Methoxyflurane: assessment of application for inclusion in the WHO Model List of Essential Medicines

Application

Application for the inclusion of methoxyflurane on the WHO Model List of Essential Medicines has been made by the manufacturer of the product, Medical Developments International Ltd of Springvale, Australia.

The application has sought to provide information required by the Expert Committee and has been laid out according to the procedure suggested (Document EB109/8 (Annex); http://www.who.int/medicines/organization/par/edl/procedures.shtml).

The drug

Methoxyflurane, a volatile liquid, was used as an anaesthetic for administration by inhalation. Other halogenated compounds used in anaesthesia include halothane and sevoflurane. However, this application relates to the use of methoxyflurane as an analgesic and involves inhalation of smaller doses. For anaesthesia, it was marketed in Australia, Germany and the USA as Penthane® but this product is no longer available. Methoxyflurane remains available as Penthrox® in Australia. Martindale does not document any other markets or proprietary brands of methoxyflurane.¹

The application specifies delivery of methoxyflurane through a proprietary (Penthrox®) inhaler, intended for single-patient use.

Indications

Section 8 of the application states that methoxyflurane is indicated as a short-term analgesic in conscious patients for minor surgical procedures, labour, dental procedures, and for emergency analgesia in pre-hospital settings (e.g. accidents, sporting and occupational injuries). These indications can be considered to be essential for the ‘health care needs of the majority of the population’ and the WHO Model List therefore includes nitrous oxide to meet such a need. (In the 2004 edition of the WHO Model Formulary, the uses of nitrous oxide include ‘analgesia for obstetric practice, for emergency management of injuries, during postoperative physiotherapy and for refractory pain in terminal illness’.)

The application suggests inclusion of methoxyflurane in the WHO Model List in section 1.3 (preoperative medication and sedation for short-term procedures) and section 2 (analgesics, antipyretics, non-steroidal anti-inflammatory medicines, medicines used to treat gout and disease modifying agents in rheumatoid disorders). However, nitrous oxide, which may be used in the same circumstances as methoxyflurane, is included in section 1.1 of the WHO Model List.

It is intended that methoxyflurane is inhaled by the patient through the hand-held inhaler Penthrox® inhaler, under the supervision of a ‘person trained in its administration’.
**Relative efficacy**

Nitrous oxide, which is already included in the WHO Model List, is the obvious comparator. The procedure for application for inclusion of new products requires a summary of comparative effectiveness in a variety of clinical settings.

The application makes reference to a number of studies that show that methoxyflurane is effective in a range of patients and a variety of circumstances where an analgesic is called for. However, it includes few references to studies that compare nitrous oxide with methoxyflurane.

Section 8.3 of the application alludes to a 1965 study (by Tomlin et al.) and states that methoxyflurane proved to be a much more effective analgesic than nitrous oxide. The application does not reveal how many patients were included in the study nor does it state the difference between the two interventions in quantitative terms. Although the application states that this study is ‘the only available comparison of the two agents’, section 8.2 reports on 15 obstetric studies and goes on to say that ‘efficacy was comparable to nitrous oxide when the trial design included this agent as a comparator’.

Section 8.3 claims a number of advantages of methoxyflurane over nitrous oxide including the more persistent analgesic effect of methoxyflurane, which might be useful when extricating trapped patients. However, no comparative clinical studies are cited to support the claim.

**Relative safety**

The procedure for application for inclusion of new products requires a summary of comparative evidence on safety. Again, the relevant comparator is nitrous oxide. However, the application does not provide any information on clinical studies comparing the safety of methoxyflurane with nitrous oxide. Side-effects of nitrous oxide generally occur on prolonged exposure and include megaloblastic anaemia, leucopenia and middle-ear damage.

A review of the literature to support this application specifically excluded correspondence in medical journals; this is unfortunate because frequently the first signals about hazards are reported as letters to editors.

Significant concerns relating to methoxyflurane are discussed below.

**Renal toxicity**

The application identifies nephrotoxicity as a major concern but goes on to say that renal problems do not occur with analgesic doses. However, a relatively superficial search revealed a report of renal failure in 2 patients following methoxyflurane analgesia over 14 and 16 days; this report is not cited in the application. The authors comment that the inhaler was withdrawn from the New Zealand market in 1984.

Methoxyflurane impairs renal function in a dose-related manner. It is likely that it has been abandoned as an anaesthetic because its nephrotoxicity is greater than that of other halogenated anaesthetics. It is metabolised slowly, resulting in prolonged production of fluoride ion and other potentially nephrotoxic metabolites.\(^1\)

*Drug Facts and Comparisons* (January 2000) includes a warning that methoxyflurane ‘may cause renal failure or damage due to release of the fluoride ion’. Prescribing information for
methoxyflurane\textsuperscript{3} notes that because of the risk of nephrotoxicity, ‘patients with pre-existing renal disease, impairment of renal function, toxaemia of pregnancy, or concurrently using tetracyclines should not receive methoxyflurane unless in the judgement of the physician the benefits outweigh the increased risk of nephrotoxic effects’.

