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RESEARCH PAPER

Speed of reversal of vecuronium neuromuscular block with different doses of neostigmine in anesthetized dogs

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Abstract

Objectives Neostigmine is routinely used to reverse non-depolarizing neuromuscular block. Given its indirect mechanism, a plateau may exist whereby increasing doses of neostigmine do not result in clinical benefit. This study was designed to measure the speed of reversal of vecuronium-induced neuromuscular block in isoflurane-anesthetized dogs after the administration of three doses of neostigmine as used in clinical practice.

Study design Prospective, crossover, randomized study.

Animals Seven adult, mixed-breed dogs with a mean ± standard deviation (SD) age of 2.0 ± 0.8 years and weight of 19.1 ± 9.1 kg.

Methods Dogs were anesthetized on three occasions with isoflurane and administered vecuronium (0.1 mg kg^{-1}) intravenously (IV). The train-of-four (TOF) ratio was measured on the pelvic limb with acceleromyography. When the second twitch of the TOF had returned spontaneously, atropine (0.03 mg kg^{-1}) and neostigmine (0.02, 0.04 or 0.07 mg kg^{-1}) were administered IV. Time to reach a TOF ratio of ≥0.9 after neostigmine administration was recorded.

Results Increasing the dose of neostigmine from 0.02 mg kg^{-1} to 0.04 mg kg^{-1} and 0.07 mg kg^{-1} resulted in significant reductions in mean ± SD reversal times (10.5 ± 2.3, 7.4 ± 1.1 and 5.4 ± 0.5 minutes, respectively) ($p < 0.0001$) and smaller coefficients of variation (22%, 15% and 10%, respectively).

Conclusions and clinical relevance Increasing the dose of neostigmine from 0.02 mg kg^{-1} to 0.04 mg kg^{-1} and 0.07 mg kg^{-1} produced faster and less variable reversal of vecuronium-induced neuromuscular block in isoflurane-anesthetized dogs. No ceiling effect was observed at this dose range.

Keywords acceleromyography, cholinesterase inhibitor, neostigmine, neuromuscular, train-of-four, vecuronium.

Introduction

Acetylcholinesterase (AChE) inhibitors such as neostigmine are used routinely to enhance the speed of recovery from non-depolarizing neuromuscular block and reduce the risk for residual paralysis. Inhibition of AChE enzymes allows endogenous acetylcholine (ACh) to accumulate in the body. The increasing concentration of ACh competes with the neuromuscular blocking agent (NMBA) for nicotinic cholinergic receptors in the neuromuscular junction, thereby curtailing the action of the NMBA and restoring neuromuscular transmission.

In different studies, and under various circumstances, neostigmine doses ranging from 0.0125 to

0.2 mg kg^{-1} have been used to reverse different non-depolarizing NMBAs in dogs (Jones 1990; Adams et al. 2006; Lorenzutti et al. 2014). Theoretically, increasing the dose of neostigmine will inhibit more AChE molecules, thus allowing the concentration of endogenous ACh to rise more rapidly and neuromuscular block to be reversed more quickly. However, because neostigmine has an indirect mechanism of action, its effects may reach a plateau at which, once the maximal AChE inhibitory effect has been attained, larger doses of neostigmine will have no additional effect on the speed of recovery as the local concentration of ACh cannot increase any further. It is not known whether that plateau may be reached with commonly used doses of neostigmine. In this study, the speed of reversal of vecuronium-induced neuromuscular block was measured in anesthetized dogs after the administration of three doses of neostigmine. The study was based on the hypothesis that, when administered at equal levels of neuromuscular block, increasing doses of neostigmine would result in shorter recovery times.

Materials and methods

This experiment was approved by the Committee of Bioethics and Animal Welfare of Villa María National University, Argentina. Seven adult, mixed-breed dogs (two intact males, five intact females) with a mean ± standard deviation (SD) age of 2.0 ± 0.8 years and weight of 19.1 ± 9.1 kg were included in this randomized crossover study. Each dog was anesthetized on three occasions, at least 1 week apart. On each occasion, the effects of one of three doses of neostigmine were studied (0.02, 0.04 or 0.07 mg kg^{-1}). The order in which the doses were administered was selected randomly by removing labels from an opaque envelope.

Food was withheld overnight and water was withheld for 2 hours prior to anesthesia. The dog was sedated with acepromazine (0.05 mg kg^{-1}; Acedan; Holliday-Scott SA, Argentina) and morphine (0.5 mg kg^{-1}; Amidiaz; Laboratorios Richmond, Argentina) administered intramuscularly (IM). General anesthesia was induced with propofol (Diprivan; AstraZeneca SA, Argentina) administered intravenously (IV) through a cephalic vein catheter until the palpebral and laryngeal reflexes were lost. Then, the trachea was intubated with a cuffed orotracheal tube. Anesthesia was maintained with isoflurane (Forane; Abbott Laboratories Argentina SA, Argentina) in oxygen (2 L $minute^{-1}$) delivered through a circle system. The isoflurane vaporizer was adjusted to 1.0–1.5% based on a clinical assessment of the depth of anesthesia and to avoid purposeful movement in response to neuromuscular monitoring. The lungs were mechanically ventilated (Máquina de Anestesia Veterinaria L1220; Leistung Ingeniería Srl, Argentina) to an end-tidal carbon dioxide tension of 35–45 mmHg (4.6–6.0 kPa). Monitoring included electrocardiography, pulse oximetry, oscillometric arterial blood pressure measurements (obtained every 5 minutes using a cuff of width approximating to 40% of the limb circumference placed on the antebrachium), capnography, and esophageal temperature measurements (Monitor Multiparamétrico; Feas Electrónica SA, Argentina). Heart rate (HR) was obtained from a lead II electrocardiogram. Heated blankets were applied to maintain esophageal temperature at 36–38 °C.

Neuromuscular function was measured at the pelvic limb with acceleromyography (AMG). The dog was positioned in left lateral recumbency and the right pelvic limb was supported parallel to the surgical table to allow the tarsus to flex freely and without opposition during nerve stimulation. Two 21 gauge hypodermic needles were placed subcutaneously over the peroneal (common fibular) nerve as it crosses the lateral head of the gastrocnemius muscle, lateral to the femorotibial joint. The needles were connected to the AMG monitor [TOF-Watch; Organon (Ireland) Ltd, Ireland] and train-of-four (TOF) stimulation was delivered every 15 seconds (60 mA, 2 Hz, pulse duration 0.2 ms). The acceleration-sensitive crystal was taped over the dorsal aspect of the paw to measure the peak acceleration of the evoked tarsal flexion, and the TOF ratio (T4:T1) was calculated. The AMG monitor was calibrated, and after at least 15 minutes of TOF stimulation, complete neuromuscular block was induced by IV administration of vecuronium (0.1 mg kg^{-1}; Vecuron; Scott Cassara, Argentina).

Initially, recovery from neuromuscular block was allowed to occur spontaneously. Neuromuscular function was monitored every 15 seconds until the second twitch (T2) of the TOF could be observed (visually). At that time, atropine (0.03 mg kg^{-1}; Klonatropina; Klonal Laboratorios, Argentina) was administered IV and immediately followed by the assigned dose of neostigmine (Neostigmina; Surar Pharma SA, Argentina) injected IV over 5 seconds. The TOF ratio was then recorded every minute until it reached a value of ≥0.9. The period between

