Dose-response Relation and Time Course of Action of Pipecuronium in Patients Anesthetized with Nitrous Oxide and Sevoflurane

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The dose-response relation of pipecuronium, the time course of its neuromuscular blocking effects, and the reversibility of the residual block by neostigmine have been investigated in patients under sevoflurane/N_2O Anesthesia using a neuromuscular transmission analyzer (Accelograph®, Biometer, Denmark). After an initial dose of pipecuronium (0.04 $mg \cdot kg^{-1}$, i.v.), the maximum block rate, onset time, the time from administration until 25% recovery and 50% recovery of control twitch height of the first response to train-of-four nerve stimulation and the interval time of administration of maintenance dose (0.005 $mg \cdot kg^{-1}$, i.v.) were 93.7 ± 7.68%, 5.0 ± 1.84, 55.4 ± 23.92, 73.0 ± 29.44 and 38.7 ± 15.50 minutes, respectively. The average intubation score (excellent; 0, good; 1 fair; 2, poor; 3) was 0.63 ± 0.56 at the level of 95.88 ± 5.06% block. Neostigmine (1.5 mg) promptly reversed the residual neuromuscular blockade induced by pipecuronium (reversal time: 10.1 ± 2.98 minutes). No side effects attributable to pipecuronium was seen in this study.

In conclusion, pipecuronium is a very useful nondepolarizing neuromuscular blocking agent especially for moderately long surgical procedure over 4–5 hours. (Key words: pipecuronium, nondepolarizing neuromuscular blockade, train-of-four, sevoflurane)

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Pipecuronium is a new, long acting, nondepolarizing neuromuscular blocking agent with a chemical structure of steroid similar to that of pancuronium and vecuronium. Agoston et al.[1], Maestrone[2] and Zwölfer et al.[3] have reported the clinical pharmacologic profile of pipecuronium. The administration of pipecuronium did not seem to be followed by either release of histamine or cardiovascular side effects, such as tachycardia and/or hypotension. The present study reports the results of an open clinical study designed to evaluate the potency, time course of action and reversibility of the pipecuronium-induced neuromuscular blockade in patients be-

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ing anesthetized with nitrous oxide and sevoflurane.

Materials and Methods

The subjects included 24 adult patients (age: 45.5 ± 11.8, body weight: 52.5 ± 8.9 kg, Male: 6, Female: 18) of ASA class 1 and 2, undergoing elective gynecologic or gastroenterologic surgery. Excluded from the study were patients with known kidney, liver or neuromuscular disorders or those taking any medication known to alter neuromuscular transmission. This open clinical trial was approved by the Medical Ethical Committee of our hospital, and the informed consent was obtained at a preoperative visit. One hour after premedication with atopine (0.01 $mg \cdot kg^{-1}$, i.m.) and hydroxidine (1 $mg \cdot kg^{-1}$, i.m.), anesthesia was induced with thiopental (3–5 $mg \cdot kg^{-1}$, i.v.) and fentanyl (4 $\mu g \cdot kg^{-1}$, i.v.). Then, the patient's lungs were ventilated using a face mask with nitrous oxide/oxygen (in a ratio of 1 to 1) to which sevoflurane was added in gradually increasing inspired concentrations up to 2.0% sevoflurane prior to endotracheal intubation. Anesthesia was maintained with 2.0% sevoflurane and 50% nitrous oxide in oxygen during operation. The inspired sevoflurane concentration (2.0%), expired concentration (1.7–1.9%) and normocapnea were sustained using a Capnomac® (Datex, Finland). In all patients the electro cardiogram (ECG), blood pressure, heart rate were monitored during anesthesia. Rectal temperature and peripheral skin temperature of the hands were maintained at 36.5 ± 0.5°C and 34.0 ± 0.5°C, respectively using a warming mattress. After induction of anesthesia, the ulnar nerve was stimulated at the wrist through cutanous electrodes connected to a nerve stimulator incorporated in a neuromuscular transmission analyzer[4] (Accelograph®, Biometer, Denmark). After obtaining supramaximal stimulation using a single twitch stimulation (1.0 Hz), the indirect adduction force of the resultant thumb twitch was measured with an acceleration transducer which was fixed with a tape on the thumb, and the responses were recorded. The pattern of the stimulation was switched to the train-of-four (TOF, 2 Hz, every 15 seconds). After stabilization of the response, pipecuronium (0.04 $mg \cdot kg^{-1}$) in 10 ml of saline solution was administered intravenously as an initial dose. Tracheal intubation was performed after obtaining maximum block and the intubation score was determined in accordance with Fahey's Table of Intubation Score[5] that is classified as excellent (score 0); vocal cords abducted, good visualization, no patient movement, good (score 1); vocal cords abducted, good visualization, diaphragmatic movement with endotracheal intubation, fair (score 2); vocal cords slightly adducted, fair visualization, coughing on intubation of trachea, poor (score 3); vocal cords adducted, difficult visualization, gross movement of the extremities and coughing with endotracheal intubation. When relaxation was not sufficient for tracheal intubation, an additional dose (0.005 $mg \cdot kg^{-1}$) was administered after determining the maximum block rate with the initial dose. When response to TOF stimulation disappeared with the initial dose, posttetanic count (PTC)[6,7] was measured. During the operation, an additional dose (0.005 $mg \cdot kg^{-1}$, i.v.) was administered when the degree of neuromuscular blockage recovered to 50% of the control twitch height of the first response to TOF stimulation as long as there was no inconvenience for the operation. After the operation, the patients were anesthetized with only 50% of nitrous oxide in oxygen and when the degree of neuromuscular blockade recovered spontaneously to the level of TOF ratio of 25%, neostig-

