Increases in heart rate and systolic blood pressure in anaesthetized dogs affected with X-linked muscular dystrophy after cisatracurium administration: a retrospective study.

Francesco Staffieri, Maria Paula Larenza, Margaret M Sleeper

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The enclosed manuscript has been read and approved by all authors, it is not under active consideration for publication elsewhere, has not been accepted for publication, nor has been published in full or in part (except in abstract form).

Valenzano, 25/09/2010

Dr Francesco Staffieri

Dipartimento dell’Emergenza e dei Trapianti d’Organo, Sezione di Chirurgia Veterinaria, Università degli Studi di Bari, Italy

Prof Sleeper Margaret

Matthew J. Ryan Veterinary Hospital, School of Veterinary Medicine, University of Pennsylvania, PA, USA

Prof Larenza Paula M

Matthew J. Ryan Veterinary Hospital, School of Veterinary Medicine, University of Pennsylvania, PA, USA

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Increases in heart rate and systolic blood pressure in anaesthetized dogs affected with X-linked muscular dystrophy after cisatracurium administration: a retrospective study.

F. Staffieri^{°*}, M. Sleeper[°], M.P.Larenza[°]

[°]Matthew J. Ryan Veterinary Hospital, School of Veterinary Medicine, University of Pennsylvania, PA, USA.

*Dipartimento dell’Emergenza e dei Trapianti d’Organo, Sezione di Chirurgia Veterinaria, Università degli Studi di Bari, Italy.

Corresponding author:

Dr F. Staffieri: Dipartimento dell’Emergenza e dei Trapianti d’Organo, Sezione di Chirurgia Veterinaria, Università degli Studi di Bari, SP per Casamassima km 3 70010, Valenzano, Bari, Italy

f.staffieri@veterinaria.uniba.it

Running title: cisatracurium in X-linked muscular dystrophy

Abstract

Background: Most patients affected with Duchenne muscular dystrophy (DMD) present with arrhythmias and cardiomyopathies. Drugs which potentially may induce tachycardia or hypertension could precipitate acute cardiac failure in these patients and should be avoided.

Methods: Thirty anesthesia records of 5 experimental male golden retriever cross-bred dogs affected with X-linked muscular dystrophy (GRDM) a model of DMD, were retrospectively reviewed (DMD group). Anesthesia records were compared with those of 10 golden retriever dogs not affected with muscular dystrophy (control group). Records were excluded if dogs received anticholinergics or vasoactive amines. Anesthesia was induced with fentanyl followed by propofol, both intravenously. After orotracheal intubation all dogs' lungs were mechanically ventilated. Anesthesia was maintained with and infusion of fentanyl and propofol (DMD group) or isoflurane in oxygen (control group). Pure O₂ was provided to the DMD group. Cisatracurium (0.1 mg kg⁻¹) was administered intravenously to all dogs. Five-min interval recordings of HR and SAP were obtained.

Results: Immediately after the administration of cisatracurium, absolute values for HR and SAP significantly increased by 78.3±37.0 beats minute⁻¹ (115.4±64.9%) and 33.0±28.3 mmHg (33.5±31.2%), respectively, in all DMD dogs, and remained significantly increased for 10 and 30 minutes, respectively. Dogs in the control group did not show significant increases of HR or SAP after cisatracurium administration. All dogs recovered from anesthesia without complications.

Conclusion: In this report, increases in HR and SAP could be associated with the administration of cisatracurium in individuals affected with X-linked muscular dystrophy. These cardiovascular changes deserve further investigation.

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Keywords: X-linked muscular dystrophy, dogs, cisatracurium, heart rate

For Peer Review

Introduction

Duchenne's muscular dystrophy (DMD) is an X-linked disease caused by mutations in the dystrophin gene, resulting in disintegration of the dystrophin glycoprotein complex, instability of the muscle cell membrane and uncontrolled influx of calcium (1). The progressive nature of the disease results in restrictive pulmonary function, multiple contractures, scoliosis and cardiomyopathy. Respiratory insufficiency and cardiomyopathy are predominant factors contributing to early morbidity and mortality (2).

