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Use of atracurium and its reversal with neostigmine in 14 pet rabbits undergoing ophthalmic surgery: a retrospective study

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Abstract

The objective of this retrospective study was to report the clinical use of atracurium and its reversal with neostigmine in pet rabbits. The medical records of 14 rabbits undergoing anesthesia for ophthalmic surgery were located through a search of the hospital's database. Demographic data and data pertaining the use of the neuromuscular blocker and its reversal were analysed. After intravenous administration of 0.44 ± 0.4 mg/kg atracurium, 11 rabbits experienced at least one of the following cardiovascular responses: hypotension, defined as systolic arterial pressure (SAP) < 75 mmHg (n=6), hypotension with decreased heart rate (HR) (n=1), hypotension with increased HR (n=1), decreased arterial blood pressure (ABP) without hypotension (n=6), decreased ABP with decreased HR (n=1), or increased HR (n=2, ABP reading could not be taken). Two of these 11 rabbits also experienced severe intra-operative hypothermia. The neuromuscular block was monitored with a train-of-four nerve-stimulation pattern, and reversed, with intramuscular 0.01-0.045 mg/kg neostigmine and 0.01-0.02 mg/kg glycopirronium, after the return of at least two out of 4 muscular twitches following nerve-stimulation. Decrease in ABP and possibly hypothermia are likely intra-operative complications when clinical doses of atracurium are administered to pet rabbits. Measures should be taken to detect their occurrence in order to treat them promptly.

Introduction

Rabbits are becoming increasingly popular as pets and, owing to a rise in their life expectancy over the last decades, anesthesia is becoming more frequently required for the surgical treatment of conditions that commonly affect geriatric rabbits, such as cancer and cataracts. Phacoemulsification is the surgical treatment for cataracts and it has been described for use in rabbits.[1] Phacoemulsification requires that the eye is completely immobilized and centrally positioned during the procedure. Ocular immobilization is also

necessary for corneal surgery and is achieved through the use of neuromuscular blocking agents (NMBAs). Pancuronium and cisatracurium have been used in New Zealand White rabbits under experimental conditions.[2] However, to the best of the authors' knowledge, the clinical use of NMBAs in pet rabbits has never been described.

The aim of this retrospective investigation was to report the clinical use of atracurium and its reversal with neostigmine in 14 anesthetized pet rabbits that underwent neuromuscular blockade in preparation for cataract or corneal surgery, and to report the observed unwanted effects and peri-anesthetic complications.

Materials and methods

The medical records of all the rabbits undergoing general Anesthesia at the Queen Mother Hospital for Animals (Royal Veterinary College) between January 2006 and January 2016 were identified through the Clinical Record Database System, and reviewed. The key word-combinations used for the preliminary search were: "rabbit + anesthesia/anesthetic", "rabbit + anesthesia/anesthetic + atracurium/NMBAs". The search was refined in order to exclude the files of rabbits that underwent anesthesia but did not receive a NMBA. Additionally, a list of the pet rabbits that underwent ophthalmic surgery, a common indication for performing a neuromuscular block, was provided by the senior ophthalmologist. Demographic data of the patients included in the study (sex, age, breed and Body Condition Score (BCS)), as well as the details pertaining to anesthesia and particularly the administration of the NMBA, its reversal and related side effects, were obtained from the anesthetic records and used for data analysis. Data were analysed with descriptive statistics, using commercially available programs and software (Microsoft Excel iOS 1.30, Microsoft Corporation; and SigmaStat 3.5.1, Systat Software, Inc. US). The Pearson correlation test was used to correlate the temperature at the end of the anesthetic and the duration of anesthesia.

