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Measurement of the activity of neuromuscular blocking agents by train-of-four and their effect on the coagulation profiles of dogs undergoing & ovariohysterectomy

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ABSTRACT

Atracurium and vecuronium, which are short-acting non-depolarising neuromuscular blocking agents, were introduced into clinical use after 1980. These two drugs, which have a short-acting duration and fewer adverse side effects, have found widespread use.The aims of this study were to determine the onset of action and duration of three neuromuscular-blocking drugs. A total of 18 dogs 1-3 years of age and weighing 17.6 kg on average were evaluated in the study. The animals were divided equally into the three drug groups: Group A = atracurium, Group V = vecuronium and Group R = rocuronium. Atracurium, rocuronium and vecuronium were administered at 0.2 mg/kg, 0.2 mg/kg and 0.4 mg/kg, respectively via the IV route. After the operation was completed, the animals in the vecuronium group were treated with 2-4 mg/kg IV sugammadex and the reversal time of the drug effect was recorded. Prothrombin time (PT), activated partial thromboplastin time (APTT), thrombin time (TT) and fibrinogen (FP) values were measured. The PT showed significant differences between the atracurium and rocuronium groups ($p<0.05$).TOF neuromuscular blockage time displayed significant differences between the atracurium (35.6±7.7 min) and rocuronium groups (26.1±2.1 min) ($p<0.05$). The onset of neuromuscular blockage time for all three agents was similar; however, rocuronium had a shorter neuromuscular blockage time. As a conclusion, our results suggest that all three neuromuscular blocking agents can be administered routinely with inhalation anesthesia for patients undergoing surgical procedures in which muscular relaxation is needed.

Key words: Atracurium, BIS monitoring, Coagulation parameters, Dogs, Recuronium, TOF monitoring, Vecuronium.

INTRODUCTION

The clinical use of muscle relaxants (neuromuscular-blocking agents) in veterinary anesthetics was first reported by Hall in 1952 (Thurmon *et al.,* 1996). With this development, the concept of “balanced anesthesia”, which includes anesthesia, analgesia and neuromuscular blocking, was introduced into the practice of veterinary medicine (Jones, 1992; Thurmon *et al.,* 1996). Atracurium and vecuronium, which are short-acting non-depolarizing neuromuscular blocking agents, were introduced into clinical use after 1980. These two drugs, which have a short-acting duration and fewer adverse side effects, have found widespread use. A long-acting non-depolarizing neuromuscular blocking agent, pipecuronium, was also developed and began being used in clinical practice. In addition to these drugs, newer neuromuscular blocking agents with reduced side effects have begun to be preferred (Jones, 1992; Hildebrand, 1995; Thurmon *et al.,* 1996).

The aims of this study were to determine the onset of action and duration of three neuromuscular-blocking drugs: (Arca and Saritas, 2017) atracurium which has been used for many years in veterinary anesthesia practice, (Auer, 2007) vecuronium which supplanted atracurium in recent years and (Balcı *et al.,* 2006) rocuronium which is a derivative of vecuronium. Train-of-four (TOF) monitoring was used to evaluate the onset and duration of action of these drugs. Coagulation parameters were evaluated as well. Another aim of this study was to determine the effect of sugammadex (frequently used in human medicine to reverse the effect of rocuronium) in dogs by using TOF monitoring to fill a gap in the literature with regard to this matter.

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MATERIALS AND METHODS

A total of 18 female dogs 1 to 3 years of age, weighing an average of 17.6 kg, brought to the clinic for ovariohysterectomy procedures, were evaluated in the study following approval by the ethics committee (permission number AKÜHADYEK-338-14 and date 20.03.2014). The dogs were randomly divided into three groups: atracurium (Group A) (n = 6), vecuronium (Group V) (n = 6) and rocuronium (Group R) (n = 6).

All dogs were fasted for 12 hours before surgery. Prior to the study, a catheter was placed in the cephalic vein for drug delivery and serum withdraw. The dogs were premedicated with 0.3 mg/kg IV midazolam (Dormicum, Roche, Turkey). After sedation, anesthesia was induced by IV bolus of propofol 5 mg/kg (Propofol 2% Abbot, Turkey). Dogs were then intubated and connected to an anesthesia system (SMS 2000 Classic Turkey) for administration of a 2% isoflurane + oxygen mixture for general anesthesia. During anesthesia, all cases were monitored using a PETAS KMA 800 Multi-Channel Monitor. Heart rate (at II. derivation) and respiratory counts were recorded.