**Hepatic effects**

Section 9.3 of the application states that ‘hepatitis is an idiosyncratic response which results from a hypersensitivity reaction’. No specific references are cited in the application.

A very quick search of the literature retrieves a number of papers on liver injury and methoxyflurane use. Although many relate to its use in anaesthesia, a number deal with hepatitis with subanaesthetic doses of methoxyflurane.\textsuperscript{4,5,6} Martindale\textsuperscript{1} mentions that there have been occasional reports of hepatic dysfunction, jaundice, and fatal hepatic necrosis.

**Other adverse effects**

Halogenated anaesthetics are associated with malignant hyperthermia; *Facts and Comparisons* advises that the patient should be monitored closely. Martindale reports that methoxyflurane is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in animals or in laboratory models.

**Interactions**

The application states that methoxyflurane has no interactions. However, the prescribing information states that it should not be given with tetracyclines because of the possibility of renal injury.

**Costs**

The application compares the cost of nitrous oxide (and morphine sulfate) with methoxyflurane delivered through the Penthrox\textsuperscript{®} device. Australian prices are used for the comparison. They show a 6\% price advantage of methoxyflurane over nitrous oxide. However, this approach is flawed since the price of oxygen–nitrous oxide is likely to vary considerably on a global basis whereas the price of methoxyflurane does not vary since it is manufactured only in Australia.

**Conclusions**

Methoxyflurane appears effective and safe as an inhaled analgesic for use in pre-hospital and obstetric settings. Currently this need is met by nitrous oxide on the WHO Model List.

Although the application seeks to provide the WHO with the required range of information, there are a number of deficiencies. It would have been useful to have been provided with the regulatory information (such as data sheets, details of the product licence) from territories where this product is being used. Furthermore, the applicant’s review of the literature (section 8.1) specifically excluded letters (missing out an opportunity for identifying signals of drug hazards) and papers by ‘anonymous authors’ (thereby potentially excluding clinical reviews in publications such as *Medical Letter*). There is some evidence of selective use of the literature; for example, the application describes a study which found that ‘subjects inhaling nitrous oxide were almost unconscious before any change in the character of painful stimuli

Methoxyflurane assessment 3 of 5 January 2005
was demonstrated’ (section 8.3); however, this finding is not consistent with the enormous clinical experience of using nitrous oxide.

The application provides little evidence from head-to-head studies of the equivalence or superiority of methoxyflurane in relation to nitrous oxide. In these circumstances, a way forward might be to compare the regulatory data/licensing information for the two.

The UK data sheet for Entonox® (mixture of 50% nitrous oxide and 50% oxygen)\(^7\) states that there are no specific contra-indications but the mixture should not be used in circumstances where excessive gases (including oxygen) in the body might be hazardous. The data sheet warns that nitrous oxide should not be given for longer than 24 hours without monitoring for megaloblastic anaemia and leucopenia. The New Zealand data sheet for methoxyflurane\(^8\) includes a number of drug-specific contra-indications including renal impairment and cardiovascular instability; the data sheet adds that the potential for renal damage is increased in patients already at risk of nephropathy (including pre-eclampsia and eclampsia) and in those taking potentially nephrotoxic drugs. There is therefore a risk – albeit minute – of serious toxicity from methoxyflurane in some patients.

An assessment of this application was marred by the lack of information on methoxyflurane. Much of the older information relates to the now discontinued use of the drug for anaesthesia. Current editions of standard textbooks (e.g. Goodman and Gilman’s *Pharmacological Basis of Therapeutics*) do not mention the drug. Furthermore, full prescribing information could be found in two sources only (Australian Prescription Products Guide and the New Zealand data sheet). The application is able to draw upon only the Australian experience of this drug. It is of interest that even in Australia, the *Australian Medicines Handbook*\(^9\) does not allude to methoxyflurane but does mention nitrous oxide for the treatment of short-term procedures. In contrast to the paucity of knowledge about methoxyflurane, there is vast worldwide experience of using nitrous oxide.

The limited global availability of methoxyflurane is disconcerting on two grounds. First, if it is a safe and effective analgesic, why has it not been registered in territories other than Australia and New Zealand? Despite its use in Australia for over 3 decades, the product does not feature in analgesic protocols in most of the world. The application does not say how long registration has been pending or proposed in territories other than Australia and New Zealand (section 11).

Second, to rely on just one supplier for a medicine that is expected to be used on a worldwide basis seems highly risky. No information is provided on how global demand would be met (remembering that the drug needs to be accompanied by a safe suitable inhaler device). Having to rely on a single supplier would also affect the cost of the product and the ability to meet demand.
**Recommendation**

It is recommended that methoxyflurane not be added to the WHO Model List because it does not meet a need that is not covered by a product already on the List. Furthermore, no compelling evidence has been provided to show that in clinical practice methoxyflurane is more efficacious or safer than the alternative; concern about its efficacy and safety is further heightened by the fact that it is registered in just two countries despite being available for over 30 years. Methoxyflurane appears to be available from one source only; this is unsatisfactory for a drug intended for worldwide use.

Dinesh K Mehta

Rachel S M Ryan

---

7. Entonox data sheet (BOC Gases) April 1995