Postoperative malignant hyperthermia and dantrolene therapy

Uwe Schulte-Sasse MD, Wolfgang Hess MD, Hans Joachim Eberlein MD

A case of malignant hyperthermia (MH) in a three-year eight-month-old girl is presented. Definite symptoms of MH developed in the awake patient 30 min after termination of anaesthesia which had lasted five hours. This postoperative MH-episode resolved promptly following intravenous administration of dantrolene (2.5 mg·kg^{-1} initially, followed by 5 mg·kg^{-1} over 12 hours). Results of serial serum samples revealed a steady increase in creatine kinase (CK) concentration with the highest value being observed at the second day, despite dantrolene therapy. The unusual occurrence of MH in the postoperative period, when the major effects of anaesthesia were no longer an important consideration, is discussed with regard to the "human stress syndrome." The necessity to give this information to people usually not familiar in diagnosing MH (e.g., medical personnel in surgical wards) is stressed.

Key words

DANTROLENE: therapeutic use; FEVER: occurrence; MALIGNANT HYPERTHERMIA: therapy; POSTOPERATIVE COMPLICATIONS: etiology.

From the Department of Anaesthesiology of the Klinikum Charlottenburg, Free University of Berlin, Germany.

Address correspondence to: Dr. Schulte-Sasse, Department of Anaesthesiology, Klinikum Charlottenburg, Free University of Berlin, Spandauer Damm 130, 1000 Berlin 19, Germany.

A baffling feature of malignant hyperthermia (MH) is the erratic nature of established triggers in malignant hyperthermia susceptible (MHS) patients. Many patients known to be MHS have had previous anaesthetics without untoward effects.[1–4] On the other hand, patients who have had documented MH reactions have successfully been subsequently anaesthetized with contraindicated drugs.[3] This information suggests that factors other than drugs and inheritance are necessary for MH to develop. The reason for the variable expression of the condition within an individual remains a mystery. Although genetic variability has been implicated in this pattern of triggering, there is evidence suggesting that other factors could be involved, as certain concurrently given drugs or environmental factors can enhance or depress the response to MH triggers.[5] Cases of MH were recognized to be "induced" in the postoperative period when obviously the major effects of anaesthesia were no longer an important consideration.[4,6–9] Therefore a more expanded concept of MH seems to develop, including the assumption that one of the other factors in MH is stress. The implication of this extends far beyond the scope of anaesthesiology.

We wish to present a case of MH in a child, who had six previous anaesthetics without hyperthermia. Definite symptoms of MH developed in the awake patient 30 min after termination of a five-hour anaesthetic. MH was treated successfully with intravenous dantrolene.

Case report

A three-year eight-month-old girl, weighing 12 kg and physically slightly retarded, was admitted to hospital with signs of elevated intracranial pressure, due to malfunction of a ventriculoatrial shunt. Direct external drainage had been done as a temporary procedure under general anaesthesia (halo-

thane, nitrous oxide, succinylcholine), the definitive revision being planned for the next day. Except for an increase in rectal temperature, from 37.5° C to 38.5° C, during the course of anaesthesia, the procedure was uneventful. Postoperatively the body temperature returned to normal. Since birth the child had undergone general anaesthesia five times for similar procedures. Although known MH-trigger substances were used, no difficulties during these previous anaesthetics were recorded. The significant past medical history was related to her congenital hydrocephalus internus.

On the morning of operation the girl was premedicated with pentobarbitone 25 mg and scopolamine 0.15 mg intramuscularly, without apparent effect. Anaesthesia was induced with nitrous oxide 6 litre·min^{-1}, oxygen 3 litre·min^{-1} and halothane 2.0 per cent given by mask. Tracheal intubation was completed without difficulty after the intravenous administration of suxamethonium, 20 mg. An intravenous saline infusion was started to ensure adequate hydration. Anaesthesia was maintained with nitrous oxide 70 per cent and oxygen 30 per cent plus halothane 0.7–1.0 per cent, respiration being assisted manually. A rectal temperature probe was placed and an initial reading of 36.5° C was recorded. As with the night before, the temperature had risen from 36.5° C to 38.0° C by the end of the procedure, which lasted five hours, without use of a heating mattress. While there was no tachycardia or change in respiratory rate accompanying the increase in temperature, the course of anaesthesia was judged to be normal. Adequate spontaneous respiration soon resumed and when the patient had regained consciousness, the trachea was extubated and the patient transferred to the ward. Thirty minutes later an increase of the rectal temperature to 41° C and of the heart rate to 200 beats·min^{-1} was noticed and the anaesthetist informed.

