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INFLUENCE OF AGE AND GENDER ON THE PHARMACODYNAMIC PARAMETERS OF ROCURONIUM DURING TOTAL INTRAVENOUS ANESTHESIA

Milan Adamus[a]*, Lumir Hrabalek[b], Tomas Wanek[b], Tomas Gabrhelik[a], Jana Zapletalova[c,d]

[a] *Department of Anesthesiology and Intensive Care Medicine, University Hospital Olomouc and Faculty of Medicine and Dentistry, Palacky University Olomouc, Czech Republic*
[b] *Department of Neurosurgery, University Hospital Olomouc and Faculty of Medicine and Dentistry, Palacky University Olomouc*
[c] *Department of Medical Biophysics, Faculty of Medicine and Dentistry, Palacky University Olomouc*
[d] *Institute of Molecular and Translational Medicine, Faculty of Medicine and Dentistry, Palacky University Olomouc*
E-mail: milan.adamus@seznam.cz

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Aims. To compare the pharmacodynamics of 0.6 mg kg^{-1} rocuronium in young and older patients of both genders during total intravenous anesthesia.

Methods. Following local ethics committee approval and informed consent, patients scheduled for surgery under total intravenous anesthesia (propofol/sufentanil) were divided into 4 study groups: 37 males aged 20-40, 40 males aged 60-75 yrs, 43 females aged 20-40 and 38 females aged 60-75 yrs. Neuromuscular block following rocuronium (0.6 mg kg^{-1}) was monitored: train-of-four [TOF] stimulation of the ulnar nerve at 15-s intervals, EMG of the adductor pollicis muscle. The onset time (from application of rocuronium to maximum depression of T_1), clinical duration (from application to 25% recovery of T_1), and time to full spontaneous recovery (from application to TOF-ratio ≥ 0.9) were determined for each patient. The Kruskal-Wallis test was used to compare differences between groups; $P<0.05$ was considered statistically significant.

Results. The onset time (median [interquartile range]) in the respective groups was 90 [80-110]^{BCD}, 135 [116-165]^{AC}, 75 [60-90]^{ABD}, and 120 [90-146]^{AC} seconds. The clinical duration was 30 [25-42]^{BCD}, 58 [53-67]^{AD}, 50 [40-65]^{AD}, and 85 [70-90]^{ABC} min. Interval to full spontaneous recovery was 59 [51-67]^{BCD}, 102 [75-106]^{A}, 76 [66-91]^{AD}, and 128 [94-137]^{AC} min. ($^{A}P<0.05$ vs. young males, $^{B}P<0.05$ vs. elderly males, $^{C}P<0.05$ vs. young females, $^{D}P<0.05$ vs. elderly females).

Conclusion. Females and older patients were more sensitive to rocuronium.

INTRODUCTION

Rocuronium (ROC) is a modern aminosteroidal neuromuscular blocking agent (NMBA) with intermediate clinical duration of action (30-50 min). Introduced into clinical practice in 1994 (ref.[1]), it is now frequently used during general anesthesia worldwide. Of the non-depolarizing NMBAs, ROC has the fastest onset (45-60 s), and to facilitate tracheal intubation in elective cases, it is gradually replacing suxamethonium[2,3].

The drug dose is usually calculated according to patient body weight. However, the effect of a number of anesthetic agents, including aminosteroidal NMBAs, can be influenced by a large number of other factors including gender[4,5] and age[6-8].

The aim of this study was to compare the pharmacodynamics (PD) of the rocuronium, following a single dose (0.6 mg kg^{-1}) in young and older males and females during total intravenous anesthesia (TIVA).

MATERIALS AND METHODS

This was a prospective, non-interventional, non-blinded, clinical study. Its protocol did not alter the routine anesthetic care at the main author's department.