Several animal models for DMD have been investigated in order to test new treatments that improve the quality of life and possibly cure the disorder (3). Among these animal models the golden retriever X-linked muscular dystrophy (GRMD) has been regarded as one of the best suited mammalian models for preclinical therapy and for specific experimental therapeutic approaches such as the use of stem cells or the testing of viral vectors (3). The myocardial involvement is much more evident in GRMD dogs than in other animal models, matching very closely the cardiac complications encountered in DMD patients (4).

It has been recognized that patients with DMD have an increased risk for complications when they undergo general anesthesia (5). In particular the use of the depolarizing muscle relaxant succinylcholine has been absolutely contraindicated because its administration is associated with life-threatening hyperkalemia (6). As cardiac autonomic function is usually altered in patients with DMD, the use of non-depolarizing neuromuscular blockers (NDNMB) with vagolytic actions (i.e. gallamine, pancuronium) should also be avoided as they may induce tachycardia and precipitate cardiac failure. Atracurium, an intermediate-acting benzyliisoquinolinium NDNMB, has been suggested as a good alternative for these patients as it lacks vagolytic actions and undergoes Hofmann's degradation (7). However, research and/or clinical data are missing to support this recommendation.

Therefore, in this context, we would like to report a case series in which cisatracurium, one of the stereoisomers of atracurium, could potentially be linked with increases of heart rate (HR) and blood pressure in a colony of GRMD which were anesthetized on several occasions as part of a translational experimental study.

Materials and Methods

DMD group

The anesthesia records (n = 30) of 5 purpose bred, experimental male golden retriever cross-bred dogs affected with X-linked muscular dystrophy, weighting between 16.3 and 22.5 kg, that underwent general anesthesia for the execution of magnetic resonance imaging (MRI) studies of the heart and hind limbs were retrospectively reviewed. Each dog was anesthetized once a month in the period of time between January 2009 and June 2009 as part of a larger study in which the benefits of gene therapy were investigated. Each dog was investigated before and after the beginning of the gene therapy. Gene therapy was performed between the first and second anesthetic episodes and has been described elsewhere (8) Briefly, the therapy consists of transferring a gene vector, a self complementary adeno-associated virus, with the dogs under general anesthesia and using a percutaneous transendocardial injection catheter under fluoroscopy guidance.

The study had been approved by the University of Pennsylvania Animal Care and Use Committee. Dogs were raised under National Institutes of Health and US department of Agriculture guidelines for the care and use of animals in research. Dogs were fasted for 8 hours (with free access to water) prior to any anesthetic episode. Dogs did not show clinical signs of cardiomyopathy at the time of the scans.

After catheterization of a cephalic vein, general anesthesia was induced in all dogs with an intravenous (IV) administration of 0.010 – 0.012 mg kg⁻¹ of fentanyl (Fentanyl Citrate USP, Hospira, Lake Forest, IL, USA) followed by 3 – 4 mg kg⁻¹ of propofol (PropoFlo, Abbott, Chicago IL, USA). The dog's trachea was intubated with a cuffed silicone tube which was connected to a small animal anesthesia machine via a circle system that was used for oxygen delivery (50 – 100 ml kg⁻¹ minute⁻¹). General anesthesia was maintained with a constant rate infusion (CRI) of propofol (0.1 – 0.2 mg kg⁻¹ minute⁻¹) using a roller pump (Vet-Pro VIP 2000, Caesarea Medical Electronics, Liechtenstein, Germany) and fentanyl (0.5 – 0.7 µg kg⁻¹ minute⁻¹) administered through a second IV catheter placed in the contralateral cephalic vein using a syringe pump (Graseby syringe pump 3400, Smith Medical MD, St. Paul MN, USA) and titrated to maintain an adequate level of anesthesia (absence of jaw tone and palpebral reflex and ventro-medial rotation of the ocular globe). The constant rate infusions were connected to the catheter via a small extension "T" set that had an independent injection port to allow for the intravenous administration of additional drugs without altering the infusion rates of fentanyl or propofol (Microbore extension set with "T" and prepierced injection site, Hospira, Lake Forest IL, USA). All dogs' lungs were mechanically ventilated using a pneumatically driven ventilator with preset volume and flow rate (Nuffield Anaesthesia Ventilator Series 200, Penlon, Abingdon, Oxon, UK). The ventilator was set to deliver a flow rate of 0.25 mL sec⁻¹ with an inspiratory to expiratory ratio (I:E) between 1 : 3 and 1 : 3.5 to achieve a peak inspiratory pressure of 10-15 cmH₂O and a respiratory rate (RR) titrated to maintain an end-tidal partial pressure of carbon dioxide (PetCO₂) between 35 and 45 mmHg. Inspiratory pressures were measured with a manometer built into the ventilator. During the entire anesthetic procedure, all dogs received an infusion of a balanced electrolyte solution (Normosol-R; Hospira, Lake Forest, IL, USA) at an approximate rate of 10 ml kg⁻¹ h⁻¹ delivered by gravity. A continuous lead II ECG, heart rate (HR), systolic blood pressures

