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RESEARCH PAPER

The influence of a continuous rate infusion of dexmedetomidine on the nociceptive withdrawal reflex and temporal summation during isoflurane anaesthesia in dogs

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Abstract

Objective To examine the influence of a low dose dexmedetomidine infusion on the nociceptive withdrawal reflex and temporal summation in dogs during isoflurane anaesthesia.

Study design Prospective experimental blinded cross-over study.

Animals Eight healthy mixed breed dogs, body weight Mean ± SD 26.5 ± 8.4 kg and age 25 ± 16 months.

Methods Anaesthesia was induced with propofol and maintained with isoflurane (F_E'ISO 1.3%) delivered in oxygen and air. After stabilization, baseline recordings (time 0) were obtained, then a dexmedetomidine bolus (1 μg kg^{-1} IV) followed by a continuous rate infusion (1 μg kg^{-1} $hour^{-1}$) or saline placebo were administered. At times 10, 30 and 60 minutes after the initial bolus, electrical stimulations of increasing intensity were applied over the lateral plantar digital nerve, and administered both as single and as repeated stimuli. The resulting reflex responses were recorded using electromyography. Data were analysed using a multivariable linear regression model and a Kruskal Wallis test for single stimulation data, and repeated measures ANOVA and paired *t*-test for repeated stimulation data.

Results The AUC for the stimulus-response curves after single stimulation were similar for both treatments at time 0. At times 10, 30 and 60 the AUCs for the stimulus-response curves were significantly lower with dexmedetomidine treatment than with placebo. Temporal summation was evident in both treatments at times 0, 10, 30 and 60 starting from a stimulation intensity of 10 mA. The magnitude of temporal summation was smaller in dexmedetomidine than in placebo treated dogs at time 10, 30 and 60, but not at time 0.

Conclusions During isoflurane anaesthesia, low dose dexmedetomidine suppresses the nociceptive reflex responses after single and repeated electrical stimulation.

Clinical relevance This experimental study confirms previous reports on its peri-operative efficacy under clinical conditions, and further indicates that dexmedetomidine might reduce the risk of post-operative chronic pain development.

Keywords dexmedetomidine, dogs, isoflurane, NWR, temporal summation.

Introduction

Pain caused by surgical interventions is common in small animal patients. During general anaesthesia the conscious perception of pain is prevented; however most general anaesthetics will not abolish nociceptive processing in the central nervous system. The use of one or more antinociceptive drugs during anaesthesia reduces the amount of general anaesthetics needed, and may contribute to reducing post operative pain (Lamont 2008).

The highly selective alpha-2-receptor agonist dexmedetomidine is the pharmacologically active enantiomer of medetomidine, and has well recognized sedative and analgesic properties (Sabbe et al. 1994; Kuusela et al. 2000; Murrell & Hellebrekers 2005; Granholm et al. 2007; Wegner et al. 2008). Due to its pharmacological profile, it has potential for use as a low-dose constant rate infusion (CRI) in order to provide peri-operative analgesia and stress reduction in small animals. Recent clinical trials documented the safety and efficacy of dexmedetomidine CRI, administered at approximately 1–3 μg kg^{-1} $hour^{-1}$, to provide intra- (Uilenreef et al. 2008) and post –operative analgesia (Lin et al. 2008; Valtolina et al. 2009) in canine patients undergoing a wide range of surgical procedures. Furthermore, an experimental study showed that a dexmedetomidine CRI, at 0.5 and 3 μg kg^{-1} $hour^{-1}$ significantly reduces isoflurane MAC determined by intermittent supramaximal electrical limb stimulation in dogs (Pascoe et al. 2006).

MAC reduction has been used as an indirect measure of the antinociceptive properties of drugs administered during inhalation anaesthesia (Quasha et al. 1980). When determining MAC the output variable is binary, the response to a supramaximal noxious stimulus does or does not elicit complex purposeful movements. MAC determination provides non-quantitative information in the single animal. In order to better understand the mechanism and the extent of antinociceptive action of dexmedetomidine under anaesthesia, the nociceptive withdrawal reflex (NWR) model, previously described in conscious dogs (Bergadano et al. 2006), could be useful. By delivering single and repeated electrical stimulations to peripheral sensory nerves, nociceptive withdrawal reflexes can be elicited and recorded electromyographically from the muscles involved in the nocifensive response. The stimulus-response curve can be characterised exactly before and after administration of an analgesic drug, allowing quantification of its efficacy on both single nociceptive reflexes and on temporal summation (Spadavecchia et al. 2005; Rohrbach et al. 2009). As temporal summation is involved in the early phase of wind-up (Arendt-Nielsen et al. 1994), its pharmacological modulation in the peri-operative settings is of particular interest as it may indicate specific drug induced effects against the development of central sensitization.

The aim of this study was to quantify the efficacy of a low dose dexmedetomidine CRI on the NWR and temporal summation evoked by electrical transcutaneous nerve stimulations in isoflurane-anaesthetized dogs.

Materials and methods

Data are given as mean ± SD if not otherwise stated.

Animals

The study was approved by the Norwegian National Animal Research Authority (Approval number S-2008/1894). Eight mixed breed dogs, four female and four male, with a mean body weight of 26.5(8.36) kg and a mean age of 25 (16.4) months were used in the study. All dogs were found to be healthy before the first experimental session based on clinical examination and blood samples evaluating haematological and biochemical parameters. The dogs were kept in separate kennels the day before and after each experiment. Food was withheld for at least 12 hours and water for at least 2 hours prior to induction of anaesthesia. All dogs were re-examined the day after each experimental session.

Study design

A cross over design, treatments separated by a 7 days wash out period, was used. The dogs were randomised in two groups of four dogs, one group received dexmedetomidine followed by placebo whereas the other group received placebo followed by dexmedetomidine. The main investigators were unaware of the treatment received.

Anaesthesia and monitoring

Before induction of anaesthesia all dogs had an intravenous (IV) catheter (Venflon Pro; Becton Dickinson Infusion Therapy, Sweden) placed in the