Postoperative malignant hyperthermia episodes in patients who received "safe" anaesthetics

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Three cases of postoperative malignant hyperthermia (MH) episodes, after what was considered to be a "safe" anaesthetic, are described. In each case the temperature rose in a delayed fashion after an uneventful anaesthetic. Treatment included intravenous dantrolene, surface cooling and ventilation with 100 per cent oxygen. Stress in the postoperative period may have been the triggering factor responsible for these reactions. Patients should be monitored well into the postoperative period as MH episodes may occur long after surgery is completed. If stress represents a significant triggering mechanism then no anaesthetic technique can be considered entirely safe.

Key words
HYPERTHERMIA: malignant, postoperative.

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Malignant hyperthermia (MH) is a life threatening emergency which arises in susceptible individuals when they are exposed to certain triggering agents. The best known triggering agents are pharmacological, particularly certain drugs used commonly during anaesthesia. If appropriate precautions are taken, the risk of MH under anaesthesia can be minimized. Precautions include avoiding volatile anaesthetics or equipment that has been exposed to them and avoiding depolarizing muscle relaxants, amide local anaesthetics, calcium, atropine and adrenergic agonists. In addition, close monitoring is necessary, particularly of temperature. Intravenous dantrolene should be available, along with cold intravenous solutions, ice and cooling blankets, should a malignant hyperthermia reaction occur.

The following case histories describe three patients who were thought to be susceptible to malignant hyperthermia and who experienced postoperative MH crises despite precautions appropriate to the circumstances.

Patient #1

A 46-year-old man was admitted for a right carpal tunnel release procedure. He had a history of obesity, alcohol abuse and smoking. The creatinine kinase (CK) level was 143 I.U./litre (normal < 105). There was no family history of MH. The patient reported one previous general anaesthetic which was uneventful.

Preoperative assessment was otherwise unremarkable. Because of the elevated CK it was decided to proceed with an anaesthetic free of the classic triggering agents for MH and to perform a muscle biopsy.

Following premedication with diazepam 25 mg p.o. and pantopon 20 mg i.m., induction consisted of Innovar® 7 ml, fentanyl 100 μg and diazepam 40 mg along with cocaine spray to the larynx. He was intubated and ventilated, using a vapour-free anaesthetic machine, with nitrous oxide and oxygen (60:40). The hour-long operation was uneventful.

The patient was transferred to the recovery room following extubation, with a rectal temperature of 35.6° C. Two and one half hours after the surgery the rectal temperature was 35.8° C and he was shivering. Four and one half hours after operation the rectal temperature was 37° C and one hour later it was 38.8° C. At this time the heart rate was 106 per minute, blood pressure 150/90 mmHg. Arterial blood gases while breathing oxygen-enriched air were $[H^+]_a$ 63 nmol/litre (pH 7.20), PCO_2 7.45 kPa (56 mmHg), PO_2 16.36 kPa (123 mmHg) and bicarbonate 22 mmol/litre.

The patient was intubated without aid of muscle relaxants and ventilated with 100 per cent oxygen. At five hours and fifty-five minutes after operation he was given dantrolene 300 mg i.v. The patient was surface cooled with a cooling blanket. He responded well to this treatment and by the seventh postoperative hour his rectal temperature was 37.2° C. He was observed overnight in the intensive care unit and the remainder of his postoperative course was uneventful. He received dantrolene 120 mg i.v. every six hours and this was decreased over five days and then discontinued.

The CK was 167 I.U./litre immediately before operation, 201 I.U./litre immediately after operation, 362 I.U./litre on the first postoperative day and peaked at 528 I.U./litre on the second postoperative day.

Muscle biopsy testing* revealed that the concentration of caffeine needed to produce a 1 gram tension was 3.0 mM (normal > 4.1) while with one per cent halothane the concentration required to produce the same tension was 0.63 mM (normal > 1.2). These results are consistent with a diagnosis of malignant hyperthermia.

Patient #2

A 16-year-old man was admitted for a septoplasty and muscle biopsy. He had received four previous uneventful general anaesthetics though they all had been given with precautions to avoid MH triggering agents. His mother had been investigated because of postoperative fevers on two occasions and results of muscle biopsy with caffeine contracture testing had been consistent with MH. The patient's preoperative assessment was otherwise unremarkable.

