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Methoxyflurane: a review with emphasis on its role in dental practice

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Abstract

Methoxyflurane was developed as an anaesthetic agent and introduced into clinical practice in 1960. It soon became evident that it possessed analgesic properties that other drugs did not. Due to toxicity concerns, it lost favour in general anaesthesia and had been largely abandoned by the late 1970's. The manufacturer withdrew it in 1999, and the Food and Drug Administration in the United States did not renew its license in 2005. It has also been withdrawn by the European Union. However, it continues to be used in Australasia, primarily as an inhaled self-administered analgesic by emergency services immediately following

trauma. It has become attractive for use in dental practice, likely due to its effectiveness as an analgesic and its additional sedative qualities. Its acceptance is controversial as its use in dentistry is largely elective. Despite its good safety record in analgesic doses, adverse reactions have been recorded. Practitioners should be well aware of risks associated with its use before considering administration, and carefully assess whether or not there are equally good alternative options that do not the carry the same risks. Methoxyflurane is reviewed below with an emphasis on its use in dental practice.

Keywords: analgesic, dentistry, inhalation, Methoxyflurane, safety

Background

The principle for methoxyflurane development initially occurred when methyl alcohol was added to Fluoroethylenes.[1] Described as the first "modern" halogenated ether, it was introduced in 1959,[2] and clinical evaluation in 100 patients was reported in 1960.[3] It was described as a second-generation halogenated inhaled anaesthetic but was withdrawn from use in many countries due to case reports of renal impairment.[4] Its use in anaesthetics declined in the 1970's due to adverse effects. Despite this, it continued to be used in some parts of the world as a self-administered inhalational preparation, for example “the Analgizer”.[5] In 1999, the manufacturers, Abbott Laboratories, voluntarily withdrew methoxyflurane from US market. FDA later revoked its license in 2005. However, it remains licensed for use in Australia (Therapeutic Goods Administration) and New Zealand (Pharmaceutical Management Agency).

The analgesic qualities of methoxyflurane were recognised shortly after its introduction for clinical use,[6] and this view was supported a few years later.[7] An assessment of six inhalation anaesthetic agents used at sub-anaesthetic concentrations found that methoxyflurane and nitrous oxide possessed both analgesic and hypnotic actions, which halothane, enflurane, isoflurane and sevoflurane did not.[8] A role for methoxyflurane was suggested in situations where general anaesthesia was a significant hazard or regional anaesthesia was deemed impractical or contraindicated.[9] In a small cohort pilot study, in children, it was deemed effective as an analgesic, with no serious adverse events, and found most useful as a bridging analgesic agent post extremity trauma.[10] Methoxyflurane as a Penthrox (Medical Developments International, Springvale, Victoria, Australia) inhaler was approved under the PBS for prescription by medical practitioners.[11,12]

Pharmacology

Methoxyflurane is 2,2-dichloro-1,1-difluoro-ethyl methyl ether. It is a clear, almost colourless liquid with a characteristic odour. At its recommended concentrations, it is non-flammable and chemically stable in the presence of light, oxygen, moisture and carbon dioxide absorbents. Methoxyflurane vapour provides analgesia when inhaled at low concentrations. Once absorbed, 50-70% is metabolized to free fluoride, oxalic acid, difluoromethoxyacetic acid, and dichloroacetic acid. The high blood gas partition coefficient of methoxyflurane was found to be of considerable benefit ensuring pain relief for a prolonged period after administration was ceased.[13] Its propensity to diffuse into fatty tissues creates a slow release reservoir for days post administration.[14] This is of particular concern in the dental setting as many anxious patients may also be obese and if they are promptly discharged they are likely to retain the drug for release over a considerable time after treatment.

Clinical Use

The pre-hospital setting:

Methoxyflurane is as a self administered inhalational analgesic in pre-hospital settings in which the patient is intentioned towards a full medical service and primary attention is allocated to monitor and assist the sedated patient. Although there are no published controlled trials of use of methoxyflurane in sub-anaesthetic doses, available data suggests that it is effective as an analgesic, particularly in the pre-hospital post-trauma setting[15-17] with its strength lying in the rapidity of pain relief onset.[18] This facilitates patient comfort prior to treatment in a hospital setting where more potent intravenous medications can be administered by personnel with appropriate training with the availability of monitoring and resuscitation facilities. It is, however, reported to be less effective in overall pain relief than fentanyl and morphine in both adults and children.[19 20] Further, there is insufficient information to support its use for procedural pain. [21] The incidence of adverse events has been reported in the literature as low/insignificant when the recommended doses are not exceeded, although deep sedation has been reported in children less than five years old.[16,21] Aside from trials of its use in pre-hospital settings, there has been minimal data on the use of methoxyflurane in the last 30 years.

