Veterinary Anaesthesia and Analgesia, 2005, **32**, 261–270

RESEARCH PAPER

Comparative study of three intramuscular anaesthetic combinations (medetomidine/ketamine, medetomidine/fentanyl/midazolam and xylazine/ketamine) in rabbits

Julia Henke* DVM, **Susanne Astner*** DVM, **Thomas Brill*** DVM, MD, **Barbara Eissner*** DVM, **Raymonde Busch†** MSc & **Wolf Erhardt*** Prof. DVM, Diplomate ECVA, Diplomate ECLAM

*Institute for Experimental Oncology and Therapeutic Research, Working Group Experimental Surgery, Munich, Germany

†Institute of Medical Statistics and Epidemiology, Munich, Germany

Correspondence: Julia Henke, Institut für Experimentelle Onkologie und Therapieforschung der TU München, Ismaningerstr. 22, 81675 München, Germany. E-mail: julia.henke@lrz.tu-muenchen.de

Abstract

Objective To compare the quality of surgical anaesthesia and cardiorespiratory effects of three intramuscular (IM) anaesthetic combinations in rabbits.

Study design Prospective randomized cross-over experimental study.

Animals Nineteen adult female chinchilla mixed-bred rabbits weighing 3.9 ± 0.8 kg.

Methods Rabbits were given one of three IM anaesthetic combinations: 0.25 mg kg^{-1} medetomidine and 35.0 mg kg^{-1} ketamine (M–K), 0.20 mg kg^{-1} medetomidine and 0.02 mg kg^{-1} fentanyl and 1.0 mg kg^{-1} midazolam (M–F–Mz) and 4.0 mg kg^{-1} xylazine and 50 mg kg^{-1} ketamine (X–K). The effects of anaesthesia on nociceptive reflexes, circulatory and respiratory function were recorded. Statistical analyses involved repeated measures ANOVA with paired Student's *t*-test applied *post hoc*. *P*-values <0.05 were considered as significant.

Results Reflex loss was most rapid and complete in M–K recipients, whereas animals receiving M–F–Mz showed the longest tolerance of endotracheal intubation (78.1 ± 36.5 minutes). Loss of righting reflex was significantly most rapid ($p < 0.05$) in the X–K group (114.7 ± 24.0 minutes). Surgical anaesthesia was achieved in 16 of 19 animals receiving M–K, in 14 animals receiving M–F–Mz, and in seven animals with X–K, but only for a short period (7.1 ± 11.6 minutes). This was significantly ($p < 0.001$) shorter than with M–K (38.7 ± 30.0 minutes) and M–F–Mz (31.6 ± 26.6 minutes). Heart rates were greatest in X–K recipients; lowest HR were seen in animals receiving M–F–Mz. Mean arterial blood pressure was significantly higher (about 88 mmHg) during the first hour in the M–K group. During recovery, the greatest hypotension was encountered in the X–K group; minimum values were 53 ± 12 mmHg. Six of 19 animals in the M–F–Mz group showed a short period of apnoea (30 seconds) immediately after endotracheal intubation. Respiratory frequency was significantly lower in this group ($p < 0.001$). Highest values for arterial carbon dioxide partial pressures ($PaCO_2$) (6.90 ± 0.87 kPa; 52.5 ± 6.5 mmHg) occurred after induction of anaesthesia in group M–F–Mz animals. There was a marked decrease in PaO_2 in all three groups (the minimum value 5.28 ± 0.65 kPa [39.7 ± 4.9 mmHg] was observed with M–K immediately after injection). Arterial PO_2 was between 26.0 and 43.0 kPa (196 and 324 mmHg) in all groups during O_2 delivery and decreased – but not <7.98 kPa – on its withdrawal. Immediately after drug injection, pH_a values fell in all groups, with lowest values after 30 minutes (7.23 ± 0.03 with M–K, 7.28 ± 0.05 with M–F–Mz, and 7.36 ± 0.04 with X–K). The X–K animals

showed significantly ($p < 0.001$) higher pH values than medetomidine recipients. During 1 hour of anaesthesia pH values in the medetomidine groups remained below those of the X–K group.

