Development of malignant hyperthermia obscured by cardiopulmonary bypass

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An episode of malignant hyperthermia occurring in a two-year-old child undergoing cardiac surgery is reported. The coincidental usage of hypothermic cardiopulmonary bypass obscured the classical presenting signs and symptoms of the syndrome. Once the clinical diagnosis was confirmed, rapid reversal was achieved with the administration of dantrolene sodium.

Malignant hyperthermia (MH) is a syndrome initiated by a hypermetabolic state of skeletal muscle. Incidence, in association with anaesthetic administration in children, is quoted at 1 in 15,000.[1] We report a case of MH in a two-year-old boy in whom the syndrome developed in association with hypothermic cardiopulmonary bypass (CPB).

Case report

A two-year-old Indian (Asiatic) boy weighing 11 kg presented for correction of an acyanotic tetralogy of Fallot.

Preoperatively the child was well. There was no family history of unusual reaction to anaesthesia. Premedication consisted of oral trimeprazine 4 $mg \cdot kg^{-1}$, two hours, and morphine 0.25 $mg \cdot kg^{-1}$ by intramuscular injection one hour preoperatively.

Anaesthesia was induced with nitrous oxide, oxygen and halothane. Monitoring (left radial artery and right internal jugular vein) and infusion cannulae were inserted, and the trachea was intubated following topical administration of two per cent lidocaine 3 $mg \cdot kg^{-1}$. Pancuronium 0.1 $mg \cdot kg^{-1}$ was used to provide muscle relaxation and increments of morphine were given to a total dose of 10 mg. Ventilation was controlled with a non-rebreathing circuit and a volume pre-set ventilator. End-tidal PCO_2 and oxygen saturation (by finger pulse oximeter) were monitored continuously with intermittent analysis of arterial blood-gases and electrolytes. Temperature was monitored by nasopharyngeal and rectal thermistor probes.

During the first hour of anaesthesia, in order to maintain end-tidal PCO_2 below 5 kPa it was necessary to increase the pre-set minute volume of ventilation from 3.0 to 4.0 $L \cdot min^{-1}$. At the time of surgical manipulation and cannulation of the heart, the heart rate increased from 100 to 150 b.p.m., oxygen saturation fell from 98 to 89 per cent and end-tidal PCO_2 rose to 6.9 kPa. These events were variously attributed to additional pancuronium administration, light anaesthesia and possible iatrogenic reversal of the intracardiac shunt. Rectal temperature was 35.5° C.

The period of CPB was uneventful and lasted 90 min. The ventricular septal defect was closed and the pulmonary outflow tract enlarged, under cardiac standstill, at a core temperature of 25° C. On rewarming, sinus rhythm resumed spontaneously at 28° C, the rate soon rising to 130 b.p.m. Calcium gluconate 10 $mg \cdot kg^{-1}$ was given IV and 25 mmol sodium bicarbonate was given to correct a meta-

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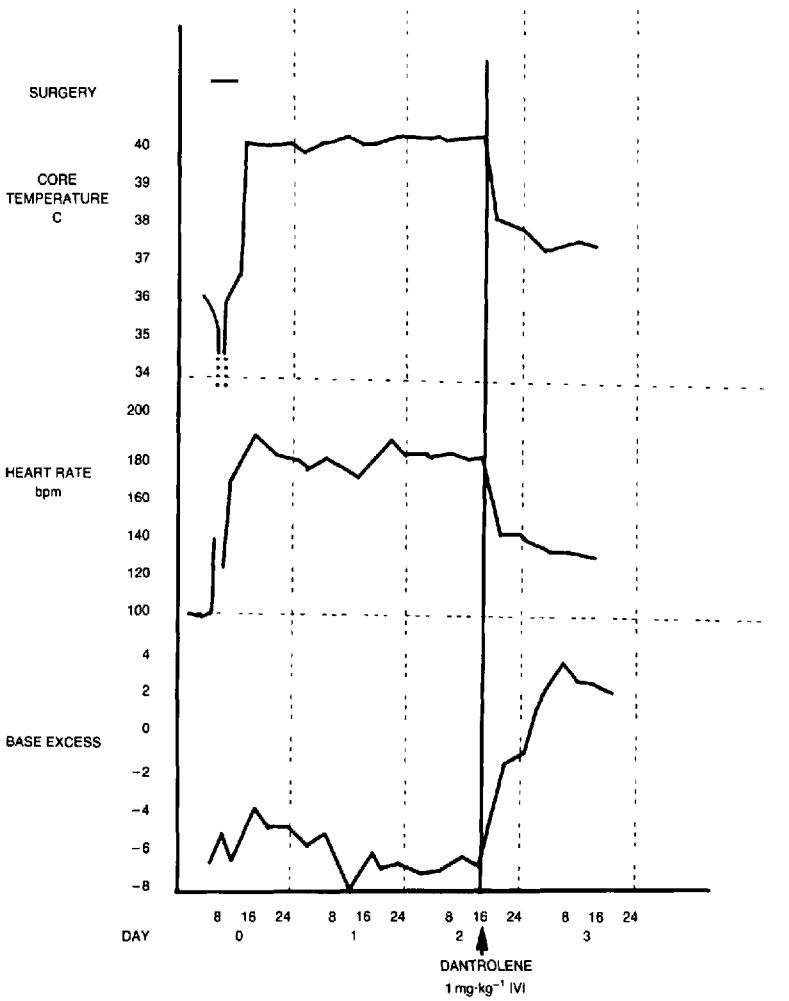

