THE ROLE OF HISTAMINE IN THE CARDIOVASCULAR EFFECTS OF ATRACURIUM

M. ADT, J.-H. BAUMERT AND H.-J. REIMANN

SUMMARY
We have investigated the effect of a bolus injection of atracurium 0.6 mg kg⁻¹ on the cardiovascular system in 16 patients undergoing aortocoronary bypass surgery. H₁- and H₂-receptor antagonists were administered to eight patients before the neuromuscular blocker. A standard anaesthetic was used comprising fentanyl, flunitrazepam, etomidate and enflurane. After administration of atracurium, haemodynamic changes and plasma histamine concentrations were measured at frequent intervals. In the first group, who received only atracurium, a brief but marked decrease in SVR and MAP occurred, accompanied by an increase in CI, together with a marked increase in plasma concentration of histamine. In the second group, who received H₁- and H₂-receptor block, there was no decrease in MAP and only a small increase in plasma histamine concentration. However, there were significant changes in SVR and CI similar to those in the atracurium group.

KEY WORDS

Changes induced by atracurium in the cardiovascular system have been documented by many investigators [1–4]. The aim of the present study was to examine these effects in detail, to see if histamine is primarily responsible for such effects.

We wished to answer the following questions: What cardiovascular changes are produced by bolus administration of atracurium 0.6 mg kg⁻¹ into the right atrium? Does administration of atracurium release a significant amount of histamine? Is it possible to prevent cardiovascular changes by prior administration of H₁- and H₂-receptor antagonists?

PATIENTS AND METHODS
The study, approved by the Local Ethics Committee, was undertaken in patients undergoing aortocoronary bypass surgery. Our exclusion criteria included a left ventricular end-diastolic pressure (LVEDP) of > 20 mm Hg, an ejection fraction (EF) of < 50 %, or both. Consequently, our patients were classified as ASA III. Additional exclusion criteria included any allergy, serious systemic disorders or congenital anomaly of the cardiovascular system.

After giving their written consent, the patients were allocated randomly to two groups of eight. In the first group (AT) atracurium only was administered, whilst in the second group (ATP) H₁- and H₂-receptor antagonists were given prophylactically. All patients had a prolonged history of cardiac disease and had previously received various types of conservative treatment, for example nitrates, calcium channel blockers, beta-adrenergic antagonists, but not antihistamines. The last medication was taken on the evening before surgery, and premedication and anti-anginal therapy were administered early in the morning, approximately 2 h before measurements were begun.

Premedication comprised flunitrazepam 2 mg orally on the evening before and on the morning of surgery 2 h before induction of anaesthesia. After i.v. and i.a. cannulae had been inserted and inserted and ECG recording commenced, anaesthesia was induced with fentanyl 0.004–0.006 mg kg⁻¹, flunitrazepam 0.008–0.01 mg kg⁻¹ and etomidate 0.16–0.2 mg kg⁻¹. These drugs were given into a running infusion of a total of 500–1000 ml of Ringer lactate. Subsequently, 0.6–1.2 % enflurane in oxygen was administered for a period of 10 min via a face mask. Shortly before tracheal intubation, patients were given additional fentanyl 0.1 mg and etomidate 8–10 mg.

This induction technique permitted tracheal intubation without complications and without administration of a neuromuscular blocker, and no serious changes were observed in the cardiovascular system. After intubation of the trachea, anaesthesia was maintained with 0.4–0.8 % enflurane in oxygen and the lungs were ventilated mechanically to normocapnia as monitored by a Datex Capnomac and checked by arterial blood-gas analysis. Via the right internal jugular vein, a triple-lumen and a pulmonary artery catheter were inserted. At the same time, dimetindene (Fenistil) 0.1 mg kg⁻¹ and cimetidine 5 mg kg⁻¹ were administered i.v. to patients in the ATP group, approximately 30 min before measurement of the control values, by infusion over a period of 10 min.