After obtaining the Hospital Ethics Committee approval and written informed consent to anesthesia, adult patients, scheduled for elective surgery under total intravenous anesthesia with tracheal intubation, muscle relaxation with single bolus dose of rocuronium and mechanical ventilation, were enrolled. The expected duration of surgery was about 60-120 min. The management of anesthesia was identical in all patients but only males and females of two age groups (20-40 and 60-75) were studied.

Exclusion criteria were ASA physical status more than 3, obesity (BMI more than 30 kg m^{-2}), anticipated difficult tracheal intubation, age outside the selected range. Patients using medication known to interfere with NMBA and those with severe renal, hepatic, metabolic, or neuromuscular diseases were not studied either. Patients in whom the initial dose of rocuronium had to be supplemented with one or several top-ups, or those in whom the reversal was administered, were also excluded. Unstable

neuromuscular blockade (NMB) monitoring was also a reason for exclusion.

A pre-anesthetic questionnaire was used to collect patients' demographic data (gender, age, weight, height, ASA physical status classification) and BMI (body mass index) was computed.

Anesthesia

We used standardized anesthetic techniques in all patients[5]. The patients were premedicated orally with diazepam 5-10 mg 1 h before the beginning of surgery. On arrival in the operating room, an intravenous cannula was inserted into a vein of the forearm contralateral to NMT (*neuromuscular transmission*) measurement. After 3-min preoxygenation, midazolam (1-3 mg) and sufentanil (0.1 μg kg^{-1}) were injected intravenously. Total intravenous anesthesia in TCI mode *(target-controlled infusion)* was induced and maintained with a Base Primea® (Fresenius Vial) infusion device. Target plasmatic concentration was initially set to 2.0 μg ml^{-1} for propofol in Schnider's model[9,10] and 1.8 ng ml^{-1} for sufentanil in Gepts's model[9,11], respectively, and adjusted according to blood pressure and heart rate during anesthesia. To facilitate tracheal intubation, neuromuscular block was induced with a single bolus dose of rocuronium (0.6 mg kg^{-1}) injected intravenously over 5 seconds. Following maximal depression of T_1 (onset time), tracheal intubation was performed. The endotracheal tube was connected to *"low-flow"* anesthetic breathing circuit with a mixture of 40 % oxygen in air; mechanical ventilation was adjusted to maintain end-tidal partial pressure of carbon dioxide (E_TCO_2) between 4.7 and 5.0 kPa. When necessary, supplemental top-ups of 5 mg rocuronium were administered. Sufentanil and propofol were discontinued 10 minutes before the end of anesthesia and extubation was not performed before full recovery from neuromuscular block (TOF-ratio ≥ 0.90). When required, the recovery was accelerated with neostigmine (0.04 mg kg^{-1}) given together with atropine (0.015 mg kg^{-1}).

Neuromuscular block and monitoring

This study was conducted in accordance with good clinical research practice in pharmacodynamic studies of neuromuscular blocking agents[12]. We used the NMT module of the AS/3™ Anaesthesia Monitor (Datex-Ohmeda) and the monitoring system was connected to the patient before induction of anesthesia. Following careful skin preparation of the right distal forearm, five skin electromyographic monitoring electrodes (H124, Kendall) were applied over the ulnar nerve and adductor pollicis muscle as appropriate. The forearm was immobilized in supination on a splint. Skin temperature was monitored using a probe placed on the dorsum of the hand from which the response to ulnar nerve stimulation was recorded. The temperature was maintained above 34 °C throughout the study period by wrapping the arm in cotton wool. After anesthesia induction, but before administration of rocuronium, the NMT monitor was calibrated using the automatic start-up-procedure. For measurements, we used TOF (train-of-four) assessed at 15-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. The height of twitch response to first im-

Table 1. Patients' demographic data.

