

COMPARATIVE STUDY OF NEUROMUSCULAR BLOCKING AND HEMODYNAMIC EFFECTS OF ROCURONIUM AND CISATRACURIUM UNDER SEVOFLURANE OR TOTAL INTRAVENOUS ANESTHESIA

ASHRAF MOUNIR AMIN*, MOHAMMAD YOSRY MOHAMMAD*
AND MONA FATHI IBRAHIM*

Abstract

Neuromuscular blockers (NMB) are important adjuvant to general anesthesia. Rocuronium bromide and cisatracurium besylate are considered relatively recently introduced non-depolarizing muscle relaxants.

Objectives: This study evaluates the enhancement of cisatracurium and rocuronium-induced neuromuscular block during anesthesia with 1.5 MAC sevoflurane or total i.v. anesthesia (TIVA), hemodynamic effects and side effects.

Methodology: 80 patients were randomly allocated into one of four equal Groups to receive either rocuronium (under sevoflurane or propofol TIVA) or cisatracurium (under sevoflurane or propofol TIVA). The NMB effects of rocuronium and cisatracurium were studied by constructing dose-effect curves. Acceleromyography (TOF-Guard) and train-of-four (TOF) stimulation of the ulnar nerve were used (2 Hz every 15 sec). Cisatracurium and rocuronium were administered in increments until depression of $T_1/T_0 > 95\%$ was reached. Hemodynamic effects of both muscle relaxants together with sevoflurane or propofol were assessed using thoracic bioimpedance.

Results: Depression of T_1/T_0 was enhanced under sevoflurane compared to TIVA. ED_{50} and ED_{95} values of both drugs were significantly lower under sevoflurane more than TIVA. Recovery index 25-75% and time to a TOF ration of 0.70 were prolonged significantly by sevoflurane compared to TIVA. Hemodynamically, rocuronium and cisatracurium did not exert significant changes, but the interaction of the relaxants and the anesthetic agents resulted in statistically significant decline in some hemodynamic parameters at certain periods which are not clinically significant and required no medications.

Conclusion: We conclude that the effects of rocuronium and cisatracurium are significantly enhanced during sevoflurane compared with propofol anesthesia and the recovery is lower.

From Anesthesia Department, Faculty of Medicine, Cairo University.

* Correspondence with Dr. Mohammad Yosry Mohammad 31 Meawen Street. East Omrania - Haram - Giza. 1st floor, flat no. 3. Post code 12551 Cairo, Egypt. Phone: 002-010-168-93-92 Fax: 002-02-3761348 E-mail: m_yosry_m@yahoo.com

Introduction

Neuromuscular blockers (NMB) have become essential parts of the anesthetist armamentarium. They aid endotracheal intubation, mechanical ventilation, reduce anesthetic requirements, prevent patient movement without voluntary or reflex muscle movement, facilitate surgery, and decrease oxygen consumption.

In the development of new neuromuscular blocking drugs, the anesthesiologist is now provided with drugs that are almost free of unwanted effects, have a time course of action that allows great control of their activity and, in most cases, allows the anesthesiologist to substitute them for succinylcholine¹.

In selecting a neuromuscular blocking agent, an anesthetist strives to achieve three competing goals: rapid adequate muscle relaxation, hemodynamic stability, and predictable complete return of skeletal muscle function.

Rocuronium bromide is a non-depolarizing muscle relaxant, with a short onset time, an intermediate duration of action and rapid recovery characteristics coupled with cardiovascular stability, with no histamine release or other side effects².

Cisatracurium has an intermediate duration of action, potent and safe with excellent cardiovascular stability and without apparent histamine release³.

Sevoflurane is a fluorinated methyl ethyl ether that has less respiratory irritation, more hemodynamic stability and more rapid emergence in comparison to isoflurane⁴. It has a low blood-gas solubility resulting in rapid uptake and elimination. These physicochemical properties allow a fast recovery, thus making it suitable for day case surgery.

Propofol (di-isopropylphenol) is a phenol which is insoluble in water. The short elimination half life and non cumulative properties of propofol should make this drug ideal for use in TIVA. Indeed propofol can be considered the best intravenous anesthetic available for TIVA⁵.

The neuromuscular blocking effects of muscle relaxants are enhanced by volatile anesthetics, a phenomenon called "potentiation". Several reasons have been postulated as the causes of this potentiation: pre-junctional effects, increased blood flow to muscles

during anesthesia, and a centrally mediated relaxation. Not all types of anesthetics enhance neuromuscular block to the same extent⁶.

Inhaled anesthetics augment the neuromuscular blockade from nondepolarizing muscle relaxants in a dose-dependent fashion, which may also depend on the duration of anesthesia.

Joo and Perks have shown that the use of volatile anesthetics results in lower ED50 and ED95 of neuromuscular blockade significantly in comparison to propofol⁴. Underestimation of the enhancement of neuromuscular block by volatile anesthetics during short procedures could result in inadvertent prolonged duration of relaxation.

A new method for monitoring neuromuscular function consists of measuring acceleration of the thumb after stimulation of a peripheral motor nerve⁷. This technique is based on Newton's second law:

$$\text{Force} = \text{mass} \times \text{acceleration}$$

Thus if mass is constant, acceleration is directly proportional to force. Accordingly, after nerve stimulation, one can measure not only the evoked force but also the acceleration of the thumb⁸.

Acceleromyography is a simple method of analyzing neuromuscular function. One requirement is that the muscle be able to move freely. During a nondepolarizing neuromuscular blockade, good correlation exists between the TOF ratio measured by this method and the TOF ratio measured with a force displacement transducer⁹. Also the precision of acceleromyography seems to be comparable to that of mechanical measurement¹⁰.

The aim of this study is to compare rocuronium to cisatracurium regarding intensity, duration of neuromuscular blockade and also the hemodynamic profile under sevoflurane or total intravenous anesthesia with propofol, as well as associated side effects.

Materials and Methods

This clinical study was conducted in Kasr et Aini University Hospital after obtaining local Ethics Committee approval and informed patient consent. Eighty adult patients of both sexes (ASA I and II) scheduled to undergo extra-thoracic moderate

elective general surgery were studied in a prospective, randomized study. Routine laboratory investigations included liver function tests, kidney function tests, complete blood picture, and coagulation profile.

Patients were randomly divided into 4 equal groups, (20 patients each). Group I (Rocuronium & Sevoflurane), Group II (Cisatracurium & Sevoflurane), Group III (Rocuronium & Propofol) and finally, Group IV (Cisatracurium and propofol). Exclusion criteria included cardiovascular diseases or drugs affecting hemodynamics, renal impairment, hepatic insufficiency, endocrine disease, neuromuscular disease or receiving drugs that interact with neuromuscular blockers and finally, difficult intubation patients grade III & IV.

