Veterinary Anaesthesia and Analgesia, 2007, **34**, 75–81 doi:10.1111/j.1467-2995.2006.00298.x

RESEARCH PAPER

Observations on the muscle relaxant rocuronium bromide in the horse – a dose–response study

Ulrike Auer DVM, **Carmen Uray** DVM & **Martina Mosing** DVM
Clinic of Anaesthesiology and Perioperative Intensive Care, University of Veterinary Medicine Vienna, Vienna, Austria

Correspondence: Ulrike Auer, Anaesthesia and Perioperative Intensive Care, University of Veterinary Medicine Vienna, Veterinärplatz 1, A-1210 Vienna. E-mail: ulrike.auer@vu-wien.ac.at

Abstract

Objective To investigate the onset and duration of neuromuscular blockade of rocuronium bromide and its associated haemodynamic effects at three doses in healthy horses.

Study design Prospective, randomized experimental study.

Animals Seven adult horses aged 3–20 (mean 10.3) years and weighing 466 ± 44 (mean ± SD) kg.

Methods Horses were anaesthetized three times with at least 2 weeks between. They were pre-medicated with 0.6 mg kg^{-1} xylazine and 0.01 mg kg^{-1} butorphanol IV. Anaesthesia was induced with 2.2 mg kg^{-1} ketamine and 0.1 mg kg^{-1} diazepam IV. Following orotracheal intubation anaesthesia was maintained with isoflurane in 100% oxygen. Intermittent positive pressure ventilation was initiated and the horses were ventilated at a respiratory rate (*fr*) of 4–8 breaths $minute^{-1}$. Neuromuscular function was monitored with an acceleromyograph. The peroneal nerve was stimulated with train-of-four (TOF) mode at 2 Hz every 15 seconds. Each horse received, in randomly assigned order, one of the three doses of rocuronium: 0.2 mg kg^{-1} (D02), 0.4 mg kg^{-1} (D04) or 0.6 mg kg^{-1} (D06) IV. Lag time, onset time, time of no response, duration of action and the TOF ratio 0.7 and 0.9 were measured. Recovery time ($T1_{25-75}$) was calculated. Vital parameters were recorded at 5-minute intervals on a standard anaesthetic record form.

Results Rocuronium produced a dose-dependent duration of action in isoflurane-anaesthetized horses. 100% block was observed in D04 and D06 but not in D02, in which the maximum decrease of the first twitch of TOF attained was 91.5 ± 16.5%. Time to $T1_{25}$ was 13.1 ± 5.5 minutes, 38.6 ± 10.1 minutes and 55 ± 9.8 minutes in D02, D04 and D06 respectively. There was a significantly shorter time for TOFR 0.9 with 0.2 mg kg^{-1} compared with 0.4 and 0.6 mg kg^{-1} rocuronium. $T1_{25-75}$ in D04 and D6 was not statistically significantly different. Heart rate, systolic, diastolic and mean arterial blood pressure increased slightly during the observation period.

Conclusion Rocuronium is an effective nondepolarizing muscle relaxant in horses under isoflurane anaesthesia. It had a dose-dependent onset and duration of action. Rocuronium did not produce significant changes in the measured cardiovascular parameters.

Keywords anaesthesia, horse, neuromuscular-blocking agents, rocuronium.

Introduction

The introduction of muscle relaxants to human anaesthesia in 1942 was a major advance as any desired degree of relaxation could be produced irrespective of the depth of anaesthesia (Griffith & Johnson 1942). The first reports of the use of muscle relaxants in horses were by Booth & Rankin (1953) with curare and by Belling & Booth (1955) with the

depolarizing agent succinylcholine. A number of nondepolarizing muscle relaxants (NDMR) including gallamine, pancuronium, atracurium and vecuronium have been introduced into equine anaesthesia in the last three decades (Dykes 1973; Klein et al. 1983; Hildebrand & Arpin 1988; Hildebrand et al. 1989; Bechara et al. 1999).

The main use of neuromuscular-blocking agents in veterinary anaesthesia is to relax skeletal muscles for easier surgical access, to prevent movement during ophthalmic, orthopaedic and abdominal procedures and to allow the initiation of IPPV. Used as part of balanced anaesthesia they reduce the dose requirement of general anaesthetic agents, which can seriously depress cardiovascular function (Hall & Weaver 1954).