	Males (M)		Females (F)		*P*-value
	Young (20–40 yr)	Elderly (60–75 yr)	Young (20–40 yr)	Elderly (60–75 yr)	
No	37	40	43	38	0.633[a]
Age (yr)	31 ± 7[BD] (29–33)	66 ± 4[AC] (65–67)	29 ± 6[BD] (28–31)	67 ± 4[AC] (66–68)	< 0.0001[b]
Weight (kg)	74 ± 9[D] (71–77)	76 ± 9[CD] (74–79)	68 ± 11[B] (65–72)	66 ± 11[AB] (63–70)	< 0.0001[b]
Height (cm)	171 ± 9[CD] (168–173)	174 ± 7[CD] (171–176)	166 ± 8[AB] (163–168)	165 ± 9[AB] (162–168)	< 0.0001[b]
BMI (kg m^{-2})	25.6 ± 3.0 (24.7–26.6)	25.4 ± 2.8 (24.5–26.2)	24.9 ± 3.0 (24.0–25.8)	24.4 ± 3.1 (23.4–25.4)	0.280[b]
ASA (1/2/3)	22/12/3	11/25/4	27/10/6	13/21/4	0.005[c]
Supramax (mA)	46 ± 15 (41–51)	43 ± 11 (39–46)	45 ± 12 (42–49)	43 ± 9 (40–46)	0.455[b]

BMI = body mass index, ASA = American Society of Anesthesiologists' Physical Status Classification, Supramax = supramaximal current
Data are mean ± SD (95% CI), or frequencies.
[a]Fisher's exact test, [b]One-way ANOVA with Tukey-Kramer multiple comparisons post-test, [c]chi-square test
[A]$p < 0.05$ vs. young males, [B]$p < 0.05$ vs. elderly males, [C]$p < 0.05$ vs. young females, [D]$p < 0.05$ vs. elderly females

Table 2. Pharmacodynamics of rocuronium in young and elderly males and females.

	Males (M)		Females (F)		*P*-value[a]
	Young (20–40 yr)	Elderly (60–75 yr)	Young (20–40 yr)	Elderly (60–75 yr)	
Onset time (s)	90^{BCD} [80–110]	135^{AC} [116–165]	75^{ABD} [60–90]	120^{AC} [90–146]	< 0.001
Clinical duration (min)	30^{BCD} [25–42]	58^{AD} [53–67]	50^{AD} [40–65]	85^{ABC} [70–90]	< 0.001
Full recovery (min)	59^{BCD} [51–67]	102^{A} [75–106]	76^{AD} [66–91]	128^{AC} [94–137]	< 0.001

Data are median [interquartile range].
[a]non-parametric ANOVA (Kruskal-Wallis test) with multiple comparisons post-test (Dunn)
$^{A}p < 0.05$ vs. young males, $^{B}p < 0.05$ vs. elderly males, $^{C}p < 0.05$ vs. young females, $^{D}p < 0.05$ vs. elderly females

