

ORIGINAL ARTICLE

Neuromuscular block monitoring after the administration of 1 mg/kg intravenous cis-atracurium in the anaesthetized pig

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Abstract

Neuromuscular blocking agents should be included as part of a balanced anaesthetic protocol to improve anaesthetic management, although doses are not always established for each species. Cis-atracurium is a benzylisoquinolinium neuromuscular blocking agent with an intermediate duration of action devoid of significant adverse effects previously used in pigs with a wide dosage range. Cis-atracurium was administered at 1 mg/kg bolus to sixteen pigs to establish its time profile and effects. The pigs were premedicated intramuscularly with 4 mg/kg azaperone, 8 mg/kg ketamine and 0.2 mg/kg morphine IM and maintained with isoflurane in oxygen. After cis-atracurium administration, neuromuscular monitoring via acceleromyography was started until the recovery of the 90% of the train of four ratio. Complete decrease in the train of four ratio was accomplished in eleven pigs. Onset of action was 70 s, with a recovery of the fourth twitch at 26 min and a recovery of a train of four ratio greater than 90% in 60 min. In conclusion, 1 mg/kg intravenous cis-atracurium in the pig allowed for a rapid onset of action and a complete recovery after 60 min although high variability in the time profile is seen.

KEYWORDS

Cis-atracurium, monitoring, neuromuscular blockade, swine

1 | INTRODUCTION

Pigs are commonly anaesthetized in biomedical research as animal models for a wide variety of procedures. Neuromuscular blocking agents (NMBAs) are an essential part of a balanced anaesthetic protocol, although reports on the drugs are sparse and large differences in doses could be seen (Goebel et al., 2008; Lowalekar et al., 2013; Sereinigg et al., 2012; Veres-Nyéki, Rieben, Spadavecchia, & Bergadano, 2012). The lack of species-specific reports involves the extrapolation of pharmacological data between species (Martin-Flores, Paré, Campoy, & Gleed, 2012). To administer a drug safely, its pharmacological properties, time course of action and possible side-effects should be known (Auer, Mosing, & Moens, 2007). Furthermore, extrapolating neuromuscular blocking agents' pharmacological data between species is risky, because overdosing could increase the

risk of prolonged neuromuscular block and underdosing could lead to difficulties in an accurate anaesthetic and neuromuscular block management.

Cis-atracurium besylate is a benzylisoquinolinium neuromuscular blocking agent with an intermediate duration of action (Lien et al., 1995; Wastila, Maehr, Turner, Hill, & Savarese, 1996). It is obtained from the racemic mixture of the ten stereoisomers of atracurium. Cis-atracurium comprises approximately 15% of the mixture. Cis-atracurium is considered three to five times more potent than a atracurium with a similar duration of block in human patients (Lepage et al., 1996; Smith, Van Miert, Parker, & Hunter, 1997).

Benzylisoquinolinium compounds are associated with histamine release and cardiovascular instability (Lepage et al., 1996; Lien et al., 1995). Atracurium besylate has been associated with histamine release after high doses and rapid intravenous injections, resulting in

TABLE 1 Data definitions for neuromuscular monitoring

Data	Definition
Onset time	Time period from the start of the injection of the neuromuscular blocking agent until the total fade of the four twitches in complete relaxation or the first of three consecutive TOF stimulations with the same amplitude in case of partial blockade
Reappearance of T1	Time period from the injection of the NMBA until the reappearance of the first twitch of the train of four
Reappearance of T4	Time period from the injection of the NMBA until the reappearance of the fourth twitch of the train of four
Moderate neuromuscular block	Time period from the reappearance of T1 to the reappearance of T4
Recovery period	Time period from the reappearance of T4 to the recovery of the 90% in the TOFR
Duration TOFR 25%—clinical effective duration	Time period from the injection of the NMBA to the recovery of a 25% of the TOFR
Duration TOFR 90%—recovery end-point	Time period from the injection of the NMBA to the recovery of a 90% of the TOFR

hypotension and compensatory tachycardia in humans, dogs and cats (Basta et al., 1982; Naguib, Samarkandi, Bakhamees, Magboul, & El-Bakry, 1995; Wastila et al., 1996). Conversely, cis-atracurium has not been associated with adverse cardiovascular effects due to histamine release even after the administration of high doses (Lepage et al., 1996; Lien et al., 1995; Wastila et al., 1996).