The latest NDMR, rocuronium bromide (ORG 9426, 2-morpholino,3-desacethyl,16-*N*-alkyl-pyrrolidion), an analogue of vecuronium, became available in 1995. In order to administer a drug safely to patients it is important that its pharmacological properties, its time course of action and the possible side effects are available. To the authors' knowledge the pharmacodynamic and cardiovascular properties of rocuronium bromide have not been documented in horses under experimental or clinical conditions.

The aim of the present study was to determine the pharmacodynamic properties and the associated haemodynamic effects of three different doses of rocuronium administered to horses under isoflurane anaesthesia.

Material and methods

Animals

Seven adult horses were classified as ASA 1 (healthy, no systemic disease), with a mean body weight of 466 ± 44 (mean ± SD) kg and 3–20 (mean 10.3) years old, were studied. The prospective, randomized experimental study protocol was approved by the National Animal Care and Welfare Committee Austria (§ 8 Tierversuchsgesetz, BGBI Nr 501/1989 i. d. F. d BGBL. I Nr 169/199). Food, but not water, was withheld for 12 hours before anaesthesia. Health status was determined on the basis of physical, biochemical and haematological examination.

Anaesthesia and monitoring

After catheter placement (Intraflon2, 12 SWG; Vycon, Ecoune, France) in the left jugular vein, horses were pre-medicated with 0.6 mg kg^{-1} xylazine (Xylasol, Dr E. Gräub AG, Berne, Switzerland) and 0.01 mg kg^{-1} butorphanol (Butomidor; Richter Pharma, Wels, Austria) mixed in a syringe and administered slowly IV. Anaesthesia was induced with 2.2 mg kg^{-1} ketamine (Narketan; 10%, Vetoquinol Austria GmbH, Vienna, Austria) and 0.1 mg kg^{-1} diazepam (Valium; Roche Austria GmbH, Vienna, Austria) in separate syringes IV. Oral endotracheal intubation was performed and the endotracheal tube was connected to a circle system (Matrx VML; Matrx Medical Inc., Orchard Park, New York, NY, USA). The horses were positioned in right lateral recumbency. Anaesthesia was maintained with 1–1.1 Vol% isoflurane (Furane; Baxter, Vienna, Austria) in 100% oxygen during the observation period and intermittent positive pressure ventilation (IPPV; Ventilator L.A., Smith, Udlose, Denmark) was initiated to maintain end-tidal carbon dioxide ($P_E'CO_2$) between 35 and 45 mmHg (4.6–5.9 kPa). A catheter (Vasocan Braunüle, 0.9 × 25 mm, B. Braun, Deutschland) was placed in the transverse facial artery for monitoring arterial blood pressure (ABP) and blood sampling for blood-gas analysis. The transducer (Combitrans Monitoring-set arteriell, Fa. Braun, Melsungen, Germany) was zeroed to the level of the sternum. Mean ABP was maintained at a minimum value of 60 mmHg by administering a continuous infusion of dobutamine (1–2 μg kg^{-1} $minute^{-1}$) (Dobutamine Solvay, Solvay Pharma GmbH, Klosterneuburg, Austria). Ringer's lactate solution was infused at a rate of 10 mL kg^{-1} $hour^{-1}$ (Ringer Lactat 'Fresenius', Fresenius Kabi, Graz, Austria). An electrocardiograph (ECG; EKG HP M1001A; Hewlett Packard, Boeblingen, Germany) with leads in the base–apex position was attached. Respiratory rate (*fr*), end-tidal carbon dioxide pressure ($P_E'CO_2$) and end-tidal isoflurane concentration ($F_E'ISO$) were monitored with a methane-insensitive side stream infrared gas analyser (HP M1026A; Hewlett Packard), connected to the Y-piece of the anaesthetic circle. Arterial blood pressure, ECG and the capnogram were continuously displayed on a monitor (HP CMS monitor; Hewlett Packard) and recorded via a laptop program (MEDKOM MLS20WIN; Hewlett Packard, Vienna, Austria) for off-line analysis. Additionally values were recorded manually at 5-minute intervals on a standard anaesthetic record form except for any marked changes observed immediately after drug administration that were recorded as they occurred. For statistical analysis

data certain time points were extracted: baseline (time of rocuronium application), $t = 1$, $t = 2$ (1 and 2 minutes after application) and $T1_{25}$ and TOFR 0.9. On recovery from anaesthesia the time and number of attempts to standing were recorded.

