Title : TIME DEPENDENT INCREASE IN SENSITIVITY TO dTC DURING ENFLURANE ANESTHESIA

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Introduction: This study compares the relative contribution of altered pharmacokinetics and pharmacodynamics to the potentiation[1,2] of d-tubocurarine (dTC) paralysis by enflurane, relative to an equipotent anesthetic concentration of halothane.

Methods: After obtaining informed consent, 7 healthy patients received enflurane 1.3-1.4% end-tidal with 70% N_2O while 7 patients received an equipotent anesthetic concentration of halothane 0.5-0.7% end-tidal with 70% N_2O. Anesthesia was induced with thiopental 4 mg/kg and the trachea intubated after giving succinylcholine 1 mg/kg IV. The force of thumb adduction produced by supramaximal ulnar nerve stimulation was measured. After induction, each patient received first a rapid infusion of dTC 16.8 µg/kg/min for 10 min, then a slower infusion of 1.2 µg/kg/min for 1-2 hours. This drug administration protocol resulted in a constant plasma concentration (Cp) within 60 min. Twenty to thirty blood samples were obtained from each patient and analyzed for dTC using a radioimmunoassay.

Data Analysis: Cp was fit to a 2 compartment pharmacokinetic model while the paralysis data was fit to a pharmacodynamic model[3] that derives the Cpss(50) or steady state plasma concentration that results in 50% paralysis - an estimate of neuromuscular junction sensitivity to dTC. The steady state paralysis resulting from the constant Cp was related to time with linear regression.

Results: There were no significant differences in the pharmacokinetics of dTC with the two anesthetics. A marked difference existed in the relationship of the steady state Cp to paralysis. With halothane, a constant Cp resulted in a constant degree of paralysis. With enflurane, in spite of a constant Cp, paralysis was not constant, rather linearly increased with time. The mean ± SD increase of paralysis was 9.0 ± 4.0% per hr. Representative patients are shown in fig 1 where steady state effect is the degree of paralysis. Analyzing only the first hr of anesthesia, the Cpss(50) of the enflurane group was 0.52 ± .13 µg/ml, significantly ($p = .05$) higher than the halothane Cpss(50) of 0.36 ± .04 µg/ml.

Discussion: With halothane, neuromuscular junction sensitivity to dTC remains constant for the duration of the anesthetic. With enflurane, there is a time dependent increase in neuromuscular junction sensitivity to dTC, apparently linear for the first 2-3 hrs of enflurane anesthesia. During the first hr of enflurane anesthesia, patients were actually less sensitive to dTC when compared to an equipotent anesthetic concentration of halothane. This differs from previous studies[1,2] where enflurane was found to potentiate dTC to a greater degree than halothane. Previous studies, however made no effort to control the time at which the study was performed, relative to the duration of enflurane anesthesia.

1. Fogdall R, Miller RD: Anesthesiology 42:173, 1975.
2. Lebowitz MH, et al: Anesthesiology 33:52, 1970.
3. Sheiner LB, et al: Clin Pharm Ther 25:358-371, 1979.

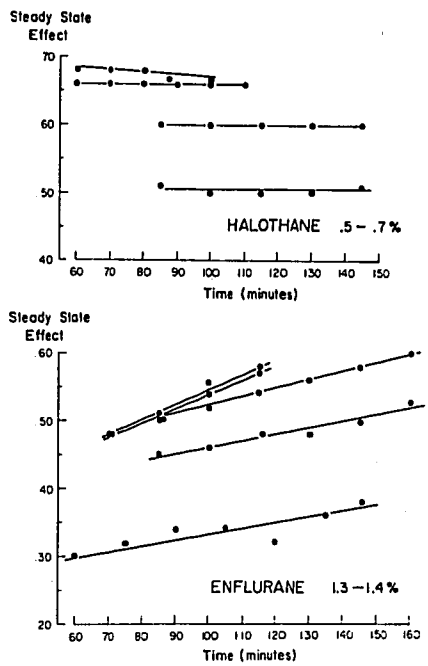

Figure 1