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Influence of Body Fat on the Onset of Vecuronium Induced Neuromuscular Blockade

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The onset time of vecuronium, a muscle relaxant, was measured after a bolus intravenous injection of 0.15 mg·kg^{-1} of vecuronium into 40 surgical patients aged 59–64 years. The onset time was then compared between male and female patients and the relationship between onset time and body fat (% of body weight) was analyzed. Arterial plasma concentrations of vecuronium were measured at 75, 195, and 375 sec after administration of vecuronium to 8 patients. The female patients (n = 23) showed a shorter onset time and more body fat than the male patients (n = 17). The onset time significantly decreased with increasing body fat in both groups. When only females with body fat of less than 30% (n = 10) were compared with the male group (all male patients had body fat of less than 30%), the body fat, onset time, and regression lines between the onset time and the body fat did not differ significantly. Except in the patient with the highest body fat, plasma concentrations at 195 and 375 sec significantly increased with increasing body fat. We concluded that the higher body fat in females is largely responsible for the faster onset of vecuronium action in females. A smaller distribution volume of vecuronium may also be one of the reasons for the faster onset of vecuronium in females.

Key words : Vecuronium, Onset time, Body fat, Plasma concentration

INTRODUCTION

Vecuronium is the muscle relaxant used most widely in Japan for tracheal intubation because it has the shortest onset time among the commercially available nondepolarizing muscle relaxants in Japan. The onset of muscle paralysis is governed by the dose, distribution/redistribution pharmacokinetics, the blood concentration-paralysis relationship which is governed mainly by muscle perfusion and blood:muscle partitioning, and pharmacodynamic factors [11]. The onset of the effects of vecuronium becomes faster with increasing body mass index (BMI) and slower with increasing age in female patients when the same dose of vecuronium per body weight is given [16]. Females are more sensitive to vecuronium than males [15]. Because vecuronium is almost completely ionized at pH 7.4, it basically does not enter the fatty tissue. Therefore, the initial distribution volume of vecuronium is similar to the blood volume, and the steady state distribution volume is close to the extracellular fluid volume [6, 13]. The blood concentrations of vecuronium shortly after intravenous administration are governed mainly by the distribution volume of vecuronium because the distribution half-life of vecuronium (10 to 20 min) is much shorter than its elimination half-life (70 to 120 min) [6, 9, 14]. Blood volume per body weight and body water per body weight, and also the initial and total distribution volume per body weight of vecuronium are lower in obese individuals than in non-obese individuals [1, 2, 14]. Therefore, obese individuals should have higher blood concentrations of vecuronium when the same dose per body weight is administered. Because women have more body fat than men [8], women should have a lower distribution volume per body weight of vecuronium and a shorter onset time than men. We administered the same dose of vecuronium

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per body weight intravenously and measured the onset time. Then we compared the onset time between males and females and correlated the onset time with body fat. In some patients, we measured plasma concentrations of vecuronium shortly after the administration of vecuronium and correlated them with body fat.

MATERIALS AND METHODS

After approval by the Tokai University Hospital Ethics Committee, a total of 40 patients (17 males and 23 females), aged 59–64 years and ASA (American Society of Anesthesiologists) physical status I or II, who were scheduled for elective surgery requiring neuromuscular blockade, participated in this study. Any patient who had a moderate to severe systemic disorder or disease was excluded. One male patient had mild to moderate diabetes mellitus, and six male and four female patients had hypertension. The patients did not have any disease affecting neuromuscular function. We arbitrarily considered them to be within the same age group. Informed consent was obtained from all patients. Midazolam at 0.05–0.06 $mg \cdot kg^{-1}$, atropine sulfate at 0.5 mg, and famotidine at 20 mg were administered intramuscularly as premedication 30 min before the induction of anesthesia. On arrival at the operating room, ECG, SpO_2, and arterial blood pressure were monitored. Intravenous infusion of Ringer's lactated solution in the dorsal region of the hand was initiated. Surface stimulating electrodes were attached to the forearm for ulnar-nerve supramaximal stimulation, and surface recording electrodes were attached over the hypothenar muscle. Muscular responses were measured electromyographically using a Relaxograph™ (NMT 100, Datex, Helsinki, Finland). A blood pressure cuff was placed on the opposite arm. After intravenous administration of fentanyl at 2 $\mu g \cdot kg^{-1}$ and midazolam at 1–2 mg, the electrical response to train-of-four (TOF) stimulation (100 μs square wave, 2 Hz) was recorded as a control. Thereafter, the ulnar nerve was stimulated repeatedly every 20 seconds. Approximately 3 $mg \cdot kg^{-1}$ of thiopental and 0.15 $mg \cdot kg^{-1}$ of vecuronium were given by bolus (5 sec) into a rapidly running intravenous line. When the first twitch height (T_1) in TOF stimulation decreased to 5% or less of the control value, indicating sufficient neuromuscular blockade for tracheal intubation [3], the trachea was intubated. Onset time was determined as the interval from the administration of vecuronium to 95% depression of T_1. In the 8 patients (3 males and 5 females) who required the direct arterial pressure monitoring during the operation, blood samples (5 ml) were collected in heparinized test tubes over 10 seconds from a radial arterial catheter at 75, 195, and 375 seconds after completion of vecuronium administration. The midpoint during each blood sampling was regarded as the blood sampling time. Plasma was separated and frozen at −20℃ after addition of NaH_2PO_4 until the assay of vecuronium concentration using the gas chromatography/selective ion monitoring mass spectrometry method [4].

