

Neuromuscular Efficacy and Histamine-Release Hemodynamic Changes Produced by Rocuronium versus Atracurium: A Comparative Study

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ABSTRACT

Background: Rocuronium and atracurium are muscle relaxants used for short-and intermediate-duration surgical procedures. This study compares rocuronium and atracurium with regard to neuromuscular efficacy, hemodynamic changes, and their effects on plasma histamine concentration.

Materials and Methods: Sixty adult patients scheduled for general surgical operations lasting less than 120 minutes were clinically randomized to receive either 0.6mg/kg rocuronium (group-1, n=30) or 0.5mg/kg atracurium (group-2, n=30). Twitch response to a course of four electrical stimulations, baseline heart rate, and mean blood pressure were monitored, as well as histamine levels through venous blood samples.

Results: The onset time of neuromuscular block was 54 ± 22 seconds in the rocuronium group, vs. 94 ± 26 seconds in atracurium group ($p=0.001$). The clinical duration of the intubating dose was 34 ± 6.9 minutes in the rocuronium group, vs. 45 ± 7.1 minutes in atracurium group ($p<0.001$). Tracheas were intubated in less than 90 seconds from the time of the injection of the muscle relaxant in only 20 of the 30 patients in the atracurium group, but in all 30 patients in the rocuronium group ($p=0.005$). Atracurium, but not rocuronium, produced significant reduction of mean arterial blood pressure and increased heart rate at all times. Atracurium resulted in a significant increase in plasma histamine concentrations at one and three minutes of 232% and 149% (as percentage changes from control values, $p<0.01$). This corresponded significantly with the decrease in mean arterial blood pressure and the increase in heart rate ($p<0.01$). Rocuronium did not result in significant changes in plasma histamine concentrations. Further, 62±10% of the patients in the atracurium group, and none of rocuronium group, had clinical signs of histamine release.

Conclusion: Rocuronium provides more suitable conditions for rapid tracheal intubation than atracurium, is associated with a shorter clinical duration, has less effect on mean arterial blood pressure and heart rate, and

has less histamine releasing potency when compared to atracurium.

Key Words: Propofol - Atracurium - Rocuronium - Histamine - Hemodynamic changes.

INTRODUCTION

The onset time, duration of a muscle relaxant and type of surgery are critical factors in choosing the appropriate muscle relaxant to achieve rapid successful tracheal intubation [1]. In cases where rapid tracheal intubation is required to secure the airway, a level of muscular relaxation sufficient for rapid and smooth intubation can currently be provided only by succinylcholine. There are, however, potentially hazardous side effects associated with its use [1,2]. Hence, the anaesthetist needs to substitute it with a rapid onset non-depolarising muscle relaxant.

Atracurium (tracrium) is a muscle relaxant frequently used for short- and intermediate-duration surgical procedures [3]. It is a benzoisoquinoline neuromuscular blocker of intermediate duration, and has a unique degradation by ester hydrolysis and Hoffman reaction [4].

The use of a high initial bolus dosage of atracurium shortens the onset time, but at the expense of a prolonged duration of action [4]. Cardiovascular stability is considered desirable in an ideal muscle relaxant [5,6].

Rocuronium (zemuron) is a steroidal non-depolarising muscle relaxant [7]. It acts by competing for cholinergic receptors at the muscle end plate and it is antagonised by anticholinesterase inhibitors [8]. The introduction of

rocuronium and atracurium considerably improved the flexibility in the clinical administration of muscle relaxants [6].

This study was designed to compare the onset time, tracheal intubating condition, the degree of histamine release and cardiovascular stability between equi-effective doses of atracurium and rocuronium in elective surgical procedures lasting less than 120 minutes, and to correlate any changes in plasma histamine levels with cardiovascular and/or cutaneous responses.

MATERIAL AND METHODS

This study was conducted at The National Cancer Institute, Cairo University, after obtaining permission from the hospital's Ethical Committee and informed patients' consent. Sixty adult patients, ASA I or II of both sexes, aged 20 to 63 years (mean 31.9), weighing 42 to 80kg (mean 58.7) and measuring 159-178cm (mean 169) tall were included in this assessor-blinded, parallel-grouped, comparative, randomized study. All patients were scheduled for elective surgical procedures lasting less than 120 minutes, requiring tracheal intubation and neuromuscular relaxation. Patients were excluded if they have muscular or endocrine disease, and if they receive antihistaminics or antibiotics potentiating the effects of muscle relaxants such as aminoglycosides 24 hours before surgery.