Results

The preliminary file search identified 180 cases, which were reduced to 14 after manual refinement of the search. Six out of 14 rabbit cases were neutered males, 6 were neutered females, and the remaining 2 were intact females. Seven different anesthetists carried out the anesthetics, while the surgeries were performed always by the same ophthalmologist (RFS). The rabbits were aged 56 ± 4 months, weighed 2.2 [1.2-2.8] kg and their BCS was 3 [2-5]/9. The represented breeds were Dwarf Lop (n=4), French Lop (n=2), Netherland Dwarf (n=1), Lop Eared (n=1), and Lion-head (n=1), with the remaining rabbits being mixed-breeds. The surgical procedures were phacoemulsification (n=13), of which one also included an iridal abscess removal, and another one that also included an automated vitrectomy, and traumatic corneal laceration repair (n=1). Topical local Anesthesia (EMLA cream, AstraZeneca UK) was used to facilitate catheterization of the auricular vein. Thereafter, buprenorphine (Buprecare, Animalcare UK; dose: 0.02 [0.01-0.03] mg/kg) and midazolam (Midazolam hydrochloride, Hameln Pharmaceuticals UK; dose: 0.3 [0.2-0.3] mg/kg) were used, either intramuscularly (IM; n=10) or intravenously (IV; n=4), to premedicate all the rabbits. Five rabbits received additional medetomidine (Domitor, Pfizer UK; dose: 0.01 [0.005-0.02] mg/kg), either IM (n=4) or IV (n=1), to deepen the level of sedation. Anesthesia was induced with either alfaxalone (n=10; Alfaxan, Jurox Australia; dose: 2 [1-2] mg/kg), propofol (Diprivan, AstraZeneca UK; n=2; 2 mg/kg) or ketamine (Ketamidor, Chanelle UK; n=2; 3 mg/kg), IV, and maintained with either sevoflurane (SevoFlo, Abbott UK; n=10; end-tidal (ET): 2 [1.6-4.7] per cent) or isoflurane (IsoFlo, Abbott UK; n=4; ET: 1.2 [1.1-1.9] per cent) in oxygen following endotracheal intubation (ETT size: 2 [2-3] mm). Intra-operatively, atracurium (Tracrium, GlaxoSmithKline UK) was administered IV as boluses (total dose: 0.44 ± 0.4 mg/kg) to the rabbits to allow myorelaxation of the peri-ocular muscles. The initial atracurium dose ranged between 0.05

and 0.3 mg/kg, with the anesthetist deciding on a particular dose based on the estimated duration of the surgery. The degree of neuromuscular block was monitored during anesthesia with a train-of-four electrical stimulation pattern (TOF-watch SX, Organon US), with the electrodes positioned over the proximal (positive pole) and distal (negative pole) ends of the peroneal nerve in one leg. Other monitoring consisted of ECG, arterial blood pressure (ABP) measurement with either the Doppler probe positioned over the palmar metatarsal artery (n=13; systolic blood pressure (SAP)), or invasively, via auricular artery catheterization (n=1; systolic, mean and diastolic blood pressures), capnography, gas analyzer and body temperature measured rectally. In each rabbit, a drop of a topical anesthetic (Proxymetacaine Hydrochloride 0.5%, Minims UK) was instilled twice, two to four minutes apart, at the start of each procedure. Eleven out of 14 rabbits experienced at least one cardiovascular response to atracurium during the anesthetic. The observed cardiovascular responses were the following: hypotension (defined as SAP < 75 mmHg)[3] (n=6), hypotension with decreased heart rate (HR) (n=1), hypotension with increased HR (n=1), decreased ABP without hypotension (n=6), decreased ABP with decreased HR (n=1), or increased HR (n=2, the ABP reading could not be obtained in this case). The details of atracurium administration and the observed effects are shown in Table 1. Peri-operatively, either metoclopramide alone (Plasil, Lepetit UK; n=2) or a combination of metoclopramide and ranitidine (Zantac, GlaxoSmithKline UK; n=9) were administered IV in 11 out of 14 rabbits to prevent the occurrence of gastrointestinal disturbances. Anesthesia lasted 180 ± 62 minutes (Table 1). After the completion of each surgery, neostigmine (Neostigmine Methylsulfate Injection, Hameln Pharmaceuticals UK; total dose: 0.02 [0.01-0.045] mg/kg) and glycopyrronium (Glycopyrronium Bromide, Accord Healthcare UK; total dose range: 0.01 [0.01-0.02] mg/kg) were administered simultaneously IM, as soon as at least two out of 4 muscular twitches could be elicited by the nerve stimulator. Twelve out of 14 rabbits received a single dose of neostigmine, which

