Changes in the Plasma Histamine Concentration after the Administration of Vecuronium Bromide

Hiromasa MITSUHATA, Shigeru MATSUMOTO, Keiji ENZAN*, Masaya YABE and Hiromichi TERADA

Clinical symptoms of anaphylactoid reaction to muscle relaxants vary from localized flush to cardiovascular collapse. Vecuronium bromide is reported to have very little histamine releasing property. However, there are some reports of anaphylaxis or anaphylactoid reaction to vecuronium. We studied plasma histamine concentration after the intravenous injection of vecuronium to confirm the histamine release. Twenty patients were randomly allocated to one of two groups, each group comprising of 10 patients: one group was to receive vecuronium 0.1 $mg \cdot kg^{-1}$ and the other 0.2 $mg \cdot kg^{-1}$ using the priming principle. Blood samples were taken prior to and 1, 3, 5, 8 and 13 min after the administration of vecuronium. The plasma histamine concentration was measured by radioimmunoassay with monoclonal antibody.

There were no significant changes in plasma histamine concentration over 13 min after the administration of vecuronium compared with the baseline value. There were also no significant differences between these two groups. We concluded that vecuronium up to 0.2 $mg \cdot kg^{-1}$ did not change the plasma histamine concentration in the patients having no previous history of allergy or atopic tendencies. (Key words: vecuronium, histamine, priming principle, radioimmunoassay)

(Mitsuhata H, Matsumoto S, Enzan K, et al.: Changes in the plasma histamine concentration after the administration of vecronium bromide. J Anesth 5: 24–29, 1991)

Some anesthetics and muscle relaxants may cause anaphylaxis or anaphylactoid reaction. Clinical symptoms of anaphylactoid reaction to muscle relaxants vary from localized skin flush to cardiovascular collapse. Fisher et al.[1] state that the life-threating anaphylactoid reactions to muscle relaxants occur more commonly than has previously been suspected, and that the mechanism is different from direct histamine release and type I hypersensitivity. It is known that d-tubocurarine has a direct histamine releasing property, and other commonly used relaxants also have more or less histamine releasing ability[2].

It is reported that vecuronium has very little histamine releasing property with intradermal test. Some authors recommend vecuronium as the relaxant of choice to the patients being atopic, asthmatic or with allergic tendency[3,4]. However some observations of systemic histaminoid reaction following vecuronium administration have been reported[5–8]. Durrani et al.[7] recommend accordingly the routine use of a priming dose as a predictive test of histamine release. Therefore, we investigated the plasma his-

Department of Anesthesiology, Hiraka General Hospital, Akita, Japan

**Department of Anesthesiology, Akita University School of Medicine, Akita, Japan*

Address reprint requests to Dr. Mitsuhata: Department of Anesthesiology, Hiraka General Hospital, 1-30 Ekimae-cho, Yokote, Akita 013 Japan

Table 1. Clinical characteristics of the patients

	0.1 mg·kg^{-1} vecuronium group	0.2 mg·kg^{-1} vecuronium group
Age (yrs)	56.3 ± 12.2	50.5 ± 13.8
Sex ratio (male/female)	7/3	5/5
Weight (kg)	59.4 ± 5.8	52.2 ± 8.0

Values represent the mean ± SD.

tamine concentration after the intravenous administration of vecuronium to confirm the histamine releasing property instead of studying the skin reaction.

Subjects and Methods

We selected 20 patients (ASA physical status class I–II) with no previous history of allergy or atopy, scheduled for the elective surgical procedures. Their clinical characteristics are shown in table 1. The protocol of this study was approved by Institutional Ethics Committee on clinical investigations. All patients were premedicated with hydroxyzine 1.5 mg·kg^{-1} and atropine sulfate 0.5 mg one hour preoperatively and were randomly allocated to one of two groups. Each group comprising of 10 patients: the first group was given vecuronium 0.1 mg·kg^{-1} (1.7 ED_{95}) and the second group 0.2 mg·kg^{-1} (3.5 ED_{95}). Vecuronium was administered according to the priming principle reported by Schwarz et al.[10] All the patients were given 6 mg·kg^{-1} of thiopental sodium intravenously 1 min after the administration of 1 mg of vecuronium as a priming does. The rest of the remaining dose from the total dose 0.1 mg·kg^{-1} or 0.2 mg·kg^{-1} in each group, was given 3 min after the administration of the priming dose. The patients were ventilated with oxygen and given only thiopental sodium over 5 min after the administration of the intubating dose of vecuronium. Thereafter enflurane was given as needed. After the administration of the priming dose of vecuronium, blood pressure and heart rate were monitored and the skin on face, trunk and limbs was observed