After insertion of IV cannula in one arm, an additional 16 G cannula was inserted into a vein in the ante-cubital fossa of the other arm for withdrawal of blood samples to estimate histamine level. No sedatives or opioids were administered before induction of anaesthesia. An IV infusion of dextrose 5% solution was started before induction of anaesthesia.

Monitoring includes ECG, pulse oximetry, indirect blood pressure (MAP) and neuromuscular function. The ulnar nerve was stimulated using the Datex-relaxograph, which delivers a supramaximal square pulse of 0.2 milliseconds in a train-of-four sequences (TOF) at 2 Hz every 12 seconds. The force of thumb adduction was measured by a transducer on a polygraph.

In all patients, anaesthesia was induced with 2ug/kg fentanyl and 2-2.5mg/kg propofol, and maintained by continuous infusion of propofol (8-10mg/kg) and 60% N₂O in oxygen. After

the patient loses consciousness (i.e. loss of eyelid reflex) and before administration of the study neuromuscular blocker (NMB), baseline TOF readings were obtained for 60 seconds. The TOF sequences were delivered every 12 seconds. After baseline TOF readings are documented, the test neuromuscular blocker was administered. The patients randomly receive an injection of equivalent doses (2xED₉₅) of either atracurium 0.5mg/kg (group-1, n=30) or rocuronium 0.6mg/kg (group-2, n=30) for tracheal intubation. Heart rate (HR) and mean arterial blood pressure (MAP) were measured just before and immediately after administration of the test drug, then one, three and five minutes after muscle relaxant administration. Baseline HR and MAP were measured as the average of the arrival and pre-induction values. Changes in HR and MAP were reported as a percentage from the baseline.

Sixty seconds after relaxant administration, intubation was attempted. If tracheal intubation was unsuccessful, the protocol allowed for another attempt at 90 seconds. The tracheal intubation conditions were evaluated on the first attempt only, and scored on a scale based on Clarke and Mirakhur grading [3] (Table 1).

Following intubation, the lungs were mechanically ventilated, and ventilation was adjusted to maintain end-tidal carbon dioxide (ETCO₂) between 35 and 40mmHg.

Venous blood samples for the histamine level were taken immediately before and at one, three and five minutes after giving the muscle relaxant. The MAP and HR were recorded at each sampling time. The samples were collected in tubes containing EDTA, and the plasma was separated and stored at -70°C for subsequent analysis. The plasma samples were analyzed by radioenzymatic assay. In both groups, patients were monitored for cutaneous flushing or other signs of histamine release, e.g. bronchospasm.

When the first twitch of TOF (T₁) recovers to 25% of the control (75% blockade), a further increment of atracurium 0.08mg/kg in group-1, or rocuronium 0.15mg/kg in group-2 was administered.

The neuromuscular effects of the muscle relaxant were assessed by TOF, and by recording the following: The onset time (time interval between the completion of the muscle relaxant

injection and the time of maximal depression of T_1); the clinical duration (time interval between the completion of the muscle relaxant injection and the return of T_1 to 25% of the control value); and the time to recovery (time interval between the completion of the muscle relaxant injection and the return of T_1 to 75% of the control). Twitch depression was expressed as reduction percentage of T_1 relative to pre-injection control.

At the end of surgery, when the twitch height recovers to 10% of its initial control height, the residual neuromuscular blocker was antagonised by neostigmine 50 ug/kg and atropine 15ug/kg.

Data were compared where appropriate with the Student's *t*-test, Wilcoxon test or Fishers exact test, all of which were performed with the SAS software package (Version 6.1). Intra-group comparisons of plasma histamine concentrations, MAP and HR were performed by analysis of variance for repeated measures with the Bonferroni adjusted *t*-test. Inter-group comparisons of the differences in plasma histamine, MAP and HR from control values were carried out using analysis of variance with the Tukey studentized range method. Differences were considered significant at $p < 0.05$. All values were given as mean + standard deviation (SD), unless otherwise specified.

