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RESEARCH PAPER

The effect of high doses of remifentanil in brain near-infrared spectroscopy and in electroencephalographic parameters in pigs

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Abstract

Objective To study the effects of a high remifentanil bolus dose on pig's electroencephalographic indices and on brain regional and global oxygenation.

Study design Prospective experimental study.

Animals Twelve healthy Large-White male pigs, age 3 months and weight 26.2 ± 3.6 kg.

Methods Anaesthesia was induced with intravenous propofol 4 mg kg^{-1}, then maintained with constant rate infusions of propofol (15 mg kg^{-1} $hour^{-1}$) and remifentanil (0.3 μg kg^{-1} $minute^{-1}$). Following instrumentation, all pigs received a 5 μg kg^{-1} remifentanil bolus. The responses of jugular venous oxygen saturation, cardiac output and cerebral oxygen saturation to the remifentanil bolus were studied. The Bispectral index, spectral edge frequency 95%, total power, approximate entropy and permutation entropy were also studied. Repeated measures ANOVA and Pearson correlation were used to analyze the effect of remifentanil bolus on these variables until 5 minutes after the bolus.

Results Cardiac output and cerebral oxygen saturation decreased significantly after the remifentanil bolus from 4.6 ± 0.9 to 3.8 ± 1.0 L $minute^{-1}$ and from 65 ± 6 to 62 ± 1% ($p < 0.05$), respectively. No significant changes were observed in the jugular venous oxygen saturation ($p > 0.05$) nor in any of the electroencephalogram derived indices ($p > 0.05$). Correlation analysis revealed strong positive significant correlations between cerebral oxygen saturation and cardiac output ($r = 0.82$, $p < 0.001$) and between cerebral oxygen saturation and approximate entropy ($r = 0.65$, $p < 0.001$).

Conclusions and Clinical Relevance The effect caused by the remifentanil bolus on the brain oxygenation seems to be better reflected by the cerebral oxygen saturation than the jugular venous oxygen saturation. The effect of remifentanil on the electroencephalogram may not be reflected in indices derived from the electroencephalogram, but the potential of the approximate entropy in reflecting changes caused by opioids on the electroencephalogram should be further investigated.

Keywords anaesthetic techniques – i.v. bolus, cerebral oxygenation, EEG, pig, remifentanil.

Introduction

It is known that the effect of remifentanil on regional cerebral blood flow is dependent on the remifentanil dose, and on the cerebral region (Lorenz et al. 2000; Wagner et al. 2001). High doses of remifentanil may decrease cerebral blood flow (Engelhard et al. 2001), particularly in the most superficial brain cortex. In normal physiological conditions, decreases/increases in cerebral blood flow result in decreasing/increasing oxygen delivery to the peripheral cortex, which could be detected by near-infrared spectroscopy (NIRS). In contrast, the brain venous blood oxygen saturation ($SVjO_2$) monitoring provides information about the global brain oxygenation, but does not provide information about regional cortex blood supply (Grocott et al. 2010).

High doses of opioids have been reported to cause a decrease in electroencephalogram derived indices such as Bispectral Index (BIS) (Sebel et al. 1981; Glass et al. 1997), and a slowing in the raw electroencephalographic patterns (Egan et al. 1996) in humans. However, other studies reported excitatory patterns caused by opioid administration in rats (Antunes et al. 2003), and even a paradoxical increase in electroencephalographic indices during opioid administration in humans (Mi et al. 1999; Barr et al. 2000; Kortelainen et al. 2009a,b). The potential of BIS to assess the depth of anaesthesia in pigs has been studied (Haga et al. 1999, 2001; Martin-Cancho et al. 2006) and, although in some studies the BIS was found not to change in accordance with anaesthetic depth at clinically relevant hypnotic concentrations (Haga et al. 1999) or not to change with nociceptive stimulation in pigs under general anaesthesia (Haga et al. 2001), it has shown correlation with increasing hypnotic concentration in other studies (Martin-Cancho et al. 2003, 2006).

The effect of opioids in the human's brain has been addressed in several studies (Lorenz et al. 2000; Engelhard et al. 2001; Wagner et al. 2001; Kortelainen et al. 2009a,b), however, there are no studies assessing the responses of BIS and other electroencephalogram-derived indices during opioid administration in pigs. Furthermore, the opioid doses used in those studies in humans are small due to the severe opioid side effects when administered at high doses in humans (Fodale et al. 2008). However, the use of high doses of opioids in clinical situations would allow us to better understand its effects in the brain oxygenation and brain metabolism.

Due to its similarities in physiology and anatomy, the pig is the most widely used laboratory animal in clinical research, which allows a more direct extrapolation of the results to humans. According to previous results (Silva et al. 2011b), the pigs seem to be more haemodynamic tolerant to high remifentanil doses than humans. This physiologic feature provides us a window of opportunity of better understanding the effect of high remifentanil doses in brain oxygenation and in brain metabolism in clinical situations similar to those observed in humans.

We hypothesized that the administration of a high remifentanil bolus dose would have depressant effects on brain regional and global oxygenation, electroencephalographic indices, and on haemodynamics in pigs under total intravenous anaesthesia with propofol and remifentanil.

Material and methods

Ethical approval for this study (Direcção Geral de Veterinária – DGV000228) was provided by the Ethical Committee from Direcção Geral de Veterinária from Ministério da Agricultura, do Desenvolvimento Rural e das Pescas, Lisbon, Portugal on 6th June 2011. All procedures were carried out under personal and project licenses approved by Direcção Geral de Veterinária.

Twelve healthy 3 months old Large White pigs, weight 26.2 ± 3.6 kg were used in this study. All pigs were submitted to general anaesthesia with propofol and remifentanil during which the methodological procedures took place. These same animals were used for another study of the physiologic effects of bleeding and volume replacement which benefited from the same monitoring setup under the same anaesthetic procedure, but started only after the end of the present study.

All pigs were premedicated with intramuscular azaperone 4 mg kg^{-1} (Stresnil, Janssen Animal Health, Belgium) 30 minutes prior to the beginning of the induction of anaesthesia. After premedication, a 22 gauge catheter was inserted in the right auricular vein for drug and fluid administration. Two three way stopcock valves were used to connect the intravenous catheter to the maintenance delivery line with lactated Ringer's, and to the lines delivering propofol 1% (Fresenius Kabi, Germany) and remifentanil 20 μg mL^{-1} (Ultiva, GSK, UK). An