

CISATRACURIUM VS. ROCURONIUM: A PROSPECTIVE, COMPARATIVE, RANDOMIZED STUDY IN ADULT PATIENTS UNDER TOTAL INTRAVENOUS ANAESTHESIA

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Aims: To compare the pharmacodynamics of cisatracurium and rocuronium-induced neuromuscular block following single dose, allowing either spontaneous or neostigmine-accelerated complete recovery.

Methods: Following the ethics committee approval and informed consent, 120 patients scheduled for elective surgery under TIVA with tracheal intubation were randomized into 4 groups with different cisatracurium (CIS, 0.10 or 0.15 mg.kg⁻¹) or rocuronium (ROC, 0.60 or 0.90 mg.kg⁻¹) doses administered. For each patient, the onset time for 95 % depression of T₁, clinical duration until 25 % recovery, recovery index (T₁ from 25 to 75 %) and time from T₁ 25 % to TOF-ratio 0.9 were determined allowing either spontaneous or induced recovery.

Results: The onset times were 277 (SD 58), 220 (46), 91 (16) and 77 (16) s for the CIS 0.10, CIS 0.15, ROC 0.60 and ROC 0.90 groups (p < 0.05), respectively, with lower variability in both ROC groups (p < 0.05). The clinical durations were 42 (7), 52 (7), 35 (11) and 52 (12) min, respectively (p < 0.05 for lower doses). Recovery index was identical in all groups allowing either spontaneous recovery - 15.9 (1.8), 15.5 (1.7), 16.1 (3.7) and 16.1 (4.0) min, or following neostigmine administration - 4.4 (0.9), 4.5 (0.8), 4.3 (0.8) and 4.7 (0.7) min for respective groups. During spontaneous recovery, the variability of DUR25-TOF90 was twice as great for ROC than CIS groups (p < 0.05), while after neostigmine administration it was uniform in all groups.

Conclusions: For equipotent doses, the onset times for CIS were approximately three times longer than for ROC. The average clinical duration for both relaxants ranged from 35 to 52 min with acceptable variability. Neostigmine administration accelerated the recovery and reduced its variability. When allowing for spontaneous recovery, less scatter was demonstrated for both CIS groups than for ROC ones.

INTRODUCTION

For many years, much effort has been made to develop neuromuscular blocking agents (NMBAs, neuromuscular blockers [NMBs], muscle relaxants, curarimimetics) with rapid onset and short duration of action¹. Two current drugs have this aim. Cisatracurium and rocuronium are non-depolarizing NMBs with an intermediate duration of action. They were introduced into clinical practice^{2,3} in 1992 (rocuronium) and 1995 (cisatracurium), respectively, and currently they are gradually replacing earlier drugs (vecuronium and atracurium). Acting on the nicotinic receptors of the neuromuscular plate, all NMBs attack one of the vital functions (spontaneous breathing) that must be simultaneously supported with mechanical ventilation of the lungs.

Almost exclusively anaesthetists use muscle relaxants; hence thorough knowledge of NMBs pharmacokinetics and pharmacodynamics is mandatory for this group of doctors.

The aim of this study was to compare the **pharmacodynamic parameters** of cisatracurium (CIS) and rocuronium

(ROC) induced neuromuscular block (NMB) following a single dose of 2 or 3 x ED₉₅, allowing either spontaneous or neostigmine-induced complete recovery. Special attention was paid to the **variability** of these parameters.

MATERIAL AND METHODS

Following approval from the local Ethics Committee and obtaining informed consent, 120 adult patients, scheduled for elective general surgery under total intravenous anaesthesia (TIVA) with tracheal intubation, muscle relaxation and mechanical ventilation, were studied. Exclusion criteria were ASA physical status more than III, age under 18 and over 75 years, obesity (BMI over > 30 kg.m⁻²), patients receiving medication known to interfere with NMBs (anticonvulsants, amino glycosides or polypeptide antibiotics), patients with anticipated difficult intubation (Mallampati score⁴ III and more), and those with diseases affecting neuromuscular transmission (myopathies).

Table 1. Demographic data.