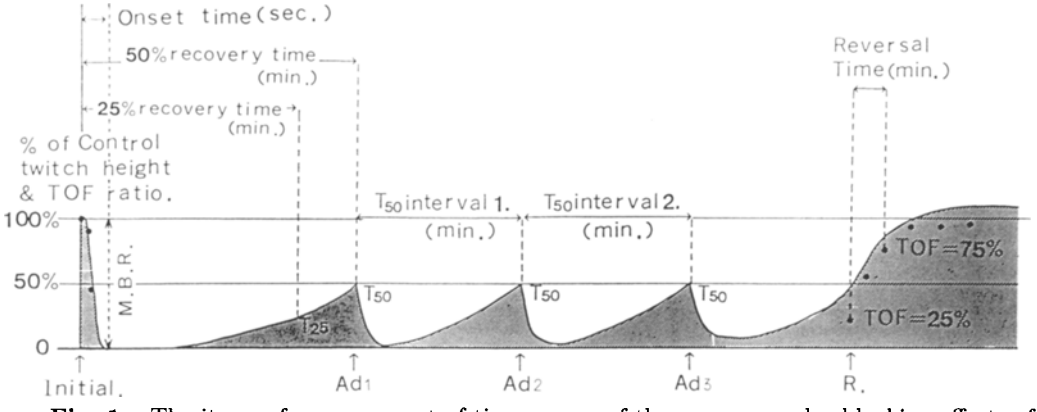

Fig. 1. The items of measurement of time course of the neuromuscular blocking effects of pipecuronium. Vertical scale is control twitch height of the first response to TOF stimulation (%) and horizontal scale is time. Dot describes TOF ratio. M.B.R.; maximum block rate.

mine (1.5 mg) and atropine (0.5 mg) in 18 ml of saline solution was administered intravenously in four divided doses[8] (each 5 ml, every 3 minutes). As figure 1 shows, the oneset time, the time from the administration until maximum block, clinical duration, the time from the administration until 25% recovery (T_{25}) and 50% recovery (T_{50}) of control twitch height of first response to TOF stimulation, maintenance dose interval (T_{50} interval), the time from additional dose to next additional dose and reversal time and the time from administration of neostigmine at TOF ratio of 25% until the recovery reached a TOF ratio of 75% were determined. All values are expressed as mean ± SD. To analyze the cumulative effect of pipecuronium, comparisons of the mean value of T_{50} interval were made using the one-way analysis of variance of repeated measurements. If there was a statistical difference, an F test was applied to determine where the difference between the T_{50} interval occurred. A *P* value less than 0.05 was regarded as significant.

Results

Table 1 shows the time course of the effects. Figure 2 shows the recording of

Table 1. The time course of neuromuscular blockade.