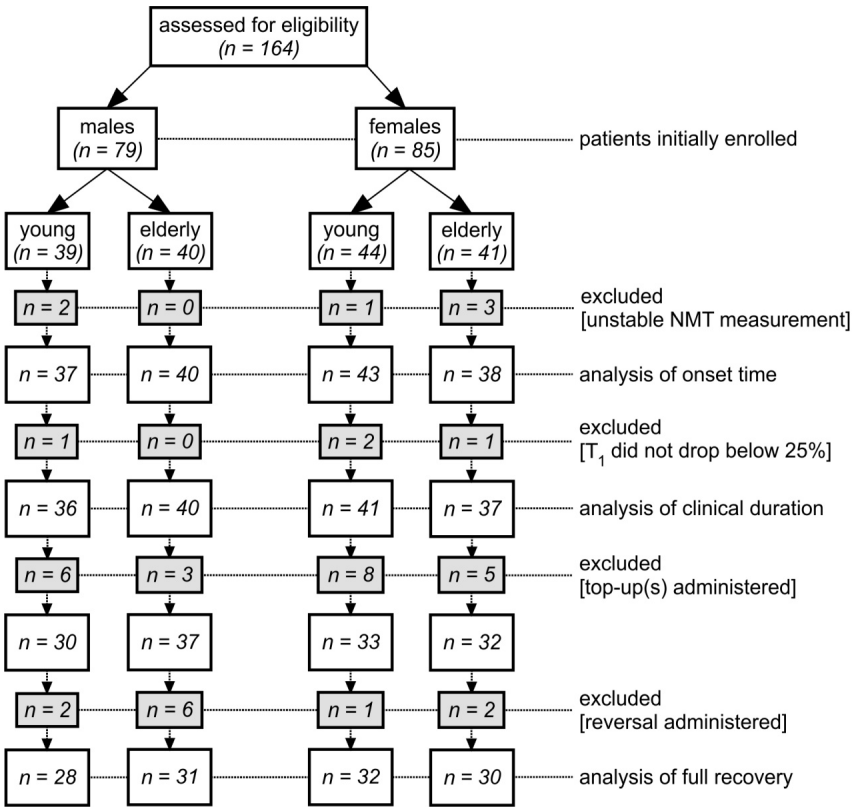

Fig. 1. Flow diagram illustrating the progress of patients through the clinical trial. Reasons for exclusion from the study are given in brackets. Young = age 20-40 yrs, Elderly = 60-75 yrs

pulse in TOF-stimulation (T_1) was used to determine the onset time and clinical duration. These NMB parameters[12] were measured in all patients:

- onset time (seconds) = time interval from the completion of the intravenous injection of rocuronium to maximal T_1 depression
- clinical duration (minutes) = time interval from the completion of the intravenous injection of rocuronium to spontaneous recovery of T_1 to 25% of the control value
- full recovery (minutes) = interval from the completion of the intravenous injection of rocuronium to spontaneous recovery to TOF-ratio 0.90, which reflects complete recovery from the block

Data were recorded and transferred into Excel spreadsheet application (Microsoft Office 2007 SP2, Microsoft Corporation) for further analysis.

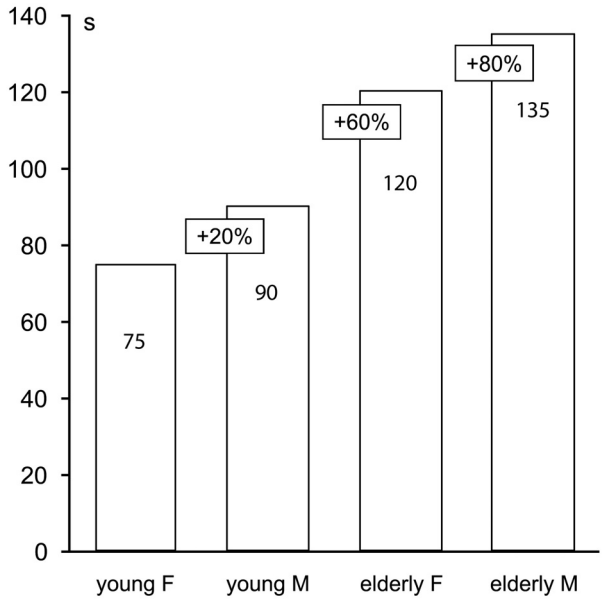

Fig. 2. Onset time in seconds (= time interval from the completion of the intravenous injection of rocuronium to maximal T_1 depression in TOF-stimulation).
Data are medians. The percentage values describe the increase compared to young females.
M = males, F = females, Young = age 20-40 yrs, Elderly = 60-75 yrs