	CIS 0.10 (n = 30)	CIS 0.15 (n = 30)	ROC 0.60 (n = 30)	ROC 0.90 (n = 30)
Age (years)	51.5 (12.6) [53.5]	50.6 (13.3) [53.0]	51.5 (14.9) [51.0]	50.9 (13.7) [51.5]
Men/Women (n)	14/16	16/14	12/18	17/13
Weight (kg)	76.5 (14.3) [79.5]	75.1 (10.8) [75.0]	74.5 (12.2) [77.0]	74.1 (11.1) [72.5]
Height (cm)	171.1 (8.2) [173]	170.7 (7.8) [170]	171.3 (9.0) [171]	171.7 (8.8) [174]
BSA (m ²)	1.90 (0.22) [1.96]	1.88 (0.16) [1.89]	1.88 (0.19) [1.89]	1.87 (0.16) [1.88]
BMI (kg.m ⁻²)	26.01 (3.72) [26.36]	25.82 (3.50) [26.72]	25.35 (3.56) [25.57]	25.16 (3.82) [25.82]
ASA classification (I/II/III)	11/16/3	9/19/2	12/14/4	9/18/3

Data are means (SD – standard deviation) [median] or frequencies, CIS and ROC – groups with different doses (mg.kg⁻¹) of cisatracurium and rocuronium administered

Pre-anaesthetic questionnaire was used to collect patients' demographic data – gender, age, weight, height, ASA classification; derived parameters (body mass index, body surface area) were computed⁵. Patients were randomly assigned to 4 groups of 30 (CIS 0.10, CIS 0.15, ROC 0.60, ROC 0.90). A method of computer-generated random numbers with blockwise randomization was used to obtain balanced sample sizes in all groups. In CIS groups, patients received cisatracurium 0.10 and 0.15 mg.kg⁻¹, respectively. In ROC groups, the respective rocuronium doses were 0.60 and 0.90 mg.kg⁻¹.

Anaesthesia

Premedication consisted of diazepam 5–10 mg orally 1 hr before the beginning of surgery. On arrival in the operating room, the electrocardiogram (ECG), haemoglobin oxygen saturation (SpO₂) and non-invasive arterial pressure (NIBP) were monitored. An intravenous cannula was inserted into a forearm vein. Datex-Ohmeda S/5™ Anaesthesia Monitor with relevant modules (ECG, NIBP, pulse oxymetry, oxygen and nitrous oxide inspiratory and expiratory concentrations, spirometry, core and skin temperature, NMT – neuromuscular transmission) was used to monitor the patient during anaesthesia and surgery.

After 3 min preoxygenation, intravenous premedication with midazolam (Dormicum®, F. Hoffmann-LaRoche, 0.05 mg.kg⁻¹) and sufentanil (Sufenta® forte, Janssen Pharmaceutica, 0.1 µg.kg⁻¹) was injected into a rapidly running infusion of normal saline. Total intra-

venous anaesthesia (TIVA) in TCI mode (target controlled infusion) was induced and maintained with the Base Primea® (Fresenius Vial) infusion device. Target plasmatic concentrations were initially set to 2.0 µg.ml⁻¹ for propofol (Propofol Abbott, Abbott Laboratories) in Schnider's model⁶ and 1.8 ng.ml⁻¹ for sufentanil in Gepts's model⁶, respectively, and adjusted according to clinical response during anaesthesia.

Sufentanil was discontinued 20 min before the end of anaesthesia and tracheal extubation was not performed before full recovery from neuromuscular block (TOF-ratio ≥ 0.90).

Neuromuscular block and monitoring

To facilitate tracheal intubation, neuromuscular block was induced with a single bolus dose of cisatracurium or rocuronium, respectively. The calculated amount of relaxant was injected over 5 s into a rapid infusion of normal saline. Following maximal depression of T₁ (onset time), direct laryngoscopy was initiated followed by tracheal intubation. The endotracheal tube was connected to closed „low-flow“ anaesthetic breathing circuit with a mixture of 40 % oxygen in air; mechanical ventilation was adjusted to maintain end-tidal partial pressure of carbon dioxide (E_TCO₂) between 4.7 and 5.0 kPa.

Neuromuscular transmission monitoring complied with GCRP (good clinical research practice)^{7,8}, using the NMT module of Datex-Ohmeda S/5™ Anaesthesia Monitor. Both oesophageal and skin temperature were

Table 2. Pharmacodynamic parameters and variability – onset time, clinical duration.

