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Influence of Volatile Anesthetics on Muscle Relaxant Effect of Vecuronium in Dogs

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Abstract: The effect of a non-depolarizing neuromuscular blocking drug, vecuronium, is reportedly potentiated by volatile anesthetics. In this study, the influences of Halothane (Hal), Isoflurane (Iso) and Sevoflurane (Sev) on the effect of vecuronium were investigated in dogs. Six treatment groups were established for 2 concentrations (1.2 and 1.8 MAC) of Hal, Iso and Sev, using 6 healthy beagles. After the induction of anesthesia with propofol, 0.1 mg kg^{-1} of vecuronium was administered and its blocking effect was observed and recorded over time employing Single Twitch (ST) and Train-of-Four (TOF) stimulations. Parameters, such as the recovery time and rate were calculated and compared among the anesthetics and between the concentrations. All anesthetics potentiated the muscle relaxant effect in a dose-dependent manner. The TOF recovery rate was significantly lower in the Sev 1.2 MAC than in the Hal 1.2 MAC group and significant differences were noted between the concentrations at recovery time points of T_1, T_2 and T_3 in the Hal group. potentiation by Hal increased in a concentration-dependent manner, whereas that by Sev was strong from the low concentration. In addition, differences in the ST and TOF recovery rates suggested that the site in the neuromuscular junction involved in vecuronium potentiation by Hal is different from that involved in potentiation by Iso and Sev. It was also suggested that the potentiation may have been due to volatile anesthetic-induced changes in the affinity for the drug.

Key words: Canine, muscle relaxants, single twitch stimulation, train-of-four stimulation, vecuronium, volatile anesthetics

INTRODUCTION

Balanced anesthesia is ideal in the veterinary field and the use of muscle relaxants is advantageous, as it makes surgery easier and reduces the amount of drugs necessary, such as anesthetics. However, there have been fewer reports and insufficient information on the pharmacological effects of muscle relaxants in the veterinary field, despite muscle relaxation being an essential condition of anesthesia.

Muscle relaxants are classified into depolarizing and non-depolarizing types and non-depolarizing blocking drugs include pancuronium, vecuronium (Musculax Intravenous®, Organon Japan), pipecuronium (Raplon®, STORM LAW FIRM,L,L,C) and rocuronium (ZEMURON®, Organon). Vecuronium is the major non-depolarizing neuromuscular relaxant in human clinical medicine because the drug is short-acting and exerts no cumulative effect, compared to another non-depolarizing neuromuscular blocking drug, pancuronium or adverse effects on the cardiovascular system.

The effect of non-depolarizing muscle relaxants is potentiated by generally employed concomitant volatile anesthetics and the prolongation and potentiation of the effect vary depending on the type of volatile anesthetic, for which various studies on the synergistic effect of muscle relaxants and volatile anesthetics have been performed involving humans (Awata, 1987; Kurahashi and Maruta, 1996; Zhou *et al*., 2001; Itagaki *et al*., 1988; Tai *et al*., 1987). However, no study on the effect of vecuronium has been performed in the clinical veterinary field. Although, the use of non-depolarizing

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neuromuscular blocking drugs in dogs has been reported (Cullen *et al*., 1980; Jones and Seymour, 1985; Jones, 1985; Jones and Young, 1991) no study on the relationship between non-depolarizing blocking drugs and volatile anesthetics has been performed.

The duration of action of a non-depolarizing neuromuscular blocking drug, vecuronium has not been closely investigated in the veterinary field. In this study, we investigated the characteristics of the influences of volatile anesthetics on the muscle relaxant effect of vecuronium.

