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Dose-response curve and time-course of effect of vecuronium in male and female patients

F. S. XUE, X. LIAO, J. H. LIU, S. Y. TONG, Y. M. ZHANG, R. J. ZHANG, G. AN, L. K. LUO

Summary

To determine the differences between men and women in the dose-response curve and the time-course of effect of vecuronium, we studied 60 adult patients (30 male and 30 female), ASA I, age 18–51 yr, undergoing elective plastic surgery. Anaesthesia was maintained with nitrous oxide 60% in oxygen; thiopentone and incremental doses of fentanyl were given as required. Neuromuscular function was assessed mechanomyographically using the train-of-four (TOF) stimulation at the wrist every 12 s. The percentage depression of T_1 was used as the study variable. The dose-response relationship of vecuronium was determined by a cumulative dose-response technique. The dose-response curve in men was shifted in a parallel fashion to the right, indicating a decrease in the sensitivity to vecuronium-induced neuromuscular block, compared with women. The ED_{50}, ED_{90} and ED_{95} of vecuronium were 23.9 (4.7), 45.4 (11.2) and 55.7 (14.3) $\mu g\ kg^{-1}$ in men and 18.4 (3.7), 33.5 (7.8) and 39.8 (9.6)$\mu g\ kg^{-1}$ in women respectively. There were statistically significant differences in these values between the two groups ($P<0.01$ in each instance). After a total dose of vecuronium 80 $\mu g\ kg^{-1}$, neuromuscular block was significantly longer in women than in men. The duration of peak effect, clinical duration, and the total duration were 18.7 (7.1), 26.6 (8.8) and 50.6 (16.0) min respectively in men and 26.0 (7.2), 37.1 (11.2) and 65.9 (20.7) min in women. They differed significantly between men and women ($P<0.005$ in each case). (*Br. J. Anaesth.* 1998; **80**: 720–724)

Keywords: neuromuscular block vecuronium; pharmacodynamics vecuronium; gender

In recent years, possible factors influencing the pharmacokinetics and pharmacodynamics of vecuronium have been studied extensively. It is well documented that increasing age,[1,2] hepatic insufficiency,[3] respiratory acidosis,[4] hypothermia,[5] obesity,[6] inhalation anaesthetic agents,[7–9] other neuromuscular blocking drugs,[10,11] aminoglycoside antibiotics,[7] and myasthenia gravis[12] make patients more sensitive to vecuronium, but there is controversy about the effect of gender on neuromuscular block produced by vecuronium. Semple and colleagues[13] reported that women required 22% less vecuronium than men to achieve the same degree of neuromuscular block. Houghton, Aun and Oh[14] showed that the condition of male patients was significantly less satisfactory than that of female patients when the trachea was intubated 60 s after administration of vecuronium 100 $\mu g\ kg^{-1}$. However, Gramstad and Lilleaasen[15] found no such difference. In addition, it is not known whether there is any difference in the time-course of action of vecuronium in men and women. It was the purpose of the present study to evaluate the influence of gender on the dose response and on the pharmacodynamics of vecuronium in healthy adult patients under nitrous oxide–oxygen–fentanyl anaesthesia.

Patients and methods

After obtaining ethics committee approval and written informed consent, we studied 60 healthy adult patients (30 male and 30 female), ASA I, aged 18–51 yr and weighing 47–84 kg, who were undergoing elective plastic surgery expected to require general anaesthesia for >120 min. All the patients were Chinese of the Han race. Patients were excluded if they had cardiac, pulmonary, renal, hepatic, neurological, psychiatric, muscular, inflammatory, malignant or endocrine disease, as were pregnant women, patients undergoing major reconstructive surgery for burns, and patients with recent exposure (within 72 h) to medications known to interfere with neuromuscular transmission. Those with a body weight more than 10% above ideal were not studied. Ideal body weight was defined as follows: for males, 110 lb + 5 lb $inch^{-1}$ above 5 ft height; for females, 100 lb + 5 lb $inch^{-1}$ above 5 ft height.[6]