(SAP) determined at the level of the radial artery by use of noninvasive oscillometric technology with a 3-minute cycling time, hemoglobin oxygen saturation (SpO₂) measured with a pulse oximeter with the infrared probe placed onto the tongue and PetCO₂ using a side stream probe and infrared technology, were continuously monitored throughout anesthesia with an MRI compatible monitor (Medrad Veris MR patient monitor, Warrendale PA, USA) and recorded every 5 minutes.

In order to improve the quality of the MRI images, a 2 minutes-long apnea was required. A bolus of cisatracurium (0.1 mg kg⁻¹; Nimbex, GlaxoSmithKline Pharma, Research Triangle Park, NC, USA) was administered via the fentanyl infusion line to facilitate apnea that was induced 10 minutes later by switching off the ventilator right before starting the cardiac sequences. To avoid inadvertent administration of fentanyl or delay in the infusion, the cisatracurium was injected as a rapid bolus directly into the intravenous catheter through the injection port of the extension line placed between the catheter and the infusion line. Mechanical ventilation was immediately restored if SpO₂ showed values below 95% and in all cases at end of the cardiac MRI sequence. At the end of the MRI study, the anesthetic agents were discontinued and animals were let to breathe spontaneously. The endotracheal tube was removed when the dogs regained the swallowing reflex. The total anesthesia time from anesthesia induction until removal of the endotracheal tube was also measured and recorded (TimeAnesth).

Control group

In order to create a control group to compare with the GRMDs the anesthesia records of all client owned golden retriever dogs which presented to the Surgery Veterinary Section of the Univeristy of Bari, Italy for elective cataract surgery between January 2007 and Dicember 2010 were retrospectively reviewed. After an initial screening process, the records of 10 male

Golden retriever dogs aged between 5 and 8.2 years old, with a body weight between 16.3 and 25.2 kg and with no clinical signs of being affected with X-linked muscular dystrophy were identified and included in the control group. General anesthesia was induced with IV administration of fentanyl ($0.010 - 0.012 \text{ mg kg}^{-1}$; Fentanest; Pharmacia & Upjohn, Italy) and propofol ($1 - 2 \text{ mg kg}^{-1}$ PropVet 1%; Esteve Hospira Inc, IL, USA) and the dog's trachea was intubated with a cuffed silicone tube. Anesthesia was maintained with a CRI infusion of fentanyl ($0.5 - 0.7 \mu\text{g kg}^{-1} \text{ minute}^{-1}$) and the inhalation of isoflurane (Isoba; Shering-Plough Spa, Italy). Isoflurane was delivered via a circle system using a small animal anesthesia machine, a precision vaporizer set between 1.5 – 2% and oxygen ($0.5 - 1 \text{ L minute}^{-1}$) as the carrier gas. The lungs of the dogs were ventilated using an electronic mechanical ventilator (Aliseo; Datex Ohmeda, Finland) set in volume controlled mode (12 ml kg^{-1}) and with respiratory rate (RR) titrated to maintain normocapnia (PetCO₂ between 35 and 45 mmHg. All dogs included in this group received an infusion of a ringer lactate solution throughout anesthesia ($5 - 10 \text{ mL kg}^{-1} \text{ h}^{-1}$). In addition, dogs received the IV administration of cisatracurium (0.1 mg kg^{-1} ; Nimbex 2; Glaxo Spa, Verona, Italy) 10 minutes before the beginning of the surgery to induce central positioning of the eye and facilitate the surgical conditions. Likewise dogs in DMD group, cardiovascular and respiratory parameters were monitored throughout anesthesia using a multiparameter anesthesia monitor (SC 6002XL; Siemens, MA, USA) and recorded every 5 minutes.