Dressings for burns:

Methoxyflurane was found to be useful as an analgesic for burns' dressings.[22,23]
Patient acceptance was good, and advantages included no undue sedation, no need for preoperative starvation, and venepuncture being avoided. Use in burn dressings for children has been variably reported, with one study of patients under five years reporting that it provided unsatisfactory analgesia,[24] while a separate study[25] reported that analgesia was deemed good or better in approximately two thirds of cases aged between four months and 13 years.

Obstetric practice:

Methoxyflurane was used extensively in obstetric practice when it became initially available. It was described as drug of choice in obstetric anaesthesia.[26] A review of 645 cases in 1962 found methoxyflurane to be a safe anaesthetic and analgesic agent, without side-effects, because only low concentrations were needed.[27] When self-administered, methoxyflurane was deemed a more effective analgesic, with less nausea and vomiting, when compared to nitrous oxide,[28] and another study found in the same year (1969) methoxyflurane similarly satisfactory, noting there were no ill effects upon the foetus.[29] Pain relief was reported up to 36-48 hours post-partum but also some drowsiness.[30] It was suggested that there was no evidence of renal dysfunction after self-administered use during labour.[31] However, a subsequent study in 1977 reported dose dependent changes in renal markers of both mothers and neonates.[32] Methoxyflurane is no longer a drug of use in obstetric practice.

Dental practice:

The use of methoxyflurane in dentistry was recommended due to its analgesic and sedative properties.[33] Safety and simplicity of administration were noted in two other reports.[34,35] An early (1960) blinded trial on methoxyflurane in dental anaesthesia did not demonstrate any particular advantage in its use.[38] A study from 1975 showed that nitrous oxide caused significantly less uncooperative behaviour than methoxyflurane.[36] In a recent study, the Penthrox inhaler provided comparable sedation to nitrous oxide when third molars were removed under local anaesthesia. [37] This study was completed on a group of healthy individuals aged between 18-30 in an oral and maxillofacial clinic with full resuscitation facilities available.

Adverse effects

In the 1960s, an emphasis on development of improved analgesics and anaesthetic drugs saw published data on fluorinated anaesthetic compounds, initially predominantly animal studies,[39-42] and proceeding into human clinical trials.[43,44] The results from one large series was encouraging,[45] with the main adverse effect in most reports appearing to be respiratory depression. As discussed above, methoxyflurane has a propensity to diffuse into fatty tissues creating a slow release reservoir for days post administration.[14] In the dental setting, if used with obese patients, this has the potential for prolonged respiratory depression for days after discharge.

Nephrotoxicity

Changes in renal function, and the potential for nephrotoxicity, were being monitored if not at the time of, then shortly after, the introduction of methoxyflurane into clinical practice.[46-48] Limitations on concentration and duration of exposure were suggested.[49] Deaths due to renal failure at analgesic doses via a penthrane analgiser have also been reported.[50] The mechanism of renal toxicity of methoxyflurane is unknown. There has been a suggested role of intrarenal generation of nephrotoxic metabolites, in particular inorganic fluoride ions.[51] More recently a new hypothesis of methoxyflurane nephrotoxicity proposed that it may result from O-demethylation which forms both fluoride and dichloroacetic acid.[52] The formation of the two compounds is unique to methoxyflurane compared to other volatile anaesthetics.

An earlier laboratory study in rats suggested that the predominant factors leading to methoxyflurane nephrotoxicity appeared to be dosage of the agent, and serum inorganic fluoride concentration. Secondary factors included the high rate of methoxyflurane

metabolism, sensitivity of the kidney to inorganic fluoride toxicity, concurrent treatment with other nephrotoxic drugs, pre-existing renal disease, repeat administration, and concurrent treatment with enzyme-inducing drugs such as phenobarbital.[53]

