# Smoking increases the requirement for rocuronium

P. Rautoma MD PhD,
N. Svartling MD PhD

**Purpose:** To compare the potency of rocuronium in non-smokers and smokers during general anaesthesia.

**Methods:** In a randomized, open clinical study, 40 patients, 17-62 yr of age, were anaesthetized with propofol, alfentanil and nitrous oxide in oxygen. After obtaining individual dose-response curves for rocuronium, bolus doses of rocuronium were given to maintain neuromuscular block at 90-99 % for 60 min. Evoked adductor pollicis electromyography (EMG) was used to monitor neuromuscular block.

**Results:** The $ED_{95}$ values (± SEM) for rocuronium were 460.5 ± 28.9 and 471.5 ± 22.1 $\mu g \cdot kg^{-1}$ for non-smokers and smokers, respectively (*P*:NS). However, doses of rocuronium to maintain 90-99 % neuromuscular block (± SEM) were 620.1 ± 46.7 and 747.4 ± 56.0 $\mu g \cdot kg^{-1} \cdot hr^{-1}$ for non-smokers and smokers, respectively ($P = 0.0504$).

**Conclusion:** The results may indicate increased metabolism of rocuronium in smokers rather than increased requirement of rocuronium at the receptor site.

**Objectif :** Comparer l'action du rocuronium chez des non fumeurs et des fumeurs pendant l'anesthésie générale.

**Méthode :** Dans une étude clinique randomisée et ouverte, 40 patients, de 17 à 62 ans, ont reçu une anesthésie avec du propofol, de l'alfentanil et un mélange de protoxyde d'azote et d'oxygène. Après avoir obtenu les courbes individuelles de dose-réponse au rocuronium, des bolus de rocuronium ont été administrés pour maintenir le bloc neuromusculaire à 90-99 % pendant 60 min. L'électromyographie (EMG) de l'adducteur du pouce a été utilisée pour surveiller le bloc neuromusculaire.

**Résultats :** Les valeurs de la $ED_{95}$ (± écart-type) ont été, pour le rocuronium, de 460,5 ± 28,9 et de 471,5 ± 22,1 $\mu g \cdot kg^{-1}$ pour les non fumeurs et les fumeurs, respectivement (*P* : NS). Cependant, les doses de rocuronium administrées pour maintenir un bloc neuromusculaire à 90-99 % (± écart-type) ont été de 620,1 ± 46,7 et de 747,4 ± 56,0 $\mu g \cdot kg^{-1} \cdot hr^{-1}$ pour les non fumeurs et les fumeurs, respectivement ($P = 0{,}0504$).

**Conclusion :** Les résultats peuvent indiquer un accroissement du métabolisme du rocuronium chez les fumeurs plutôt qu'un accroissement des besoins en rocuronium au site récepteur.

From the Department of Anaesthesia, Töölö Hospital, University of Helsinki, Helsinki, Finland.
*Address correspondence to*: P. Rautoma MD PhD, Department of Anaesthesia, Maria Hospital, Lapinlahdenkatu 16, 00180 Helsinki, Finland. Fax: 358-9-31063378.
*Accepted for Publication March 31, 1998.*

TOBACCO smoke has enzyme-inducing properties; enhanced biotransformation of many drugs metabolized by the cytochrome P-450 mixed function oxidase pathway.[1] It has been proposed that smokers have an enhanced hourly need of vecuronium to maintain neuromuscular block (NMB) compared with non-smokers.[2] However, the $ED_{95}$ for vecuronium was also higher in smokers than in non-smokers. Therefore, it was proposed that the effect of smoking on the need for vecuronium may be explained by increased requirement of vecuronium at the receptor site, although increased metabolism of vecuronium in smokers could not be excluded. There are no data about the elimination pathway of rocuronium in humans, but it has been found that about 33% of rocuronium is recovered in the urine over 24 hr with no metabolites detected.[3] Therefore, rocuronium appears to be eliminated primarily via the liver. In the cat, hepatic uptake and biliary excretion have been shown to be the dominant mechanisms of rocuronium clearance.[4] We are not aware of specific connections of vecuronium or rocuronium elimination with the P-450 system. Rocuronium has a shorter onset time than vecuronium and, by using rocuronium instead of vecuronium in an otherwise similar study, it might be possible to find out which of the above theories holds true.

## Patients and methods

The study protocol was approved by the local Ethics Committee. All patients were white, ASA I-II, age 17-62 yr and came for minor surgery requiring general anaesthesia. Twenty non-smokers (10 female, 10 male) and 20 smokers (10 female, 10 male) gave written informed consent. Inclusion criteria were: no medication or disease known to affect NMB, body weight index < 27, and weekly alcohol consumption ≤ 20 units (1 unit = one drink or a glass of wine). Smokers inhaled 10 or more cigarettes daily. Passive smokers were excluded from the study.

