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Hemolysis and Hyperkalemia Complicate Malignant Hyperpyrexia During Anesthetic Death

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ABSTRACT: A healthy, 15-year-old male received a thiopental, nitrous oxide, oxygen, enflurane anesthetic for appendectomy. Cardiac arrest, following succinylcholine administration, was associated with marked hyperkalemia (potassium levels 8.7 to 11.6 meq), hemolysis (hematocrit fall from 41.7 to 26.6%, plasma hemoglobin 27 mg/dL), and creatine phosphokinase (CPK) elevation (8900 units). Vigorous resuscitative therapy including dantrolene was unsuccessful.

The diagnosis of malignant hyperthermia was made by the marked CPK elevation on blood samples drawn during resuscitation and analyzed by the Medical Examiner's Office.

KEYWORDS: pathology and biology, anesthetics, hyperthermia

Malignant hyperthermia (MH) is an incompletely understood inherited disease, of autosomal dominance, associated with rapid fulminant hypermetabolism. During the hypermetabolic state, there is sudden loss of control of intracellular ionized calcium. In muscles, the resultant continuous linkage of actin and myosin causes adenosine 5′-triphosphate (ATP) to be broken down into adenosine 5′-diphosphate (ADP), with production of considerable amounts of heat. In the attempt to reconvert the excessive amounts of ADP back to ATP, more heat is liberated, more carbon dioxide produced, and when oxygen demand exceeds oxygen supply in the hypermetabolic state, lactic acidosis ensues [*1*].

While the disease might be triggered by anxiety or immoderate exercise, anesthetic agents have been the almost exclusive triggering factor in the published clinical reports. Halothane and succinylcholine seem to be unusually sensitive triggers, but most other anesthetics have been linked as well. In a typical case, anesthesia is induced with an ultrashort barbiturate or by inhalation of the halogenated agent. Succinylcholine may be given to faciliate intubation; a second dose of succinylcholine may be administered as commonly the jaw muscles are

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inadequately relaxed. Soon tachycardia appears, the temperature begins to rise, and increased muscle tone makes surgery difficult. Blood gas analysis shows marked metabolic acidosis, hypercarbia, and a profounded reduction in the oxygen tension, considering the oxygen percentage used for ventilation. If untreated, cardiac arrest ensues, which is refractory to therapy. Dantrolene is a specific therapeutic drug, and if given early enough during the event, will produce a remarkable reversal of the phenomenon. A handful of patients have been reported who have had repetition of the process within two days; in these patients fatal hyperkalemia seems to be the terminal event.

Surprisingly, in susceptible individuals, the phenomenon is not always triggered by each anesthetic. One patient has been reported who had twelve anesthetics without difficulty, but the thirteenth caused a fatal hyperthermic response [*2*].

Case Report

The case being presented is that of a 15-year-old male who presented to the hospital with a 24-h history of periumbilical pain, associated with nausea and one episode of vomiting immediately before admission. Past history was negative except for an uncomplicated undescended testis repair eight years previously under halothane, nitrous oxide, oxygen anesthesia. He had received several injections of lidocaine for dental work. Physical examination showed right lower quadrant tenderness and rebound pain. The admission hematocrit was 41.7%, the white blood cell count was 16 300. At 1115 h he received 300 mg of thiopental to induce anesthesia, followed by 80 mg of succinylcholine. Muscle relaxation was inadequate for intubation, so an additional 40 mg was administered. Oxygen and nitrous oxide in equal parts and enflurane were the anesthetic agents employed. At 1140, after the skin incision, an additional 40 mg of succinylcholine was administered to facilitate the surgeon's entrance into the abdominal cavity. The patient had an immediate bradycardia, which was refractory to 0.4 mg of atropine. Asystole followed within seconds, which progressed to refractory ventricular fibrillation. Dantrolene (0.9 mg/kg per body weight) was administered at 1322.

His rectal temperature was 37.2°C (99°F) at 1200, 37.8°C (100°F) at 1230, following which it gradually fell to 35°C (95°F) at 1430.

