J Anesth (1998) 12:185–188

Journal of
Anesthesia

Comparison of respiratory sparing effect between pancuronium and three new nondepolarizing muscle relaxants in rats

MISATO KANEKO and LU HUA

Department of Anesthesiology, Jikei University School of Medicine, 3-25-8 Nishishinbashi, Minato-ku, Tokyo 105, Japan

Abstract

Purpose. There is a large difference in sensitivity between respiratory muscles and other limb muscles. This phenomenon, known as the respiratory sparing effect (RSE), is well established with *d*-tubocurarine, pancuronium, and succinylcholine. The purpose of this study is to evaluate the RSE of these new relaxants, vecuronium, pipecuronium, and ORG9426.

Methods. The study was done in vivo using rats. Mechanical twitch responses of tibialis anterior muscle and diaphragm stimulated with the sciatic nerve and phrenic nerve, respectively, were recorded simultaneously to monitor neuromuscular transmission. Changes of mechanical twitch responses from both muscles were compared following the injection of four kinds of muscle relaxants (pancuronium, picuronium, recuronium, and ORG9426).

Results. T, D (%) represents the maximum depression in tibialis anterior and diaphragm, respectively. T − D (%), which means the sensitivity difference between the two kinds of muscle, was calculated by subtracting D from T. The T − Ds of pancuronium, pipecuronium, vecuronium, and ORG9426 were 86.0 ± 2.6%, 81.4 ± 1.9%, 77.7 ± 2.1%, and 74.6 ± 2.7%, respectively.

Conclusions. The results indicated that the blockade produced by each muscle relaxant was lower in the diaphragm than in the anterior tibialis muscle. T − D was significantly smaller with vecuronium or ORG9426 than with pancuronium.

Key words: Respiratory sparing effect, Nondepolarizing muscle relaxants, Diaphragm, Anterior tibialis muscle

Address correspondence to: M. Kaneko

Received for publication on July 22, 1997; accepted on June 15, 1998

Introduction

The white, red, respiratory, laryngeal muscles and the muscles in the limbs are all skeletal muscles. However, it has been reported that these muscles exhibit differences in sensitivity to muscle relaxants. The assessment of this difference in sensitivity between the respiratory muscles and muscles in the limbs is clinically important. This phenomenon is referred to as the respiratory sparing effect (RSE). The RSE of muscle relaxants such as *d*-tubocurarine (dTc), pancuronium, and succinylcholine is well established [1]. However, the RSE of newly introduced muscle relaxants, namely, vecuronium, pipecuronium, and rocuranium (ORG9426), has not been sufficiently established. In the present paper, the RSEs of pancuronium and the new relaxants, pipecuronium, vecuronium, and rocuronium, were examined in vivo using rats.

Materials and methods

Pentobarbital ($4\,mg \cdot kg^{-1}$) and urethane ($50\,mg \cdot kg^{-1}$) were administered intraperitoneally to anesthetize 31 Sprague-Dawley rats. Tracheostomy was then performed, and while a respirator (type-683; Harvard, Cambridge, MA, USA) was used to control respiration, a cannula was inserted into the jugular vein to administer each relaxant. Expired carbon dioxide gas concentration was measured using Respina (IH26, NEC Sanei, Tokyo, Japan) to stabilize ventilation during testing. A horizontal incision was made at the sternum to open the chest, and the phrenic nerve was isolated. Then the center of the tendon in the diaphragm was attached with silk thread to an isometric forced transducer (type 45072, NEC Sanei, Tokyo, Japan). Bipolar platinum electrodes were inserted in the thoracic cavity to stimulate the phrenic nerves bilaterally by administering square wave supramaximal electrical stimulation

(width, 0.3 ms; 0.1 Hz interval) using a stimulator (SEN-7103, Nihon Koden, Tokyo, Japan). The mechanical twitch response (MTR), the response of a muscle to electrical stimulation, was measured by the forced transducer. The anterior tibialis muscle was selected to represent the muscles in the limbs, and the tendon of the muscle was attached to another forced transducer to measure MTR. Isometric contraction was used to measure MTR in both the diaphragm and the anterior tibial muscle. Another pair of bipolar platinum electrodes were placed on the sciatic nerve through the hip muscle. The same mode of stimulation was given to the sciatic nerve as to the phrenic nerve. Both muscles were stimulated simultaneously. A polygraph recorder (Nippon Denki Sanei, type 45072, Tokyo, Japan) was used to record the responses from the diaphragm in channel 1, and those from the anterior tibialis muscle were recorded in channel 2. In order to prevent lowering the body temperature, a heat lamp was used. Core temperatures were measured by thermocouple probes placed on the rectum and esophagus.