RESULTS

The patients were demographically comparable in both groups. The onset time of neuromuscular block was significantly shorter in the rocuronium group than in atracurium group ($p = 0.001$).

Intubation Score:

At the time of successful intubation, intubating conditions were rated similar in both groups, and the tracheas were intubated at the first laryngoscopy in all patients. However, tracheas were intubated in less than 90 seconds from the time of the injection of the muscle relaxant in only 20 of the 30 patients in the atracurium group, but in all 30 patients in the rocuronium group ($p = 0.005$, Table 2). The clinical duration of the intubating dose of the muscle relaxant was significantly shorter in the rocuronium group than in atracurium group ($p < .001$). The spontaneous recovery time from intubating dose was nearly similar in both groups, ($p = 0.1$, Table 3).

Cardiovascular Data:

Atracurium produced significant reduction in MAP (Fig. 1) and increase in HR (Fig. 2) at all times; the peak changes were seen at 3 minutes ($p < 0.015$).

For all patients in both groups, the mean control plasma histamine concentration was 727 ± 324 pg/ml, and it did not change significantly after the administration of propofol (Table 4).

The administration of atracurium in a dose of 0.6mg/kg resulted in an increase in mean plasma histamine concentrations at one and three minutes (expressed as percentage changes from control values), 232% and 149%, respectively ($p < 0.01$) (Table 5). This increase in plasma histamine concentration corresponded with the decrease in MAP (Fig. 4) and the increase in HR (Fig. 5). However, administration of rocuronium 0.5mg/kg did not produce significant changes in MAP (Fig. 1), HR data (Fig. 2), or significant changes in plasma histamine concentrations (Fig. 3), where $p < 0.1$. These hemodynamic effects correlated significantly with plasma histamine concentrations, where $p < 0.01$ (Fig. 4,5). In both groups, by five minutes, plasma concentration of histamine had returned to control values (Fig. 3).

In addition, $62 \pm 10\%$ of the patients in the atracurium group had clinical signs of histamine release, with development of mild-to-moderate erythema over the trunk and face. There was no correlation between plasma histamine concentrations after atracurium and cutaneous manifestations. None of rocuronium group patients showed signs of histamine release or any hemodynamic changes of clinical or statistical significance.

Table (1): Grading of intubation scores.

Intubating score	Condition	Description
4	Excellent	Jaw relaxed, vocal cords immobile, no diaphragmatic movement.
3	Good	Jaw relaxed, vocal cords immobile, some diaphragmatic movement.
2	Poor	Jaw relaxed, vocal cords moving, "bucking," or coughing.
1	Inadequate	Jaw relaxed, vocal cords closed.

Table (2): Intubation scores at 60 seconds.

Group	Intubation time <90 sec	Inadequate	Poor	Good	Excellent
	N (%)	N (%)	N (%)	N (%)	N (%)
Rocuronium	30 (100)	0 (0)	3 (10)	7 (23)	20 (67)
Atracurium	20 (67)	0 (0)	2 (7)	12 (43)	16 (53)

Table (3): Neuromuscular data.

Group	Time to Spontaneous Recovery (min.)	Clinical Duration (min.)	Onset (sec.)
Rocuronium	53+6.2	34+6.9	54+22
Atracurium	58.9+7.56	45+7.1	94+26

Values are mean ± SD

Table (4): Plasma histamine concentrations (pgm/ml).

Group	Control	One minute after Propofol	Time after NM blockers		
			One minute	Three minutes	Five minutes
Atracurium	900±100	1100±125	2200±160	1610±125	1350±140
Rocuronium	1100±120	1300±140	1490±149	1200±170	1250±175

Values are mean ±SD, NM= neuromuscular blockers,

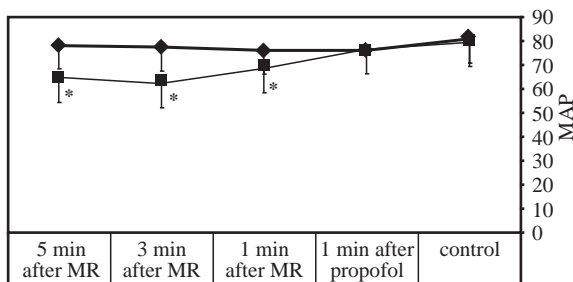


Fig. (1): Mean arterial blood pressure variables (MAP) before and after administration of rocuronium —◆— and atracurium —■— MR = muscle relaxant, * significant value compared to the other group, $p<0.01$.