All patients received midazolam 0.05 mg.kg⁻¹ I.M. one hour before surgery. An intravenous line was secured in the arm opposite to that connected to the neuromuscular monitoring equipment. Anesthesia was induced with propofol 2-2.5 mg.kg⁻¹ and fentanyl 1 µg.kg⁻¹. Oxygen and nitrous oxide mixture (50:50%) were used in all Groups. Groups I and II patients were allowed to sustain spontaneous ventilation with a face mask with 2 MAC sevoflurane for 10-15 minutes, then rocuronium and cisatracurium were given in gradual incremental doses till reaching ED₉₅ as judged by accelerograph. Groups III and IV patients received a standard propofol infusion at 6-12 mg.kg⁻¹.h⁻¹. Rocuronium and cisatracurium were given in gradual incremental doses till reaching ED₉₅ as judged by accelerograph. The patients were anesthetized before operating the stimulator, as the stimulator could be painful to an awake patient.

Lungs were mechanically ventilated, followed by laryngoscopy and orotracheal intubation when ED₉₅ was reached. Anesthesia was maintained in Group I and II with 2 MAC sevoflurane and with propofol, 100 µg.kg⁻¹.min⁻¹ in Groups III and IV. End-tidal PCO₂ was adjusted to 32-36 mmHg, skin temperature above the monitored muscle were measured and maintained between 32°C and 35°C by passive warming (wrapping of the patient arm in a cotton blanket). The arterial pressure cuff was placed on the opposite arm.

When adductor response was reached to T_{25%} (time to recovery of T₁ to 25% of baseline), clinical relaxation was maintained by a second bolus of rocuronium (0.1 mg/kg) or cisatracurium (0.015 mg/

kg) till the end of the operation.

Neuromuscular Monitoring

By the use of **TOF-guard** (biometer, Denmark) the following variables of neuromuscular block were obtained for all groups:

1 - *Depression of T₁ of the train-of-four:* Cumulative increments of 100 µg.kg⁻¹ rocuronium were given in Groups I and III, while increments of 15 µg.kg⁻¹ cisatracurium were given in Groups II and IV. The subsequent dose was administered after at least 3 min and only if three consecutive twitches of identical amplitude were demonstrated (steady state of onset). Increments were given until depression of the first twitch of at least 95% was achieved during sevoflurane or total i.v. anesthesia (*equi-effective dose: identical end-point instead of identical doses*).

2 - *Cumulative dose-response curves:* They were obtained by non-linear regression in the four Groups, showing values of ED₅₀, Ed₉₅, Ed₉₅/ED₅₀ ratio and the slope of the regression curve in the four Groups of the study.

3 - *Clinical duration:* Time after injection of the last cumulative dose of muscle relaxant until 25% recovery of T₁.

4 - *Recovery index:* Time interval during which T₁ recovered from 25% to 75% of control. Time to TOF_{0.7}: Time required for return of TOF ratio to 0.7.

Fig. 1
The TOF-Guard connected to the patient
before starting stimulation

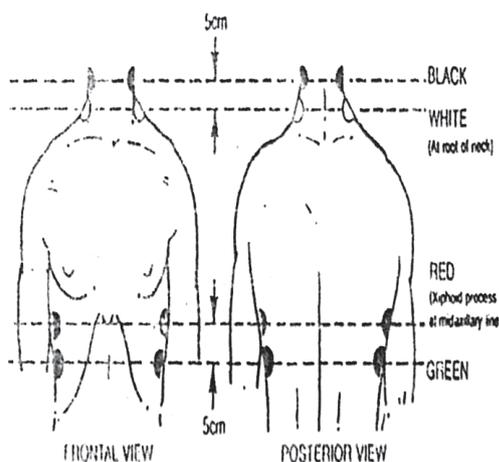


TOF-Guard: It is a relatively new microprocessor controlled neuromuscular transmission monitor

based on accelerometry. Four supramaximal stimuli of 60 mA were given every 0.5 seconds (2HZ), and each set (train) is repeated by the monitor every 15 seconds to the ulnar nerve at the wrist. Electrodes are placed over the ulnar nerve on the medial side of the wrist. The transducer is positioned so that its flat side is placed on the finger in such a way that the movement is perpendicular. The temperature probe is placed over the skin of adductor pollicis muscle; it can read between 16.0 to 41.5 C°. The data are stored on a memory card and transferred to a computer (Fig. 1).

Hemodynamics: Hemodynamic parameters were monitored at; before administration of general anesthesia, after administration of general anesthesia and just before administration of muscle relaxant, then at 1, 3, 5, 10, 15, 20 minutes after muscle relaxant and then every 10 minutes up to 90 minutes. The following parameters were monitored: heart rate, mean arterial blood pressure (by Agilent M 1166A monitor), cardiac index and stroke index were monitored non-invasively by thoracic bioimpedance (BOMED/NCCO M3-R7) cardiodynamic monitor. Electrodes are applied to the patients' neck and chest as shown in Fig. 2. After recovery data were measured, conventional doses of neostigmine 0.045 mg/kg with atropine 0.01 mg/kg were given, followed by continued hemodynamic and oxygenation monitoring and management of postoperative complications: e.g. pain, nausea and vomiting.

Fig. 2
The drawing indicating proper placement of Thoracic Bioimpedance electrodes



Statistical Analysis

Data were presented as mean (SD), or mean (95% CI), as appropriate. Statistical analysis was performed using the software package statistica® 5.0 for Windows®. Values were compared among the groups using analysis of variance (ANOVA) with post hoc Newman-Keul's test. Repeated measures ANOVA were used for comparison of hemodynamic parameters. Chi-square test was used for analysis of categorical data. Statistical significance was set when $P < 0.05$. Dose-response curves were constructed by non-linear regression using the known pharmacological model:

$$\text{Response} = \text{Max} - \frac{\text{Max}}{\text{Max} + \left(\frac{\text{Dose}}{\text{ED}_{50}}\right)^{\text{Slope}}}$$

Where *Max* is the maximum possible response (100% in the present case), ED_{50} is the median effective dose and *Slope* is the slope of the regression curve. Both ED_{50} and *Slope* were estimated as regression parameters. ED_{95} , the dose which produces the desired response in 95% of patients, was calculated from the equation of the regression curve.

The 95% confidence interval (CI) was calculated for ED_{50} , ED_{95} , the ratio $\text{ED}_{95}/\text{ED}_{50}$, and the slope of the curve. If the experiment is to be repeated a hundred times under the same conditions, the calculated values of the previously mentioned parameters will fall within the 95% CI in 95 of these hundred times; i.e. it can be said with 95% confidence that the calculated values of the parameter will fall within the 95% CI.