Data analysis and exclusion criteria

The records of anesthetic episodes of either group were excluded from further analysis if cardiovascularly active drugs such as atropine, dopamine, dobutamine or phenylephrine were administered. In order to analyze the changes induced by the administration of cisatracurium on the HR and SAP, the values collected 15 (-15), 10 (-10) and 5 (-5) minutes before and 5

(5), 10 (10), 15 (15), 20 (20), 25 (25) and 30 (30) minutes after the administration of cisatracurium (TimeCIS) were considered for the statistical analysis. The absolute increase or decrease in HR (Δ HR) and SAP (Δ SAP) within 30 minutes after cisatracurium administration was calculated compared to the values at TimeCIS. In order to normalize the data among the different anesthetic episodes Δ HR and Δ SAP were computed as percentage of their absolute values at TimeCIS (Δ HR% and Δ SAP%, respectively). The time (minutes) in which the maximum change in HR and SAP occurred was reported for every anesthetic episode as TimeHR and TimeSAP, respectively.

Statistical analysis

All data were evaluated with descriptive statistics and normal distribution was assessed using the Kolmogorov-Smirnow test. A one-way analysis of variance (ANOVA) for repeated measures followed by a Bonferroni test was used for comparisons of HR and SAP among the study times and between each anesthetic episode of the DMD group. A one-way ANOVA was used to compare the parameters between the control and the DMD group. Non-parametric individual variables were compared among each DMD dog using Friedman's tests followed by Dunnett tests.

Results

DMD group

All dogs recovered successfully from each anesthetic episode. No dog showed SpO₂ values < 95% during the entire anesthetic episode including the 2-minutes long apnea. Of all anesthesia records (n = 30), 7 (one from each dog and another two from dogs 4 and 5) were excluded from statistical analysis. Reasons for exclusion of these records included the

administration of atropine sulfate (n = 5) and/or dopamine (n = 4) during anesthesia to treat bradycardia and/or hypotension that occurred before TimeCIS.

Observed differences for $\Delta\text{HR}\%$ (%), ΔHR (beats minute⁻¹), $\Delta\text{SAP}\%$ (%), ΔSAP (mmHg), Time HR (min), Time SAP (min) were not statistically significant among dogs.

All anesthesia records that met the inclusion criteria showed increases in HR and SAP after the administration of cisatracurium. The HR was significantly higher compared to TimeCIS at 5, 10, 15, 20, 25 and 30 minutes while SAP was significantly higher only at 5 and 10 minutes after TimeCIS (Figures 1 and 2). The average TimeHR and TimeSAP were 10.2 ± 5.3 min and 8.0 ± 2.9 min respectively. At these time points, the mean ΔHR was 78.3 ± 37.0 beats/min, which represented a $\Delta\text{HR}\%$ of $115.4 \pm 64.9\%$ and the mean ΔSAP was 33.0 ± 28.3 mmHg, which represented a $\Delta\text{SAP}\%$ of $33.5 \pm 31.2\%$. Values for PetCO₂ were statistically significantly different from baseline values only at min 15 (Figure 3). Mean anesthesia time was 219.5 ± 16.3 min. No other evaluated physiologic parameter showed statistically significant differences compare with baseline after TimeCIS. All other analyzed parameters in DMD group did not show statistically significant differences among anesthetic episodes.

