Accelerated Reversal of Pancuronium Blockade with Divided Administration of Neostigmine

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During the recovery from anesthesia, neostigmine is often administered to reverse the effects of nondepolarizing blocking agents. In our department, it has been a rule to administer the reversal drugs as slowly as possible in order to avoid a vagotonic effect on the cardiovascular systems. According to Payne et al.,[1] the neostigmine itself might have neuromuscular blocking properties depending upon the methods of administration. To date there have been very few studies on such methods and the ideal one has not yet been found.

The present study was designed to evaluate the rate of recovery of the Train-of-Four (TOF) ratio after administration of neostigmine by either a one slow bolus injection or a divided injection.

Methods and Materials

The subjects of the study included 24 adulut patients (ASA class 1–2, Age 20–66 years) undergoing elective gynecologic or gastroenterologic surgery. All the patients were free from neuromuscular, renal, or hepatic diseases and were not taking any drugs known to interfere with neuromuscular functions. Informed consent was obtained. All Patients were premedicated with atropine (0.01 mg/kg, im), and hydroxyzine (1 mg/kg, im) 90 min preoperatively. In all the patients, anesthesia was induced with thiopental (5 mg/kg, iv) and with 50% nitrous oxide in oxygen and enflurane (1.5–2.0%). Ventilation was controlled and adjusted to maintain normocapnea, and end tidal CO_2 was monitored by a Datex infrared CO_2 analyzer. After the patients were sleeping, the ulnar nerve was stimulated at the wrist with square wave supramaximal stimuli of a 200 μsec. duration, delivered in a train-of-four (TOF) sequence at 2 Hz every 15 sec. The stimuli was delivered using a peripheral nerve sitimulator which had been incorporated in the Accelograph®. The resultant contraction of the adductor pollicis was recorded using a acceleration transducer and neuromuscular function analyzer (Accelograph®, Biometer Inernational, Denmark). After stabilization of the twitch recording, succinylcholine was administered and tracheal intubatin was carried out at maximum block. For further paralysis, pancuronium (0.08–0.15 mg/kg, iv) was used. At the end of surgery, when spontaneous recorvery had begun and the TOF ratio returned to 20–25%, the patients were randomly allocated into two groups. In group A (n = 12). The reversal drugs (neostigmine 1.5 mg, atropine 0.5 mg and lactate Ringer solution 16 ml) were con-

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Table 1. Recovery rate of TOF ratio

	Group A		Group B
No.	Recovery rate (%/min)	No.	Recovery rate (%/min)
1	2.78	1	6.25
2	4.17	2	8.33
3	5.0	3	4.17
4	4.55	4	5.56
5	5.0	5	5.56
6	5.0	6	7.14
7	2.0	7	8.33
8	5.0	8	8.33
9	5.0	9	10.0
10	4.17	10	8.33
11	3.57	11	3.13
12	3.85	12	5.56
mean ± SD	4.17 ± 0.98	mean ± SD	6.72 ± 2.0

level of significance: $P < 0.05$

tinuously administered intravenously at a rate of 4 ml/min from the point when the TOF ratio was 20–25%. In group B (n = 12), the patients were intermittently administered one fourth of the same dosage every three minutes from the same recovery point. The TOF ratio was recorded continuously and the reversal time was measured; the reversal time was the period taken from when the TOF ratio value was 25% to when it was 75%. The recovery rate of the TOF ratio was calculated. A paired t-test was performed to assess the mean recovery rate of the TOF ratios of the two groups. A P value of less than 0.05 was considered statistically significant.

Results

The recovery rates of the TOF ratios were 4.17 ± 0.98%/min in group A and 6.72 ± 2.0%/min in group B. The group B recovered significantly faster than the group A. All the samples of the recovery rate of the TOF ratio are summarized in table 1. The trends of the TOF ratio in group A were towards a sigmoid curve in 9 out of the 12 patients and the TOF ratio in group B (10 out of 12) increased linearly. Typical recordings of the TOF ratio during the reversal phase is shown in figure 1 and an explanation of the difference of the recovery phase in group A and B is expressed in figure 2.

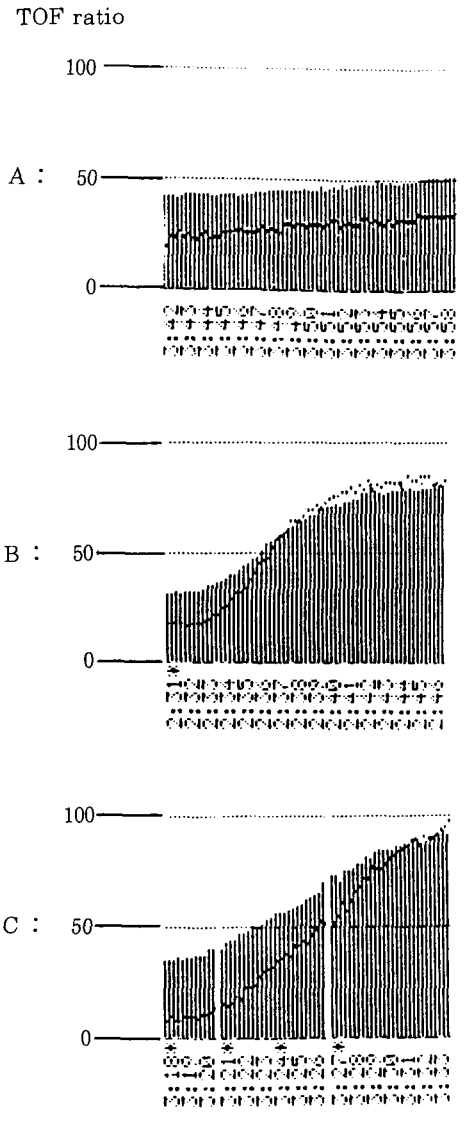

Fig. 1. Typical recording of the TOF ratio during reversal is shown. The TOF ratio is expressed by dots. In panel A, spontaneous recovery of the TOF ratio is traced. The recovery of the TOF ratios which was induced by neostigmine in a one-bolus-slow-injection and divided doses are shown in panels B and C, respectively. The above data was recorded by the trend mode of TOF of Accelograph®.