Results

Demographic data: there was no significant difference among the four Groups of the study as regards age, weight, gender distribution, or duration or surgery (Table 1).

Hemodynamic parameters

Heart rate: Changes in heart rate are shown in Table 2. Significant changes at certain times of the study are marked with *. There was no significant difference among the four Groups at baseline as well as all through the study period. General anesthetic administration resulted in a non significant decrease of heart rate in the four Groups of the study.

Table 1
Demographic and operative data of patients in the four Groups of the study [mean (SD) or ratio].

	Group I (n = 20)	Group II (n = 20)	Group III (n = 20)	Group IV (n = 20)
Age (year)	35 (8.9)	34 (8.8)	35 (7.8)	37 (6.5)
Gender (M/F)	12/8	9/11	13/7	11/9
Weight (kg)	73 (3.9)	70 (5.2)	73 (5.09)	74 (3.9)
ASA status (I/II)	15/5	14/6	16/4	13/7
Duration of operation (min)	72 (8.8)	71 (7.1)	69 (5.8)	74 (9.2)

Mean arterial pressure: As shown in Table 3, there was no significant difference among the four Groups at baseline as well as all through the study period as regards MAP. Mean arterial pressure showed non significant decrease as a result of administration of general anesthetics. Significant changes at certain times of the study are marked with *.

Table 3
Mean arterial pressure (mmHg) in the four Groups of the study [mean (SD)]

	Group I (n = 20)	Group II (n = 20)	Group III (n = 20)	Group IV (n = 20)
Baseline	89 (5.3)	87 (4.2)	86 (4.7)	89 (6.0)
Before MR	84 (8.4)	82 (8.5)	80 (6.2)	83 (7.9)
1	84 (6.5)	81 (5.9)	79 (6.4)*	81 (7.3)*
3	82 (7.5)*	81 (7.6)*	79 (5.4)*	81 (7.4)*
5	84 (8.4)	82 (8.1)	80 (6.2)	82 (7.3)*
10	83 (9.5)*	80 (4.1)*	81 (6.3)	84 (7.3)
15	84 (6.3)	78 (6.9)*	83 (5.5)	84 (6.9)
20	85 (8.2)	80 (6.8)*	81 (7.4)	84 (8.9)
30	82 (7.7)*	79 (6.2)*	81 (6.9)	85 (7.6)
40	83 (8.0)*	82 (7.7)	81 (7.7)	85 (8.6)
50	83 (7.1)*	81 (6.8)	79 (7.4)*	85 (8.9)
60	80 (7.0)*	81 (7.8)*	80 (7.8)	83 (7.6)
70	84 (7.6)	80 (6.4)*	79 (7.2)*	83 (8.7)*
80	82 (8.0)*	81 (8.1)	80 (8.1)	85 (6.4)
90	82 (8.2)*	77 (7.4)*	79 (7.6)*	84 (8.6)

* P < 0.05 compared to baseline values before induction of anesthesia.

Table 2
Heart rate (beats/min) in the four Groups of the study [mean (SD)]

	Group I (n = 20)	Group II (n = 20)	Group III (n = 20)	Group IV (n = 20)
Baseline	75 (4.9)	76 (5.6)	76 (6.4)	77 (2.8)
Before MR	72 (5.2)	73 (6.3)	71 (5.8)	72 (5.5)
1	73 (7.5)	73 (6.8)	72 (9.0)	73 (5.5)
3	71 (6.6)	73 (6.7)	71 (6.5)*	71 (4.9)*
5	72 (6.3)	72 (5.3)	71 (7.3)	71 (3.6)*
10	71 (6.3)	72 (5.9)	71 (7.9)	72 (5.3)*
15	72 (6.3)	73 (5.9)	70 (8.4)*	73 (5.1)
20	71 (6.3)	72 (8.1)	73 (7.1)	73 (4.8)
30	71 (6.3)	72 (6.8)	71 (9.1)*	72 (4.4)*
40	70 (7.2)	71 (6.6)	71 (5.9)	73 (5.0)
50	72 (7.5)	73 (6.5)	72 (7.8)	72 (5.5)
60	70 (6.4)	73 (7.0)	71 (7.5)*	73 (5.4)
70	72 (7.2)	71 (6.0)	71 (8.0)	72 (5.0)*
80	70 (6.4)	72 (6.4)	72 (6.2)	71 (3.4)*
90	71 (5.1)	74 (6.7)	71 (8.4)*	71 (5.5)*

* P < 0.05 compared to baseline values before induction of anesthesia.

Cardiac index (CI): As shown in Table 4, there was no significant difference among the four Groups at baseline as well as all through the study period as regards CI. CI showed non significant decrease as a result of administration of general anesthetics in all Groups. Significant changes at certain times of the study are marked with *.

Table 4
Cardiac index (L/min/m²) in the four Groups of the study
[mean (SD)]

	Group I (n = 20)	Group II (n = 20)	Group III (n = 20)	Group IV (n = 20)
Baseline	3.4 (0.34)	3.5 (0.38)	3.4 (0.29)	3.5 (0.25)
Before MR	3.1 (0.45)	3.3 (0.40)	3.2 (0.35)	3.3 (0.37)
1	3.1 (0.38)	3.3 (0.37)	3.2 (0.33)	3.4 (0.37)
3	3.2 (0.32)	3.3 (0.45)	3.2 (0.37)	3.4 (0.37)
5	3.2 (0.38)	3.2 (0.35)	3.2 (0.37)	3.3 (0.28)
10	3.2 (0.48)	3.2 (0.49)*	3.3 (0.36)	3.5 (0.29)
15	3.1 (0.37)	3.2 (0.39)*	3.2 (0.34)	3.3 (0.42)
20	3.0 (0.32)*	3.1 (0.45)*	3.2 (0.46)	3.3 (0.40)*
30	3.1 (0.35)	3.2 (0.37)*	3.1 (0.32)*	3.3 (0.31)
40	3.0 (0.40)*	3.1 (0.49)*	3.1 (0.37)*	3.3 (0.38)
50	3.1 (0.39)	3.2 (0.40)	3.2 (0.34)	3.3 (0.22)
60	3.0 (0.33)*	3.1 (0.37)*	3.1 (0.38)*	3.2 (0.30)*
70	3.0 (0.30)*	3.3 (0.40)	3.2 (0.37)	3.3 (0.41)*
80	3.0 (0.37)	3.2 (0.36)	3.1 (0.37)	3.3 (0.30)
90	3.0 (0.38)*	3.2 (0.28)*	3.2 (0.40)	3.3 (0.26)*

* $P < 0.05$ compared to baseline values before induction of anesthesia.

