MALIGNANT HYPERTHERMIA INDUCED BY CURARE

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INTRODUCTION

Is CURARE safe for malignant hyperthermia susceptible (MHS)* patients? Denborough¹ and King² have claimed that it is indeed so, although they do not report any human clinical or experimental data to support this contention. Hawthorne³ states that the muscle tone of one of his hyperthermic patients appeared to decrease after infusion of curare. However, this patient did not recover. Harrison has found that curare alone does not trigger malignant hyperthermia (MH) in swine⁴ and that pretreatment with curare prevents initiation of MH by succinylcholine, although not by halothane.⁴⁻⁶ Such animal data cannot, however, be extrapolated to man since the aetiologies of human and porcine MH do not appear to be identical.⁷⁻¹⁸ Furthermore, in some human subjects, as we have previously reported,¹³⁻¹⁶ curare does not relieve rigidity and may even worsen an MH crisis induced by drugs such as halothane or succinylcholine.

In this paper we will describe two cases of MH in which curare was the probable triggering drug. Each episode occurred in a member of a known MH family and developed in spite of preventive precautions such as prophylactic cooling and avoidance of potent inhalational anaesthetic agents and depolarizing skeletal muscle relaxants.

CASE 1

A 13-year-old Caucasian male required anaesthesia for subacute bowel obstruction secondary to volvulus. The immediate preoperative temperature was normal. Prior to the occurrence of volvulus, this boy was healthy, with normal muscle strength and no localized muscle abnormalities. Haematocrit was 40 per cent and the serum potassium was normal. Twenty relatives had had a non-rigid form of MH, eight of whom had expired during or immediately following anaesthesia. These facts were known to the attending anaesthesiologists. They therefore cooled the patient prophylactically for one hour prior to surgery with a K-thermia blanket and monitored heart action by an EKG oscilloscope.

Premedication was atropine 0.6 mg and chlorpromazine 50 mg. During the preoperative cooling period a lytic cocktail of meperidine 100 mg, chlorpromazine 50

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*MHS (Malignant Hyperthermia Susceptible). A patient known to carry an MH gene but either fully recovered from an acute MH crisis or not yet anaesthetized with triggering agents.

mg, and promethazine 50 mg was infused in divided doses. Immediately prior to induction the rectal temperature was 97° F. Anaesthesia was induced with nitrous oxide and oxygen. Curare 30 mg was infused to facilitate intubation and to provide relaxation of the abdominal muscles. Immediately following intubation the temperature began to rise rapidly and reached a maximum of 103.5° F five minutes after the administration of curare. During this five-minute period the heart rate accelerated from 78 per minute to 120 per minute.

No further curare was given. Cooling with the hypothermia blanket was intensified and ice bags were placed in the groin and axilla. Hyperventilation was instituted with a Bird ventilator. During the next 135 minutes (i.e. 140 minutes from induction) the temperature gradually fell to 97.5° F and during this period, the operation was completed. No skeletal muscle rigidity occurred at any time throughout the anaesthetic period. In the recovery room, blood gases were within normal limits. In spite of the minimal administration of anaesthetic drugs, consciousness did not return for several hours. No haemoglobinuria or myoglobinuria could be detected during the convalescent period.

Eventually, the patient made a complete mental and physical recovery. One year later, serial creatine phosphokinase (CPK) estimations were 25, 55 and 50 i.u. (normal $\leq$ 40 i.u.).

CASE 2

An eight-year-old Caucasian male developed acute appendicitis with a maximum temperature of 100.4° F. His prior health had been good. Muscle development was normal and he had no localized muscle weaknesses. Preoperative laboratory findings were Hb 13.3 Gm%; Hct 39 per cent; WBC 26,000, differential normal; serum Na 130 mEq/L; serum Cl 98 mEq/L; serum K 3.6 mEq/L; CO₂ content 25 mEq/L; total serum Ca 4.9 mEq/L; ionized serum Ca 2.5 mEq/L; urinalysis 1+ protein, 1+ acetone, no blood; serial CPK 160 i.u. and 90 i.u. (normal $\leq$ 130 i.u.). It was known that 11 relatives had suffered acute MH episodes of the rigid variety and that six of these had died during the crises.

Premedication was omitted. In the operating theatre, the child was placed on a K-thermia mattress at 60° F and attached to an EKG monitor. Oesophageal temperature immediately prior to anaesthesia was 100.5° F. Following induction with curare 3 mg and diazepam 20 mg, a number 5 portex cuffed tracheal tube was passed without difficulty. A further 12 mg of curare was then given and the patient was hyperventilated manually with N₂O:O₂, 5:2. Within fifteen minutes the heart rate rose to 140 per minute, the systolic blood pressure (BP) to 169 mm Hg and the oesophageal temperature to 105° F.