When we saw the child, she exhibited tachypnoea and failed to respond to commands. There was no apparent rigidity, cardiac arrhythmia or change in blood pressure. An arterial blood gas revealed a compensated metabolic acidosis: PO_2 11.20 kPa (84 mmHg), PCO_2 2.14 kPa (16 mmHg), pH 7.34, BE −13 mmol·$litre^{-1}$. The diagnosis of MH was made and emergency therapy was started immediately. The trachea was reintubated and the lungs ventilated with pure oxygen, a dantrolene infusion (2.5 mg·kg^{-1} over 15 min) was given via a central venous catheter. Venous blood at this time showed: creatine kinase (CK) 54 U·$litre^{-1}$, K 6.6 mmol·$litre^{-1}$, glucose 12.4 mmol·$litre^{-1}$. The therapy with dantrolene was accompanied by such supportive measures as surface cooling, correction of the metabolic acidosis with $NaHCO_3$, infusion of dextrose five per cent (40 ml·hr^{-1}), and administration of heparin (10 Units·kg^{-1}·hr^{-1} for two days). Within 30 min body temperature had fallen to 37.7° C, heart rate to 130 beats·min^{-1} and cooling was stopped. In order to prevent a recurrence of MH, the dantrolene infusion was continued for the following 12 hours (5.0 mg·kg^{-1}).

Results of analyses of serial serum samples revealed a steady increase in serum enzyme concentrations with the highest values being observed at the second postoperative day (Table). The CK isoenzyme pattern was normal. While urine myoglobin remained within normal limits, there was a marked increase in serum myoglobin on the first postoperative day (Table). Following the MH-episode prolonged coagulation times and a decreased platelet count were present (Table). Hepatic function was not impaired, as assessed by normal values of alkaline phosphatase and pseudocholinesterase.

Sixteen hours after the crisis the trachea was extubated. At that time the child did not obey commands, and there was only some motor activity of the extremities in response to painful stimuli. During the following hours the clinical condition of the girl improved gradually. By the evening of the first postoperative day the patient could answer questions posed by her father. During the first 48 hours following the crisis the child was unable to stand or walk without help, due to muscle weakness. On the third day after operation she was transferred to the ward. Bearing in mind the psychological state of the child, the central venous catheter was removed and further blood analyses were dispensed with, when serum enzyme concentrations began to decline. On the sixth postoperative day she was discharged in good physical and mental condition.

A full anaesthesia-history at this time revealed one suspect episode: Following the first revision of an initially instituted ventriculo-peritoneal shunt, both the operation and halothane anaesthesia proceeded smoothly, but when back on the paediatric ward the six-week-old girl developed marked tachycardia (maximum 200 beats·min^{-1}) and tachypnoea

TABLE Results of laboratory tests

	Day of operation				*After operation*		
	15.30 h	*17.00 h*	*18.00 h*	*22.00 h*	*1st day*	*2nd day*	*3rd day*
Creatine kinase (<70 Units·litre^{-1})	54	76	128	202	458	1042	408
α-hydroxybutyric dehydrogenase (50–140 Units·litre^{-1})					1184		400
Glutamic oxaloacetic transaminase (5–18 Units·litre^{-1})					588	2110	400
Glutamic pyruvic transaminase (5–19 Units·litre^{-1})					345	1728	1035
Myoglobin, serum (1–41 μg·litre^{-1})					700		174
Prothrombin time (Quick's test) (75–140 per cent)					35	34	58
Partial thromboplastin time (24–39 sec)					33	46	25
Plasma thrombin time (12–16 sec)					15.5	17.8	15.8
Fibrinogen (2.0–4.0 g·litre^{-1})					1.95	2.06	1.67
Platelet count (150,000–300,000 per mm^3)					138,000		149,000

NOTE: Therapy with dantrolene was started at 15.45 h (2.5 mg·kg^{-1}) over 15 min followed by an infusion over 12 hours (5.0 mg·kg^{-1}).

(maximum 60 respirations·min^{-1}). No signs of infection were present and the rectal temperature was 38° C. Laboratory tests such as blood gases or creatine kinase were not done. Thirty-six hours later both heart rate and respiration had returned spontaneously to normal. The postoperative course, as judged by the paediatricians, was uneventful!

On investigation of her immediate relatives the patient's mother was found to have an abnormal CK-level of 180 U litre^{-1}.