Control group

All dogs recovery successfully form anesthesia. All anesthesia records met the inclusion criteria. Mean $\pm$ SD values of HR, SAP and PetCO₂ for each evaluated time point are reported in figures 1, 2 and 3. Mean values for HR, SAP and PetCO₂ were comparable between each studied time point. The mean ΔHR was 1.2 ± 0.3 beats minute⁻¹ corresponding to a $\Delta\text{HR}\%$ of $1.4 \pm 0.5\%$ that occurred at a mean TimeHR of 5.2 ± 0.9 minutes. The mean value of ΔSAP was 1.5 ± 0.4 mmHg corresponding to a $\Delta\text{SAP}\%$ of $1.5 \pm 0.2\%$ that occurred at a mean TimeSAP of 10.3 ± 1.2 minutes. All the other evaluated physiological parameters did not show statistically significant difference after TimeCIS.

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Mean values for Δ HR, Δ HR %, Δ SAP and Δ SAP % were statistically significant lower in the control group compared with the DMD group ($P < 0.01$).

Discussion

Intra-anesthetic increases in HR and SAP occur as a response to the activation of the autonomic system and could be induced by several determinants such as nociception, changes in anesthetic depth, hypovolemia, hypercarbia, hypoxemia and administration of anticholinergic and/or adrenergic agents among many others. Nevertheless, in these GRMD dogs, most of these factors were ruled out as potential contributors for the observed effects because dogs were not moved and remained in the same position during the entire procedure, in a closed MRI, at a fairly constant propofol/fentanyl infusion and crystalloid rates, showing values of $SpO_2 > 95\%$, without the administration of vasoactive agents or nociceptive stimuli and having always the same anesthetist performing all anesthetics. Although hypercarbia can cause both, increases in HR and SAP, in the present report the apnea-related increases in $PetCO_2$ probably occurred when discontinuing the ventilator 10 min after the administration of Cisatracurium, as seen in the significantly increased $PetCO_2$ values observed at 15 min. Therefore, it is possible that in the present report these changes in HR and SAP are related with the IV administration of clinically used doses of Cisatracurium. The mild hypercarbia recorded after the apneustic episode may have contributed with the highest values observed for HR and SAP at that point and also with the duration of the increases in HR.

Interestingly, cisatracurium, like gallamine, pancuronium and atropine, behaved in vitro as a type 2 atrial muscarinic receptor (M2) antagonist (9). However, the results of the present study suggest that cisatracurium administration to anesthetized golden retriever dogs with no

signs of being affected with X-linked muscular dystrophy does not affect HR and SAP in the same manner as when equivalent doses are administered to GRMDs. Despite that anesthesia was maintained with different general anesthetics (i.e. propofol vs isoflurane) it is unlikely that the administration of isoflurane to the control group would blunt potential cisatracurium-induced vagolytic responses in this group.. Reports of patients anesthetized with volatile agents or propofol infusions receiving cisatracurium do not associate cardiovascular changes with the administration of this NDNMB (10, 11). In addition, the results of this study are in agreement with previous reports in which cisatracurium was administered to healthy mongrel dogs or dogs of different breeds affected with portosystemic shunt and did affect HR or blood pressure values (9, 12). Similarly, only minor cardiovascular changes were observed in surgical patients not affected with DMD that received 2-5 x ED₉₅ of Cisatracurium (13). In another study in which the cardiovascular effects of Cisatracurium were evaluated in hemodynamically stable patients undergoing cardiovascular bypass, the administration of this NDNMB at a bolus dose of 6-8 x ED₉₅ only caused small decrease in HR and no changes in mean arterial pressure (14).

Another possible factor to consider is the role which gene therapy might have played in the increased autonomic responses observed in the DMD group after cisatracurium administration. The gene treatment was directly injected into the myocardium of these dogs and could have potentially influenced their cardiac autonomic function. However, this hypothesis is improbable considering that the transgene which was used in these GRMDs is not expressed in the nervous system (8). Moreover, the first anesthetic episode was performed before the myocardial injection of the gene vector and the fact that the increases in HR and SAP were comparable among anesthetic episodes, including that very first one, supports the theory that gene therapy was not the reason for the augmented autonomic response observed after cisatracurium administration in the DMD group.