was 0.01 mg/kg in 10 cases and 0.02 mg/kg in 2 cases. Two of the rabbits that had received 0.01 mg/kg required additional neostigmine to achieve full recovery from the neuromuscular block. Of these two rabbits, one received an additional 0.01 mg/kg 20 minutes after the first dose, while the other received an additional 0.05 mg/kg, followed by doses of 0.01 and 0.02 mg/kg given at 20 minute-intervals. The rectal temperature recorded at recovery was 36.4 ± 2 °C. Despite the continuous use of active warming throughout anesthesia, postoperative hypothermia (rectal temperature < 37.7 ºC)[3] was recorded in 8 out of 14 rabbits. Of these, two rabbits that were severely hypothermic at the end of the anesthetic (rabbit 1 = 30.3°C and rabbit 4 = 33 °C; Table 1), had experienced a decrease in ABP after atracurium administration. One of these two rabbits had the longest anesthetic time (rabbit 1 = 242 minutes; Table 1), while in the other anesthesia lasted 200 minutes (rabbit 4; Table 1). There was no association between the temperature at the end of the anesthetic and the duration of anesthesia (Pearson correlation coefficient = -0.34; P = 0.24). Rabbits 1 and 4 experienced a prolonged recovery characterized by slow increase in body temperature, which reached 37°C after 2 and 3 hours, respectively, after the end of anesthesia.

Food intake was encouraged postoperatively through syringe feeding. Once the rabbits were fully recovered from anesthesia, meloxicam (Metacam, Boerhinger Ingelheim UK; 0.5 mg/kg) was administered IV as post-operative analgesia. Additional buprenorphine (0.02 mg/kg IV) was administered in 5 cases. Long-term complications were not observed.

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Table 1 Details of intra-operative atracurium administration and related cardiovascular effects in 11 out of 14 pet rabbits anaesthetized to undergo ophthalmic surgery

Rabbit	Anesthetic protocol	Total atracurium (mg/kg, IV)	Details of atracurium administration	Agent/ ET range per cent	Duration of anesthesia (minutes)	Cardiovascular effects within 5 minutes from atracurium administration / intra-operative complications	End T (°C)
1	BMKS	0.2	One single dose given at the beginning of surgery	Sevo/ 1.9-3	242	SAP (Doppler) decreased from 105 to 75 mmHg and normalized within 20 minutes HR remained unchanged (180 bpm) Intra-operative hypothermia	33
2	BMAS	0.15	Two doses, of 0.1 and 0.05 mg/kg, given at 40 minute intervals	Sevo/ 3-4.7	200	SAP could not be measured (Doppler) Transient increase in HR (from 230 to above 250 bpm) that lasted 20 minutes after the first atracurium dose (0.1 mg/kg)	38.3
3	BMAS	0.6	Four doses, of 0.2 (n=2) and 0.1 (n=2) mg/kg, given at 20 minute intervals	Sevo/ 2.1-2.9	220	SAP could not be measured (Doppler) Transient increase in HR (from 250 to 320 bpm) that lasted 20 minutes, after the second atracurium dose (0.2 mg/kg) Intra-operative hypothermia	36
4	BMAS	0.5	Five doses (0.1 mg/kg each), given at 20-30 minute intervals	Sevo/ 1.6-2.5	200	SAP (Doppler) decreased from 140 to 115 mmHg, and from 145 to 120 mmHg, after first and second atracurium doses, respectively HR remained unchanged (160 bpm) Intra-operative hypothermia	30.3
5	BMKS	0.65	Three doses (0.3, 0.2 and then 0.15 mg/kg), given at 30-60 minute intervals	Sevo/ 1.8-2.6	180	Intra-operative hypotension: SAP, MAP and DAP (invasive measurement via auricular artery) decreased from 115 to 85, from 90 to 60, and from 50 to 35 mmHg, respectively, and normalized within 20 minutes	35.6