Now known to be MHS, the young girl was readmitted five months after the postoperative hyperthermic crisis for removal of a non-functioning ventricular catheter left in place during a former procedure. Biochemical assays of interest and diagnostic importance revealed no abnormalities. Oral dantrolene was given during the 24 hours before the operation (4 mg·kg^{-1}). The surgical procedure, necessitating an 1½-inch incision on the neck, was done using a pancuronium/fentanyl/nitrous oxide/oxygen IPPV technique following induction of anaesthesia with intramuscular methohexitone sodium (100 mg). Rectal temperature during induction was 36.5° C initially and increased to 37.0° C over the next 30 min. The course of the two-hour procedure was uneventful and after arrival on the ward the child was awake and in a good condition. There were no clinical or laboratory signs of increased metabolism. In the evening, however, a blood sample revealed an increase in serum creatine kinase (31 to 424 U·litre^{-1}, isoenzyme pattern normal) and glutamic oxaloacetic transaminase (12 to 27 U·litre^{-1}). Similar to the hyperthermic crisis five months before, the increase in enzyme activities continued until next evening (CK: 940 U·litre^{-1}, GOT: 35 U·litre^{-1}). As there was no concomitant deterioration in the clinical or psychological condition, the girl was discharged on the second postoperative day when the abnormal laboratory findings were returning to normal.

Discussion

Evidence of hypermetabolism, a *conditio sine qua non* in diagnosing MH,[10,11] was present in the first episode, as indicated by metabolic acidosis and rise in body temperature. Active MH results in increased

permeability of muscle: the elevated serum potassium, myoglobin, CK and other enzymes found in skeletal muscle reflect a loss of integrity of muscle cell membranes. In combination with further symptoms such as tachycardia, tachypnoea, unresponsiveness, hyperglycaemia, and changes in coagulation factors, which all are reported to be typical for MH, there is good evidence supporting the diagnosis of MH. Moreover, the mother's abnormal CK-level, the postoperative suspect episode with tachycardia and tachypnoea when the child was six weeks old, and the complete reversal of clinical symptoms by dantrolene within 30 minutes provides further confirmation.

However, the case presented differs somewhat from many episodes of MH recently reported: Harrison[12] showed that the administration of dantrolene in the established porcine MH syndrome is followed by a decrease in the elevated CK level. We observed the same course of CK blood level (a steady decrease after administration of dantrolene) in a previously reported episode of MH in man, successfully treated with dantrolene.[13] In the case presented here, CK values were within normal limits during the full-blown syndrome. During the following 40 hours, however, serum enzyme concentration steadily increased, despite dantrolene, suggesting a discrepancy between disappearance of the clinical signs (i.e., tachycardia, tachypnoea, hyperthermia) and the termination of events within the muscle cells. Obviously there is considerable uncertainty in judging cell metabolism by means of those insensible parameters. Reports[4,14–16] in which patients survived the initial severe episode only to succumb to a recrudescence of the process many hours later, emphasized that continuation of dantrolene therapy is mandatory even if classical signs of MH have subsided following initial treatment.

Metabolic acidosis during MH is mainly a reflection of accelerated lactic acid formation in the muscles. In this case unequivocal evidence of metabolic acidosis was present. No degree of spontaneous hyperventilation will result in a hypocapnia of the magnitude observed unless there is metabolic stimulation. Arterial blood analysis might show respiratory acidosis if the patient is unable to increase ventilation as metabolism increases. Fortunately our patient was breathing spontaneously and therefore was able to compensate for the marked metabolic acidosis by hyperventilation, maintaining an arterial pH of 7.34 and preventing hypoxaemia at the same time.

As in many other episodes of MH, our patient also had myoglobinaemia. Obviously the capacity of plasma proteins to bind myoglobin was of sufficient magnitude to prevent myoglobinuria. Urinary output remained satisfactory, probably because of the mannitol contained in the dantrolene preparation.

The striking feature of this case was the onset of MH during the postoperative period. Beldavs *et al.*[6] have argued that the delay in onset of symptoms indicates low grade susceptibility of the patient due to a relative mild genetic defect and that therefore fairly large and prolonged concentrations of anaesthetic agents are required to trigger a MH episode. The fact that several MHS patients had been previously anaesthetized using contraindicated drugs without developing MH raises serious doubt as to the role of incomplete penetrance of the MH gene(s) as an important reason why susceptibility infrequently expresses itself.[1–4] It seems possible that the small intraoperative increase in body temperature in our case indicates a low grade smoldering of the syndrome, which was triggered in the beginning of anaesthesia and, as on the night before, could very well have ended as an undiagnosed abortive form of MH.

