

## Pharmacodynamic behaviour of rocuronium in the elderly

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*This study compared the potency and time course of action of rocuronium (ORG 9426) in elderly and young patients during nitrous oxide-opioid anaesthesia. One hundred ASA physical status I-II patients (60, aged 65–80 yr, and 40, aged 20–45 yr) were studied by measuring the force of contraction of the adductor pollicis in response to train-of-four stimulation of the ulnar nerve. After induction of anaesthesia with thiopentone and maintenance with N<sub>2</sub>O/O<sub>2</sub> and fentanyl, rocuronium 120, 160, 200, or 240 µg · kg<sup>-1</sup> was administered to determine dose-response curves. When maximum block had been obtained, further rocuronium to a total of 300 µg · kg<sup>-1</sup> was given. Additional doses of 100 µg · kg<sup>-1</sup> were administered when the first twitch height (T<sub>1</sub>) had recovered to 25% control. At the end of surgery neuromuscular blockade was allowed, whenever possible, to recover spontaneously until T<sub>1</sub> was 90% of control before administration of neostigmine. There was no difference in the potency of rocuronium in the elderly and the younger patients. The ED<sub>50</sub> was 196 ± 8 (SEE for the mean) in elderly, vs 215 ± 17 µg · kg<sup>-1</sup> in young patients (NS). When individual cumulative dose-response curves were constructed, the ED<sub>50</sub> was 203 ± 7 (SEM) and 201 ± 10 µg · kg<sup>-1</sup> in the elderly and the young respectively (NS). However, the onset of maximum neuromuscular block was slower in the elderly 3.7 ± 1.1 (SD) vs 3.1 ± 0.9 min, P < 0.05). The time to 25% T<sub>1</sub> recovery was longer in the elderly (11.8 ± 8.1 vs 8.0 ± 6.5 min, P < 0.05) as was the recovery index, time from 25 to 75% T<sub>1</sub> recovery (15.5 ± 6.2 vs 11.2 ± 4.9 min, P < 0.05). The duration of neuromuscular block after each maintenance dose was longer*

*in the elderly (P < 0.01) and increased gradually with time. It is concluded that rocuronium is an intermediate-acting neuromuscular blocking drug with a similar potency in elderly and young patients, but the onset and recovery of neuromuscular blockade are slower in the elderly.*

*Cette étude compare la puissance et l'évolution temporelle de l'effet du rocuronium (ORG 9426) chez des patients âgés et des jeunes pendant une anesthésie au protoxyde d'azote associé à un opiacé. Cent patients ASA classes I-II (60 sujets de 60 à 80 ans et 40, de 20 à 40 ans) font l'objet de l'étude qui consiste à mesurer la force de contraction de l'adducteur court du pouce en réponse à la stimulation du nerf cubital au train de quatre. Après l'induction de l'anesthésie au thiopental et le maintien au N<sub>2</sub>O/O<sub>2</sub> avec fentanyl, du rocuronium est administré aux doses de 120, 160, 200 et 240 µg · kg<sup>-1</sup> pour déterminer la relation dose effet. Une fois le block maximum obtenu, on donne une dose supplémentaire de rocuronium jusqu'à un total de 300 µg · kg<sup>-1</sup>. On ajoute des doses de 100 µg · kg<sup>-1</sup> dès que la première contraction (T<sub>1</sub>) revient à 25% du contrôle. A la fin de la chirurgie, on laisse le block récupérer spontanément, lorsque c'est possible, jusqu'à ce que T<sub>1</sub> atteigne 90% du contrôle avant d'administrer de la néostigmine. On ne retrouve pas de différence de puissance pour le rocuronium entre les patients jeunes et les patients âgés. La DE<sub>50</sub> est de 196 ± 8 (SEE pour la moyenne) chez les patients âgés vs 215 ± 17 µg · kg<sup>-1</sup> chez les jeunes (NS). Lorsqu'on construit des courbes dose-effet individuelles cumulatives, la DE<sub>50</sub> est respectivement de 203 ± 7 (SEM) et de 201 ± 10 µg · kg<sup>-1</sup> chez les personnes âgées et les jeunes (NS). Cependant le block neuromusculaire survient plus lentement chez le sujet âgé (3,7 ± 1,1(SD) vs 3,1 ± 0,9 P < 0,05). La période de recouvrement de T<sub>1</sub> à 25% se prolonge dans le groupe âgé (11,8 ± 8,1 vs 8,0 ± 6,5 min, P < 0,05) de même que l'index de récupération (5,5 ± 6,2 vs 11,2 ± 4,9 min, P < 0,05). La durée du block neuromusculaire après chaque dose de maintien est plus longue pour le groupe âgé (P < 0,01) et augmente progressivement avec le temps. On conclut que le rocuronium est un myorelaxant à action intermédiaire dont la puissance ne diffère pas chez les patients âgées et les jeunes. Son d'action débute plus lentement et sa durée de récupération est plus longue chez le sujet âgé.*

### Key words

ANAESTHESIA: geriatric;  
NEUROMUSCULAR RELAXANTS: rocuronium (ORG 9426).

