Duchenne muscular dystrophy and malignant hyperthermia - two case reports

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The case histories are presented including the anaesthetic and postoperative management, of two children, a two-year-old with undiagnosed Duchenne muscular dystrophy (DMD) and a three-year-old with known DMD. The child with undiagnosed DMD had no symptoms of DMD and had received halothane twice before, without succinylcholine, with no apparent difficulty. Following an uneventful induction of anaesthesia with halothane, nitrous oxide and O_2, succinylcholine resulted in bilateral masseter muscle spasm and then, in rapid sequence, ventricular tachycardia and cardiac arrest. Resuscitation was difficult, prolonged and associated with hyperkalaemia ($K^+ = 12.57\ mEq \cdot L^{-1}$), severe metabolic and respiratory acidosis, high peripheral venous pressure and massive hepatospleenomegaly, but not hyperthermia. The patient was finally resuscitated but died two days later. Skeletal muscle biopsy results were consistent with malignant hyperthermia. The second patient was known to have DMD but did not receive prophylactic or intraoperative dantrolene nor have his anaesthetic machine flushed with oxygen for an extended period prior to induction of anaesthesia. This child was anaesthetized with fentanyl and N_2O and, with the exception of a high intraoperative heart rate (155–160 beats·min^{-1}), had an uncomplicated anaesthetic and operation (intraoperative axillary temperatures ranged between 36.8–37.9° C). Postoperatively his temperature rapidly increased to 38.8° C and then 40.3° C and he became metabolically acidotic. Intravenous administration of dantrolene for 48 hours reduced the temperature and allowed normal recovery and discharge. A postoperative muscle biopsy was consistent with DMD. These case reports confirm that children with DMD have the potential for developing malignant hyperthermia during or after anaesthesia and therefore should be prepared preoperatively and managed intraoperatively accordingly.

Key words

ANAESTHESIA: paediatric; ANAESTHETICS: succinylcholine, halothane; COMPLICATIONS: cardiac arrest, hyperkalaemia, hyperthermia; GENETIC FACTORS: Duchenne's muscular dystrophy.

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Anaesthesia in patients with Duchenne muscular dystrophy can result in rhabdomyolysis,[1–3] cardiac arrest,[4,5] and death.[4] Similar problems can occur in patients with malignant hyperthermia.[6] Halothane and succinylcholine have been incriminated as triggering agents for the hyperthermic syndrome and skeletal muscle has been identified as the target organ in both diseases.[7] Numerous case reports have suggested an association of malignant hyperthermia and Duchenne muscular dystrophy.[8–14] This report describes two children, one with diagnosed and the other with undiagnosed Duchenne dystrophy, who suffered reactions during or following general anaesthesia. Postoperative muscle biopsies and laboratory studies suggested that both children had Duchenne muscular dystrophy and malignant hyperthermia.

Case reports

Case no. 1

The patient was an active healthy 15 kg two-year-old male outpatient scheduled for silicon implant and lacrimal duct exploration of the right eye. He was seen as an outpatient, at which time no unusual features of his development or family history were

TABLE Case no.1 – laboratory values

	Minutes after onset of ventricular fibrillation						*Minutes after resumption of sinus tachycardia*	
Arterial blood gases	*20*	*23*	*25*	*30*	*40*	*50*	*10*	*20*
pH	6.93	6.94	6.94	6.93	6.98	6.89	7.07	7.2
PO_2 (mmHg)	15.3	13.4	12.5	21.7	21.8	44.5	451.5	452.0
PCO_2 (mmHg)	82.0	84.4	82.4	93.4	70.6	71.4	37.3	21.9
O_2sat (%)		3.4			13.8	46.7	99.7	99.8
HCO_3 (mEq·L^{-1})		12.0			15.5	12.6	10.1	8.6
B.E. (mEq·L^{-1})		−16.2			−15.0	−20.1	−19.6	−17.4
Calcium (mg·dL^{-1})	0.611	0.746	0.855	1.026	0.978	1.162	1.097	1.041
Potassium (mEq·L^{-1})	12.57	11.30	9.05	7.58	6.90	6.13	4.27	4.73

noted. He had undergone two previous eye operations and bilateral myringotomy with halothane anaesthesia (without succinylcholine) with no intraoperative or postoperative problems or complication.

After premedication with atropine, 0.2 mg IM, 60 minutes before arrival in the operating room, anaesthesia was induced without difficulty using halothane, 0.25 to 2.75 per cent, and 50 per cent nitrous oxide in oxygen. A 20-gauge intravenous catheter was introduced into a foot vein. The concentration of halothane was decreased to 1.5 per cent and atropine, 0.1 mg, followed by succinylcholine, 40 mg, was given intravenously. One minute later, endotracheal intubation was attempted but the mouth was difficult to open because of bilateral masseter spasm. During the next 15 seconds, ventilation became difficult and an ashen colour was noted. Within the following 30 seconds, masseter spasm abated, all muscular tone decreased, the patient became flaccid and the cardiac rhythm deteriorated into ventricular tachycardia (with a rate of approximately 120 beats·min^{-1}) and then ventricular fibrillation.

