Comparison of neuromuscular effects, efficacy and safety of rocuronium and atracurium in ambulatory anaesthesia

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Purpose: To compare the neuromuscular effects, efficacy, and safety of equi-effective doses of rocuronium and atracurium in ambulatory female patients undergoing surgery.

Methods: Forty-one patients undergoing laparoscopic gynaecological surgery were randomized to receive 2 × ED_{90} rocuronium (0.6 mg·kg^{-1}; n = 20) or atracurium (0.5 mg·kg^{-1}; n = 21) during intravenous propofol/alfentanil anaesthesia with N_2O/O_2 ventilation. Neuromuscular block was measured with a mechanomyogram eliciting a train-of-four (TOF) response at the wrist. Intubation conditions 60 sec after administration of muscle relaxant and immediate cardiovascular disturbances or adverse events during the hospital stay were noted by blinded observers.

Results: Compared with atracurium, rocuronium was associated with a shorter onset time (59.0 ± 22.2 *vs* 98.6 ± 41.4 sec; $P < 0.001$) and clinical duration of action (33.3 ± 7.1 *vs* 44.7 ± 7.2 min; $P < 0.001$), but longer spontaneous recovery index (9.6 ± 2.41 *vs* 6.9 ± 1.89 min; $P = 0.023$) and a similar time to spontaneous recovery to TOF 70%; 53 ± 6.31 *vs* 59.2 ± 7.59 min; $P = 0.139$). Tracheal intubation was accomplished in < 90 sec in all patients receiving rocuronium but in only 14 of 21 patients receiving atracurium. The incidence of adverse events and the cardiovascular profiles for the two drugs were similar, although one patient receiving atracurium experienced transient flushing of the head and neck.

Conclusion: Rocuronium has minimal side effects, provides conditions more suitable for rapid tracheal intubation, and is associated with a shorter clinical duration than atracurium. Once begun, the spontaneous recovery profile of rocuronium is slightly slower than that of atracurium.

Objectif : Comparer les effets neuromusculaires, l'efficacité et la sécurité de doses à effet équivalent de rocuronium et d'atracurium chez des patientes devant subir une chirurgie ambulatoire.

Méthode : Quarante-deux patientes réparties au hasard et devant subir une laparoscopie gynécologique ont reçu 2 x ED_{90} de rocuronium (0,6 mg·kg^{-1} ; n = 20) ou d'atracurium (0,5 mg·kg^{-1} ; n = 21) pour une anesthésie intraveineuse avec propofol et alfentanil sous ventilation avec N_2O et O_2. Le blocage neuromusculaire a été mesuré à l'aide d'un mécanomyogramme enregistrant, au poignet, une réponse en train-de-quatre (TDQ). Pendant le séjour à l'hôpital, des observateurs impartiaux ont noté l'état de l'intubation 60 s après l'administration du relaxant musculaire, et les perturbations cardiovasculaires ou les réactions indésirables immédiatement après leur survenue.

Résultats : Comparé à l'atracurium, le rocuronium a été associé à une induction plus courte (59,0 ± 22,2 *vs* 98,6 ± 41,4 s ; $P < 0,001$) et à une action clinique plus brève (33,3 ± 7,1 *vs* 44,7 ± 7,2 min ; $P < 0,001$), mais à un index de récupération spontanée plus long (9,6 ± 2,41*vs* 6,9 ± 1,89 min ; $P = 0,023$) et à une durée similaire de récupération spontanée au TDQ 70 % (53 ± 6,31 *vs* 59,2 ± 7,59 min ; $P = 0,139$). L'intubation endotrachéale a eu lieu en moins de 90 s chez toutes les patientes qui ont reçu du rocuronium mais chez seulement 14 des 21 patientes ayant reçu de l'atracurium. L'incidence de réactions indésirables et les profils cardiovasculaires ont été semblables avec les deux médicaments, quoiqu'une patiente ayant reçu de l'atracurium ait manifesté des bouffées vasomotrices à la tête et au cou.

Conclusion : Le rocuronium présente moins d'effets secondaires, permet une intubation endotrachéale plus rapide et est associé à un effet clinique plus court que l'atracurium. Une fois amorcée, la récupération spontanée est légèrement plus lente qu'avec l'atracurium.