From the time of intubation until measurement of baseline values, a period of 40–50 min had elapsed, during which time cardiovascular variables remained...
unchanged. Atracurium 0.6 mg kg\(^{-1}\) was then administered as an undiluted bolus over 2 s into the right atrium. During the measurement period, the patients were not stimulated by additional manipulations and were not given further medication. The following variables were measured: heart rate (HR), systolic arterial pressure (SAP), mean arterial pressure (MAP), diastolic arterial pressure (DAP), pulmonary arterial pressure (PAP), pulmonary capillary wedge pressure (PCWP), cardiac index (CI), systemic vascular resistance (SVR), pulmonary vascular resistance (PVR) and plasma histamine concentration.

ECG, HR, SAP, MAP, DAP, PAP and RAP were measured continuously and calculated for every 7.5 s. Cardiac output (CO; triple measurements within 15 % of each other) using the thermodilution technique on an SAT-1 cardiac output computer (Edwards Laboratories) and PCWP were measured; CO was then converted into CI. Blood samples for measurement of plasma histamine concentration were taken from the right atrium via the triple-lumen catheter and were cooled immediately in iced water. Plasma concentrations of histamine were measured, using the method of Lorenz and co-workers, slightly modified [5–7]. This method is based on a combination of ion exchange chromatography on Dowex 50 WX 8 chromatograph and fluorimetric measurement and has a coefficient of variation of 7 % for plasma histamine concentrations greater than 0.5 ng ml\(^{-1}\), 10 % between 0.5 and 0.1 ng ml\(^{-1}\), and 33 % for concentrations less than 0.1 ng ml\(^{-1}\) [8]. Measurements started 30 s after injection and were repeated at 1, 2, 3, 5, 10 and 15 min after administration of atracurium.

**Statistics**

Because a normal distribution of data cannot be assumed, and only a small number of patients were studied, we have used median values (50th percentile) together with the 95 % confidence intervals (given in parentheses). Data were analysed using the Wilcoxon rank sum test on the 5 % (P < 0.05) and 1 % (P < 0.01) levels to compare measurements with baseline values. In the same manner, the U test by Wilcoxon, Mann and Whitney was used to obtain a between-group comparison. Correlations between plasma histamine concentration and cardiovascular variables were calculated by Spearman’s rank correlation test (\(r_s\) values).

**RESULTS**

There was no difference between groups in age, height, weight (table I) or preoperative medication (table II). Male patients predominated.

<table>
<thead>
<tr>
<th>Group</th>
<th>Height (cm)</th>
<th>Weight (kg)</th>
<th>Age (yr)</th>
<th>LVEDP (mm Hg)</th>
<th>EF (%)</th>
<th>Sex (M/F)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AT</td>
<td>171.5</td>
<td>76.0</td>
<td>62.0</td>
<td>14.5</td>
<td>68.0</td>
<td>7/1</td>
</tr>
<tr>
<td>(n = 8)</td>
<td>(167-191)</td>
<td>(63-113)</td>
<td>(39-73)</td>
<td>(8-17)</td>
<td>(66-70)</td>
<td></td>
</tr>
<tr>
<td>ATP</td>
<td>168.5</td>
<td>73.8</td>
<td>53.5</td>
<td>11.0</td>
<td>66.0</td>
<td>7/1</td>
</tr>
<tr>
<td>(n = 8)</td>
<td>(161-178)</td>
<td>(61-90)</td>
<td>(41-73)</td>
<td>(5-20)</td>
<td>(60-72)</td>
<td></td>
</tr>
</tbody>
</table>

In group AT, with the exception of two patients, HR differed only slightly from the baseline value of 49.5 (95 % confidence intervals 44-52) beat min\(^{-1}\) during the measurement period. In group ATP also, there was little change from the control value of 53.5 (47-70) beat min\(^{-1}\) (table II).

In group AT, MAP decreased significantly (P < 0.05) from a baseline value of 71.0 (66-83) mm Hg to a minimum of 62.0 (38-76) mm Hg after 2 min and increased towards the end of the measurement period to slightly greater than control values (table III). In four patients there was a marked decrease in MAP of 15-20 mm Hg (to 61, 53, 48 and 38 mm Hg); in three patients there was only a slight reduction of 10 mm Hg and in one patient there was no change. In contrast, in group ATP, MAP decreased only very slightly from 76.5 (65-83) mm Hg to 75.0 (56-84) mm Hg, after 2 min with a value of 76.5 (62-88) mm Hg at the end of the measurement period.

