Ketamine Does Not Trigger Malignant Hyperthermia in Susceptible Swine

Mark Dershwitz, MD, PhD, Frank A. Sréter, MD, PhD, and John F. Ryan, MD

DERSHWITZ M, SRÉTER FA, RYAN JF. Ketamine does not trigger malignant hyperthermia in susceptible swine. Anesth Analg 1989;69:501–3.

The use of ketamine in individuals susceptible to malignant hyperthermia (MH) is controversial. We describe our experience with ketamine used for induction and/or maintenance of anesthesia in our herd of swine inbred for susceptibility to MH. A total of 76 MH-susceptible swine were given a total of 112 general anesthetics using ketamine as the induction drug. In 34 of these anesthetics, anesthesia was also maintained with ketamine. Signs of MH did not develop in response to ketamine in any of the pigs.

Key Words: HYPERTHERMIA, MALIGNANT. ANESTHETICS, INTRAVENOUS—ketamine.

In recent years, the list of anesthetics to be avoided in patients suceptible to malignant hyperthermia (MH) has been shrinking (1). Many of the drugs used in anesthesia, including lidocaine, curare, nitrous oxide (N_2O), and epinephrine, initially implicated as triggers of MH episodes, have now been recognized to be safe for the MH individual. Ketamine may still be considered a controversial anesthetic; it is a drug that is not routinely used with the MH-susceptible patient (2). The concern regarding the use of ketamine in MH may stem from its stimulatory effects on the sympathetic nervous system, which cause an increase in circulating catecholamine levels. While elevated blood levels of catecholamines accompany an MH episode, the infusion of catecholamines does not, by itself, trigger MH (3).

Although we have routinely employed ketamine via the intramuscular route as an induction anesthetic in our work with MH-susceptible swine, we have not experienced an untoward reaction to the drug. We describe here our experience with a total of 76 MH-susceptible pigs given 112 general anesthetics using ketamine as the induction drug. In 34 of the anesthetics, ketamine was also used for maintenance of anesthesia.

Methods

The study was approved by the Subcommittee on Animal Care of the Massachusetts General Hospital. A herd of Pietrain pigs, inbred for susceptibility to MH, was maintained at the research farm of the Boston Biomedical Research Institute and fed commercial pig chow ad libitum. Offspring of sows and boars known to be susceptible to MH were weaned at age 6–8 weeks. For determination of MH susceptibility, the following procedure was employed. The pig was given ketamine, 10 mg/kg, via an intramuscular injection in the rump. After approximately 10 min, a 22–24 gauge Teflon intravenous catheter was inserted into an ear vein without response from the pig, a normal saline infusion begun, and electrocardiogram (ECG) leads applied. The pig was then given 2% halothane and 67% N_2O in oxygen (O_2) by an anesthesia face mask, allowed to breathe spontaneously, and observed for signs of MH. The diagnosis of MH was made according to criteria previously described by Gronert and Theye (4).

Once an episode of MH occurred, the pig was given dantrolene, 1 mg/kg intravenously. This dose of dantrolene was repeated until the hind limbs were supple and vital signs had returned to normal values. The pigs were allowed to recover and, when awake, were returned to the farm.

Supported in part by NIH National Research Service Award GM11656 (to MD) and Center Grant GM15904 (FAS and JFR).

Received from the Department of Anaesthesia, Massachusetts General Hospital and Harvard Medical School, and the Department of Muscle Research, Boston Biomedical Research Institute, Boston, Massachusetts. Accepted for publication May 9, 1989.

Address correspondence and reprint requests to Dr. Mark Dershwitz, Dept. of Anaesthesia, Massachusetts General Hospital, Boston, MA 02114.

Table 1. Responses of Swine Inbred for Susceptibility to MH to the Administration of Ketamine, Halothane, and Succinylcholine

Number of Inbred Pigs Tested for MH Susceptibility	78
Number of Halothane-positive Pigs	36 (46%)
Number of Halothane + Succinylcholine-positive Pigs	40 (51%)
Total Number of MH-susceptible Pigs	76 (97%)
Number of Pigs Nonresponsive to Halothane + Succinylcholine Challenge	2 (3%)
Number of Episodes of General Anesthesia Induced with Ketamine Administered to MH-susceptible Pigs	112
Number of Episodes of MH Occurring after Ketamine But before Halothane or Succinylcholine	0
Number of Episodes of General Anesthesia Induced and Maintained with Ketamine Administered to MH-susceptible Pigs	34
Number of Episodes of MH Occurring during Ketamine Anesthesia	0

We have employed MH pigs in 34 experiments in which the pigs' survival at the end of the experimental procedure—e.g., for obtaining blood samples, muscle biopsies, and electrophysiologic measurements—was desirable and an episode of MH undesirable. For such experiments, the pigs were administered ketamine intramuscularly, as described above, and given incremental doses of ketamine, 0.5 mg/kg intravenously, as needed to maintain cooperation, while breathing room air.

Results

Table 1 summarizes our experience with our inbred MH herd. We tested a total of 78 pigs for susceptibility to MH, and found that in 36 (46%) an MH episode was triggered when they breathed halothane alone, while another 40 (51%) required succinylcholine in addition to halothane in order to cause an episode of MH. All of the halothane-responders and 38 of the halothane-plus-succinylcholine-responders survived their MH episode. The two pigs that died after succinylcholine challenge suffered cardiac arrest and the absence of electrical activity on ECG shortly after succinylcholine administration, presumably as a result of succinylcholine-induced hyperkalemia. Two pigs failed to develop signs of MH after 15 min of halothane administration followed by succinylcholine (1 mg/kg).