Conclusions Surgical anaesthesia was induced in most animals receiving medetomidine-based combinations. Arterial blood pressure was maintained at baseline values for about 1 hour after M–K. Transient apnoea occurred with M–F–Mz and mandates respiratory function monitoring. Oxygen enrichment of inspired gases is necessary with all three combinations. Endotracheal intubation is essential in rabbits receiving M–F–Mz.

Clinical relevance The quality of surgical anaesthesia was greatest with M–K. All combinations allowed recoveries of similar duration. It is theoretically possible to antagonize each component of the M–F–Mz combination.

Keywords α_2-agonist drugs, anaesthesia, fentanyl, intramuscular, ketamine, medetomidine, midazolam, rabbit, xylazine.

Introduction

Rabbits are sensitive to anaesthetics and so have been generally regarded as unsafe subjects. Supporting this, Fehr (1984) reported 5.8% deaths under xylazine-ketamine anaesthesia. Rabbits are easily stressed and consequently may have high plasma catecholamine concentrations during induction of anaesthesia, which may increase risk (Hall et al. 2001; Haberstroh & Henke 2004). Intramuscular (IM) administration of anaesthetic combinations – particularly xylazine/ketamine – have been popular in the past. However, in the authors' experience, the analgesic properties of this combination is insufficient for major surgery and in many cases significant hypotension develops; this may contribute to the reported mortality. Moreover, rabbits display wide inter-individual variability in response to anaesthetics and show strain- and sex-specific differences (Avsaroglu et al. 2003). The most common complications during anaesthesia in small mammals are due to respiratory depression (Sedgwick 1986; Hall et al. 2001; Haberstroh & Henke 2004). The dose of anaesthetic required to provide surgical anaesthesia is very close to the dose that can cause respiratory arrest (Erhardt 1984). It is well documented that most anaesthetic techniques in rabbits produce a marked and prolonged hypotension, especially when anaesthesia lasts longer than 1 hour (Sanford & Colby 1980; Lipman et al. 1990; Marini et al. 1992).

Anaesthesia with combinations of agents – each of which can be antagonized by specific antagonists – has potential advantages. Each component may potentiate each other's actions, lower individual dose requirements, and therefore produce surgical anaesthesia more safely (Erhardt et al. 1986/87; Henke et al. 1993, 1996, 1998, 2000; Roberts et al. 1993). In one combination examined in the current study, medetomidine replaced xylazine in combination with ketamine, because its higher α_2-receptor specificity has been reported to confer greater analgesic and sedative-hypnotic properties. This enables the ketamine dose to be reduced (Verstegen et al. 1991). Fentanyl is a short-acting synthetic derivative of morphine which has potent analgesic properties. It causes only minimal changes in circulatory variables although it can cause marked respiratory depression. Midazolam, a benzodiazepine, causes minimal haemodynamic and respiratory changes and was chosen because of its water solubility and therefore can be mixed with other water-soluble substances in a single syringe.

In the present study, we investigated the anaesthetic and cardiorespiratory effects of three IM anaesthetic combinations based on medetomidine with either ketamine or fentanyl and midazolam or xylazine with ketamine in mixed-bred chinchilla rabbits. Another aim was to establish a completely reversible anaesthetic technique using medetomidine, fentanyl and midazolam, with the aim of i) avoiding complications associated with a long recovery and ii) allowing rapid reversal during emergencies. Partial antagonism of ketamine-containing combinations is not recommended, particularly in the early stages of anaesthesia, because of the undesirable effects of ketamine alone in rabbits (Hedenqvist et al. 2002).

Materials and methods

Animals

Adult female rabbits (chinchilla, cross-bred, $n = 19$), with a mean body mass of 3.9 ± 0.8 kg, were obtained from a commercial supplier (Charles River, Sulzfeld, Germany). They were group-housed (maximum of 10 individuals per group) with dust-reduced wood shavings as bedding. Floor area