It is recognized that the autonomic system function is affected in patients with Duchenne muscular dystrophy and that the severity of the disease significantly correlates with the impairment of the autonomic function (i.e. significant decrease in parasympathetic activity and a significant increase in sympathetic activity with severe disease) (15). This situation characterizes a variety of arrhythmias typical of both, the early and late phase of the disease (16). Although up-regulation of nicotinic receptors with low affinity for some NDNMBs and prolonged paralysis after administration of NDNMBs have been reported in patients affected with DMD (17) little is known about the autonomic system activity and drug(s) interacting with nicotinic and/or muscarinic receptors in these patients. Therefore, in the present report, it can only be hypothesized that a pre-existing imbalance of the autonomic system and/or an amplified antagonistic effect of Cisatracurium on M2 atrial receptors augmented the sympathetic tone in these GRMD dogs resulting in significantly increased HR and SAP values. Although these increases (115% for HR and 33% for SAP) may be well tolerated in patients with normal myocardial function, they potentially could precipitate acute cardiac failure in patients with severe cardiomyopathies, which are present in 90% of patients affected with DMD (18).

To the authors' knowledge, this is the first report describing significant autonomic responses potentially associated with the administration of cisatracurium in anesthetized subjects affected with X-linked muscular dystrophy. An anecdotal report, described the use of atracurium to facilitate endotracheal intubation in a 12-year boy affected with DMD (7). The absence of vagolysis with atracurium combined with the ability to allow reversal to occur without using neostigmine and atropine was recognized as a significant advantage and atracurium was regarded as the most suitable NDNMB to use in patients with DMD. However, it is suspected that Cis-isomer of atracurium, Cisatracurim, caused the observed increases in HR and SAP in these GRMDs. Therefore, until research and clinical trials

demonstrate its safety, the use of Cisatracurium in DMD patients should be considered with caution.

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For Peer Review

Figure 1.

Figure 2.

Figure 3.

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Figure 1. Mean heart rate and the respective SDs (bars) obtained from anesthetized dogs affected (continuous line) and not affected (interrupted line) with X-linked muscular dystrophy, which received cisatracurium (CIS). * Statistically significantly different compared to the value at CIS within the same group ($P < 0.05$ ANOVA)

Figure 2. Mean systolic blood pressure and the respective SDs (bars) obtained from anesthetized dogs affected (continuous line) and not affected (interrupted line) with X-linked muscular dystrophy, which received cisatracurium (CIS). * Statistically significantly different compared to the value at CIS within the same group ($P < 0.05$ ANOVA)

Figure 3. Mean end-tidal partial pressure of carbon dioxide (EtCO_2) and the respective SDs (bars) obtained from anesthetized dogs affected (continuous line) and not affected (interrupted line) with X-linked muscular dystrophy, which received cisatracurium (CIS). * Statistically significantly different compared to the value at CIS within the same group ($P < 0.05$ ANOVA)

Mean heart rate and the respective SDs (bars) obtained from anesthetized dogs affected (continuous line) and not affected (interrupted line) with X-linked muscular dystrophy, which received cisatracurium (CIS). * Statistically significantly different compared to the value at CIS within the same group (P < 0.05 ANOVA)

256x156mm (72 x 72 DPI)

Mean systolic blood pressure and the respective SDs (bars) obtained from anesthetized dogs affected (continuous line) and not affected (interrupted line) with X-linked muscular dystrophy, which received cisatracurium (CIS). * Statistically significantly different compared to the value at CIS within the same group (P < 0.05 ANOVA)
256x156mm (72 x 72 DPI)

Mean end-tidal partial pressure of carbon dioxide (EtCO₂) and the respective SDs (bars) obtained from anesthetized dogs affected (continuous line) and not affected (interrupted line) with X-linked muscular dystrophy, which received cisatracurium (CIS). * Statistically significantly different compared to the value at CIS within the same group (P < 0.05 ANOVA)

256x156mm (72 x 72 DPI)