Atypical malignant hyperthermia with persistent hyperkalaemia during renal transplantation

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A 35-year-old 110 kg male developed marked hyperkalaemia, hyponatraemia, hypercapnia and hyperthermia during living-related renal transplantation under anaesthesia with oxygen–nitrous oxide, isoflurane and muscle relaxation with atracurium. This is the first report of successfully treated malignant hyperthermia triggered by isoflurane during renal transplantation with early appearance and persistent (to 12 hours after surgery) electrolyte abnormalities.

Malignant hyperthermia (MH) is a hypermetabolic state that can be triggered by a variety of stresses and agents including several anaesthetics.[1–4] We describe the case of a living-related renal transplant recipient under isoflurane anaesthesia with an atypical manifestation of MH in which severe hyperkalaemia and hypercapnia occurred but serum levels of creatine phosphokinase (CPK) did not increase greatly.

Case report

A 35-year-old 110-kg man in chronic renal failure from medullary cystic kidney disease was scheduled to receive a kidney from his 27-year-old brother. The patient had had three previous operations without apparent difficulty: two (repair of a knee injury and an appendectomy) under general anaesthesia (for which records were not available) and a more recent procedure under local anaesthesia (revision of an arteriovenous fistula). He had no other medical problems. His ECG showed normal sinus rhythm, and a chest *x*-ray was normal. Dialysis was performed 24 hr before surgery; at the end of the dialysis, the serum potassium level was 4.8 $mEq \cdot L^{-1}$. At this time he was given 200 mg of azathioprine and 100 mg prednisone IV. Two hours before surgery, the haemoglobin concentration was 8.2 $g \cdot L^{-1}$, haematocrit 24 per cent, BUN 79 $mg \cdot dl^{-1}$, serum creatinine 15.4 $mg \cdot dl^{-1}$, serum potassium 4.5 $mEq \cdot L^{-1}$ and serum sodium 139 $mEq \cdot L^{-1}$.

On arrival at the operating room at 0900, the patient had a pulse rate of 70 beats $\cdot min^{-1}$ and arterial blood pressure of 122/83 mmHg. Monitors included an ECG, a finger plethysmograph, an oxygen analyzer (Hewlett-Packard), a central venous pressure catheter, Dinamap blood pressure cuff, Portex oesophageal stethoscope with a thermistor, a peripheral nerve stimulator, and end-tidal carbon dioxide ($P_{ET}CO_2$) levels (Hewlett-Packard). Induction was with 400 mg of thiopentone and 100 μg of fentanyl. Tracheal intubation was facilitated by administration of 50 mg of atracurium. Anaesthesia was maintained with nitrous oxide and oxygen (2 $L \cdot min^{-1}$ total flow) and 0.5 to 1.0 per cent isoflurane. Additional doses of atracurium were added as needed, to a total of 150 mg. The last dose of atracurium (30 mg) was given at 12:00. No muscle rigidity was observed either during induction or throughout the case. Ventilation was controlled with a semiclosed system (Drager Narkomed II ventilator).

The first two hours of the surgery were uneventful. Blood pressure was 120–145 mmHg systolic and 70–85 mmHg diastolic, pulse rate was 60–70 beats $\cdot min^{-1}$, $P_{ET}CO_2$ was 32–35 mmHg, central venous pressure was 15–20 cm H_2O and oesophageal temperature was 36.2° C. At 1100 the potassium increased to 6.7 $mEq \cdot L^{-1}$. The table shows the changes that occurred in arterial and venous blood gases and electrolytes.