	CIS 0.15 (n = 30)	CIS 0.15 (n = 30)	ROC 0.60 (n = 30)	ROC 0.90 (n = 30)
ONSET TIME (s)	B,C,D 277 (58) [283]	A,C,D 220 (46) [220]	A,B,D 91 (16) [90]	A,B,C 77 (16) [75]
Variability of ONSET TIME (s)	C,D 44 (36) [33]	C,D 35 (29) [30]	A,B 11 (11) [10]	A,B 12 (11) [8]
CLINICAL DURATION DUR25 (min)	B,C,D 42 (7) [40]	A,C 52 (7) [52]	A,B,D 35 (11) [34]	A,C 52 (12) [53]
Variability of CLINICAL DURATION (min)	6 (3) [6]	D 5 (4) [4]	8 (7) [5]	B 10 (7) [9]

Data are means (SD – standard deviation) [median], CIS and ROC – groups with different doses (mg.kg⁻¹) of cisatracurium and rocuronium administered

ONSET – onset time, DUR25 – clinical duration

^A p < 0.05 vs. CIS 0.10, ^B p < 0.05 vs. CIS 0.15, ^C p < 0.05 vs. ROC 0.60, ^D p < 0.05 vs. ROC 0.90

continuously recorded. Thenar skin temperature was monitored using a probe placed on the dorsum of the hand from which the response to ulnar nerve stimulation was recorded. Skin temperature over the thenar muscles was maintained above 34 °C throughout the study period by wrapping the arm in cotton wool. After induction, but before administration of the neuromuscular blocking drug, the NMT monitor was calibrated using the automatic start-up-procedure, and we then applied 0.1 Hz single twitch stimulation before relaxant injection. After maximal neuromuscular block had been established, we switched to TOF stimulation assessed at 12 s intervals by stimulation of ulnar nerve with four rectangular impulses at 2 Hz, duration 0.2 ms and supramaximal current. The evoked electromyographic response of adductor pollicis muscle was monitored. All data reflecting the effect of neuromuscular blocker (TOF-ratio, T₁ value) were wirelessly transferred⁹ to a PC, displayed on the screen and stored for further processing.

For each consecutive patient, spontaneous recovery until 25 % of T₁ was allowed (clinical duration). At this point, each group was divided into 2 subgroups of 15 patients (the randomization described previously). While in the SPONT subgroup, the patients were allowed to recover from the block spontaneously, in the NEOST subgroup the recovery course was accelerated with neostigmine (Syntostigmin, Hoechst-Biotika, 0.04 mg.kg⁻¹) administered with atropine (Atropin, Hoechst-Biotika, 0.015 mg.kg⁻¹). The following pharmacodynamic parameters were measured in all patients:

1. **ONSET TIME** (s) = time interval from the completion of the intravenous injection of the relaxant to maximal T₁ depression
2. **DUR25** (min) = **CLINICAL DURATION** – time interval from the completion of the intravenous injection

of the relaxant to spontaneous recovery of T₁ to 25 % of the control value

3. **DUR25-75** (min) = **RECOVERY INDEX** – time interval from the end of clinical duration (T₁ = 25 %) to 75 % recovery of T₁ (T₁ = 75 %)
4. **DUR25-TOF90** (min) = interval from the end of clinical duration (T₁ = 25 %) to TOF-ratio 0.90, which reflects complete recovery from the block
5. For each drug, the **VARIABILITY** of all pharmacodynamic parameters was determined by subtracting the actual value of a given parameter from its respective mean. The larger the variability of a parameter the less accurate was the prediction of duration of this parameter.

Statistical support

Statistical calculations were carried out using the software packages SPSS for Windows v. 14.0, Systat SigmaStat for Windows v. 3.5 and Systat SigmaPlot for Windows v. 10.0. The sample size was determined by performing a power analysis based on a previous study⁹. From the data, we calculated that 29 patients in each group would be sufficient to find a significant difference of 30 % or more in onset time between groups (0.05 two-way significance level [α = 0.05], 80 % power [β = 0.2]). Depending on the character and distribution of the data, a variety of parametric and nonparametric tests were used for statistical analysis. To compare the physical characteristics of the groups, analysis of variance (ANOVA) or Kruskal-Wallis test were performed. The chi-square test was used to compare distribution by sex and ASA classification. The pharmacodynamic variables between two groups with different doses of the same relaxant administered were compared using unpaired Student's t-test or Mann-Whitney rank sum test; analysis of variance (ANOVA) was applied when comparing all groups. If the overall comparison revealed

Table 3. Pharmacodynamic parameters and variability – recovery characteristics.