The aim of this study was to monitor the neuromuscular function via acceleromyography (AMG) and to establish a neuromuscular block time course of action after the administration of 1 mg/kg intravenous cis-atracurium in anaesthetized experimental pigs.

2 | MATERIALS AND METHODS

2.1 | Animals

The present experimental study was approved by the Animal and Human Experimentation Ethics Committee of the Universitat Autònoma de Barcelona under protocol numbers CEEAH 2621 and DMAH 8232.

Sixteen crossbreed (Landrace × Large White) female pigs were included in the study. The pigs aged from 2 to 5 months old (3.5 ± 1.3 months old; $M \pm SD$) and weighed 39.3 ± 17.1 kg ($M \pm SD$) and ranged from 22 to 69.7 kg. All the pigs included in this study were anaesthetized for cyanoacrylate tissue adhesion testing. Pigs were obtained from the Farm Service in the Universitat Autònoma de Barcelona. The

pigs were housed in a 12-hr light/dark cycle, temperature was maintained between 18 and 22°C, and humidity was maintained between 40% and 60%. Pigs were fed with a commercial flour and water ad libitum.

Food was withheld for 12 hr before the experimental procedure. A complete blood count and a biochemical profile were obtained for each pig prior to anaesthesia.

Pigs were excluded from the study if any abnormality that could affect neuromuscular blockade was seen in the biochemical profile, blood pH or temperature. At the same time, pigs were excluded if significant neuromuscular monitoring data were missing during the experimental procedure.

2.2 | Anaesthetic procedure

Pigs were premedicated intramuscularly with 4 mg/kg azaperone (Stresnil, Esteve, Spain), 8 mg/kg ketamine (Ketamidol, Karizoo, Spain) and 0.2 mg/kg morphine (morphine 2%; B. Braun, Spain) and anaesthetized with 4% isoflurane (IsoVet; B. Braun, Spain) in 100% oxygen via a facemask. An intravenous catheter was placed in the auricular vein, and tracheal intubation was accomplished with an endotracheal tube. Anaesthesia was maintained with 2%–2.5% isoflurane in 100% oxygen.

After intubation, the pigs were positioned in dorsal recumbency. The popliteal artery was catheterized with an arterial catheter kit (Arteriofix, B. Braun VetCare, Spain) to obtain arterial blood samples for arterial blood gas analysis and to monitor the invasive arterial blood pressure. Heart rate, SpO_2 , $EtCO_2$ and oesophageal temperature were also monitored throughout the experimental procedure with a multiparametric monitor (B. Braun VetCare; Spain) and recorded every 10 min. Anaesthesia lasted for 240 min. Mechanical ventilation was initiated after tracheal intubation. Mechanical ventilation was performed in a pressure-controlled mode with a rebreathing circuit, and ventilator settings were established to maintain an $EtCO_2$ between 35 and 45 mmHg (Dräger Fabius Plus; Dräger; Spain). Peak pressures values varied from 12 to 15 cmH₂O, respiratory rate was set from 14 to 18 breaths/min, and inspiratory: expiratory ratio was 1:2–1:3. Central temperature measured in the mid-cervical oesophagus was maintained within 37–39°C via thermoblanquet. Fluid therapy was provided via 0.9% saline (NaCl 0.9%, B. Braun, Spain) administered through the auricular catheter at 5–10 mL/kg/h depending on the arterial blood pressure values. Arterial blood gas analyses were performed from the catheter placed in the popliteal artery right before cis-atracurium administration and at 30, 90 and 240 min with an arterial blood sample analyser (i-STAT 1 Analyser, Abbot Point of Care, Illinois, USA).

2.3 | Neuromuscular monitoring

Acceleromyography (TOF Watch SX, Organon Ltd, Dublin, Ireland) was used to monitor neuromuscular blockade in the pigs.