Stroke index (SI): As shown in Table 5, there was no significant difference among the four Groups at baseline as well as all through the study period. Stroke index showed non significant decrease after administration of general anesthetics in all Groups. Significant changes at certain times of the study are marked with*.

Neuromuscular Monitoring

Depression of T₁ of the train-of-four: Administration of muscle relaxants resulted in a variable

degree of depression of the T₁ twitch of the train-of-four stimulation in the four Groups of the study. To reach the end-point of at least 95% depression of the T₁ twitch, all patients required at least two increments of muscle relaxants. Most patients required a third increment, while a few patients required a fourth increment. The mean depression (as percent of baseline) resulting from administration of increments of muscle relaxants are shown in Table 6. No patient in group II required a fourth increment of muscle relaxant.

Table 5
Stroke index (ml/m²) in the four Groups
of the study [mean (SD)]

	Group I (n = 20)	Group II (n = 20)	Group III (n = 20)	Group IV (n = 20)
Baseline	52 (6.8)	53 (5.7)	52 (5.1)	53 (3.8)
Before MR	47 (8.9)	49 (7.2)	51 (7.0)	52 (5.7)
1	47 (7.0)	50 (7.8)	52 (7.2)	53 (6.9)
3	49 (7.1)	49 (7.4)	52 (7.0)	54 (5.7)
5	49 (7.8)	49 (6.1)	51 (6.9)	53 (4.9)
10	49 (8.7)	49 (7.7)	53 (7.1)	54 (5.8)
15	48 (7.8)	48 (7.6)	52 (8.0)	52 (4.9)
20	47 (5.5)*	47 (7.4)*	50 (8.2)	51 (6.7)
30	48 (8.5)	48 (6.1)	50 (6.9)	52 (5.8)
40	47 (7.9)	48 (8.2)*	50 (7.2)	51 (6.4)
50	47 (7.4)*	48 (5.7)	51 (6.3)	52 (4.9)
60	47 (7.0)	48 (4.7)	50 (7.1)	50 (4.8)
70	46 (6.5)*	48 (6.0)	51 (6.5)	51 (6.6)
80	48 (8.3)	49 (6.8)	50 (5.8)	53 (4.2)
90	47 (7.1)*	48 (5.4)*	51 (6.9)	52 (4.5)

* $P < 0.05$ compared to baseline values before induction of anesthesia.

Cumulative dose-response curves: Figures 3 through 6 represent the cumulative dose-response curves in the four Groups of the study. The thin lines represent the 95% confidence intervals of the regression line. The narrow confidence intervals imply low inter-individual variability in the response to muscle relaxants. It can be shown from the cumulative dose-response curves that a plateau is reached as the dose approaches the ED₉₅. From the cumulative dose-

response curves, the ED₅₀ and the ED₉₅ were calculated in each of the four Groups. The values of ED₅₀, ED₉₅, the ED₉₅/ED₅₀ ratio and the slope of the regression curve in the four Groups are shown in Table 3-9, together with their 95% confidence intervals. Values of ED₅₀ and ED₉₅ in the sevoflurane Groups were significantly lower than those in the propofol Groups for each muscle relaxant.

*Table 6
Depression (%) of T₁ of the train-of-four relative to baseline values after increments of muscle relaxant in the four Groups of the study [mean (SD)].*

	Group I	Group II	Group III	Group IV
First increment	27 (9.2) [n = 20]	36 (4.4) [n = 20]	14 (4.8) [n = 20]	13 (4.3) [n = 20]
Second increment	90 (7.2) [n = 20]	93 (2.0) [n = 20]	78 (6.8) [n = 20]	78 (3.9) [n = 20]
Third increment	97 (1.8) [n = 15]	98 (1.8) [n = 20]	95 (3.1) [n = 20]	90 (3.2) [n = 20]
Fourth increment	100 (0.0) [n = 2]	[n = 0]	100 (1.2) [n = 6]	97 (1.8) [n = 16]

Fig. 3

Cumulative dose-response curve for rocuronium in patients anesthetized with sevoflurane. Horizontal bars represent the individual observations. The thick solid line represents the best-fit regression line. The upper and the lower thin solid lines represent the 95% confidence limits of the regression line.

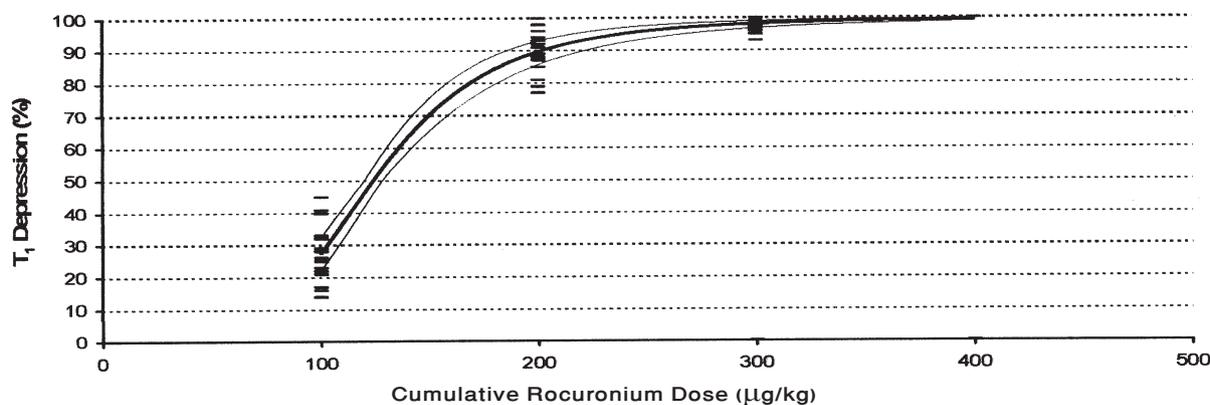


Fig. 4

Cumulative dose-response curve for cisatracurium in patients anesthetized with sevoflurane. Horizontal bars represent the individual observations. The thick solid line represents the best-fit regression line. The upper and the lower thin solid lines represent the 95% confidence limits of the regression line.