After an overnight fast, patients were premedicated with diazepam 0.2 mg kg^{-1}, meperidine 1 mg kg^{-1} and atropine 0.01 mg kg^{-1} i.m. 1 h before anaesthesia. Anaesthesia was induced with thiopentone 4–6 mg kg^{-1} and fentanyl 2–4 $\mu g\ kg^{-1}$. After topical anaesthesia with 2% lidocaine, the trachea was intubated without the aid of a neuromuscular blocking drug. Anaesthesia was maintained with nitrous oxide and oxygen in the ratio 3:2 (total flow 5 l min^{-1}), and intermittent bolus doses of thiopentone. For analgesia, bolus doses of fentanyl 2 $\mu g\ kg^{-1}$ were given if there were clinical signs of inadequate analgesia (heart rate or

F. S. XUE, MD, FCAA, X. LIAO, MD, FCAA, J. H. LIU, MD, FCAA, S. Y. TONG, MD, FCAA, Y. M. ZHANG, MD, FCAA, R. J. ZHANG, MD, FCAA, G. AN, MD, FCAA, L. K. LUO, MD, FCAA, Department of Anaesthesiology, Plastic Surgery Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Ba-Da-Chu Road, Shi-Jing-Shan District, Beijing, People's Republic of China, 100041. Accepted for publication January 28, 1998.

Correspondence to F. S. X.

Table 1 Patient characteristics. Values are mean (SD) (range)

	Male ($n=30$)	Female ($n=30$)
Age (yr)	28.3 (8.1) (18–49)	29.5 (7.7) (20–51)
Weight (kg)	58.6 (10.8) (47–84)	57.2 (9.2) (48–75)
Height (cm)	165.4 (8.7) (160–180)	163.7 (9.2) (158–176)
Duration of surgery (h)	3.6 (1.1) (2.3–6.2)	3.8 (1.3) (2.8–6.1)
Temperature (°C)	36.5 (0.4) (36.5–37)	36.4 (0.4) (36.4–37)
Haemoglobin (g dl^{-1})	14.8 (1.5) (12.5–16.7)	14.7 (1.5) (13–16.6)

mean arterial pressure >20% above baseline values). Ventilation was controlled to maintain $P_{E'CO2}$ at 4–5 kPa.

Inspired and end-tidal concentrations of oxygen, carbon dioxide and nitrous oxide were measured continuously and displayed digitally with an anaesthetic gas analyser (Capnomac Ultima, Datex). A cannula was placed in the radial or femoral artery for sampling. Arterial pH, Pa_{O2}, Pa_{CO2} K^+, Na^+, Cl^- and ionized calcium were determined with a blood-gas-electrolyte analyser Model-5 (Nova Biomedical Company, Hoboken, USA) before and during surgery. Total plasma protein and albumin were measured with an automatic biochemical analyser Type-550 (Corning Medical, Oberlin, OH, USA). Thenar skin temperature was monitored using a thermocouple placed on the dorsum of the hand, from which the response to ulnar nerve stimulation was recorded. Skin temperature over the thenar muscles was maintained above 32°C throughout the study period by wrapping the arm in cotton-wool.

Neuromuscular function was assessed using mechanomyography of the thenar muscles. The ulnar nerve was stimulated at the wrist with a nerve stimulator in train-of-four (TOF) mode (Myotest MK, Biometer, Odense, Denmark) through surface electrodes. Supramaximal, square-wave impulses of 0.2 ms duration at 2 Hz were administered every 12 s. The hand and forearm were immobilized in supination and abduction on a splint, and the fingers were strapped in extension. Evoked muscle contraction of the adductor pollicis was quantified isometrically by a force displacement transducer, amplified, and recorded continuously on a polygraph. The first response (T_1) of the TOF stimulus was used as the parameter for pharmacodynamic measurements. The dose-response relationship for vecuronium in the two groups was determined using a cumulative dose-response technique according to Donlon and colleagues.[16] A total dose of vecuronium 40 μg kg^{-1} was given in four doses of 10 μg kg^{-1}. Each dose of vecuronium was injected as an i.v. bolus over <5 s into a rapidly running i.v. infusion. Five min were allowed for stabilization of the response to TOF stimulation before giving the first dose of vecuronium. The mean of 10 T_1 responses, immediately preceding the first administration of vecuronium, was accepted as the control with which all subsequent T_1 responses were compared. Each dose increment was given (at times t1, t2 and t3, respectively) only after the effect of the previous dose had reached a stable response, defined as three equal (±1%) consecutive T_1 responses, or when 5 min had passed with no decrease in T_1 from control. If 90% or more T_1 depression was achieved after the second incremental dose, the third incremental dose was not used.