A cannula was inserted into the femoral artery directly to measure arterial blood pressure and to monitor the circulatory system. A muscle relaxant was administered by either bolus or continuous infusion. A continuous infusion pump (type 355, Sage Instruments, Cambridge, MA, USA) was used to administer muscle relaxants. The concentration of the four muscle relaxants solutions was $50\,\mu g \cdot ml^{-1}$.

In the single-injection experiments, a muscle relaxant was administered with the doses to adjust to maintain MTR at 5% to 10% of the control. In addition, the maximal depression time (time to maximal depression from injection), percent of maximal depression, and recovery time (time required to recover to 90% to 100% of the control value) were measured.

In the continuous infusion experiments, the infusion rate was adjusted at 0.43 to $1.91\,\mu g \cdot min^{-1}$ to maintain the MTR at 10% to 20% (T_{10}–T_{20}) of the control in the anterior tibialis muscle. The percent of maximal depression of the diaphragm was measured when the anterior tibialis muscle blockade was maintained with MTR 10% to 20% of the control. Results were expressed as the mean ± standard error of the mean (SEM). Student's *t*-test was used for statistical analysis, with a *P* value of less than 0.05 being considered significant.

Results

Figure 1 shows representative recordings of the single-injection and the continuous infusion of pancuronium with diaphragm (D) and anterior tibialis muscle (T). Either in the bolus injection or in the continuous infusion, the neuromuscular blockade of pancuronium was greater in the anterior tibialis muscle than in the diaphragm. The difference in blockade between the two muscles (T − D) was greater in the continuous infusion than in the single injection.

Table 1 summarizes the responses of the diaphragm and the anterior tibialis muscle to each muscle relaxant

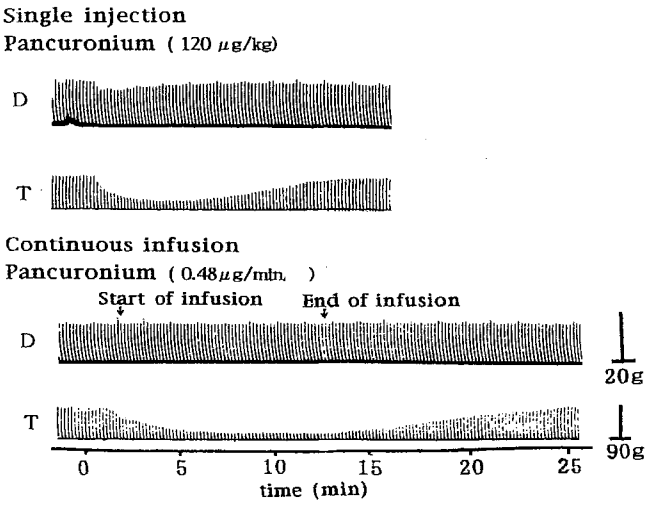

Fig. 1. Neuromuscular blocking effects produced by single injection or continuous infusion of pancuronium. D and T represent diaphragm and anterior tibialis muscle, respectively

Table 1. Neuromuscular blocking effects produced by intravenous single injection of muscle relaxants

Blocking agents (no. of cases)	Dose ($mg \cdot kg^{-1}$)[a]	Neuromuscular block (%)		Differences (T. − D.) (%)	Time to maximal effect (s)[b]		Time for recovery (s)[c]	
		T	D		T	D	T	D
Pancuronium (7)	0.11 ± 0.01	90.0 ± 3.2**	17.1 ± 2.6	72.9 ± 3.5	98.4 ± 16.8	51.3 ± 6.3	395.0 ± 65.2*	181.7 ± 55.9
Pipecuronium (7)	0.04 ± 0.00	93.9 ± 2.8**	18.6 ± 5.5	75.3 ± 6.6	88.3 ± 13.7**	48.2 ± 8.3	381.0 ± 53.5**	165.0 ± 14.6
Vecuronium (8)	0.21 ± 0.01	80.4 ± 4.9**	13.3 ± 3.3	67.1 ± 5.4	52.0 ± 5.4**	24.5 ± 3.2	85.6 ± 14.6	54.0 ± 11.6
ORG9426 (7)	0.60 ± 0.05	87.8 ± 5.3**	44.0 ± 11.5	43.8 ± 8.4##	51.6 ± 9.0*	28.7 ± 2.2	107.5 ± 17.6*	56.0 ± 6.9

T., Tibialis anterior muscle; D., diaphragm muscle.
[a] Mean ± SEM.
[b] From start of injection.
[c] Recovery time from T90 to T100.
* $P < 0.05$, ** $P < 0.01$ (comparison between T. and D.), ## $P < 0.01$ (comparison with pancuronium).