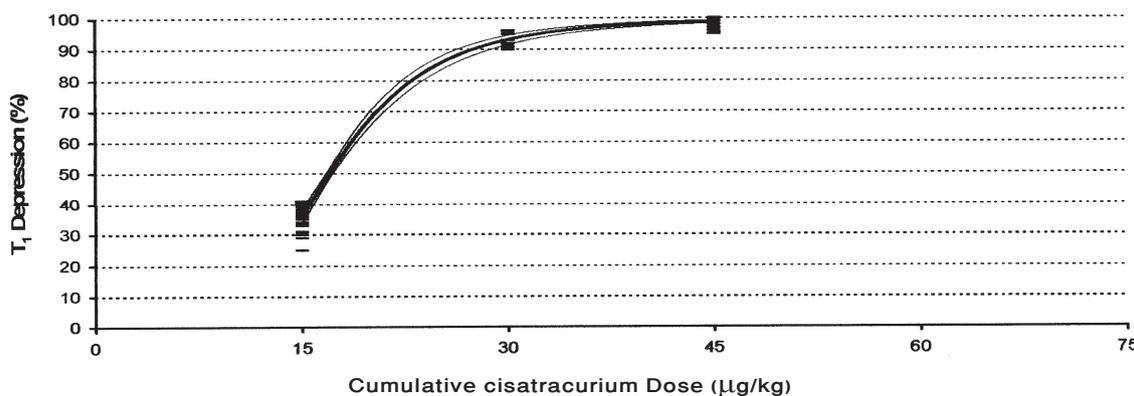


Fig. 5
Cumulative dose-response curve for rocuronium in patients anesthetized with propofol. Horizontal bars represent the individual observations. The thick solid line represents the best-fit regression line. The upper and the lower thin solid lines represent the 95% confidence limits of the regression line.

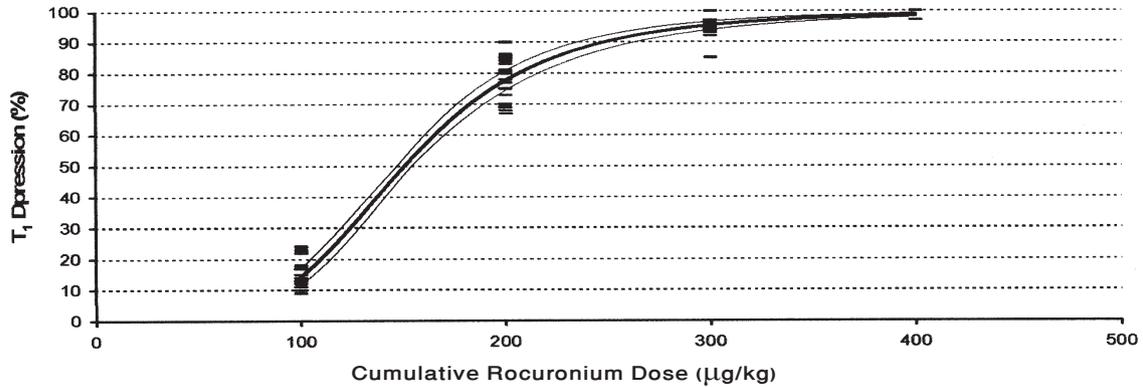
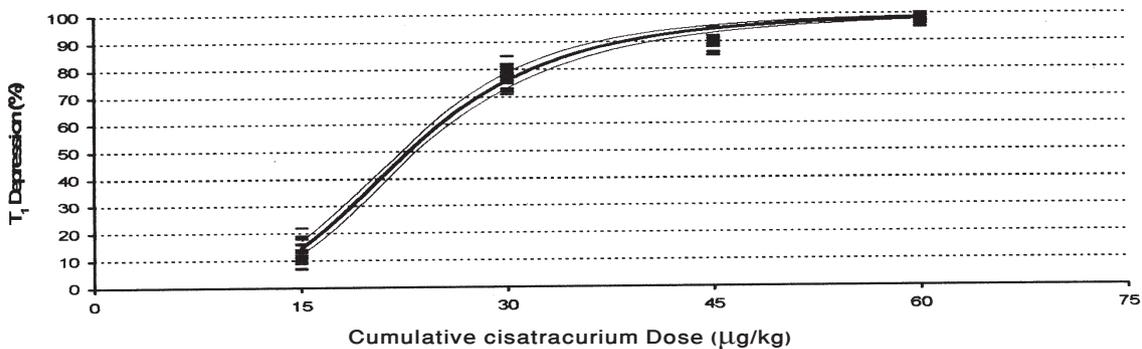


Fig. 6
Cumulative dose-response curve for cisatracurium in patients anesthetized with propofol. Horizontal bars represent the individual observations. The thick solid line represents the best-fit regression line. The upper and the lower thin solid lines represent the 95% confidence limits of the regression line.



However, the slope of the curve and the ED₉₅/ED₅₀ ratio were comparable among the Groups (Table 7). The cumulative dose-response curve was shifted to the left with sevoflurane anesthesia as compared to

propofol anesthesia for each of the muscle relaxants (Fig. 7 & 8). The slope of the curve was not much affected by changing the anesthetic.

Table 7:
Values of ED₅₀, ED₉₅, ED₉₅/ED₅₀ ratio and the slope of the regression curve in the four Group of the study.

		Group I	Group II	Group III	Group IV
ED ₅₀ (µg/kg)	Mean	124	17	150*	23†
	95% CI	119.9 to 128.0	16.8 to 17.2	146.8 to 153.9	22.3 to 23.3
ED ₉₅ (µg/kg)	Mean	238	32	295*	46†
	95% CI	215.1 to 267.1	30.5 to 34.2	276.1 to 316.2	43.2 to 49.0
ED ₉₅ /ED ₅₀	Mean	1.92	1.90	1.96	2.01
	95% CI	1.68 to 2.23	1.77 to 2.04	1.79 to 2.15	1.86 to 2.20
Slope	Mean	4.519	4.600	4.376	4.205
	95% CI	4.002 to 5.035	4.293 to 4.907	4.088 to 4.665	3.956 to 4.453

* P < 0.01 compared with group I. † P < 0.01 compared with group II.

Fig. 7
Comparison between the cumulative dose-response curves of rocuronium under sevoflurane versus propofol anesthesia.