Mattress temperature was reduced to 30° F and cold gastric lavage and cold lactated Ringer's solution were administered. The operation was completed one hour after induction, at which time the oesophageal temperature was 103° F, systolic BP 106 mm Hg, and the heart rate was 130 per minute. The pH was 7.32; Paco₂ = 45.4 mm Hg (in spite of hyperventilation); base excess = -3.1 mEq; total CO₂ content 23.9 mEq/L; serum Cl 104 mEq/L; serum Na 134 mEq/L; and serum K 4.4 mEq/L.

On arrival in the recovery room, 75 minutes after induction, the oesophageal temperature was 101.5° F, BP was 120/60, and the heart rate was 120 per minute. During the next six hours a fever of 105° F again occurred, but was controlled with further cooling measures.

Eventually, the patient recovered completely, both mentally and physically, and he was discharged after 13 days' hospitalization. Several months later, serum CPK were 25, 50 and 80 i.u. (normal $\leq$ 40 i.u.).

DISCUSSION

Was the fever observed during anaesthesia in these two patients due to MH or to infection? The latter possibility seems unlikely for the following reasons:

1. The pre-anaesthetic fevers were mild and there was nothing to suggest a worsening of the patient's condition immediately following induction, sufficient to account for the high fevers during anaesthesia.

2. Sudden release of bacteria into the blood stream by surgical stimulation could not be responsible for the sudden spiking hyperthermia, since fever occurred in each instance prior to the initial surgical incision.

3. Fever due to infection would be unlikely to rise at such a rapid rate while vigorous cooling measures were underway.

4. Furthermore, fever secondary to infection usually subsides, rather than rises, during anaesthesia (especially in children) since cessation of muscle activity and vasodilatation initiated by the anaesthetic agents result in lowered heat production and accelerated heat loss.

5. In addition, even without the inhibiting effect of anaesthesia, fever in each patient developed much more quickly than would be expected for either acute appendicitis or volvulus, conditions which are usually associated with only modest temperature rises.

6. Finally, the high temperatures in both patients subsided and remained normal with the use of hyperventilation and cooling alone and without the aid of antibiotics.

Thus, MH appears to be the probable cause of the hyperthermia in these two patients. The question then is, which of the several agents used by the anaesthetists could be the triggering drug? In case 1, the several administrations of meperidine, promethazine and chlorpromazine prior to induction did not initiate a temperature rise. Moreover, nitrous oxide, which was employed in both cases, has been repeatedly demonstrated to be safe for MH patients^{13,17-20} as have meperidine^{18,20} and diazepam.¹⁷ In fact, a number of relatives of these same two patients have been uneventfully anaesthetized with various combinations of nitrous oxide, meperidine, and diazepam. The only possible triggering agent common to both anaesthetics, therefore, is curare. Curare is additionally implicated since the marked and rapid rise in temperature in each patient commenced immediately following its infusion and was in each instance accompanied by tachycardia (a consistent feature of known MH crises).

The clinical course of these two cases suggests that curare is a fairly weak triggering agent since no skeletal muscle rigidity was detected in spite of careful observa-

tion; no irregularity of heart action accompanied the tachycardia; disturbances of blood gases, electrolytes and other biochemical parameters were mild or absent; and both patients survived.

It might also be argued that the relatively benign nature of these MH episodes was due to an inherently mild muscle defect, since serial CPKs in both subjects were either normal or only minimally elevated, neither manifested any muscle abnormality and the survival rate in each family significantly exceeded the average of 64 per cent.²¹ Alternatively, the fever and manifestations of MH may have been mild because of the prophylactic cooling, early recognition and prompt and effective therapy.

The combined evidence of two mild cases of MH probably induced by curare plus the observation that curare worsens already established MH, contraindicates this drug for elective use in anaesthesia for patients suspected to have malignant hyperthermia.

RÉSUMÉ

Les auteurs rapportent deux cas d'hyperthermie maligne survenus après administration de curare.

Le premier cas survint chez un garçon de 13 ans opéré pour sub-occlusion intestinale secondaire à un volvulus, et le second chez un garçonnet de 8 ans opéré pour appendicite aiguë.

Les deux enfants avaient une histoire familiale d'hyperthermie maligne et il était connu que plusieurs membres de leur famille respective étaient morts de cette complication.

Ils présentèrent tous deux une hyperthermie (à 103.5° F et à 105° F) après administration de curare, sans cependant présenter de rigidité musculaire. Ces épisodes survinrent malgré la prise de précautions (refroidissement préalable et non utilisation d'agents dépolarisants et d'agents d'anesthésiques puissants).

Les deux interventions purent être poursuivies, et les températures furent abaissées graduellement grâce aux matelas réfrigérants (placés au préalable), à l'application de sacs de glace, à l'usage de solutés froids et dans un cas à un lavage gastrique avec du soluté froid.

Les deux enfants s'en tirèrent sans séquelles.

Les auteurs concluent que l'usage du curare est contre-indiqué lorsqu'il y a possibilité d'hyperthermie maligne.

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