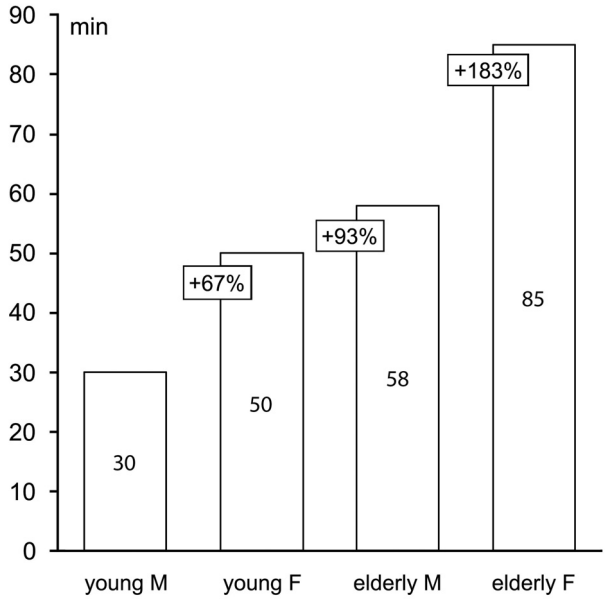

Fig. 3. Clinical duration in minutes (= time interval from the completion of the intravenous injection of rocuronium to spontaneous recovery of T_1 to 25% of the control value in TOF-stimulation).
Data are medians. The percentage values describe the increase compared to young males.
M = males, F = females, Young = age 20-40 yrs, Elderly = 60-75 yrs

Statistical analysis

For calculations, we used the statistical software package InStat v. 3.10 (GraphPad Software, San Diego, California, U.S.A.). Comparisons between the groups were made using a one-way ANOVA with multiple comparisons post-test (Tukey-Kramer), non-parametric ANOVA (Kruskal-Wallis test) with multiple comparisons post-test (Dunn), chi-square, or Fisher's exact test, as appropriate. The results are expressed as means ± SD (95% CI) or medians [interquartile range (IQR)], or frequencies; *P*-values less than 0.05 were considered statistically significant.

RESULTS

The patients' demographics are summarized in Table 1. Males were significantly taller ($P<0.0001$) and heavier ($P<0.0001$) than females but the body mass index was comparable in both sexes. The older patients (both males and females) were assigned higher ASA classification.

164 patients (79 males, 85 females) were initially enrolled in the study. Fig. 1 shows the flow diagram illustrating the progress of patients through the clinical trial. Six patients were excluded because of unstable neuromuscular monitoring. In four patients, the T_1 did not fall below 25%, so the clinical duration was not determined. During surgery, the initial dose of rocuronium had to be supple-

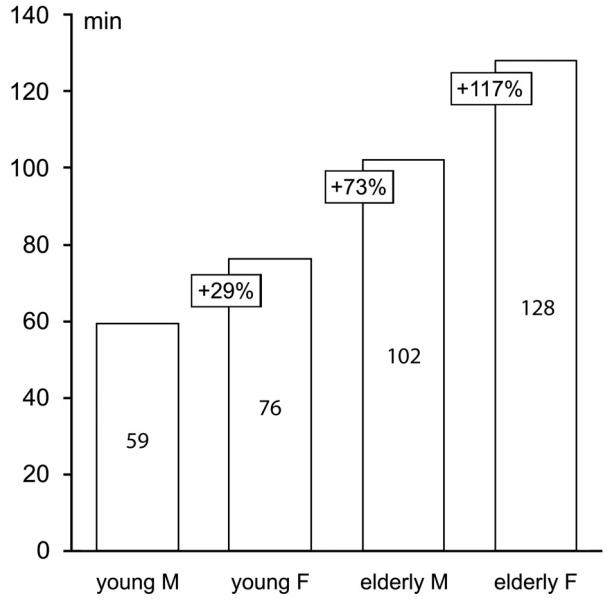

Fig. 4. Interval to full recovery in minutes (= interval from the completion of the intravenous injection of rocuronium to spontaneous recovery to TOF-ratio 0.90, which reflects complete recovery from the block).
Data are medians. The percentage values describe the increase compared to young males.
M = males, F = females, Young = age 20-40 yrs, Elderly = 60-75 yrs

mented with one or several top-ups in 22 cases. In 11 patients, reversal was necessary due to a residual block at the end of surgery. The resulting number of patients in whom the interval to full spontaneous recovery was obtained was 121.