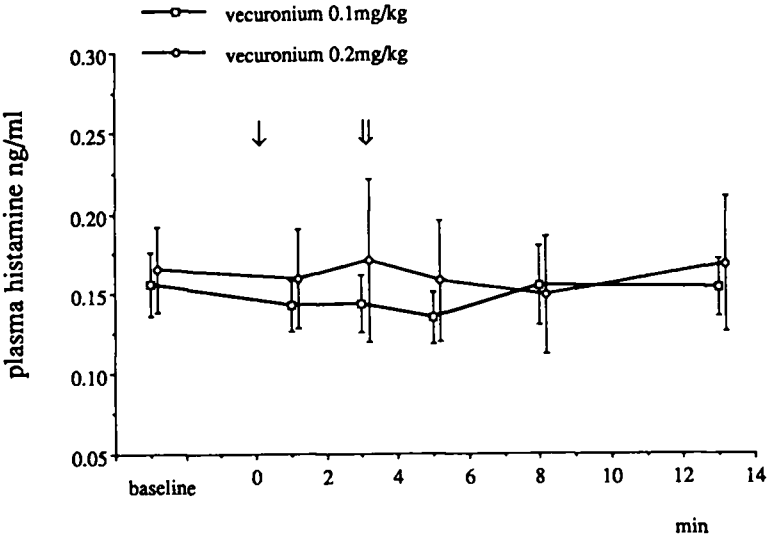

Fig. 1. Changes in plasma histamine concentration before and after the administration of 0.1 mg·kg^{-1} and 0.2 mg·kg^{-1} vecuronium bromide.

Values represent the mean ± SE. Arrow denotes the administration of 1 mg vecuronium as a priming dose. Wide arrow denotes the administration of 0.1 mg·kg^{-1} of 0.2 mg·kg^{-1} vecuronium as an intubating dose.

Table 2. Histamine concentration ($ng \cdot ml^{-1}$) before and after the administration of vecuronium

	histamine concentration ($ng \cdot ml^{-1}$)					
	baseline	1 min	3 min	5 min	8 min	13 min
0.1 $mg \cdot kg^{-1}$ vecuronium group	0.156±0.020 (0)	0.142±0.016 (−3.7±9.3)	0.143±0.003 (−6.6±5.9)	0.134±0.016 (−12.8±4.0)	0.154±0.025 (−1.4±7.4)	0.152±0.018 (2.1±8.8)
0.2 $mg \cdot kg^{-1}$ vecuronium group	0.165±0.027 (0)	0.159±0.031 (−0.6±9.0)	0.170±0.051 (−0.3±16.3)	0.157±0.038 (−8.5±9.9)	0.148±0.037 (−10.1±12.2)	0.167±0.042 (−1.0±12.5)

Values represent the mean ± SE. Values in parenthesis represent per cent changes from baseline.

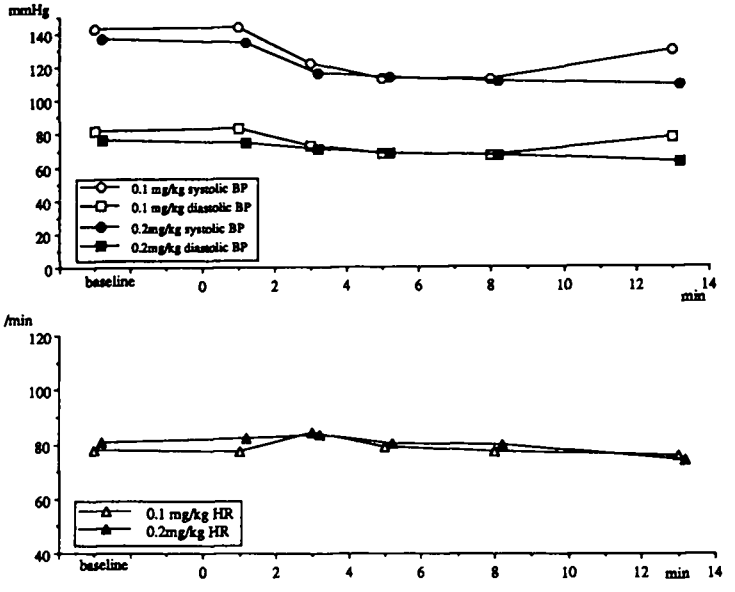

Fig. 2. Changes of systolic and diastolic blood pressures, and heart rate before and after the administration of 0.1 $mg \cdot kg^{-1}$ and 0.2 $mg \cdot kg^{-1}$ vecuronium bromide.

Values represent the mean ± SE.

for the flush for 13 min.