A typical monitor display of heart rate and systolic and diastolic pressures from a patient in group AT is shown in figure 1.

CI (table III) in group AT increased significantly (P < 0.05), from 2.02 (1.5-2.7) litre min\(^{-1}\) m\(^{-2}\) to 2.33 (1.7-3.0) litre min\(^{-1}\) m\(^{-2}\) after 1 min, and at the end of the measurement period was slightly greater than the baseline value. Group ATP exhibited a significant (P < 0.01) increase from 2.28 (1.8-3.9) litre min\(^{-1}\) m\(^{-2}\) to 2.63 (2.3-3.6) litre min\(^{-1}\) m\(^{-2}\) after 1 min, followed by a decrease to 2.48 (1.7-3.4) litre min\(^{-1}\) m\(^{-2}\) at the end of the measurement period. Increased values were present in all patients, mainly 0.5-1.0 litre min\(^{-1}\) m\(^{-2}\).

SVR (table III) decreased significantly (P < 0.05) in group AT from 1421 (632-1920) dyn s cm\(^{-5}\) after 2 min, to 1021 (560-1419) dyn s cm\(^{-5}\) and increased again to baseline value at the end of the measurement period. Apart from the one stable patient, this decrease occurred in all other patients at the same time, but with different baseline values. In group ATP, SVR also decreased significantly (P < 0.01) from 1286 (816-1828) dyn s cm\(^{-5}\) to 1010 (656-1434) dyn s cm\(^{-5}\) after 1 min, and at the end of the measurement period exhibited a value of 1301 (703-1530) dyn s cm\(^{-5}\). In three patients, however, the changes were only very slight.

Plasma histamine concentration (table III) increased significantly (P < 0.01) in group AT from 0.30 (0.2-0.4) ng ml\(^{-1}\) to a maximum of 1.50 (0.4-1.9) ng ml\(^{-1}\) after 1 min, and after a period of 10 min returned to control value. However in five patients, values of 1.6-2.3 ng ml\(^{-1}\) and in one 3.6 ng ml\(^{-1}\) were observed. In group ATP there was a transient but significant increase (P < 0.05), from 0.2 (0.1-...
0.3) ng ml\(^{-1}\) to 0.40 (0.3–0.6) ng ml\(^{-1}\) after 30 s, followed by a rapid return to baseline after 3 min, without exceeding 0.6 ng ml\(^{-1}\) in any patient. 

Correlations in group AT were \(r_s = -0.476\) for MAP and \(r_s = -0.571\) for SVR with plasma histamine concentration after 1 min and \(r_s = 0.607\) for CI with plasma histamine concentration after 2 min.

All other measured variables, which were considered of less importance for this study, are presented in table IV.

### Discussion

Lorenz and Doenicke [9], defined a plasma concentration of histamine 0.3 ng ml\(^{-1}\) in healthy volunteers as normal and the pathological value at which clinical symptoms may be expected as 1.0 ng ml\(^{-1}\). It should be noted that local concentrations of histamine in organs and tissues may be much greater than those measured in venous blood [10–13].

According to Lorenz and Doenicke [9, 14], the plasma histamine concentration may be correlated with clinical effects as follows: for concentrations of less than 1 ng ml\(^{-1}\), a systemic reaction is not expected—only reddening or itching of the skin is possible (grade I); with concentrations greater than 1 ng ml\(^{-1}\), tachycardia, mild hypotension and eventual shortness of breath may occur (grade II); with concentrations greater than 12 ng ml\(^{-1}\), life-threatening hypotension with ventricular fibrillation and bronchospasm may be expected (grade III).