						HR increased from 220 to 240 bpm after the second (0.2 mg/kg) atracurium bolus, normalized within 20 minutes Intra-operative hypothermia	
6	MedBMAS	0.5	Four doses, of 0.2 (n=1) and 0.1 (n=3) mg/kg given at 20-55 minute intervals	Sevo/ 1.9-3.1	120	SAP (Doppler) decreased from 90 to 20, and then from 150 to 115 mmHg, after the first (0.2 mg/kg) and the second (0.1 mg/kg) atracurium boluses, respectively; the hypotension that occurred after the first bolus lasted 25 minutes despite IV fluid resuscitation (10 ml/kg Lactated ringer and 5 ml/kg 4% succinylated gelatin Ringer's solution, IV) and ephedrine administration (0.1 mg/kg IV) HR remained unchanged (180 bpm)	39.1
7	BMAS	0.4	Two doses of 0.2 mg/kg, given at 70 minute intervals	Sevo/ 1.9-3.1	208	SAP (Doppler) decreased from 110 to 90 mmHg after the first atracurium bolus and normalized within 10 minutes HR remained unchanged (200 bpm) Intra-operative hypothermia	36.2
8	MedBMAS	0.5	Four doses, of 0.2 (n=1) and 0.1 (n=4) mg/kg, given at 20-45 minute intervals	Sevo/ 1.9-2.6	190	Intra-operative hypotension: SAP (Doppler) decreased from 95 to 22 mmHg after the first (0.2 mg/kg) atracurium bolus; hypotension lasted 25 minutes despite fluids resuscitation (10 ml/kg Hartmann's solution and 5 ml/kg 6% tetrastarch solution, IV) and ephedrine administration (0.1 mg/kg IV) HR remained unchanged	39.1
9	MedBMAI	0.3	Three doses, of 0.1 mg/kg each,	Iso/ 1.1-1.4	125	Intra-operative hypotension: SAP (Doppler) decreased	36.5

			given at 20-60 minute intervals			from 100 to 60 mmHg after the second atracurium bolus (0.1 mg/kg); hypotension lasted 25 minutes despite IV fluid resuscitation (5 ml/kg Hartmann's solution, IV) and ephedrine administration (0.05 mg/kg IV) HR decreased from 250 to 230 bpm and lasted 25 minutes after the second atracurium bolus Intra-operative hypothermia	
10	MedBMAI	0.6	Five doses, of 0.2 (n=1) and 0.1 (n=5) mg/kg, given at 20-70 minute intervals	Iso/ 1.1-1.9	150	SAP (Doppler) decreased from 90 to 60 mmHg, and from 110 to 90 mmHg, after the first (0.2 mg/kg) and the second (0.1 mg/kg) atracurium boluses, respectively; the effect lasted for 20 minutes after each bolus HR remained unchanged (190 bpm) Intra-operative hypothermia	36.8
11	MedBMAS	0.75	Five doses, of 0.2 (n=2), 0.1 (n=3) and 0.05 mg/kg (n=1), given at 15-40 minute intervals	Sevo/ 2.2-3.1	155	SAP (Doppler) decreased from 150 to 130 mmHg, and from 170 to 70 mmHg, after the first (0.2 mg/kg) and the second (0.1 mg/kg) atracurium bolus, respectively; the effect lasted for 20 minutes after each bolus HR remained unchanged (200 bpm) Intra-operative hypothermia	36

Table legend

B: buprenorphine; M: midazolam; K: ketamine; Sevo: sevoflurane; Iso: isoflurane; A: Alfaxalone; Med: Medetomidine; ET: end-tidal concentration; SAP: systolic arterial pressure; MAP: mean arterial pressure: DAP: diastolic arterial pressure; HR: heart rate; bpm: beats per minute; end T (temperature): rectal body temperature measured at the end of general anaesthesia. Hypothermia and hypotension are defined as SAP < 75 mmHg and rectal temperature < 37.4 ºC (Gallego 2017).