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Rocuronium (ORG 9426) is an aminosteroidal neuromuscular blocking drug with an intermediate duration of action. Its major difference from vecuronium is its more rapid onset of action which is probably a result of its lower potency.<sup>1</sup> Studies in animals showed that rocuronium is about one fifth as potent as vecuronium and has insignificant cardiovascular effects. The duration of action was similar to vecuronium but its onset of block was about twice as rapid.<sup>2,3</sup> In general, these effects have been confirmed in humans,<sup>4-6</sup> although in one study the mean time to maximum effect was 4.6 min.<sup>7</sup> However, all these studies have been performed in young and middle aged adults.

Pharmacokinetic and pharmacodynamic studies of the nondepolarizing neuromuscular blocking drugs d-tubocurarine,<sup>8</sup> metocurine,<sup>8</sup> pancuronium,<sup>9-11</sup> alcuronium,<sup>12</sup> and vecuronium<sup>11,13,14</sup> have shown prolonged duration of neuromuscular blockade and slower recovery from neuromuscular block in the elderly mainly as a result of decreased renal and hepatic elimination. There is conflicting evidence concerning the effects of atracurium. As the elimination of atracurium is mainly independent of liver and kidney function, age-related changes in organ function would not be expected to modify its pharmacological activity and this has been confirmed in two studies.<sup>15,16</sup> However, one report suggested that the elimination of atracurium may be prolonged in the elderly as a result of an increase in volume of distribution.<sup>17</sup> Dose-response studies have shown that the potencies of atracurium, pancuronium and vecuronium are no different in the young from the elderly.<sup>18,19</sup> However, haemodynamic changes with aging may cause delayed onset of neuromuscular blockade.<sup>20</sup>

Rocuronium is the first of the recently introduced neuromuscular blocking drugs which has an onset of action which is rapid enough to compete with succinylcholine to facilitate tracheal intubation. However, as the onset characteristics have only been described in younger subjects it seemed to be important to determine whether they were also present in the elderly and whether aging would lead to a longer duration of action which might prejudice the use of rocuronium in the elderly. Thus, the purpose of this study was to compare the pharmacodynamic behaviour of rocuronium in young and elderly patients.

### Methods

The protocol was approved by the Hospital Ethics Committee. After informed consent had been obtained, 100 adult patients (60 aged 65-80 yr, and 40 aged 20-45 yr) ASA physical status I or II, scheduled for elective surgery were entered into the study. Patients with hepatic, renal, or neuromuscular disease were excluded. Other exclusion criteria included women of child-bearing poten-

tial, abnormality of serum electrolyte concentrations, personal or family history of plasma cholinesterase deficiency, malignant hyperthermia, recent treatment with any medication known or suspected of interfering with neuromuscular function, and known allergy to benzyl alcohol, opioids or other medications used during anaesthesia.

Diazepam, 10 mg *po*, was administered approximately one hour before the anticipated start of surgery. In the operating room, the ECG and SpO<sub>2</sub> were monitored continuously, and arterial blood pressure was measured, non-invasively, every three minutes. Anaesthesia was induced with thiopentone, 2-8 mg · kg<sup>-1</sup>, and fentanyl, up to 4 µg · kg<sup>-1</sup>, and was maintained with N<sub>2</sub>O/O<sub>2</sub> and increments of fentanyl (50-100 µg) as required.

The ulnar nerve was stimulated supramaximally using a Relaxograph (Datex Instrumentation Corp., Helsinki, Finland) and via surface electrodes at the wrist, with square-wave pulses of 0.2 msec duration delivered at a frequency of 2 Hz for 2 sec (train-of-four, TOF) and repeated every ten seconds. The hand and forearm were immobilized in a splint. The force of contraction of the adductor pollicis was measured with a force displacement transducer (Grass FT-10) and recorded on paper.