At 1210 $P_{ET}CO_2$ had increased from a previous average of 34 mmHg to 69 mmHg in about five minutes without evidence of circuit malfunction and potassium had increased to 7.3 $mEq \cdot L^{-1}$ The patient was ventilated

Key words

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manually (FiO_2 1.0) requiring a rapid ventilatory rate and a tidal volume of about one litre to keep $PETCO_2$ at 55 mmHg. At 1215, the venous PO_2 of 20 mmHg indicated an increased A–V difference for O_2 due to either decreased cardiac output or increased O_2 uptake. Considering the stability of blood pressure and increasing $PETCO_2$, the diagnosis of malignant hyperthermia was likely; it was decided to complete the operation since the surgeons had started the vascular anastomosis. Shortly thereafter at 12:30, heart rate rose from 85 to 118 beats · min^{-1}, and peaked T waves occurred on the ECG, indicating hyperkalaemia. The patient was given a glucose-insulin infusion (ten units) and 90 mEq of sodium bicarbonate for treatment of hyperkalaemia and acidosis. The patient's temperature began to rise at a rate of 0.1°C every two minutes, and a hyperdynamic circulatory pattern was apparent from the peripheral pulses and the iliac artery. Bags of frozen saline were placed in the axillae, on the groin and around the neck. The patient was connected to an anaesthesia machine having no vaporizers and fresh soda lime, stored especially for such an instance; anaesthesia was continued with 100 per cent O_2, incremental doses of fentanyl (to a total of 700 μg) and 3 mg diazepam. Before the vascular clamps were removed, the patient was given furosemide 1 mg · kg^{-1} and mannitol 1 g · kg^{-1} IV.

At 12:30, after 200 mg of dantrolene and an additional 90 mEq of sodium bicarbonate, $PETCO_2$ began to decrease and ventilation was slowed to 15 breaths · min^{-1}. Heart rate decreased from 120 beats · min^{-1} to 100 beats · min^{-1} at 13:45. However, at this time large T waves consistent with marked hyperkalaemia (8.6 mEq · L^{-1}) occurred on ECG, along with a short run of ventricular tachycardia that resolved spontaneously. Administration of an additional glucose-insulin infusion (ten units) and 1 g of calcium chloride resolved these electrocardiographic abnormalities. At this point, the surgeons were implanting the ureter into the bladder.

During the rest of the operation an additional 140 mg of dantrolene was administered (total 3 mg · kg^{-1}). Vital signs were stable, and temperature remained constant at 37.3°C. End-tidal CO_2 levels fell to 26 mmHg and potassium was 7.8 mEq · L^{-1}. Total urinary output was 650 ml. Fluids administered intraoperatively consisted of 2.7 L of saline, 1.5 L of lactated Ringer's solution and two units of packed red blood cells.

On arrival at the Intensive Care Unit, the patient was given 200 mg of dantrolene; the CPK level was 271 units · L^{-1} (upper limit of normal range 230 units · L^{-1}). While in the ICU, the patient remained stable, and temperature did not increase. Dantrolene 200 mg IV, was given every 6 hr for 24 hr, following which the drug was given orally for another 24 hr. Twelve hours after surgery, the CPK level was 475 units · L^{-1}, serum potassium 5.1 mEq · L^{-1}, serum sodium 128 mEq · L^{-1} and serum creatinine 7.9 mg · dL^{-1}. Urinary output was 13 L during the same period. Creatinine phosphokinase levels peaked (862 units · L^{-1}) 36 hr later, at which time serum potassium was 4.5 mEq · L^{-1}. The rest of the postoperative period was uneventful.

The patient's brother had previously received thiopentone and succinylcholine during anaesthetic induction and marked fasciculations were noted. Since no other abnormalities were detected the case proceeded under isoflurane anaesthesia. After this episode of malignant hyperthermia, the patient stated that he had had frequent leg cramps, as did his son, especially after ingestion of caffeine. He also said that an uncle had been "packed in ice" after an operative procedure. However, the patient refused to undergo muscle biopsy.