FIGURE 1 Perioperative trends in temperature, heart rate and base excess.

bolic acidosis (base excess $-7\,mmol \cdot L^{-1}$). At a nasopharyngeal temperature of 36° C and rectal temperature of 33° C CPB was successfully discontinued.

On completion of surgery the heart rate had risen to 160–170 b.p.m. At an FiO_2 of 0.5, arterial pH was 7.42, PaO_2 35 kPa, $PaCO_2$ 4.0 kPa, base excess $-4\,mmol \cdot L^{-1}$; serum electrolyte concentrations were: sodium, $128\,mmol \cdot L^{-1}$ and potassium $4.3\,mmol \cdot L^{-1}$.

From the time of discontinuation of CPB the rectal temperature rose progressively and had reached 40° C one hour after the patient's return to the intensive care unit. The heart rate had risen to 185 b.p.m. The patient's subsequent course is represented in Figures 1 and 2. Temperature remained elevated at 40° C despite acetylsalicylic acid 60 mg suppositories given four hourly, and ice packs to axillae and groins at peaks of temperature up to 41° C.

A sinus tachycardia, of 170 to 190 b.p.m. persisted despite otherwise stable haemodynamic

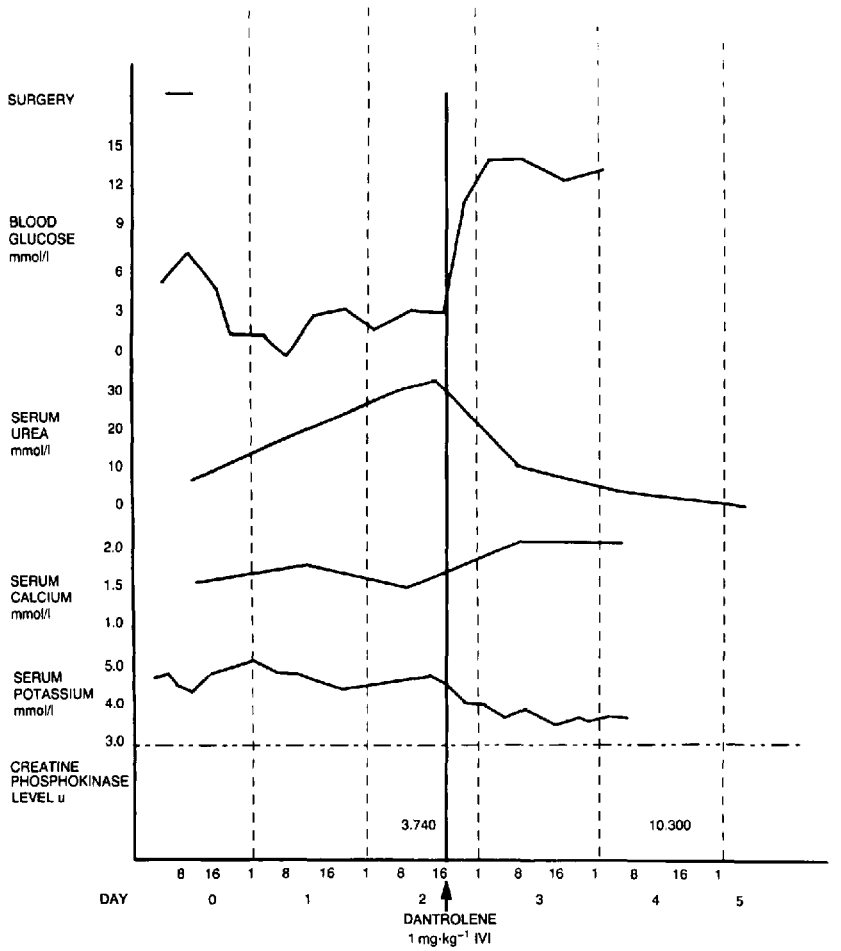

FIGURE 2 Perioperative biochemical trends.

