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Neuromuscular blockade with rocuronium bromide for ophthalmic surgery in horses

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Abstract

Purpose The production of a central eye to ease surgical access for intraocular surgery is generally dependent on the depth of anesthesia. The aim of this study was to evaluate the eyeball position under muscle relaxation with rocuronium during general anesthesia.

Material and methods Twenty horses, body weight 480 ± 62 kg; age 12.6 ± 6.2 years (mean ± SD) were anesthetised for various ophthalmic surgeries. Horses were premedicated with acepromazine, xylazine, and butorphanol intravenously and anesthesia induced with ketamine and diazepam. Anesthesia was maintained with isoflurane in 100% oxygen and 0.6 mL/kg/h of an infusion containing midazolam, ketamine, and xylazine diluted in 500 mL 0.9% NaCl. Horses were mechanically ventilated. Neuromuscular function was assessed with an acceleromyograph (TOF-Guard®) and the N. peroneus superficialis was stimulated every 15 s with a train-of-four stimulation pattern. A dose of 0.3 mg/kg rocuronium was administered intravenously. The changes in the eyeball position were recorded.

Results The dose of 0.3 mg/kg rocuronium produced a 100% neuromuscular block in all horses. Onset time and clinical duration of block was 2.38 ± 2.02 min (range 0.5–8) and 32 ± 18.6 min (range 7.7–76.2), respectively. The globe rotated to central position within 31 ± 2.8 s. The whole iris was visible after 42 ± 7.7 s in all horses. No additional bolus of rocuronium was necessary for any surgery.

Conclusion Neuromuscular blockade with rocuronium bromide can be used safely to facilitate ophthalmic surgery in equines.

Key Words: eye globe, horse, neuromuscular blocking agent, rocuronium

INTRODUCTION

The introduction of muscle relaxants to human anesthesia in 1942 was a major advance since any desired degree of relaxation could be produced irrespective of the depth of anesthesia.[1] The first reports of the use of muscle relaxants in horses were by Booth[2] with curare and by Belling[3] with the depolarizing agent succinylcholine. A number of nondepolarizing muscle relaxants including gallamine, pancuronium, atracurium, and vecuronium have been introduced into equine anesthesia in the last three decades.[4–8] More recently the effects of different doses of the nondepolarizing muscle relaxant rocuronium bromide have been documented for horses.[9]

Muscle relaxants are often used as part of balanced anesthetic protocol because they reduce the requirement of general anesthetic agents which can seriously depress cardiorespiratory function.[10] However neuromuscular blocking agents (NMBA) cause a dose-dependent paralysis of the respiratory muscles and as a consequence intermittent positive-pressure ventilation (IPPV) is required. Muscle relaxants are also used if a motionless, centrally positioned eye is needed during intraocular or corneal surgery.[11] The effects of the NMBA rocuronium on the extraocular muscles and the position of the eye are not documented in horses.

The purpose of this clinical study was to determine the effect of rocuronium bromide on skeletal and extraocular muscle relaxation and to evaluate the position of the eye in horses.

MATERIAL AND METHODS

The study design was a prospective clinical study. The study population were horses undergoing ophthalmologic surgery,

classified as ASA (American Society of Anesthesiologists) I–II and subject to an anesthesia protocol which included intravenous administration of 0.3 mg/kg rocuronium and neuromuscular monitoring with acceleromyography.

Anesthesia and monitoring

After catheterization of the left jugular vein (Intraflon2, 12 G; Vycon, Ecoune, France) horses were sedated with 0.03 mg/kg acepromazine (Vanastress®; Vana GmbH, Vienna, Austria). Thirty minutes later the horses were premedicated with 0.6 mg/kg xylazine (Xylasol; Dr. E. Gräub AG, Berne, Switzerland) and 0.01 mg/kg butorphanol (Butomidor; Richter Pharma, Wels, Austria) mixed in a syringe and slowly administered intravenously. Anesthesia was induced with 2.2 mg/kg ketamine (Narketan 10%; Vetoquinol Austria GmbH, Vienna, Austria) and 0.1 mg/kg diazepam (Valium; Roche Austria GmbH, Vienna, Austria) in separate syringes intravenously. Oral endotracheal intubation was performed and the tube connected to a large animal circle system (Matrx VML; Matrx Medical Inc., Orchard Park, USA). The horses were positioned in lateral recumbency. A balanced anesthesia was maintained with isoflurane (Furane; Baxter, Wien, Austria) in 100% oxygen and a continuous rate infusion of 0.6 mL/kg/h of an infusion containing 15 mg midazolam (Midazolam Mayrhofer Pharmazeutika, Linz, Austria), 1000 mg ketamine, and 250 mg xylazine diluted in 500 mL 0.9% NaCl (0.9% NaCl; Fresenius Kabi, Graz, Austria). The transverse facial artery was catheterized (Vasocan Braunüle, 0.9 × 25 mm; B. Braun, Deutschland, Germany) to monitor arterial blood pressure (ABP) and to allow blood sampling for blood gas analysis. The transducer, (Combitrans Monitoring-set arteriell; Fa. Braun, Melsungen, Germany) was zeroed to the level of the sternum. An electrocardiograph (EKG HP M1001A; Hewlett Packard, Boeblingen, Germany) was connected and the leads fixed in the base–apex position. Respiratory rate, end-tidal carbon dioxide pressure ($PE'CO_2$) and end-tidal isoflurane concentration (FE´ISO) were monitored with a methane insensitive side stream infrared gas analyzer (HP M1026A; Hewlett Packard), sampling respiratory gas from the Y-piece of the anesthetic circle system. ABP, ECG, heart rate (HR), and the capnogram were continuously displayed on a monitor (HP CMS monitor; Hewlett Packard). Relevant data were also recorded manually at 5-min intervals on a standard anesthetic record form. IPPV (Ventilator L.A.; Smith, Udlose, Denmark) was initiated immediately after intubation. The settings of the ventilator were adjusted to maintain $PE'CO_2$ between 35 and 45 mmHg (4.6–5.9 kPa). During recovery the time and number of attempts to standing were recorded and quality of recovery scored with an extended scoring sheet developed by Donaldson *et al.*[12]