Reasoning forces us to assume additional environmental factors in order to trigger the full blown picture with all its typical and life-threatening symptoms. Consideration of reports[4,6–9] in which MH was "induced" postoperatively leads to the impression that the time of onset of MH might vary considerably with different drug exposure and that severity or rapidity of MH episodes cannot be correlated with genetic predisposition unless these modifying factors have been controlled.

It is wise to give appropriate information, concerning the delayed onset of MH, to people usually not familiar in diagnosing MH (e.g., medical personnel on surgical wards). Excitement might play a role in recurrent episodes of human MH, for it seems unlikely that anaesthetic agents would retrigger the syndrome in the recovery room. One might have to postulate a role for the "human stress syndrome" in order to explain this case.[17,18] The onset of pain in the recovery room following anaesthesia represents a significant stress and might induce MH-reactions even when anaesthesia has

been conducted with non-triggering agents.[8] Since the work of Gronert *et al.*[19] the role of the sympathetic nervous system seemed to be of minor if any importance in triggering MH. But later Gronert himself presented a case showing some definite signs of MH in the absence of anaesthesia, which was successfully treated with dantrolene.[20] In the meantime more reports point in the same direction, namely triggering of some or all of the symptoms of MH caused by influences other than anaesthetics or suxamethonium.[21–23] These newer publications might lead to a renaissance of the "human stress syndrome" – an analogon to the porcine stress syndrome. Whether "stress" in humans plays the same important role as in pigs is not clear at the present time.[24] Besides the possible or probable importance of physical or psychological stress, there might be a number of so far unknown factors, which could trigger MH in individuals genetically prone to the syndrome. The only conclusion at the time is, that MH probably is not confined to the state of anaesthesia.

Marked elevations in CK-levels remained unchanged in patients with a history of myopathy, when treated with high doses of oral dantrolene.[25] The belief in the "membrane stabilizing" action of the hydantoin derivate dantrolene[26,27] is also contradicted by the postoperative increase in CK activity despite dantrolene pretreatment in the girl not given any agent known to trigger MH. Knowing the patient's history and ignoring the small increase in temperature of the nearly uncovered child following anaesthesia induction it is difficult to relate the elevation in CK-activity to the minor surgical trauma or the intramuscular injection of methohexitone.[28,29] While there were no signs of increased metabolism the changes in CK-level must be interpreted as an exaggerated response to minor stimuli indicating the unspecific manifestation of a myopathy.

References

1 *Britt BA, Kalow W.* Malignant hyperthermia: a statistical review. Can Anaesth Soc J 1970; 17: 293–315.

2 *Pueschel, K, Schubert-Thiele I, Hirth L, Benkmann HG, Brinkmann B.* Malignant hyperthermia during the 13th general anaesthesia. Der Anaesthesist 1978; 27: 488–91.

3 *Halsall PJ, Cain PA, Ellis FR.* Retrospective analysis of anaesthetics received by patients before susceptibility to malignant hyperpyrexia was recognized. Br J Anaesth 1979; 51: 949–54.

4 *Kolb ME, Horne ML, Martz, R.* Dantrolene in human malignant hyperthermia. A multicenter study. Anesthesiology 1982; 56: 254–62.

5 *Gronert GA, Milde JH.* Variations in onset of porcine malignant hyperthermia. Anesth Analg 1981; 60: 499–503.

6 *Beldavs J, Small V, Cooper DA, Britt BA.* Postoperative malignant hyperthermia: a case report. Can Anaesth Soc J 1971; 18: 202–12.

7 *Faust DK, Gergis SD, Sokoll MD.* Management of suspected malignant hyperpyrexia in an infant. Anesth Analg 1979; 58: 33–5.

8 *Grinberg R, Edelist G, Gordon A.* Postoperative malignant hyperthermia episodes in patients who received "safe" anaesthetics. Can Anaesth Soc J 1983; 30: 273–6.

9 *Kripke BJ, Blanck TJJ, Sizemore DA, Cumunale FL, Christiansen J, Gruener R.* Association of postanaesthetic hyperthermia with abnormal muscle characteristics: a case report. Can Anaesth Soc J 1983; 30: 290–4.

