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RESEARCH PAPER

Induction of anaesthesia with remifentanil after bolus midazolam administration in Landrace/Large White swine

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Abstract

Objective To investigate an alternative combination for anaesthesia induction in swine.

Study design Randomized experimental study, blinded.

Animals Forty-five Landrace/Large White swine with 20.0 ± 1.5 kg body weight.

Methods Pulse oximetry, heart rate (HR) and blood pressure were measured after premedication with ketamine, midazolam and atropine as well as after intubation following induction with a fixed dose of 0.2 mg kg^{-1} midazolam combined with 1, 2, 3, 4 or 5 μg kg^{-1} remifentanil (groups R1, R2, R3, R4 and R5, respectively). Intubation was evaluated using a numerical scoring system assessing jaw relaxation, resistance to the laryngoscope, vocal cord position, vocal cord movement and response to intubation. The time required to intubate and necessity for an additional midazolam dose were recorded. Baseline and post-intubation variables were compared with paired *t* tests, whereas for differences between the remifentanil groups the Spearman's rank correlation coefficient was estimated. Multivariate regression analysis was performed to disentangle the effect of remifentanil dose and the additional midazolam.

Results Higher dose of remifentanil was associated with better vocal cord position ($p < 0.001$), better response to intubation ($p < 0.001$), shorter time required for intubation ($p = 0.030$) and less frequent necessity for additional administration of midazolam ($p = 0.004$). In total, 39.5% of the animals required additional midazolam. In groups R1, R4 and R5, there were decreases in HRs ($p = 0.009$, $p = 0.008$ and $p = 0.032$, respectively) between baseline and post-intubation phase; in groups R3 and R4, there were decreases in systolic blood pressure ($p = 0.040$ and $p = 0.019$, respectively). In the multivariate analysis, remifentanil dose was not associated with the observed changes in haemodynamic variables. One animal developed apnoea and four electrocardiographic anomalies; all resolved without pharmaceutical interventions.

Conclusions and clinical relevance: A combination of 0.2 mg kg^{-1} midazolam with 4 or 5 μg kg^{-1} remifentanil may provide an alternative method of anaesthesia induction for swine.

Keywords endotracheal intubation, midazolam, remifentanil, swine.

Introduction

Swine are commonly used as animal models in biomedical research. They undergo specialised procedures which often require not only endotracheal intubation and mechanical ventilation but also the selection of specific anaesthetic agents that will not interfere with the research goals (Swindle & Sistino

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2015). The study of different anaesthetic combinations that will accommodate various experimental purposes is essential.

Several drugs and drug combinations have been suggested as anaesthesia induction schemes prior to intubation for swine. Most consist of or include a general anaesthetic such as propofol or thiopental (Smith & Swindle 2008; Swindle & Sistino 2015). The use of remifentanil combined with propofol for the same purpose has been studied on humans (Grant et al. 1998; Alexander et al. 1999; Bouvet et al. 2009; Naziri et al. 2015) and swine (Demestiha et al. 2010).

In human anaesthesia practice, remifentanil is commonly combined with midazolam as an intubation anaesthetic regimen (Cattano et al. 2012; Song et al. 2012; Fukuda 2015). Our hypothesis was that a remifentanil–midazolam combination would also produce adequate anaesthesia induction for intubation of swine. The present study was carried out in order to investigate this alternative combination. The primary aim was to confirm our hypothesis that it is feasible to use a remifentanil–midazolam combination for swine intubation. A secondary aim was to investigate the effect of different doses of remifentanil in this proposed anaesthetic regimen.

Materials and methods

Animals

Landrace/Large-White swine were purchased from the same registered farm breeder (Validakis, Koropi, Greece). In order to achieve 90% power for the detection of 0.3-point incremental change in intubation quality scores (per 1 μg change in remifentanil dose, assuming a SD of the scores equal to 0.5 in each dose group), six animals per group was the minimum necessary number. The sample size calculation was performed with GPower 3.1.9.2 software (University of Dusseldorf, Germany). A total of 45 female animals (nine per group) were recruited for the study to account for potential drop-outs. Q2

All animals were housed in 2 m^2 pens alone or in pairs. The animal house had a controlled environment of light/dark cycle (lights on from 7:00 A.M. to 7:00 P.M.), temperature (21 ± 2 °C), relative humidity (50–70%) and ventilation (15 air changes per hour). Animals were fed commercial food (S/100 MangimeCompleto per Suini, Galtieri S.P.A., Italy) and were fasted overnight. All had *ad libitum* access to water. They were allowed to acclimatize to laboratory conditions for 1 week prior to the experiment. The study was carried out at the ***, which conforms to the European Directive 2010/63/EU for the Protection of Animals used for Scientific Purposes. The procedures for this protocol were performed on animals which were to be intubated for other licenced studies (Licence Number: 23, 2980, 2981) after receiving approval from the director of the centre and following the authorization procedures according to the national legislation (PD 56/2013). This manuscript was drafted in accordance to ARRIVE Guidelines. Q3

Experimental design

Personnel

The staff of the *** administered premedication to all animals and prepared the remifentanil and midazolam doses. The veterinarian (*.*.) was responsible for administering the anaesthetics, intubating and evaluating the conditions of endotracheal intubation in order to avoid inter-observer biases. The senior investigator (*.*.) monitored the animals and recorded the data. Both were unaware of the dose delivered.

Group assignment

Each animal was randomly assigned to be administered one of five remifentanil doses (1, 2, 3, 4 or 5 μg kg^{-1} body weight; groups R1, R2, R3, R4 or R5, respectively). The instruction sheets were printed in advance on separate sheets of paper, the group names were covered, the sheets were shuffled and one sheet was randomly picked prior to premedication. The exclusion criterion was the inability to adequately deliver the intramuscular (IM) premedication at the pen.

Premedication

A mixture of ketamine hydrochloride (30 mg kg^{-1}; Imalgene 100 mg mL^{-1}; Merial, France), midazolam (0.75 mg kg^{-1}; Dormicum 50 mg 10 mL^{-1}; Roche, Greece) and atropine sulphate (0.05 mg kg^{-1}; Demo, Greece) was injected IM into the neck muscles as premedication. The animals were then left isolated for 10 minutes and transferred to the operating room.

Monitoring

Oxygen saturation values were obtained with a pulse oximeter sensor placed on the lower lip of the pig

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