

# A case of hepatitis attributable to repeated exposure to methoxyflurane during its use for procedural analgesia

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## Clinical record

A 33-year-old woman was admitted to our service for investigation and management of acute hepatitis. She reported symptoms of nausea, fatigue, pruritus and right upper abdominal discomfort. The symptoms had first occurred 3 weeks earlier, resolving over 5 days, then recurred 2–3 days before presentation.

The symptoms were temporally related to varicose vein sclerosing procedures, of which she had had three in total. The first procedure occurred 4 weeks before admission, with no subsequent side effects. It was after the second procedure, 1 week later, that symptoms first developed. The final procedure occurred a week before admission. During each procedure, the patient was given methoxyflurane as an inhaled analgesic administered from a 3 mL disposable cartridge. Other medications administered during the procedures were the sclerosing agent sodium tetradecyl sulfate and fexofenadine. There was no history of exposure to alcohol or to other prescription or over-the-counter medications. The patient had no risk factors for viral hepatitis, and there was no history of hepatitis or liver disease in her family. Clinical examination revealed jaundice and mild tender hepatomegaly only.

Initial investigations showed hepatic enzymosis, with an elevated alanine transaminase level (2710 U/L [reference range, < 34 U/L]) and hyperbilirubinaemia (bilirubin 92 µmol/L [reference range, < 20 µmol/L]). Markers of liver synthetic function (albumin and prothrombin time)

were within normal limits, as were full blood counts, electrolyte levels and renal function.

Abdominal ultrasound demonstrated a normal-sized spleen and mild hepatomegaly, with an increased liver echotexture. Doppler sonography of the portal vein was normal. Serological tests for hepatitis A, B and C, Epstein–Barr virus, cytomegalovirus and HIV were negative. Iron and copper studies and levels of  $\alpha$ -1-antitrypsin, antinuclear antibodies, antimitochondrial antibodies, anti-liver/kidney microsomal antibodies, anti-smooth-muscle antibodies and antinuclear cytoplasmic antibodies were all normal. Paracetamol was undetectable.

Bilirubin levels continued to rise over the following 8 days (peaking at 202 µmol/L), although liver synthetic function remained normal throughout this time. A liver biopsy revealed evidence of resolving acute hepatitis with confluent perivenular hepatocyte dropout and bridging necrosis. There was no evidence of cholestasis or underlying fibrosis.

The pathological diagnosis was of an idiosyncratic drug reaction, with the implicated drug being methoxyflurane. The patient's condition continued to improve, with resolution of symptoms over 4 weeks and associated normalisation of liver enzyme and bilirubin levels. She has since remained well, and has been advised to avoid future exposure to methoxyflurane. ◆

Methoxyflurane, a short-chain halogenated ether, is a volatile anaesthetic agent. It was used for inhalational anaesthesia in the 1960s, but was withdrawn from use for this purpose when newer anaesthetic agents with more acceptable side effects became available.<sup>1,2</sup> Methoxyflurane also has significant analgesic properties at subanaesthetic concentrations,<sup>3</sup> and is thought to have minimal side effects in analgesic doses.<sup>4</sup> These properties led to its adoption for use as an analgesic in a variety of settings for over 40 years.<sup>4</sup> It is widely used by paramedic services in Australia,<sup>5</sup> and has recently been studied for use in procedural analgesia in children and adults.<sup>4,6</sup> It is provided in single-dose, pre-filled delivery devices (Pentrox, Medical Developments International, Melbourne, Vic), allowing accurate dosing and convenient delivery. In 2010, Pentrox was added to the Australian Schedule of Pharmaceutical Benefits as an item available free of charge for doctors' bags.

Although subanaesthetic doses of methoxyflurane (in the form of Pentrox) are used widely in Australia by ambulance services for prehospital analgesia, there is a paucity of data on its efficacy and safety. A recent observational case series and a review article found no significant side effects associated with its use for this purpose.<sup>4,5</sup> Over three million inhalers have been dispensed in Australia since 1970,<sup>4</sup> with the majority of doses administered for single-episode analgesia.

Hepatotoxicity resulting from the use of methoxyflurane as an inhalation agent in general anaesthesia is well described.<sup>1–3</sup> However, hepatotoxicity associated with low doses of methoxyflurane for analgesic purposes appears to be rare. Three cases of hepatitis complicating methoxyflurane use (at subanaesthetic doses) during

labour have been reported.<sup>7,8</sup> In another case report, repeated exposure in the form of misuse of methoxyflurane was found to be associated with hepatotoxicity.<sup>9</sup>

The mechanisms of methoxyflurane-induced hepatotoxicity are unclear and may be multiple. Adverse effects of halogenated ethers are thought to be related to immune-mediated, direct toxic effects of metabolites and/or host idiosyncrasy.<sup>1</sup> Reactive intermediates formed during metabolism of methoxyflurane can lead to tissue acetylation, with proteins modified by acetylation forming neoantigens that may trigger an immune response.<sup>1</sup> Drug re-exposure has also been implicated as a factor contributing to methoxyflurane-induced hepatitis.<sup>2</sup> Although unproven, it is possible that our patient's repeated exposure to the drug may have contributed to the development of hepatitis through dose-dependent toxicity.

In the prehospital setting, where methoxyflurane is being widely used, the side effect profile is minimal.<sup>5</sup> It seems the exposure to methoxyflurane in our patient was the likely cause of acute hepatitis, and it may be that repeated exposure was a contributing

## Lessons from practice

- Taking a history of all medication exposures is important in assessing acute hepatitis.
- Repeated exposure to methoxyflurane may increase the risk of acute hepatitis.
- Reporting of suspected adverse drug reactions, such as this case, are important to raise awareness of possible rare side effects of commonly used medications. ◆

factor. This observation has implications for the way methoxyflurane is prescribed, including its use for procedural analgesia in cases in which several procedures (and hence, repeated dosing) are required.

### Competing interests

None identified.

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