J Anesth (1994) 8:387–391

Journal of
Anesthesia
© JSA 1994

Does sex difference influence the neuromuscular blocking potencies of vecuronium?

Ikuo Yoneda[1], Tatsuya Ura[2], Tetsuji Nakai[2], Masaaki Harada[2], and Tetsuo Sato[2]

[1] Medical Division, Air Staff Office, Japan Air Self-Defense Force, Defense Agency, 9-7-45 Akasaka, Minato-ku, Tokyo, 107 Japan
[2] Department of Anesthesiology, National Defense Medical College, Tokorozawa, 359 Japan

Abstract: One hundred and fifty patients of ASA class I–II undergoing elective surgery were given vecuronium 0.1 mg·kg^{-1} under fentanyl- (NLA), halothane, enflurane, isoflurane, or sevoflurane anesthesia, and the spontaneous recovery was monitored to study the sex differences as to onset time, duration [(T_1, train of four (TOF)], and recovery index (T_1, TOF). The onset time was significantly shorter in women than in men under isoflurane and sevoflurane anesthesia. No significant differences were seen between the sexes in terms of duration and recovery index of both T_1 and TOF. We suggest that the results regarding onset time were due to the differences in distribution volume and extracellular fluid volume influenced by the proportions of lean body mass, fat tissue, and the occasional menstruation in women. It remains unclear, however, whether or not the effects of volatile gases to the sensitivity of receptors may contribute to the observed sex difference. Similar durations and recovery indexes in any anesthetic method indicate that the drug's rate of elimination is similar between the sexes. In conclusion, female patients favor the rapid onset of vecuronium when used under isoflurane or sevoflurane, but the recovery from the paralysis seems to be the same between the sexes regardless of the type of general anesthesia used.

Key words: Sex difference—Vecuronium—Volatile anesthetics

Introduction

Before administering muscle relaxants to a patient under general anesthesia, the patient's age, weight, body surface area, and the condition of the main organs must be known, but the gender is rarely of concern to anesthesiologists. It is well known that women have less muscle and more adipose tissue in general, and that men are physically stronger than women. Could these big differences give rise to differences in the response to neuromuscular blocking agents? Although a lot of drugs have been investigated pharmacologically with respect to sex differences with some positive results [1], we cannot simply extrapolate those results to muscle relaxants because of their unique pharmacodynamic properties. This study was designed to clarify whether or not there are sex differences in the response to muscle relaxants by clinically monitoring the neuromuscular blockade with vecuronium, one of the most frequently used nondepolarizing muscle relaxants, under several general anesthetics.

Address correspondence to: I. Yoneda
Received for publication on August 11, 1993; accepted on March 24, 1994

Materials and methods

One hundred and fifty patients of ASA class I–II (aged 15–65 years) undergoing elective surgery were selected for the study and allocated to five groups according to the type of general anesthesia. Informed consent was obtained from all participants. None of the patients had clinical or biochemical evidence of hepatic or renal disease, nor were they receiving medication known to influence neuromuscular transmission. The anesthetics chosen were NLA (O_2-N_2O-fentanyl-droperidol), F (O_2-N_2O-halothane), E (O_2-N_2O-enflurane), I (O_2-N_2O-isoflurane), and S (O_2-N_2O-sevoflurane). Demographic details of the patients included in this study are shown in Table 1.

After the patient was transferred to the operation room, ECG and pulse oximeter were monitored continuously, and the heart rate and blood pressure were measured every 5 min. To monitor the neuromuscular transmission by electromyogram (EMG), the stimulus surface electrodes were placed over the ulnar nerve near the wrist, and the recording electrodes on the hypothenar muscles. After making the patients sleep