Neuromuscular monitoring and definition of pharmacodynamic parameters

Neuromuscular function was assessed using an acceleromyograph (TOF-Guard; Organon Teknika NV, Turnhout, Belgium). The N. peroneus superficialis of the upper hind limb was stimulated. The acceleration transducer was fixed to the dorsal tip of the hoof using adhesive tape. Method of limb fixation and position of the electrodes were as described by Bechara et al. (1999) and Jones & Prentice (1976) and adapted for the acceleromyography by Auer et al (2002). The nerve was electrically stimulated in a train-of-four (TOF) mode at 2 Hz (four stimuli delivered over 2 seconds) every 15 seconds with two needle electrodes placed subcutaneously directly over the nerve. Electrical stimulation and corresponding response was continuously recorded on a memory card in the TOF-Guard for off-line analysis. After instrumentation the current needed for supramaximal stimulation (twitch height remaining constant despite increasing electrical current) was determined.

The lag time (LT; time from end of injection to first depression of the first twitch = T1 of TOF) and onset time (OT; time from end of injection to total disappearance of all four twitch responses in case of total relaxation) were determined. If partial relaxation occurred, the first of three consecutive TOF stimulation with identical amplitude of the first twitch was defined as OT (Viby-Mogensen et al. 1996). Time of 100% block (TonR, time from onset in case of total relaxation with no detectable responses to TOF stimulation till return of the first twitch of TOF), $T1_{25}$ and $T1_{75}$ (the time from end of injection until 25% and 75% recovery of the first twitch from baseline value) was determined. $T1_{25}$ is also defined as the clinical duration of action. The train-of-four ratio (TOFR) was calculated by the TOF-Guard, dividing the fourth twitch height by the first twitch height. The times to reach a TOFR of 0.7 (TOFR 0.7) and 0.9 (TOFR 0.9) were then determined. The recovery time from neuromuscular block ($T1_{25-75}$, time of the first twitch height of TOF to increase from 25% to 75% of baseline values) was calculated (see Fig. 1).

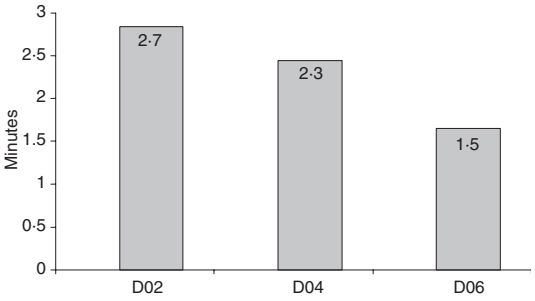

Figure 1 Onset time of 0.2, 0.4 and 0.6 mg kg^{-1} rocuronium bromide in horses, time in minutes, 100% block only in D04 and D06.

Additionally the changes in the eyeball position and rotation of the eyeball in central position were noted.

Study design

The horses were anaesthetized three times and randomly assigned to receive one of the three treatments at an interval of at least 2 weeks. All horses received one bolus of rocuronium bromide (Esmeron 50 mg 5 mL^{-1}, N.V. Organon, NL-53540 BH Oss, the Netherlands) IV when responses to initial nerve stimulation were stable for 5–10 minutes. Rocuronium was administered at three different doses: 0.2 mg kg^{-1} (D02; $n = 7$), 0.4 mg kg^{-1} (D04; $n = 7$) and 0.6 mg kg^{-1} (D06; $n = 7$) as a rapid bolus injection. When T1 recovered to 75% and no further increase were seen for 3 minutes, the rocuronium in D04 and D06 was antagonized with neostigmine 7 μg kg^{-1} (Normastigmin, Sigmapharma Wien, Vienna, Austria) to avoid residual paralysis of skeletal muscles during recovery from anaesthesia.