The BMI was calculated as $weight \cdot (height/100)^{-2}$. The body fat was calculated from height (cm) and weight (kg) based on Hume's equation [12], i.e. fat-free mass = $(0.194786Ht + 0.296785Wt - 14.012934)/0.73$ in males and $(0.344547Ht + 0.183809Wt - 35.270121)/0.73$ in females.

Clinical characteristics of the patients and the onset time of vecuronium were expressed as means ± standard deviation. Differences between males and females were analyzed by the unpaired *t*-test. A P value of less than 0.05 was considered to indicate statistical significance. Linear regression analysis was used to correlate the onset time with body fat, and the plasma concentrations of vecuronium with body fat. Regression lines were fitted using the least-squares method. The correlation coefficient "r" was considered as statistically significant at a probability of less than 0.05.

RESULTS

Clinical characteristics of patients and onset time of vecuronium

There were no significant differences in age and BMI between the male and female patients. The male patients had significantly less body fat ($P < 0.001$) and significantly longer onset time than female patients ($P < 0.05$) (Table 1). Comparisons of body fat and onset time between male patients and the 10 female patients with body fat of less than 30% (all male patients had a body fat less than 30%) indicated that the body fat and the onset time did not differ significant-

Table 1 Clinical characteristics of patients and onset time of vecuronium in males and females

	Males (n = 17)	Females (n = 23)	
Age (years)	61.8 ± 1.7	61.5 ± 1.7	N.S.
Height (cm)	161.9 ± 4.9	151.5 ± 5.1	$P < 0.001$
Weight (kg)	61.9 ± 7.0	52.4 ± 7.3	$P < 0.001$
BMI ($kg \cdot m^{-2}$)	23.7 ± 3.2	22.9 ± 3.4	N.S.
Body fat (%)	20.0 ± 5.4	29.8 ± 7.4	$P < 0.001$
Onset time (sec)	165 ± 44	136 ± 36	$P < 0.05$

Data are means ± SD. N.S. = not significant. BMI (body mass index) = weight·(height/100)$^{-2}$.
Body fat is expressed as % of total body weight according to Hume's equation. Onset time is the interval from the administration of vecuronium to 95% depression of first twitch height (T_1) in train-of-four (TOF) stimulation.
Significant differences were analyzed between males and females.

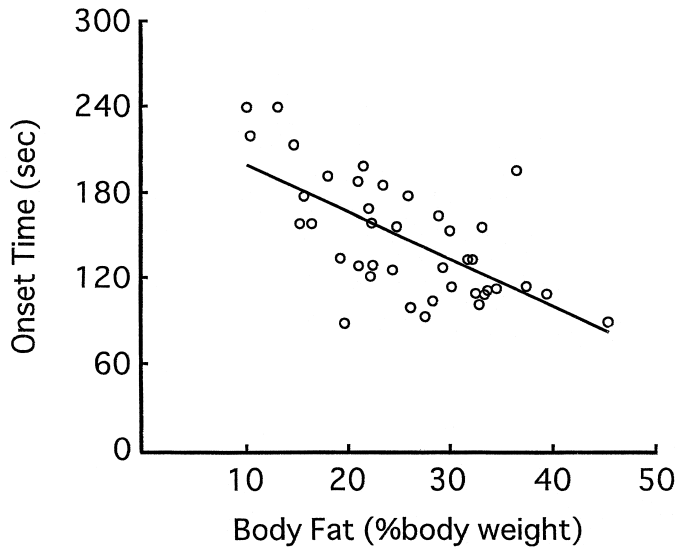

Fig. 1 Relationship between the onset time of vecuronium and body fat in 40 patients aged 59–64 years. The onset time (y), determined as the interval from the administration of vecuronium to 95% depression of T_1 in TOF stimulation, became shorter with increasing body fat (x). $y = -3.3x + 233$ ($r = -0.65$, $P < 0.001$)

ly between males and females. The body fat and onset time in the females were 23.4 ± 5.6% and 153 ± 41 sec, respectively (data not shown).

Relationship between onset time and body fat

The equations used to calculate the onset time (y) and the body fat (x) were y (sec) = − 5.1x + 267 ($r = -0.63$, $P < 0.01$, $n = 17$) in males and $y = -4.6x + 261$ ($r = -0.64$, $P < 0.05$, $n = 10$) in females with body fat of less than 30%. These lines did not differ significantly. Therefore, we correlated onset time with body fat for all subjects (n = 40). The equation was $y = -3.3x + 233$ ($r = -0.65$, $P < 0.001$) (Fig 1).