After the pigs were positioned, the right forelimb was extended horizontally and strapped on a box, to avoid excessive movement of the limb, as described by Madsen et al. (2014). The hoof was allowed to move freely. Once positioned, the limb was shaved, washed and rubbed

with an abrasive material. Skin electrodes were placed on the palmar side of the right forelimb over the ulnar nerve. The proximal electrode was placed 2–3 cm distal from the elbow joint. The distal electrode was placed separated by 4 cm. The acceleration transducer was secured in the hoof with tape, between the two toes. The AMG monitor peripheral temperature sensor was taped near the accelerator transducer to monitor the peripheral temperature in the monitored limb.

Once a stable anaesthetic plane was achieved, the acceleromyographic monitor, TOF Watch SX monitor, was started. Calibration of the monitor, supramaximal stimulation and stable baseline value were performed and obtained following the recommendations described in the “Good clinical research practice in pharmacodynamic studies of neuromuscular blocking agents II: the Stockholm revision” (Fuchs-Buder et al., 2007). After a baseline value was achieved, 1 mg/kg intravenous cis-atracurium (Nimbex, GlaxoSmithKline, Spain) was administered over 5 s via the auricular catheter. The administration dose was based on an unpublished pilot study as an effective dose to achieve 100% decrease in the train of four ratio (TOFR) neuromuscular blockade in the anaesthetized pig. After cis-atracurium administration, neuromuscular function was monitored with a train of four (TOF) pattern every 15 s until the TOFR exceeded 90% during 2 min, which was considered the recovery end-point. All neuromuscular function data were recorded and saved in a computer using the TOF Watch SX computer software (TOF Watch SX Monitor version 2.5; Organon Ltd., Ireland). The software allowed registering the height of each one of the four TOF twitches (T1, T2, T3 and T4), the TOFR count and the peripheral temperature. After recording, all data were analysed to obtain the parameters to establish the time course of the neuromuscular block (Table 1).

Weight, blood pH and the neuromuscular function data are expressed as median (range). Cardiovascular values, temperature, end-tidal carbon dioxide and partial pressure of carbon dioxide are expressed as $M \pm SD$.

3 | RESULTS

Pigs weighed 39.3 (22.0–69.7) kg. Blood pH was 7.44 (7.41–7.45). Central oesophageal and peripheral temperature, end-tidal carbon dioxide and partial pressure of carbon dioxide values are shown in Table 2. Heart rate (HR) and systolic (SAP), mean (MAP) and diastolic (DAP) arterial blood pressure values are presented in Figure 1.

Thirteen pigs were included in the neuromuscular blocking profile analysis after cis-atracurium administration. Three pigs were excluded from the study because of incomplete data record. A complete fading of the four twitches with a 100% decrease in the TOFR (TOFR = 0%) count was achieved in eleven of thirteen pigs (85%). Two of the pigs (15%) maintained the first TOF twitch (T1) after cis-atracurium administration.

The onset time for cis-atracurium was 70 (41–170) s. The duration of moderate neuromuscular block was 7 (5–9 min) with a re-appearance time of T1 of 18 (12–28) min and a re-appearance time of the fourth twitch (T4) of 26 (18–36) min. The recovery period, as defined from the re-appearance of T4 to the recovery of a TOFR 90%,

TABLE 2 Arterial blood pH, central and peripheral temperatures, end-tidal carbon dioxide values (EtCO_2) and arterial partial pressure of oxygen (PaCO_2) values during anaesthetic monitoring after the administration of 1 mg/kg intravenous cis-atracurium in the pig