Statistical analysis

Pharmacodynamic parameters (LT, OT, $T1_{25}$, $T1_{75}$, $T1_{25-75}$, TOFR 0.9) between DO2, DO4 and DO6 were subjected to paired Student's *t*-test for determination of statistical significance for parameters with a normal distribution and the Wilcoxon rank sum test for non-normally distributed parameters. Vital parameters were analysed within doses with ANOVA for repeated measurements between baseline and $t = 1$, $t = 2$ and time points $T1_{25}$ and TOFR 0.9. Results were expressed as mean ± SD and differences were considered significant if $p < 0.05$.

Table 1 Physiological variables recorded after 0.2, 0.4 and 0.6 mg kg^{-1} rocuronium bromide IV in mechanically ventilated isoflurane-anaesthetized horses ($n = 7$)

Parameter/dose	0.2 mg kg^{-1}	0.4 mg kg^{-1}	0.6 mg kg^{-1}
HR (beats $minute^{-1}$)	41 ± 16	37 ± 7	38 ± 7
SAP (mmHg)	95 ± 5	95 ± 9	99 ± 6
DAP (mmHg)	49 ± 6	53 ± 7	52 ± 8
MAP (mmHg)	62 ± 5	70 ± 6	69 ± 13
$P_{E'}CO_2$ (mmHg)	36.4 ± 6.1	36.8 ± 6.3	40.7 ± 5
$P_{E'}CO_2$ (kPa)	4.8 ± 0.9	4.9 ± 0.9	5.4 ± 0.6
$F_{E'}ISO$ (%)	1.01 ± 0.2	1.02 ± 0.3	1.05 ± 0.1

HR, heart rate; SAP, DAP and MAP, systolic, diastolic and mean arterial blood pressure; $P_{E'}CO_2$, end-tidal carbon dioxide partial pressure; $F_{E'}ISO$, end-tidal isoflurane concentration.

Results

Rocuronium produced a dose-dependent duration of action in isoflurane-anaesthetized horses. Results are expressed as mean ± SD (range). The OT was inversely related to the dose, with the highest dose (DO6) inducing the fastest onset of complete block in 1.5 ± 0.6 minutes. 100% block was observed in D04 and D06 but not in D02, in which the maximum decrease of TOF attained was 91.5 ± 16.5%. $T1_{25}$ returned in 13.1 ± 5.5 minutes, 38.8 ± 10.1 minutes and 55 ± 9.8 minutes in D02, D04 and D06 respectively. There was a statistically significant shorter time to reach TOFR 0.9 with 0.2 mg kg^{-1} compared with 0.4 and 0.6 mg kg^{-1} rocuronium. $T1_{25-75}$ in D04 and D6 was not statistically significantly different. The administration of neostigmine at the end of recovery in G04 and G06 produced no further increase of T1 or TOFR. The pharmacodynamic parameters are shown in Table 2. The results of OT and $T1_{25}$ and TOFR 0.9 are illustrated in Figs 2 and 3.

The $P_{E'}CO_2$ remained stable with mechanical ventilation. HR, systolic, diastolic and mean BP increased slightly, but were not statistically significant after administration at all the three doses. There were no major changes observed throughout the procedures. The administration of neostigmine produced no effect on HR and BP (Table 1). No deleterious side effects, such as bradycardia, dysrhythmias or life-threatening anaphylactic reaction (hypotension, change in mucous membrane colour, etc.) occurred during or following the administration of rocuronium. In all horses the eyeball rotated

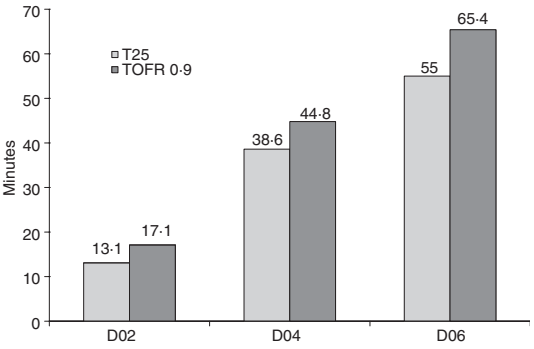

Figure 2 Clinical duration and end point of time course of action of 0.2, 0.4 and 0.6 mg kg^{-1} rocuronium bromide in horses. T25 = clinical duration = $T1_{25}$; TOFR 0.9 = train-of-four ratio.