Table 1. Characteristics of patients

Group	Gender	*n*	Age (years)	Height (cm)	Weight (kg)	ChE[a] (U/ml)
NLA	Female	24	45.1 ± 2.4	155.0 ± 1.1*	51.9 ± 1.4*	3.3 ± 0.1
	Male	17	43.3 ± 4.0	167.0 ± 1.1	63.8 ± 2.3	3.8 ± 0.2
F	Female	13	41.9 ± 4.5	154.4 ± 2.2*	53.7 ± 2.7*	3.8 ± 0.3
	Male	16	38.2 ± 4.2	169.6 ± 1.5	67.7 ± 2.8	3.5 ± 0.5
E	Female	13	41.9 ± 3.4	154.3 ± 1.2*	52.0 ± 1.6*	3.0 ± 0.2
	Male	13	38.2 ± 4.6	170.0 ± 1.5	61.2 ± 2.4	3.6 ± 0.2
I	Female	10	35.6 ± 4.0	151.8 ± 2.6*	52.2 ± 2.2*	3.8 ± 0.5
	Male	17	37.0 ± 3.8	169.0 ± 1.8	63.9 ± 2.5	3.4 ± 0.3
S	Female	16	48.3 ± 3.2	156.2 ± 1.3*	53.6 ± 1.9*	3.1 ± 0.4
	Male	11	47.6 ± 5.7	166.3 ± 3.0	62.4 ± 3.6	3.6 ± 0.4

Values are expressed as mean ± SEM.
* $P < 0.05$ versus men in the same anesthetic group.
ChE, cholinesterase; NLA, O_2-N_2O-fentanyl-droperidol; F, O_2-N_2O-halothane; E, O_2-N_2O-enflurane; I, O_2-N_2O-isoflurane; S, O_2-N_2O-sevoflurane.
[a] Normal range; 2.40–4.30 U/ml.

with 3–5 mg·kg^{-1} thiopental, supramaximal stimuli with train-of-four (TOF) impulses at 20-s intervals were given (Relaxograph, Datex, Helsinki, Finland). The evoked compound electromyogram was amplified, integrated, and recorded on a thermal printer. After the calibration and baseline recording, the patients were slowly induced with the chosen method of general anesthesia ventilated by mask, that is, under O_2 (2 l · min^{-1}) —N_2O (4 l·min^{-1})—X (X corresponding to NLA, halothane, enflurane, isoflurane, or sevoflurane). NLA consisted of 5 μg·kg^{-1} intravenous fentanyl and 250 μg·kg^{-1} intravenous droperidol, followed by reinjections of 2 μg·kg^{-1} fentanyl when the clinical evidence of inadequate analgesia was observed. In other anesthetic groups, the end-tidal concentration of the volatile gases were adjusted to stay throughout the study at the predetermined value of 1 MAC under 100% O_2 (i.e., 0.75% for halothane, 1.68% for enflurane, 1.15% for isoflurane, and 1.71% for sevoflurane), which was continuously monitored (Ultima, Datex). Vecuronium 0.1 mg·kg^{-1} was given after 10 min of general anesthesia with the end-tidal concentration kept at the specified value, and then the trachea was intubated at the time of maximum blockade or when T_1 became 0. No additional muscle relaxants were given thereafter, and spontaneous recovery was monitored throughout surgery. End-tidal CO_2 was maintained within the range of 40 ± 2 mmHg by accommodating mechanical ventilation (Ultima, Datex). When the recovery from vecuronium paralysis was not complete at the end of surgery, reversal with neostigmine/atropine mixtures was given to the patient. If the recovery had not achieved 75% for both T_1 and TOF before reversal, the data were excluded from this study.

Onset time was defined as the time from injection to the maximum depression of T_1. Duration and recovery index of T_1 were defined as the time from the administration of vecuronium to the 25% recovery of the control value and the time from 25% to 75% recovery of the control, respectively. Duration and recovery index of TOF were defined as the time from administration to 25% and the time from 25% to 75% recovery of TOF, respectively (Fig. 1).

The measured values were expressed as mean ± SEM. Differences between the sexes were analyzed using Student's *t*-test, and $P < 0.05$ was considered statiscally significant.

Results

The mean values of height and weight were significantly greater in men than in women in every anesthetic group, but no significant differences were evident in age or cholinesterase (Table 1).

