

## Decreasing Enflurane Concentrations and *d*-Tubocurarine Neuromuscular Blockade

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To study the effect of decreasing the concentration of enflurane on a combined enflurane-*d*-tubocurarine (*d*TC) neuromuscular blockade, six ASA class I or II patients were studied using a continuous infusion of *d*TC and a sequence of decreasing end-tidal concentrations of enflurane. A constant infusion of *d*TC and a 2.2 per cent end-tidal concentration of enflurane decreased twitch tension to 8 per cent of control. Maintaining this same infusion rate of *d*TC, but decreasing the end-tidal concentration of enflurane to 1.35 and 0.5 per cent, increased the twitch tension to 57 and 91 per cent of control, respectively. The authors conclude that the enflurane contribution to muscle relaxation dissipates in a dose-dependent manner as the end-tidal concentration of enflurane is reduced. This factor may provide additional safety for patients because the anesthetic produces a component of relaxation that is readily reversible with time without the use of acetylcholinesterase inhibitors. (Key words: Anesthetics, volatile; enflurane. Neuromuscular relaxants: *d*-tubocurarine.)

INHALED ANESTHETICS enhance the neuromuscular blockade of nondepolarizing relaxants in a dose-dependent manner.<sup>1</sup> Of the currently available inhaled anesthetics, enflurane is one of the most potent in augmenting the neuromuscular blockade from nondepolarizing neuromuscular blockers.<sup>2</sup> Presumably, elimination of an inhaled anesthetic should result in less neuromuscular blockade from a nondepolarizing muscle relaxant such as *d*-tubocurarine (*d*TC). The effect of eliminating the enflurane in reversing a combined enflurane-nondepolarizing muscle relaxant neuromuscular blockade has not been reported. This study was undertaken to quantitate the effect of decreasing the concentration of enflurane on a *d*TC-induced neuromuscular blockade.

### Method

Six adult surgical patients, ASA classification I or II, were studied intraoperatively. Informed consent was granted by each patient for participation in the study

which was approved according to the guidelines of the University of California San Francisco Committee on Human Research. The patients were undergoing either plastic or neurosurgical procedures. Their mean age was  $23.8 \pm 7.6$  years ( $\pm$ SD) and mean weight  $64.8 \pm 12.3$  kg.

One hour after administration of 10 mg diazepam orally, anesthesia was induced with 1-3 mg/kg thiopental and continued with increasing concentrations of enflurane in 60 per cent nitrous oxide and oxygen. Endotracheal intubation was accomplished without administration of muscle relaxants, although 4 per cent lidocaine, 4 ml, was sprayed into the trachea prior to intubation. Ventilation was controlled to maintain an end-tidal  $P_{CO_2}$  of 30-40 mmHg. Esophageal temperature was kept within 34.5-36.0° C.

A Grass S-44 stimulator was used to apply supra-maximal square wave pulses of 0.15-ms duration and 0.15 Hz to thin-walled 27-gauge needle electrodes placed one inch apart near the ulnar nerve at the wrist. The resultant thumb adduction was measured by a force displacement transducer (Grass FT-10) and recorded continuously on a polygraph. Control twitch tension was established after induction of anesthesia and before any muscle relaxants were administered or enflurane concentrations were increased to more than 1.2 per cent end-tidal.

When surgery began 30-45 min after induction of anesthesia, enflurane was increased to a 2.2 per cent end-tidal concentration. Simultaneously, a *d*TC infusion was begun and adjusted to produce a constant 10 per cent of control twitch tension as determined by at least 30 min of observation. The *d*TC infusion was continued at this rate for the remainder of the study. After one hour of 2.2 per cent end-tidal enflurane concentration and 30 min of unchanging twitch tension, the end-tidal enflurane concentration was decreased to 1.35 per cent. After one hour at 1.35 per cent end-tidal concentration, enflurane concentration was decreased to 0.5 per cent end-tidal where it was maintained for one hour. Small doses (100-300  $\mu$ g) of fentanyl were administered at 0.5 per cent end-tidal enflurane concentration to four patients to augment anesthesia. At the end of the hour at each enflurane dose level, a blood sample was obtained from the arm opposite that being used to administer *d*TC. Plasma concentrations of *d*TC were determined by radioimmunoassay.<sup>3</sup> The coefficient of variation of the as-

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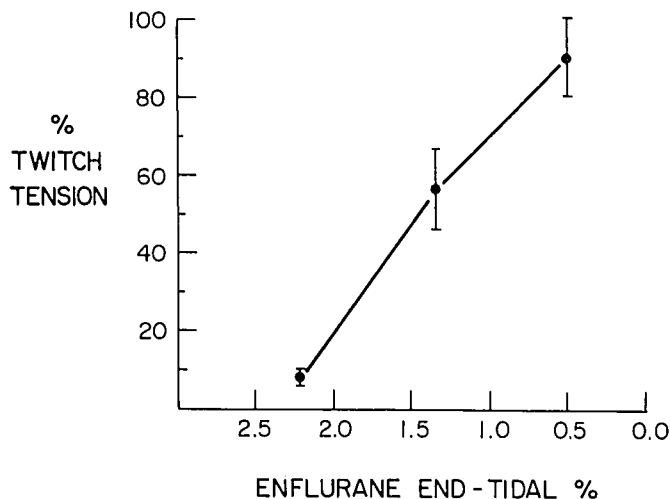


FIG. 1. Relationship between percentage of control twitch tension and enflurane end-tidal concentration during continuous infusion of  $dTC$ . Each point and vertical bracket represent mean  $\pm$  SD for six patients.

say at three different concentrations was 8 per cent, with a lower limit of sensitivity of 0.05  $\mu\text{g/ml}$ . End-tidal enflurane concentration and  $P_{\text{CO}_2}$  were measured continuously by mass spectrometry.