Table 2 Pharmacodynamic parameters of rocuronium in isoflurane-anaesthetized horses (time in minutes)

Parameter	0.2 mg kg^{-1}	0.4 mg kg^{-1}	0.6 mg kg^{-1}
LT (minutes)	0.6 ± 0.2 (0.2–1)	0.5 ± 0.2 (0.2–1)[c]	0.3 ± 0.1 (0.2–0.5)[b,c]
OT (minutes)	2.7 ± 0.6 (1.5–3.5)[a,b]	2.3 ± 1.4 (1–6)[c]	1.5 ± 0.6 (0.75–2.5)[b,c]
TonR (minutes)	NA	27.7 ± 6.5 (18–46.2)[c]	40.7 ± 8.4 (29.0–53.7)[b,c]
$T1_{25}$ (minutes)	13.1 ± 5.5 (7–23)[a,b]	38.6 ± 10.1 (25.2–64.0)[c]	55.0 ± 9.8 (40.5–72.2)
$T1_{75}$ (minutes)	NA	51.8 ± 11.4 (37.2–74.0)	74.9 ± 9.1 (65.7–89.5)
$T1_{25-75}$ (minutes)	NA	11.3 ± 2.4 (6.25–17.0)	9.6 ± 2.2 (7.5–11.7)
TOFR 0.7 (minutes)	14.2 ± 6.6 (4.5–26)[a,b]	41.9 ± 9.2 (31.5–70.0)[c]	58.6 ± 11.5 (43.2–78.0)[b,c]
TOFR 0.9 (minutes)	17.1 ± 6.3 (5.75–30.2)[a,b]	44.8 ± 6.5 (35–78)[c]	65.4 ± 10.8 (49.0–83.5)
mA	52 ± 9 (39–60)	54 ± 8 (35–60)	50 ± 8.5 (40–60)

Values are expressed as mean ± SD (range).
Statistically significant difference: [a]between DO2 and DO4, [b]between DO2 and DO6, [c]between DO4 and DO6 ($p < 0.05$).
LT, lag time; OT, onset time; TonR, time of no response; T1, first twitch of train-of-four; TOFR, TOF ratio; mA, milli ampere; $T1_{25}$, clinical duration; $T1_{25-75}$, recovery time; NA, data not available.

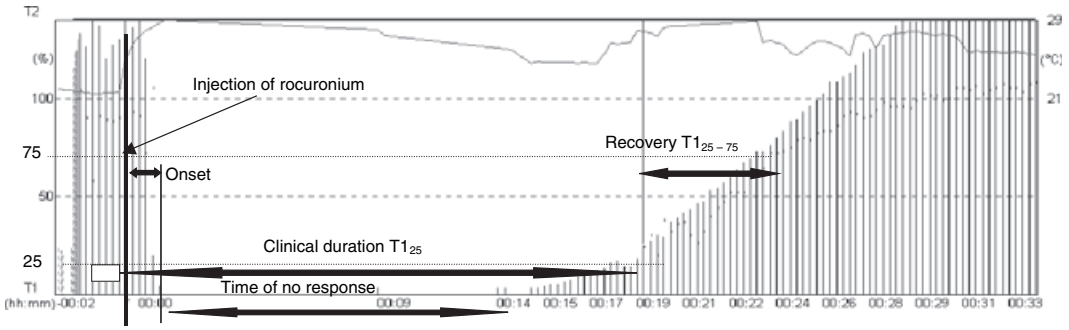

Figure 3 Graphic of a train-of-four (TOF) stimulation recorded on the memory card of the TOF-Guard of 0.4 mg kg^{-1} rocuronium in horse 3, illustrating the pharmacodynamic parameters measured. The upper thin line indicates the skin temperature and has no relevance in animals.

to the central position within the OT and remained there till the end of observation period.

Duration of anaesthesia was 45 ± 4.5 minutes in D02, 73 ± 6.3 minutes in D04 and 90 ± 5.8 minutes in D06. Time to standing was 37.4 ± 16.6 minutes in D02, 53 ± 28.6 minutes in D04 and 43.7 ± 18.9 minutes in D06. The average number of attempts to standing was 1.71 ± 0.95 in all three groups. Recovery was smooth and no evidence of post-anaesthetic muscle weakness was observed.