Cardiopulmonary resuscitation was initiated immediately and all anaesthetic gases were discontinued. An endotracheal tube was easily placed in the trachea, a Foley catheter was inserted into the urinary bladder and rectal and oesophageal temperature probes were also inserted. Following this the ventricular fibration became slower and the patient became asystolic with occasional ventricular contractions.

Over the next 20 minutes, the patient was refractory to all resuscitative efforts which included multiple intravenous bolus doses of epinephrine (100 to 150 μg), calcium gluconate (100 mg), lidocaine (20 mg), sodium bicarbonate (10–15 mEq), and numerous attempts at electric defibrillation. Pulses were barely palpable but a catheter was finally introduced into the right femoral artery 20 minutes after beginning the resuscitation. The initial arterial blood gases, serum electrolytes, and calcium concentrations are displayed in the Table.

Treatment of hyperkalaemia (12.57 mEq·L^{-1}) included dextrose 50 per cent (50 ml) and regular insulin (five, then ten units) intravenously and hyperventilation. Continuous backflow of venous blood into the venous catheter in the foot suggested high venous pressure and necessitated high hydrostatic pressure for fluid administration. Examination of the abdomen indicated massive congestion of the liver and spleen as both organs were easily palpable three to four fingerbreaths below the costal margins.

Serial arterial blood samples over the next twenty minutes revealed a gradual decrease in potassium concentration to 6.13 mEq·L^{-1}. Finally, approximately one hour after beginning the resuscitation, the patient's heart rhythm returned to sinus tachycardia and muscle tone returned to normal. Blood pressure stabilized at 120/70 mmHg, heart rate at 150–160 beats·min^{-1}, and respiration became spontaneous at 30–32 breaths·min^{-1}.

With resumption of normal perfusion, the patient's liver and spleen returned to their preoperative subdiaphragmatic positions and were no longer palpable in the abdomen. His intravenous catheter, which had formerly necessitated high hydrostatic

pressures to maintain flow during the resuscitation, began running at normal hydrostatic pressures. There was no urine output until the resumption of a sinus heart rhythm. The urine was then tea coloured for the following three hours.

The initial temperature was 35.1° C rectally (ten minutes after induction of anaesthesia). Temperature remained at this level until one hour after resuscitative attempts were begun when it rose to 36.8° C, eight minutes after sinus rhythm had been restored. Concern for the possibility of delayed malignant hyperthermia resulted in the administration of dantrolene, 15 mg intravenously. At no time during the resuscitation or for the 12 hours afterward did the temperature rise above 37.0° C. Two hours after the start of anaesthesia, the patient was taken to the ICU intubated and comatose.

Twenty-four hours after cardiac arrest the patient's neurologic status had deteriorated. At the time of transfer from the operating room, his pupils were 3–4 mm, sluggish, and unequally reactive to light. Spontaneous movements of the upper extremities were present. A day later he no longer had spontaneous extremity movements, reflexes, or evident EEG activity. The serum CPK obtained at the end of resuscitation was 314,026 $IU \cdot L^{-1}$ (normal 72–376 $IU \cdot L^{-1}$). The urine was positive for myoglobin. A muscle biopsy was obtained for calcium uptake studies.

The child's blood pressure and urine output began to decrease in spite of large volumes of intravenous fluids, a variety of cardiac inotropes and vasopressors and other resuscitative efforts and he expired 48 hours after the cardiac arrest.

Autopsy findings of the brain were compatible with anoxia. Congestion of the lungs and kidneys was also present. Histopathologic examination of a specimen of rectus femorus muscle by ATPase, NADH (dihydronicotinamide adenine dinucleotide), Gamori trichrome, and haemotoxyn and oeosin stains demonstrated changes consistent with Duchenne muscular dystrophy. The muscle had the following abnormalities: variation of fibre size, atrophy, degeneration with necrosis of muscle fibres, internalization of nuclei, and an increase in fibrous and fatty tissue. In addition, calcium uptake studies were interpreted as being consistent with malignant hyperthermia: calcium uptake by thin sections was 5.3 μmol Ca/g muscle/min (normal 6.5–13 μmol Ca/g muscle/min),[15] actomyosin ATPase activity was 0.17 μmol phosphate/g muscle/min (normal 0.11–0.17 μmol phosphate/g muscle/min).