MATERIALS AND METHODS

Animals: A cross-over study was performed using 6 beagles (3 males and 3 females) weighing 14.5±1.92 kg (mean±SD), which were healthy based on blood chemistry and X-ray radiography. Anesthesia was induced by the bolus administration of 7 mg kg^{-1} of propofol and intubation was performed, followed by maintenance through the inhalation of an anesthetic at the experimental concentrations. The anesthetic concentrations were established based on the Minimum Alveolar Concentration (MAC): Halothane (Hal) (Fluothane®, Takeda Pharmaceutical, Osaka, Japan), 1.2 and 1.8 MAC groups (end-tidal: 1.0 and 1.5%, respectively); isoflurane (Iso) (Isoflu®, Dainippon Pharmaceutical, Osaka, Japan), 1.2 and 1.8 MAC groups (end-tidal: 1.5 and 2.7%, respectively) and sevoflurane (Sev) (Sevoflurane®, Maruishi Pharmaceutical, Osaka, Japan), 1.2 and 1.8 MAC groups (end-tidal: 2.8 and 4.1%, respectively) (6 groups in total). Sodium lactate-Ringer's solution (Lactated Ringer's Solution®, Fuso, Osaka, Japan) was continuously administered at 10 mL/kg/h after the induction of anesthesia until completion of the experiment to maintain the circulating blood volume. To prevent body temperature reduction, a warm mat kept at 37°C or higher was used during the experiment. P_{CO2} under anesthesia was maintained at 35-40 mmHg on a monitor (BP-508®, Nihon Colin, Tokyo, Japan) using a ventilator (Model 2000 Anesthesia Ventilator; Hallowell EMC, Pittsfield, MA) and recorded every 5 min. Electrocardiogram, SpO_2, blood pressure and body temperature measurements were also carried out using the same monitor and recorded every 5 min.

A TOF watch (TOF Watch®, Schering-Plough Corporation, Tokyo, Japan) was used as a neuromuscular monitor. Referring to the neuromuscular function monitoring method reported by Cullen *et al*. (1980), the animal was retained in a recumbent position on a restrainer, a stimulation electrode was set to stimulate the right foreleg ulnar nerve and an acceleration transducer was set at the foreleg digit tip. Regarding the stimulation method, Single Twitch stimulation (ST) and Train-of-Four stimulation (TOF) were used. The stimulation intensity was 15 mA and ST stimulation was set at 0.1 Hz. The muscle relaxation monitor was calibrated and a control value was established. Anesthesia was induced after completion of the above setting and after 30 min, a bolus administration of 0.1 mg kg^{-1} of vecuronium (Musculax Intravenous®, Schering-Plough Corporation, Tokyo, Japan) was given via an intravenous cannula. After vecuronium administration, each of the above stimulations was loaded 3 times per minute. Induced flexion reactions of the foreleg were measured and the ST and TOF ratios were recorded over time. The ST and TOF ratios recorded for one minute 3 times were averaged and regarded as the one-minute values.

Analysis: The ST and TOF ratios were plotted with time: 2 curves for anesthetics and anesthetic concentrations were prepared in each animal.

The following calculations were performed using the data from the above experiment: 3-1, 25, 50, 75, 90% recovery times (Fig. 1a).

Based on the method reported by Wright *et al*. (1995), the time after vecuronium administration at which the recovery reached 25% in the recovery phase was designated as the 25% recovery time. Similarly, the 50, 75 and 90% recovery times were calculated 3-2, 25-75% recovery rate (Fig. 1b).

The measured values were plotted in the 25-75% interval. An approximation line was determined from the scatter plot and its slope was calculated as the recovery rate, 3-3 T_1, T_2 and T_3 recovery times.

The time points at which TOF-induced contractions (T_1, T_2 and T_3) were noted were designated as T_1, T_2 and T_3 recovery times, respectively.

Statistical analysis: The above measurement items were subjected to Bartlett's test among the anesthetics at the same MAC to confirm homogeneity. When the distribution was homogenous, one-way layout ANOVA was performed and the Bonferroni multiple comparison test was employed as a post-hoc test. When the distribution was not homogenous, the Kruskal Wallis test was performed and the Dunn test was employed as a post-hoc test. On comparison between the concentrations of the anesthetic (1.2 MAC and 1.8 MAC), the F-test was performed to confirm homogeneity. When the distribution was homogenous, Student's t-test was employed and when the distribution was not homogenous, the Mann-Whitney U-statistic test was employed. $p<0.05$ was regarded as significant in all tests.

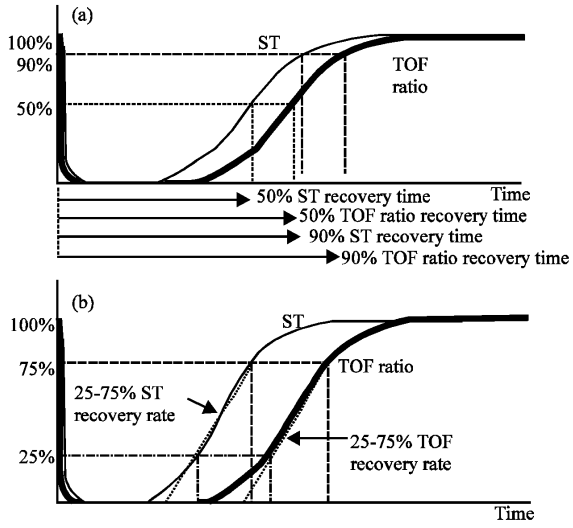

Fig. 1: The schema of analyzed data. The calculated data from the ST and TOF ratios were shown schematically in the figure. (a) 50% ST recovery time, 50% TOF ratio recovery time, 90% ST recovery time and 90% TOF ratio recovery time and (b) 25-75% ST recovery rate and 25-75% TOF recovery rate