Discussion

Rocuronium produced a dose-dependent duration of neuromuscular blockade in isoflurane-anaesthetized horses. This NMBA fulfils most of the criteria of an ideal muscle relaxant (Savarese & Kitz 1975) with a rapid onset, intermediate duration of action, non-depolarizing action and lack of cardiovascular side effects.

The OT in this study was within 3 minutes and correlated with the dose. Within this onset the eyeball achieved a central position in all horses. The fast onset could be an advantage of rocuronium in comparison with atracurium, the usual NMBA in horses that has an OT of 3–9 minutes depending on the dose (Hildebrand & Arpin 1988). The outcome of this study is that a dose of 0.2 mg kg^{-1} rocuronium in horses could be a useful option in ophthalmic surgery to achieve a central position of the globe of the eye together with a short duration of action. In comparison with 0.1 mg kg^{-1} atracurium, rocuronium has a fast OT of 3 minutes and short clinical duration of 13 minutes (Senior et al. 2001).

Species variation in the duration of action of rocuronium makes it difficult to apply information obtained from one species to another. In the present study, a dose of 0.6 mg kg^{-1} of rocuronium produced a 100% blockade with a duration of action ($T1_{25}$) of 55 minutes. The same dose produced a duration of action in dogs of 20 minutes and in cats of 13 minutes (Adams et al. 2000; Auer & Mosing 2006; Auer 2006).

Techniques for monitoring neuromuscular blockade in horses have been described (Bowen 1969; Jones & Prentice 1976) including mechanomyography and electromyography. Stimulation of the peroneal nerve (Klein et al. 1983) with mechanomyography has been reported. Acceleromyography is a relatively new technique for monitoring neuromuscular blockade and Bechara et al. (1999) used different nerve-muscle units to demonstrate that the acceleromyography was a reliable technique in horses. Stimulation of the peroneal nerve with an acceleromyograph, in the manner described, was feasible in this study. On closer examination there are some restrictions of the method. Minimal changes in the position of the limb or of the needle electrodes may lead to the response of the single twitch of a TOF not reaching the baseline values before drug administration. The TOF ratio always recovered to baseline. Despite this restriction we recommend that acceleromyography is applicable for use in the clinical setting. The fixation of the limb needs no special device such as a cast as required with mechanomyography, the equipment is not expensive, easily applied and is an improvement compared with visual-tactile evaluation of the responses to nerve stimulation.

In humans the TOF ratio of more than 0.8 is defined as a desirable level of recovery because it is associated with full restoration of diaphragmatic function. This indicates adequate neuromuscular

activity and suggests, but does not guarantee, recovery of full upper airway protection and ventilatory function (Eriksson 2003). In horses the ability to perform sustained full muscle activity is assessed when the horse is able to stand and maintain that position. Currently, no information is available concerning the TOF ratio which guarantees adequate recovery of neuromuscular function in horses. In the present study, a TOF ratio of 0.9 was defined as the end point of duration of action of rocuronium. This parameter as discussed above appears to be reliable and safe and should guarantee an adequate recovery without residual muscle weakness.

In D04 and D06 antagonism with neostigmine was performed as an additional safeguard although a TOF ratio of 0.9 existed. No further increase of the response of T1 was seen as a result of neostigmine administration. The dose of neostigmine used was low compared with other studies (Cullen 1996; Hall et al. 2001) and was chosen in an attempt to avoid residual paralysis of skeletal muscle.

Cardiovascular changes following immediately after the administration of rocuronium in this study were not observed. The increase in heart rate and ABP observed over the whole period were not associated with the administration of rocuronium. Rocuronium has a mild vagolytic action that leads to a slight but transient increase in heart rate that is occasionally observed in humans (Khuenl-Brady et al. 1995). Another reason may be the use of dobutamine to provide an adequate BP. The slight increase in heart rate and ABP due to the effect of rocuronium may be an advantage in equine anaesthesia, where arterial hypotension, especially during inhalational anaesthesia, is a common problem.

Conclusion

Rocuronium administration in the horse provided predictable neuromuscular blockade, without haemodynamic changes, in isoflurane-anaesthetized horses. The large variation between the individuals in response to a given dose of rocuronium makes monitoring of the neuromuscular block essential.

Acknowledgement

The authors thank Organon Austria who supported this study by making the drug available.

