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Histamine-release haemodynamic changes produced by rocuronium, vecuronium, mivacurium, atracurium and tubocurarine

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Summary

We have examined the effects of different benzylisoquinolinium and steroidal neuromuscular blocking compounds on plasma concentrations of histamine, heart rate and arterial pressure in surgical patients. A single, rapid (5-s) bolus of mivacurium 0.2 mg kg^{-1}, atracurium 0.6 mg kg^{-1}, tubocurarine 0.5 mg kg^{-1}, vecuronium 0.1 mg kg^{-1} or rocuronium 0.6 mg kg^{-1} was administered to 75 patients ($n = 15$ in each group). Anaesthesia was induced with thiopentone 6 mg kg^{-1} i.v. and maintained with isoflurane and 70 % nitrous oxide in oxygen. Venous blood samples were obtained before induction, 1 min after thiopentone and 1, 3 and 5 min after administration of the neuromuscular blocking drug. Mivacurium, atracurium and tubocurarine caused 370 %, 234 % and 252 % increases in plasma histamine concentrations at 1 min, respectively. Corresponding values at 3 min were 223 %, 148 % and 157 %, respectively. These changes were significant ($P < 0.01$) at 1 and 3 min. In contrast, the rocuronium and vecuronium groups had no significant changes in either plasma histamine concentrations or haemodynamic variables. (*Br. J. Anaesth*. 1995; **75**: 588–592)

Key words

Histamine. Neuromuscular block, atracurium. Neuromuscular block, mivacurium. Neuromuscular block, rocuronium. Neuromuscular block, tubocurarine. Neuromuscular block, vecuronium.

Histamine is released by benzylisoquinolinium compounds such as mivacurium, atracurium and tubocurarine, causing skin flushing, decreases in arterial pressure and systemic vascular resistance and increases in heart rate [1–6]. Although steroidal neuromuscular blocking drugs are not associated with histamine release in typical clinical doses [6–8], there are several reports of hypotension and possible histamine release induced by vecuronium in surgical patients [9–11]. A notable exception is the drug ANQ 9040 that has been shown to trigger considerable histamine release at twice its ED_{95} [12].

Although the histamine releasing potencies of all currently available neuromuscular blocking drugs have been reported [1–8], comparative data do not exist. Therefore, this study was designed to compare the histamine releasing potencies and haemodynamic changes induced by different benzylisoquinolinium compounds (mivacurium, atracurium and tubocurarine) and steroidal neuromuscular blocking drugs (rocuronium and vecuronium).

Patients and methods

After obtaining local Ethics Committee approval and informed patient consent, we studied 75 ASA I or II unpremedicated patients of both sexes, aged 18–60 (mean 32.8) yr and weighing 45–91 (mean 68.4 (SD 11.1)) kg. All patients were undergoing elective procedures, had no neuromuscular, renal or hepatic disease and were not receiving any drugs known to interfere with neuromuscular function. Patients with recent exposure (previous 3 months) to antihistamines or antidepressants or known or suspected to have an allergy to narcotics, neuromuscular blocking drugs or other medications used during general anaesthesia were excluded. Patients were allocated randomly to one of five groups ($n = 15$ in each).

In the operating room, a 20-gauge radial arterial cannula was inserted using local anaesthesia before induction of general anaesthesia. Electrocardiogram and invasive arterial pressure were monitored continuously using HP M1166 A, Model 68 S, with write-out capability in the event of the need for documentation of possible rhythm disturbances. Haemoglobin oxygen saturation was monitored by pulse oximetry. After insertion of an i.v. cannula in one arm and an additional cannula in the opposite forearm for blood collection, the first sample was obtained. Estimated fluid deficits were replaced over 2 h with lactated Ringer's solution (1.5 ml kg^{-1} h^{-1} of fasting) before induction of anaesthesia.

Anaesthesia was induced with thiopentone 6 mg kg^{-1} i.v. and maintained with isoflurane (1.0 % inspired) and 70 % nitrous oxide in oxygen via a face mask. A second sample was obtained 1 min after

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Table 1 Histamine concentrations and cardiovascular variables before and after administration of mivacurium 0.2 mg kg^{-1}, atracurium 0.6 mg kg^{-1}, tubocurarine 0.5 mg kg^{-1}, vecuronium 0.1 mg kg^{-1} or rocuronium 0.6 mg kg^{-1} (mean (SD)). * $P < 0.01$ *vs* control values (within-group comparisons); ‡ $P < 0.05$ *vs* vecuronium and rocuronium groups (between-group comparisons for the differences from control values); ¶ $P < 0.05$ *vs* mivacurium group (between-group comparisons for the differences from control values)