Pig number	1	2	3	4	5	6	7	8	9	10	11	12	13
Parameter													
pH	7.40 (7.40–7.52)	7.41 (7.38–7.45)	7.42 (7.37–7.47)	7.45 (7.40–7.48)	7.44 (7.41–7.46)	7.44 (7.41–7.46)	7.42 (7.37–7.45)	7.43 (7.38–7.44)	7.42 (7.41–7.44)	7.44 (7.40–7.50)	7.50 (7.43–7.52)	7.41 (7.39–7.49)	7.46 (7.44–7.51)
Central temperature (°C)	38.3 ± 0.3	37.7 ± 0.6	38.1 ± 0.3	37.1 ± 0.8	37.1 ± 0.9	37.9 ± 0.4	37.2 ± 0.1	37.6 ± 0.7	37.0 ± 0.3	36.9 ± 0.7	37.2 ± 0.7	37.4 ± 0.5	37.1 ± 0.7
Peripheral temperature (°C)	36.6 ± 0.2	36.3 ± 0.5	36.4 ± 0.2	35.5 ± 0.3	35.5 ± 0.4	36.2 ± 0.3	36.5 ± 0.4	35.9 ± 0.1	36.3 ± 0.2	36.7 ± 0.1	36.3 ± 0.3	35.9 ± 0.7	36.4 ± 0.2
EtCO_2 (mmHg)	40 ± 5	42 ± 4	42 ± 3	45 ± 3	43 ± 1	44 ± 3	39 ± 3	41 ± 4	42 ± 2	45 ± 2	37 ± 3	39 ± 3	40 ± 4
PaCO_2 (mmHg)	50.3 ± 7.7	46.3 ± 6.3	46.6 ± 2.8	53.1 ± 4.1	48.1 ± 1.8	41.1 ± 12.7	50.3 ± 5.2	50.3 ± 2.9	44.8 ± 11.7	48.4 ± 7.4	42.6 ± 8.2	50.0 ± 7.7	47.6 ± 3.8

Arterial blood pH is presented as median (range). Central and peripheral temperatures, EtCO_2 and PaCO_2 are presented as $M \pm SD$.

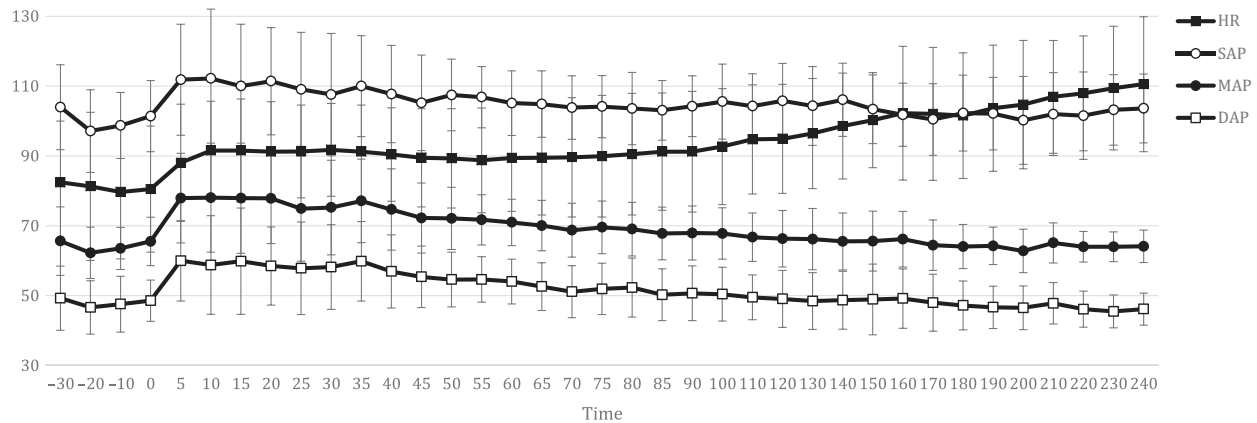


FIGURE 1 $M \pm SD$ values for heart rate and systolic, mean and diastolic arterial blood pressure before and after the administration of an intravenous 1 mg/kg cis-atracurium bolus. Heart rate is expressed as beats/min. Systolic, mean and diastolic arterial blood pressures are expressed as mmHg

