

Sevoflurane Triggers Malignant Hyperthermia in Swine

To the Editor:—Potent inhalational anesthetics have been shown to trigger malignant hyperthermia (MH) in susceptible (MHS) swine,^{1,2} and are not recommended for use in human subjects susceptible to the condition.^{3,4} A new volatile anesthetic, fluoromethyl hexafluoroisopropyl ether (Sevoflurane; Travenol Laboratories, Morton Grove, IL), has the favorable pharmacologic properties of rapid induction, rapid emergence, absence of cardiac arrhythmias, and lack of explosive hazard,^{5,6} but its ability to trigger MH in susceptible patients is unknown. We report the results of our investigation on sevoflurane administration to five purebred Poland China swine, previously screened for high susceptibility to MH by standard halothane challenge.

An MHS pig was handled and restrained in a routine manner while nitrous oxide (80 per cent) and oxygen (20 per cent) were administered by mask. After 60 min, no evidence of MH was observed in response to the stress of restraining and masking. Several days later, administration to this pig of sevoflurane by mask, 4–6 per cent in oxygen, produced limb rigidity within 6 min; all four limbs were rigid by 11 min and the pig died after bradycardia and cardiac arrest and before resuscitation could be initiated.

A second pig given 6 per cent sevoflurane in oxygen by mask developed limb rigidity and apnea within 8 min. The pig was intubated and mechanically ventilated. Sevoflurane was discontinued at 15 min; arterial blood-gas values were: P_{O_2} 195 torr; P_{CO_2} 118 torr; pH 6.79. Administration of dantrolene, 2 mg/kg, intravenous (iv), and bicarbonate, 2 mEq/kg, iv, at this time and again 15 min later resulted in complete recovery, with the pig standing and awake at 53 min from the initial sevoflurane administration.

In order to obtain cardiovascular as well as metabolic data in three other MHS swine, anesthesia was induced with thiopental, 10 to 15 mg/kg, iv. The pigs were given atropine, 0.4 mg/kg, iv, intubated, and ventilated with 70 per cent nitrous oxide and 30 per cent oxygen while catheters were inserted into the femoral artery and vein and into the pulmonary artery (Swan-Ganz). In two of these pigs, supplemental doses, 100 mg, iv, of thiopental were given to complete catheter placement. The third pig

received local anesthetic, 2 per cent lidocaine, at the cut-down site in place of thiopental supplements. The two pigs given additional thiopental did not develop MH for the 60 min of observation. At this time, a bolus iv injection of succinylcholine, 3 mg/kg, resulted in instant rigidity in one pig and marked fasciculation and hypotension in the other. Both pigs developed fulminant MH after the succinylcholine injection. The two agents appeared to act synergistically, since the onset of MH was more rapid than that produced by succinylcholine alone.⁷

The third pig, which received no thiopental supplements, developed MH symptoms including acidosis (pH_a 7.03) and hypercapnia (89 torr), within 21 min of sevoflurane administration. All three pigs responded to MH therapy but recovery was prolonged over 24 hours.

Since sevoflurane triggered MH in three of five MHS swine, sevoflurane may be hazardous in susceptible patients.

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Questions Regarding a Time-dependent Increase in Sensitivity to *d*-Tubocurarine during Enflurane Anesthesia

To the Editor:—Stanski *et al.*¹ conclude that the sensitivity to *d*-tubocurarine (*d*Tc) increases during the course of enflurane anesthesia. I cannot accept this conclusion without requesting additional analysis of their data.

Their conclusion pivots on the assumption that steady state plasma concentrations of *d*Tc were achieved to the same extent in the halothane group (4 patients) and the enflurane group (5 patients). Did the authors analyze their steady state *d*Tc concentrations in the same manner as their linear analysis of their paralysis data shown in their figure 2? What were the results? Why does their two-compartment mammillary model, which they use to describe and analyze their pharmacokinetic data in their table 1 and figure 1, overestimate the *d*Tc concentrations be-

tween 50 and 160 min, and underestimate the concentrations thereafter? Is this a random error or an inherent bias of their model?

These questions become more relevant as we examine several dose response curves for these same drug combinations published previously by investigators from the same institution. The figure presented here (fig. 1) shows the data from three clinical studies of the maximum per cent twitch depression resulting from bolus doses of pancuronium or *d*Tc during halothane or enflurane anesthesia. The doses of pancuronium are multiplied by 10 to facilitate display on the same coordinates.

Curves B and C show the reduced doses of pancuronium required to produce similar degrees of paralysis during enflurane,² as compared to halo-

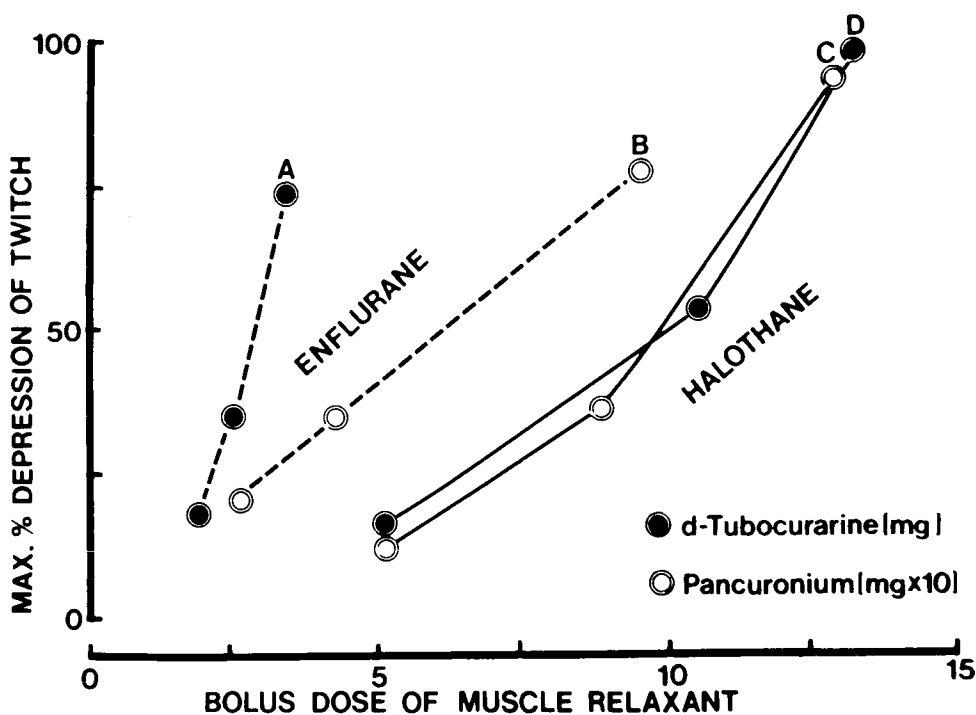


FIG. 1. The mean values of the maximum percent depression of twitch response following bolus doses of either *d*-tubocurarine (closed circles ●) or pancuronium (open circles ○) during either enflurane (broken lines ---) or halothane (solid lines —) anesthesia as described in previous studies.²⁻⁴