	Control	1 min after thiopentone	Time after blocking drug (min) 1	3	5
Histamine concn (pg ml^{-1})					
Mivacurium (n = 15)	568 (201)	640.5(250)	2099.1 (429)*‡	1264.5 (496)*‡	881.9 (426)
Atracurium (n = 15)	781.3 (365)	854.8 (263)	1826.3 (529)*‡	1440 (487)*‡	980.2 (387)
Tubocurarine (n = 15)	780 (361)	768.8 (351)	1965.8 (564)*‡	1370 (419)*‡	845.1 (402)
Vecuronium (n = 15)	700.9 (262)	660.7 (237)	643.7 (234)	632 (288)	533.2 (348)
Rocuronium (n = 15)	816.4 (391)	908.8 (403)	1095 (404)	822.9 (279)	754.1 (319)
Mean arterial pressure (mm Hg)					
Mivacurium (n = 15)	76.0 (8.3)	72.7 (8.4)	64.8 (9.2)*‡	58.1 (7.2)*‡	62.0(7.8)*
Atracurium (n = 15)	78.7 (6.6)	75.6 (6.2)	67.8 (6.5)*‡	61.0 (6.3)*‡	63.6 (6.5)*
Tubocurarine (n = 15)	75.3 (5.4)	71.2 (6.9)	64.8 (8.2)*‡	57.2 (4.9)*‡	60.7 (5.1)*
Vecuronium (n = 15)	75.7 (7.4)	72.1 (7.9)	73.1 (7.2)	74.3 (7.1)	74.7 (7.4)
Rocuronium (n = 15)	79.3 (6.4)	75.1 (5.9)	75.1 (6.1)	75.9 (6.6)	76.9 (6.7)
Heart rate (beat min^{-1})					
Mivacurium (n = 15)	71.0 (2.9)	74.9 (2.9)	81.2 (5.1)*‡	82.3 (4.6)*‡	76.5 (6.1)‡
Atracurium (n = 15)	74.5 (6.8)	78.1 (7)	87.1 (7.3)*‡	90.6 (6.1)*‡¶	86.5 (5.3)*‡¶
Tubocurarine (n = 15)	72.7 (7.4)	76.3 (7.3)	82.9 (7.4)*‡	87.0 (7.9)*‡	83.1 (5.9)*‡¶
Vecuronium (n = 15)	75.5 (4)	79.0 (4.1)	77.0 (4.1)	75.1 (4.6)	75.0 (3.9)
Rocuronium (n = 15)	67.1 (4.7)	70.7 (4.5)	69.9 (4.2)	69.0 (4.6)	67.8 (4.4)

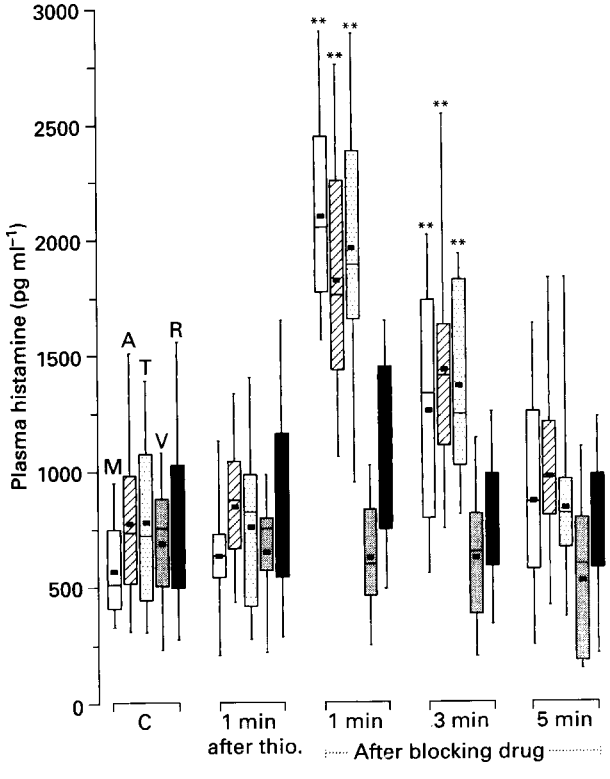

Figure 1 Plasma concentrations of histamine after administration of mivacurium (M), atracurium (A), tubocurarine (T), vecuronium (V) and rocuronium (R). Lower and upper borders of the box = 25th to 75th percentiles; horizontal line within the box = median, marking 50th percentile; rectangular symbols in the box = mean; extended bars = ranges. C = Control, thio = thiopentone. ** $P < 0.01$ compared with control values.