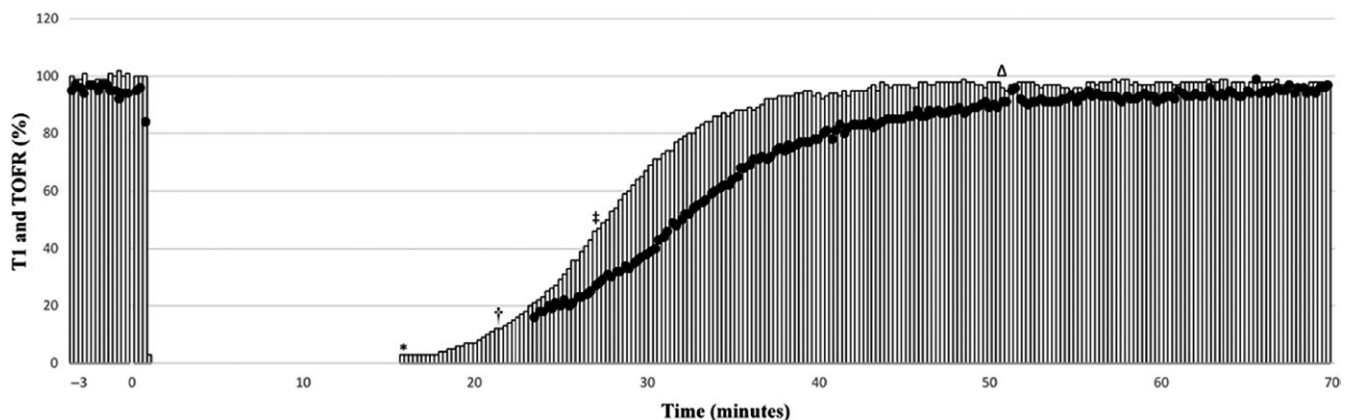


FIGURE 2 Evolution of the neuromuscular blockade monitoring in a pig before and after cis-atracurium administration. Magnitude of the first twitch (T1) heights (bar graph) and train of four ratio (TOFR) values (black dots). * Recovery of T1. † Recovery of T4. ‡ Recovery of a TOFR of $\geq 25\%$. Δ Recovery of a TOFR of $\geq 90\%$

was 28 (8–68) min. The time to a recovery of a TOFR 25% was 30 (18–38) min. The time from injection to the recovery of TOFR 90% was 60 (32–94) min. Figure 2 shows the neuromuscular blocking profile of cis-atracurium in one pig as well as the main recovery points. All the thirteen pigs included in the study recovered uneventfully from cis-atracurium neuromuscular blockade.

4 | DISCUSSION

This study reports the neuromuscular blockade time course of action after a single intravenous bolus of 1 mg/kg of cis-atracurium in experimental pigs.

Objective monitoring of the neuromuscular blockade should be mandatory to improve postoperative outcomes and diminish complications such as residual curarization or upper airway obstruction, due to the high variability seen in NMBA's time profile. AMG is, nowadays, one of the most used methods in neuromuscular blockade monitoring, although mechanomyography is still considered the

gold standard (Fuchs-Buder, Schreiber, & Meinstelman, 2009). In the present study, AMG was used to establish the time profile of cis-atracurium in the pig due to its ease of use for research purposes obtaining objective and repeatable measurements (Madsen et al., 2014). The recovery point was fixed in a TOFR $\geq 90\%$ to avoid postanaesthetic complications and allow for a full recovery of the laryngeal muscles as recommended in human medicine (Fuchs-Buder et al., 2007).

The ulnar nerve was used for electrical stimulation as described by Madsen et al. (2014). This monitoring site allowed for repeatable measurements without the possibility of inadvertent movements of the limb as it was fixed in a box. However, other monitoring sites have been described in the pig, such as the peroneal nerve (Tutunaru et al., 2017).

Cis-atracurium has been administered in experimental pigs as part of a balanced anaesthetic technique in several experimental procedures with doses ranging from 0.2 to 15 mg/kg (Goebel et al., 2008; Lowalekar et al., 2013; Sereinigg et al., 2012). That variation in cis-atracurium doses could lead to suboptimal effects or increases in

neuromuscular blockade and the occurrence of postoperative complications. Our objective was to study the time profile and effects of 1 mg/kg cis-atracurium and to test its effectiveness in the pig.

