Suspected recurrence of malignant hyperthermia after post-extubation shivering in the intensive care unit, 18 h after tonsillectomy

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A 25-yr-old man, subsequently shown to be malignant hyperthermia (MH) susceptible by in vitro contracture testing, developed MH during anaesthesia for tonsillectomy. Prompt treatment, including dantrolene, led to rapid resolution of the metabolic crisis. Eighteen hours later the patient’s trachea was extubated in the ICU, when he had been stable and apyrexial overnight. Twenty minutes after extubation, an episode of shivering was followed by the onset of tachycardia, hypertension, tachypnoea and a rapid increase in temperature. Recurrence of MH was suspected and the patient was given another dose of dantrolene with good clinical effect. Shivering in this patient may have been an indicator or a causative factor of recurrence of MH.

Keywords: malignant hyperthermia; complications, shivering; pharmacology, dantrolene; surgery, otolaryngological

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Malignant hyperthermia (MH) is an uncommon consequence of general anaesthesia. Although fulminant cases are now rarely seen because of early diagnosis and management, including the use of dantrolene, the clinical course of MH may not be straightforward. There are various recognized presentations,1 and prolonged reactions requiring repeated doses of dantrolene have been described.2,3 We report the case of an episode of MH which was recognized and treated promptly, with rapid recovery, but which was complicated by an apparent recurrence after a period of post-extubation shivering, 18 h after operation.

Case report
A 25-yr-old, 80-kg man presented for elective tonsillectomy. His medical history included mild asthma, treated with inhaled salbutamol, no known allergies and two previous uneventful anaesthetics for foot surgery. His family anaesthetic history was unremarkable.

No premedication was given. Anaesthesia was induced with thiopental 400 mg and succinylcholine 100 mg. Intubation was complicated by some stiffness on opening the mouth and an irregular bradycardia which, on treatment with glycopyrrolate 400 µg, resulted in tachycardia of 150 beat min⁻¹. Initially, anaesthesia was maintained with 1% isoflurane and nitrous oxide in oxygen, with morphine 10 mg for analgesia. The patient’s arterial pressure was increased (170/90 mm Hg) on transfer to the operating theatre and the surgeon commented on difficulty in opening the mouth and insertion of the Boyle–Davis gag. Atracurium 35 mg was given, but an increasing end-tidal carbon dioxide partial pressure of 10–12 kPa was noted in spite of manual ventilation. Fifteen minutes after induction, isoflurane was discontinued on suspicion of MH and surgery was completed rapidly while propofol was used to maintain anaesthesia. The patient’s skin temperature was measured at 37.9°C. Dantrolene 80 mg (1 mg kg⁻¹) was administered with saline 1 litre i.v. and the patient was transferred to the intensive care unit (ICU).

On arrival in the ICU, the patient’s temperature, measured with an axillary probe, was 36.8°C, heart rate 105 beat min⁻¹ and arterial pressure 140/70 mm Hg. Initial blood tests showed a potassium concentration of 4.7 mmol litre⁻¹, pH 7.37, PCO₂ 4.9 kPa, PO₂ 26.1 kPa, SB 22, base excess –3 (intubated, FiO₂ 0.5) and creatine kinase 2409 iu litre⁻¹ (normal range 0–190 iu litre⁻¹). No further dantrolene was given.

The patient was sedated with propofol and alfentanil, and the lungs ventilated overnight. No other drugs were given and maintenance fluid requirements were provided with 4% glucose–0.18% saline. He remained stable and apyrexial with good urine output. Potassium and blood-gas analysis remained normal, although subsequent urine analysis revealed a myoglobin concentration of 64 800 µg litre⁻¹ (normally not detected), and serum creatine kinase...
concentration increased to 92.182 iu litre\(^{-1}\), 6 h after admission.

The following morning axillary temperature was 36.8°C. He was cardiovascularly stable and blood-gas analysis showed pH 7.48, \(P_{CO_2}\) 3.9 kPa, \(P_{O_2}\) 11.9 kPa, SB 25 and base excess 0 (intubated, \(F_{O_2}\) 0.35). Sedation was discontinued, he rapidly resumed spontaneous respiration and the trachea was extubated without difficulty when fully conscious. Approximately 20 min after extubation, he developed generalized shaking, typical in appearance to post-anaesthetic shivering. This was associated with an increase in heart rate from 80 to 130 beat min\(^{-1}\), increasing spontaneous ventilatory frequency from 10 to 26 bpm, hypertension of 190/90 mm Hg (previously 110/60 mm Hg) and a decrease in \(S_{A_2}O_2\) from 99% to 94% (\(F_{O_2}\) 0.35 via face mask). He appeared peripherally vasoconstricted with some generalized skin mottling. He remained fully conscious, although very anxious, throughout this deterioration. The axillary probe indicated a rapid increase in temperature. Pethidine 20 mg i.v. terminated shivering within minutes but temperature continued to increase to 39.4°C, an increase of 2.6°C in 50 min. A single dose of dantrolene 80 mg was administered 15 min after pethidine and active cooling with ice packs was initiated (Fig. 1). At this time, blood-gas analysis showed pH 7.41, \(P_{CO_2}\) 4.6 kPa, \(P_{O_2}\) 11.1 kPa, SB 23 and base excess –2 (extubated, \(F_{O_2}\) 0.6, spontaneous ventilatory frequency 26 bpm). After administration of dantrolene, heart rate, arterial pressure and peripheral perfusion improved rapidly and temperature reduced slightly, although it remained greater than 37.5°C for another 7 h. Potassium concentrations and arterial blood-gas values remained within the normal range.