### Table II. Preoperative cardiovascular therapy (No. of patients)

<table>
<thead>
<tr>
<th>Group</th>
<th>(\beta)-Blockers</th>
<th>Calcium antagonists</th>
<th>Nitrates</th>
<th>Digitalis</th>
</tr>
</thead>
<tbody>
<tr>
<td>AT</td>
<td>5</td>
<td>8</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>(n = 8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATP</td>
<td>5</td>
<td>4</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>(n = 8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table III. Important cardiovascular and plasma histamine (PHC) variables (median values (95% confidence limits)) for both groups.

<table>
<thead>
<tr>
<th>Time after injection of atracurium (min)</th>
<th>0.5</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>5</th>
<th>10</th>
<th>15</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td>49.5</td>
<td>49.5</td>
<td>49.5</td>
<td>50.5</td>
<td>50.5</td>
<td>49.5</td>
<td>50.0</td>
</tr>
<tr>
<td>ATP</td>
<td>53.5</td>
<td>53.0</td>
<td>55.0</td>
<td>55.5</td>
<td>54.5</td>
<td>56.0</td>
<td>55.5</td>
</tr>
<tr>
<td>MAP</td>
<td>71.0</td>
<td>73.5</td>
<td>67.0*</td>
<td>62.0*</td>
<td>66.0</td>
<td>75.0*</td>
<td>75.0*</td>
</tr>
<tr>
<td>(mm Hg)</td>
<td>(66–83)</td>
<td>(67–89)</td>
<td>(38–76)</td>
<td>(54–84)</td>
<td>(62–86)</td>
<td>(71–87)</td>
<td>(69–93)</td>
</tr>
<tr>
<td>ATP</td>
<td>76.5</td>
<td>77.5</td>
<td>75.0</td>
<td>76.0</td>
<td>76.0</td>
<td>79.0</td>
<td>79.0</td>
</tr>
<tr>
<td>CI</td>
<td>2.02</td>
<td>2.33*</td>
<td>2.28*</td>
<td>2.22</td>
<td>2.23*</td>
<td>2.36*</td>
<td>2.17</td>
</tr>
<tr>
<td>(litre min(^{-1}) m(^{-2}))</td>
<td>(1.5–2.7)</td>
<td>(1.7–3.0)</td>
<td>(1.8–3.0)</td>
<td>(1.6–2.7)</td>
<td>(1.6–2.7)</td>
<td>(1.6–3.0)</td>
<td>(1.6–3.1)</td>
</tr>
</tbody>
</table>

\*P < 0.05; **P < 0.01

### Table IV. Important cardiovascular and plasma histamine (PHC) variables (median values (95% confidence limits)) for both groups.

![Fig. 1. SAP, DAP and HR of one patient in group AT: copy of original monitor display. The arrow indicates the injection of atracurium.](https://academic.oup.com/bja/article-abstract/68/2/155/298208)
ever, in more recent work the author has questioned his cut-off level of 1 ng ml\(^{-1}\) for systemic reactions [15].

In this group, in study AT, after atracurium 0.6 mg kg\(^{-1}\) there was significant histamine release in at least six of eight cases. Lorenz and colleagues [15], Buzello [16] and Hunter [17] are in agreement that atracurium may cause a slight histamine reaction, and Tryba [1] investigated this reaction further and observed that doses of 0.4 and 0.6 mg kg\(^{-1}\) were able to cause histamine release in four to six of 10 patients.

Using doses of atracurium similar to or greater than those in our study, Scott and co-workers [18, 19] found increased plasma concentrations of histamine. In common with other investigators [20, 21], they found that this increase could be avoided by slow injection or fractionated administration of the drug. Where authors have failed to observe histamine release with doses exceeding 0.3 mg kg\(^{-1}\) we may assume that cardiovascular measurements were not made frequently enough, that other medications were given, or that direct measurement of plasma histamine was not carried out [2, 3, 22, 23]. In our study, we allowed 40–50 min to elapse between induction of anaesthesia and beginning the measurements to obviate the effects of other drugs [9, 10]. The small baseline values of 0.2–0.3 ng ml\(^{-1}\) in both groups confirms that we were successful.

A small increase in concentration of plasma histamine occurred in the ATP group treated with antihistamines. However, plasma concentration of histamine increased to 0.6 ng ml\(^{-1}\) in only two patients, and in all others, reached a maximum of 0.4 ng ml\(^{-1}\); thus cardiovascular changes would not be expected to occur.