TOF monitoring

The electrodes of the TOF device (TOF-Watch® S, Organon, Ireland) were placed on the ulnar nerve and the first phalanx. Measurements were taken at 15 and 30 minutes before and after the application of neuromuscular blocking agents to determine the drugs' onset and duration of action. Atracurium, vecuronium, and rocuronium were administered intravenously to the related groups at a dose of 0.2 mg/kg, 0.2 mg/kg, and 0.4 mg/kg, respectively. After the operation was completed, the animals in the vecuronium group were treated with 2-4 mg/kg IV sugammadex (Bridion, Merck Sharp & Dohme, Germany) and the reversal time of the drug effect was recorded.

BIS monitoring

The temporofrontal region of the dogs were shaved prior to anesthesia administration and fat on the skin was removed with ether. Sensors consisting of five electrodes typically used in humans were placed for BIS monitoring (Covidien, Complete Monitoring System, Norwood, MA, USA). Three sensors were placed in the frontal region and two in the pre-auricular temporal region (Saritas *et al.,* 2013). After the sensors were connected to the BIS monitor, values were recorded in all three groups before and after anesthesia induction, after neuromuscular blocking agent application, and after the anesthesia process.

Surgical procedure

A routine ovariohysterectomy was performed with a median laparotomy by the same researcher under aseptic conditions after general anesthesia was established. All operations were completed in approximately 25-30 minutes. After surgery, animals were hospitalized and cefazolin was administered intramuscularly 20 mg/kg for five days. At the end of the 10th postoperative day, sutures were removed.

Measurement of coagulation parameters

Venous blood samples were collected in citrate tubes before anesthesia and during general anesthesia at 15 and 30 minutes. Prothrombin time (PT, seconds), active partial thromboplastin time (APTT, seconds), thrombin time (TT, seconds) and fibrinogen (FP, mg/dl) measurements were performed with a semi-automatic coagulometer (MT4C Coagulation Analyzer, Tokra Medical, Turkey).

Statistical analysis

To determine the differences between group results for the onset and duration of action values, a Mann-Whitney U test was applied. To determine the differences between group results for clotting factor values, a Bonferroni Test was performed and the ANOVA test was used for repeated measurements to assess differences over time within the group. Data are presented as mean ± standard deviation. A $p < 0.05$ was considered significant.

RESULTS AND DISCUSSION

The neuromuscular-blocking duration was 35.6 ± 7.7 min in the atracurium group and 26.1 ± 2.1 min in the rocuronium group. There was a significant difference between these two groups in terms of neuromuscular blocking time ($p < 0.05$). After the neuromuscular blocking was reversed with sugammadex in the vecuronium group, the duration of inactivation was 45 ± 5.4 sec for TOF 25% and 96 ± 16.8 sec for TOF 75% (Table 1).

Table 1: Onset and duration of action times for atracurium (Group A), vecuronium (Group V) and rocuronium (Group R) groups n=6, (Mean±SD).

Groups	Onset of action (Sec)		Duration of action (Min)	
	TOF %75	TOF %25	TOF %25	TOF %75
Group A	38.8±16.1	122.5±17.2	31.6±7[a]	35.6±7.7[a]
Group V	43.5±8.4	98.3±24.8	-	-
Group R	45.0±19.7	95.5±8.9	22.5±1.7[b]	26.1±2.1[b]
P	0.75	0.23	0.043	0.054

[ab]Superscript letters indicate a significant difference between the values having different letters in the same column. Since the vecuronium group was reversed by sugammadex at the end of the operation, the duration of action for this group was not included in the statistical evaluation.

Table 2: Coagulation factor analysis results for atracurium (Group A), vecuronium (Group V) and rocuronium (Group R) (n=6) (Mean±SD).

	Groups	PT (sec)	APTT (sec)	TT (sec)	FP(mg/dl)
0	Group A	6.4±1.7	15±5.6	10.05±3.1	346.3±186.5
	Group V	10.03±0.2	15.1±2.6	10.8±1.2	384.5±196.5
	Group R	11.9±1.2	11.2±4.1	10.8±1.04	424.5±240.5
15	Group A	8.2±2.1	12±4.4	11.7±2.3	452.1±200.9
	Group V	9.06±2.3	14.08±1.8	11.2±7.4	485.3±86.4
	Group R	11.9±0.8	13.8±3.3	11.7±1.1	426.3±64.6

A significant difference was determined between the atracurium and rocuronium groups in terms of PT levels ($p < 0.05$), whereas there was no significant difference between the vecuronium and rocuronium groups. The alterations observed in APTT, TT and FP levels among the groups were not statistically significant (Table 2).