	CIS 0.10 (n = 30)		CIS 0.15 (n = 30)		ROC 0.60 (n = 30)		ROC 0.90 (n = 30)	
	SPONT (n = 15)	NEOST (n = 15)	SPONT (n = 15)	NEOST (n = 15)	SPONT (n = 15)	NEOST (n = 15)	SPONT (n = 15)	NEOST (n = 15)
RECOVERY INDEX DUR25-75 (min)	B,D,F,H 15.9 (1.8) [16.3]	A,C,E,G 4.4 (0.9) [4.7]	B,D,F,H 15.5 (1.7) [15.5]	A,C,E,G 4.5 (0.8) [4.7]	B,D,F,H 16.1 (3.7) [15.7]	A,C,E,G 4.3 (0.8) [4.3]	B,D,F,H 16.1 (4.0) [16.3]	A,C,E,G 4.7 (0.7) [4.6]
Variability of RECOVERY INDEX (min)	F,H 1.5 (0.8) [1.6]			G 0.7 (0.4) [0.5]	F,H 2.8 (2.3) [1.9]	A,E,G 0.6 (0.5) [0.6]	D,F,H 3.1 (2.3) [2.9]	A,E,G 0.6 (0.5) [0.5]
DUR25-TOF90 (min)	B,D,F,H 49.2 (8.0) [49]	A,C,E,G 11.5 (2.8) [12]	B,D,E,F,H 52.5 (7.0) [54]	A,C,E,G 11.7 (2.7) [12]	B,C,D,F,G,H 43.1 (13.1) [41]	A,C,E,G 9.8 (2.0) [10]	B,D,E,F,H 56.7 (12.9) [56]	A,C,E,G 10.0 (2.7) [10]
Variability of DUR25-TOF90 (min)	F 6.3 (4.5) [5.8]	E,F,G 2.3 (1.4) [1.5]	F 5.2 (4.5) [3.5]	E,F,G 2.2 (1.3) [2.0]	B,D,F,H 10.7 (7.1) [8.9]	A,B,C,D,E,G 1.6 (1.3) [1.1]	B,D,F,H 10.6 (6.9) [9.7]	E,G 1.9 (1.9) [1.1]

Data are means (SD – standard deviation) [median],

CIS and ROC – groups with different doses ($\text{mg}\cdot\text{kg}^{-1}$) of cisatracurium and rocuronium administered
DUR25-75 – recovery index, DUR25-TOF90 – time interval from the end of clinical duration (T_1 25 %) to TOF-ratio 0.9, SPONT – spontaneous recovery, NEOST – neostigmine-induced recovery

^A $p < 0.05$ vs. CIS 0.10 SPONT, ^B $p < 0.05$ vs. CIS 0.10 NEOST, ^C $p < 0.05$ vs. CIS 0.15 SPONT, ^D $p < 0.05$ vs. CIS 0.15 NEOST, ^E $p < 0.05$ vs. ROC 0.60 SPONT, ^F $p < 0.05$ vs. ROC 0.60 NEOST, ^G $p < 0.05$ vs. ROC 0.90 SPONT, ^H $p < 0.05$

a statistical significance, appropriate post hoc tests were done. The results are expressed as means (SD – standard deviation) [median] or frequencies. The accepted significance level was 0.05.

(DUR25-TOF90 interval) was more consistent with lower variability in both CIS groups.