The dose used in the present study was established from an unpublished pilot study in which different doses of cis-atracurium were tested in order to achieve a total fade of the four TOF twitches with a TOFR of 0% via AMG. Each dose was tested in two different pigs. Doses of 0.5, 0.7, 0.85 mg/kg failed to reach the objective, whereas 1 mg/kg cis-atracurium intravenous dose decreased the TOFR to 0% in the two pigs tested. However, during the realization of the study, a total decrease in the TOFR was not achieved in all the pigs tested. Two of thirteen pigs maintained the first TOF twitch after cis-atracurium administration. At the same time, wide variations are seen in neuromuscular blocking course of action. Onset time and moderate neuromuscular block duration show little differences between pigs. On the other hand, wide differences are seen in the recovery period, that ranged from 8 to 68 min, and the time to a recovery of a TOFR $\geq$ 90%, which ranged from 32 to 94 min. Neuromuscular blockade could be affected by factors including anaesthetics and physiologic variables such as temperature or pH (Clutton, 2007). Inhalants could increase the intensity and duration of the neuromuscular blocking effects of NMBAs (Kastrup et al., 2005; Wulf, Kahl, & Ledowsky, 1998) while injectable anaesthetics do not seem to affect neuromuscular blockade (Kastrup et al., 2005). However, in the present study, isoflurane was used as the maintenance anaesthetic in all the animals. Inhaled isoflurane concentrations were adjusted between 2% and 2.5% to maintain a stable anaesthetic plane before cis-atracurium administration and during all the procedure. Isoflurane was used in the present study as it has been demonstrated to not affect significantly the duration and recovery of cis-atracurium in human patients in contrast to sevoflurane and desflurane (Wulf et al., 1998). However, end-tidal isoflurane concentrations could not be measured during the present study and these could have influenced to some extent in the duration and recovery times of neuromuscular blockade.

Body temperature and arterial blood pH were controlled during the whole procedure. Cis-atracurium is degraded through Hofmann elimination depending on body temperature and pH. Hypothermia and acidosis decrease the elimination rate, increasing the duration of cis-atracurium blockade (Kisor et al., 1996). Simultaneously, it is important to measure and control peripheral temperature as low temperatures at the monitoring site could influence the muscular contraction strength, increasing indirectly the duration of the neuromuscular blockade (Heier, Caldwell, Sessler, Kitts, & Miller, 1989; Thornberry & Mazumdar, 1988). In human medicine, core temperatures should be maintained above 36°C while peripheral temperatures should be always above 32°C to avoid neuromuscular monitoring interferences (Heier et al., 1989; Thornberry & Mazumdar, 1988). In the present study, central temperature was measured in the oesophagus and maintained between 37 and 39°C, as normal temperature in pigs is higher than humans' temperature. At the same time, peripheral temperatures were maintained above 35.5°C, maintaining a maximum difference between peripheral and

central temperature of less 4°C following the above-mentioned studies in human medicine.

