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Puzzles in Malignant Hyperthermia

THE DISTURBING REPORT by Fitzgibbons[1] in this issue of ANESTHESIOLOGY contradicts some widely held beliefs about malignant hyperthermia (MH). Malignant hyperthermia occurred in a susceptible patient pretreated with dantrolene who also was not given any agent that triggers MH. Why?

First, was this episode really MH? The primary episode in the operating room involved an increase in oxygen consumption, as evidenced by an increased Pa_{CO_2} despite an increase in minute ventilation. Anaerobic metabolism also increased, as evidenced by a base excess that remained zero despite administration of bicarbonate, 50 mEq/30 kg. The recurrence of MH in the recovery room probably involved an increase in oxygen consumption, since Pa_{CO_2} increased from 23 to 67 torr within a 40-minute period during initially supported and then spontaneous ventilation. Base excess remained zero, indicating no metabolic acidosis. Both episodes reverted promptly with therapy, the former in response to various drugs plus intravenously administered dantrolene, and the latter in response to dantrolene alone. The diagnosis of MH does seem incontrovertible.

Second, why did MH occur at all? Some of the "safe" anesthetic agents and muscle relaxants have been incriminated as weak triggers in humans,[2-4] but, overall, they have been used repeatedly and safely in known susceptible patients.[5] While preoperative stress coincident with inadequate sedation[6] or intraoperative stress associated with light anesthesia[7] might be a factor in causing an episode of MH, it is likely that neither of these was present in the Fitzgibbons case.

However, none of this begins to explain why MH can occur in the absence of exposure to potent volatile agents or succinylcholine. In genetically susceptible pigs, the mechanism seems to be related to acetylcholine release and nonspecific sympathetic-mediated alterations in blood flow and heat loss.[8] These factors are generally well controlled during anesthesia and skeletal muscle relaxation with non-triggering agents. We have observed only a few episodes of porcine MH during such anesthesia. These have occurred only during light levels of anesthesia and incomplete relaxation of skeletal muscle. Whether these data obtained from swine apply to man is difficult to ascertain.

The third problem with the Fitzgibbons report is that orally administered dantrolene taken preoperatively failed to prevent MH. The presence of subjective muscle weakness indicates that the dantrolene had been absorbed and was affecting skeletal muscle. Perhaps the magnitude of the effect was inadequate for protection, and the subsequent intravenously administered increment of dantrolene, 1 mg/kg, achieved the necessary level.

The ultimate effectiveness of dantrolene given alone again[9] suggests that the cardiac manifestations of MH are secondary to sympathetic stimulation.[10] This further implies that otherwise unexplained myocardial abnormalities in these patients[11] or reputed episodes of sudden death unrelated to anesthesia[12] may result from repeated intermittent sympathetic hyperactivity secondary to episodes of muscle hypermetabolism occurring during ordinary activities. Such episodes of MH in awake humanbeings are probably rare events in an already rare population.[9]

Combining the clinical observations and experimental data, we currently recommend that susceptible patients who need anesthesia should receive:

1) Dantrolene, 4 mg/kg, given orally in three or four divided doses in the 24-hour period before anes-

thesia. This avoids the marked muscle weakness that occurs with larger doses[13] and yet exceeds by a comfortable margin the average effective intravenous therapeutic dose of 2.5 mg/kg.* Because muscle effects are apparent within several hours,[9] a longer period of pretreatment seems unnecessary. Flewellen and Nelson found in porcine MH that profound weakness is necessary before dantrolene protects against triggers of MH.[14] Confirmation in man is understandably lacking; therefore, susceptible patients should always be given non-triggering agents.

2) Comfortable to heavy preanesthetic medication[6] with tranquilizers (no phenothiazines),[15] barbiturates, and/or opiates. Atropine should be given intravenously in small doses only as needed.

3) Ester local anesthetic agents for regional block. Amide agents are probably also safe in small amounts, *e.g.*, for dental use, when it is unlikely that high blood levels could result.[16]

4) Nitrous oxide–barbiturate–opiate–tranquilizer–pancuronium for general anesthesia. Combinations of these agents have been used most frequently in the management of susceptible patients.[5,16]

5) Adequate monitoring.[16] This varies with the complexity of the operative procedure and need not arbitrarily include an arterial catheter. However, the anesthesiologist must anticipate even the remote possibility of a need for blood-gas analysis.

An episode of MH can be violent and life-threatening, and it necessitates immediate appropriate action.[16] Until we understand the mechanism of human MH triggering, no anesthetic regimen can guarantee safety, as illustrated by the Fitzgibbons case.

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