10 *Britt BA.* Etiology and pathophysiology of malignant hyperthermia. Fed Proc 1979; 38: 44–8.

11 *Gronert GA.* Malignant hyperthermia. Anesthesiology 1980; 53: 395–423.

12 *Harrison GG.* Control of malignant hyperpyrexic syndrome in MHS swine by dantrolene sodium. Br J Anaesth 1975; 47: 62–5.

13 *Schulte-Sasse U, Tarnow J, Eberlein HJ.* Successful treatment of malignant hyperthermia with dantrolene-sodium and uneventful re-anaesthesia after oral dantrolene-prophylaxis. Der Anaesthesist 1982; 31: 241–4.

14 *Mathieu A, Bogosian AJ, Ryan JF, Grone RK, Crocker D.* Recrudescence after survival of an episode of malignant hyperthermia. Anesthesiology 1979; 51: 454–5.

15 *Fitzgibbons DC.* Malignant hyperthermia follow-

ing preoperative oral administration of dantrolene. Anesthesiology 1981; 54: 73–5.

16 *Fletcher R, Blennow G, Olsson AK, Ranklev E, Törnebrandt K.* Malignant hyperthermia in a myopathic child. Prolonged postoperative course requiring dantrolene. Acta Anaesthesiol Scand 1982; 26: 435–8.

17 *Wingard DW.* Malignant hyperthermia: a human stress syndrome? Lancet 1974; IV: 1450–1.

18 *Jardon, OM.* Physiologic stress, heat stroke, malignant hyperthermia – a perspective. Milit Med 1982; 147: 8–14.

19 *Gronert GA, Milde JH, Theye RA.* Role of sympathetic activity in porcine malignant hyperthermia. Anesthesiology 1977; 47: 411–5.

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

21 *Goekoop JG, Carbaat PATh.* Treatment of neuroleptic malignant syndrome with dantrolene. Lancet 1982; III: 49–50.

22 *Haegy JM, Laplatte G, Gollner JL, Eulry F, Clement R, Schneider F.* Hyperthermie maligne d'effort chez un sujet ayant une ichtyose familiale commune. Rôle favorisant d'un deficit en carnitine musculaire. Nouv Presse Med 1982; 11: 115–7.

23 *Lydiatt JS, Hill GE.* Treatment of heat stroke with dantrolene. JAMA 1982; 246: 41–2.

24 *Denborough MA, Galloway GJ, Hopkinson KC.* Malignant hyperpyrexia and sudden infant death. Lancet 1982; IV: 1068–9.

25 *Bertorini T, Palmieri G, Bhattacharya S.* Beneficial effects of dantrolene sodium in exercise-induced muscle pains: Calcium mediated? Lancet 1982; I: 616–7.

26 *Bianchi CP.* Cell calcium and malignant hyperthermia. *In*: Gordon RA, Britt BA, Kalow W. (eds.) International symposium on malignant hyperthermia. Springfield: CC Thomas 1973; 147–51.

27 *Plötz J, Braun J, Stallenberger R.* The inhibitory effect of dantrolene on the rise of serum-creatine-kinase activity after combined use of halothane and suxamethonium in man. Der Anaesthesist 1981; 30: 338–42.

28 *Meltzer HY, Mrozak S, Boyer M.* Effect of intramuscular injections on serum creatine phosphokinase activity. Am J Med Sci 1970; 259: 42–8.

29 *Nevins MA, Saran M, Bright M, Lyon LJ.* Pitfalls in interpreting serum creatine phosphokinase activity. JAMA 1973; 224: 1382–7.

Résumé

On rapporte un cas d'hyperthemie maligne chez une enfant de trois ans et huit mois. Les symptômes classiques d'hyperthermie maligne sont apparus chez la patiente éveillée trente minutes après la fin d'une anesthésie qui avait duré cinq heures. Cet épisode de MH à été rapidement contrôlé par l'administration intraveineuse de dantrolène (2.5 mg·kg^{-1}) comme dose d'amorce et maintenue ensuite par une dose de (5 mg·kg^{-1}) pendant douze heures. Les mesures sériées de la créatine-kinase plasmatiques ont démontré une augmentation régulière des concentrations, dont le pic est apparu au deuxième jour en dépit du traitement au Dantrolène. L'apparition inhabituelle de MH dans la période post-opératoire, alors que les effets de l'anesthésie semblent sans importance nous amène à discuter du "syndrome de stress humain". On souligne l'importance qu'il y a de bien renseigner le personnel soignant sur ce sujet.