The data were evaluated by analysis of linear regression and by analysis of variance. Statistically significant differences were assumed at  $P < 0.05$ .

### Results

Each decrease in the end-tidal concentration of enflurane significantly lessened the magnitude of neuromuscular blockade (fig. 1). At the initial end-tidal concentration of 2.2 per cent, twitch tension was  $8 \pm 2$  per cent (mean  $\pm$  SD) of control. Reduction of enflurane to 1.35 per cent end-tidal concentration increased twitch tension to  $57 \pm 11$  per cent of control, and a further decrease of enflurane to 0.5 per cent end-tidal concentration resulted in a twitch tension of  $91 \pm 10$  per cent of control. The per cent twitch tension increased in a linear manner as the end-tidal concentration of enflurane was decreased. The regression equation for this data is  $Y = -49X + 118$ .

Serum  $dTC$  levels did not vary markedly during the study (fig. 2). At enflurane end-tidal concentrations of 2.2, 1.35, and 0.5 per cent the serum  $dTC$  concentrations did not differ significantly.

The mean times ( $\pm$ SD) from reduction of inspired enflurane concentration to the first perceptible (2 per cent) increase in twitch tension, and attainment of unchanging twitch tension (for at least 10 min) were  $1.6 \pm 0.5$  and  $41.3 \pm 11.2$  min, respectively.

### Discussion

Enflurane enhances the neuromuscular-blocking properties of nondepolarizing muscle relaxants. This effect is due partially to a change in the sensitivity of the neuromuscular junction to nondepolarizing relaxants caused by enflurane.<sup>4</sup> Our results indicate that elimination of approximately 1.8 per cent (1.0 MAC) of enflurane produced a mean increase in the twitch tension of 84 per cent of control, a greater than 90 per cent reversal of the initial depression of twitch tension. This reversal was not due to altered elimination of  $dTC$  since our experimental approach maintained constant serum  $dTC$  levels. By keeping enflurane end-tidal concentration below 2.5 per cent, we also avoided any depression of twitch tension by enflurane alone.<sup>5</sup>

Enflurane enhancement of nondepolarizing neuromuscular blockade increases about 9 per cent per hour.<sup>6</sup> We designed our study so that the change in twitch tension caused by sequential changes of enflurane end-tidal concentration would be opposite the decrease in twitch tension caused by the time-dependent increase in enflurane enhancement of  $dTC$  neuromuscular blockade.

There are limitations to extrapolating from our results to other clinical situations. We measured changes in twitch tension from changing enflurane end-tidal concentrations over a wide anesthetic dose range (1.8 per cent). The initial dose level, 2.2 per cent end-tidal concentration enflurane (with 60 per cent nitrous oxide) probably exceeds that used in most clinical situations. Thus, if the range of change of enflurane end-tidal concentration is smaller, or if the initial dose level is not as high as the one we used, it would be reasonable to expect a smaller reversal effect from the elimination of enflurane. Another limitation is the time required for the reversal effect. A time interval of 1.6 min from reduction of inspired enflurane concentration to the first 2 per cent increase in twitch tension is consistent with a rapid reduction in anesthetic concentration in the vessel-rich group of tissues, which include the brain and neuromuscular junction.<sup>7</sup> The time required to attain steady

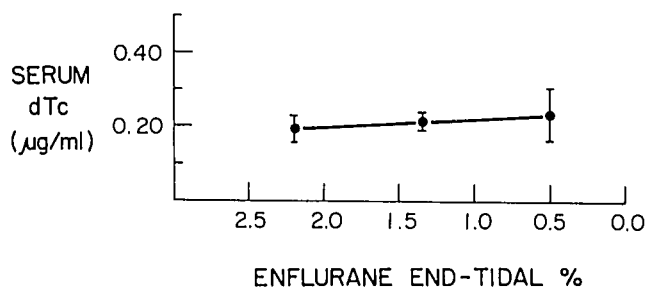


FIG. 2. Relationships between concentration of  $dTC$  in serum and enflurane end-tidal concentration during continuous infusion of  $dTC$ . Each point and vertical bracket represent mean  $\pm$  SD for six patients.

twitch tension, 41 min, correlates with the slower rate of anesthetic partial pressure reduction in many tissues, including muscle bulk.<sup>8</sup> These data indicate that the contribution of anesthetic elimination to reversal effect might require 30 to 60 min.

Our results indicate that the anesthetic contribution to muscle relaxation dissipates in a dose-dependent manner as the end-tidal concentration of enflurane is reduced. This factor may provide additional safety for patients whose anesthetic is one of the more potent muscle relaxant enhancing agents. First, these anesthetics reduce the dose of neuromuscular-blocking drugs necessary to achieve satisfactory muscle relaxation. Decreasing the administered dose of relaxants should decrease the probability of muscle relaxant associated complications, such as autonomic side effects or prolonged neuromuscular blockade that is difficult to reverse. Second, the anesthetics which significantly enhance nondepolarizing neuromuscular-blocking drugs provide a component of relaxation which is readily reversible with time without the use of acetylcholinesterase inhibitors.

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