The individual dose-response relationship was examined by least squares linear regression of the logarithm of each dose against a probit transformation of the depression of T_1, from which the doses required for 50%, 90%, and 95% T_1 depression (ED_{50}, ED_{90} and ED_{95}, respectively) were calculated. The regression lines were tested to determine if they deviated from parallelism.[17] If they did not, ED_{50}, and ED_{95} values were compared between the groups. Parallelism was tested using one-way analysis of variance followed by the Student-Newman-Keuls multiple range test of the steepness coefficients of the regression lines (α).

When maximal depression of the T_1 response had occurred after the final increment, additional doses of vecuronium 40 μg kg^{-1} or 50 μg kg^{-1} (total dose 80 μg kg^{-1}) were given. If the resulting depression of the T_1 was 100%, duration of peak effect (time from injection of total dose of vecuronium 80 μg kg^{-1} to recovery of T_1 response to 5%), clinical duration (time from injection to 25% recovery), total duration (time from injection to 90% recovery), and recovery index (time from 25% to 75% recovery) were estimated.

All data were stored on disk and analysed with POMS statistical software Version 2.1 (Shanghai Scientific and Technical Publishers, Shanghai, People's Republic of China). An analysis of covariance was used to compare the dose-response curves of the two groups. The possible effects of age, weight, and gender on the peak depression of the T_1 response to a given dose of vecuronium were analysed by multiple linear regression; the significance of added regressors was tested using the F test. Statistical comparisons of other data between and within groups were carried out using the unpaired and paired Student's *t* test, respectively. Data are expressed as mean (SD). $P<0.05$ was considered significant.

Results

The patient characteristics of the two groups were comparable (table 1). All patients had stable haemodynamics and were normothermic throughout the study. There were no significant differences between male and female patients in arterial blood gas data or plasma electrolytes before and during surgery. However, the concentrations of total plasma protein and albumin in the women were decreased by 8–10% and 11–16% respectively compared with those in the men ($P<0.01$) (table 2).

The third incremental dose was not used in four women and two men because 90% or more of T_1 depression was achieved after the second incremental dose. The times of administration of the first (t1), second (t2), and third (t3) increments were 4.7 (1.3) min, 9.5 (2.1) min, and 12.6 (3.1) min respectively in the men, and 4.6 (1.2) min, 9.4 (2.5) min, and 12.1 (2.8) min in the women. There was no statistically significant difference between the two groups ($P>0.05$). When all the patients were considered together, the patient's age and weight were not significantly correlated with the peak depression of

Table 2 Arterial blood gas data, electrolyte concentrations, total plasma protein (TPP) and albumin before and during surgery in the male and female patients. Values are means (SD). $^{+}$Calcium = ionized calcium. ★$P<0.01$, compared with preoperative value; †$P<0.01$, compared with male patients

	Male ($n=30$)		Female ($n=30$)	
	Before surgery	During surgery	Before surgery	During surgery
pHa	7.40 (0.03)	7.44 (0.04)	7.41 (0.02)	7.43 (0.03)
Pa_{CO2} (kPa)	5.3 (0.2)	4.5 (0.3)★	5.4 (0.2)	4.6 (0.2)★
Pa_{O2} (kPa)	12.6 (0.8)	19.2 (1.2)★	12.7 (1.0)	19.6 (1.2)★
K^+ (mmol l^{-1})	4.3 (0.3)	4.2 (0.2)	4.2 (0.2)	4.0 (0.2)
Na^+ (mmol l^{-1})	144.3 (3.5)	145.8 (2.8)	143.7 (3.2)	145.2 (2.8)
Cl^- (mmol l^{-1})	105.3 (1.7)	108.4 (1.3)	104.5 (1.3)	105.8 (2.0)
$^{+}$Calcium (mmol l^{-1})	1.18 (0.02)	1.08 (0.02)	1.09 (0.03)	1.04 (0.02)
TPP (g l^{-1})	65.1 (7.8)	63.5 (8.6)	59.7 (8.2)†	57.4 (7.3)†
Albumin (g l^{-1})	46.9 (8.7)	45.1 (7.69)	41.8 (4.8)†	38.2 (5.7)†

Table 3 Coefficients (b_i), standard errors and corresponding values of F and P for the fitted $Y=b_0+b_1X_1+b_2X_2+b_3X_3+b_4X_4$, where Y = the peak twitch depression; X_1=age in yr; X_2 = body weight in kg; X_3 = log dose in μg kg^{-1}; and $X_4=1$ for females, 0 for males

