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Prevention of Porcine Malignant Hyperthermia by Epidural Block

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Malignant hyperthermia in susceptible swine was completely blocked by epidural anesthesia with lidocaine. Incomplete epidural anesthesia modified the disease but did not prevent it. These studies indicate the importance of the nervous system in the triggering of malignant hyperthermia. (Key words: Hyperthermia, malignant; Anesthetic technique, peridural.)

MALIGNANT HYPERTHERMIA (MH) in both man[1,2] and swine[3] has been well described. Much of the experimental work on MH has tended to focus on the role of skeletal muscle in this disease,[4] with little regard for the effect of the central nervous system. However, we have been impressed by the rapid onset of skeletal-muscle rigidity in unpremedicated susceptible swine and its apparent relationship to the excitement phase of anesthesia. Also, we have noticed that in the same pig, MH may be more easily triggered when the pig is excited prior to induction of anesthesia than when it is calm. These observations led us to consider the role of the central nervous system in the initiation of MH.

We have been unable to find any report of MH in man occurring during epidural anesthesia. Since lumbosacral epidural anesthesia is a recognized technique in swine, we used this approach to produce nervomuscular blockade prior to induction of MH by general anesthesia. This report describes our findings in susceptible swine when halothane was administered with and without epidural anesthesia.

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Methods

Eleven susceptible swine were used. Each was anesthetized at least twice. The swine were maintained in a controlled environment and fed a standard swine diet and water *ad lib.* Susceptibility to MH was confirmed in all unpremedicated swine by administration of halothane (vaporized in a Copper Kettle) in oxygen by face mask, using a Fink valve in a nonrebreathing system. For identification of the disease, high concentrations of halothane (4 to 10 per cent) were used as tolerated for induction of anesthesia. This exposure to halothane served as the initial control anesthesia for each pig and was designated Control I. Since each pig served as its own control, it received the same concentration for each subsequent anesthetization as it had received for identification. Following induction, the concentration of halothane was reduced to 1 to 1.5 per cent for maintenance of anesthesia.

Malignant hyperthermia was identified by the onset of extensor rigidity and increase in rectal temperature subsequent to induction of anesthesia with halothane. Anesthesia was discontinued shortly after MH was identified and the pig allowed to recover. If rectal temperature continued to increase 5 minutes after termination of halothane administration, external cooling, hyperventilation and sodium bicarbonate, iv, were given to aid recovery.

GROUP I

Group I, three male and three female swine, consisted of five purebred Poland China and one crossbred swine, ranging in weight from 17 to 136 kg and in age from 2 to 15 months. After the first exposure (Control I), a recovery period of at least two weeks was allowed before the swine were again

TABLE 1. Time of Halothane Administration to Susceptible Swine

	Group I		Group II	
	Pig	Time (Min)	Pig	Time (Min)
Control I	35	2	6	3
	0	2	9	2
	65	3	1	6
	4	3	12	5
	61	5	3	2
	81	13		
Mean ± SD		4.6 ± 4.2		3.6 ± 1.8
Epidural (with halothane)	35	5	6	15
	0	10	9	7
	65	12	1	3
	4	14	12	15
	61	28	3	1
	81	48		
Mean ± SD		19.5 ± 16		8.2 ± 6.6
Control II	0	4		
	4	9		
	61	7		
	81	5		
Mean ± SD		6.3 ± 2.2		

exposed to anesthesia. Each pig was then restrained with a snout-holder. The skin over the lumbosacral region was clipped, cleaned, and infiltrated with 2 ml 2 per cent lidocaine. A 0.036-inch-diameter vinyl catheter was inserted several centimeters into the lumbosacral epidural space through a 2–4-inch 17-gauge thin-wall needle. After the needle was withdrawn, 2 per cent lidocaine was injected into the catheter to produce continuous epidural anesthesia. The amounts of lidocaine used ranged from 2 to 3 mg/kg (mean 2.8 ± 0.4 mg/kg). Epidural anesthesia was considered good if motor activity of the hind limbs was totally blocked. In one of those pigs, the block also extended to give a partial block of the forelegs. Rectal temperature was monitored throughout the experiment. As soon as the block was complete, halothane anesthesia was started. After induction, the halothane concentration was reduced and administration continued for periods as long as 48 minutes. In each case, cessation of anesthesia was an arbitrary decision of the anesthetist. Each animal was allowed at least two weeks to recover from anesthesia and then again exposed to halothane alone (Control II), without epidural anesthesia. One pig in this group became pregnant (table 1, pig 65), and one died from an anesthetic accident unrelated to the experiment (table 1, pig 35) so these two did not receive halothane again after the epidural block with halothane anesthesia (table 1).