Premedication comprised 10 mg diazepam *po* 30-60 min before induction of anaesthesia which was with 2.5 $mg \cdot kg^{-1}$ propofol and 20 $\mu g \cdot kg^{-1}$ alfentanil. A 2:1 $N_2O/O_2$ mixture was used as a fresh gas. During maintenance of anaesthesia, propofol was administered as a continuous infusion of 6-12 $mg \cdot kg^{-1} \cdot hr^{-1}$ and alfentanil was given in incremental doses up to 50 $\mu g \cdot kg^{-1} \cdot hr^{-1}$.

Neuromuscular block was monitored by adductor pollicis electromyographic (EMG ) response to supramaximal ulnar nerve stimulation (Relaxograph™, Datex, Finland). A 2 Hz train-of-four (TOF) stimulation was given every 20 sec with a pulse width of 100 μsec. The two stimulating electrodes were positioned over the ulnar nerve, the recording electrode over the adductor pollicis muscle, the indifferent electrode on the volar surface on the base of the forefinger and the ground electrode between the stimulating and the recording electrodes. The NMB monitor was calibrated after induction of anaesthesia and before administration of rocuronium. The calibration was repeated until unchanged responses were recorded for three minutes. A dorsal splint was used to maintain immobility. No thumb pretension was used. The skin temperature in the hand where EMG was monitored was kept > 33C. Warm blankets were used when needed. Opposite hands were used for monitoring of EMG and drug administration. Rocuronium was injected in five seconds into a freely running *iv* line.

After calibration, the first dose of 150 $\mu g \cdot kg^{-1}$ rocuronium was given. Following maximal neuromuscular response, a second identical dose of rocuronium was administered if the maximal NMB was ≤ 30%; if it was > 30%, then a second dose of 90 $\mu g \cdot kg^{-1}$ rocuronium was administered. Thereafter, stabilization of response was again awaited and an individual third dose of rocuronium was given to create an individual dose-response curve for rocuronium.[5-6] Tracheal intubation was performed when the EMG response (the block of the first response ($T_1$) of the train of four) was ≤ 15% of the baseline. Neuromuscular block was maintained at 90-99% ($T_1$/control = 1-10%) for 60 min by giving bolus doses of rocuronium (20% of the estimated individual $ED_{95}$ ($T_1$/control = 5%)) when needed. At the end of anaesthesia, a TOF ratio of ≥ 0.70 was awaited for in every patient.

The dose of rocuronium consumed hourly was calculated excluding the doses needed to generate the dose- response data. The final individual $ED_{95}$ values for rocuronium and slopes of the dose-response curves were determined by least square linear regression analysis of the log-dose and probit-response values.[5-8] Thereafter, the mean and standard deviation for ED-doses and for slopes of the dose-response curves were analyzed. The dose-response curves were compared statistically by computer calculated log-probit regression analysis. For analysis of demographic data, analysis of variance (ANOVA) followed by Scheffe's test was used. For other between-group statistical analysis, Student's unpaired two-tailed t test was used. A $P$ value of 0.05 was regarded as statistically significant.

## Results

The main results of this study are presented in the Table.

Mean end-tidal $CO_2$ was 4.80% (NS) and skin temperature 34.1°C ($P$:NS). The median ages for non-smokers and smokers were 36 (range 17-62) and 32 (range 17-48) yr, respectively ($P$:NS). The median weights of non- smokers and smokers were 69 (range

TABLE Hourly consumption of rocuronium, slope of the dose-response curve, $ED_{95}$ and $ED_{95}$·$hr^{-1}$ values for rocuronium in non-smokers and smokers.
Values are mean ± 95% confidence limits.
* indicates statistically significant difference between the groups (ANOVA and Scheffe's test).

| | *Non-smokers* | *Smokers* |
|---|---|---|
| Consumption ($\mu g \cdot kg^{-1} \cdot hr^{-1}$) | 620.1 (526.6-713.6)* | 747.4 (635.3-859.5)* |
| Slope (probit·$log^{-1}$) | 5.92 (5.41-6.43) | 6.11 (5.65-6.59) |
| $ED_{95}$ ($\mu g \cdot kg^{-1}$) | 460.5 (402.8-518.1) | 471.5 (427.3-515.7) |
| Ratio ($ED_{95} \cdot hr^{-1}$) | 1.36 (1.21-1.52)* | 1.60 (1.42-1.77)* |

43-94) and 68 (range 50-85) kg, respectively (*P*:NS).

The time required to construct the individual dose-response curves for rocuronium was eight minutes, in both groups. After the third individual bolus dose of rocuronium, the NMB was 94 (range 86-99)% (*P*:NS).To analyze maintenance requirements of rocuronium, non-smokers needed approximately seven and smokers eight bolus doses of rocuronium in one hour ($P < 0.05$). The final $T_1$ recovery when TOF-ratio was ≥ 0.70 was 87% of the initial calibration value (NS).

