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Comparison of ketamine–dexmedetomidine–methadone and tiletamine–zolazepam–methadone combinations for short-term anaesthesia in domestic pigs

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ABSTRACT

Cardiorespiratory effects, quality of induction, depth of anaesthesia and quality of recovery were compared in pigs anaesthetised with 8 mg/kg ketamine, 20 μg/kg dexmedetomidine and 0.2 mg/kg methadone (KDM, $n = 18$) or 8 mg/kg tiletamine–zolazepam and 0.2 mg/kg methadone (TZM, $n = 9$). Anaesthesia with KDM was partially reversed in nine animals with 0.2 mg/kg atipamezole (KDM*at*). Sedation was observed earlier in the TZM group (47.2 ± 25.3 s) than the KDM group (91.5 ± 37.4 s). Sternal and lateral recumbency were achieved earlier in the TZM group (76.3 ± 36.5 s and 132.1 ± 30.5 s, respectively) than in the KDM group (149.1 ± 58.7 s and 249.2 ± 84.0 s, respectively). PaO_2, SaO_2 and PaO_2:FiO_2 were lower in the TZM group (68.7 ± 4.1 mmHg, 93.4 ± 1.4% and 327.2 ± 19.9 mmHg, respectively) than in the KDM group (80.4 ± 5.9 mmHg, 95.7 ± 1.0% and 380.4 ± 25.6 mmHg, respectively). Fshunt and $P_{(A-a)}O_2$ were higher in the TZM group (24.0 ± 11.8% and 31.4 ± 3.8 mmHg, respectively) than in the KDM group (13.4 ± 3.2% and 20.7 ± 7.4 mmHg, respectively). Times from drug injection to first head movements, sternal recumbency and standing/walking were significantly shorter in the KDM group (45.1 ± 10.5, 48.4 ± 12.6 and 54.4 ± 17.8 min, respectively) than in the TZM group (57.8 ± 11.4, 93.1 ± 14.2 and 165.7 ± 56.6 min, respectively). The median recovery score was higher in the TZM group than in the KDM*noat* and KDM*at* subgroups. Both drug combinations provided adequate anaesthesia for minor procedures lasting about 30 min, but TZM was associated with a poor recovery and oxygenation.

Introduction

Short-term anaesthesia of domestic pigs is often required in biomedical research for minor surgical or diagnostic procedures (Hastings et al., 1982; Swindle et al., 1994; Nunes et al., 2007; Grasso et al., 2009; Staffieri et al., 2012; Jordan et al., 2014). The ideal anaesthetic protocol in pigs should provide fast and reliable immobilisation, minimal cardiovascular and respiratory depression, and adequate analgesia and muscle relaxation.

Pigs are difficult to handle and restrain due to their temperament and resistance to sedative drug combinations (Brodbelt and Taylor, 1999; Heinonen et al., 2009; Lee et al., 2010; Linkenhoker et al., 2010). Restraint for IM administration of drugs seems to be less stressful than for intravenous (IV) injection (Henrikson et al., 1995). The combination of two or more drugs (balanced anaesthesia) targeting specific clinical effects (hypnosis, analgesia and muscle relaxation) represents the current best standard for injectable IM anaesthesia in pigs in terms of safety and efficacy (Nishimura et al., 1992).

Cyclohexane anaesthetic drugs (ketamine and tiletamine) are commonly used for sedation and anaesthesia in pigs, since they produce rapid and reliable immobilisation after IM administration, with a high margin of safety and few cardiopulmonary side effects (Lin et al., 1993; Boschert et al., 1996). These drugs produce a state of dissociative anaesthesia resulting from an electrophysiological dissociation between the limbic and cortical system, do not usually depress the cardiovascular or respiratory systems and have significant analgesic effects (Reves et al., 2005; Craven, 2007). Tiletamine is more potent than ketamine and is commercially available in combination with the benzodiazepine tranquiliser zolazepam (Telazol) in a 1:1 combination. The major collateral effects of dissociative drugs are muscle rigidity, ataxia and excitatory effects during recovery (Lin et al., 1993). To counteract these side effects, α2 agonists (xylazine, detomidine and medetomidine) and opioids (butorphanol and buprenorphine) are commonly combined with dissociative drugs for short-term anaesthesia in pigs (Nishimura et al.,

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1992; Sakaguchi et al., 1992, 1995, 1996; Brodbelt and Taylor, 1999; Heinonen et al., 2009; Lee and Kim, 2012; Santos González et al., 2013). However, there are few reports of the use of dexmedetomidine and methadone in this species (Hermansen et al., 1986; Sano et al., 2010; Santos et al., 2015).