Following premedication with diazepam 15 mg p.o. and pantopon 15 mg i.m., anaesthesia was induced with Innovar® 7 ml diazepam 35 mg and fentanyl 300 μg. He was intubated and ventilated using a vapour-free machine, with nitrous oxide and oxygen (60:40). The hour-long operation was uneventful. He was taken to the recovery room still intubated and ventilated, with a rectal temperature of 36.4° C. After one half hour in the recovery room the rectal temperature was 36.5° C, heart rate 115 per minute and blood pressure 190/80 mmHg. The trachea was extubated one and one half hours after arrival in the recovery room. Three hours after operation the rectal temperature was 37.9° C and by four hours it was 38.3° C. Peripheral venous blood gases were: $[H^+]$ 66 nmol/litre (pH 7.18), PCO_2 7.45 kPa (56 mmHg), PO_2 5.72 kPa (43 mmHg) and bicarbonate 21 mmol/litre.

At this time he was treated with tracheal intubation and ventilation with 100 per cent oxygen. He was surface cooled with a cooling blanket and with ice. Dantrolene 100 mg i.v. was first given at four hours and twenty minutes after arriving in the recovery room and a further 60 mg was given one half hour later. He was given sodium bicarbonate 50 meq i.v. along with diazepam 20 mg and Innovar® 2 ml. He was transferred to the intensive care unit for further treatment and monitoring. Dantrolene was given in a dose of 400 mg every six hours and this was decreased over three days and then discontinued.

The serum lactate at six hours after surgery was 5 mmol/litre (normal < 1.9). He had transient myoglobinuria. There was generalized muscle swelling and tenderness in the postoperative period. The patient responded to therapy and was discharged on the sixth postoperative day with no apparent ill effects from the experience.

The CK was 182 IU/litre immediately before operation and it peaked at 1005 IU/litre on the first day after operation.

Caffeine contracture testing revealed that the

*Dr. B.A. Britt, University of Toronto.

concentration of caffeine required to produce a 1 gram tension was 2.2 mM without halothane (normal > 4.1) and 0.3 mM with halothane (normal > 1.2). This is consistent with malignant hyperthermia.

Patient #3

A 26-year-old man was admitted for a left hemithyroidectomy because of a thyroid nodule. He was clinically and biochemically euthyroid. He had experienced one previous general anaesthetic without difficulty. He was otherwise healthy. He reported that his sister and an aunt had both experienced postoperative difficulties, the nature of which was unclear. It was decided he would be given an anaesthetic free of MH triggering agents.

Following premedication with diazepam 15 mg p.o. and pantopon 15 mg i.m., anaesthesia was induced with Innovar® 3 ml, sodium thiopentone 300 mg and fentanyl 100 μg i.v. Muscle relaxation was achieved with a total of 8 mg of pancuronium. The trachea was intubated and he was ventilated using a vapour-free machine and nitrous oxide and oxygen (50:50). The two and one half hour operation was uneventful. The patient was taken to the recovery room still intubated and ventilated, with a rectal temperature of 35.0° C.

After one hour in the recovery room he was shivering and his vital signs were: blood pressure 190/90 mmHg, pulse 70 beats per minute and rectal temperature 35.7° C. He received diazepam 20 mg i.v. in divided doses over one half hour. By three hours after operation his rectal temperature was 38.5° C. Blood gases (FIO_2 = 1.0) were $[H^+]_a$ 34 nmol/litre (pH 7.47), PCO_2 3.59 kPa (27 mmHg), PO_2 27.12 kPa (204 mmHg) and bicarbonate 19 mmol/litre. At this time his blood pressure was 200/150 mmHg and pulse was 110 beats per minute. He was ventilated with 100 per cent oxygen and surface cooling was initiated. Dantrolene 300 mg i.v. was first given three hours after arrival in the recovery room. By four and one half hours after operation the rectal temperature was 37.1° C. The patient received a further 100 mg of dantrolene. He was transferred to the intensive care unit for observation and the remainder of his postoperative course was uneventful.

The patient's preoperative CK was 28 I.U./litre. It was 98 I.U./litre immediately after operation and peaked at 379 I.U./litre on the first postoperative day. Muscle biopsy was not done.

Discussion

The three case histories described are similar. All three patients had previous general anaesthetics without known problems. Two had a family history of perioperative problems and the third had an unexplained elevated CK.

All three patients were given anaesthetics free of the classic triggering agents for malignant hyperthermia.

The operations were uneventful and the patients arrived in the recovery room in a mildly hypothermic state. They all developed signs and symptoms of malignant hyperthermia in the postoperative period. All had a rise in rectal temperature, two developed a metabolic and respiratory acidosis, two developed hypertension, all developed a heart rate over 100 beats per minute and two were shivering.