Two of these swine had an incomplete epidural block on one occasion each. In both swine, there was partial motor paralysis of one hind leg and good block of the other. These attempts at epidural block were followed by the administration of halothane. These animals were then allowed to recover, and the epidural anesthesia was repeated at least two weeks later, at which time a good block was obtained.

GROUP II

Group II consisted of four crossbred (same litter) and one Poland China swine, ranging in weight from 9 to 110 kg and in age from 2 to 15 months (four female and one male). These animals were handled as Group I, with the following exceptions. In all five, problems were encountered with the administration of the epidural anesthesia, and an incomplete block was obtained prior to the administration of halothane. However, there was evidence of some motor block in all animals. Since the aim of the experiment did not allow use of premedication, problems were encountered in restraint of the swine for placement of the epidural catheter, especially in the crossbred swine, which tended to be less docile than the Poland China. The difficulties encountered in obtaining good epidural anesthesia in these swine are reflected in a much higher concentration of lidocaine administered (9.25 ± 7.5 mg/kg).

Results

GROUP I

The data for this group are listed in table 1 and figure 1. Brief exposure of unpremedicated susceptible swine to halothane resulted in rapid development of muscular rigidity and an increase in rectal temperature (Con-

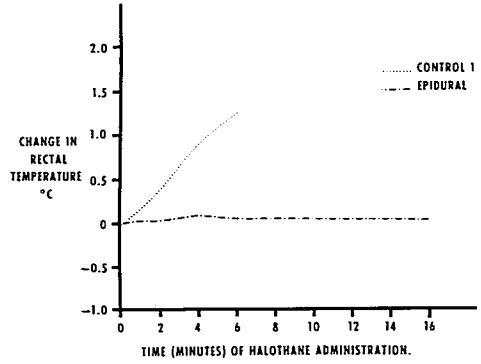

FIG. 1. Change in rectal temperatures in Group I.

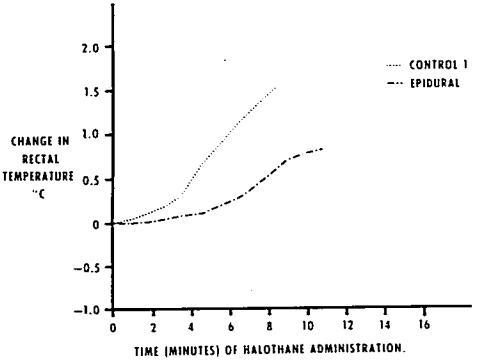

FIG. 2. Change in rectal temperatures in Group II.

trol I, fig. 1). Within two minutes the syndrome was obvious, with marked muscle rigidity in all extremities and increasing temperature. Shortly thereafter, the anesthetic was arbitrarily discontinued to ensure survival of the animals.

The effects of the epidural block were dramatic. Although forelimb extensor rigidity occurred as rapidly with halothane as during both control exposures, the hind limbs remained totally relaxed. In addition, there was no evidence of rising body temperature (fig. 1). The change in rectal temperature was significantly ($P < .001$) less in those animals receiving epidural anesthesia. The pig in which epidural block affected the forelegs also had complete relaxation of the right forelimb that had motor blockade, while the left forelimb, which was not totally blocked, became rigid.

The two pigs of this group that had inadequate epidural anesthesia developed a pattern intermediate between their control anesthetizations and their experimental anesthetizations with complete epidural block. Their average exposure time was 4.5 minutes. Again, their forelegs became rigid as in the control experiments. However, there

was a slight delay in the occurrence of rigidity in the hind limbs. Both these pigs developed MH.

Group II

The pattern seen in this group of swine was similar to the pattern seen in Group I (table 1). In all of these swine epidural anesthesia was incomplete. When halothane was administered, rigidity was initially seen in the forelegs and later in the hind legs. In one pig, which had complete block of only one hind leg, rigidity developed in the incompletely blocked leg only and not in the totally blocked leg. The epidural blocks did not prevent MH. Four of these swine died from MH. In the fifth animal, rigidity was present in all four legs, but halothane was discontinued immediately, and the pig recovered from the MH. Although the rate of temperature increase was faster in the control exposure than when epidural block was attempted (fig. 2), this difference was not statistically significant.