Predictors	Coefficient	SE	F	P
Intercept	−1.8825	0.098	—	—
Age (yr)	0.0026	0.002	1.63	0.203
Weight (kg)	0.098	0.04	3.48	0.0587
Log dose (μg/kg)	4.54	0.144	991.2	<0.0001
Gender (F:M)	0.52	0.065	64.7	<0.0001

Table 4 Dose-response data. Values are mean (SD). ★$P<0.01$ compared with male patients

	Males ($n=30$)	Female ($n=30$)
ED_{50} (μg kg^{-1})	23.9 (4.7)	18.4 (3.7)★
ED_{90} (μg kg^{-1})	45.4 (11.2)	33.5 (7.8)★
ED_{95} (μg kg^{-1})	55.7 (14.3)	39.8 (9.6)★
Slope (probit/log)	4.4 (0.7)	4.7 (0.8)

T_1 following each dose of vecuronium. However, there were significant correlations between the peak depression of T_1 and gender, and the peak depression of T_1 and the cumulative log doses of vecuronium (table 3). The effect of interactions between gender and log doses was tested and no significance was achieved, thereby supporting the assumption that the regression lines for the two genders were parallel. The mean percentage depression of T_1 after administration of vecuronium 10, 20, 30, and 40 μg kg^{-1} was 8.1 (5.0), 39.3 (17.8), 68.3 (16.1), and 84.3 (8.8)% respectively in men, and 15.1 (11.4), 58.8 (16.4), 84.9 (10.6) and 93.8 (5.3)% in women. In each instance, the difference between the two groups was significant ($P<0.05$).

The cumulative dose-response curve of vecuronium in men was shifted in a parallel fashion to the right (fig. 1), indicating a reduced sensitivity to vecuronium-induced neuromuscular block compared with women. The effective doses calculated by linear regression are shown in table 4. There were significant differences in the ED_{50}, ED_{90} and ED_{95} of vecuronium between men and women. However, the slope of the dose-response curve of vecuronium in the males was not significantly different from that in females.

Using post-tetanic count stimulation at 50 Hz, all the patients were shown to have 100% depression of the twitch response after receiving a total dose of vecuronium 80 μg kg^{-1}. Vecuronium-induced neuromuscular block was significantly longer in women than in men. The duration of peak effect, clinical

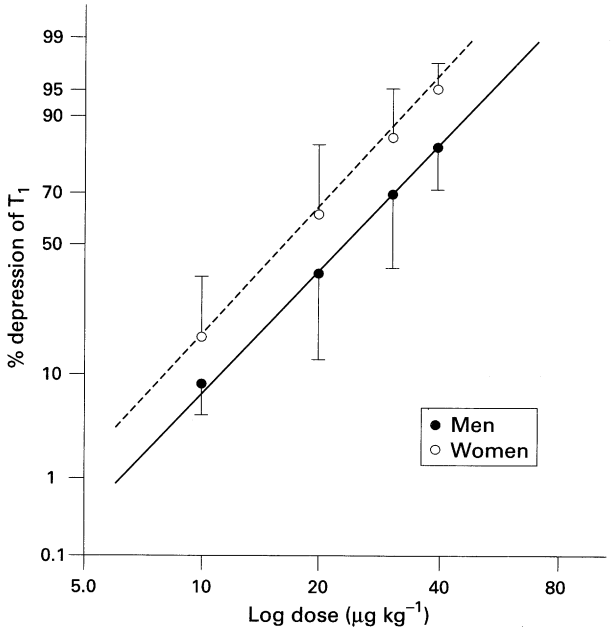

Figure 1 Dose-response curves of vecuronium in men and women. Points express the mean depression of T_1 after administration of each dose of vecuronium. Vertical bars represent SD.

duration and total duration differed significantly between the two groups. However, the recovery index in the males did not differ from that in the females (table 5).