parameters. A metabolic acidosis (base excess of -6 to $-8\,mmol\cdot L^{-1}$), persisted (Figure 1) despite hourly administration of 10 mmol sodium bicarbonate.

Initially maintenance fluid infusion was half strength Darrows solution (Na^+ 61, K^+ 17, Cl 51, lactate 27) with ten per cent dextrose. However, blood sugar concentrations decreased (Figure 2) necessitating infusion of 20 per cent dextrose, with intermittent bolus injection of 50 per cent dextrose to prevent hypoglycaemia. Serum potassium rose to $5.0\,mmol\cdot L^{-1}$ within four hours before the Darrows solution was changed to one-half normal saline, and no further potassium was administered. Total serum calcium was low ($1.5\,mmol\cdot L^{-1}$) despite calcium gluconate supplementation (Figure 2).

Serum urea increased dramatically from 7.0 $mmol\cdot L^{-1}$ to $30\,mmol\cdot L^{-1}$ by day two (Figure 2), despite continued urine production augmented by an infusion of $5\,\mu g\cdot kg^{-1}\cdot min^{-1}$ of dopamine and a dose of 10 mg furosemide. The serum to urine osmolality ratio decreased, indicating established renal failure. Throughout, oxygenation and carbon dioxide elimination remained satisfactory. No

attempt was made to wean the patient from ventilatory support while investigating the persistent hypermetabolic state.

There was no evidence of muscle rigidity or myoglobinuria, and although the spectre of MH was raised on day one, it was not until the result of the creatine kinase (CK) estimation was obtained on day two, that the diagnosis was seriously considered. A CK of 3,740 units (normal value – less than 150 u) in conjunction with the other available evidence was considered sufficient indication to administer intravenous dantrolene.

Within one hour of administration of a dose of dantrolene of 1 $mg \cdot kg^{-1}$ on the afternoon of the second postoperative day, the temperature had fallen to 38° C, the heart rate to 140 b.p.m. and the base excess to $-2\,mmol \cdot L^{-1}$. The blood sugar increased and these trends continued with an associated fall in blood urea and potassium concentrations, and an increase in serum calcium. The child was weaned from ventilatory support on day three and made an uncomplicated recovery. CK on day four was 10,300 units, but had fallen to 940 units by day seven.

Subsequently it was revealed that three months previously the patient had undergone cardiac catheterisation under morphine/cyclizine sedation. Following this investigation he developed a severe "spell" characterised by cyanosis, pyrexia (41° C), acidosis and convulsions. He was treated with topical cooling and administration of intravenous diazepam, propranolol, glucose and sodium bicarbonate. He made an uneventful recovery. This poorly documented incident was attributed to shunt reversal, caused by a "reaction" to contrast material at angiography.

The patient's father was found to have a resting CK of 450 u; however, all efforts to persuade the family to undergo definitive investigation for MH susceptibility by muscle biopsy have failed.

Discussion

Malignant hyperthermia has engendered much interest since the initial full description of the syndrome by Denborough *et al.*[2] in 1962. Two international symposia,[3,4] and recent reviews of the syndrome,[5,6] and the role of dantrolene,[7] in its management have contributed much to our recognition and understanding of the condition. While hypothermic cardiopulmonary bypass has been used in the treatment of MH[8] and a patient with proven MH susceptibility has been successfully managed for surgery requiring CPB,[9] we are unaware of any previous report of the development of the syndrome coincidentally wtih CPB. We suggest that this delayed the diagnosis in our case by obscuring the classical signs and symptoms of presentation.

Development of symptoms of MH can vary from insidious to fulminant.[10] The latter is usually associated with the concurrent administration of halogenated inhalational agents and succinylcholine. In the case reported halothane was the most likely triggering agent, though trimeprazine has been implicated in the past.[11]

In our patient the rising end-tidal PCO_2 and heart rate, with falling oxygen saturation, observed immediately pre-bypass, may have been the result of the development of MH. CPB with core cooling to 25° C reduced the hypermetabolism until the rewarming period.