Neuromuscular blockade and monitoring

Neuromuscular function was assessed during anesthesia using an acceleromyograph (TOF-Guard®; Organon Teknika NV, Turnhout, Belgium). The peroneus superficialis nerve of the upper pelvic limb was stimulated. Two needle electrodes were inserted subcutaneously where the nerve crosses the lateral crest of the head of the tibia and can be palpated as a mobile cordlike structure. An acceleration transducer was fixed to the dorsal tip of the hoof using adhesive tape. Stimulation of this nerve causes extension of the hoof. Electrical stimulation was done in a train-of-four (TOF) mode at 2 Hz (four stimuli delivered over 2 s) every 15 s and corresponding response was continuously recorded on a memory card of the TOF-Guard® for off-line analysis. If the response to a stimulus was too weak the sensitivity of the transducer was increased by activating the amplification mode (default ×5). After instrumentation the current then needed for supramaximal stimulation (when twitch height remains constant despite increasing electrical current) was determined.

When responses to nerve stimulation recorded by acceleromyography were stable all horses received one bolus of 0.3 mg/kg rocuronium bromide (Esmeron 50 mg/5mL; N.V. Organon, NL-53540 BH Oss, The Netherland) intravenously. When TOF ratio did not recover to base line value following surgery or at the end of anesthesia, rocuronium was antagonized with neostigmine 0.007 mg/kg (Normastigmin; Sigmapharma Wien, Austria) to avoid residual paralysis of skeletal muscles during recovery.

The lag time (LT, time from end of injection to first depression of the first twitch 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. Time of 100% block (TonR, time from onset of total relaxation with no detectable responses to TOF stimulation till return of the first twitch of TOF), and $T1_{25}$ (the time from end of injection until 25% 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 automatically calculated by the TOF-Guard, dividing the fourth twitch height by the first twitch height. The time from end of injection of rocuronium to recovery to a TOFR of 0.9 (DURTOFR 0.9) was determined.

The change in globe position was recorded manually and time for the globe to rotate and to remain in central position (iris fully visible) was measured with a stop watch.

Statistical methods

Data are given as mean and standard deviation (± SD) and range (minimum – maximum). For HR and MAP an ANOVA was done to find significant changes over time. Significance was set when $P < 0.05$.

RESULTS

Twenty client-owned horses of different breeds with a body weight of 480 ± 62 kg and age 12.6 ± 6.2 years (mean and SD) were included in the study. Ten horses underwent conjunctival flap surgery, five horses keratectomy, three were enucleated and two horses underwent lens extraction. Mean

Table 1. Pharmacodynamic parameters following intravenous injection of 0.3 mg/kg rocuronium in anesthetised horses (time in min, mean ± SD, range)

Parameter	Mean ± SD	Range
LT (min)	0.75 ± 0.3	0.25–1.5
OT (min)	2.4 ± 2.0	0.5–8
TonR (min)	20.5 ± 12.3	4.5–47
$T1_{25}$ (min)	32.0 ± 18.6	7.7–56.2
DURTOFR 0.9 (min)	36.1 ± 19.4	19.9–84.3
mA	50 ± 10	30–60

LT = lag time; OT = onset time; TonR = Time of no response; T1 = first twitch of TOF; TOFR = train-of-four ratio; mA = mille Ampere; $T1_{25}$ = mean clinical duration.

duration of anesthesia was 78 ± 27 min and mean surgery time was 57 ± 26 min. Mean time from induction of anesthesia to the injection of rocuronium was 15 ± 12 min.

An increased amplification (×5) of the accelerograph was needed in 10/20 horses. The dose of 0.3 mg/kg rocuronium produced a 100% neuromuscular block in all horses. Onset time was 2.4 ± 2.02 min (range 0.5–8). Mean clinical duration ($T1_{25}$) was 32 ± 18.6 min (range 7.7–56.2). Other pharmacodynamic parameters are listed in Table 1.