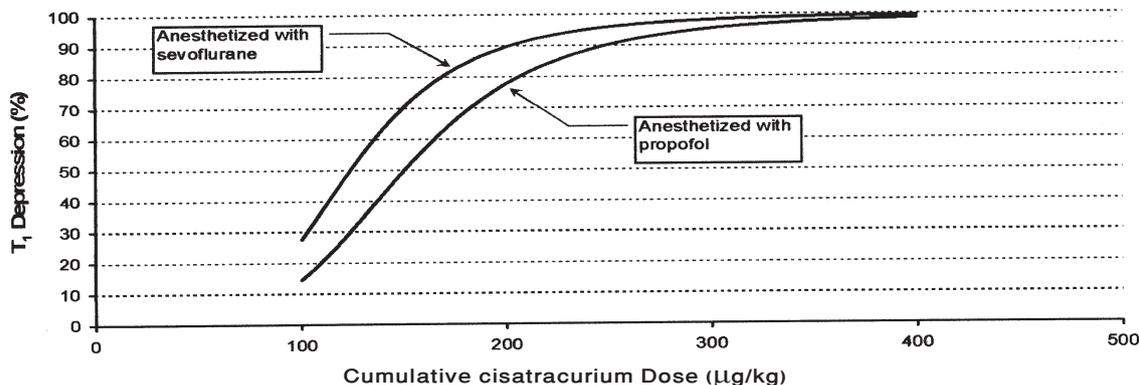
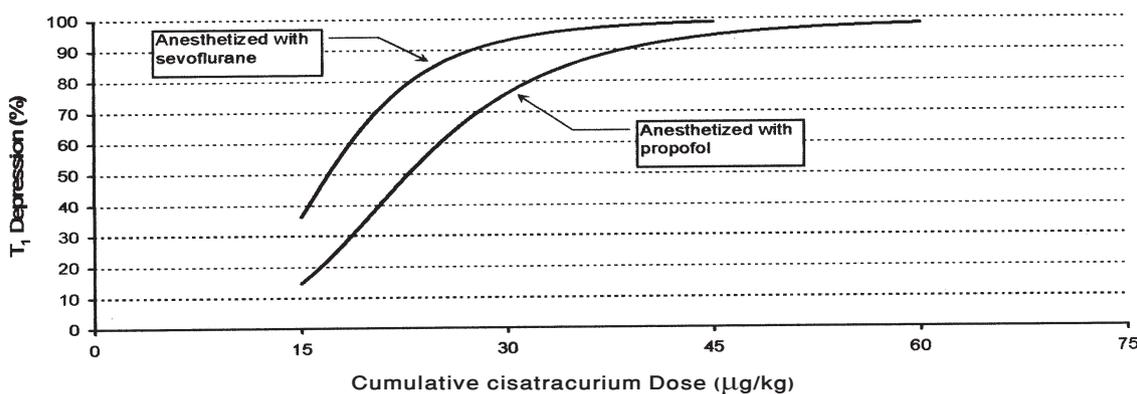


Fig. 8
Comparison between the cumulative dose-response curves of cisatracurium under sevoflurane versus propofol anesthesia.



Recovery from muscle relaxation: Time to recovery of T₁ to 25% of baseline (T_{25%}) was not significantly different with the different anesthetics or muscle relaxants; while time to recovery of T₁ to 75% of baseline (T_{75%}), the recovery index (the difference between T_{75%} and T_{25%}) and time required for return of TOF ratio to 0.7 (TOF_{0.7}) were significantly prolonged by the use of sevoflurane compared with propofol, and were significantly longer with cisatracurium than rocuronium (Table 8).

Recorded Side Effects

Three patients in the propofol with rocuronium Group elicited pain on drugs injection and postoperative phlebitis. Also we report two cases of postoperative nausea and vomiting in the sevoflurane Groups, one in each Group.

Table 8
Recovery criteria in the four Groups of the study [mean (SD)]

	Group I (n = 20)	Group II (n = 20)	Group III (n = 20)	Group IV (n = 20)
T _{25%} (min)	18 (4.8)	19 (4.5)	15 (3.3)	16 (6.3)
T _{75%} (min)	31 (8.0)*	37 (8.9)**	23 (5.8)	30 (10.1)†
Recovery index (min)	13 (3.3)*	18 (4.5)**	9 (2.5)	14 (3.8)†
TOF _{0.7} (min)	36 (7.8)*	44 (6.4)**	29 (6.2)	34 (6.7)†

T_{25%} = time to recovery of T₁ to 25% of baseline; T_{75%} = time to recovery of T₁ to 75% of baseline; Recovery index = the difference between T_{75%} and T_{25%}; TOF_{0.7} = time necessary for the TOF ratio to return to 0.7. *P < 0.05, same muscle relaxant, different anesthetic, † P < 0.05, same anesthetic, different muscle relaxant.

Discussion

This comparative study determined the influence of sevoflurane on the dose response relationship of either rocuronium or cisatracurium compared to a TIVA with propofol as well as hemodynamic effects of both relaxants under the two anesthetics. The neuromuscular blocking effect of rocuronium and cisatracurium were enhanced by sevoflurane. The interaction between sevoflurane and both neuromuscular blocking drugs (NMBD) led to increased intensity of block and prolongation of recovery in comparison to TIVA with propofol.

Usually, potentiation of NMBD by volatile anesthetics results predominantly in prolongation of the duration and recovery of neuromuscular block¹¹. Recovery was prolonged significantly by the volatile anesthetic sevoflurane under the conditions of the present study. The prolongation of the effect of rocuronium or cisatracurium during sevoflurane anesthesia is probably caused by a faster and more complete equilibrium among the end-tidal, blood, and muscle concentrations of sevoflurane because of its smaller muscle-gas partition coefficient, resulting in slower recovery, as seen in all groups under sevoflurane anesthesia¹². As regarding the potency (augmentation of depression of T_1), we determined the anesthesia-related effects of cisatracurium or rocuronium but not the absolute potency data.

The cumulative dose technique may underestimate the potency of neuromuscular blocking agents. However, administration of both, cisatracurium and rocuronium was standardized and the use sevoflurane or TIVA with propofol was randomized; thus the cumulative pattern of cisatracurium and rocuronium administration would have similar effects in all groups.

In the present study values of ED_{50} and ED_{95} in the sevoflurane Groups were significantly lower than those in the propofol Groups for each muscle relaxant. The values of mean ED_{50} and ED_{95} of rocuronium were lower during sevoflurane anesthesia than with TIVA. Similarly the values of mean ED_{50} and ED_{95} of cisatracurium were lower during sevoflurane anesthesia than with TIVA. However, the slope of the curve and the ED_{95}/ED_{50} ratio were comparable among the Groups. The cumulative dose-response curve was shifted to the left with sevoflurane anesthesia as compared to

propofol anesthesia for each of the muscle relaxants. It was found that degree of potentiation (ratio of ED_{50} during TIVA/ ED_{50} during volatile anesthesia) was 1.2 for sevoflurane in both types of relaxants.