Table 2. Neuromuscular blocking effects produced by continuous intravenous infusion of muscle relaxants

Blocking agents (no. of cases)	Neuromusuclar block (%)[a]		Differences (T. − D.) (%)
	T.	D.	
Pancuronium (7)	91.1 ± 1.9**	5.1 ± 1.5	86.0 ± 2.6
Pipecuronium (7)	89.2 ± 1.1**	8.0 ± 1.9	81.4 ± 1.9
Vecuronium (8)	84.3 ± 1.7**	6.6 ± 1.6	77.7 ± 2.1#
ORG9426 (7)	87.3 ± 1.6**	12.6 ± 3.0	74.6 ± 2.7##

T., Tibialis anterior muscle; D., diaphragm muscle.
[a] Mean ± SEM.
* $P < 0.05$, ** $P < 0.01$ (comparison between T. and D.).
# P 0.05, ## $P < 0.01$ (comparison with pancuronium).

in the single-injection experiments. For all four muscle relaxant, the blockade in the anterior tibialis muscle was greater than that in the diaphragm.

Furthermore, the onset and recovery times in the diaphragm were significantly shorter ($P < 0.05$) than those in the anterior tibialis muscle. These tendencies were quite pronounced in rats treated with pancuronium and pipecuronium.

Table 2 summarizes the responses of the diaphragm and the anterior tibialis muscle to the four muscle relaxants in the continuous infusion experiments. The difference in sensitivity between the diaphragm and the tibialis anterior muscle was significantly more apparent in continuous infusion than in single injection for the four muscle relaxants.

The neuromuscular blockade in the diaphragm was significantly lower than that in the anterior tibialis muscle. The differences in maximal blockade between the two muscles were greater with pancuronium or pipecuronium than with vecuronium or rocuronium. The differences in sensitivity between the two muscles were significantly smaller with vecuronium or rocuronium than with pancuronium.

Discussion

As early as 1951, Paton and Zaimis [2] reported that there was a difference between the respiratory muscles and the muscles in the limbs with respect to the sensitivity of these muscles to dTc. Because the majority of reports published after 1951 were clinical reports, there were limitations on experimental procedures.

Studies of sensitivity differences between muscles in the limbs and the respiratory muscles have been carried out. In such studies, using limb muscles such as the adductor pollicis muscle or the anterior tibialis muscle, information on MTR has been obtained without difficulty. However, in the case of the respiratory muscles (the diaphragm or intercostal muscle), to get information about neuromuscular transmission it might be essential to monitor the electromyogram [3,4], respiratory movement [5], grip strength [6], or shift in gastroesophageal pressure [7]. Because two different standard measurements of MTR were used to examine the function of the respiratory muscles and the muscles in the limbs, it was uncertain whether data could be correctly and objectively analyzed. In this study, MTR of the diaphragm was measurable while the chest was kept open. So the functions of the respiratory muscles and the muscles in the limbs could be compared, because MTRs of the diaphragm and the anterior tibialis muscle were assessed simultaneously.

The previous studies of sensitivity to muscle relaxant in these muscles used single injection of muscle relaxants. During in vivo experiments, the amount of blood flow to the diaphragm is greater than that to the anterior tibialis muscle, possibly resulting in the neuromuscular junctions in the diaphragm being exposed to a larger number of muscle relaxant molecules than those in the anterior tibialis muscle. Thus a comparison of MTRs between the two muscles does not accurately reflect the sensitivity of either muscle as a whole. Consequently, in the present study, continuous infusion of each muscle relaxant was introduced so that the two muscles were exposed to equal serum concentrations of the muscle relaxant.