Discussion

The main finding of this retrospective investigation was that the intra-operative administration of atracurium to pet rabbits undergoing ocular surgery resulted in decreased ABP in the majority of the patients, and that this effect, although transient and self-limiting, was in some cases profound and refractory to treatment with fluids and vasopressors. Another interesting finding is that the two most severe episodes of hypotension were observed in rabbits that had received a first, relatively low-dose of atracurium, which supports the assumption that this effect may not be dose-dependent.

In all the 14 rabbits, the observed cardiovascular changes occurred within 5 minutes from the administration of atracurium. Moreover, in 8 of these rabbits the physiological response occurred before the beginning of surgery, when the mechanical stimulation of the eye globe had not started yet, which rules out a possible role of the oculocardiac reflex in causing the decrease in ABP. This supports the hypothesis of a causal, rather than only temporal association between the NMBA and the physiological response.

Atracurium is known to cause vasodilation – and, possibly, hypotension - in various animal species, through release of histamine into the bloodstream.[4] The vasodilation may trigger a baroreceptor reflex, which ultimately results in tachycardia as an attempt of the heart to compensate, and therefore prevent the cardiac output from decreasing critically.[5] Interestingly, in 6 of the 9 rabbits that experienced decrease in ABP after atracurium injection the heart rate remained unchanged and even decreased in one subject. This unusual finding may be explained by the peculiar physiology of the baroreceptor reflex of rabbits, in which hypotension can elicit a complex autonomic response which involves both the sympathetic and the parasympathetic components.[6,7] Clinically, the net result of this complex interaction may be tachycardia, unchanged heart rate, or even bradycardia.

Severe hypothermia was observed in two of the patients of this report. In these two rabbits, both of which had experienced decrease in ABP following atracurium

administration, the rectal body temperature decreased steadily during surgery despite the use of active warming devices and was critically low at the end of the anesthetic. Owing to a large surface area to body mass ratio and a high basal metabolism, rabbits are particularly prone to develop hypothermia during Anesthesia.[8] Inhalational anesthetic agents are known to further contribute to intra-operative hypothermia by inhibiting central thermoregulatory control and by causing arterial and venous vasodilation,[9,10] which facilitates the dissipation of body heat through redistribution of the latter from the body core to the periphery. It is possible that atracurium exacerbated the drop in body temperature leading to severe hypothermia in some cases, by enhancing the vasodilatory effect of the anesthetic gases used.

One recent study demonstrated that rabbits require sevoflurane ET concentrations of 3.9 ± 0.2 to maintain unconsciousness in the absence of nociceptive stimulation.[11] The delivery of sevoflurane and isoflurane in the rabbits of the current investigation was titrated to effect at the discretion of the anesthetist in charge, based on the results of the clinical monitoring of each patient. This resulted in sevoflurane end tidal concentrations that were slightly lower than those reported by Terada and colleagues, a finding that can be explained by the concomitant use of other anesthetic and analgesic drugs that presumably decreased the MAC of sevoflurane.

The choice of timing and dosing of neostigmine to reverse the block was also at the anesthesists' discretion, and different clinicians opted for different doses, within the recommended dose-range, based on the total dose of atracurium received by each rabbit. However, all the anesthesists chose to administer the reversal agent IM, and only when at least two out of 4 twitches were elicited by the nerve stimulator. This is in agreement with the guidelines published for human patients that recommend not to administer neostigmine when the block is still profound.[12]

In conclusion, hypotension and, possibly, hypothermia are likely intra-operative complications when clinical doses of atracurium are administered to pet rabbits. Extra care should be taken in the presence of underlying conditions that may exacerbate the cardiovascular effects of atracurium, namely hypovolemia, compromised cardiac function, high risk of intra-operative haemorrhage and concomitant use of inhalational anesthetic agents.

Ethics approval

The study was conducted under approval of the Social Science Research Ethical Review Board (SSRERB) of the Royal Veterinary College (license number: URN SR 2017-1275). The manuscript (number CSS 01875) was approved for publication by the Vice Principal for Research of the Royal Veterinary College for compliance with Good Research Practice Policy on Publications.

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