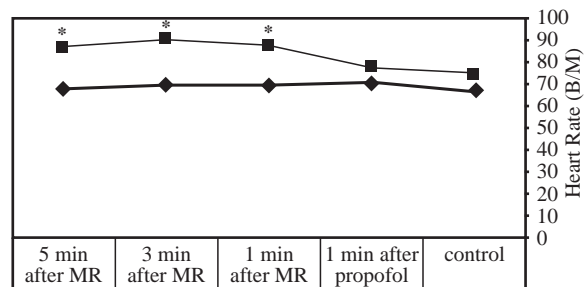


Fig. (2): Heart rate variables before and after administration of rocuronium —◆— and atracurium —■— MR = muscle relaxant, * Significant value compared to the other group, $p<0.01$.

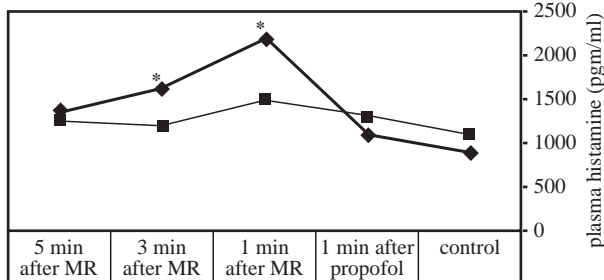


Fig. (3): Plasma concentrations of histamine (pgmm1-1) before and after administration of atracurium —◆— and rocuronium —■— MR = muscle relaxant, *Significant value compared to the other group, $p<0.01$.

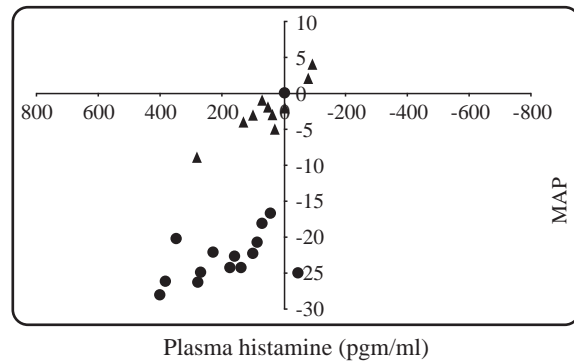


Fig. (4): Correlation of percentage changes from control values for plasma concentrations of histamine and mean arterial blood pressure (MAP) in patients 3 minutes after administration of atracurium ● and rocuronium ▲.

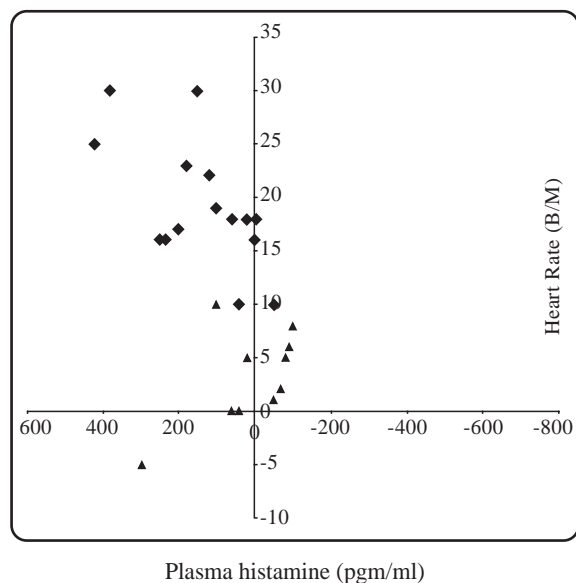


Fig. (5): Correlation of percentage changes from control values for plasma concentrations of histamine and heart rate in patients 3 minutes after administration of rocuronium ▲ and atracurium ◆.