From the results of this study, it was found that the blockade rate in the diaphragm was smaller than that in the anterior tibialis; the maxima blockade in the diaphragm was established earlier than that in the anterior tibialis muscle; and the recovery from blockade in the diaphragm was faster than in the anterior tibialis muscle. So far, no valid explanation has been offered for RSE, and some researchers have proposed that RSE is caused by a difference in the affinity of receptors as agonists and antagonists. Taylor et al. [8] conducted in vitro experiments (these include no pharmacokinetic factors such as age, liver and renal function, body temperature, and blood flow) which indicated that the sen-

sitivity to nondepolarizing muscle relaxants was the greatest in slow muscle, the anterior tibialis muscle, and lowest in the diaphragm. It might be on these findings that the sensitivity of each muscle differed. This difference in sensitivity could be due to differences in the number of receptors, in the type of neurotransmitter used to stimulate the muscle, or in the sensitivity of the muscles to acetylcholine. Smith et al. [9] reported that there was a decrease in the catabolism of acetylcholine as well as an increase in the secretion of acetylcholine in the diaphragm. Also, Waud et al. reported that the diaphragm had a greater margin of safety of neuromuscular transmission than the peripheral muscles. The results of this study may explain the difference in sensitivity in the two muscles [10].

We have reported that RSE can be observed with well-known muscle relaxants such as dTc, gallamine, alcuronium, and toxiferine, using the same methods. Recently, many new muscle relaxants have been introduced. However, the locus of activity of these newly developed nondepolarizing muscle relaxants varies according to their kinds (presynaptic membrane or postsynaptic membrane). Therefore, in the present study, experiments were conducted to clarify whether RSE could be observed with newly introduced muscle relaxants, and whether there were differences of RSE between and the newly developed relaxants and pancuronium. The results revealed that RES was also observed when using the newly developed muscle relaxants. However, the RSE of pancuronium was greater than that of vecuronium or ORG9426. Our finding agreed with the previous reports [11–13] in that the RSE of these two new relaxants was neither nonexistent not great.

In the present study, the RSE of vecuronium and ORG9426 was weak. It is known that pancuronium and dTc strongly affect the postsynaptic membrane. However, vecuronium is known to be a unique nondepolarizing muscle relaxant, because it affects both the presynaptic and postsynaptic membranes [13]. Consequently, it can be inferred that the functions of vecuronium are different from those of pancuronium and dTc, and that these differences might be responsible for the changes in RSE.

References

1. Amaki Y (1984) Decreased sensitivity of rat diaphragm to neuromuscular blocking agent (in Japanese with English abstract). Masui (Jpn J Anesthesiol) 33(2):120–124
2. Paton WD, Zaimis EJ (1951) The action of *d*-tubocurarine and of decamethonium on respiratory and other muscles in the cat. J Physiol 112:311–331
3. Laycock JRD, Donati F, Smith CE, et al. (1988) Potency of atracurium and vecuronium at the diaphragm and the adductor pollicis muscle. Br J Anaesth 61:286–291
4. Gilly H, Hirschi MM, Steinbereithner K (1988) Pharmacodynamics of ORG8764, atracurium, and vecuronium: a comparison of vocal cord, diaphragm, and tibial muscle relaxation. Anesthesiology 69(3A):A481
5. Hackett G, Hughes R, Payne JP (1986) Recovery of spontaneous breathing following neuromuscular blockade with atracurium. Br J Anaesth 58:494–497
6. Foldes FF, Monte AP, Brunn HM, et al. (1961) Studies with muscle relaxants in unanesthetized subjects. Anesthesiology 22(2):230–236
7. Derrington MC, Hincocha N (1988) Comparison of neuromuscular blockade in the diaphragm and the hand. Br J Anaesth 61:279–285
8. Taylor DB, Prior RD, Bevan JA (1964) The relative sensitivities of the diaphragm and other muscles of the guinea pig to neuromuscular blocking agents. J Pharmacol Exp Ther 143:187–191
9. Smith CE, Donati F, Bevan DB (1988) Potency of succinylcholine at the diaphragm and at the adductor pollicis muscle. Anesth Analg 67:625–630
10. Waud BE, Waud DR (1972) The margin of safety of neuromuscular transmission in the muscle of the diaphragm. Anesthesiology 37:417–422
11. Chauvin ML, Lebrault C, Duvaldestin P (1987) The neuromuscular blocking effect of vecuronium on the human diaphragm. Anesth Analg 66:117–122
12. Plaud B, Meistelman C, Donati F (1991) Organon 9426 neuromuscular blockade at the adductor muscles of the larynx and the adductor pollicis in man. Anesthesiology 75–3A:A784
13. Day NS, Blake GJ, Standaert FG, Dretchen KL (1983) Characterization of the train-of-four response in fast and slow muscles: effect of *d*-tubocurarine, pancuronium and vecuronium. Anesthesiology 58:414–417