The venous blood samples were taken slowly with a plastic syringe through the 16G argyle Medicut catheter®, placed in femoral vein, prior to the injection of the priming dose, and 1, 3, 5, 8, and 13 min thereafter. Blood was immediately transfered into an iced tube containing ethylenediamine-tetraacetic acid (EDTA 2Na) and centrifuged at 1–4°C within 20 min for 5 min. Plasma was separated and stored at −80°C until assay was performed. Plasma histamine concentration was measured with radioimmunoassay using HISTAMINE RADIOIMMUNOASSAY KIT® (Immunotech S.A. Marseille, France, Eiken, Tokyo).

Data are expressed as the mean ± SE. The statistical analysis was performed using one-way analysis of variance, Wilcoxon single rank test, and Mann-Whiteny U test, with a P values of < 0.05 considered statistically significant.

Results

The baseline value of plasma histamine was 0.16 ± 0.02 $ng \cdot ml^{-1}$ in the first group, and 0.17 ± 0.03 $ng \cdot ml^{-1}$ in the second group. There were no significant changes in plasma histamine concentration over 13 min after the administration of the priming dose, namely, the variation from the baseline level was from −12.8 ± 4.0% to +2.1 ± 8.8% in the first group, and from −10.1 ± 12.2% to −1.0 ± 12.5% in the second group. There

were also no significant differences between the two groups (table 2).

The blood pressure and heart rate did not change significantly in either group compared with the baseline value, although the systolic pressure slightly decreased after the administration of thiopental sodium (fig. 2). None of the patients showed skin flush in either group.

Discussion

It is stated that histamine is easily liberated from the white blood cells, if sampling, transportation and storage is improperly performed[11]. Therefore, we took blood samples from large vein through 16G indwelling catheter, and handled them very carefully to exclude any errors. In this study, plasma histamine was measured by radioimmunoassay with monoclonal antibody against N-methylhistamine, which is more sensitive than the radioenzymatic analysis, which was frequently used in many previous reports on plasma histamine after the vecuronium administration. The sensitivity of latter method is 0.1 $ng \cdot ml^{-1}$ histamine[12].

Histamine concentration obtained from 20 patients in this study was 0.16 ± 0.01 $ng \cdot ml^{-1}$, which corresponds to the previously reported value of 0.05 to 0.2 $ng \cdot ml^{-1}$ [13]. Our results revealed that vecuronium did not induce direct histamine release either after the administration of 1 mg vecuronium as a priming dose, or after the administration of a full dose in either group. The administration of vecuronium in vivo[14–16] and in vitro[17] has revealed no change in histamine concentration measured by radioenzymatic analysis, it is obvious that vecuronium up to 3.5 times of ED_{95} (0.2 $mg \cdot kg^{-1}$) dose not release histamine. The maximal histamine level in this study (0.33 $ng \cdot ml^{-1}$) was quite low compared with the level which causes symptoms, that is 1.61 ± 0.30 $ng \cdot ml^{-1}$ [18]. Consequently, we consider that vecuronium up to 3.5 times of ED_{95} can be used safely in patients with no history of allergy or previous reaction to muscle relaxants.

Since halothane is reported to reduce d-tubocurarine-induced histamine release in vitro[19], no inhalational anesthetic was used during this study. All the patients were premedicated with hydroxyzine, which is not considered to alter the plasma histamine level, because it binds to H_1-type receptors and does not inhibit the release of histamine.

In this study, the plasma histamine concentration did not change significantly after the administration of vecuronium in the priming principle to the patients with no previous history of allergy or atopic tendency. The histaminoid reaction due to administration of some muscle relaxants is stated to occur mainly in the patients with history of allergy. However, Lavery et al.[5] reported a systemic histaminoid reaction with erythema on face and entire trunk, and hypotension in a 40-years-old female with no history of allergy. Clayton et al.[6] also reported the similar erythema over arms and trunk after the vecuronium administraion in a 7-year-old boy with atopic tendency. They confirmed that this cutaneous reaction was due to the direct histamine release. Durrani et al.[7] reported a patient with breathing difficulty accompanied by no clinical symptoms of bronchospasm 7 min after the administration of priming dose of 1 mg of vecuronium. This patient has no previous history of allergy or reaction to any other intravenous anesthetics. O'Callaghan[8] has reported the bronchospasm, which occured in a patient with no evidence of direct histamine release or IgE-mediated reaction. The observations of anaphylaxis following vecuronium administration have been also reported[20]. Therefore, vecuronium should be given very carefully not only to the patients with history of allergy, but also to the patients with no previous history of allergy. It is also worth mentioning that the patients with previous allergic reaction to other muscle relaxants have some possibilities of cross-reactivity to vecuronium[21].