The initial laboratory studies, drawn immediately after 100 meq of sodium bicarbonate administration showed pH 7.16, $PaCO_2$ 7 kPa (52 torr), PaO_2 47.5 kPa (357 torr), sodium 128 meq, and potassium 11.5 meq. Vigorous resuscitation attempts continued for 3 h. One hour after the arrest, the potassium values varied between 8.7 to 11.6 meq. The hematocrit was noted to be 26.6% and the plasma hemoglobin was 27 mg/dL.

All unused blood samples were transferred with the body to the Medical Examiner's Office. Subsequent analyses showed the creatine phosphokinase (CPK) to be 3740 units at 1200, and 8900 units at 1430.

Discussion

Sudden massive hemolysis is almost unheard of during anesthesia. Hemolysis following toxic drug administration can be ruled out as stock solutions of drugs were used and no other patient had a similar event following the administration of these drugs or the use of the same anesthetic machine.

Increased fragility of erythrocytes has been reported in both malignant hyperthermia susceptible humans and pigs, but the degrees of increased fragility have been of no major clinical significance [*3,4*]. The hyperkalemia of recrudescent malignant hyperthermia is allegedly associated with increased muscle membrane permeability, but in those patients reported, the free hemoglobin levels in the plasma have not been stated [*5*].

This patient's anesthetic induction and early course were entirely uneventful except for the

subtle clue of inadequate relaxation following the initial dose of succinylcholine. His clinical picture was that of massive hemolysis (approximately one third of his red blood cell mass), refractory hyperkalemia, and unsuccessful cardiac resuscitation. The diagnosis of malignant hyperthermia is confirmed by the CPK value, 35 times normal within 20 min of the arrest, and almost a threefold further increase over the next 2½ h.

The diagnosis of malignant hyperthermia was considered during the resuscitation, but considered to be of low probability. Dantrolene was administered, but considering the massive hemolysis and hyperkalemia, would most probably have been ineffective in any dose. During retrospective review, the diagnosis of malignant hyperthermia was again considered and confirmed by determination of CPK levels in the saved blood samples.

We have been unable to find any other reports of malignant hyperthermia presenting first by hyperkalemic cardiac arrest, associated with massive hemolysis.

Conclusion

Lessons to be learned in investigating anesthetic deaths include: (1) save samples of blood drawn during resuscitative attempts for possible subsequent analysis, (2) consider malignant hyperthermia if young patients have *unexplained* death during anesthesia, and (3) if malignant hyperthermia is a possible cause of death, determine creatine phosphokinase levels on the available blood.

References

[1] Britt, B. A. and Kalow, W., "Malignant Hyperthermia: Aetiology Unknown!," *Canadian Anaesthetists' Society Journal*, Vol. 17, No. 4, July 1970, pp. 316-330.

[2] Britt, B. A., "Malignant Hyperthermia Alert," *Bulletin No. 6*, Norwich Eaton Pharmaceuticals, Inc., May 1983.

[3] Zsigmond, E. K., Penner, J., and Kothary, S. P., "Normal Erythrocyte Fragility and Abnormal Platelet Aggregation in MH Families: A Pilot Study," in *2nd International Symposium on Malignant Hyperthermia*, J. A. Aldrete and B. A. Britt, Eds., Grune and Stratton, New York, 1978, pp. 213-219.

[4] Heffron, J. J. A. and Mitchell, G., "Influence of pH, Temperature, Halothane and Its Metabolites on Osmotic Fragility of Erythrocytes of Malignant Hyperthermia-Susceptible and Resistant Pigs," *British Journal of Anaesthesia*, Vol. 53, 1981, pp. 499-504.

[5] Mathieu, A., Bogosian, A. J., Ryan, J. F., Crone, R. K., and Crocker, D., "Recrudescence after Survival of an Initial Episode of Malignant Hyperthermia," *Anesthesiology*, Vol. 51, No. 5, Nov. 1979, pp. 454-455.

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