Patients received, by random allocation, one of four doses of rocuronium (120, 160, 200, or 240 µg · kg<sup>-1</sup>) within 1-2 min of the start of recording. When maximal block had been achieved (three consecutive T<sub>1</sub> responses of equal magnitude) a supplemental dose of rocuronium was given so that each patient had received a total of 300 µg · kg<sup>-1</sup>. The trachea was intubated at maximal block or when T<sub>1</sub> was less than 10% of control. During surgery additional doses of rocuronium were given, 100 µg · kg<sup>-1</sup>, whenever T<sub>1</sub> returned to 25% control. At the end of surgery, neuromuscular activity was allowed, whenever possible, to recover spontaneously until T<sub>1</sub> reached 90% control. At this time neostigmine, 20-40 µg · kg<sup>-1</sup>, and atropine were given if the TOF ratio was less than 0.7.

Dose-response relationships were calculated for T<sub>1</sub> by linear regression of the logit transformation of twitch depression and the logarithm of rocuronium dose. These regression lines were used to determine the ED<sub>50</sub>, ED<sub>90</sub>, and ED<sub>95</sub> values. Dose-response data were also obtained in each patient by analysis of the cumulative effect of the two doses given. The logit transformation of T<sub>1</sub> was plotted against the logarithm of the cumulative dose given, and the ED<sub>50</sub>, ED<sub>90</sub>, and ED<sub>95</sub>, were determined for each patient. The onset time was the interval between injection of rocuronium and maximal T<sub>1</sub> depression. The duration of block was defined as the time from the injection of the second dose until T<sub>1</sub> had recovered to 25% of control. The duration of action of maintenance doses

TABLE I Demographic data

Age yr	M:F	Weight kg	Height cm	Duration min
<i>Young (n = 40)</i>				
33.7 ± 8.0	30:10	70.5 ± 12.8	172.3 ± 8.0	78.0 ± 39.4
<i>Elderly (n = 60)</i>				
71.6 ± 4.2	26:34	68.7 ± 13.0	162.2 ± 12.0	110.0 ± 53.9
<i>P</i> < 0.001	< 0.01	NS	< 0.01	< 0.05

was defined as the interval between the injection of the maintenance dose of rocuronium (administered at a  $T_1$  of 25% of control), and the return of  $T_1$  to 25% of control. After the final dose of rocuronium, the times at which  $T_1$  recovered to 10%, 25%, 50%, 75%, and 90% were recorded and the recovery index (25–75%  $T_1$  recovery time) was calculated.

Values are presented, unless stated otherwise, as the mean ± SD. Statistical comparisons between the groups of young and elderly patients were performed using analysis of variance, paired and unpaired Student's *t* test, and Bonferroni's correction for multiple comparisons where appropriate. Dose-response curves were evaluated using regression analysis. Analysis of covariance was used to compare the regression lines. The  $ED_{50}$ ,  $ED_{90}$ , and  $ED_{95}$  calculated by the single dose method are given as means ± standard error of the estimate of the mean (SEE). The level of significance was set at  $P < 0.05$ .

## Results

Patients in the elderly group had a greater proportion of women, were shorter but not different in weight, and were undergoing longer procedures than those in the younger group (Table I).

The potency of rocuronium was similar in the young and old. The  $ED_{50}$ , calculated by the single dose method, was 196 ± 8 (SEE) in the elderly and 215 ± 17  $\mu\text{g} \cdot \text{kg}^{-1}$  in young patients. When individual cumulative dose-responses were constructed the  $ED_{50}$  was 203 ± 7 (SEM) and 201 ± 10  $\mu\text{g} \cdot \text{kg}^{-1}$  (NS) in the elderly and young respectively (Table II). Although the dose-response curves appear to diverge there was no statistical difference in their slopes or position. Following the second dose of rocuronium (total 300  $\mu\text{g} \cdot \text{kg}^{-1}$ ), the maximum block was not different between the two groups (Table III).