Premedication with H_1 and H_2 antagonist is recommended to the patients considered to be sensitive to non-depolarizing muscle relaxants[8]. Hydroxyzine, which is commonly used as a sedative in premedication, is reported to raise significantly the threshold for

histamine-induced tachycardia[18]. Moreover, the combined use of H_1 and H_2 antagonist significantly raised the histamine dose to elicit the responses during sequential infusion of histamine in volunteers[18]. Because there are some possibilities for anaphylaxis or anaphylactoid reaction to occur following the administration of muscle relaxants in any patients, the preanesthetic medication with hydroxyzine is recommended when the administration of non-depolarizing muscle relaxants was anticipated.

In summary, we measured the plasma concentration of histamine following the administration of vecuronium in the priming principle in the patients with no previous history of allergy or atopic tendency. There were no significant change in plasma concentration of histamine, and no clinical allergic reaction such as hypotension and skin flush was observed. The effects of vecuronium on the patients having history of allergy or atopy can not be concluded from this study, and remained to be clarified.

(Received Mar. 22, 1990, accepted for publication Jul. 18, 1990)

References

1. Fisher MM, Munro I: Life-threatening anaphylactoid reactions to muscle relaxants. Anesth Analg 62:559–564, 1983
2. Galletly DC: Comparative cutaneous histamine release by neuromuscular blocking agents. Anaesth Intens Care 14:365–369, 1986
3. Booiji LHDJ, Krieg N, Crul JF: Intradermal histamine releasing effect caused by Org-NC 45. Acta Anaesthesiol Scand 24:393–394, 1980
4. Robertson EN, Booij HDJ, Fragen RJ, Crul JF: Intradermal histamine release by 3 muscle relaxants. Acta Anaesthesiol Scand 27:203–205, 1983
5. Lavery GG, Hewitt AJ, Kenny NT: Possible histamine release after vecuronium. Anaesthesia 40:389–390, 1985
6. Clayton DG, Watkins J: Histamine release with vecuronium. Anesthesia 39:1143–1144, 1984
7. Durrani Z, O'Hara J: Histaminoid reaction from vecuronium priming: A case report. Anesthesiology 67:130–132. 1987
8. O'Callaghan AC, Scadding G, Watkins J: Bronchospasm following the use of vecuronium. Anaesthesia 41:940–942, 1986
9. McBride P, Bradley D, Kaliner M: Evaluation of radioimmunoassay for histamine measurement in biologic fluids. J Allergy Clin Immunol 82:638–646, 1988
10. Schwarz S, Ilias W, Lacker F, Maryhofer O, Foldes FF: Rapid tracheal intubation with vecuronium: The priming principle. Anesthesiology 62:388–391, 1985
11. Watkins J: Tests in vivo and in vitro of hypersensitivity response, Guide to immediate anaesthetic reactions. Edited by Watkins, J, Levy, CJ. London, Butterworths, 1988, pp. 101–115
12. McBride P, Bradley D, Kaliner M: Evaluation of a radioimmunoassay for histamine measurement in biologic fluids. J. Allergy Clin Immunol 82:638–646, 1988
13. Holgate ST, Robinson C, Church MK: Mediators of immediate hypersensitivity, Allergy: Principles and practice. Edited by Middleton, E, Reed, CE, Ellis, EF, Adkinson, NF, Yunginger, JW. ST. Louis, C.V. Mosby, 1988, pp. 135–163
14. Basta SJ, Savarreses JJ, Ali HH, Sunder N, Moss J, Gionfriddo M, Embree P: Vecuronium does not alter serum histamine within the clinical dose range. Anesthesiology 59:A273, 1983
15. Goudsouzian NG, Young ET, Moss J, Liu LMP: Histamine release during the administration of atracurium or vecuronium in children. Br J Anaesth 58:1229–1233, 1986
16. Cannon JE, Fahey MR: Large doses of vecuronium and plasma histamine concentration. Can J Anaesth 35:350–363, 1988
17. North FC, Kettelkamp N, Hirshman CA: Comparision of cutaneous and in vitro histamine release by muscle relaxants. Anesthesiology 66:543–546, 1987
18. Kaliner M, Shelhamer JH, Ottesen EA: Effects of infused histamine: correlation of plasma histamine levels and symptoms. J Allergy Clin Immunol 69:283–289, 1982
19. Kettlekamp NS, Austin DR, Downes H, Cheek DBC, Hirshman CA: Inhibition of d-tubocurarine-induced histamine release by halothane. Anesthesiology 66:666–669, 1987
20. Moneret-Vautrin DA, Laxenaire MC, Mouton C: Anapylaxie croisée avec le vécuronium. Ann Fr Anesth Réanim 3:467, 1984

21. Harle DG, Baldo BA, Fisher MM: Cross-reactivity of metocurine, atracurium, vecuronium and fazadinium with IgE antibodies from patients unexposed to these drugs but allergic to other myoneural blocking drugs. Br J Anaesth 57:1073–1076, 1985