Dexmedetomidine is the latest α2 adrenoceptor agonist available for veterinary use; it is an enantiomer of medetomidine and provides sedative and analgesic effects (Pypendop et al., 2011). α2 agonists exert their sedative effects through stimulation of α2 adrenoceptors in the brain, decreasing release of noradrenaline (norepinephrine). Sedation results from decreased activity of ascending neural projections to the cerebral cortex and limbic system (Stenberg, 1986). Analgesia appears to be the result of both cerebral and spinal effects, possibly in part mediated by serotonin and the descending endogenous analgesia system (Sinclair, 2003).

Methadone is a synthetic μ opioid agonist with potent and short acting (about 4 h) analgesic and sedative effects (Lamont and Mathews, 2007). Methadone has pharmacological properties qualitatively similar to those of morphine, the prototypical opioid analgesic, but possessing additional antagonistic affinity for N-methyl-D-aspartate (NMDA) receptors, thus contributing to analgesia by minimising central nervous system sensitisation (Ebert et al., 1995).

Considering the unique and advantageous characteristics of dexmedetomidine and methadone, the aim of this study was to evaluate the physiological effects of an anaesthesia protocol that includes these drugs in comparison with a traditional protocol to produce short-term anaesthesia in pigs undergoing skin and mucosal biopsies. Ketamine–dexmedetomidine–methadone and tiletamine–zolazepam–methadone combinations were evaluated in terms of quality of induction, depth of anaesthesia, quality of recovery, and cardiovascular and respiratory effects. The study did not consider situations in which pigs are intended for food production, since only ketamine is licensed for food producing animals among the drugs tested.[1]

Materials and methods

Animals

Twenty-seven Landrace × Large white pigs (22 female, 5 male) were used in this study. Food was withheld for 24 h and water was withheld for 2 h before the administration of drugs to prevent any possible adverse effects, such as vomiting during the anaesthetic or recovery periods. The study protocol was approved by the Ethics Committee of the University of Perugia (approval number 2013-027R; date of approval 6 September 2013). Pigs were involved in another experimental study in which four skin biopsies (dorsal thoracic area) and two mucosal biopsies (ventral aspect of the tongue) were collected with a cutaneous punch (0.6 mm diameter) under general anaesthesia. The aim of the surgical study was to compare the quality of incisions and degree of thermal injury produced by different surgical instruments and their effects on reepithelialisation. The number and allocation of the pigs among groups were based on the main surgical experimental study. Physical examination carried out the day before the experiment, including measurement of rectal temperature (T, °C), heart rate (HR, beats/min) and respiratory rate (RR, breaths/min), had shown the pigs were healthy. The experiments were carried out at room temperature (18–20 °C). The mean body weights (TZM 41.0 ± 6.1 kg; KDM 40.5 ± 6.6 kg) and ages (TZM 86.6 ± 7.4 days; KDM 85.2 ± 6.6 days) were similar in both groups.

Study design

Eighteen animals (KDM group) were anaesthetised IM with a combination of ketamine (8 mg/kg; Ketavet 100, 100 mg/mL, Intervet), dexmedetomidine (20 μg/kg; Dexdomitor, 0.5 mg/mL, Elanco Animal Health) and methadone (0.2 mg/kg; Eptadone, 10 mg/mL, Molteni Farmaceutici). Nine animals (TZM group) received a combination of tiletamine–zolazepam (8 mg/kg; Zoletil 100, 100 mg/mL, Virbac) and methadone (0.2 mg/kg) IM. Pigs in the KDM group were further divided in two subgroups of nine animals each based on the administration (KDM*at*) or not (KDM*noat*) of atipamezole (0.2 mg/kg; Antisedan, 5 mg/mL, Elanco Animal Health) during recovery. All animals were injected into the neck muscles caudal to the base of the ear (splenius and brachiocephalic muscles). Randomisation of pigs among treatment groups was performed using Research Randomizer.[2]

The times from injection of drugs to the first signs of sedation, and to sternal and lateral recumbency, were recorded. The quality of induction was assessed using a descriptive score ranging from 1 (excellent) to 4 (poor; see Appendix: Supplementary Table S1). Ten minutes after administration of drugs, pigs with inadequate induction (scores 3–4; one pig in the KDM group) received an additional dose of ketamine (1 mg/kg, IV; KDM group) or tiletamine–zolazepam (1 mg/kg, IV; TZM group); these animals were excluded from the study. When the induction was adequate (scores 1–2), pigs were approached, blindfolded and placed in left lateral recumbency; animals were not intubated and breathed room air (fraction of inspired oxygen, FiO_2 0.21).