RESULTS

120 patients were enrolled in the study. All groups (CIS 0.10 – CIS 0.15 – ROC 0.60 and ROC 0.90, respectively) were comparable with regard to sex, age, weight, height, BSA, BMI, and ASA classification (Tab. 1). No complications attributable to the study or anaesthesia were observed. The pharmacodynamic findings related to neuromuscular block are summarized in Tab. 2 and 3. Following induction of the block, both ROC doses provided the fastest onset time with lowest variability. Clinical duration of the block was dose dependent in both groups, being 42 (SD 7) and 52 (7) min, respectively, for CIS groups and 35 (SD 11) and 52 (12) min, respectively, for ROC groups. During spontaneous recovery, the recovery index was almost uniform for all four groups and the same applies when the blockade was antagonized with neostigmine. The course of complete recovery from the block

DISCUSSION

Neuromuscular block is an essential part of balanced general anaesthesia. However, widespread use of muscle relaxants, often based on empiricism and superficial look at the commercial information, is frequently associated with unacceptably high incidence of adverse effects. Basically, two categories of potential complications related to the use of neuromuscular blockers can be identified:

1. Adverse effects that are undesirable under any circumstance (e.g. histamine liberation, anaphylactoid or anaphylactic reaction¹⁰).
2. Adverse reactions caused by increased effect (e.g. improper dosage) and/or by incorrect timing (e.g. post-operative residual curarization).

The incidence of anaphylactic and anaphylactoid reactions occurring during anaesthesia is estimated between 1 in 10,000 and 1 in 20,000 anaesthesias¹⁰. Neuromuscular blocking agents represent the most frequently involved

substances¹⁰, with a range of 50 % to 70 %. Rocuronium (43.1 %) and succinylcholine (22.6 %) are the most frequently incriminated NMBs¹⁰⁻¹⁶. Compared to atracurium, the risk of histamine release following cisatracurium is markedly reduced but sporadic reports on anaphylactic reactions are available¹⁷. In our study, there were no signs of anaphylaxis during anaesthesia. However, the number of patients studied was too small to draw conclusions.

The ease of intravenous injection of muscle relaxant, resulting in neuromuscular block, contrasts with clinically serious consequences following its application and with considerable interindividual variability. Particularly at the end of anaesthesia, this may present a problem; in one patient, the effect of a single bolus dose of NMB may have fully subsided, while in the other one, there is a significant degree of block still present¹⁸⁻²⁰.

The only solution for this potentially life-threatening condition is adequate perioperative neuromuscular monitoring²¹⁻²³.

Today, rocuronium is a non-depolarizer with the fastest onset. In this study, the onset times of equipotent doses were three times longer for CIS than for ROC. From this point of view, ROC is superior to CIS (and to any non-depolarizing NMB available today, too) and with special precautions, it can safely be used for rapid sequence induction^{9,24-26}. Fast onset, flexibility and promptness of response make ROC also suitable for a computer-controlled closed-loop system for automatic regulation of neuromuscular block during anaesthesia²⁷.

As far as the clinical duration until 25 % recovery is concerned, there was a significant difference both between CIS 0.10 vs. CIS 0.15 and ROC 0.60 vs. ROC 0.90, respectively. When comparing the equipotent doses of the two relaxants, the clinical duration following lower doses (CIS 0.10 vs. ROC 0.6) was different (42 (SD 7) vs. 35 (11) min, respectively) but no significant difference could be demonstrated for the larger ones (CIS 0.15 vs. ROC 0.90) (ref.^{28,29}).

Both NMBs had identical recovery indices, irrespective of the dose administered. This applied both to spontaneous and induced recovery. It means, when the muscle strength recovered to 25 %, further course and subsiding of the block was fairly uniform^{29,30}. The DUR25-TOF90 interval reflects the time necessary for the complete recovery from the neuromuscular block. Following neostigmine administration, this interval was identical for all four groups^{30,31}. When allowing for spontaneous recovery, the variability of this index was twice as great for ROC than for CIS.

Based on the dose administered, the course of recovery was better predicted for CIS than ROC. This may be advantageous at the end of anaesthesia when considering neostigmine administration to prevent postoperative residual curarization^{17,31-33}.

CONCLUSION

ROC is unbeatable in its onset speed. In both doses, it produced fast and deep neuromuscular blockade. For equipotent doses, the onset times for CIS were approximately three times longer than for ROC. Both relaxants provided adequate blockade of average clinical duration ranging from 35 to 52 min with acceptable variability. In all groups, neostigmine administration accelerated the recovery and decreased its variability. When allowing for spontaneous recovery, less scatter was demonstrated for both CIS groups than for ROC ones.

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