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SHORT COMMUNICATION

Transnasal administration of a combination of dexmedetomidine, midazolam and butorphanol produces deep sedation in New Zealand White rabbits

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Abstract

Objective To study the sedative and cardiorespiratory effects of transnasal (TN) administration of a combination of dexmedetomidine (DEX), midazolam (MID) and butorphanol (BUT) administered through a nasal catheter to rabbits undergoing diagnostic procedures.

Study design Descriptive cross-sectional experimental study.

Animals Eight healthy New Zealand White rabbit does (12 ± 1 months old, 3.5 ± 0.3 kg).

Methods DEX (0.1 mg kg^{-1}), MID (2 mg kg^{-1}) and BUT (0.4 mg kg^{-1}) were mixed (DMB) in a syringe and applied to the rabbits' nasopharyngeal mucosa after the accurate catheterization of one nostril. The onset, duration and quality of effects including analgesia were scored using a numeric rating scale of sedation for rabbits. Continuous monitoring of vital parameters was performed via clinical and multiparametric recording. Physiological variables were explored using repeated measures ANOVA for parametric data or Friedman's test for non-parametric data. Tukey's or Dunn's *post hoc* multiple comparisons test was used depending on normality. The statistical significance was set at $p < 0.05$.

Results Loss of the righting reflex, deep sedation and profound analgesia ensued simultaneously at 1.4 ± 1.1 minutes after DMB administration. These effects lasted 45 minutes before subsiding into moderate sedation, which lasted for an additional 25 minutes. Residual central nervous system impairment persisted up to 100 minutes. Blood pressure dropped progressively over time by 50%, whereas respiratory frequency decreased by 70%, consistent with moderate hypoxemia and hypercarbia.

Conclusion and clinical relevance The TN route is a reliable and effective means for administration of DEX, MID and BUT to rabbits. The overall profound sedative effects and analgesic proprieties of the DMB combination can be selectively reversed depending on the needs of the procedure. Oxygen supplementation and careful monitoring are mandatory even in healthy subjects. The DMB protocol should be cautiously used in rabbits with cardiovascular or respiratory deficiencies.

Keywords butorphanol, dexmedetomidine, midazolam, nasal, rabbit.

Introduction

In rabbits, anaesthetic induction using single parenteral drugs requires high doses, leading to apnoea, hypoxemia, inability to control anaesthetic depth and at times prolonged recovery. Ketamine alone produces inconsistent anaesthetic and analgesic effects in rabbits while its combination with midazolam produces a light to medium plane of anaesthesia. The addition of butorphanol to the ketamine/midazolam combination increases the duration of anaesthesia (Hedenqvist et al. 2002). More recently, a combination of midazolam–fentanyl–medetomidine, which can be reversed by specific antagonists, has been reported as an effective anaesthetic in rabbits, producing surgical anaesthesia (Henke et al. 2005).

The dextrorotatory enantiomer of medetomidine, dexmedetomidine (DEX), is a highly selective alpha-2 adrenergic receptor agonist. The respiratory depressant effects of DEX have been studied in rabbits by Nishida et al. (2002), who reported a reduction in respiratory frequency (f_R) and tidal volume (V_T) unaccompanied by profound hypoxemia or hypercapnia. The water-soluble formulation and powerful sedative effect of DEX are suitable requisites for mucosal absorption; in fact, DEX can be effectively administered via the intranasal route in humans and animals (Schnellbacher et al. 2012).

Midazolam (MID) produces intense tranquilization in rabbits, along with good muscle relaxation and synergistic effects with other anaesthetics or opioids. The pharmacological features of MID favour its oral and intranasal absorption, as shown in children and dogs (Eagleson et al. 2012). In rabbits, intranasal administration of 2 mg kg^{-1} MID has an onset time of 3 minutes and duration of approximately 25 minutes (Robertson & Eberhart 1994). Although MID exerts little depressant effects on the cardiovascular and respiratory systems, in rabbits, the combination of MID with other anaesthetic agents requires careful monitoring of respiratory function (Henke et al. 2005; Hedenqvist et al. 2013).

Butorphanol tartrate (BUT) is a powerful agonist-antagonist opioid analgesic with minimal cardiorespiratory side effects in rabbits (Portnoy & Hustead 1992), although its combination with MID causes mild hypoxemia (Schroeder & Smith 2011). The water-soluble formulation of butorphanol and its high concentration are good candidates for transmucosal absorption, as shown by its intranasal administration in humans.

Given the pharmacological qualities of DMB and the remarkably deep sedation observed in captive hares after its transnasal (TN) administration (personal observations), we were inspired to observe its sedative and cardiorespiratory effects in rabbits. The choice of the TN route rather than the intranasal one was as a result of the large volume of solution that would need to be administered.

We hypothesized that the TN administration of the DMB combination would induce profound sedation with tolerable cardiorespiratory depression in New Zealand White rabbits.

Materials and methods

Animals and housing

This study was approved by the welfare regulation committee (CESA) of the University 'Federico II' of Naples under project license number 2011/0087561. All animals were handled in accordance with the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH Publication No. 85-23, revised 1996). The study was undertaken, between 08.00 and 16.00 hours, in a mobile anaesthesia lab set up on the farm where the animals were born and raised.

Eight, American Society of Anesthesiologists physical status (ASA) I, New Zealand White rabbits (brood females) with a mean ± SD of 12 ± 1 months and body weight of 3.5 ± 0.3 kg were randomly selected from a rabbit colony free from common rabbit pathogens. Twenty-four hours prior to the execution of the study, the animals were assessed healthy based on physical, haematological and biochemical examinations, identified using ear tags and transferred to individual flat-deck cages (70 × 50 × 50 cm) for acclimatization in their own barn (temperature, 20–22 °C; humidity, 40–60%; 12:12 hour light–dark cycle). A commercial pellet diet (Liverini pellets, Italy), autoclaved hay and water were available *ad libitum*.

Study design

At the time of the study, one assistant gently restrained each rabbit in a sitting position at the edge of the examination table by means of a fabric towel with the head exposed. The rectal temperature (T °C), heart rate (HR), respiratory frequency (f_R) and pulse-