The PD data are listed in Table 2. The shortest onset time was in young females (median 75, IQR 60–90 s), the clinical duration was shortest in young males (median 30, IQR 25–42 min), and finally, the interval to full recovery was shortest in young males (median 59, IQR 51–67 min). Fig. 2-4 show a percentage prolongation of these values in the other respective groups.

DISCUSSION

Our study confirmed a significant variability in the above parameters for the two genders and age groups of patients in response to 0.6 mg kg^{-1} rocuronium.

The **onset times** were shorter in females and were prolonged with aging in both genders. To make a NMB, rocuronium has to reach the neuromuscular junction. Lower cardiac output, prolonged circulation time, and decreased muscle blood flow with slower biophase equilibration may participate in the slower onset time in the elderly[13]. The **clinical duration** was significantly longer in females. Moreover, aging was associated with further prolongation of clinical duration in both males and females. Finally, **full spontaneous recovery** until TOF-ratio 0.9 was longer in females and it was further delayed in elderly patients of both genders. The highest differences were in the parameters describing the **length** of rocuronium effect (clinical duration and interval to full recovery). For example, in elderly females, the clinical duration was nearly three times longer than in young males.

Not only were differences in gender and age demonstrated in this study. There was a significant spread of PD parameters within respective groups (see Tab. 2). For example, in elderly females, the median clinical duration was 85 min with lower and upper quartiles 70 and 90 min. This signifies that in only 50% of these cases, the clinical duration was in the range 70 to 90 min.

This inevitably has important clinical implications. Residual block is one of the most dangerous adverse effects of incorrect use of NMBA. Based on the clinical signs, the assessment of postoperative residual curarization (PORC) is not reliable and hence even significant degrees of residual paralysis are not detected[14]. Due to a large variability in the effect of NMBA (rocuronium inclusive), the duration cannot precisely be predicted[15]. A long interval from the administration of an intermediate NMBA does not guarantee adequate recovery[16]. Without NMB monitoring, the anesthesiologist cannot be sure about the exact muscle strength at the end of anesthesia[17-19]. Residual block not only reduces the coordination of pharyngeal muscles but also decreases the sensitivity of carotid chemoreceptors. Consequently, the patient with even small degrees of PORC cannot respond to hypoxia by increasing ventilation[20]. This may increase the risk of postoperative pulmonary complications[21].

Today, rocuronium is one of the most often used non-depolarizing neuromuscular blockers worldwide. It is a very potent drug and if incorrectly used, it increases morbidity in surgical patients[22,23]. One can only speculate that its high popularity is further enhanced by the introduction of sugammadex into clinical practice. Sugammadex as a selective relaxant-binding agent has the ability to reverse the neuromuscular blockade induced by rocuronium and vecuronium[24,25]. From the pharmacological point of view, sugammadex definitely has many advantages over the older reversal drugs such as neostigmine[2,26-28]. However, compared to neostigmine, it is much more expensive[29]. All these facts constitute a rationale for a thorough knowledge of the PD of rocuronium and its correct use.

Gender

There is increasing evidence for gender differences in the pharmacokinetics (PK) and PD of anesthetic drugs and NMBA (ref.[30,31]). Females have 20-30 % greater sensitivity to the effects of aminosteroidal muscle relaxants[4,5]. This is probably due to different PK of aminosteroidal NMBA. In females, there is higher percentage of body fat, lower percentage of muscle mass and lower percentage of water and hence smaller distribution volume of rocuronium. In addition, the degradation and elimination of rocuronium are influenced by gender. Liver microsomal enzymes have different activity in males and females. In females, the glomerular filtration and renal clearance are lower so the elimination of rocuronium is decreased. In contrast, benzylisocholines undergo Hofmann elimination (a chemical process dependent on pH and temperature). Thus, tight physiological control of pH and temperature results in little variability in this biodegradation pathway without significant gender differences[5,32].

