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Cimetidine and Succinylcholine: Potential Interaction and Effect on Neuromuscular Blockade in Man

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Cimetidine, a histamine H_2 receptor antagonist, is often used as a premedication to increase gastric fluid *p*H. Cimetidine decreases liver blood flow[1] and inhibits microsomal drug metabolism.[2] In addition, *in vitro* inhibition of pseudocholinesterase activity by cimetidine has been demonstrated.[3] Since succinylcholine is metabolized by pseudocholinesterase formed in the liver, a potential exists for interaction between cimetidine and succinylcholine. Indeed, one recent study has demonstrated a markedly prolonged time to recovery of neuromuscular function after succinylcholine in patients receiving cimetidine *versus* controls during halothane anesthesia.[4] This prospective study was designed to determine the effect of cimetidine premedication on the onset and duration of succinylcholine-induced neuromuscular blockade in patients anesthetized with nitrous oxide and fentanyl.

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METHODS AND MATERIALS

This study was approved by the institution's Human Investigation Committee, and written informed consent was obtained from each patient. The subjects were 20 adult patients, ASA physical status 1 or 2, scheduled for elective surgery. The patients were randomly allocated into two groups of 10 each. Group 1 patients received cimetidine 400 mg p.o. at bedtime and 400 mg p.o. 90 min prior to induction of anesthesia. Group 2 patients acted as controls and did not receive cimetidine. No other premedication was given.

After placement of an arterial blood pressure cuff and EKG electrodes, anesthesia was induced with thiopental 4–6 mg/kg iv and maintained with fentanyl 3–5 μg/kg iv and N_2O, 67% in O_2. Succinylcholine 1 mg/kg iv was administered 3 min after thiopental.

Neuromuscular blockade was monitored with a force transducer (Grass FT-10) which measured adductor pollicus twitch tension in response to supramaximal ulnar nerve stimulation at 0.15 Hz, delivered for a duration of 0.15 ms *via* 25-gauge needles placed subcutaneously. A strip chart continuously recorded the force transducer measurements from 2 min before to 50 min after succinylcholine administration.

Times to initial twitch depression and to maximal neuromuscular blockade and the magnitude of neuromuscular block were measured, as were times to 10, 25, 50, 75, and 90% recovery of initial twitch tension. Student's *t* test was used to test statistical significance between groups, with $P < 0.05$ considered significant.

TABLE 1. Characteristics of Succinylcholine-induced Neuromuscular Block and Recovery With and Without Cimetidine Premedication

	Maximal Block (%)	Time to Initial Twitch Height Depression (min)	Time to Maximal Block (min)	Time to Recovery (min)				
				10%	25%	50%	75%	90%
Cimetidine	98.0 ± 6.3	0.7 ± 0.3	1.4 ± 0.7	7 ± 2	8 ± 2	9 ± 3	10 ± 3	10 ± 3
Control	98.8 ± 3.8	0.7 ± 0.2	1.6 ± 0.4	7 ± 2	8 ± 2	9 ± 3	10 ± 3	11 ± 3

All values are mean ± SD.

RESULTS

Maximal neuromuscular block (twitch tension depression) and times to initial and maximal twitch depression for the two groups are shown in table 1. The administration of cimetidine had no effect on the neuromuscular blockade produced by succinylcholine. Times to various % recovery (10, 25, 50, 75, and 90%), a measure of duration of neuromuscular blockade, are also shown in table 1. There was no significant difference at any % recovery of initial twitch height from succinylcholine between patients given cimetidine and controls.

DISCUSSION

Cimetidine alters the effects of many drugs commonly used during anesthesia, including opioids,[5] benzodiazepines,[6] and beta adrenergic blockers.[1] Proposed mechanisms for cimetidine-induced changes are a reduction in liver blood flow[1] and inhibition of liver microsomal enzyme systems.[2]

After iv injection of a dose of succinylcholine, the drug is distributed throughout the extracellular space and to the neuromuscular junction. The plasma levels and the clinical effects of succinylcholine dissipate because of its breakdown in plasma. Pseudocholinesterase levels must be markedly reduced before any prolongation of succinylcholine-induced neuromuscular block occurs, and cimetidine should not have any effect on pseudocholinesterase produced before its administration. Thus, a prolonged effect of succinylcholine after cimetidine would not be expected unless cimetidine levels proved to be high enough to cause major reductions in pseudocholinesterase levels.

In a recent laboratory study,[3] it was found that cimetidine significantly inhibits pseudocholinesterase, the minimum cimetidine concentration producing a significant inhibition (50%) of pseudocholinesterase activity being 2.1×10^{-3} M. However, during chronic cimetidine treatment in man, serum drug levels are 0.5×10^{-5} to 2.0×10^{-5} M.[3] Based on *in vitro* analysis of pseudocholinesterase inhibition by cimetidine, one would predict less than 1% inhibition of pseudocholinesterase activity *in vivo* at these serum cimetidine concentrations.[3]

The predictions based on *in vitro* analysis, as noted above, are consistent with the findings of our study. In contrast to a previous study,[4] we found no differences in the duration of succinylcholine-induced neuromuscular blockade between cimetidine-treated and control groups. The reason for the discrepancy between our results and those reported previously[4] is unclear.

We used a force transduction method to monitor neuromuscular blockade; in contrast, the earlier study[4] employed the evoked EMG. Nevertheless, it is difficult to impute this difference in monitoring methodology as the reason why the previous study demonstrated a 150% increase in the duration of action of succinylcholine in patients given prior cimetidine, whereas ours showed no difference.

The earlier study[4] employed halothane/N_2O anesthesia while we used fentanyl/N_2O. Whether this is enough to explain the qualitative difference in results remains problematic. If it is sufficient, then one would have to infer either a cimetidine-halothane-succinylcholine interaction, or inhibition by fentanyl of a cimetidine-succinylcholine interaction, neither of which has been reported. We view neither of these as likely, and therefore suggest that cimetidine and succinylcholine do not interact to produce clinically relevant prolongation of succinylcholine-induced neuromuscular blockade.

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