No significant changes in BIS values were detected in all groups. BIS values were determined as 100 before anesthesia, dropping to 40-60 after anesthesia induction and remaining at the same level of 40-60 after the neuromuscular blocking agents were applied, then rising to 75-85 when the anesthesia was discontinued.

Because the duration of action of muscle relaxants may be prolonged in cases requiring additional dosage applications, neuromuscular monitoring is recommended during long-term operations under inhalation anesthesia. Accurate monitoring is useful for determining the dose of both the muscle relaxant and its antagonist. To prevent permanent paralysis or muscle weakness during the recovery process, monitoring should be performed until muscle function returns completely. Responses to peripheral nerve stimulation can be evaluated to determine the degree of neuromuscular blocking (Pollard, 2005; Martinez and Keegan, 2007). Electromyography or mechanomyography is considered the scientific standard in monitoring the effects of neuromuscular blocking agents under experimental conditions. Acceleromyography is the recommended technique in clinical trials with neuromuscular blocking agents (Turgut, 2000).

In this study, the action levels and durations of single-dose muscle relaxants were determined by giving a stimulus at the elbow area where the ulnar nerve exists and measuring the response at the paw area via TOF electrodes placed in those areas. The TOF method has been used in many studies because of its practicality when compared to other monitoring methods described in previous studies. It has been reported that inhalation anesthetics increase neuromuscular blocking by non-depolarizing drugs depending on the dose (Miller *et al.,* 1971; Fogdall and Miller, 1975; Ngai, 1975; Stansky *et al.,* 1979; Cannon *et al.,* 1987; Oyos, 1994; Nagahama *et al.,* 2006). (The clinical duration of action of rocuronium has been reported to be prolonged in both humans and dogs (Kumar *et al, 2017*; Sink *et al*, 2017) with isoflurane anesthesia (Quill *et al.,* 1991; Oris, 1993). The results of a study by Kastrup *et al*. (2005) showed that the duration of neuromuscular blocking with atracurium in dogs under Sevoflurane was approximately 15 min longer than that of a Total Intravenous Anesthesia (TIVA) group. Nagahama *et al*. (2006) reported that the infusion rate of vecuronium in dogs should be reduced twofold with sevoflurane and isoflurane anesthesia compared to propofol anesthesia.

In this study, anesthesia induction in all three groups was performed with IV propofol administered to dogs premedicated with midazolam, and general anesthesia was maintained with the inhalation anesthetic isoflurane. The study was designed to test the effects of different muscle relaxants using the same anesthesia protocol, thus, testing of the effects of muscle relaxants with different anesthesia protocols was not performed. In our study, the time of onset of action was 38.8 ± 16.1 sec (T75) in Group A, 43. 5 + 8.4 sec in Group V and 45.0 ± 19.7 sec in Group R. There was no significant difference between the values of the onset of actions (T75) using the same anesthesia protocol ($p > 0.05$). The T25 values of the onset of action in groups were 122.5 ± 17.2 sec, 98.3 ± 24.8 sec and 95.5 ± 8.9 sec and there was again no significant difference between the groups ($p > 0.05$). It was determined that the blocking action activated more quickly in group A and muscle relaxation time in group R was shorter but these differences were not significant. These results also support the information in the literature.

In the study performed by Auer (2007), rocuronium was used at a 0.6 mg/kg dose and the duration of clinical action of rocuronium (T25) in a propofol-anesthetized group was 20.87 ± 5.29 min. In our study, the duration of clinical action of rocuronium (T25) was 22.5 ± 1.7 min. On the other hand, clinical duration (T25) in Group A was 31.6 ± 7 min. Since Group V was reversed by sugammadex, it was not included in the statistical analysis. In our study, T25 values for group A were longer than group R and the difference was significant ($p < 0.05$). Our results coincide with the results of Auer (2007). On the other hand, the researcher applied rocuronium at a dose of 0.6 mg/kg in a TIVA group and sufficient muscular relaxation was obtained with a 0.4 mg/kg dose of rocuronium during our ovariohysterectomy operations in dogs. This finding is also noteworthy.

The duration of clinical effect T75 was not measured in group V, 35.6 ± 7.7 min in Group A and 26.1 ± 2.1 min in Group R. According to these measurement results, Group A duration was significantly longer than Group R ($p < 0.05$).