The onset of maximum block after the first and second doses of rocuronium was more rapid in the young than the elderly. There was no difference in the time to maximum block among the different doses of rocuronium. Recovery to 25%  $T_1$  was also more rapid in the young as was the recovery index (Table III). Maintenance doses,

TABLE II Potency of rocuronium in young and elderly patients

	Single dose method $\mu\text{g} \cdot \text{kg}^{-1}$ (mean ± SEE)	Cumulative method $\mu\text{g} \cdot \text{kg}^{-1}$ (mean ± SEM)
<i>Young</i>		
$ED_{50}$	215 ± 17	201 ± 10
$ED_{90}$	419 ± 34	329 ± 18
$ED_{95}$	521 ± 42	390 ± 24
<i>Elderly</i>		
$ED_{50}$	196 ± 8	203 ± 7
$ED_{90}$	315 ± 14	311 ± 11
$ED_{95}$	369 ± 16	367 ± 14

TABLE III Times to maximum block after first ( $t_1$  max) and second ( $t_2$  max) doses of rocuronium, times to 25% recovery of  $T_1$ , recovery index, and maximum block after rocuronium 300  $\mu\text{g} \cdot \text{kg}^{-1}$ 

$t_1$ max min	$t_2$ max min	$max_2$ block %	25% recovery min	Recovery index min
<i>Young</i>				
3.13 ± 0.89 <i>n</i> = 40	2.7 ± 1.0 40	81.4 ± 17.7 40	8.0 ± 6.5 40	11.2 ± 4.9 22
<i>Elderly</i>				
3.72 ± 1.1 <i>n</i> = 60	3.9 ± 1.5 60	84.6 ± 16.3 60	11.8 ± 8.1 60	15.5 ± 5.7 41
<i>P</i> < 0.01	< 0.001	NS	< 0.05	< 0.01

100  $\mu\text{g} \cdot \text{kg}^{-1}$ , lasted for longer in the elderly (Figure). In those patients who received at least six increments of rocuronium and for whom data collection was complete at each interval ( $n = 30$  after combining both groups) there was a gradual increase in duration of each maintenance dose from a mean of 11.9 ± 4.1 min of the first two increments to 16.5 ± 6.7 min following the fifth increment ( $P < 0.0001$ ).

## Discussion

This study demonstrates that rocuronium is a neuromuscular blocking drug of low potency ( $ED_{50}$  200  $\mu\text{g} \cdot \text{kg}^{-1}$ ) and intermediate duration (time to 25% recovery after 1.5 ×  $ED_{50}$  – 8–12 min, recovery index 11–16 min) and with a rapid (3–4 min) onset of block compared with other non-depolarizing muscle relaxants. In the elderly, the onset and recovery of block are slightly slower than in the young, but the potency is similar.

In the present study, doses from 120 to 240  $\mu\text{g} \cdot \text{kg}^{-1}$  were given initially to establish dose-response relationships. The calculated  $ED_{50}$  (215 and 196  $\mu\text{g} \cdot \text{kg}^{-1}$  in the young and elderly respectively) was within that range.

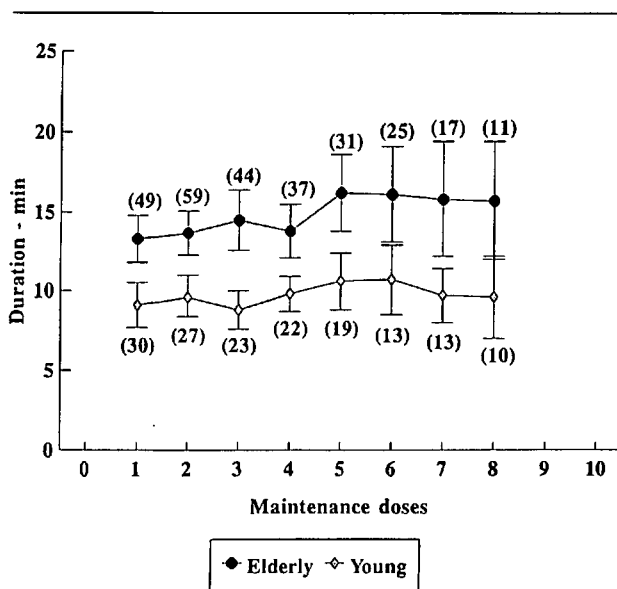


FIGURE Duration of maintenance doses administered at 25%  $T_1$  recovery. Data are included from all patients ( $n$ ) at each interval.

Thus, the accuracy of the  $ED_{50}$  estimates is greater than that of the  $ED_{90}$  and  $ED_{95}$  values ( $315\text{--}521 \mu\text{g} \cdot \text{kg}^{-1}$  which are outside the dose range tested, and are extrapolations. To obtain more accurate estimates of the  $ED_{90}$  and  $ED_{95}$ , a two-dose cumulative technique was used, similar to a method used for atracurium.<sup>21</sup> The two-dose technique was found to yield, for atracurium, results which were comparable with those obtained with the single-dose method.<sup>21</sup> This is in contrast to giving four to six successive doses of atracurium or vecuronium, which tends to overestimate the  $ED_{90}$  and  $ED_{95}$ ,<sup>22-24</sup> probably because some distribution and/or elimination is more likely to occur when a large number of doses are administered over a longer time.

