropriately

Adverse Reactions

The principle adverse reactions are:

1. Nausea/ vomiting (uncommon).

2. Nephrotoxicity:

    - Both the **free fluoride** and the **oxalic acid** can cause **irreversible** renal damage in large doses.

      Dose-related nephrotoxicity seen with **clinical** doses appears related to a *combination* of free fluoride and dichloroacetic acid.

3. Respiratory depression (excessive dosing/ and or comorbidities).

4. CNS depression (excessive dosing/ and or comorbidities).

5. CVS:

    - Bradycardia
    - Hypotension
    - Arrhythmias
    - Hepatotoxicity

6. Malignant hyperthermia (rare - but lethal if unrecognized)

Dosing

Standard dosing is up to 3 mls of the methoxyflurane, delivered via the inhaler device.

Note that poor administration technique will lead to ineffective analgesia.

Avoid administration in confined spaces if possible - well ventilated spaces are preferred.

The patient should **self administer** because if the conscious state becomes significantly the device will fall from the hand, (and so limit further exposure).

Because of the risk of cumulative dose related nephrotoxicity, the maximum recommended dosing for the inhaler device is:

- 6 mls per day
- 15 mls per week
- Should **not** be used on **consecutive days**

These total maximum doses should not be exceeded.

After use, replace the top back onto the bottle and place used inhaler and bottle in sealed plastic bag and dispose of responsibly through normal waste.

Appendix 1

Method of methoxyflurane inhaler use:

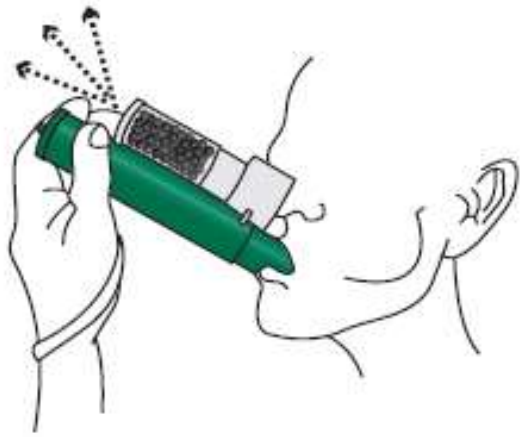
The inhaler device is strapped around the patient's wrist. Methoxyflurane is then inhaled via the inhaler. The gas that is exhaled (partly) through the nose is absorbed by the activated charcoal in the carbon canister, and so reduces atmospheric pollution and the exposure of others.

1 Check AC Chamber is pre-inserted into dilutor hole of Penthrox Inhaler.

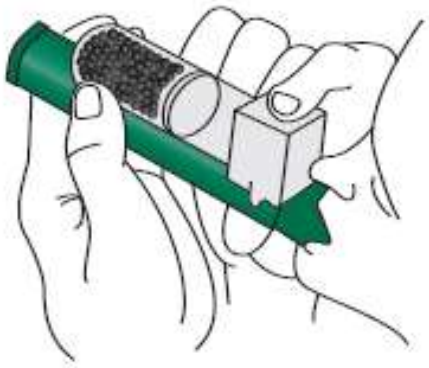
2 Tilt Penthrox Inhaler and slowly pour all of the contents of 3mL Penthrox bottle into base of Penthrox Inhaler while rotating the Penthrox Inhaler.

3 Shake lightly.

4 Place wrist-loop around patient's wrist. Patient inhales through mouthpiece of Penthrox Inhaler to obtain relief. First few breaths should be gentle, and then breath normally through Penthrox Inhaler.

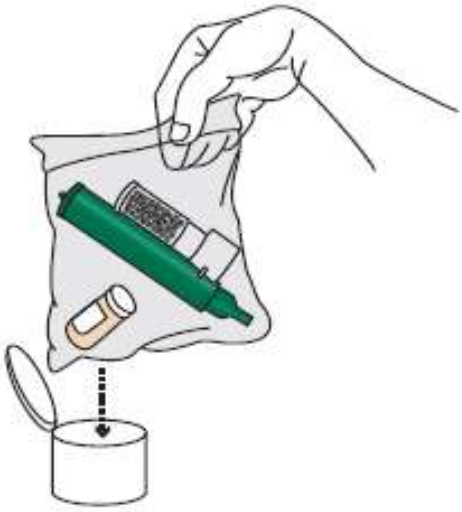


5 Patient exhales through mouthpiece of Penthrox Inhaler. The AC Chamber adsorbs exhaled vapours.



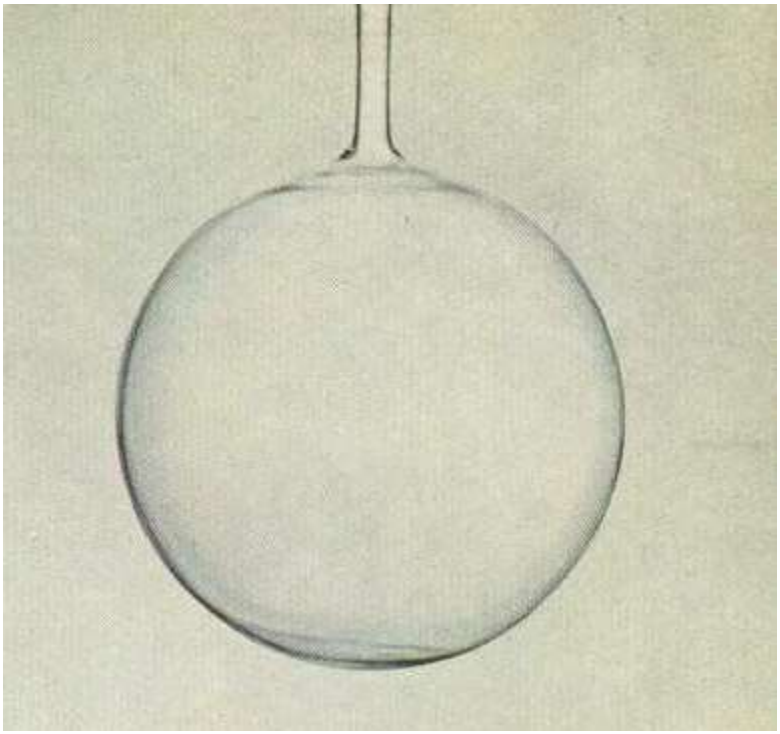
6 If stronger relief is required, patient can cover dilutor hole on top of AC Chamber with finger when inhaling.

7 Patient uses intermittently (but sufficiently) to maintain adequate relief during treatment.



8 Replace cap on 3mL Penthrox bottle, place used Penthrox Inhaler in sealed plastic bag, and dispose of responsibly after treatment.

Appendix 2



Fluorine (from Life Science Library, "Matter", 1963).

A flask of fluorine. Its name is derived from "fluo" or "flow". It is one of the most reactive of the non-metals, only a few of the inert gases can resist it. It can corrode pure platinum, an element that withstands corrosion from most other chemicals. In a stream of fluorine gas wood will spontaneously burst into flame. The development of organo-fluorine chemistry was actually a spin-off from the Manhattan Project which required fluorine to be produced on the industrial scale for the first time. The fluorinated hydrocarbon ether anesthetics were one such spin-off.

Elemental symbol:	**F**
Atomic number	9
Atomic weight:	18.99
Melting point:	−219.67 °C
Boiling point:	−188.11 °C
Classification:	Gas
Physical Appearance:	Pale yellow gas.

References

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Acknowledgments:
Paramedic Scott Clarke
Paramedic Elia Petzierides
April 2015