Hepatotoxicity

There have been a number of reports of hepatotoxicity, some non-fatal[54-57] and some fatal.[58-60] Repeated exposure,[61] even in sub-anaesthetic concentrations,[62] may be a risk factor. One conclusion drawn in a further report of two obstetric cases was that idiosyncratic hepatitis will continue to occur unpredictably in a very few patients.[63] In 2008, a review of adverse drug reactions with halogenated anaesthetics, focused on adverse organ effects (including hepatic and renal) that were attributable to anaesthetic metabolism and/or degradation. It was stated that none of the currently available halogenated anaesthetics cause clinically significant changes in renal function[2] but the licence for the use of methoxyflurane had been withdrawn[64] in the USA by the time this article was published. A manufacturer-funded study (which indicated there was no conflict of interest) found no difference in event rates for cardiac/renal/hepatic/disease plus diabetes and cancer, between those who received Methoxyflurane, and those who did not, in the pre-hospital setting.[65]

Illicit use and occupational hazards

There are a number of papers documenting diverse medical problems as a result of methoxyflurane abuse: renal[57], psychiatric[66], multisystem[67], and ocular.[68] Attention to the potential for occupational hazards for anaesthetists was drawn,[69] and rare but significant occupational exposure problems have been reported including hepatic and renal effects; specifically, these were significantly elevated levels of blood urea nitrogen, serum uric acid, serum glutamic oxaloacetic transaminases (SGOT) and serum glutamic pyruvic

transaminases (SGPT) three days after exposure to Methoxyflurane, emphasising the need for good scavenging.[32] Exacerbation of subclinical myasthenia (reversible lethargy, muscular weakness and ptosis) in a nurse anaesthetist has also been reported.[70]

Access and Availability of Information

Availability of methoxyflurane is not limited to ambulance and Emergency Department but available for purchase by health professionals. According to an Australian manufacturer's website, it can be purchased by a dentist with provision of a "Dental Registration Certificate/Card". [71] The available product information guide contains comprehensive information. [72] Contraindications include patients with renal impairment and failure, hypersensitivity to fluorinated anaesthetics, cardiovascular instability, respiratory depression, head injury or loss of consciousness. Caution is highlighted for those with liver disease and diabetes, the elderly and the obese and patients on enzyme inducing drugs. Additionally, health care workers regularly exposed to patient using methoxyflurane inhalers are encouraged to be aware of relevant occupation health and safety guidelines for use of inhalational agents. Dental use is analogous to other usages. The maximum stated daily dose of 2 bottles x 3ml and no more than 15ml (5 bottles) in a week for all patients. Regarding operation of a vehicle after administration, this is suggested to be at the discretion of the treating doctor, however a minimum of 24 hours would seem prudent. [72]

Guidelines for the use of methoxyflurane in Dental Practice

1. Safety in the use of methoxyflurane can only be possible if used in accordance with the manufacturer's instructions and anxiolysis guidelines of the Dental Board of Australia. A sound knowledge of potential adverse events should precede embarkation of its use.

2. Although the product is readily available, it should be known that the use of methoxyflurane is governed under the anxiolysis guidelines of the Dental Board of Australia. There is a clear requirement for training on the correct use of methoxyflurane with the need for oxygen, airway management skills and life support skills.

3. Patient selection requires that a full and current patient medical history be taken by the clinician with particular relevance to strict and relative contraindications.

4. Prior to use, dentists should carefully consider whether or not there are alternatives to methoxyflurane that do not carry the same risk of adverse reactions.

5. Should the procedure require anything more than simple anxiolysis or analgesia, methoxyflurane is not indicated, and the patient should be referred.

6. A clear and concise discussion on its intended use should be had with the patient prior to its use. This should not occur at the same appointment that this is intending to be used.

7. Methoxyflurane should not be used with any other sedative medication, as it is likely that this will be both harmful and illegal if dentist is not an endorsed Dental Sedationists.

8. Extreme care should be taken to not allow misuse of methoxyflurane. It is not appropriate to override patient control by holding the device to the patient's mouth during administration.

9. Patients should be monitored after administration of methoxyflurane and should not operate machinery or drive a vehicle until they have completely recovered from the effects of the drug, and it is recommended that this be at least 24 hours.

10. Dentists and patients must be well informed of the possibility of developing late complication.

11. Similar to that recommended for the use of methoxyflurane in the ambulance setting to reduce the risk of occupational exposure to methoxyflurane, no single Dentist should

administer more than two doses of methoxyflurane in any given day.

Conclusions on use in dentistry

Adverse effects are rare when Methoxyflurane is administered in analgesic doses. However its legitimate role and limitations in the dental surgery are unclear. There is a lack of recent and well-designed studies describing or supporting its use in routine dental practice. Practitioners, at a minimum, must be aware of the risks of this drug to their patients, their staff and themselves. Current regulations for the use of inhalational sedatives used in dentistry call for formalized training of the practitioner and the requirement of appropriate surgery and ventilation design. These regulations should apply to the use of Methoxyflurane.

