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SHORT COMMUNICATION

Effects of continuous intravenous infusion of morphine and morphine-tramadol on the minimum alveolar concentration of sevoflurane and electroencephalographic entropy indices in dogs

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Abstract

Objective To compare the effects of continuous rate infusions (CRIs) of intravenous (IV) morphine and morphine-tramadol on the minimum alveolar concentration (MAC) of sevoflurane, and on electroencephalographic entropy indices in dogs.

Design Prospective study.

Animals Eight young, healthy German shepherds, weighing 26.3 ± 3.1 kg (mean ± SD).

Methods Anaesthesia was induced and maintained with sevoflurane. A standard tail-clamp technique was used for MAC determination. Within one anaesthetic period, MAC was first determined during sevoflurane anaesthesia alone (MAC_B); then during morphine infusion (MAC_M), (loading dose 0.5 mg kg^{-1}IM; CRI, 0.2 mg kg^{-1} $hour^{-1)}$ then finally during morphine-tramadol infusion (tramadol loading dose 1.5 mg kg^{-1}IV; CRI, 2.6 mg kg^{-1} $hour^{-1}$) (MAC_{MT}). At each change, periods of 45 minutes were allowed for equilibration. Stated entropy (SE), response entropy (RE), and RE-SE differences were measured five minutes prior to and during tail clamping.

Results The MAC_B was 2.1 ± 0.3vol%. The morphine and morphine-tramadol infusions reduced MAC to 1.6 ± 0.3vol% and 1.3 ± 0.3vol%, respectively. MAC was decreased below baseline more during morphine-tramadol than during morphine alone (39 ± 9% *versus* 25 ± 6%, respectively; $p = 0.003$). All SE and RE and most RE-SE differences were increased significantly ($p < 0.05$) over pre-stimulation in all groups when the dogs responded purposefully to noxious stimulation. When no response to noxious stimulation occurred, the entropy indices did not change.

Conclusion and clinical relevance In dogs, combined morphine-tramadol CRI decreased sevoflurane MAC more than morphine CRI alone. Entropy indices changed during nociceptive responses in anaesthetized animals, suggesting that entropy measurements may be useful in determining anaesthetic depth in dogs.

Keywords dog, entropy, minimum alveolar concentration, morphine, sevoflurane, tramadol.

Introduction

The administration of morphine decreases the minimum alveolar concentration (MAC) of inhalational anaesthetics and intravenous (IV) infusion of morphine reduces the MAC of isoflurane by up to 48% in dogs (Muir et al. 2003). The efficacy of sevoflurane MAC-sparing effects of morphine infusion has not

yet been reported in dogs. Tramadol, a synthetic opiate analgesic structurally related to morphine and codeine, has a weak affinity for μ-opioid receptors and inhibits the re-uptake of both norepinephrine and serotonin in the central nervous system (Grond & Sablotzki 2004). This drug has sevoflurane MAC-sparing effects in dogs (Seddighi et al. 2009; Itami et al. 2013).

Entropy is a relatively new method of electroencephalogram (EEG) signal processing for monitoring anaesthetic depth in humans, based on the fact that anaesthesia diminishes brain neuronal activity and electroencephalographic activity (March & Muir 2005). To date, however, there are limited studies that have evaluated the ability of spectral entropy to determine anaesthesia depth or to assess the analgesic and anaesthetic effects of drugs in dogs (Otto 2008; Morgaz et al. 2011). The present study was designed to compare the effects of continuous rate infusions (CRIs) of IV morphine and of morphine-tramadol on sevoflurane MAC, and, at the same time, evaluate the ability of spectral entropy to assess depth of anaesthesia of sevoflurane in dogs.

Materials and methods

This study was approved by the Kasetsart University Animal Care and Use Committee (ID number ACKU 03256).

Animals

Eight healthy German shepherd dogs (four males and four females) were enrolled in the study. The dogs weighed (mean ± SD) 26.3 ± 3.1 kg and were 1–1.5 years old. Food was withheld overnight prior to the experiment. Each dog was anaesthetized on one occasion only, during which time the experimental protocol outlined below was performed.

Anaesthesia and general monitoring

Anaesthesia was induced with sevoflurane (Sevorane; Aesica Queenborough Limited, UK), delivered by face-mask. Once anaesthetized, and following endotracheal intubation (internal diameter, 9–10 mm) the dogs were connected to an-F circuit and sevoflurane in oxygen (2 L minute^{-1}) was administered to maintain anaesthesia from a G.E. Datex-Ohmeda Aespire100 anaesthetic machine (Datex-Ohmeda Inc., WI, USA). Dogs were positioned in left lateral recumbency. Ventilation was controlled to maintain the end-tidal carbon dioxide partial pressure between 35 and 45 mmHg (4.7 and 6 kPa). A 20-gauge (2.5 cm) catheter (Becton Dickinson Infusion Therapy System Inc., UT, USA) was inserted into a cephalic vein for infusion of lactated Ringer's solution (A.N.B. Laboratories Co., Ltd., Thailand) at 5 mL kg^{-1} hour^{-1}. Heart rate and rhythm, oesophageal temperature, pulse oximetry (SpO_2), and invasive femoral artery blood pressure (via a 20-gauge (2.5 cm) catheter in a femoral artery) were monitored continuously using a multiparameter physiological monitor (Datex-Ohmeda CARESCAPE Multifunctional Anaesthesia Monitor; GE Healthcare, Finland). A circulating warm-water blanket (Soarmed Medical-Tech Co., Ltd., Taiwan) and hot air (Breeze; Laboratorios Cair S.L., Spain) were used to maintain a normal body temperature (37.8–38.9 °C).

Respiratory rate, end-tidal sevoflurane concentration ($F_E'SEVO$), and end-tidal CO_2 ($P_E'CO_2$) were measured using a Drager Vamos Plus infrared gas analyser (Drager Medical, Germany). Gas samples were obtained at a rate of 150 mL minute^{-1} via a catheter placed inside the endotracheal tube at the level of the carina. At the start of each experiment, the gas analyser was calibrated with standard gases (1% sevoflurane in 5% CO_2 and 70% N_2O), supplied by the manufacturer (Air Liquide Healthcare America Corporation, PA, USA).

Study protocol

A period of 45 minutes of sevoflurane anaesthesia was allowed for equilibration. MAC_B (MAC of sevoflurane) was then determined. Following this determination, dogs received an intramuscular loading dose of 0.5 mg kg^{-1} morphine (M&H Manufacturing Co., Ltd., Thailand) followed by a CRI of at 0.2 mg kg^{-1} hour $^{-1}$. A period of 45 minutes equilibration was allowed, then MAC of sevoflurane with morphine (MAC_M) was determined. With the morphine CRI continuing, the dogs then received an IV loading dose of 1.5 mg kg^{-1} tramadol (Harson Laboratories, India) followed by a CRI of 2.6 mg kg^{-1} hour^{-1}, and after a further 45 minute period of equilibration, the MAC of sevoflurane in combination with morphine and tramadol (MAC_{MT}) was determined. A flow-chart of the experimental protocol is provided in supporting information (Fig. S1). Sevoflurane and CRIs were discontinued at the end of the study and dogs were taken to a postoperative recovery ward and allowed to recover.