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THE onset time and duration of action of muscle relaxants and the type of surgery are critical factors in choosing the appropriate drug to achieve rapid, successful tracheal intubation. Rocuronium and atracurium are frequently used muscle relaxants for short to intermediate duration surgical procedures. Rocuronium is a nondepolarizing muscle relaxant of intermediate duration that differs from its analogue, vecuronium, by having a rapid onset of action.[1] At doses of approximately 2 × ED_{90} (0.6, 0.1, and 0.33 mg·kg^{-1} for rocuronium, vecuronium, and succinylcholine, respectively[2,3]), the onset time of rocuronium is shorter than that of vecuronium and approaches that of succinylcholine, making it a useful component of a rapid sequence induction of anaesthesia.[2] Rocuronium has a duration of action that is similar to that of vecuronium,[3] demonstrates little or no cumulative effect,[4] and is only minimally influenced by the type of anaesthetic technique.[5] Furthermore, the cardiovascular stability of rocuronium has been demonstrated by observing no changes in heart rate and blood pressure in response to doses of up to 0.9 mg·kg^{-1}.[1,6]

Atracurium has been used extensively since its introduction by Stenlake in 1983,[7] particularly in the area of ambulatory anaesthesia. Because of its unique degradation by ester hydrolysis and the Hoffman reaction,[8] anaesthetists have felt able to allow their patients to recover spontaneously from muscle relaxation induced by atracurium, thus obviating the need for reversal drugs and their alleged contribution to emetic sequelae after general anaesthesia.[9] Atracurium is, however, associated with hypotension and tachycardia, the magnitude of which is dose dependent and related to an increase in plasma histamine concentration.[10]

Rocuronium has been shown to have a faster onset and shorter duration of action than atracurium in children[11] and in adults undergoing dental[12] and cervical spine[13] surgery who were anaesthetized with both intravenous and inhalation anaesthetics. The objective of the present study was to compare the neuromuscular effects, safety, and efficacy of equi-effective doses (2 × ED_{90}) of rocuronium and atracurium in an unique population of female ambulatory patients undergoing gynaecological, laparoscopic surgery while anaesthetized with *iv* agents supplemented with nitrous oxide only. We tested the hypothesis that rocuronium provided better intubating conditions sooner after administration with fewer side effects than atracurium, yet provided a clinical duration of action that is similar to that of atracurium.

Methods

The study was approved by the Institutional Review Board of the Cleveland Clinic Foundation. After obtaining informed consent, 41 patients undergoing laparoscopic, gynaecological, ambulatory surgery were entered into this assessor-blinded, parallel group, comparative, randomized study. The patients were admitted to the study if they were between 18 and 65 years of age and were ASA I or II. Patients with known renal, hepatic, or neuromuscular disorders, patients receiving drugs known to modify the action of neuromuscular blocking agents, patients who weighed >100 kg and patients in whom pregnancy could not be excluded did not participate in the study.

The patients were premedicated with 1-2 mg midazolam up to 90 min before the induction of anaesthesia. Anaesthesia was achieved by an infusion of propofol (1.8 mg·kg^{-1}) and alfentanil (9 μg·kg^{-1}) *iv*, and the lungs were ventilated with nitrous oxide 70% in oxygen via a face mask. A control recording of neuromuscular transmission for each patient was obtained with a mechanomyogram (Myograph 2000, Biometer International A/S, Odense, Denmark). The force of contraction of the adductor pollicis was recorded after stimulation of the ulnar nerve at the wrist by four supramaximal square wave impulses of 200 μsec in duration delivered at 2 Hz every 12 sec through surface electrodes. The outstretched arm was enveloped in a cotton blanket and plastic bag to minimize heat loss. Patients were monitored with an oesophageal stethoscope and an electrocardiograph, and by sphygmomanometry, pulse oximetry, and mass spectrometry to measure the concentration and percentage of inspired and expired gases.

After obtaining a satisfactory control recording of the mechanomyogram for two minutes, the patients were randomized to receive equivalent doses (2 × ED_{90}) of either rocuronium (0.6 mg·kg^{-1}; n = 20) or atracurium (0.5 mg·kg^{-1}; n = 21), which were each administered as a bolus dose injected over five seconds into a fast flowing *iv* infusion. Sixty seconds after the administration of the muscle relaxant, laryngoscopy was performed and intubating conditions were assessed by the same anesthesiologist (WM) who was blinded to the muscle relaxant that had been given. If tracheal intubation was unsuccessful, the protocol allowed for another attempt at 90 sec and, if again unsuccessful, then a third attempt at 120 sec. The tracheal intubation conditions were evaluated on the first attempt only and scored on a scale described by Clarke and Mirakhur.[14] Possible tracheal intubation conditions were excellent (jaw relaxed, vocal cords apart and immobile, no diaphragmatic movement), good (jaw relaxed, vocal cords apart and immobile, some diaphragmatic movement), poor (jaw relaxed, vocal cords moving, substantial diaphragmatic movement),

or inadequate (jaw not relaxed, vocal cords closed).