Alternatively, it has been reported an important influence of individual variation in neuromuscular blockade in people and dogs after the administration of vecuronium, atracurium, rocuronium and cis-atracurium (Adams, Robinson, Senior, & Jones, 2001; Clutton, 2007; Dabaene, Plaud, Dilly, & Donati, 2003; Varposhti, Heidari, Safavi, Honarmand, & Raeesi, 2011; Yamamoto, Uchida, Yamamoto, Ito, & Makita, 2011). In dogs, cis-atracurium duration of action ranged from 5 to 50 min after a single 0.1 mg/kg dose. Yamamoto et al. (2011) also showed that even though the majority of patients recover from rocuronium blockade within 1 hr from the last administration, more than one-third of the patients needed from 1 to 2 hr to recover from neuromuscular blockade. Even more, Claudius, Skovgaard, and Viby-Mogensen (2010) studied the arm-to-arm variation in neuromuscular monitoring in the same patients using acceleromyography under controlled procedures. Interestingly, they found differences in NMB recovery between arms. While one of the arms recovered a TOFR $>$ 90%, the time to reach the same TOFR in the other arm could be prolonged by 20% or more. Even though this individual variation is reported in the literature, the details of its importance and the reason why it affects neuromuscular blockers to that extent are sparse. Some authors tried to explain individual variation due to differences in drug disposition and pharmacokinetics (Adams et al., 2001). Cis-atracurium pharmacokinetics were measured for every pig (results presented in a different manuscript); however, no association was seen between pharmacokinetics and neuromuscular blockade duration. Other causes of individual variation in neuromuscular blockade recovery include electrolytic imbalances and pathologies such as myasthenia gravis (Clutton, 2007). In the present study, a complete biochemical profile was performed on every pig and no signs of neuromuscular disease were appreciated in any pig. Finally, as demonstrated by Claudius et al. (2010), an arm-to-arm variation in neuromuscular blockade recovery of more than 20% was seen in human patients. However, they are not able to explain why these variations were present, although they suspect about some differences in physiological characteristics of the arms. In the present study, the right forelimb was used for neuromuscular monitoring. It could be possible that a similar effect could have played an important role during neuromuscular monitoring and some pharmacodynamic differences could be explained due to a limb or monitoring site effects. Nevertheless, more studies should be performed to explain how this individual variation affects the neuromuscular blockade duration.

Some studies in the literature have reported an increase in arterial pressure and heart rate after cis-atracurium administration. Jurado, Mosing, Kutter, Boretti, and Bettschart-Wolfensberger (2012) observed increases in heart rate and mean arterial blood pressure in a dog after a cis-atracurium overdose. Staffieri, Sleeper, and Larenza (2011) also observed increases in arterial blood pressure and heart rate in dogs affected by X-link muscular dystrophy. In the present study, increases in HR and arterial blood pressure were seen 5 min after cis-atracurium administration in the pig. Cis-atracurium

is now known to have antagonistic effects on M2 muscarinic receptors (Sanches Bornia, Bando, Machinski, Pereira, & Alves-Do-Prado, 2009; Staffieri et al., 2011). These effects on M2 receptors could result in increases in heart rate and arterial blood pressure if high doses of cis-atracurium are administered. Jurado et al., 2012 observed an increase in heart rate and arterial blood pressure when four boluses of 0.1 mg/kg cis-atracurium were administered to a dog, achieving a final dose of 0.4 mg/kg. In the present study, doses of 1 mg/kg cis-atracurium were needed to achieve a complete decrease in the TOF count and TOFR in the pigs. Compared to other cis-atracurium studies in the pig, where the neuromuscular blockade end-point was to achieve a decrease in TOF count to ≤ 2 twitches, the dose administered in the present study was up to three times higher (Tutunaru et al., 2017). These high doses may increase the possibility that cis-atracurium acts on M2 receptors and affects cardiovascular values. Nevertheless, heart rate and arterial blood pressure values were always within normal limits, and the changes were not considered clinically important. However, further research should be performed to assess the cardiovascular effects of cis-atracurium in the pig.

Finally, no signs of histamine release were observed after cis-atracurium injection in the pigs. Signs of histamine release include a decrease in arterial pressure with an increase in heart rate (Lien et al., 1995; Wastila et al., 1996), erythema and bronchospasm (Lepage et al., 1996; Naguib et al., 1995). These results agree with other reports in which no histamine release was found after cis-atracurium injection (Lepage et al., 1996; Wastila et al., 1996). Nevertheless, histamine concentrations should be measured in future studies to confirm these observations.

In conclusion, the administration of 1 mg/kg intravenous cis-atracurium in the pig allows for a rapid onset of neuromuscular blockade with a TOFR depression greater than 97% and a recovery of 90% of the TOFR of 60 min although great variability is seen between pigs.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

5 | AUTHOR CONTRIBUTION

AAg designed the study; prepared the experimental process, data acquirement and analysis; and drafted the manuscript. XM designed the study and prepared the experimental process and manuscript revision. FG interpreted the results and involved in manuscript preparation and revision. AAn designed the study and involved in manuscript revision and final draft acceptance.

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