Title: Atracurium: Clinical Strategies for Preventing Histamine Release and Attenuating the Hemodynamic Response

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Introduction: The histamine releasing property of tubocurarine occurs within the clinical dose range and a correlation between the level of plasma histamine and the extent of hypotension has been demonstrated.[1] Recently, it has been shown that atracurium will also release small amounts of histamine at the extreme upper end of the clinical dose range (0.6 mg/kg).[2] When plasma histamine is elevated to about 200 percent of control values, there is a clinically and statistically significant change in heart rate and arterial blood pressure. The present study was designed to examine clinical strategies for preventing histamine release by atracurium and attenuating the hemodynamic response.

Methods: Twenty-seven (ASA Class I or II) patients gave institutionally approved informed consent to the study and were assigned to one of three subgroups. Premedication consisted of 0.1 mg/kg morphine I.M. and 0.2 mg/kg diazepam orally. Anesthesia was induced with fentanyl 5 μg/kg and thiopental 5 mg/kg I.V. Heart rate (by tachograph), EKG and intra-arterial blood pressure were monitored continuously. After a stable 10 minute base line period, a single 5 second bolus of atracurium, 0.6 mg/kg was administered to patients in Group I. Patients in Group II received the same dose of atracurium slowly (over 75 seconds). The patients in Group III were pre-treated with cimetidine 4 mg/kg I.V. and chlorpheniramine 0.1 mg/kg I.V. 15 minutes before induction. They were then given atracurium 0.6 mg/kg as a 5 sec bolus. Maximum changes in heart rate and arterial pressure were recorded. Plasma samples were drawn immediately before injection of atracurium and at two and five minutes after injection. These samples were analyzed for histamine by an isotope radioenzymatic assay technique described previously.[3]

Results: The data displayed in Table 1&2 are mean values expressed without standard error to conserve space. Patients in Group I demonstrated a significant increase in plasma histamine levels at the two minute value. Seven patients (77%) in this group showed clinical signs of histamine release such as skin flushing, brief fall in arterial pressure or slight increase in heart rate lasting 2 to 5 minutes. A moderate rise in histamine levels at the 2 minute sample in Group II approached, but did not reach statistical significance ($.1>P>.05$). None of the patients in Groups II or III showed clinical signs of histamine release.

Discussion: The significant increase in plasma histamine levels in Group I in association with a reduction of mean arterial pressure to 82% of control values and a mean increase in heart rate to 108% of control is nearly identical to observations in a previous study.[2] It has been shown that small time differences in the rate of administration of intravenous drugs can lead to significant changes in the likelihood of generating clinically significant histamine release.[1] In this study, administration of a high dose of atracurium slowly over 75 seconds appeared to completely prevent increases in serum histamine and any associated hemodynamic response. Antihistamine pre-treatment also attenuated the hemodynamic response despite the moderate increase in histamine levels. We conclude that histamine release by large doses (0.6 mg/kg) of atracurium and any associated hemodynamic response can be prevented by administering the dose slowly over 75 seconds. In addition, the hemodynamic response can also be attenuated by pre-treatment with intravenous H_1 and H_2 receptor antagonists.

Table 1

	n	Percent of Control MAP	HR
Group I 5 sec bolus	9	82	108
Group II 75 sec dose	9	95	97
Group III H_1 + H_2 prophylaxis	9	96. 2	102.3

Table 2

	Plasma Histamine pg/ml Control	+2mins	+5 mins
Group I 5 sec bolus	715	1415*	1086
Group II 75 sec dose	954	949	939
Group III H_1 + H_2 prophylaxis	751	1107	854

MAP = mean arterial pressure
HR = heart rate
*$p<0.05$ (one way analysis of variance)

References:
1. Moss J, Philbin DM, Rosow CE et al: Klin Wochenschr 60:891-95, 1982.
2. Basta SJ, Savarese JJ, Ali HH et al: Br J Anaesth 55:105S, 1983.
3. Moss J, Rosow CE, Savarese JJ, et al: Anesthesiology 55:19, 1981.