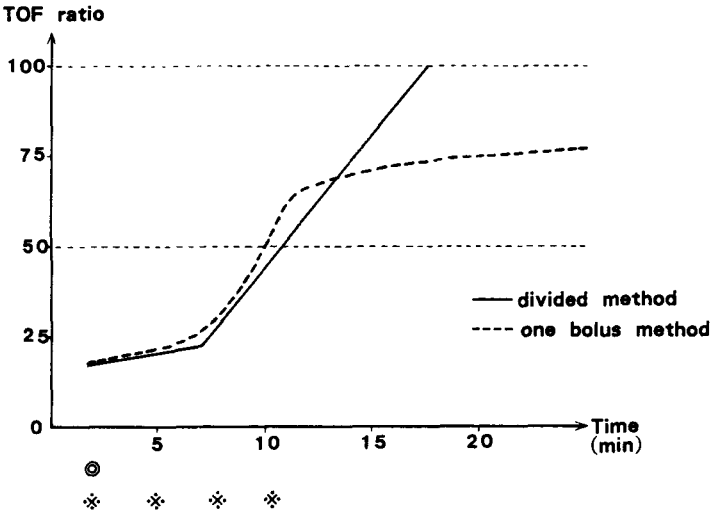

Fig. 2. The recovery of the TOF ratio which was induced by the one bolous method and divided method is illustrated. When a reversal drug was administered in a one bolus injection, the trace of the TOF ratios showed sigmoid curve. The divided dose of a reversal drug caused a linear increase of the TOF ratios to nearly a TOF ratio of 100% . At the mark of double circle, a reversal drug was administered in a single bolus. At each ※ mark, one fourth of the above reversal drug was administered in divided doses every three minutes.

Discussion

In our department, when the anesthesiologists administer the reversal drugs, they have used the one-bolus-slow- injection method or divided injection method to avoid a critical vagotonic effect on the cardiovascular system. Concerning such side-effects, there was no clinical difference between the two methods as far as we have experienced. However, from the point of reversal effects, the divided method was clinically observed to be more effective than the one-bolus-slow-injection. In order to demonstrate the above phenomenon quantitatively we designed the present study. Conversely, Abdulatif[2] and Naguib[3] and Kim[4] et al. studied the reversal effect of divided doses of neostigmine on the basis of the following hypothesis. The onset time of the nondepolarizing muscle relaxants can be shortened significantly when small doses of the same or different nondepolarizing muscle relaxant are administered rather than a single sufficient dose. This is the so-called "priming principle". Likewise, the hypothesis that administration of neostigmine in divided doses accelarates the antagonism of neuromuscular blockade would be achieved. They then obtained results that supported their hypothesis. We also obtained the same results in spite of using a slightly different method. To explain this phenomenon, Abdulatif and Naguib used the idea of a "margin of safety" in enzyme inhibition that was demonstrated by Barber[5]. Accordig to Barner's report, facilitation of twitch height did not occur when cholinesterase was inhibited less than 85%. Facilitation was linearly related to enzyme inhibition between 85% and 98% inhibition. Therefore, a large proportion of acetylcholinesterase could be inhibited without an effect on neuromuscular function. This suggests a "margin of safety" in enzyme inhibition similar to that seen during the blockade of neuromuscular transmission by nondepolarizing muscle relaxants. By analogy to the priming principle, the initial relatively ineffective dose of neostigmine will cause partial enzyme inhibition and therefore will decrease the margin of safety of the acetylcholinesterase enzyme, allowing a more profound effect of the second dose. However, the obvious difference between the recovery rate by the TOF ratios of the one-bolus-slow-injection and the divided injection was found when the TOF ratio exceeded 50% as far as we have observed. Consequently, the factor that would cause the diference between the two recovery conditions was speculated to exist in the latter part of recovery phase. This tendency can be also recognised in the studies carried out by Abdultif and Kim[4]. Considering the above, it would not

be possible to explain the difference of the two recovery courses solely on the concept of a "margin of safety" in enzyme inhibition. Further study will be necessary to reveal the mechanism of the accelerated reversal by divided administration of anticholinesterase.

In conclusion, from a clinical view, it is recommended to administer neostigmine in a 0.4 mg dose every three minutes until an adequate recovery of neuromuscular function is achieved. If anesthesiologists administer neostigmine in a one-bolus-injection, they have to take into consideration that the speed of recovery from blockade is slow when the TOF ratio is above 50%.

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HONORS

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CORRECTION

In the article entitled "Effects of Anesthetic and Related Agents on Calcium-induced Calcium Release from Sarcoplasmic Reticulum Isolated from Rabbit Skeletal Muscle" (J Anesth 3: 1–9, 1989), there are errors in the units of measurement. On page 5, legend of table 1, third sentence should have read "···138 n mol Ca^{2+}/mg protein/min···," not "···138 μM Ca^{2+}/min···," as printed. On page 6, first sentence in the legend for table 2 should have also read "···SR (n mol Ca^{2+}/1.5 mg protein)," not "···SR (μM Ca^{2+}/mg SR protein)."