	Mean ± SD	
onset time (min.) n=24	5.0	1.84
maximum block rate (%) n=24	93.7	7.68
T_{25} (min.) n=24	55.4	23.92
T_{50} (min.) n=20	73.0	29.44
T_{50} interval 1 (min.) ※ n=17	38.7	15.50
T_{50} interval 2 (min.) ※ n=12	31.8	9.60
T_{50} interval 3 (min.) ※ n=8	28.9	8.49
T_{50} interval 4 (min.) ※ n=6	29.2	9.51
T_{50} interval 5 (min.) ※ n=5	33.7	9.91
Revarsal Time (min.) n=22	10.1	2.98

※ There was no significant difference among the mean times of T_{50} interval each other.

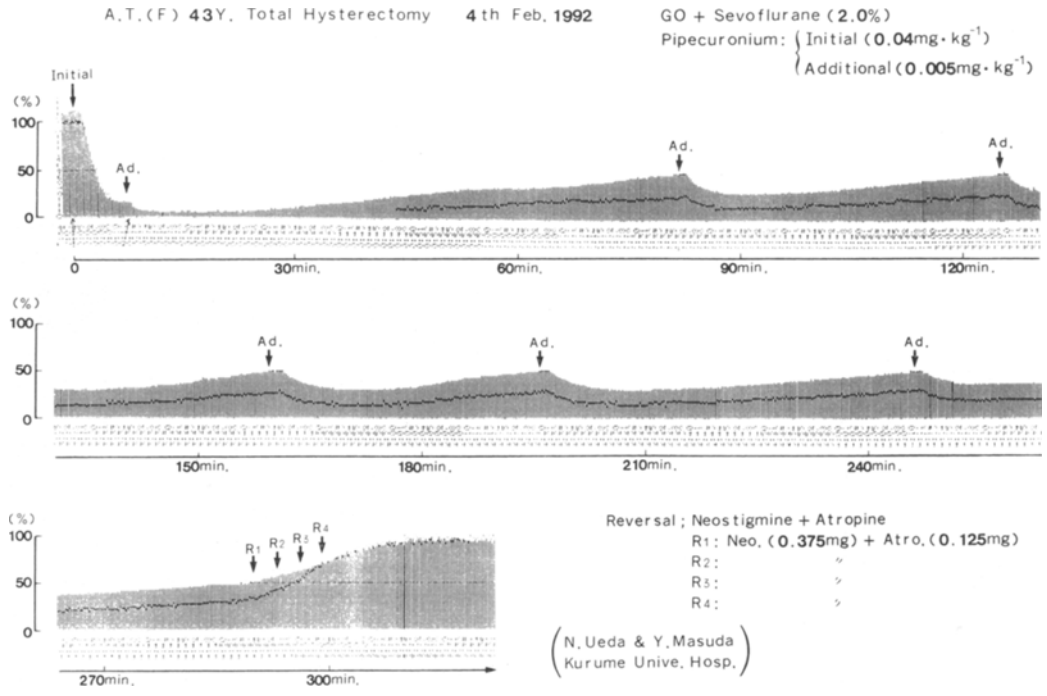

Fig. 2. Typical recording of time course of the neuromuscular blocking effects of pipecuronium. Initial dose and additional dose were 0.04 mg·kg^{-1} and 0.005 mg·kg^{-1}, respectively.

Neostigmine was administered when TOF ratio reached 25%, and residual block was antagonized to the level of 100% of control twitch height and TOF ratio of 100% in 15 min latter. This measurement was made using a neuromuscular transmission analyzer, Accelograph®.

a typical time course of the neuromuscular blocking effect of pipecuronium.

Table 2 shows the intubation scores and the degree of neuromuscular blockade when intubation was performed.

There were no obvious changes in heart rate, blood pressure, ECG findings and other side effects that could be attributed to the administration of pipecuronium.