Onset time was significantly longer in women than in men under isoflurane and sevoflurane anesthesia [2.0 ± 0.1 min (women), 2.7 ± 0.2 min (men) in I and 2.2 ± 0.1 min (women), 3.3 ± 0.4 min (men) in S], but no significant differences were found under NLA, F, or E (Fig. 2)

As to duration and recovery index of T_1, no significant differences were evident between the sexes, though there was large interindividual variability in the recovery index (Figs. 3, 4). Duration and recovery index of TOF showed less variability than those of T_1, but there were no significant differences between the sexes, either (Figs. 5, 6).

Discussion

Sex-linked differences in drug kinetics are known in a limited number of substances such as certain antibiotics, a few tricyclic antidepressants, lithium carbon-

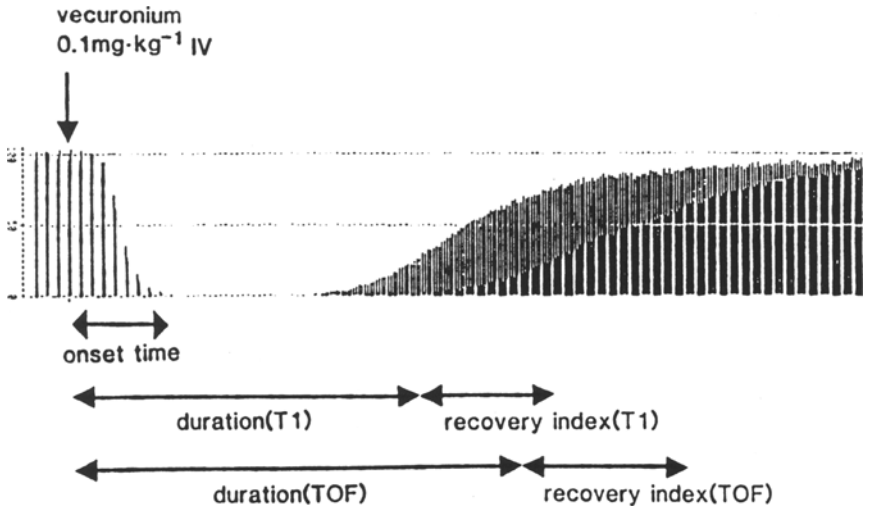

Fig. 1. A recording of spontaneous recovery from the 0.1 mg·kg^{-1} vecuronium bolus injection, and the definitions of onset time, duration [T_1 and train of four (TOF)], and recovery index (T_1 and TOF)

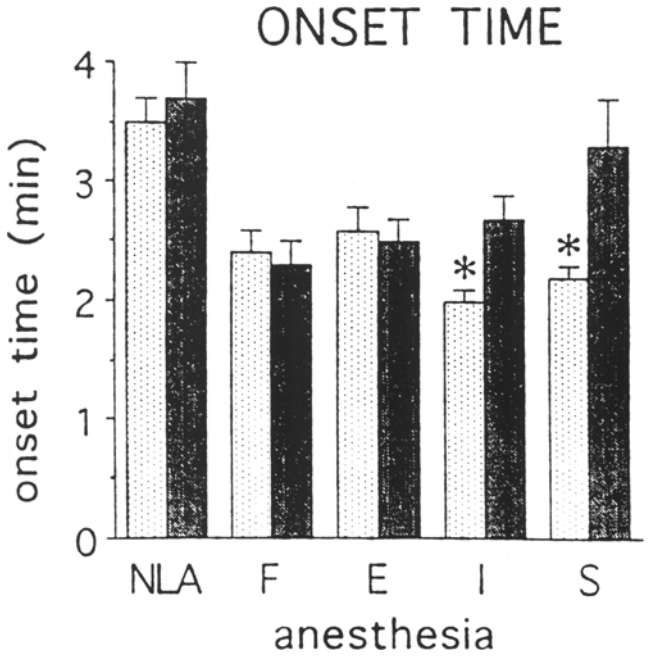

Fig. 2. Relationship of sex, anesthesia, and onset time. Under isoflurane and sevoflurane anesthesia, onset time was prolonged in women compared with men. Values are mean ± SEM. $^*P < 0.05$ *vs* men. *Shaded bars*, women; *solid bars*, men