thiopentone injection. Three minutes later, a single bolus of mivacurium 0.2 mg kg^{-1}, atracurium 0.6 mg kg^{-1}, tubocurarine 0.5 mg kg^{-1}, vecuronium 0.1 mg kg^{-1} or rocuronium 0.6 mg kg^{-1} was administered over 5 s to patients in groups I to V, respectively. Samples 3, 4 and 5, were obtained 1, 3 and 5 min after administration of the neuromuscular blocking drug. Heart rate and mean arterial pressure were recorded at each sampling point. Intubation of the trachea was performed after blood sampling to avoid the cardiovascular response to laryngoscopy. Ventilation was controlled manually after administration of the neuromuscular blocking drugs. Thereafter, the study was concluded, tracheal intubation was performed and anaesthesia continued as appropriate for surgery.

Venous blood samples were obtained in Vacutainer tubes containing ethylenediaminetetraacetate (EDTA) and placed immediately on ice. Cold centrifugation was performed rapidly, the plasma separated and stored at −70 °C for later analysis. The plasma samples were analysed by radioenzymatic assay using [methyl^{-3}H]*S*-adenosylmethionine (^{3}H-SAM) and histamine *N*-methyltransferase (HNMT) (DuPont NEW Research Products). HNMT catalyses the transfer of the [^{3}H]methyl group from tritiated *S*-adenosylmethionine (^{3}H-SAM) to histamine, forming [^{3}H]tele-methylhistamine. This product is isolated by solvent extraction and quantitated by liquid scintillation counting. This technique is sensitive to 1–2 pg using a 25-ml sample [13, 14]. A 25-ml plasma sample is used in the enzyme reaction. Variability of the assay is less than 10 %. Each sample is assayed in duplicate with or without a 500-pg histamine standard. In addition, a HNMT-dependent blank and a 500-pg histamine external standard are included in every assay to monitor assay conditions. In these tubes, the sample is replaced by an equal volume of water [13, 14].

All statistical analyses were carried out using BMDP statistical package, release 7.01 (University of California Press, Berkeley, CA, USA). Within-group comparisons of plasma histamine con-

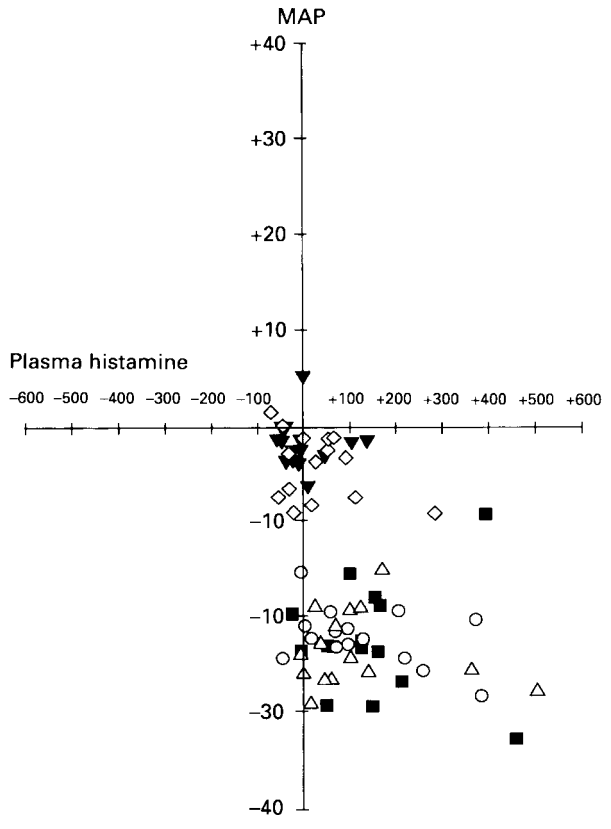

Figure 2 Correlation of percentage changes from control values for plasma concentrations of histamine and mean arterial pressure (MAP) in patients, 3 min after administration of mivacurium 0.2 mg kg^{-1} (■), atracurium 0.6 mg kg^{-1} (○), tubocurarine 0.5 mg kg^{-1} (△), vecuronium 0.1 mg kg^{-1} (▼) or rocuronium 0.6 mg kg^{-1} (◇) ($n = 75$, $r = -0.38$, $P < 0.001$).