Detailed further questioning of the family was unproductive. Examination of one of the three previous anaesthetic records (all of which were unavailable preoperatively) revealed some increase in heart rate (120–170 beats·min^{-1}) and an elevation in temperature (36.5° to 38° C) over a two-hour period during a myringotomy and tear duct operation. The other two anaesthestic records were unremarkable. All three previous anaesthetics included halothane but not succinylcholine.

Case no 2

The patient was an apparently healthy three-year-old 15 kg boy until six months prior to admission when he was noted by his mother to climb and walk up stairs slowly. A blood sample analyzed for CPK at that time was 1600 $IU \cdot L^{-1}$. He was subsequently admitted to the hospital for muscle biopsy to rule out Duchenne muscular dystrophy.

Preoperatively, the patient had some deltoid muscle weakness but no Gower's sign (because of weakness of the lumbar and gluteal muscles the patient must climb up on his legs to rise from the floor). The calves were symmetrically hypertrophied. Review of systems was otherwise unremarkable. The patient had no previous operations and his family history was negative for any anaesthetic related complications. A repeat CPK was 6,600 $IU \cdot L^{-1}$.

On arrival in the induction suite, a blood pressure cuff was applied to the left arm, a precordial stethoscope placed on the chest and lead II EKG continuously recorded. Anaesthesia was induced with methohexitone, 350 mg per rectum, and nitrous oxide 50 per cent in oxygen via a face mask. A 24-gauge catheter was inserted into the left wrist and the patient was given fentanyl, 42 μg, and atracurium, 7 mg, intravenously prior to endotracheal intubation with a 5.0 mm endotracheal tube. A temperature probe was placed in the rectum. Anaesthesia was maintained with fentanyl and nitrous oxide 50 per cent in O_2.

The intraoperative course was uneventful (arterial blood pressure ranged between 100–110/70 mmHg, and axillary temperature between 36.8 to 37.9° C) with the exception of a heart rate of 155–160 beats·min^{-1} during the 90-minute opera-

tion. The child was extubated and taken to the recovery room. On arrival, his temperature was 38.8° C within 15 minutes. Arterial blood gases at this time were as follows: pH 7.26, PO_2 74.6 mm Hg, PCO_2 38 mmHg and base excess −9.5 mEq·L^{-1}. Dantrolene 40 mg was given intravenously as a bolus and an infusion was begun at an initial rate of 10 mg·kg^{-1}·hr^{-1}. Sodium bicarbonate, 20 mEq, was also administered intravenously, and ice and alcohol baths started. Repeat arterial blood gases and serum electrolytes revealed pH 7.35, PO_2 89.6 mmHg, PCO_2 36.6 mmHg, base excess −4.8 mEq·L^{-1}, potassium 4.18 mEq·L^{-1}, and sodium 135 mEq·L^{-1}. A small volume of urine (65 ml) was obtained after insertion of a Foley catheter. During the 90 minutes the patient was in the recovery room, his maximum temperature was 40.3° C (rectal), and there was no cardiac irritability or muscle rigidity. Following this he was transferred to the intensive care unit.

Over the next 24 hours, the patient's vital signs were stable but his rectal temperature remained at 39.0° C. Dantrolene 10 mg·kg^{-1}·day^{-1} was continued intravenously for 48 hours (total dose 300 mg) and there were no further temperature rises. Postoperative CPK was 4,704 IU·L^{-1}. There was myoglobinaemia, but not myoglobinuria. The muscle biopsy results were reported as consistent with Duchenne dystrophy, using the same criteria as previously described. It was not possible to obtain calcium uptake or caffeine contracture studies.

Discussion

These case reports indicate that patients with Duchenne muscular dystrophy (DMD) are susceptible to malignant hyperthermia (MH). They also suggest that patients with DMD should receive similar preoperative and intraoperative therapy as is usually given those patients suspected of having MH. There are only a few reports which have documented the occurrence of malignant hyperthermia in patients with DMD using both clinical and laboratory (muscle biopsy, enzyme, Ca^{++} uptake and/or halothane induced muscle contraction) studies.

Unfortunately, our first patient had no symptoms of DMD and a previous anaesthetic record, which was only suggestive of possible MH, was unavailable prior to the last operation. The patient experienced some of the classic signs of MH immediately after administration of succinylcholine. These included master spasm,[16–18] increased metabolism (arterial blood gases demonstrating a markedly elevated $PaCO_2$ in spite of a correctly placed endotracheal tube),[19] hyperkalaemia,[20] and venous constriction resulting in hepatosplenic congestion and backflow of blood into the intravenous catheter tubing.[6,21,22] Though there was never a significant temperature rise, this is not inconsistent with MH in a small child whose heat loss exceeds production and whose circulation was at a virtual standstill for many minutes.*

The second child, who was suspected of having DMD, first experienced hyperthermia in the postoperative period. The clinical course emphasizes the importance of taking the same precautions in patients with known or suspected DMD as in patients with MH. Unfortunately, in this case the anaesthesia machine was not flushed with oxygen before use nor the child pretreated with dantrolene. A small amount of volatile anaesthetic remaining in the anaesthetic machine circuitry may have been sufficient to trigger the posoperative hyperpyrexic response, despite the use of a nitrous oxide–narcotic technique. Fortunately, this child had an uninvolved postoperative course after institution of appropriate therapy.