Upon successful tracheal intubation, anaesthesia was continued with nitrous oxide 70% and 30% oxygen and an *iv* infusion of propofol and alfentanil adjusted to the surgical stimulus. Ventilation was adjusted to maintain normocapnia, thereby avoiding the increase in P_aCO_2 and the respiratory acidosis typically associated with laparoscopic surgery. Additional muscle relaxation was achieved, if clinically required, by supplementary doses of the initial muscle relaxant assigned to the patient, to whom the anesthesiologist remained blinded (either 0.1 $mg \cdot kg^{-1}$ rocuronium or 0.08 $mg \cdot kg^{-1}$ atracurium). The neuromuscular blockade was allowed to recover spontaneously, but the block was reversed with neostigmine and glycopyrrolate if the TOF ratio was <70% (TOF 70%) at the end of surgery.

The neuromuscular effects of the muscle relaxants were assessed by recording the onset time (time interval between the completion of injection of the muscle relaxant and the time of maximal depression of the first twitch of the TOF, T1), the clinical duration (time interval between the completion of the injection of the muscle relaxant and return of T1 to 25% of control value), recovery index (time interval during which T1 recovered from 25% to 75% of control), and time to recovery (time interval between the completion of the injection of the muscle relaxant and return to TOF 70%). The recovery index and time to recovery could not be measured in patients who received more than one dose of muscle relaxant or in patients whose surgery was complete before TOF 70%.

In addition to routine cardiovascular monitoring, the heart rate and blood pressure were specifically noted prior to the administration of the intubating dose of rocuronium or atracurium and 2, 5, 10, and 15 min after administration of the muscle relaxant and before surgical incision. While the patient was in the hospital, any adverse event, including histamine-related symptoms, was clinically assessed and recorded by an observer blinded to the randomization schedule. The presence of cutaneous reactions, such as flushing, redness, wheels, hives, or erythema of the arms, face, and trunk, of each patient were noted before the administration of the induction agent, after induction but before the initial dose of rocuronium or atracurium, and after administration of the muscle relaxant.

Data were compared where appropriate with Student's t test, Wilcoxon test, or Fisher's exact test, all of which were performed with the SAS Software Package (Version 6.1). Differences were considered significant at $P < 0.05$, and all values are given as mean ± standard deviation (SD).

Results

The patients were demographically similar in both groups (Table I). Complete twitch suppression was achieved in all patients, but the time to ablation (onset time) was shorter in the rocuronium group than in the atracurium group (59.0 ± 22.0 *vs* 98.6 ± 41.4 sec; $P < 0.001$; Table II). Intubating conditions were rated as similar in both groups, and the tracheas were intubated at the first laryngoscopy in all patients. However, tracheas were intubated in <90 sec from the time of the injection of the muscle relaxant in only 14 of the 21 patients in the atracurium group but in all 20 patients in the rocuronium group ($P = 0.005$; Table III). Three patients in the rocuronium group and six patients in the atracurium group were reported to have experienced one or more adverse events ($P = 0.454$), none of which were severe. One patient in the atracurium group experienced transient flushing of the head and neck. The most frequent adverse event was nausea and vomiting (two patients in the rocuronium group; three patients in the atracurium group). No difference was noted between the groups in the percent changes in heart rate or systolic and diastolic blood pressures at the designated time intervals, which were before surgical incision in all cases (Table IV).

The clinical duration of the intubating dose of muscle relaxant was shorter in the rocuronium group than in the atracurium group (33.3 ± 7.1 *vs* 44.7 ± 7.2 min; $P < 0.001$; Table II). No patient in the atracurium group received additional muscle relaxant during surgery, whereas five patients in the rocuronium group required additional doses of relaxant (one

TABLE I Demographic Characteristics

Group	*Age (yr)*	*Height (cm)*	*Weight (kg)*	*ASA Class (1,2)*
Rocuronium	33.1 ± 7.0	164.3 ± 7.0	63.6 ± 10.6	15,5
Atracurium	32.5 ± 6.6	165.3 ± 8.1	71.3 ± 15.8	15,6
P	0.7	0.7	0.07	1