These findings are in accordance with observations of Scott and colleagues (atracurium 0.6 mg kg\(^{-1}\), prophylactic cimetidine 0.4 mg kg\(^{-1}\), chlorpheniramine 0.1 mg kg\(^{-1}\) [19] and Lorenz and colleagues (atracurium 0.5 mg kg\(^{-1}\), ranitidine and dimetindene) [15], but not with another investigation by Scott and co-workers [18], where he documented increased histamine release after atracurium 0.8 mg kg\(^{-1}\) with the same prophylaxis. A possible explanation for our own findings could be block of histamine release from mast cells caused by the prophylaxis, as has been demonstrated in vitro [24, 25].

In group AT, the most important effect was transient hypotension lasting approximately 1 min (Table III). In three patients, a marked decrease in MAP (minima 38, 48 and 53 mm Hg, baseline value approximately 70 mm Hg) was observed. During our preliminary studies it was sometimes necessary to intervene in the patient head-down. However, the effect was obviously self-limiting, as confirmed by the short half-life value of plasma histamine. Therefore, we did not intervene in the three aforementioned cases, and there were no complications.

The cause of the decrease in MAP was a marked, transient decrease in SVR. These phenomena coincided with the increase in plasma histamine concentration. In spite of measurable histamine release, heart rate remained unchanged. However, a distinct increase in CI was observed in all patients and may be explained by a combination of a cardiac histamine effect and the decrease in SVR.

Cardiovascular reactions after administration of atracurium are still controversial, being classified differently by various investigators. Several investigators found no significant cardiovascular changes with doses of atracurium 0.2–0.4 mg kg\(^{-1}\) [3, 21, 22, 26] and in isolated cases even with 0.5 mg kg\(^{-1}\) [27]. Dose dependence was investigated
further by Hilgenberg and Stoelting using atracurium 0.2 and 0.4 mg kg\(^{-1}\) [21]. Scott and colleagues using 0.6 and 0.8 mg kg\(^{-1}\) [18, 19] and by Tryba and colleagues [1], as mentioned above. Scott's group reported a cardiovascular reaction (decrease in MAP, increase in HR, CI not measured) with atracurium 0.6 mg kg\(^{-1}\) and greater, whereas Tryba's group, using 0.4 mg kg\(^{-1}\), reported changes in six of 10 patients (decrease in MAP, HR unchanged, CI not measured); both authors classified the changes as histamine-mediated.

In our study, the decrease in mean arterial pressure was prevented completely in group ATP. Other authors who also used combined H\(_1\)-H\(_2\)-receptor block found similar block of cardiovascular reactions [19, 28–30]. Other authors here reported stability of MAP and concluded that the prophylaxis was devoid of cardiovascular effects [31, 32] and completely or at least “significantly” effective [29, 30, 33].

The cardiovascular effects, not only of atracurium but also of histamine, are still debatable. Whereas the combination of tachycardia/arrhythmia, decrease in SVR and increase in CI is regarded as “histamine-typical” [9, 12], some authors have reported hypertension or bradycardia or various other combinations [1, 9, 29, 34]. Lorenz and colleagues stated that systemic reactions at comparable plasma histamine concentrations vary from one “releaser” to another, as does the efficacy of H\(_1\) and H\(_2\)-receptor block [15]. Absence of tachycardia in our patients, of course, could be a result of the preoperative medication, but Ferres and colleagues [2] found significant tachycardia in patients with coronary artery disease and similar preoperative therapy after atracurium 0.5 mg kg\(^{-1}\).

There is also the possibility that the variability in cardiovascular response is a reflection of the fact that these changes are produced by a network of other mechanisms and mediators that might be activated by histamine. This concept could provide an explanation for the relatively low correlations between HR, MAP, CI, SVR and plasma histamine concentration in the present study, and is supported by the findings that, after block of histamine receptors and at very low plasma histamine concentrations, there are still significant changes in cardiovascular variables after injection of atracurium.

REFERENCES