RESULTS AND DISCUSSION

P_{CO2} was maintained at 35-43 mmHg on the monitor during anesthesia and the mean body temperature was maintained at 37.2-38.1°C. In all dogs, SpO_2 was 97.3±1.5% (mean±SD), the heart rate was 105.1±17.4 and systolic and diastolic blood pressures were 97.65±22.23 and 48.74±10.0 mmHg, respectively but the blood pressure tended to decrease under anesthesia with 1.8 MAC Hal and Iso.

ST and TOF: Both parameters rapidly decreased after muscle relaxant administration (Fig. 2 and 3) and recovered within about 10 min but the recovery tended to be delayed at a higher concentration of all anesthetics.

ST and TOF recovery times: There were no significant differences in the ST or TOF recovery times among the 1.2 MAC Hal, Iso and Sev and 1.8 MAC Hal, Iso and Sev groups. On comparison between the Hal concentrations, all ST and TOF recovery times excluding the 25% TOF recovery time were significantly delayed in the 1.8 MAC group (Fig. 4 and 5). No significant differences were noted between the concentrations for Iso or Sev.

Recovery rate (25-75%): On comparison among the anesthetics, the TOF recovery rate was significantly lower in the Sev 1.2 MAC than in the Hal 1.2 MAC group

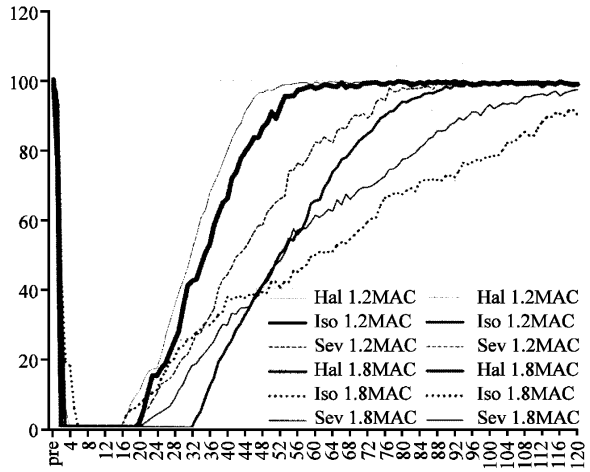

Fig. 2: Time-course ST

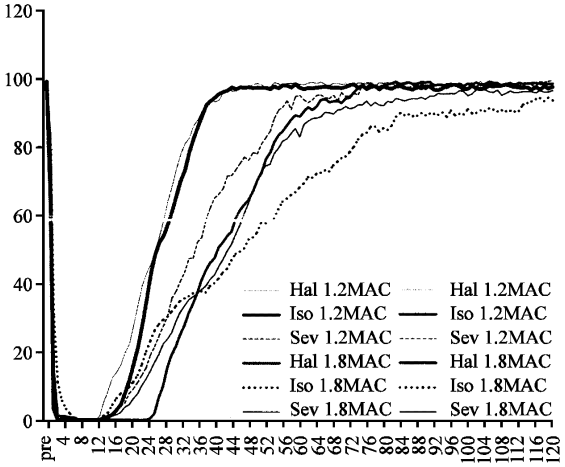

Fig. 3: Time-course TOF

(Hal 1.2 MAC: 9.3±1.14 vs. Sev 1.2 MAC: 5.2±1.14). No significant difference was noted among the 1.8 MAC Hal, Iso and Sev groups but the recovery rate tended to be lower in the Sev and Iso than in the Hal group ($p = 0.064$) (Fig. 6).

On comparison between the concentrations, the recovery rate shown by the TOF curve was significantly lower in the Hal 1.8 MAC than in the Hal 1.8 MAC group (1.2 MAC: 9.2±2.54 vs. 1.8 MAC: 3.9±1.35).

On comparison between the Iso 1.2 MAC and Iso 1.8 MAC groups, the recovery rate was significantly lower in the 1.8 MAC group on both ST and TOF curves (ST: 1.2 MAC: 9.4±3.27 vs. 1.8 MAC: 3.5±2.45) (TOF: 1.2 MAC: 5.6±1.03 vs. 1.8 MAC: 2.2±1.42).