The patient was discharged from hospital 3 days after operation, after receiving preliminary family counselling. The results of subsequent in vitro contracture testing at the MH Investigation Unit, Leeds, were: static 0.5% halothane test threshold, 3 g tension generated at 2% halothane, and static caffeine test threshold 2.0 mmol litre\(^{-1}\), confirming his susceptibility to MH.

**Discussion**

This case represents a fairly typical scenario—an episode of MH associated with ENT surgery in a young male patient who had undergone previous uneventful anaesthetics.\(^4\) The metabolic crisis initially resolved with a single dose of dantrolene 1 mg kg\(^{-1}\). This is the recommended starting dose, with further doses given up to 10 mg kg\(^{-1}\) if the clinical situation does not improve.\(^5\) It is suggested that early diagnosis and management may limit the severity of the metabolic derangement and thus the required dose of dantrolene\(^1\) \(^3\) \(^6\) ; doses exceeding 4 mg kg\(^{-1}\) are rarely required.\(^7\) The effective therapeutic concentrations of dantrolene for treatment of MH are not known, but an estimated dose of 2.4 mg kg\(^{-1}\) has been suggested based on muscle weakness in healthy volunteers.\(^8\) It is possible that the clinical improvement seen with dantrolene 1 mg kg\(^{-1}\) may mask a partially treated condition, with sub-therapeutic plasma dantrolene concentrations.

Recurrence of MH, requiring further doses of dantrolene after early successful treatment of an MH episode, may be uncommon, but has been described in previous case reports.\(^2\) \(^3\) \(^9\) It is unclear if the metabolic crisis is re-initiated by new trigger factors or re-emerges as serum dantrolene decreases to less than effective therapeutic concentrations. However, recognition of the risk of recurrence has led to the suggestion that a repeat dose of dantrolene 2.4 mg kg\(^{-1}\) should be given 10–12 h after the first dose (the elimination half-life of the drug).\(^7\) Such prophylaxis against recurrence was not considered for our patient as his clinical condition indicated an apparent complete recovery.

It has been shown that isolated postoperative pyrexia does not indicate an MH reaction and patients demonstrating such a sign in the absence of other features of MH are unlikely to be MH susceptible.\(^10\) Additionally, instability of body temperature after an MH reaction has been noted previously which resolved without further administration of dantrolene.\(^11\) It is difficult to prove a true recurrence of the MH reaction in our patient, but suspicion was increased as the increase in temperature was both substantial and rapid and was associated with cardiorespiratory instability. The clinical grading scale of Larach and colleagues\(^12\) ranks the possible recurrence of MH in this patient as 4, or ‘somewhat greater than likely to be MH’. As successful management of MH depends on the initiation of treatment while the disease is reversible,\(^13\) it would be difficult not to treat such a patient early with dantrolene.

Interpretation of blood-gas values can be very helpful in diagnosing an episode of MH during the attack. Unfortunately, in our case, interpretation of arterial gases before and during the episode of shivering was problematic. The patient was sedated and ventilated when the first sample was obtained but, for the second, he was awake, extubated, breathing spontaneously and extremely anxious in response to his condition. These results alone offer relatively little help in either aiding or refuting a diagnosis of MH.
Pethidine was given before dantrolene in an attempt to control the shivering seen after extubation because of its value in postoperative shivering. Shivering stopped, but temperature continued to increase, associated with continuing cardiovascular instability. Dantrolene was then given with good clinical effect. Although it is possible that the acute increase in temperature in our patient could be explained by shivering, shivering may have been causally related to the recurrence of MH, not simply associated with it. Among the many reports of MH, we can find only two which mention shivering. Both report an abnormal reaction in a patient known to be MH susceptible who was given a trigger-free anaesthetic and who was treated as for MH. Our case suggests two possibilities. First, shivering may herald the initiation of MH or second, shivering may re-initiate the MH response in association with sub-therapeutic or absent dantrolene concentrations.

In summary, recurrence of MH in this patient could not be excluded, despite apparently adequate initial treatment, and we believe that the second dose of dantrolene was warranted in this case. However, the importance of the case report lies in the unusual clinical course presented. The occurrence of shivering in patients following treated MH may be a valuable early clinical sign, heralding further clinical developments associated with MH.

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References