In the present study, and irrespective of the method used, the  $ED_{50}$ s were similar in the young and elderly. However, because the  $ED_{90}$  and  $ED_{95}$  obtained by the single-dose technique were extrapolations, the values were similar in the young ( $ED_{95} = 390 \mu\text{g} \cdot \text{kg}^{-1}$ ) and elderly ( $ED_{95} = 367 \mu\text{g} \cdot \text{kg}^{-1}$ ) adults.

These results agree with previous studies of rocuronium in young adults<sup>4-6</sup> and suggest that it is an intermediate-duration muscle relaxant with a more rapid onset of action than vecuronium<sup>25-27</sup> or atracurium<sup>26,27</sup> but longer than succinylcholine.<sup>28</sup> The longer duration of action of metocurine,<sup>8</sup> d-tubocurarine,<sup>8</sup> and pancuronium<sup>9</sup> in the elderly has been associated with decreased plasma clearance and prolonged elimination half-life. Pharmacokinetic studies of rocuronium have now been performed in young and elderly patients. In the young,

rocuronium was found to be similar to vecuronium. The liver appears to be a more important route of elimination than the kidney: only one third of the administered dose appeared in the urine within 24 hr.<sup>5</sup> The duration of action of vecuronium is prolonged in the elderly<sup>13</sup> but, surprisingly, some studies have failed to provide a pharmacokinetic explanation. Rupp *et al.* examined the pharmacokinetic and pharmacodynamic behaviour of vecuronium after discontinuing its administration by infusion. They showed that although plasma clearance of vecuronium was reduced in the elderly, this was matched by a decreased volume of distribution, and the terminal half-life was unaffected.<sup>11</sup> More recently, it has been demonstrated that, after bolus injection, the plasma clearance of vecuronium is reduced and its terminal half-life prolonged in the elderly.<sup>14</sup> Similar findings were given in a preliminary report of the pharmacokinetic behaviour of rocuronium.<sup>29</sup> The most likely reason for the prolonged duration in the elderly is a decrease in renal and hepatic perfusion associated with aging.

The onset of action of rocuronium at the adductor pollicis is more rapid than for other currently available non-depolarizing neuromuscular blocking drugs except for gallamine.<sup>30</sup> Rocuronium is also the least potent non-depolarizing relaxant and Bowman *et al.* have demonstrated a relationship between potency and the onset time for a series of aminosteroidal compounds.<sup>1</sup> The reason is related to the large proportion of receptors which need to be occupied before the development of neuromuscular block - i.e., the "margin of safety."<sup>31</sup> This is more easily and rapidly achieved by providing large numbers of molecules of a low potency compound. The onset time will be more rapid at higher doses -  $2\text{--}3 \times ED_{95}$ . Under these conditions, with onset defined as the time to complete block, basic principles indicate that onset must be more rapid with higher doses. In addition, the onset of rocuronium blockade, like pancuronium,<sup>32</sup> is directly related to age. However, to provide ideal conditions for tracheal intubation the onset of action of neuromuscular blocking drugs at the larynx is more important than at the thumb. Recently, it has been demonstrated that the onset of action of vecuronium<sup>33</sup> and succinylcholine<sup>34</sup> is more rapid at the laryngeal adductor muscles than at the adductor pollicis. Consequently, it is likely that good intubating conditions following equipotent doses are likely to be achieved earlier after rocuronium than after vecuronium. Successful tracheal intubation has been reported within one minute after rocuronium,  $1000 \mu\text{g} \cdot \text{kg}^{-1}$ .<sup>5</sup> Preliminary studies suggest that intubating conditions after rocuronium,  $600 \mu\text{g} \cdot \text{kg}^{-1}$ , may match those following succinylcholine,  $1 \text{ mg} \cdot \text{kg}^{-1}$ .<sup>35</sup> However, succinylcholine has the additional advantage of rapid recovery which is not matched by rocuronium.

In conclusion, it has been demonstrated that rocuronium is an intermediate-acting neuromuscular blocking drug with a rapid onset of action. Onset and recovery are delayed slightly in the elderly. Further studies are required to determine its place to facilitate tracheal intubation.

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