Discussion

The aim of this study was to determine if there was any difference between the sexes in the dose-response data and the time-course of action of vecuronium. We used strict exclusion criteria and controlled other factors known to interfere with

Table 5 Vecuronium pharmacodynamic data in patients with 100% neuromuscular block following administration of a total dose of 80 μg kg^{-1}. Duration of peak effect = time from completion of injection to recovery of T_1 to 5%; clinical duration = time from injection to 25% recovery; total duration = time from injection to 90% recovery; recovery index = time from 25% to 75% recovery. Values are mean (SD). ★$P<0.005$ compared with male patients

	Male ($n=30$)	Female ($n=30$)
Duration of peak effect (min)	18.7 (7.1)	26.0 (7.2)★
Clinical duration (min)	26.6 (8.8)	37.1 (11.2)★
Recovery index (min)	16.5 (7.0)	19.7 (8.1)
Total duration (min)	50.6 (16.0)	65.9 (20.7)★

neuromuscular block: there was no significant difference in the distribution of age or weight in the two groups and all the patients were Chinese of the Han race; the study drug was produced in Oss, Netherlands, in a single factory; the output variable, percentage twitch depression, was measured using the same neuromuscular function monitor in all patients; all the anaesthetic agents were given by the same anaesthetist and comparable anaesthetic equipment and drugs were used in all the subjects; and end-tidal carbon dioxide was kept in the normal range.

We used the incremental cumulative dose technique to evaluate the dose-response relation of vecuronium. Some investigators have found that the cumulative dose technique may underestimate the potency of neuromuscular blocking drugs that are rapidly distributed and eliminated.[18–20] However, the use of vecuronium was consistent throughout the study, and thus the degree of redistribution would have been similar in the two groups of patients. To improve the accuracy of the cumulative dose-response technique for vecuronium, we also restricted the number of doses to three.[15] The aim of the study was not to provide an absolute potency estimate, but to determine any sex-related effect on the neuromuscular block produced by vecuronium. When all patients in the present study are considered together, the mean effective doses and clinical duration of vecuronium are similar to the results of previous studies using a nitrous oxide–opioid technique without any potent inhalation anaesthetics.[9 19 21 22]

Our results showed that women were significantly more sensitive to vecuronium than men. The ED_{50}, ED_{90} and ED_{95} of vecuronium in the women were decreased by 23%, 26% and 29% respectively compared with the men, and the duration of peak effect, clinical duration, and total duration were prolonged by 39%, 40%, and 30%. These results are in keeping with those of previous studies in which there were also sex-related differences in the pharmacodynamic data on vecuronium.[13 14] In addition, pancuronium 100 $\mu g\,kg^{-1}$, the monoquaternary analogue of vecuronium, has a shorter onset time in women than men. However, Gramstad and Lilleaasen[15] demonstrated that there was no difference in pharmacodynamic responses to vecuronium and pancuronium between men and women. The differences among these studies are possibly attributable to differences in selection of samples, anaesthetic techniques and observation methods.

The exact reason for the differences in the sensitivity to vecuronium between the sexes is still unclear. The most likely reason in this respect is the known difference in body build between the sexes, men having a greater percentage of muscle mass and a lower percentage of fat than women.[23] A larger dose of neuromuscular blocking drug is needed when there is less fat and more muscle.[24] The volume of distribution, in $ml\,kg^{-1}$, is most likely decreased by the presence of more adipose tissue in females. A lower dose of muscle relaxant is required to produce the comparable neuromuscular block when the volume of distribution is decreased. In addition, vecuronium is mainly eliminated by the liver and there are sex-related differences in the activity of certain microsomes in the liver. Previous studies demonstrated that some drugs, which are mainly eliminated by the liver, are more rapidly metabolized and produce lower plasma levels in men than in women.[25]

The pharmacological effect of a drug is highly dependent on the degree of plasma protein binding. Duvaldestin and Henzel[26] showed that the protein-bound fraction of vecuronium was 30% and vecuronium is mainly bound to plasma albumin. Our results showed that the concentrations of total plasma protein and albumin were higher in the men than in the women ($P<0.01$). Following administration of vecuronium, the concentration of unbound drug and the ratio of the protein-unbound/bound in plasma were increased in the females because of their lower concentration of plasma protein. The increase in the unbound fraction of vecuronium in the women makes more drug available to the tissue and receptor sites.

In conclusion, this study suggests that there are gender-related differences in the dose-response and pharmacodynamics of vecuronium. Women were significantly more sensitive to vecuronium than men, requiring about 30% less drug to achieve the same degree of neuromuscular block. After the same dose of vecuronium, the clinical duration was significantly longer in the women compared to the men.

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