Mean ± SD

TABLE II Neuromuscular Transmission Data

Group	*Onset (sec)*	*Clinical duration (min)*	*Recovery index (min)*	*Time to recovery (min)*
Rocuronium	59.0 ± 22.2 (n = 20)	33.3 ± 7.1 (n = 20)	9.6 ± 2.41 (n = 10)	53 ± 6.31 (n = 10)
Atracurium	98.6 ± 41.4 (n = 21)	44.7 ± 7.2 (n = 19)	6.9 ± 1.89 (n = 6)	59.2 ± 7.59 (n = 6)
P	< 0.001	< 0.001	0.02	0.1

Mean ± SD

TABLE III Frequency Distribution of Intubation Scores at 60 sec and Time to Intubation

Group	Excellent	Good	Poor	Inadequate	Intubation time <90 sec
Rocuronium n(%)	13(65)	5(25)	2(10)	0(0)	20(100)
Atracurium n(%)	11(52)	9(43)	1(5)	0(0)	14(70)
P		[———0.708———]			0.005

TABLE IV Mean Percent Changes in Cardiovascular Variables from Baseline

	Heart Rate		*Systolic Blood Pressure*		*Diastolic Blood Pressure*	
	Rocuronium	*Atracurium*	*Rocuronium*	*Atracurium*	*Rocuronium*	*Atracurium*
[Baseline	*77.7 ± 13.6*	*79.8 ± 13.9*	*113 ± 16.8*	*113.2 ± 15.9*	*66.7 ± 12*	*63.8 ± 9.9]*
	bpm		*mmHg*		*mmHg*	
2 min	0.17 ± 0.07	0.10 ± 0.06	0.05 ± 0.04	-0.07 ± 0.04	-0.05 ± 0.05	-0.01 ± 0.06
P	0.65		0.67		0.72	
5 min	0.04 ± 0.05	-0.01 ± 0.04	-0.01 ± 0.04	-0.06 ± 0.04	-0.05 ± 0.05	-0.03 ± 0.05
P	0.5		0.4		0.87	
10 min	-0.05 ± 0.04	-0.1 ± 0.04	-0.05 ± 0.04	-0.06 ± 0.04	-0.04 ± 0.05	-0.02 ± 0.06
P	0.37		0.87		0.97	
15 min	-0.03 ± 0.05	-0.07 ± 0.04	0.01 ± 0.05	0.05 ± 0.06	0.06 ± 0.06	0.17 ± 0.08
P	0.61		0.43		0.43	

Mean ± SD; *P* values are between groups at each time interval.

patient - one dose; two patients - two doses; one patient - three doses; one patient - five doses). These five patients were not included in the determination of the recovery index or the time to recovery.

Surgery was of sufficient duration in 10 patients in the rocuronium group and in six patients in the atracurium group to allow observation of spontaneous recovery from the intubating dose of muscle relaxant. The mean time from injection of the muscle relaxant to TOF 70% (recovery time) was similar in both groups, whereas the recovery index was slightly longer in the rocuronium group (9.6 ± 2.41 *vs* 6.9 ± 1.89 min; $P = 0.023$; Table II).

Discussion

This study of the effects of rocuronium and atracurium is unique because of its randomized, assessor-blinded design in an ambulatory surgery, female patient population, and because the patients received intravenous anaesthesia supplemented only with N_2O. The principal clinical findings of this study support, in part, the hypothesis being tested and are in general agreement with other reports in the literature about rocuronium and atracurium.[11-13,15-17] Rocuronium, given as an *iv* bolus dose after the induction of anaesthesia in patients undergoing ambulatory laparoscopic surgery, was associated with a shorter time to tracheal intubation (onset times of 59.0 *vs* 98.6 sec for rocuronium and atracurium, respectively) and a higher rate of successful intubation at <90 sec (100% *vs* 70% for rocuronium *vs* atracurium, respectively) than atracurium. However, the clinical duration of action was shorter for rocuronium (33.3 min) than that for an equi-effective dose of atracurium (44.7 min). Also, although the time to recovery for each drug was similar (53 *vs* 59 min), the recovery index for rocuronium was longer than that for atracurium (9.6 *vs* 6.9; $P < 0.023$ min). These different pharmacodynamic profiles were not associated with any difference between the two drugs in their cardiovascular profiles before skin incision or in the incidence of side effects for the duration of the study.