References

1. Miller Jr WT, Fager EW, Griswold PH. The Addition of Methyl Alcohol to Fluoroethylenes. Journal of the American Chemical Society 1948;70(1):431–2.
2. Kharasch ED. Adverse drug reactions with halogenated anaesthetics. Clin Pharm and Therapeutics 1978;84(1):158-62.
3. Artusio JF, Van Poznak A, Hunt RE, et al. A clinical evaluation of methoxyflurane in man. Anesthesiology 1960;21(5):512–7.
4. Jakobsson J. Desflurane: a clinical update of a third generation inhaled anaesthetic. Acta Anaesthesiologica Scandinavica 2012;56:420-32.
5. Wexler RE. Analgizer: Inhaler for supervised self-administration of inhalation anesthesia. Abbott Park, Illinois: Abbott Laboratories, 1968.
6. Torda TAG. The analgesic effect of methoxyflurane. Anaesthesia 1963;18(3):287–9.
7. Siker E et al. Effect of sub-anaesthetic concentrations of halothane and methoxyflurane on pain threshold in conscious volunteers.Anesthesiology 1967;28(2):337-42.
8. Tomi K, Mashimo T, Tashiro C, et al. Alterations in pain threshold and psychomotor response associated with subanaesthetic concentrations of inhalational anaesthetics in humans. British J Anaesthesia 1993;70(6):684–6.
9. Reier C. Methoxyflurane analgesia: a clinical appraisal and detailed description of stage I in man.Anesth Analg 1970;49(2):318-22.
10. Babl F, Barnett P, Palmer G, Oakley E, Davidson A. A pilot study of inhaled Methoxyflurane for procedural analgesia in children. Pediatric Anesthesia 2007;17(2):148–53.
11. Australian Government Department of Health. PBS Schedule for Methoxyflurane. URL:'http://www.pbs.gov.au/pbs/search?term=methoxyflurane.' Accessed December 2014.

12. National Prescribing Service. Methoxyflurane (Penthrox) for analgesia (doctor's bag listing). NPS RADAR. Canberra, Australia: National Prescribing Service, Department of Health and Ageing, 2010.
13. Crankshaw DP. Methoxyflurane for relief of acute pain: interpretation of uptake and elimination curves(abstract). Anesthesiology 2005;103(Supplement):A756.
14. Medical Developments International Pty. Ltd. Penthrox (methoxyflurane) inhalation: product information. Springvale, Victoria, Australia: Medical Developments International Limited, 2009.
15. Buntine P, Thom O, Babl F, Bailey M, Bernard S (2007). Prehospital analgesia in adults using inhaled methoxyflurane. Emergency Medicine Australasia 2007 19(6):509–14.
16. Babl FE, Jamison SR, Spicer M et al. Inhaled Methoxyflurane as a prehospital analgesic in children. Emergency Medicine Australasia 2006;18:404-10
17. Chin R, McCaskill M, Browne G, Lam L. A randomised controlled trial of inhaled methoxyflurane pain relief in children with upper limb fracture (abstract). Journal of Paediatrics and Child Health 2002;38(5):A13–4.
18. Johnston S, Wilkes GJ, Thompson JA, Ziman M, Brightwell R (2011). Inhaled methoxyflurane and intranasal fentanyl for prehospital management of visceral pain in an Australian ambulance service. Emergency Medicine Journal 2011;28(1):57–63.
19. Middleton PH,Simpson PM, Sinclair G, Dobbins TA, Math B, Bendall JC. Effectiveness of morphine, fentanyl and methoxyflurane in prehospital setting. Prehosp Emerg Care 2010;14:439-47.
20. Bendall JC, Simpson PM, Middleton PM. Effectiveness of prehospital morphine, fentanyl, and methoxyflurane in pediatric patients Prehosp Emerg Care 2011;15:158-65.
21. Grindlay J, Babl FE. Efficacy and safety of methoxyflurane analgesia in the emergency department and prehospital setting. Emergency Medicine Australasia 2009;21(1):4–11.
22. Packer KJ, Titel JH. Methoxyflurane analgesia for burns dressings: experience with the Analgizer. British Journal of Anaesthesia 1969;41(12):1080–5.
23**.** Marshall M, Ozorio HP. Analgesia for burns dressing using methoxyflurane.Br J Anaesth 1972;44(1):80-2.
24. Laird SM, Gray BM. Intermittent inhalation of methoxyflurane and trichloroethylene as an analgesic in burns dressings procedures. Br J Anaesth1971;43:149–59.
25. Firn S. Methoxyflurane analgesia for burns dressings and other painful ward procedures in children. Br J Anaesth 1972;44 (5):517–22.
26. Boisvert M, Hudon F. Clinical evaluation of methoxyflurane in obstetrical anaesthesia: A report on 500 cases. Canadian Anaesthetists' Society Journal 1962; 9(4):325-30.
27. Romagnoli A, Korman D. Methoxyflurane in obstetrical anaesthesia and analgesia. Canadian Anaesthetists' Society Journal 1962; 9 (5):414–8.
28. Jones PL, Rosen M, Mushin WW et al. Methoxyflurane and nitrous oxide as obstetric analgesics. I. A comparison by self-administered intermittent inhalation. Br Med J. 1969;3:259-62.
29. Barber IJ, Jr, Barnett HA, Williams CH, Adriani J. Comparison of methoxyflurane and parenteral agents for obstetric analgesia. Anesth Analg. 1969 Mar-Apr;48(2):209–216.
30. Major V, Rosen M, Mushin WW. Methoxyflurane as an obstetric analgesic: a comparison with trichloroethylene. British Medical Journal 1966;2(5529):1554–61.
31. Rosen, M.; Latto, P.; Asscher, A. Kidney function after methoxyflurane analgesia during labour. British Medical Journal 1972;1(5792):81–83.
32. Dahlgren BE. Influence of methoxyflurane-nitrous oxide analgesia during childbirth on renal and hepatic function. British journal of anaesthesia 1977;49:1271-7.
33. Grainger JG, Harris NK. Methoxyflurane (penthrane) analgesia in dentistry. Dent