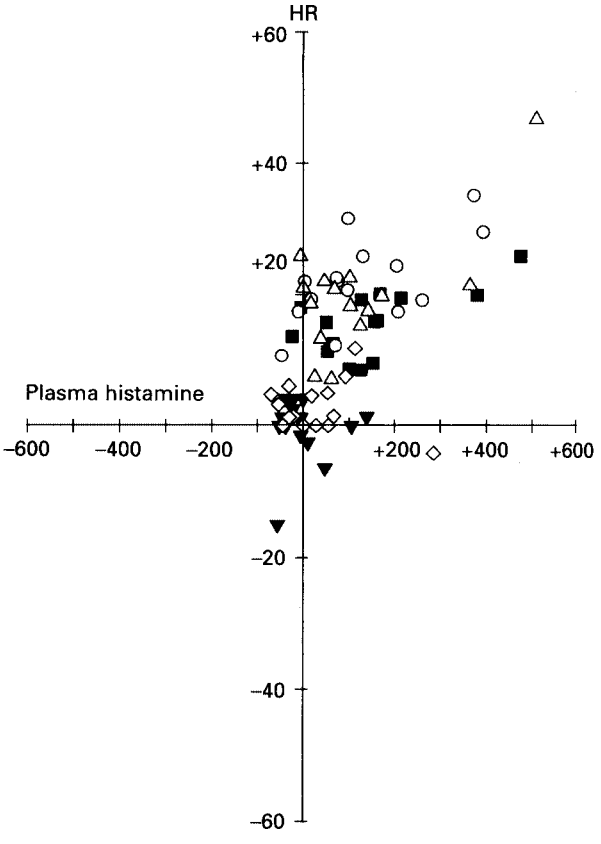

Figure 3 Correlation of percentage changes from control values for plasma concentrations of histamine and heart rate (HR) in patients, 3 min after administration of mivacurium 0.2 mg kg^{-1} (■), atracurium 0.6 mg kg^{-1} (○), tubocurarine 0.5 mg kg^{-1} (△), vecuronium 0.1 mg kg^{-1} (▼) or rocuronium 0.6 mg kg^{-1} (◇) ($n = 75$, $r = 0.37$, $P < 0.01$).

centrations, mean arterial pressure (MAP) and heart rate (HR) were performed by analysis of variance for repeated measures with the Bonferroni adjusted paired *t* test. Between-group comparisons of the differences in plasma histamine, MAP and HR from the control values were carried out using analysis of variance with the Tukey studentized range method. For all statistical comparisons, differences were considered significant when $P < 0.05$. All results are expressed as mean (SD) unless otherwise specified.

Results

The mean control plasma histamine concentration for all patients was 729 (SD 327) pg ml^{-1}. Plasma concentrations of histamine did not change significantly after administration of thiopentone (table 1, fig. 1). Administration of mivacurium 0.2 mg kg^{-1}, atracurium 0.6 mg kg^{-1} or tubocurarine 0.5 mg kg^{-1} resulted in increases ($P < 0.01$) in plasma histamine concentrations at 1 and 3 min but, as has been reported previously [1–3, 6], there was wide inter-subject variability within each group, as indicated by the large SD (table 1, fig. 1). In groups I–III there were mean increases in plasma histamine concentrations of 370 %, 234 % and 252 % at 1 min, respectively. Corresponding increases at 3 min were 223 %, 148 % and 157 %, respectively. The changes in plasma histamine concentrations after rocuronium 0.6 mg kg^{-1} or vecuronium 0.1 mg kg^{-1} were not significant (table 1, fig. 1). In all groups, by 5 min, plasma concentrations of histamine had returned to control values.

In the mivacurium, atracurium and tubocurarine groups, the increases in plasma histamine concentrations corresponded with the decrease in MAP and increase in HR. The peak changes in haemodynamic variables were seen at 3 min and the absolute values are presented in table 1. No rhythm disturbances were noted. The mean peak changes in MAP are shown in table 1. Mivacurium, atracurium and tubocurarine produced significant reductions in MAP at all times. However, vecuronium and rocuronium did not produce significant reductions in MAP. A similar pattern of changes was seen in the HR data. These changes correlated significantly ($P < 0.01$) with plasma histamine concentrations. Individual responses of MAP and HR compared with changes in histamine concentrations (expressed as percentage changes from control values), 3 min after administration of different neuromuscular blocking drugs, are presented in figures 2 and 3, respectively. In 11 (73 %) patients in the mivacurium group and nine (60 %) patients in the atracurium and tubocurarine groups, there were clinical signs of histamine release, with development of mild to moderate erythema over the trunk and face. There was no relationship between plasma histamine

concentrations after mivacurium, atracurium and tubocurarine and cutaneous manifestations. None of the patients in vecuronium and rocuronium groups showed signs of histamine release or any haemodynamic changes of clinical or statistical significance.