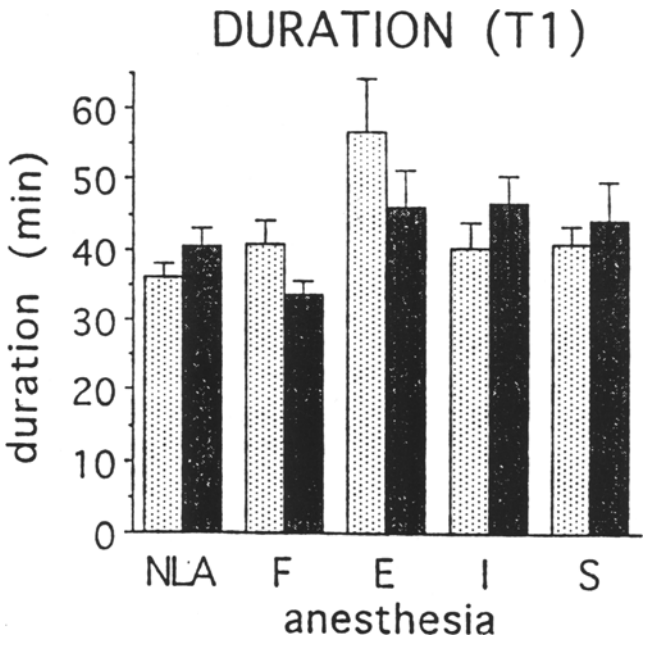

Fig. 3. Relationship of sex, anesthesia, and duration of T_1. No significant difference between sexes were found. Values are mean ± SEM. *Shaded bars*, women; *solid bars*, men

ate, aspirin, and hexobarbitone [1,2]. The results are not one-sided, and the mechanism remains unclear. For example, oral administration of antibiotics such as rifampicin, chloramphenicol, and tetracycline was more effective in women than men [3]. The effect of antidepressants such as nortriptyline [4] and imipramine [5] was also stronger in women. On the other hand, some antibiotics such as kanamycin [6] and gentamycin [7] were shown to be more effective in men, as were anticonvulsants such as phenytoin, phenobarbitone, and primidone [8]. Hexobarbitone made female rats sleep four times longer than male rats [9]. On the other hand, there are very few systematic human studies on the influence of sex on the potency of muscle relaxants.

Theoretically, the causes of differences in drug kinetics are due to differences in the drug's absorption, distribution, metabolism, and excretion. In other words, the possible factors that may make differences due to sex are: (1) body composition, (2) protein binding, (3)

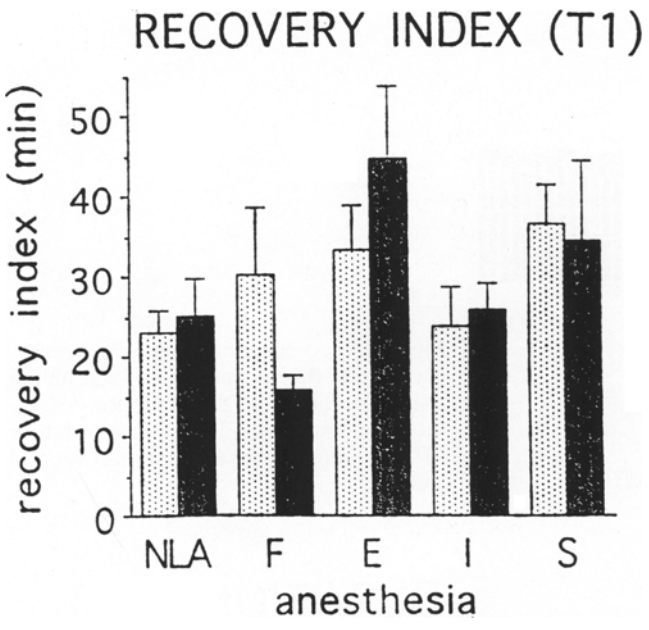

Fig. 4. Relationship of sex, anesthesia, and recovery index of T_1. No significant difference between sexes were found. Values are mean ± SEM. *Shaded bars*, women; *solid bars*, men