Anaesth Sedat 1973;2(2):10-13.
34. Dragon A, Goldstein I. Methoxyflurane: preliminary report on analgesic and mood modifying properties in dentistry. J American Dental Association 1967;75(5):1176–81.
35. Josephson CA, Schwartz W. The Cardiff inhaler and Penthrane. A method of sedation analgesia in routine dentistry. Journal of the Dental Association of South Africa 1974;29 (2): 77–80.
36. Edmunds D, Rosen M. Inhalation sedation for conservative dentistry. A comparison between nitrous oxide and methoxyflurane. British Dental Journal 1975;139(10):398–402.
37. Abdullah WA, Sheta SA, Nooh NS. Inhaled Methoxyflurane (Penthrox) sedation for third molar extraction: a comparison to nitrous oxide sedation. Aust Dent J 2011;56:296-301
38. Unkles RD, Lawson JIM. Methoxyflurane in dental anaesthesia: a blind trial. Brit J Anaesthesia 1965;37(6): 422-7.
39. Van Poznak A, Artusio JF. Anesthetic properties of a series of fluorinated compounds: I. fluorinated hydrocarbons. Toxicology and Applied Pharmacology 1960;2 (4): 363–73.
40. Van Poznak A, Artusio JF. Anesthetic properties of a series of fluorinated compounds: II. fluorinated ethers. Toxicology and Applied Pharmacology 1960;2:374-8.
41. Siebecker KL, James M, Bamforth BJ et al. The respiratory effect of methoxyflurane on dog and man. Anesthesiology 1961;22(1):143.
42. Millar RA, Morris ME (1961). "A study of methoxyflurane anaesthesia". Canadian Anaesthetists' Society Journal 8 (3): 210–5.
43. Wyant GM, Chang CA, Rapicavoli E. Methoxyflurane (penthrane): a laboratory and clinical study. Canadian Anaesthetists' Society Journal 1961;8(5):477–87.
44. McIntyre JWR, Gain EA. Methoxyflurane. Canadian Anaesthetists' Society Journal 1962;9(4):319–24.
45. McCaffrey FW, Mate MJ. Methoxyflurane (Penthrane): a report of 1200 cases. Can Anaes Soc J 1963;10(2):103-13.
46. Paddock, RB, Parker JW, Guadagni NP. The effects of methoxyflurane on renal function. Anesthesiology 1964; 25:707–8.
47. Crandell WB, Pappas, MacDonald A. Nephrotoxicity associated with methoxyflurane anesthesia. Anesthesiology 1966;27 (5):591–607
48. Jones NO. Methoxyflurane nephrotoxicity – a review and a case report. Canadian Anaesthetists' Society Journal 1972;19(2):152-9.
49. Cousins MJ, Mazze RI (1973). Methoxyflurane nephrotoxicity: a study of dose response in man (abstract). Journal of the American Medical Association 1973l225(13): 1611–6.
50. Toomath, R.; Morrison, R. Renal failure following methoxyflurane analgesia". The New Zealand medical journal 1987;100(836):707–708.
51. Kharasch ED, Hankins D, Thummel K. Human kidney Methoxyflurane and Sevoflurane metabolism. Intrarenal fluoride production as a possible mechanism of Methoxyflurane nephrotoxicity. Anesthesiology 1995;82(3):689-99.
52. Kharasch ED, Schroeder JL, Liggitt HD et al. New insights into the mechanism of Methoxyflurane nephrotoxicity and implications for anesthetic development (part 2): identification of nephrotoxic metabolites. Anesthesiology 2006;105(4):737-45.
53. Mazze RI. Methoxyflurane nephropathy. Environmental Health Perspectives 1976:1111–9.
54. Klein NC, Jeffries GH. Hepatotoxicity after methoxyflurane administration. Journal of the American Medical Association 1966;197(12):1037–9.
55. Brenner AI, Kaplan MM. Recurrent hepatitis due to methoxyflurane anaesthesia. New England Journal of Medicine 1971;284(17):961–2.
56. O'Rourke KM, McMaster S, Lust KM. A case of hepatitis attributable to repeated exposure to methoxyflurane during its use for procedural analgesia. Med J Aust