The clinical durations of action of rocuronium and atracurium, which were the primary endpoint for the pharmacodynamic portion of the study, reflect those values described in the literature for these muscle relaxants when they are given during balanced anaesthesia both with[12,13] and without[2,16] volatile drugs. In our study, rocuronium had a clinical duration approximately 11 min shorter than an equi-effective dose of atracurium, which makes rocuronium ideally suited to surgery of predictably short duration. We were able to follow the spontaneous recovery in 16 patients up to 70% TOF recovery and found that the time to recovery was similar for the two drugs. Similar equivalency in time to recovery has been reported by Hans *et al.*[13] However, Hans *et al.*[13] reported a longer recovery index for atracurium (17.8 ± 4.2 min) than after

rocuronium (13.8 ± 4.1 min), whereas the recovery time for rocuronium in this study was slightly longer than that for atracurium (9.6 ± 2.41 *vs* 6.9 ± 1.89 min; $P = 0.023$). The difference between the results of these two studies probably reflects the interaction of the volatile anaesthetic enflurane used in the study by Hans *et al.*[13] with the neuromuscular blocking effects of the muscle relaxants. The difference in the recovery index of the two muscle relaxants observed in this study confirms a clinical perception of slower recovery from rocuronium than from atracurium. The difference in the recovery profile prompted, in part, the rationale for this study, and is due, most probably, to the different mechanisms whereby the two drugs are cleared from the plasma. The rapid rate of recovery from atracurium, once begun, is an attractive property because one can anticipate a rapid return of function, thus avoiding the need for reversal drugs in many cases. Recovery from rocuronium, however, is a little slower, and the use of reversal drugs is recommended should prompt return of function be required.

Our work confirms the observations of others that, when measured at the adductor pollicis, rocuronium has the most rapid onset of action of the muscle relaxants of intermediate duration, although some workers have demonstrated an even more rapid paralysis of the adductor muscles of the vocal cords.[15] This rapidity of action has enabled the intubating conditions produced by rocuronium (0.6 $mg \cdot kg^{-1}$) to be rated as not different from those produced by succinylcholine in a direct comparison in patients undergoing outpatient anaesthesia with propofol and alfentanil.[2] In a study of young children, Scheiber *et al.*[11] observed better intubating conditions at the time of completed intubation in patients given rocuronium than those given atracurium or vecuronium. We were unable to score a qualitative difference in the conditions of tracheal intubation between rocuronium and atracurium, but in all the patients who received rocuronium the tracheas were intubated in <90 sec from the time of injection of the muscle relaxant compared with only 14 (70%) of those who were given atracurium. This result suggests a subtle difference in the quality of intubating conditions provided by the two drugs that was not apparent in the gross scoring that we employed, despite our using the same anesthesiologist who was blinded to the study drugs used to intubate the tracheas in all patients.

We chose to compare the neuromuscular effects of equi-effective doses of the two drugs using the 2 × ED_{90} determined by Wierda *et al.*[16] and Sokoll *et al.*[17] for rocuronium and atracurium, respectively. There is more agreement in the literature as to the potency of rocuronium than that of 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. We felt that the ED_{90} obtained from single-dose injections of muscle relaxant during balanced anaesthesia as described by Sokoll *et al.*[17] provided the most accurate assessment of potency. We consequently chose a rocuronium:atracurium potency ratio of 1.2:1.

The patients in the study experienced few adverse events during the course of the anaesthesia and during their stay in the Postanaesthesia Care Unit. The type of surgery was laparoscopic gynaecological ambulatory surgery, so it was not surprising that the most frequent events were symptoms of emesis.[18] Doses of atracurium >0.4 $mg \cdot kg^{-1}$ are frequently associated with cutaneous erythema as a consequence of an increase in plasma histamine concentration, and such a reaction was noted in one patient in the atracurium group.[15] Histamine release has been shown to be insignificant following doses of rocuronium up to 1.2 $mg \cdot kg^{-1}$,[20] and no cutaneous reaction was noted in any patient in the study who received rocuronium.

The cardiovascular stability of both drugs at the doses used was also demonstrated. There were no differences between the drugs in the changes in heart rate and blood pressure in the 15 min after intubation and before skin incision from control measurements obtained before the induction of anaesthesia. The changes from control were minimal for both drugs. An increased heart rate induced by tracheal intubation that might be expected was not noted in this study, perhaps because any increase had diminished by the two minute time of measurement, or the muscle relaxants may have obtunded such a heart rate increase.

In conclusion, rocuronium has a more rapid onset of action, provides conditions suitable for more rapid tracheal intubation, and has a shorter clinical duration of action than an equi-effective dose of atracurium during propofol and alfentanil anaesthesia in patients undergoing ambulatory surgery. These advantages of rocuronium, in addition to the cardiovascular stability and minimal side effects associated with rocuronium, make this neuromuscular relaxant a desirable choice for rapid tracheal intubation in surgical procedures of relatively short duration.

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