T_1, T_2 and T_3 recovery times: There were no significant differences among the anesthetics. On comparison

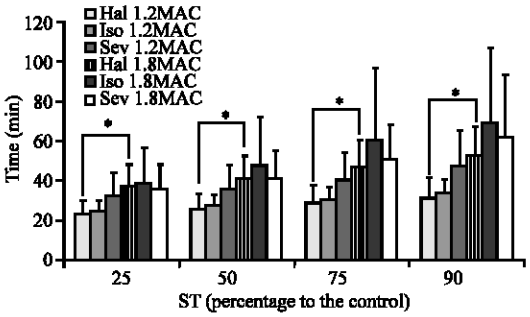

Fig. 4: ST recovery time *p<0.05

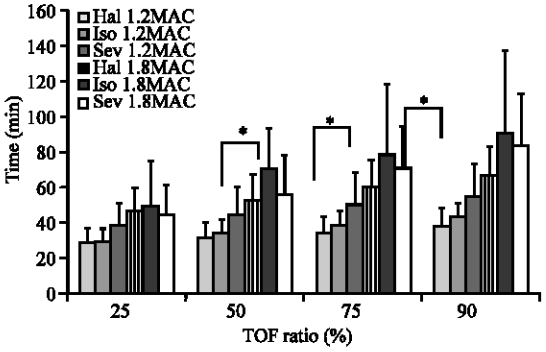

Fig. 5: TOF recovery time *p<0.05

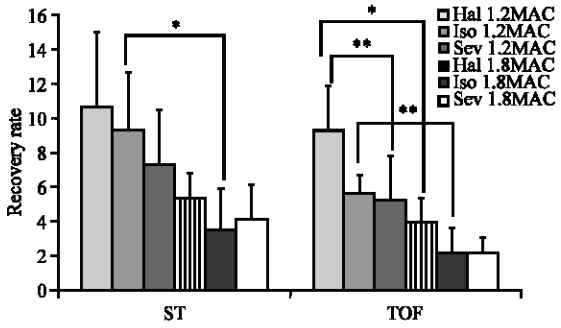

Fig. 6: 25-75% recovery rate *p<0.05, **p<0.01

between the concentrations, T_1, T_2 and T_3 were significantly delayed in the Hal 1.8 MAC compared to the Hal 1.2 MAC group (Fig. 7).

To monitor neuromuscular function in dogs, the facial, ulnar, fibular and tibial nerves are stimulated with a needle electrode (Thurmon *et al*., 1996). We selected ulnar nerve stimulation and monitoring was favorable.

Stimulation patterns include ST, TOF and tetanic stimulations, Post-Tetanic Twitch (PTT) and double-burst stimulation. Saitoh *et al*. (1994) investigated the influences of volatile anesthetics (Hal, Iso, Enflurane (Enf) and Sev) on recovery from severe neuromuscular

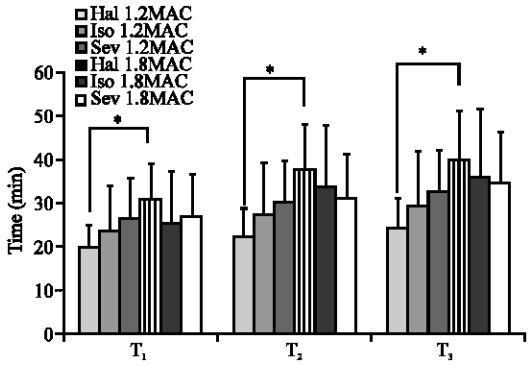

Fig. 7: T_1, T_2 and T_3 recovery times *p<0.05

blockade using the Post-Tetanic Count (PTC) and ST in humans based on the degree of recovery of PTC and ST at the time of reflex movement recovery after vecuronium administration and stated that ST and TOF stimulations well-reflected the influences of volatile anesthetics on the neuromuscular blocking effect.

In ST, a single supramaximal stimulus is loaded and clinically, 0.1 or 1 Hz is used. When the neuromuscular function is monitored based on ST, it is necessary to establish a control ST height (height of contraction) before muscle relaxant administration. ST gradually decreases after muscle relaxant administration and the rate of reduction as a percentage to the control is presented as the level of muscular relaxation.