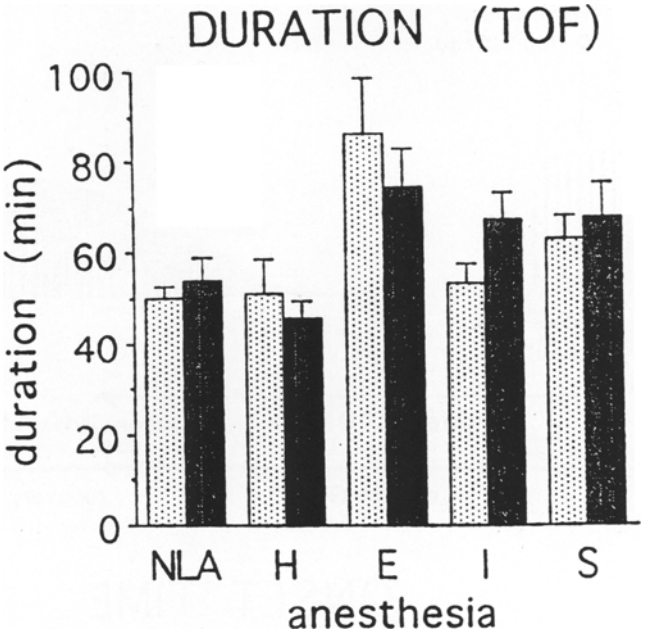

Fig. 5. Relationship of sex, anesthesia, and duration of TOF. No significant difference between sexes were found. Values are mean ± SEM. *Shaded bars*, women; *solid bars*, men

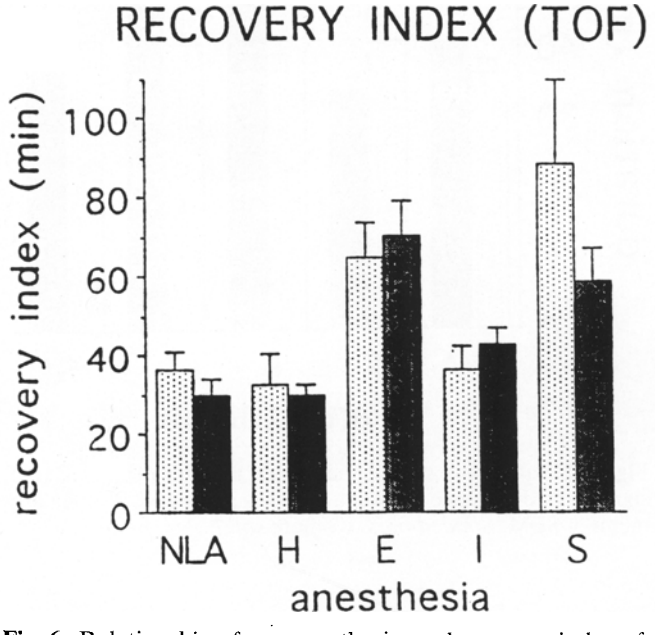

Fig. 6. Relationship of sex, anesthesia, and recovery index of TOF. No significant difference between sexes were found. Values are mean ± SEM. *Shaded bars*, women; *solid bars*, men

plasma enzyme activity, (4) metabolism in the liver, (5) hepatic or kidney excretion, and (6) receptor sensitivity. The peculiar property of muscle relaxants may well require special consideration for the its unique behavior.