## Discussion

In this study, the $ED_{95}$ values for rocuronium did not differ between non-smokers and smokers. Also, the slopes of the dose-response curves for rocuronium did not statistically differ between the groups. However, in our similar previous study with vecuronium, the $ED_{95}$ values for vecuronium were > 20 % higher for smokers than for non- smokers.[2] This difference between vecuronium and rocuronium could be explained by the structural differences between these NMBAs. More likely, this could also be explained by the time required to construct the individual dose-response curves. This time was longer for vecuronium than for rocuronium (12 *vs* 8 min, respectively). This was due to the shorter onset time of rocuronium compared with vecuronium, and more metabolization of NMBA during construction of the dose-response curves could have happened in the former study.

In this study the $ED_{95}$ value for rocuronium was higher than in previous studies. This was probably due to the use of an EMG method instead of mechanomyography of measuring NMB and a relatively low rate (every 20 sec) of stimulation.[9]

The hourly consumption of rocuronium was increased in smokers by about 20% ($P = 0.05$). This is in accordance with a previous study with vecuronium which showed that smokers consumed about 30% more NMBA than non-smokers, although it should be kept in mind that this result in the present study was statistically borderline.[2] These results may indicate increased metabolism of steroidal NMBAs in smokers. If the theory on nicotinic receptors were to explain the differences between non-smokers and smokers,[10] then the $ED_{95}$ values for rocuronium should also differ between non-smokers and smokers.

An altered mechanism of action of NMBA on the neuromuscular junction has also been proposed to be involved. Kroeker *et al.* have found that smokers require less atracurium than non-smokers.[11] This contrasts with the results presented here. However, it must be kept in mind that atracurium is eliminated by Hoffmann elimination and ester hydrolysis, not in the liver by P-450 mixed oxidase pathway.[12]

We conclude that smokers consume more rocuronium than non-smokers during similar anaesthesia, and NMB should be carefully monitored in order to avoid inadequate NMB which may disturb the surgeon. The exact mechanism for this phenomenon remains unclear, but the most probable explanation could be the increased metabolism of rocuronium in smokers. A pharmacokinetic-pharmacodynamic study would give a definitive answer both to the concentration-effect relationship, and to whether smoking does actually increase the clearance of rocuronium.

## Acknowledgement

We are grateful for Martina Bachmann MD PhD, for statistical analysis of the results.

## References

1 *Dawson GW, Vestal RE.* Smoking and drug metabolism. Pharmacol Ther 1982; 15: 207–21.
2 *Teiriä H, Rautoma P, Yli-Hankala A.* Effect of smoking on dose requirements for vecuronium. Br J Anaesth 1996; 76: 154–5.
3 *Wierda JMKH, Kleef UW, Lambalk LM, Kloppenburg WD, Agoston S.* The pharmacodynamics and pharmacokinetics of ORG 9426, a new non-depolarizing neuromuscular blocking agent, in patients anaesthetized with nitrous oxide, halothane and fentanyl. Can J Anaesth 1991; 38: 430–5.
4 *Khuenl-Brady K, Castagnoli KP, Canfell PC, Caldwell JE, Agoston S, Miller RD.* The neuromuscular blocking effects and pharmacokinetics of ORG 9426 and ORG 9616 in the cat. Anesthesiology 1990; 72: 669–74.
5 *Meretoja OA, Wirtavuori K.* Two-dose technique to create an individual dose-response curve for atracurium. Anesthesiology 1989; 70: 732–6.
6 *Rautoma P, Erkola O, Meretoja OA.* Potency and maintenance requirement of atracurium and vecuronium given alone or together. Acta Anaesthesiol Scand 1995; 39: 220–3.

7 *Litchfield JT Jr, Wilcoxon F.* A simplified method of evaluating dose-effect experiments. J Pharmacol Exp Ther 1949; 53: 99–113.
8 *Donlon JV Jr, Savarese JJ, Ali HH, Teplik RS.* Human dose-response curves for neuromuscular blocking drugs: a comparison of two methods of construction and analysis. Anesthesiology 1980; 53: 161–6.
9 *Meretoja OA, Taivainen T, Brandom BW, Wirtavuori K.* Frequency of train-of-four stimulation influences neuromuscular response. Br J Anaesth 1994; 72: 686–7.
10 *Taylor P.* Agents acting at the neuromuscular junction and autonomic ganglia. *In*: Goodman Gilman A (Ed.). The Pharmacological Basis of Therapeutics, 9th ed. New York: McGraw Hill Inc., 1996: 177–97.
11 *Kroeker KA, Beattie WS, Yang H.* Neuromuscular blockade in the setting of chronic nicotine exposure. Anesthesiology 1994; 81: A1120.
12 *Basta SJ, Ali HH, Savarese JJ, et al.* Clinical pharmacology of atracurium besylate (BW 33A): a new non- depolarizing muscle relaxant. Anesth Analg 1982; 61: 723–9.