On TOF stimulation, 4 consecutive stimuli are loaded for 2 sec at 0.5 sec intervals. Muscle contractions induced by the 4 stimuli are designated as T_1, T_2, T_3 and T_4 following the order and the height rate of the 4th (T_4) to the initial (T_1) reaction (T_4/T_1) is designated as the TOF ratio. This rate is decreased (attenuation) by non-depolarizing blocking as the severity of the blocking of neuromuscular transmission increases within a specific range and contraction disappeared in order from T_4. During recovery, contraction appears in order from T_1. The biggest advantage of TOF is that the control value before muscle relaxant administration is not necessarily required, unlike ST and evaluation can be initiated from any muscular relaxation phase.

Application of these stimuli in horses and dogs in veterinary care have been reported (Cullen *et al*., 1980; Thurmon *et al*., 1996), based on which we stimulated the ulnar nerve with ST and TOF to evaluate the effects of the drugs.

The duration of the action of vecuronium and the recovery rate varied among the anesthetics, demonstrating that volatile anesthetics influenced vecuronium's action. The TOF recovery rate was different among the anesthetics and between the concentrations,

while no marked differences were noted in the ST recovery rate, suggesting that the ST and TOF recovery rates reflect the characteristics of the influences of volatile anesthetics. Bowman and Webb (1976) discovered that the force and duration of tetanic stimulation-induced muscle contraction after the administration of hexamethonium, pancuronium and d-tubocurarine varied among the drugs in cats. They observed that a ganglion blocker, hexamethonium, specifically inhibited only the maintenance of tetanic stimulation-induced muscle contraction (tetanus fade) but showed no influence on the height of ST-induced contraction, small doses of pancuronium and tubocurarine induced tetanus fade, similarly to hexamethonium and the tetanic stimulation induced muscle contraction was reduced when the doses were increased. They reported that neuromuscular blocking drugs not only competitively antagonize the receptor on the fascia side (postjunctional effect) but also act on nerve fibers and inhibit Acetylcholine (ACh) release (prejunctional effect). Stanec and Baker (1984) confirmed the pre and postjunctional effects of d-tubocurarine and pancuronium in humans using tetanic stimulation. They observed that the tetanic stimulation-induced maximum muscle contraction and duration of contraction were different between d-tubocurarine and pancuronium, pointing out the possibility that the action site of non-depolarizing blocking drugs in the neuromuscular junction is not only the fascial end-plate (postjunctional effect) but also the synapse itself (prejunctional effect) and the rate of the effects varies among drugs, leading to different durations of muscle contraction. They stated that the rate of the pre and postjunctional effects is associated with the affinities for the nerve fiber and fascial end-plate of the drug and the fade is considered to be caused by the prejunctional effect. In the study, no difference was noted in the ST recovery rate among the anesthetics, while the TOF recovery rate was significantly lower in the Sev 1.2 MAC than in the Hal 1.2 MAC group, suggesting that potentiation by the anesthetics is mainly due to the prejunctional effect.

The TOF recovery rate was significantly lower in the 1.2 MAC Sev than in the 1.2 MAC Hal group, indicating that potentiation of the action of vecuronium by Sev at 1.2 MAC is significantly stronger. Awata (1987) reported that potentiation by Sev was the strongest based on the relative potency of vecuronium under volatile anesthetics, to which the findings are consistent. The T_1, T_2 and T_3 recovery times were not significantly different between the Sev concentrations but all recovery times were significantly lower in the 1.8 MAC than in the 1.2 MAC Hal group. The potentiation of vecuronium by Sev was the strongest among the volatile anesthetics at 1.2 and 1.8 MAC based on the recovery time but the potentiation by Hal was considered to most markedly increase in a concentration-dependent manner. These findings suggested that the order of strength of volatile anesthetics to potentiate the action of vecuronium alters depending on the anesthetic concentration, for which further investigation is necessary.

The major volatile anesthetics used in the clinical veterinary field differently potentiated the action of vecuronium. No abnormal values assumed to be associated with vecuronium were noted in the respiratory or circulatory items monitored throughout the experiment, suggesting the safety of the drug. There are vecuronium antagonists, such as neostigmine and edrophonium but these are anti-cholinesterases and exert marked effects on the cardiovascular system. Therefore, a low dose is desirable for the administration of antagonists in consideration of safety for arousal.

CONCLUSION

This study confirmed that the volatile anesthetics potentiate vecuronium in dogs. All volatile anesthetics used are employed frequently and concomitantly with vecuronium in the veterinary field. Consideration of the potentiation of vecuronium by the volatile anesthetics may facilitate safe anesthesia.

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