Discussion

The maximum block rate by an initial bolus injection of 0.04 mg·kg^{-1} pipecuronium under sevoflurane anesthesia in our study and 0.05 mg·kg^{-1} pipecuronium under isoflurane anesthesia studied by Wierda et al.[9] was 93.7 ± 7.68 and 98.0 ± 1.3%, respectively. This suggests that the clinical ED_{95} of pipecuronium is between 0.04 and 0.05 mg·kg^{-1}. The onset time in our study and that reported by Wierda et al.[9] were 5.0 ± 1.84 and 6.4 ± 0.4 minutes, respectively. Althouth we used a 0.01 mg·kg^{-1} smaller initial dose than Wierda, et al.[9] did, we obtained a 1.4 minute earlier onset time. This may be due to the fact that the effect of intensifying the neuromuscular blockade by sevoflurane is stronger than that by isoflurane. The clinical duraiton of 25% recovery (T_{25}) in our study and that reported by Wierda et al.[9] was 55.4 ± 23.9 and 50.0 ± 4.3 minutes, respectively. The additional dose (0.005 mg·kg^{-1}) was administered at the time point of 50% recovery in our study and the time point of 25% recovery with a 0.025 mg·kg^{-1} additional dose in the study of Wierda et al.[9] Although the additional dose of the former was 1/5 of the latter, the

Table 2. Intubation score and the degree of blockade where intubation was performed

Patient No.	Intu. Score	degree of blockade (%)
No. 1	0	100 (PTC=8)
No. 2	1	100 (PTC=10)
No. 3	1	95
No. 4	1	90
No. 5	0	100 (PTC=15)
No. 6	1	88
No. 7	0	100 (PTC=7)
No. 8	1	100 (PTC=15)
No. 9	1	90
No. 10	0	100 (PTC=11)
No. 11	2	80
No. 12	1	95
No. 13	0	100 (PTC=7)
No. 14	0	100 (PTC=3)
No. 15	0	95
No. 16	1	95
No. 17	1	95
No. 18	0	100 (PTC=6)
No. 19	1	95
No. 20	1	98
No. 21	0	90
No. 22	1	100 (PTC=8)
No. 23	1	95
No. 24	0	100 (PTC=4)
mean ± SD	0.63 ± 0.56	95.88 ± 5.06

difference in the duration of maintenance was only 1/2 of the latter. This suggests that the augmentation of the nondepolarizing neuromuscular blocking effect of sevoflurane is stronger than that of isoflurane, even when we take into consideration the shorter recovery time from 25 to 50% than from 0 to 25%. In this study, no significant difference was found among each interval time of additional administration. Considering our data and the report by Agoston, et al.[1], pipecuronium is considered to have no or only a minimal cumulative effect. We also evaluated the intubation condition with pipecuronium at the induction of anesthesia because few studies have evaluated the intubation condition with this agent. The average intubation score of 0.63 at a 95% block which was obtained about 5 minutes after administration, is considered to be good enough for the routine clinical anesthesia. However, considering that the frequency of excellent intubating condition (score zero) was only 41.8% (10 out of 24 cases) and eight of the 10 cases were intubated under an intense neuromuscular blockade in which there was no response to TOF stimulation, we believe that the initial dose must be increased from 0.04 to 0.05 $mg \cdot kg^{-1}$ and we must wait until the disappearance of the response to TOF stimulation which is equivalent to a level of below PTC 6–7 to perform excellent intubation. To evaluate the antagonistic effect of neostigmine against residual neuromuscular blockade, we administered neostigmine at the time of 25% TOF ratio and the TOF ratio became 75% after 10.1 minutes on average. This shows that the neuromuscular blockade induced by pipecuronium can be easily and promptly antagonised by neostigmine. Agoston et al.[1] reported that the residual neuromuscular blockade was antagonized to the level of TOF ratio of 70% within 5 minutes of the administration of neostigmine. Considering the recovery speed from a

TOF ratio of 70% to 75% was slower[7], the time of recovery to a TOF ratio of 75% was similar to that in our study. Zwölter et al.[3] studied the cardiovascular effect of pipecuronium on the coronary artery bypass graft surgery. They found no significant difference in heart rate, phasic and mean arterial, phasic and mean pulmonary artery pressure, pulmonary artery occlusion pressure or cardiac index. Although intensive observation were not made, we found no obvious changes in blood pressure, pulse rate or ECG that could be considered as side effects of pipecuronium.

In conclusion, under the sevoflurane anesthesia (2.0%), the initial pipecuronium dose should be 0.04–0.05 $mg \cdot kg^{-1}$ and additional doses of 0.005 $mg \cdot kg^{-1}$ should be administered every 30 minutes starting 70 minutes after the initial dose to provide appropriate muscle relaxation for the upper and lower abdominal surgical procedure. However, since the sensitivity of the patient to any nondepolarizing neuromuscular blocking agent may differ considerably, neuromuscular monitoring is recommended.

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