Relationships between onset time and body fat, and between plasma concentrations of vecuronium and body fat in 8 patients

The onset time significantly decreased with increasing body fat ($y = -4.4x + 274$, $r = -0.94$, $P < 0.001$). There was a significant increase of plasma concentrations at 195 and 375 sec as the body fat increased in

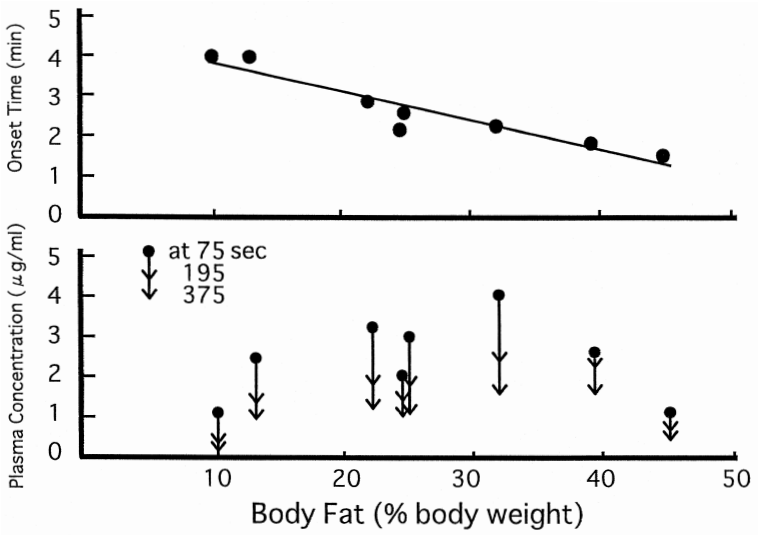

Fig. 2 Upper panel: Relationship between the onset time of vecuronium and body fat in 8 patients whose plasma concentrations of vecuronium were measured. Onset time decreased with increasing body fat ($r = -0.94$, $P < 0.001$).
Lower panel: Relationship between the plasma concentrations of vecuronium and body fat. Each arrow indicates the plasma concentrations at each time blood samples were obtained, i.e., the starting point of each arrow indicates the vecuronium concentration 75 sec after intravenous administration of vecuronium and the arrows below the starting point indicate concentrations at 195 and 375 sec, respectively. Plasma concentrations at 195 and 375 sec significantly increased with increasing body fat, except for the patient with the highest body fat.

7 out of 8 patients ($r = 0.85$, $P < 0.02$ and $r = 0.87$, $P < 0.02$, respectively) (Fig 2). The remaining patient was an obese patient with the highest body fat at 45.1%.

DISCUSSION

Our study confirmed that onset of the action of vecuronium is more rapid in females than in males and that the females have more body fat than the males. The onset became faster with increasing body fat both in males and in females. In a comparison between the groups with body fat within the same range, i.e. less than 30%, the onset time and regression lines between the onset time and body fat were not significantly different between males and females. Overall, there was a relatively high correlation between onset time and body fat in all 40 patients. In the 8 patients whose plasma concentrations of vecuronium were measured, the onset time clearly decreased with increasing body fat, and plasma concentrations increased with increasing body fat, except for the patient with the highest body fat. The onset time of muscle relaxants is influenced by many factors such as cardiac output, muscle perfusion, blood concentrations of muscle relaxants, and the drug partition coefficient between blood and the biophase. We compared the onset time of vecuronium among patients without serious systemic disorders within the same age group to exclude factors other than body fat as much as possible. Although 6 male and 4 female patients with hypertension were included in this study, differences in the onset time and body fat between non-hypertensive patients and hypertensive patients were not statistically significant both in the male group (166 ± 38 vs. 163 ± 57 sec, 20.1 ± 4.4 vs. 19.9 ± 7.4%) and the female group (134 ± 36 vs. 147 ± 42 sec, 29.1 ± 7.9 vs. 33.1 ± 3.2%). Accordingly, our results indicated that the difference in the onset time between males and females depended

on the difference of body fat, i.e. difference of the distribution volume of vecuronium. Most of the patients with high body fat probably had higher blood concentrations of vecuronium when the same dose of vecuronium per body weight was given. If the same dose of vecuronium per lean body mass had been given, the onset time might not have differed between males and females. One obese female patient with body fat of 45.1% had a short onset time in spite of low plasma concentrations. Although it is difficult to explain this phenomenon based on only one case, the following reasons can be considered. The circulation time might be shorter in some obese individuals [2]. Arterial plasma concentrations of vecuronium might have been higher if her blood samples were obtained earlier [7, 10]. Blood flow per gram of muscle might be increased in some obese individuals [5]. Some obese individuals might have different pharmacodynamics of vecuronium from non-obese individuals. The actual reason, however, remains uncertain.

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