Aging

Aging is accompanied by many physiological and pathophysiological changes that affect, like gender, the PK of various drugs[7,8]. The elderly are more often severely ill and may suffer from other diseases (co-morbidity). Their physical status, described by ASA, is generally worse than that of young patients. Elderly people often use drugs, which, although they control the concomitant diseases well (e.g. hypertension, ischemic heart disease or diabetes mellitus), can be a source of significant interactions. When prescribing drugs for seniors, polypragmasia is very common. For this reason, the risk of drug interactions is further increased with potential iatrogenic injury to the patient.

With aging, the structure and composition of body tissues change together with impaired organ functions, especially liver and kidney. However, the extent and onset of these changes is highly variable and rather than calendar age, the biological age is more important. Decrease in the total body water leads to lower central compartment and so a higher plasma concentration is usually reached following a single bolus dose of ROC. The lean body weight is lower. A higher content of fat tissue may potentially increase the clinical duration and interval to full recovery from rocuronium-induced blockade in the elderly.

There are numerous changes in the neuromuscular junction with advancing age (e.g. decrease in the number of motor units, decreased number of preterminal axons, proliferation of extrajunctional receptors, decreased amount of acetylcholine in each motor neuron, or decreased amount of acetylcholine released in response to stimulation) (ref.[33]). However, the differences between young and elderly in the PD of ROC are not probably conditioned by the changes in the neuromuscular junction. The ED_{95} of ROC is similar in elderly (0.4 mg kg^{-1}) and young (0.5 mg kg^{-1}) patients[34]. When the elderly have the same plasmatic concentration of neuromuscular blocker as do young adults, they also have the same degree of neuromuscular block. Differences in PD, therefore, are probably due to differences in PK of the ROC in the elderly population[35].

In summary, with aging, the essential factors involved in different reactivity to NMBA are reduced protein binding, changes in the composition of body tissues (muscle/fat/water), drug metabolism and elimination (renal, liver), and finally, PD parameters[7,8,37].

Our study has limitations. As we used a firm study protocol, there were significant dropouts (see Fig. 1). The data were collected during routine operations and under no circumstance did the protocol of the study alter the maintenance of anesthesia. The main source of dropouts (20%) was the requirement for supplemental top-up(s) during surgery or the need for reversal at the end of anesthesia.

When assigning patients to groups according to age (20-40, or 60-75 years), we omitted the range of 41-59 years[7]. The reason for this was to separate sufficiently the two age groups studied. From a methodological point of view, the standard classification (e.g. to a younger group of 20-65 years and those aged more than 65 years) is not entirely correct. With this kind of thinking, a 65-year old patient would be qualified as "young" while a 66-year old would belong to "seniors". In this example, the clinical significance of the difference of one year is minimal, but for classifying into a particular group, it is crucial. This imperfection could be addressed by fuzzy logic but our approach to the division, creating a large enough "window" (41-59 years), we consider clinically correct.

For logistic reasons, we chose a non-interventional and non-blinded trial design. However, only the main author (MA) was responsible for the anesthetic management of all cases and a standardized technique was used for neuromuscular monitoring throughout the study. In all patients, the depth of anesthesia was computer-controlled (TCI) with identical target levels of respective anesthetic agents (propofol and sufentanil). TIVA was preferred to inhalation anesthesia to eliminate the influence of a volatile agent on the depth of muscle relaxation. We studied relatively healthy patients, mostly ASA 1 or 2. From this point of view, our results cannot be automatically transferred to other types of anesthesia (volatile anesthetic) and/or different patients.

CONCLUSION

The effect of ROC is significantly influenced by both gender and age. In females, the onset time is shorter and clinical duration and full spontaneous recovery from rocuronium-induced block is longer than in males. These differences are further accentuated with aging and in addition, significant inter-individual variability of the effect of ROC exists. As the clinical examination cannot determine the degree of NMB exactly, these facts constitute evidence that neuromuscular monitoring is essential for safe use of rocuronium in surgical patients.

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Preliminary results were presented at meeting Euroanaesthesia 2011, Amsterdam, the Netherlands, June 11-14, 2011 (ref.[37]).

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