The globe was positioned ventromedially in all horses prior to administration of rocuronium. After rocuronium injection the globe began to rotate to a central position within 31 ± 2.8 s. The whole iris was visible after 42 ± 7.7 s in all horses. This rotation to a central position occurred within the lag time and remained until recovery to a TOF ratio of 0.9 (DURTOFR 0.9). This was sufficiently long to perform all surgeries and no additional boli of rocuronium were necessary.

Of 20 horses seven did not receive neostigmine to antagonise rocuronium, in seven horses the drug was given before and in six horses after TOF returned to 0.9.

There were no significant differences in HR and blood pressure at any time point of observation compared with baseline. The quality of nonassisted recovery was scored excellent to good in all twenty horses. The average numbers of attempts to standing was 1.6 ± 0.5. No evidence of post anesthetic muscle weakness was observed.

DISCUSSION

In this study a single bolus of rocuronium produced an adequate period of ocular muscle relaxation and a central position of the eye to allow ophthalmic surgery.

Independently of the used protocol, the eyes of the horse turn medially and ventrally in the orbit which partially or totally obscures the cornea. A reliable method to produce a central eye is to use nondepolarizing muscle relaxants which results in a central immobile eye independent of the depth of anesthesia.

Rocuronium fulfills most of the criteria of an ideal muscle relaxant with a rapid onset, intermediate duration of action, nondepolarizing properties and lack of cardiovascular side effects.[13] Rocuronium produces a dose-dependent duration of neuromuscular blockade in isoflurane anesthetized horses.[9] The dose of 0.3 mg/kg used in this study was ideal for routine ophthalmologic surgeries. It produces a complete neuromuscular block of moderate duration and guarantees a central position of the globe within 1 min.[9] The time for the globe to reach the central position was shorter than the onset time of the muscle relaxant effect of rocuronium as measured by peripheral nerve stimulation. The surgery time was longer than the duration of neuromuscular blockade as monitored by the TOF guard. However all surgery could be completed as the globe remained in a central position also when the muscle relaxant effect was no longer present. In dogs this effect is well documented.[9,14,15] The shorter onset time for NMBA action at the level of the ocular muscles suggest that the muscles of the globe are more sensitive to NMBA than skeletal muscles. Typically, NMBA produce striated muscle paralysis, beginning with the ocular muscles followed in order by the muscles of the face, extremities, abdomen, and finally the intercostals and diaphragmatic muscles.[16] This sequence may be due to differences in number and density of acetylcholine receptors for different muscle fiber types and this has been demonstrated in cats.[17,18] In man ocular muscles have greater number and a more diffuse distribution of postsynaptic acetylcholine receptors than most other skeletal muscles.[19] No information exist about the structural differences between extra ocular muscles and peripheral muscles, e.g. of the pelvic limb in horses.

Alternatively the globe can be physically moved and stabilized using stay sutures or clips but these procedures can produce undesired distortion of ocular structure. Other techniques to produce extraocular muscle relaxation can also be obtained with ophthalmic nerve block or a retrobulbar block.[20,21] Local anesthetics injected directly into a muscle mass or around nerve fibers or nerve endings block the neuromuscular transmission of impulses effectively and isolate muscle fibers from nervous influence. This method has several disadvantages in comparison to an injection of a drug in a peripheral vein. A retrobulbar block needs some skills by the anesthetist and there is a delay before the full degree of relaxation is obtained. There is a risk of perforation the globe, laceration of the optic nerve and retrobulbar hemorrhage. Furthermore, injection of a high volume of local anesthetic will produce proptosis and can increase intraocular pressure (IOP).[22] Lidocaine is the most used local anesthetic and side effects following systemic absorption of large doses lidocaine or accidental intravenous administration vary but include convulsions of a tonic-clonic nature, followed by central nervous depression, respiratory depression and ultimately respiratory arrest as well as bradycardia and hypotension.[23] Horses are reported to be more sensitive showing CNS stimulation related to exposure of the brain to lidocaine rather than a defined concentration in blood.[24–26]

Increases in IOP are best avoided during ophthalmic surgery. No data about the influence of NMBA on IOP are available in horses. IOP significantly decreased 3 min after injection of rocuronium in dogs.[15]

An important fact when using NMBA is the range in duration of muscle relaxation. In two horses of this study the clinical duration was longer than 60 min. There is no explanation for this variation in these horses. Many facts, e.g. anesthetic protocol, underlying disease and age but also unknown reasons can influence the various duration of muscle relaxation in man.[27] This unpredictable prolongation is a good argument for objective monitoring.

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. Neostigmine was chosen in an attempt to avoid residual paralysis of skeletal muscle and a low dose was used based on previous studies.[28,29] No adverse reaction could be documented after administration of neostigmine to reverse rocuronium in this study or the ones cited.[9]

A disadvantage of the use of nondepolarizing muscle relaxants is that in addition to the eye muscles also the respiratory muscles will be paralyzed and that IPPV is mandatory. The safe use of NMBA needs equipment and knowledge to perform IPPV.

CONCLUSION

If the need of IPPV and the availability of a NMBA antagonist are recognized, a single dose of 0.3 mg/kg rocuronium bromide can be safely administered to produces a reliable relaxation of the ocular muscles for a time sufficient to perform routine ophthalmic surgery.

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