Discussion

This patient experienced hyperkalaemic, hypermetabolic and hyperthermic states compatible with MH. The following occurrences suggested this diagnosis: a rapid increase in the end-tidal concentration of CO_2 without change in the ventilatory pattern, a low oxygen partial pressure in venous blood, and a steady increase in temperature 3 hr after induction of anaesthesia. The slow onset of these signs may have been related to the use of an halogenated anaesthetic[5] and decreased reflex responsiveness (by thiopentone) or neuromuscular transmission (by a non-depolarizing drug).[1] This delayed clinical course, lack of muscle rigidity and relatively slight increase in CPK could be described as a non-rigid type of malignant hyperthermia.[5]

The marked increase in the serum potassium level that occurred approximately 90 minutes after induction was the first abnormality; initially this was attributed to renal failure. However, since baseline potassium values were normal and sodium decreased simultaneously to very low values, these changes could be explained by an unusually early disruption of cell membrane homeostasis as a part of the MH syndrome. In fact, end-expiratory PCO_2, temperature and pulse rate did not change until the onset of major changes in sodium and potassium (Table), suggesting that electrolyte abnormalities (as a reflection of membrane abnormalities) preceded hypermetabolism in this MH reaction. End-stage renal disease with previous electrolytes disturbances may play a role in this atypical response. Similarly, it is interesting to speculate if the late intra- and postoperative hyperkalaemia were related to some aspect of renal failure in spite of high urinary output. This situation might indicate a residual membrane alter-

TABLE Changes in arterial and venous blood gases and electrolytes

Time	Heart rate beats·min^{-1}	Temp. °C	$P_{ET}CO_2$ mmHg	pH	$PaCO_2$ mmHg	PaO_2 mmHg	Sodium mEq·L^{-1}	Potassium mEq·L^{-1}	Base excess mEq·L^{-1}
0700							139	4.5	
0900	70	36.2	32						
0930	64	36.2	32						
1000	60	36.2	32						
1030*	68	36.2	33	7.35	36	54	135	5.2	−5.1
1100	65	36.0	34	7.37	37	184	128	6.7	−2.7
1130	60	36.1	35						
1200	70	36.0	35						
1210	85	36.5	69	7.14	69	223	121	7.3	−6.2
1215*	110	37.8	55	7.11	84	20			
1230	118	38.4	43	7.15	55	201	119	7.4	−9.0
1300	110	38.0	42						
1330	95	37.5	41						
1345	100	37.5	30	7.58	27	517	117	8.6	+5.5
1355	85	37.3	24	7.57	24	453	119	7.8	+3.1
1400	85	37.1	22						
1430	76	37.1	26	7.50	30	282	119	7.7	+1.0

*From venous blood.

ation during normal temperature, $P_{ET}CO_2$ and pulse rate.

Although it has been reported that hyperkalaemia increases whole body metabolism in MH susceptible pigs[2] and induces abnormal contraction in susceptible human muscles in *vitro*,[3] its relative contribution in this case could not be directly evaluated. Calcium administration (for the treatment of hyperkalaemia) is against the traditional teaching that calcium is contraindicated during an MH reaction. However, higher doses of calcium reportedly do not trigger MH in the heart or whole body of the highly susceptible Pietrain pig, a finding probably related to the large difference between intra- and extracellular concentration of free ionized calcium.[2] The role of inhalation agents as triggers of MH is well known. Nitrous oxide is less likely to be a specific triggering agent[6] and its use is considered safer than isoflurane, which probably initiated the MH reaction in three patients[7–9] although they had received succinylcholine for intubation. Recently, MH was reported during a pyelolithotomy in a patient anaesthetized with epidural bupivacaine and isoflurane in which vecuronium was the only neuromuscular blocking drug used.[10] Halothane and vecuronium were used in the only report of MH during renal transplantation.[5] Atracurium has been given to MH-susceptible pigs[11,12] and patients[13,14] without adverse effects. In summary, a successful management of a non-rigid type of MH in a living-related renal transplantation patient during isoflurane anaesthesia is described in which electrolyte abnormalities preceded signs of hypermetabolism.

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Résumé

Un homme 35 ans pesant 110 kg a développé une hyperkaliémie marquée, une hyponatrémie, une hypercapnie et une hyperthermie durant une transplantation rénale faite sous anesthésie à l'isoflurane/protoxyde d'azote et atracurium. Ceci est le premier cas rapporté d'une hyperthermie maligne déclenchée par l'isoflurane durant une transplantation rénale avec un début précoce et des anomalies électrolytiques persistantes (12 heures après chirurgie).