When ventilation is controlled, increased CO_2 production will be more accurately represented by mixed venous PCO_2 than $PaCO_2$,[1] and monitoring of end tidal CO_2 may be of value in early recognition of the syndrome.[12]

While postoperative pyrexia is not an unusual observation following hypothermic CPB,[13] the temperature usually peaks at eight hours after which it decreases towards normal,[14] thus the persistence of a pyrexia of greater than 39° C into the first postoperative day required explanation. Sepsis was excluded by blood cultures and other appropriate investigations, while other causes such as drug reaction, blood transfusion reaction, and malfunction of heated humidifiers were also considered.[15]

The elevated CK level helped confirm the earlier suspicion that the clinical syndrome represented MH. While CK levels commonly rise 24 hours after surgery these are usually in the range 100–200 per cent of normal,[16] in the absence of myocardial infarction or acute rhabdomyolysis. Thus an elevated CK may be an indicator of MH, though in the multicentre dantrolene study, five of 11 patients had CK levels below 1000 u.[17]

High output, or non-oliguric, renal failure as occurred in our patient may be seen in association with MH.[18] Preventative measures recommended include IV fluids and the use of osmotic diuretics such as mannitol.[6] Such therapy may be inappropri-

ate in a patient recovering from open heart surgery, particularly with diversion of blood flow to the lungs. Hyperkalaemia is a common observation in MH.[5,6] The modest rise observed in this case was managed simply by avoidance of potassium in infusion fluids; serum potassium fell soon after dantrolene administration necessitating resumption of potassium maintenance administration.

In contrast, the serum sodium rose from 128 $mmol \cdot L^{-1}$ to a peak of 144 $mmol \cdot L^{-1}$ on day two. This rise was attributed to the use of one-half normal saline as a maintenance infusion, in addition to the frequent administration of sodium bicarbonate in attempts to treat the persistent metabolic acidosis. Britt and Kalow[1] have described a patient in whom serum sodium rose to 192 $mmol \cdot L^{-1}$ as a consequence of excessive sodium bicarbonate administration.

While hyperglycaemia, due to catecholamine effects, occurs during active MH,[5] in this case the blood sugar remained low despite considerable dextrose administration. A fall in serum calcium is another characteristic finding;[1,5] however, calcium commonly decreases as a consequence of CPB,[15] so the relevance of this finding is uncertain. While intraoperative diagnosis may be difficult,[5] it is apparent that greater attention should have been paid to the rising end-tidal PCO_2[6,12] and a label of "shunt reversal" was given too readily to the desaturation and tachycardia observed pre-bypass. An index of suspicion is essential for MH diagnosis and timeous intervention.[6]

Stress-related MH episodes may occur in susceptible man,[6,19] similar to the pig, and in the absence of a recognised trigger it may be possible to attribute the episode post-catheterisation to such a cause, though documentation was incomplete.

The neuroleptic malignant syndrome (NMS) may be associated with trimeprazine used as premedication in the case reported and also implicated in MH.[11] However, NMS is usually associated with large dose antipsychotic therapy and develops over days to weeks[20] rather than minutes to hours as is the cause with MH.

Dantrolene is the definitive treatment[7,17] and while dosage up to 10 $mg \cdot kg^{-1}$ may be required, in the case reported here there was dramatic reversal of the signs and symptoms of the syndrome after a single dose of 1 $mg \cdot kg^{-1}$ IV. We propose that this favourable response to a small dose given late may have been a result of attenuation of the MH reaction by hypothermic CPB after the halothane exposure. The absence of rigidity and myoglobin production suggests that this was a mild expression of the syndrome. Dantrolene in animals may cause myocardial depression, both contractile and of impulse conduction and caution in its use has been advised in the cardiac patient.[7,9]

While we have been unable to obtain confirmation of the diagnosis by muscle biopsy, the preponderance of evidence would suggest MH susceptibility in this family and they have been advised accordingly.

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Résumé

Un épisode d'hyperthermie maligne ayant survenu chez un enfant de 2 ans subissant une chirurgie cardiaque est rapporté. L'utilisation de l'hypothermie lors de la circulation extra-corporelle a obscursi les signes classiques ainsi que les symptômes annonçants ce syndrome. Lorsque le diagnostic clinique a été confirmé, le rétablissement rapide a été acquis avec l'administration du dantrolène.