Isoflurane and Enflurane are inhalation anesthetics that increase the severity and duration of neuro-muscular

blockage. These agents affect blockage in two ways: (Arca and Saritas, 2017) they depress the central nervous system and increase the duration and severity of blocking and (Auer, 2007) they also cause a deprivation of the motor end plate secretion of acetylcholine in the periphery (Jones, 1992; Thurmon *et al.,* 1996; Hall and Clarke, 1999). Our research was planned with this information in mind and general anesthesia was provided with isoflurane in all three groups. Thus, muscle relaxants that were the subject of the study were also tested for the maximum duration of action in dogs under isoflurane anesthesia. In this respect, the method used in this study was novel.

BIS is a specific, practical, continuous, numerical EEG parameter, developed in 1985 by Aspect Medical Systems of Natick Massachusetts, that measures the direct effects of hypnosis on the brain during anesthetic and sedative application (Ganidagli *et al.,* 2001; Morgan *et al.,* 2004; Hans *et al.,* 2005; Balcı *et al.,* 2006). This commercially available version of EEG parameters was approved by the Food and Drug Administration (FDA) in 1996 and is the only device approved by the FDA for visualization of the effects of anesthesia in the brain. It was developed as a result of efforts to evaluate EEG in a simple and reliable way in various situations such as neurological diseases, cerebral ischemia, and monitoring of anesthetic activity (Ganidagli *et al.,* 2001; Tosun *et al.,* 2003). In recent years, BIS monitors, which quantitatively monitor EEG signals, have been used to evaluate the depth of anesthesia (Belda *et al.,* 2010; Belda *et al.,* 2012; De Mattos Junior, 2011; Saritas *et al.,* 2013; Saritas *et al.,* 2014a; Saritas *et al.,* 2014b). BIS, which is the numerical value of EEG derivations, was used in the evaluation of central nervous system (CNS) depression in humans. It has been reported in humans that the depressive effects of sedatives and anesthetics on the CNS correlate with BIS (Greene *et al.,* 2003; Saritas *et al.,* 2013; Saritas *et al.,* 2014a; Saritas *et al.,* 2014b). Usage of BIS in the evaluation of CNS depression with isoflurane, sevoflurane and propofol anesthesia in dogs was reported previously; however, research involving BIS in veterinary practice is limited (Greene *et al.,* 2003; Belda *et al.,* 2012; Saritas *et al.,* 2013; Saritas *et al.,* 2014a; Saritas *et al.,* 2014b). It was determined that the effect of muscle relaxants on BIS values is limited in humans; however, no such studies have been conducted on dogs (Kumar *et al.,* 2018).

In this study, deep anesthesia (surgical plane) was initiated in the three groups and muscle relaxants were then administered. The lack of correlation between the measurements made before and after giving muscle relaxants suggests that muscle relaxants do not change BIS values. For this reason, no statistical calculations were made between the groups and arithmetic values were determined considering the BIS value alternating in the range of 40-60. Because ovariohysterectomy (Ugwu *et al,* 2018) operations were performed in all three groups, the duration of surgery (was less than 30 minutes, and only a single dose of muscle relaxant was required. To determine whether the use of muscle relaxants in dogs as infusions in longer operations has an effect on BIS or not, additional studies are needed.

There is not a single test evaluating all hemostatic components. For this reason, a few hemostatic tests are usually performed to determine the nature of hemostatic disorders (Turgut, 2000). Coagulation profiles are evaluated by determining PLT, PT, aPTT, TT, FP, fibrin degradation product levels and the aspects that play a role in clotting factor IX (Hohenhaus, 2000). Extrinsic (tissue factor, factor VII) and diffuse system aspects (factors V and X, prothrombin, fibrinogen) are assessed for PT (Turgut, 2000).

In this study, blood samples were taken from the three groups of dogs before applying anesthesia and muscle relaxants and at 15 and 30 minutes after the administration of muscle relaxants. PT, aPTT, TT and FP levels were measured using a semi-automatic coagulometer. There are a few reference values reported for dogs in a limited number of sources. Arca and Saritas, (2017), reported that reference ranges were 8-11.8 seconds for PT, 7.5-10.5 seconds for aPTT and 10.7-16.4 seconds for TT.

Statistical analysis of PT, aPTT, TT and FP values found no differences between the groups following drug administration when compared to the initial values ($p > 0.05$).

CONCLUSION

It is concluded that the three muscle relaxant agents evaluated did not change or compromise the coagulation parameters and can be used in surgical patients.

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