Discussion

We have demonstrated that administration of benzylisoquinolinium compounds (mivacurium 0.2 mg kg^{-1}, atracurium 0.6 mg kg^{-1} or tubocurarine 0.5 mg kg^{-1}) over 5 s resulted in significant increases in plasma histamine concentrations (table 1, fig. 1). This was accompanied by facial erythema and significant haemodynamic changes (table, figs 2, 3). In contrast, administration of rocuronium 0.6 mg kg^{-1} or vecuronium 0.1 mg kg^{-1} caused no significant changes in plasma histamine concentrations or in haemodynamic state at any time (table 1, fig. 1).

In this study, the mean peak increases in plasma concentrations of histamine at 1 min were 370 %, 234 % and 252 % of the control values after administration of mivacurium, atracurium and tubocurarine, respectively. Similar results have been reported by Basta and colleagues [4], who found 192.1 % and 410 % increases in histamine concentrations from control values after atracurium 0.6 mg kg^{-1} and tubocurarine 0.5 mg kg^{-1}, respectively. Similarly, Naguib, Abdulatif and Absood [6] found that the mean peak plasma concentration of histamine increases by 240 % at 1 min after tubocurarine 0.5 mg kg^{-1}. Savarese and colleagues [1] reported that the peak increase in plasma histamine concentration (at 2 min) after administration of mivacurium 0.2 mg kg^{-1} over 10–15 s, was 194.4 %. Basta and colleagues [4] also noted that increases in plasma histamine concentration of this magnitude (200 % or more) resulted in clinically and statistically significant changes in heart rate and arterial pressure in healthy patients. However, within 5 min of administration of benzylisoquinolinium compounds, plasma histamine concentrations returned to control values whereas administration of rocuronium 0.6 mg kg^{-1} or vecuronium 0.1 mg kg^{-1} was associated with minimal haemodynamic effects or histamine release. Similar observations have been reported by other investigators [7, 8].

The changes in haemodynamic variables observed in this study are consistent with those of other investigators [1–8]. Previous studies have found that when mivacurium 0.2 mg kg^{-1} or atracurium 0.6 mg kg^{-1} is administered rapidly, in approximately 30 % and 78 % of patients, respectively, increases in histamine occur and are associated with decreases in arterial pressure and increases in heart rate [1, 2]. Doenicke and colleagues [15] reported that after mivacurium 0.21 mg kg^{-1}, systolic arterial pressure decreased by 42 %, heart rate increased by 60 % and histamine concentration increased to 40 ng ml^{-1} in one patient. The clinical manifestations of liberation of histamine have been attributed to several mechanisms. Histamine has a positive inotropic and chronotropic effect on the myocardial H_2 receptors; there is some evidence that its chronotropic effect may result in part from liberation of catecholamines [16]. While ganglionic block secondary to administration of tubocurarine has been demonstrated to occur in various species [17], the peripheral venous and arteriolar dilatation via stimulation of vascular H_1 and H_2 receptors can result in a significant degree of hypotension and carotid sinus-mediated reflex response to histamine-induced peripheral vasodilatation [3, 18]. Other substances liberated by mast cell degranulation, such as tryptase [19] or prostaglandins [18], may also play a role.

Vecuronium rarely produces significant release of endogenous histamine. Cannon and colleagues [7] noted that vecuronium resulted in direct release of large amounts of histamine in one of 20 patients in their study. We did not observe any significant changes in plasma histamine concentrations after vecuronium administration. The sporadic occurrence of evidence of histamine release after vecuronium in clinical practice and the occasional case with unusually severe effects [9–11, 20] may be a result of different methodology, for example vecuronium cross-reactivity with chemically-related compounds [20, 21].

Administration of thiopentone did not result in any significant changes in haemodynamic variables or in plasma concentrations of histamine (fig. 1). These results are similar to those reported by other investigators [3, 6, 22]. Lorenz and colleagues [22] reported that plasma concentrations of histamine in five patients 20 s after an i.v. bolus dose of thiopentone 5 mg kg^{-1} were 3 ng ml^{-1} and were not associated with significant changes in heart rate and arterial pressure.

The doses of different neuromuscular blocking drugs selected in this study have clinical relevance. The dose of tubocurarine (0.5 mg kg^{-1}) represents only 1 $\times$ ED_{95} [23]. The doses of other drugs used in this study were approximately 2—2.5 $\times$ ED_{95}.

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