DISCUSSION

In this study, the neuromuscular and cardiovascular characteristics of equipotent doses of rocuronium and atracurium were evaluated. Neither hypnotic nor opioid drugs were used after administration of the muscle relaxant, which means that the intubating conditions resulted from the neuromuscular block. The onset times of neuromuscular block of atracurium in this study were similar to that reported elsewhere [9,10]. Chetty, et al. compared 1.75x ED₉₀ (0.45mg/kg) doses of rocuronium to similar doses of atracurium (0.35mg/kg) and vecuronium (0.075mg/kg) in day-case dental procedures under N₂O/O₂ isoflurane anaesthesia. They found rocuronium to have a shorter onset time with a reduced clinical duration when compared to the patients receiving atracurium or vecuronium [9]. Whalley, et al. compared 2xED₉₀ doses of rocuronium 0.6mg/kg and atracurium 0.5mg/kg during intravenous propofol/alfentanil anaesthesia with N₂O/O₂ ventilation. They found faster onset times and shorter clinical duration with rocuronium, but a slower recovery rate index and spontaneous recovery to 70% TOF [10].

The neuromuscular effects of 2xED₉₀ determined by Wierda, et al [11] and the ED₉₀

described by Sokoll, et al., [12] after single-dose injection of the muscle relaxant during balanced anaesthesia provided the most accurate assessment of potency. Consequently, we choose rocuronium: atracurium potency ratio of 1.2:1. There is more agreement in the literature as to the potency of rocuronium than for atracurium because the dose response curves for atracurium have been generated in different patient age groups from bolus, as well as cumulative drug administration, and in the presence of volatile and balanced anaesthesia [13].

The choice of induction drug undoubtedly influences intubation conditions [13]. As demonstrated by Skinner, et al., the successful rate of intubation using rocuronium was higher when propofol instead of etomidate was used for induction [14]. Weiss, et al. showed that in non-premedicated patients anaesthetized with fentanyl/thiopentone, the intubation conditions at one minute following 0.7mg/kg rocuronium were not as favorable as those following 0.9mg/kg rocuronium or 1.5mg/kg succinylcholine [15].

This study demonstrates that administration of atracurium 0.5mg/kg resulted in significant increases in plasma histamine concentrations. This was accompanied by facial erythema and significant haemodynamic changes. In contrast, administration of rocuronium 0.6mg/kg caused no significant changes in plasma histamine concentrations or in hemodynamic state at any time.

In this study, the mean peak increase in plasma histamine at one minute was 232% after administration of atracurium. Similar results have been reported by Basta and colleagues, who found 192.1% increase in histamine concentrations from control values after administration of atracurium 0.6mg/kg [16]. They also noted that the increase in plasma histamine concentrations of 200% or more resulted in clinically and statistically significant changes in heart rate and arterial pressure in healthy patients. However, within five minutes of administration of atracurium, plasma histamine concentrations returned to control values, whereas administration of 0.6mg/kg rocuronium was associated with minimal hemodynamic effects or histamine release. Similar observations have been reported by other investigators [17,18].

The changes in hemodynamic variables observed in this study are consistent with those of other investigators [19]. Previous studies have found that when mivacurium 0.2mg/kg or atracurium 0.6mg/kg is administered rapidly, in approximately 30% and 78% of patients, respectively, increases in histamine concentrations occur and are associated with decrease in arterial pressure and increase in heart rate.

The clinical manifestations of histamine have been attributed to several mechanisms [20]. Histamine has a positive inotropic and chronotropic effect on the myocardial H₂ receptors; there is some evidence that its chronotropic effect may result in part from liberation of catecholamines [21]. Other substances liberated by mast cell degranulation, such as tryptase [22] or prostaglandins [23], may also play a role.

Administration of propofol did not result in significant changes in haemodynamic variables or in plasma histamine concentrations. These results are similar to those reported by Yang, et al., who showed that propofol produced more stable hemodynamics than thiopental [24].

Conclusion:

In conclusion, rocuronium provides more suitable conditions for rapid tracheal intubation, and is associated with a shorter clinical duration compared to atracurium. Rocuronium has less effect on MAP, HR and has less histamine releasing potency than atracurium.

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