References

Adams WA, Senior JM, Dugdale AHA, et al. (2000) Clinical use of the nondepolarising muscle relaxant rocuronium (Org 9426) in dogs. Proceedings of the 7th world congress of Veterinary Anaesthesia, Berne, Switzerland. p. 86.

Auer U (2006) Clinical observations on the use of the muscle relaxant rocuronium bromide in the dog. Vet J (doi: 10.1016/j.tvj.2005.11.014).

Auer U, Mosing M (2006) A clinical study of the effects of rocuronium in isoflurane-anaesthetized cats. Vet Anaesth Analg 33, 224–228.

Auer U, Mosing M, Uray C (2002) Comparison of the neuromuscular blocking effect of rocuronium on the M. levator nasolabialis and Mm. extensorii of the limb in horses. In: Proceedings of the Association of Veterinary Anaesthesia Meeting, Crete, Greece, p. 76 (abstract).

Bechara NJ, Fantoni DT, De Moraes Barros PS, et al. (1999) The TOF-Guard neuromuscular transmission monitor and its use in horses. Cienc Rural 29, 57–62.

Belling TH, Booth NH (1955) Studies on pharmacodynamics of succinylcholine chloride in horses. J Am Vet Med Assoc 126, 37–42.

Booth NH, Rankin AD (1953) Studies on the pharmacodynamics of curare in the horse: I. Dosage and physiologic activity of d-tubocurarine. Am J Vet Res 14, 51–55.

Bowen JM (1969) Monitoring neuromuscular function in intact animals. Am J Vet Res 30, 857–859.

Cullen LK (1996) Muscle relaxants and neuromuscular block. In: Lumb and Jones' Veterinary Anaesthesia (3rd edn.). Thurmon JC, Tranquilli WJ, Benson GJ (eds). Williams and Wilkins, Pennsylvania, USA. pp. 337–364.

Dykes HM (1973) Evaluation of a muscle relaxant. Pancuronium bromide. J Am Vet Med Assoc 225, 745–746.

Eriksson LI (2003) Evidence-based practice and neuromuscular monitoring. Anesthesiology 98, 1037–1039.

Griffith HR, Johnson GE (1942) The use of curare in general anaesthesia. Anesthesiology 3, 418–420.

Hall LW, Weaver BMQ (1954) Some notes on balanced anaesthesia for the dog and cat. Vet Rec 66, 491–493.

Hall LW, Clarke KW, Trim CM (2001) Relaxation of skeletal muscles. In: Veterinary Anaesthesia (10th edn.). Hall LW, Clarke KW (ed.). Saunders, London. pp. 149–178.

Hildebrand SV, Arpin D (1988) Neuromuscular and cardiovascular effects of atracurium administered to healthy horses anaesthetized with halothane. Am J Vet Res 49, 1066–1071.

Hildebrand SV, Holland M, Copland VS, et al. (1989) Clinical use of the neuromuscular blocking agents atracurium and pancuronium for equine anaesthesia. J Am Vet Med Assoc 195, 212–219.

Jones RS, Prentice DE (1976) A technique for the investigation of the action of drugs on the neuromuscular junction in the intact horse. Br Vet J 132, 226–230.

Khuenl-Brady KS, Sparr H, Pühringer F (1995) Rocuronium bromide in the ICU: dose finding and pharmacokinetics. Eur J Anaesthesiol 12, 79–80.

Klein L, Hopkins AS, Beck E, et al. (1983) Mechanical response to peroneal nerve stimulation in halothane-anaesthetized horses in the absence of neuromuscular blockade and during partial nondepolarizing blockade. Am J Vet Res 44, 781–785.

Savarese JJ, Kitz RJ (1975) Does clinical anaesthesia need new neuromuscular blocking agents? Anesthesiology 42, 236–241.

Senior JM, Robinson KJ, Price CM, et al. (2001) Clinical use of atracurium in horses undergoing ophthalmic surgery. Vet Anaesth Analg 28, 207.

Viby-Mogensen J, Engbaek J, Eriksson LI, et al. (1996) Good clinical research practice (GCRP) in pharmacodynamic studies of neuromuscular blocking agents. Acta Anaesthesiol Scand 40, 59–74.

Received 30 December 2005; accepted 10 May 2006.