Houghton et al. [10] reported that there were no differences between mean onset time and mean duration of vecuronium between both sexes, but that women had significantly better intubating conditions. Donati and Bevan [11] found that the onset time of pancuronium was shorter in women under enflurane anesthesia; they suggested that this could have been due to differences in the apparent distribution volume and body composition. In our study, only the onset time in two anesthetic methods revealed differences. This is most probably the result of unequal absorption or distribution. As to distribution, like Donati suggested, we must first consider body composition. Men have higher relative proportions of lean body mass, and women have more adipose tissue. The menstrual cycle may influence the extracellular fluid (ECF) as well. When we consider the reason for our results, it is possible that the low volume of ECF due to the smaller proportion of lean body mass, more fat tissue, and the occasional menstruation might have accelerated the onset time in women. Thus, it is reasonable to think that the same amount of vecuronium per kg body weight in women reaches the receptor sites faster and in higher concentration to attain the threshold level.

The similarities of duration or recovery index of both sexes mean not only that the drug's metabolism and rate of elimination made little differences but also that the long time course compared with the onset time value masked the differences, if any, of the onset times. We evaluated the sex differences in TOF with negative re-

sults, indicating that presynaptic and postsynaptic relationship does not differ between the sexes.

In our vecuronium study, the plasma cholinesterase (pChE) activities were not different among the group suggesting little participation of the enzyme. Vecuronium depends on the liver and kidney for elimination, and so pChE appears not to play a role in the modulation of neuromuscular blocking capability in vecuronium.

Metabolism in the liver and excretion by the kidney per se do not account for the differences between the sexes on the physiological basis, and our results on duration and recovery support the idea that as long as the major organs are intact, the muscle relaxants act similarly. Receptor sensitivity is not well investigated as to sex difference, and we cannot explain our results in this regard.

It is well known that the anesthetic methods with volatile gases enhance the neuromuscular blocking potencies in both sexes, but the sex differences regarding the onset time of vecuronium were evident only with isoflurane and sevoflurane. The reason why only isoflurane and sevoflurane exhibited sex differences on onset times is not clear. Both gases, having potent muscle relaxing properties, are also known as rapid inducers due to their smaller blood-gas partition coefficients, which might be one of the reasons why these two agents are faster enhancers of vecuronium. In other words, the small sex difference in onset time might be enhanced when the muscle mass is rapidly paralyzed by volatile gases. This, however, is a subject for future investigation.

In conclusion, under NLA, halothane, enflurane, isoflurane, or sevoflurane anesthesia, there were no significant sex differences on the potentiation of vecuronium except the onset times under isoflurane and sevoflurane. To clarify the reason for the results, further study is needed, including the relationship between sex and the type of inhalational agent used.

References

1. Giudicelli JF, Tillement JP (1977) Influence of sex on drug kinetics in man. Clin Pharmacokinet 2:157–166
2. Menguy R, Desbaillets L, Masters YF, et al. (1972) Evidence for a sex-linked difference in aspirin metabolism. Nature 239:102–103
3. Scotti R (1973) Sex differences in blood levels of some antibiotics. Chemotherapy 18:205–211
4. Hammer W, Sjoqvist F (1967) Plasma levels of monomethylated tricyclic antidepressants during treatment with imipramine-like compounds. Life Sci 6:1895–1903
5. Moody JP, Tait AC, Todrick A (1967) Plasma levels of imipramine and desmethylimipramine during therapy. Brit J Psychiatry 113:183–193
6. Nielsen B, Sorensen AW, Szabol L, et al. (1973) Kanamycin serum half-life and renal function: age and sex. Dan Med Bull 20:144–149
7. Perrier D, Gilbaldi M (1973) Estimation of drug elimination in renal failure. J Clin Pharmacol 13:458–462
8. Travers R, Reynolds EH, Callagher B (1972) Variation in response to anticonvulsants in a group of epileptic patients. Arch Neurol 27:29–33
9. Quinn GP, Axelrod J, Brodie BB (1958) Species, strain and sex differences in metabolism of hexobarbitone, amidopyrine, antipyrine and aniline. Biochem Pharmacol 1:152–159
10. Houghton IT, Aun CST, Oh TE (1992) Vecuronium: an anthropometric comparison. Anaesthesia 47:741–746
11. Donati F, Bevan DR (1986) The influence of patient's sex, age and weight on pancuronium onset time. Can Anaesth Soc J 33: S86