Discussion

The development of MH in Poland China swine in which anesthesia was induced with thiopental and subsequently maintained with halothane has been documented by Jones *et al.*[3] The sequence of events of this syndrome consists of gradual onset of skeletal-muscle rigidity, usually associated with tachycardia, hypercarbia, and metabolic acidosis followed by hyperpyrexia. When inhalation anesthetic agents such as halothane are administered to susceptible swine in the absence of premedicants or intravenous anesthetics, the speed of onset of skeletal muscle rigidity is greatly enhanced, usually occurring first in the hind limbs. This rigidity is often coincident with the excitement stage of induction. Body temperature starts to rise shortly after rigidity is observed, hyperventilation and tachycardia are frequently present, and the mortality rate rises rapidly if the general anesthetic is continued.

In the swine used in this study, rapid onset of skeletal-muscle rigidity in all four limbs was observed shortly after beginning induction of halothane anesthesia. All these swine survived this initial challenge. The second control was to ensure that the disease did not change with age and increasing body weight. As can be seen from the data, only slight prolongation of the halothane administration in the second control exposure caused high mortality. The adverse effect of prolonging the halothane anesthesia has been observed in our other experiments also. Because of this, we were reluctant to prolong general anesthesia during the first few experiments with epidural anesthesia. We arbitrarily terminated anesthesia after observing the beneficial effect of the epidural block. In subsequent experiments, we extended the duration of anesthesia to 48 minutes without difficulty.

The data demonstrate that intact pathways between the spinal cord and skeletal muscle are necessary for development of porcine MH. When blockade was complete, the muscle remained unresponsive. Thus, while skeletal muscle is probably the main site of aberrant metabolism and energy production in MH, it does not react to halothane *in vivo* after epidural anesthesia. This was best seen in Group I. In the presence of a complete block of the hind limb, rigidity typical of MH was observed in the forelimbs only, while the hind limbs remained relaxed. In addition, the pig in which the epidural block extended to the forelegs developed rigidity in the unblocked leg, while the blocked leg remained relaxed. Although not as dramatic, the same effect was seen with incomplete block. Onset of rigidity in the hind legs was delayed and occurred in the less-well-blocked extremity first.

It is also clear that heat production was curtailed in the presence of epidural anesthesia. Although the effect on the unblocked half of the body was typical of MH, the Group I pigs remained normothermic or slightly hypothermic. Assuming the triggered part of the body was producing excess heat, as we suspect, the pig was able to compensate by increasing heat loss. A likely cause could be vasodilatation produced by the epidural block, which enhanced heat loss by conduction and radiation. Another explanation could be decreased heat production by the blocked segment owing to muscle inactivity, which compensated for increased heat

production, thus maintaining normothermia. Although the hyperventilation that often occurs with MH can be a source of heat loss, it did not occur in these pigs. Since sweating is not a normal source of heat loss in pigs, it probably was not a factor in this study.

It is interesting that we were able to block MH with lidocaine epidural anesthesia, since lidocaine is said to be contraindicated in susceptible patients.[5] We do not feel that our results were brought about by a systemic effect of lidocaine, because rigidity still occurred in the unblocked muscles. On the other hand, it may be that the much higher dosage of lidocaine used in Group II, where incomplete epidural blocks were obtained, contributed to the deaths of four of these swine.

In summary, this study demonstrates the need for an intact nervous system for initiation of porcine MH. Since unblocked segments developed clinical MH, the suppression seen was not a systemic effect of lidocaine. Newer evidence in our laboratory indicates that MH occurs with transection of the spinal cord, but at a delayed rate, eliminating the necessity of intact pathways from the brain for the onset of MH. It appears that local neural mechanisms, possibly a reflex, are essential for the disease to occur.

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Drugs and Their Use

GLIPIZIDE A new antidiabetic agent of the sulfonlurea type, glipizide, is undergoing clinical trials in Europe. ^{14}C-labelled glipizide was administered as a 5-mg oral dose to five healthy men and as a 1-mg intravenous dose to three healthy men. One hour after administration the subjects began engaging in their usual occupations. After the first four hours they ingested a normal diet. The drug was almost completely absorbed from the gastrointestinal tract within two hours. Sixty-five per cent of the orally or intravenously administered drug was eliminated in the urine as glipizide and its metabolites in the first 24 hours. Almost no additional urinary elimination occurred during the next three days. The serum insulin concentration increased fourfold 10 minutes after intravenous and one hour after oral administration of glipizide. The increased insulin levels lasted three hours after oral glipizide and less than one hour after intravenous glipizide. An increase in serum insulin that occurred six hours after glipizide was thought to have resulted from food intake. The mean blood glucose concentration of three subjects who received 1 mg intravenously decreased from 62 to 37 mg/100 ml in 30 minutes. Blood glucose changes following oral glipizide were not marked.

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