The diagnosis was made late in the postoperative period, with the first dose of dantrolene being given an average of four hours and twenty five minutes after arrival in recovery room. All patients responded to surface cooling, ventilation with 100 per cent oxygen and intravenous dantrolene, and were discharged with no ill effects from their experience.

Muscle biopsies from two patients, on caffeine contracture testing, proved to be consistent with malignant hyperthermia. All three patients had a rise in CK.

The behaviour of our three patients raises three questions.

First, what were the triggering agents for these reactions? Despite anaesthetics considered to be "safe" in the presence of MH susceptibility, all three patients developed malignant hyperthermia. Their intraoperative courses were uneventful but problems arose well into the postoperative period. Could stress be responsible? Wingard[2] discussed stress as a triggering agent for malignant hyperthermia. Gronert[3] described a patient who had a malignant hyperthermia-like reaction that was brought on by stress unrelated to surgery or anaesthesia. Inadequate postoperative analgesia may present a significant stress. Perhaps more generous analgesia would have prevented the reactions seen in our patients.

As noted earlier, all our patients were mildly

hypothermic on arrival in recovery room, their average temperature being 35.7° C. That, along with the shivering noted in two of our patients, may have represented another stress.

If indeed stress such as pain and hypothermia are the triggering agents in our three cases, then no anaesthetic can be entirely safe in a susceptible patient.

Secondly, what are the risks of elective muscle biopsy in suspected malignant hyperthermia patients? Our centre has conducted anaesthesia for approximately 30 such patients in the last three years. All anaesthetics involved a protocol of close monitoring and absence of pharmacological triggering agents. Only three cases of malignant hyperthermia were seen and they were all treated successfully, with no residual ill effects. Our series is small but it would suggest that the risk of carefully conducted "safe" anaesthetics is low. For the moment we must weigh the risk against the benefit in deciding whether to proceed with elective muscle biopsy in these patients.

Patients for muscle biopsy should not be pretreated with dantrolene as it may interfere with the muscle testing.[4] Further, preoperative dantrolene administration is not a guarantee that malignant hyperthermia will not occur.[5]

Thirdly, how long should MH-susceptible patients be monitored after operation? All three patients had their crises diagnosed late in the recovery period. Our hospital protocol dictates monitoring of patients in the recovery room until all vital signs have been stable for four hours. Aldrete[6] suggests monitoring the patient routinely for 12 hours after operation. One should be aware that MH episodes can arise at any time in the perioperative period. It would seem advisable to carry out procedures on suspected malignant hyperthermia patients early in the morning to minimize the stress of a long preoperative wait, as well as to allow a longer period for observation of the patient in the recovery room. For similar reasons, it would be disadvantageous to do procedures on Fridays because the level of monitoring may tend to fall on the weekend that follows.

References

1 *Kalow W, Britt BA, Richter A.* The caffeine test of isolated human muscle in relation to malignant hyperthermia. Can Anaesth Soc J 1977; 24: 678–94.

2 *Wingard DW, Gatz EE.* Some observations on stress susceptible patients. *In*: Aldrete JA, Britt BA, eds. Second International Symposium on Malignant Hyperthermia. New York. Grune and Stratton. 1978; 363–72.

3 *Gronert GA, Thompson RL, Onofrio BM.* Human malignant hyperthermia: Awake episodes and correction by dantrolene. Anesth Analg. 1980; 59: 377–8.

4 *Lambert W.* Dantrolene and caffeine contracture test. Can Anaesth Soc J (Letter) 1980; 27: 304.

5 *Fitzgibbons DC.* Malignant hyperthermia following preoperative oral administration of dantrolene. Anesthesiology 1981; 54: 73–5.

6 *Aldrete A.* Advances in the diagnosis and treatment of malignant hyperthermia. Acta Anaesthesiol Scand 1981; 25: 477–83.

Résumé

On rapporte trois cas post-opératoires d'hyperthermie maligne (MH) après ce qu'on avait considéré être une anesthésie sans danger. Dans chacun des cas, la température monta avec retard après l'administration de l'anesthésie. Le traitement comprit l'infusion de dantrolène par voie intraveineuse, le refroidissement de surface et la ventilation avec 100 pour cent d'oxygène. Le stress pendant la période post-opératoire est peut-être l'élément qui a déclenché ces réactions. Les patients devraient être sous surveillance électronique pendant la période post-opératoire car des instances de MH peuvent intervenir bien après l'intervention chirurgicale. Si le stress est un mécanisme de déclenchement important, aucune technique d'anesthésie n'est à considérer sans danger.