Using a single-dose technique for rocuronium, Oris et al.¹³ reported a lower ED_{50} during halothane, isoflurane and enflurane anesthesia compared to TIVA using a cumulative dosing technique. Similarly, Lowry et al.¹⁴ demonstrated a significant increase in the apparent potency of rocuronium during anesthesia with 1.5 MAC of sevoflurane compared with propofol anesthesia. The study of Xue et al.¹⁵ estimated the potency of rocuronium during sevoflurane and thiopental-nitrous oxide anesthesia and found values in broad agreement with our results. Thomas et al.¹⁶ investigated the interaction between the cumulative dose requirements of cisatracurium and anesthesia with isoflurane, sevoflurane, desflurane or propofol using closed-loop feedback control. They found that in comparison to propofol, isoflurane, sevoflurane and desflurane reduce the cumulative dose requirements of cisatracurium by 42%, 41% and 60%, respectively to maintain a 90% depression of T_1 of TOF. Kopman et al.¹⁷ suggested that drug potency may be more intense under N_2O anesthesia compared with total IV anesthesia (TIVA).

Regarding the clinical duration, we found that it was not significantly different with the different anesthetics or muscle relaxants. Lowry et al.¹⁴ demonstrated that the time course of action after a bolus dose of rocuronium 0.6 mg/kg that was studied in patients anesthetized with 66% nitrous oxide in oxygen and 1.5 minimum alveolar anesthetic concentration of sevoflurane or isoflurane, or a propofol infusion did not differ significantly among groups. Similarly Wulf et al.¹¹ concluded that following equi-effective dosing of rocuronium ($T_1 > 95\%$), the clinical duration to 25% T_1 recovery during desflurane, isoflurane, sevoflurane and total intravenous anesthesia did not result in significant difference among these groups.

Regarding recovery in the present study, $T_{75\%}$, the recovery index and $TOF_{0.7}$ were significantly prolonged by the use of sevoflurane compared with propofol, and were significantly longer with cisatracurium than rocuronium. Reid et al.¹⁸ demonstrated that recovery from rocuronium induced neuromuscular block was slowed in the presence of potent volatile

agents in comparison to TIVA, and that this effect is more marked in patients receiving sevoflurane. Similarly Bock et al.¹⁹ studied recovery characteristics of rocuronium during 1.25 MAC of isoflurane, desflurane, and sevoflurane or propofol anesthesia in 84 patients using electromyography. After 120 min, the cumulative infusion rate of rocuronium required to obtain twitch depression of 90-95%, recovery index was prolonged under isoflurane, sevoflurane and desflurane anesthesia, in comparison to propofol. There were no significant differences between the three potent inhalation anesthetics in relation to recovery characteristics of rocuronium.

Cisatracurium is the only neuromuscular blocker that is both free of histamine-releasing properties and that undergoes organ-independent Hofmann elimination¹. Other studies²⁰⁻²¹ demonstrated that hemodynamically stable patients receiving a rapidly administered bolus dose of 6-8 x ED₉₅ of cisatracurium did not have hemodynamic changes that would be expected with a histamine-releasing compound. However, with bolus administration of rocuronium, some studies documented an increase in heart rate (HR), pulmonary vascular resistance (PVR), stroke index (SI) and cardiac index (CI), with decreased pulmonary capillary wedge pressure (PCWP), whereas other studies found no hemodynamic changes¹.

In our study, propofol and sevoflurane anesthesia induced non statistically significant hypotension and bradycardia in all Groups before administration of the muscle relaxants. There were no evidences of any significant clinical cardiovascular changes (Heart rate, MAP, SI, CI) when comparing post induction values to those after administration of cisatracurium or rocuronium, but there were statistically significant decline in MAP and CI at certain periods in comparison to preinduction values, attributed to the interaction between the relaxant used and maintenance agents. Heart rate in sevoflurane groups did not change significantly from baseline all through the study period, whereas some readings of heart rate in the propofol Groups were significantly lower than their baseline. SI in the propofol Groups remained comparable to baseline all through the study period whereas, SI decreased significantly relative to its baseline in the sevoflurane Groups at some points of study. However, these points of decline in all previous hemodynamic

parameters, although statistically significant, but are clinically not significant and required no medications to treat adverse hemodynamic events.

Researches²² found no clinical significant hemodynamic changes after rocuronium administration, but differed from others²³ that showed that a dose of 0.9 mg/kg rocuronium (3x ED₉₅) caused some cardiovascular effects (10-15% increase in mean arterial pressure and 5-10% increase in heart rate). These effects although statistically significant, are not likely to be clinically important, however, our study showed absence of statistically significant difference before and after administration of rocuronium due to the small dose equaling ED₉₅ that was given in increments.

Naguib et al.²⁴ found that administration of rocuronium 0.6 mg.kg⁻¹ caused no significant changes in plasma histamine concentrations or in hemodynamic state at any time. Mark et al.²⁵ found that the hemodynamic profile of a 0.6 mg.kg⁻¹ bolus of rocuronium was acceptable for patients with coronary artery disease, and changes that occurred would not promote increases in myocardial oxygen demand or further decreases in oxygen supply. Although CVP and MPAP decreased significantly, rocuronium had no effect on PCWP, SVR, MAP, or CI. Overall, these results indicate that clinical doses of rocuronium are not associated with hemodynamic instability in ASA class 3 and 4 patients undergoing cardiac surgery.

Consistent with our results, Taivainen et al.²⁶ compared the cardiovascular effects of a rapidly administrated IV dose of cisatracurium 0.15 mg.kg in infants and children during nitrous oxide-opioid anesthesia and found that changes in heart rate and arterial pressure were negligible, furthermore, there were no signs attributable to possible histamine release. Similarly, Carroll²⁷ observed the hemodynamic stability after administration of cisatracurium 0.15 mg.kg⁻¹ in patients were undergoing elective coronary artery bypass and concluded that cisatracurium is suitable relaxant when hemodynamic stability is important.

Three of our patients in propofol with rocuronium Group elicited pain on drugs injection and postoperative phlebitis. Cheong and Wong²⁸ found that rocuronium in particular, causes intense discomfort at the site of injection in conscious patients. When administered

in a subparalysing dose, 50-100% of patients report discomfort. Also in our study, we reported two cases of postoperative nausea and vomiting in the sevoflurane Groups. In most meta-analyses, propofol was associated with a lower frequency of PONV when used for total intravenous anesthesia in the absence of N₂O. In one meta-analysis, the rate of PONV was lower with the use of propofol when compared with sevoflurane⁴.

From the previous clinical study, the effects of rocuronium and cisatracurium are enhanced by sevoflurane, in comparison to TIVA with propofol anesthesia, and the recovery is slower. Particular attention should be paid to monitoring of neuromuscular block

during sevoflurane anesthesia with careful titration of relaxants' doses to avoid inadvertent prolongation of recovery. The combination of sevoflurane and cisatracurium resulted in the longest duration of recovery between Groups and recommended for long procedures while the combination of rocuronium and TIVA with propofol resulted in the shortest duration of recovery in comparison to all Groups and recommended for short and day case procedures.

