Title: COMBINED H1 AND H2 RECEPTOR BLOCKADE ATTENUATES THE CARDIOVASCULAR EFFECTS OF HIGH DOSE ATRACURIUM FOR RAPID SEQUENCE ENDOTRACHEAL INTUBATION

Authors: M.P. Hasking, M.D., R.L. Lennon, M.D., and G.A. Gronert, M.D.

Affiliation: Departments of Anesthesiology, Mayo Clinic, Rochester, Minnesota 55905 and University of California, Davis, California 95616

Introduction. Large doses of atracurium (1.5 mg/kg IV, six times the ED95) have been reported to provide adequate conditions for endotracheal intubation without succinylcholine. However, this dose can result in significant hypotension, presumably secondary to mast cell degranulation and histamine release. Histamine receptor blockade has been reported to provide only partial modulation of this response (2). Pilot studies in rabbits (unpublished data), however, indicated that attenuation of systemic hypotension could be achieved if an adequate interval between administration of histamine receptor blockers and dosing of atracurium occurred.

Methods. Four groups of seven adult patients, ASA physical status Class I or II, were planned for study: a control group, an H1 blocked group (1 mg/kg diphenhydramine), an H2 blocked group (4 mg/kg cimetidine), and a combined H1 and H2 blocked group (diphenhydramine 1 mg/kg + cimetidine 4 mg/kg). All patients were monitored by V5 of the ECG, a pulse oximeter, blood pressure cuff, and intraarterial radial catheter zeroed at midcardiac level. Stimulating electrodes were placed over the ulnar nerve and a Grass S88 stimulator was used to deliver a supramaximal 0.2 ms square wave pulse at 0.1 Hz. Thumb adductor force was quantitated by a Grass FT10 transducer, with a resting load of 250-300 gm and recorded on a chart recorder. All patients were treated with the appropriate histamine receptor blocker(s) 30 min prior to administration of atracurium. Anesthesia was induced with thiopental and fentanyl and maintained with 70% N2O and 30% O2 with incremental doses of fentanyl. After a 10 min equilibration period, a baseline histamine level was drawn and atracurium 1.5 mg/kg IV was administered. Heart rate, blood pressure and thumb adductor force were continuously recorded by polygraph. Histamine levels were drawn at 2 and 5 min postinfusion. Histamine levels were determined by a double isotope enzymatic assay technique. Intravenous hemodynamic data were analyzed by ANOVA. Intergroup comparisons utilized a correlated t test, significance equals p < 0.05.

Results. Combined H1 and H2 receptor blockade resulted in minimal variation in mean arterial pressure (MAP) from time 0, decreasing 8 mmHg at 2 min and 7 mmHg at 3 min (Figure). This pattern differed significantly from the control group in which MAP decreased 30 mmHg at 2 min (p < 0.05) and 25 mmHg at 3 min (p < 0.05). Individual H1 receptor blockade resulted in moderate attenuation of changes in MAP not significantly different from control. H2 receptor blockade alone resulted in profound decreases in MAP in the first three patients and this study group was terminated.

Histamine levels correlated with hemodynamic changes, peaking at 2 min and declining slightly at 5 min (Table). Discussion. These results demonstrate that combined H1 and H2 receptor blockade significantly attenuates the hypotensive effect of high dose atracurium. An adequate interval between pretreatment with histamine receptor blockers and administration of atracurium was required to allow equilibration with tissue and obtain peak antagonist effect. This method has been demonstrated to exert an antagonist effect on recently discovered H3 receptors which act to auto-inhibit synthesis and release of histamine. This may account for enhanced histamine release and the profound decreases in MAP in the isolated H2 blockade group. Based on these observations: 1) we do not recommend high dose atracurium for rapid sequence induction in patients on chronic H2 receptor antagonist therapy; and 2) with combined H1 and H2 receptor blockade 30 minutes prior to induction, high dose atracurium may provide the anesthesiologist with another safe, effective alternative to succinylcholine.

References

Comparison of changes in mean arterial pressure in control, H1, H2, and combined H1 and H2 receptor blockade groups as a function of time after 1.5 mg/kg atracurium IV. * or + = p < 0.05

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Control 2 min</th>
<th>5 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>7</td>
<td>349 ± 52</td>
<td>6904 ± 1044*</td>
</tr>
<tr>
<td>H1 Blockade</td>
<td>7</td>
<td>381 ± 52</td>
<td>6594 ± 3244*</td>
</tr>
<tr>
<td>H2 Blockade</td>
<td>3</td>
<td>410 ± 34</td>
<td>10465 ± 2344*</td>
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<tr>
<td>Combined Blockade</td>
<td>7</td>
<td>671 ± 216</td>
<td>11060 ± 5612</td>
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</tbody>
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* p < 0.05 compared to control