None of the pigs developed any signs of MH in the interval between the administration of ketamine and halothane. In addition, 34 procedures were performed on known MH-susceptible pigs under ketamine anesthesia, again without any signs of MH.

Discussion

A number of literature reports have linked ketamine with the production of an MH episode. Mogensen et al. described MH episodes in two patients in whom anesthesia was induced with ketamine and who subsequently received also halothane and succinylcholine (5). Both patients had received halothane and succinylcholine during earlier anesthetics without developing MH, and the authors considered that the ketamine had been the agent to trigger the episodes. It is more likely that these case reports reflect the often observed phenomenon of an MH-susceptible individual in whom MH was not triggered during the first exposure to a known triggering agent.

Roervik and Stovner reported a child who developed fever and elevated creatine phosphokinase (CPK) levels after two separate operations for squint (6). She had been given halothane and succinylcholine for the first operation and had developed prolonged jaw rigidity after the administration of succinylcholine. Her serum CPK level on the first postoperative day was 1240 U/L (normal 15–78 U/L). The second operation was performed 6 months after the first, and she was given ketamine for induction and maintenance of anesthesia. At the end of the procedure, arterial blood gas data included a pH of 7.28, Pco_2 of 36 mm Hg, Po_2 of 145 mm Hg, and base excess = −9.3 mmol/L. Her serum CPK level was 67 U/L at the time of induction and 840 U/L on the second postoperative day. While the diagnosis of MH in this patient is likely, the causal effect of ketamine is unknown.

Lees and Macnamara described a child with Lowe's (oculocerebralrenal) syndrome who was given ketamine anesthesia for a muscle biopsy (7). He developed a tonic-clonic seizure and a fever to 39.8°, but no rigidity. The increase in temperature probably represents a postictal fever, not MH.

Cardan et al. presented a case that they described as MH following ketamine anesthesia (8). The patient had been given epidural anesthesia for an appendectomy. Because the epidural was ineffective, general anesthesia was induced with ketamine followed by succinylcholine. She subsequently developed a fever of 41.5°. Plasma CPK levels peaked on the second postoperative day at 1140 U/L (normal < 50 U/L). The use of succinylcholine and the expected febrile response to appendicitis obscure the diagnosis of the causes of fever in this patient.

Rasore-Quartino et al. related a fatal episode of MH in a child who underwent muscle biopsy for diagnosis of myopathy (9). His illness was characterized by hypotonia, ptosis, inability to ambulate, and

the absence of muscular hypertrophy. Because an intravenous catheter could not be inserted, the patient was premedicated with atropine and meperidine and then given ketamine for the surgery, all intramuscularly. The patient did not awaken; he developed fever, metabolic acidosis (lowest pH was 7.15, 44 hr postoperatively), and elevated CPK levels (4700 U/L, normal 10–70 U/L). Initially he was hypotonic, but developed muscle hypertonia 29 hr postoperatively. He died 60 hr after surgery. The delay in the development of rigidity, in combination with the reported metabolic abnormalities and associated coma, suggests that the rigidity was a result of some unidentified central nervous system (CNS) or metabolic pathology.

No other cases of MH linked to ketamine usage have been reported. Considering the frequency with which it is applied in anesthesia and the prevalence of susceptibility to MH, if ketamine were capable of acting as a trigger for MH, it is most likely that such cases would have been described by now.

There are also reports of the safe use of ketamine in potentially MH-susceptible individuals. Wadhwa and Tantisira described a patient with an elevated resting CPK level and a brother who had died from MH. The patient was given ketamine anesthesia for a parotidectomy (10). Meltzer et al. showed that ketamine does not increase CPK levels in normal human volunteers (11), while Harrison et al. reported that in five MH-susceptible pigs, where MH had been triggered with halothane, anesthesia had been safely induced with ketamine (12).

Our data support the contention that ketamine is a safe anesthetic agent in the MH-susceptible individual. The pig is an excellent model for human MH, and drugs shown to be capable of triggering MH in the pig have done so in susceptible humans. The two MH-susceptible pigs in our series who did not develop MH following exposure to halothane and succinylcholine exemplify the similarity between pigs and humans in that MH does not develop in the presence of MH susceptibility during every exposure to MH-triggering drugs.

In the literature reviewed above, only the case reported by Roervik and Stovner describes an episode that was likely to be MH and in which no other causative anesthetic is apparent. Because of the age of this report, it is impossible to determine whether there were complicating factors present, such as residual halothane in the anesthetic system. There are two reports, however, of known MH-susceptible patients who were pretreated with dantrolene and yet experienced MH episodes under general anesthesia, even though no known trigger had been administered (13,14).

When ketamine is the agent of choice for a particular procedure in an MH-susceptible patient, it may be used. Since even the pretreatment with dantrolene and the use of nontriggering drugs has been associated with the development of MH, the anesthesiologist must be as vigilant as possible in monitoring the patient. The use of end-tidal carbon dioxide (15,16) and oxygen saturation monitoring is especially valuable. The anesthesiologist must be alert to the rare but possible occurrence of MH and ensure the immediate availability of dantrolene for MH-susceptible patients.

We are grateful to Norwich-Eaton Pharmaceuticals for providing the dantrolene and to Messrs. Lawrence Murphy and Robert Jeannotte for their assistance in raising the MH-susceptible swine.

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