When cardiovascular stability is of importance, the use of rocuronium and cisatracurium are recommended, as well as sevoflurane (producing more stable heart rate than TIVA with propofol).

References

1. MOORE E AND HUNTER J: The new neuromuscular blocking agents: do they offer any advantages? *Br J Anaesth*; 2001, 87:912-25.
2. LEVY J, DAVIS G AND DUGGAN J: Determination of the hemodynamics and histamine release of rocuronium (ORG 9426) when administered in increased doses under N₂O/O₂ – sufentanil anesthesia. *Anesth Analg*; 1994, 78:318-21.
3. WASTILA W, MAEHR R AND TURNER G: Comparative pharmacology of cisatracurium (51W89), atracurium, and five isomers in cats. *Anesthesiology*; 1996, 85:169.
4. JOO H AND PERKS W: Sevoflurane versus propofol for anesthetic induction: a meta-analysis. *Anesth Analg*; 2000, 91:213-9.
5. SCHUTTLE J AND IHMSEN H: Population pharmacokinetics of propofol: a multicenter study. *Anesthesiology*; 2000, 92:727-38.
6. THOMAS M, HEMMERLING A, SCHUETTLER H AND SCHWILDEN H: Desflurane reduces the effective therapeutic infusion rate (ETI) of cisatracurium more than isoflurane, sevoflurane, or propofol. *Can J Anesth*; 2001, 48:532-537.
7. EIKERMANN M, GROEBEN H, HÜSING J AND PETERS J: Acceleromyography of adductor pollicis predicts recovery of respiratory function from neuromuscular blockade. *Anesthesiology*; 2003, 98:1333-7.
8. JENSEN E, VIBY-MOGENSEN J AND BANG U: The Accelograph: A new neuromuscular transmission monitor. *Acta Anaesthesiol Scand*; 1988, 32:49.
9. MAY O, KIRKEGAARD NIELSEN H AND WERNER M: The acceleration transducer – an assessment of its precision in comparison with a force displacement transducer. *Acta Anaesthesiol Scand*; 1988, 32:239-43.
10. HARPER N, MARLEW R AND STRNAG T: Monitoring neuromuscular block by acceleromyography: Comparison of the Mini-Accelograph with the Myograph 2000. *Br J Anaesth*; 1994, 72:411-4.
11. WULF H, LEDOWSKI T, LINSTEDT U AND DIETFRID J: Neuromuscular blocking effects of rocuronium during desflurane, isoflurane, and sevoflurane anaesthesia. *Can J Anaesth*; 1998, 45:526-532.
12. ZHOU J AND LIU J: The solubility of volatile anesthetics in human tissues. *Anesth Analg*; 2001, 93:234-8.
13. ORIS B, CRUL J, VANDERMEERSCH E AND VAN AKEN H: Muscle paralysis by rocuronium during halothane, enflurane, isoflurane, and total intravenous anesthesia. *Anesth Analg*; 1993, 77:570-3.
14. LOWRY D, MIRAKHUR R, MCCARTHY G, CARROLL M AND MCCOURT K: Neuromuscular effects of rocuronium during sevoflurane, isoflurane, and intravenous anesthesia. *Anesth Analg*; 1998, 87:936-40.
15. XUE F, LIAO X, TONG S, LIU J, AN G AND LUO L: Dose-response and time-course of the effect of rocuronium bromide during sevoflurane anaesthesia. *Anaesthesia*; 1998, 53:25-30.
16. THOMAS M, HEMMERLING A, SCHUETTLER H AND SCHWILDEN H: Desflurane reduces the effective therapeutic infusion rate (ETI) of cisatracurium more than isoflurane, sevoflurane, or propofol. *Can J Anesth*; 2001, 48:532-537.
17. KOPMAN W, CHIN J AND MALIK R: The Effect of Nitrous Oxide on the Dose-Response Relationship of rocuronium. *Anesth Analg*; 2005, 100:1343-1347.
18. REID J, BRESLIN D, MIRAKHUR R AND HAYES A: Neostigmine antagonism of rocuronium block during anesthesia with sevoflurane, isoflurane or propofol. *Can J Anaesth*; 2001, 48:351-5.
19. BOCK M, KLIPPEL K, NITSCHKE B, BACH A, MARTIN E AND MOTSCH J: Rocuronium potency and recovery during steady-state desflurane, sevoflurane, isoflurane or propofol anesthesia. *Br J Anaesth*; 2000, 84:43-7.
20. LIEN C, BELMONT M AND ABALOS A: The cardiovascular effects and histamine-releasing properties of 51W89 in patients receiving nitrous oxide/opioid/barbiturate anesthesia. *Anesthesiology*; 1995, 82:1131-8.
21. KONSTADT S, REICH D, STANLEY T, DePERIO M, CHUEY C AND SCHWARTZBACH C: A two-center comparison of the cardiovascular effects of cisatracurium (Nimbex™) and vecuronium in patients with coronary artery disease. *Anesth Analg*; 1995, 81:1010-14.
22. SHORTEN G, UPPINGTON J AND COMUNALE M: Changes in plasma catecholamine concentrations and haemodynamic effects of rocuronium and vecuronium in elderly patients. *Eur J Anaesthesiol*; 1998, 15:335-41.
23. ROBERTSON E, HULL J, VERBEEK A AND BOOIJ L: A comparison of rocuronium and vecuronium: The pharmacodynamic, cardiovascular and intra-ocular effects. *Eur J Anaesthesiol*; 1994, Suppl, 9:116-121.
24. NAGUIB M, SAMARKANDI A, BAKHAMEES H AND EL-BAKRY A: Histamine-release haemodynamic changes produced by rocuronium, vecuronium, mivacurium, atracurium and tubocurarine. *Br J Anaesth*; 1995, 75:588-592.
25. MARK E, KENNETH P, WILLIAM C AND LEONARD L: Haemodynamic effects of rocuronium bromide in adult cardiac surgical patients. *Can J Anaesth*; 1998, 45:139-43.
26. TAIIVAINEN T, MEAKIN G AND MERETOJA O: The safety and efficacy of cisatracurium 0.15 mg/kg during nitrous oxide anaesthesia in infants and children. *Anaesthesia*; 2000, 55:1407-1051.
27. CARROLL M, MIRAKHUR R AND LOWRY D: Neuromuscular blocking effects and train-of-four fade with cisatracurium: comparison with other nondepolarizing relaxations. *Anesthesia*; 1998, 53:1169-1173.
28. CHEONG K AND WONG W: Pain on injection of rocuronium influence of two doses of lidocaine pretreatment. *Br J Anaesth*; 2000, 84:106-7.