2011;194(8):423-4.
57. Brennan R, Pearlstein A, Miller S. Computed Tomography of the kidneys in a patient with Methoxyflurane abuse. J Computer assisted tomography 1988;12(1):155-6.
58. Lischner MW, MacNabb GM, Galambos JT. Fatal hepatic necrosis following surgery. Possible relation to methoxyflurane anesthesia. Archives of Internal Medicine 1967;120 (6): 725–8.
59. Stefanini M, HerlandA, Kosyak, EP. Fatal massive necrosis of the liver after repeated exposure to methoxyflurane. Anesthesiology 1970;32(4):374–8.
60. Min KW, Cain GD, Sabel JS, Gyorkey F. Methoxyflurane hepatitis. Southern Medical Journal 1977;70 (11): 1363–4.
61. Rubinger D, Davidson JT, Melmed RN. Hepatitis following the use of methoxyflurane in obstetric analgesia. Anesthesiology 43(5):593–5.
62. Okuno T, Takeda M, Horishi M, Okanoue T, Takino T. Hepatitis due to repeated inhalation of methoxyflurane in subanaesthetic concentrations. Canadian Anaesthetists' Society Journal 1985;32(1):53–5.
63. Delia JE, Maxson WS, Breen JL. Methoxyflurane hepatitis: two cases following obstetric analgesia. International Journal of Gynaecology & Obstetrics 1983;21 (1): 89–93.
64. Penthrane (Methoxyflurane) inhalation liquid. Food and Drug Administration Federal Register 2005 September 6;70(171):53019.
65. Jacobs IG. Health effects of patients given Methoxyflurane in the pre-hospital Setting: a data linkage study. The Open Emergency Medicine Journal 2010;3:7-13.
66. De Francisco, C. Pentrane dependence: A case report. The British journal of psychiatry: The Journal of Mental Science 1971;119(553):609–10.
67. Klemmer, P.; Hadler, N. Subacute fluorosis: A consequence of abuse of an organofluoride anesthetic. Annals of Internal Medicine 1978;89(5 Pt 1):607–11.
68. Novak, M.; Roth, A.; Levine, M. Calcium oxalate retinopathy associated with methoxyflurane abuse. Retina 1988;8 (4):230–236.
69. Corbett, T.; Ball, G. Chronic exposure to methoxyflurane: A possible occupational hazard to anesthesiologists. Anesthesiology 1971;34 (6): 532–537.
70. Elder, B.; Beal, H.; Dewald, W et al. Exacerbation of subclinical myasthenia by occupational exposure to an anaesthetic. Anaesthesia and Analgesia 1971;50(3):383–7.
71. Documentation Requirements for the Supply of Methoxyflurane (Penthrox). Mega Medical Equipment and Gases Australia. URL:http://www.megamedical.com.au/_literature_115956/Penthrox_Product_Information. Accessed May 2015.
72. Penthrox product information. Medical Developments Internation. URL: http://www.medicaldev.com/wp/wp-content/uploads/2014/09/Penthrox-PI_v10.pdf. Accessed May 2015.