Depth of anaesthesia (anaesthesia score) (Laricchiuta et al., 2012) was assessed by checking palpebral, pedal, auricular and anal reflexes, jaw tone, presence of voluntary movements and reaction to painful stimuli (blood sampling, ear notching), scored from 1 (deep anaesthesia) to 6 (very light sedation; see Appendix: Supplementary Table S2). If the anaesthesia score was 5–6 (one pig in TZM group), pigs received an additional dose of ketamine (1 mg/kg, IV; KDM group) or tiletamine–zolazepam (1 mg/kg, IV; TZM group) and these animals were excluded from the study.

Monitoring and data collection

Heart rate, RR, T, oxygen haemoglobin saturation (SpO_2, %), non-invasive systolic, diastolic and mean arterial pressures (SAP, DAP, MAP, respectively, mmHg; HB100 multiparametric monitor, Foschi) and depth of anaesthesia were recorded at the time of the first approach (T0) and after 10 (T10), 20 (T20) and 30 (T30) min. Skin and tongue biopsies were collected between T10 and T30; no other surgical interventions were performed. An arterial (femoral artery) blood sample was collected at T20 (3 mL BD Preset syringe, BD). Arterial samples were analysed immediately using a portable blood gas analyser (i-STAT Portable Clinical Analyzer, Abbott). The measured and calculated parameters were pH, partial arterial pressure of carbon dioxide ($PaCO_2$, mmHg), partial arterial pressure of oxygen (PaO_2, mmHg), base excess (BE, mmol/L), haematocrit (Hct, %), bicarbonate concentration (HCO_3^-, mmol/L), haemoglobin concentration (tHb, g/dL), oxygen haemoglobin saturation (SaO_2,%), concentrations of Na^+, K^+ and Ca^{2+} (mmol/L), arterial CO_2 (TCO_2, vol%), and concentration of glucose (mg/dL). The alveolar to arterial oxygen gradient [$P_{(A\text{-}a)}O_2$], PaO_2:FiO_2 ratio (mmHg) and estimated shunt fraction (Fshunt,%) were calculated (Araos et al., 2012). All parameters were corrected for the rectal temperature measured at the time of sampling.

The $P_{(A\text{-}a)}O_2$ was calculated as:

$$P_{(A-a)}O_2 = ([P_B - PH_2O] \times FiO_2 - PaCO_2/R) - PaO_2$$

where P_B is the barometric pressure, PH_2O is the water vapour pressure, FiO_2 is the inspired oxygen fraction and R is the respiratory exchange ratio, assumed to be 0.9 (Cohen et al., 1995). The PH_2O was corrected for the rectal temperature recorded at the time of arterial blood collection (Mackenzie, 1963).

The *F*shunt was calculated as:

$$F\text{shunt}: ([Cc'O_2 - CaO_2]/[Cc'O_2 - CaO_2 + 3.5\,\text{mL/dL}]) \times 100$$

where $Cc'O_2$ is the pulmonary end-capillary oxygen content, CaO_2 is the arterial oxygen content and 3.5 mL/dL is an approximate fixed value of the arterial-to-mixed venous oxygen content difference.

The $Cc'O_2$ and CaO_2 were calculated as follows:

$$Cc'O_2 = Hb \times 1.31 \times Sc'O_2 + 0.0031 \times Pc'O_2$$

$$CaO_2 = Hb \times 1.31 \times SaO_2 + 0.0031 \times PaO_2$$

where Hb is the haemoglobin concentration (g/dL), 1.31 is the oxygen-carrying capacity of haemoglobin (mL/g) (Larimer, 1959), $Sc'O_2$ is the pulmonary end-capillary oxygen saturation, 0.0031 is the solubility coefficient of oxygen in porcine plasma and $Pc'O_2$ is the pulmonary end capillary partial pressure of oxygen (mmHg).

Pulmonary end-capillary partial pressure of oxygen was assumed to be equal to PAO_2 (alveolar partial pressure of oxygen); for $PAO_2 > 100$ mmHg, pulmonary end capillary oxygen saturation was assumed to be 100% (i.e. 1), whereas for $PAO_2 \leq 100$ mmHg, pulmonary end capillary oxygen saturation was calculated from the actual PAO_2 via the same method. FiO_2 was always assumed to be 0.21 because pigs were breathing room air.

Recovery from anaesthesia

At T30, pigs were moved to a recovery box to observe recovery from anaesthesia; pigs in the KDM*at* subgroup received 0.2 mg/kg atipamezole IM. Times between injection of anaesthetic drugs and the first head movements, sternal recumbency and standing/walking were recorded. Times between atipamezole administration

[1] See: http://ec.europa.eu/health/files/eudralex/vol-5/reg_2010_37/reg_2010_37_en.pdf (accessed 28 December 2014).

[2] See: http://www.randomizer.org (accessed 28 December 2014).