Presumably this potentially disasterous complication could have been averted had appropriate precautions been taken before and during operation. These would include: flushing the anaesthetic machine with air or oxygen overnight, use of a fresh disposable anaesthetic circuit, preoperative dantrolene prophylaxis, intraoperative and possibly postoperative dantrolene administration, complete avoidance of potent volatile agents, succinylcholine, lidocaine, calcium, sympathomimetics, quinidine and digoxin and a high index of suspicion and thus preparedness to rapidly diagnose and treat evidence of MH in patients with DMD.

Some authors[23] might feel our recommendations are very aggressive, since MH may only occur in a minority of patients with DMD and even in our two cases the data are consistent with rather than diagnostic of MH. However, this may be true because children with DMD usually have short exposures to anaesthetics due to short or limited

*Ryan J, Boston MA, personal communication.

operations (eye examinations, eye muscle corrections, muscle biopsies, etc.) and often don't receive succinylcholine. Indeed, Flewellen[24] recommends administration of halogenated volatile agents to children with DMD because of their long record of safe utilization.

We believe it is important to maintain a high degree of suspicion of the potential for MH in children with any signs of DMD coming to operation. While our first patient was just two years old, an age when most children with DMD begin to have symptoms, he had no detectable motor difficulties. However, he had had several eye muscle operations and one anaesthetic record that, in retrospect, demonstrated subtle increases in heart rate and temperature after exposure to halothane. Since he was an outpatient, these records were not immediately available. Even if they were, it is difficult to know whether they would have been recognized without careful, more time-consuming scrutiny, a commodity which should not but seems to have less value in our modern cost-effective approach to medical care. The second child was suspected of having DMD; unfortunately, all appropriate measures were not taken. Until better screening is available, suspicion, a good history, careful (perhaps even time-consuming) reviews of old charts and pretreatment in children with any suggestion of DMD or MH are necessities in all children coming to operation.

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Résumé

Les auteurs présentent l'histoire de cas incluant la conduite anesthésique et post-opératoire de deux enfants l'un âgé de deux ans avec une dystrophie musculaire de Duchenne (DMD) non diagnostiquée et l'autre de trois ans avec une DMD connue. L'enfant avec une DMD non diagnostiquée n'avait aucun symptôme de dystrophie et avait reçu l'halothane deux fois au préalable avec le succinylcholine sans aucune difficulté apparente. Suite à une induction sans incident avec l'halothane, protoxyde d'azote et oxygène, l'administration de succinylcholine provoqua un spasme bilatéral du muscle masseter ainsi qu'une séquence rapide de tachycardie ventriculaire et arrêt cardiaque. La réanimation était difficile, prolongée et associée à une hyperkaliémie ($K^+ = 12.57\ mEq \cdot L^{-1}$), une acidose métabolique et respiratoire sévère, une pression veineuse centrale élevée et une hypatosplenomegalie massive sans hyperthermie. Le patient était finalement réanimé mais le patient décéda deux jours plus tard. Une biopsie musculaire post-opératoire prouva l'hyperthermie maligne. Le deuxième patient connu atteint de DMC et n'ayant pas reçu ni prophylactiquement ni en période opératoire du dantrolene a subu une anesthésie sans que la machine soit nettoyée avec l'oxygène pour une période étendue avant l'induction de l'anesthésie. Cet enfant était anesthésié avec le fentanyl et le protoxyde d'azote. A l'exception d'une fréquence cardiaque per-opératoire élevée (155–160 battements/min.) aucune complication anesthésique ou opératoire n'a été mentionnée (température axillaire per-opératoire variée entre 36.8–9° C). Malheureusement en période post-opératoire sa température augmenta rapidement jusqu'à 38.8° C et 40.3° C et présenta une acidose métabolique. L'administration intraveineuse de dantrolene pour 48 heures a diminué la température et conduit à un rétablissement normal. Une biopsie musculaire post-opératoire démontrait une DMD. Ces deux cas confirment que les patients atteints de DMD présentent le potentiel de développer une hyperthermie maligne durant et après l'anesthésie et doivent par conséquent être préparés en conséquence en période pré-opératoire et per-opératoire.