

Infusion of Pentobarbital and Fentanyl Combination for Long-Term Anaesthesia in Pigs

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Abstract: The cardiopulmonary and clinical effects of the infusion of pentobarbital sodium in combination with fentanyl for long-term anaesthesia in 9 pigs were investigated. Pigs were premedicated with i.m. atropine at a dose of 0.05 mg/kg and azaperon at a dose of 2 mg/kg. General anaesthesia was induced with i.v. thiopental sodium at a dose of 3.3 mg/kg. After induction of anaesthesia, the pigs were intubated and supplied with oxygen during anaesthesia. Anaesthesia was maintained with an i.v. infusion of pentobarbital-sodium at a dose of 45 mg/kg/h and fentanyl at a dose of 0.026 mg/kg/h. Arterial blood pressure, blood gas analyses, arterial haemoglobin saturation (SpO₂), end-tidal CO₂ concentration (ETCO₂), rectal temperature and heart rate were monitored 20, 40, 65, 90, 115, 140, 165, 190 and 215 min after induction. ETCO₂, SpO₂, pH and blood gas values did not change significantly over time. Temporal changes in arterial blood pressure and heart rate were detected; however, significant differences in heart rates and systolic arterial pressure were not detected. Diastolic arterial pressure increased significantly with time. Rectal temperature was significantly below the baseline value after 65, 90 and 115 min, and then increased significantly 190 and 215 min after anaesthetic administration. It was concluded that infusion of a combination of pentobarbital and fentanyl was suitable for prolonged anaesthesia in pigs.

Key Words: Pentobarbital, fentanyl, infusion, anaesthesia, pig.

Domuzlarda Uzun Süreli Anesteziler İçin Pentobarbital ve Fentanil Kombinasyonunun İnfüzyonu

Özet: Bu çalışmada, domuzlarda uzun süreli anesteziler için infüzyon şeklinde uygulanan pentobarbital ve fentanyl kombinasyonunun kardiyopulmoner ve klinik etkileri incelenmiştir. Çalışmada 9 domuz kullanılmıştır. Tüm domuzlarda, 0,05 mg/kg atropin ve 2 mg/kg azaperon intramusküler yolla uygulanarak premedikasyon sağlanmıştır. Anestezinin induksiyonu için 3,3 mg/kg tiyopental sodyum intravenöz olarak uygulandı. İndüksiyondan sonra domuzlar entübe edilmiş ve bir respiratore bağlanarak tüm anestezi boyunca oksijenle ventile edilmiştir. Anestezinin devamı için 45 mg/kg/saat pentobarbital sodyum ve 0,026 mg/kg/saat fentanil i.v. infüzyon şeklinde uygulanmıştır. Arteriyel kan basıncı, kan gazları, SpO₂, ETCO₂, rektal vücut ısısı ve kalp frekansı induksiyondan sonra 20, 40, 65, 90, 115, 140, 165, 190 ve 215. dakikalarda kayıt edildi. ETCO₂, SpO₂, pH ve kan gazları seviyesinde anlamlı değişiklikler gözlenmedi. Kalp frekansı ve sistolik kan basıncında anlamlı olmayan değişiklikler saptanmıştır. Diastolik kan basıncında istatistiksel yönden anlamlı düşüşler gözlemlendi. Rektal vücut ısısında 65, 90, 115. dakikalarda anlamlı düşüşler gözlenirken, müteakiben 190 ve 215. dakikalarda istatistiksel olarak anlamlı artışlar gözlemlendi. Pentobarbital ve fentanil infüzyonunun domuzlarda uzun süreli anesteziler için uygun olduğu sonucuna varıldı.

Anahtar Sözcükler: Pentobarbital, fentanil, infüzyon, anestezi, domuz.

Introduction

The use of pigs as an animal model in biomedical research has increased steadily, because their anatomic and physiological similarities to human beings are being increasingly appreciated (1,2). For this purpose, small

immature conventional pigs and miniature pigs are preferred. However, both types can be nervous and noisy when handled, and may require chemical restraint or anaesthesia in many situations (3).

Barbiturates can be used for general anaesthesia, and the pharmacologic effects in swine are similar to those in other species. The pig is prone to apnea secondary to their administration, and this use of dilute solutions (1-2.5%) for intravenous (i.v.) bolus injections is recommended (4). The severe cardiopulmonary depression associated with the prolonged administration of these agents may be alleviated by using continuous i.v. infusions rather than repeated i.v. boluses (5,6). Pentobarbital is an intermediate-acting barbiturate, more cardiodepressant than thiobarbiturates and may require prolonged recovery times postoperatively due to its slower metabolism by the liver (7-9).

Fentanyl is the most commonly used agent for opioid infusion techniques in swine. The agents may be used alone for induction or following light sedation to facilitate i.v. access. Fentanyl is given as an i.v. bolus (50 µg/kg) after initiating a continuous i.v. infusion of 30-100 µg/kg/h (7,9-12). Opioid infusion techniques produce a profound bradycardia during the i.v. bolus phase that can be controlled with anticholinergics. Fentanyl (0.005 mg/kg i.v.) combined with thiopental (12.5 mg/kg i.v.) for induction followed by fentanyl (0.005 mg/kg/h), thiopental (2 mg/kg/h) and midazolam (0.25 mg/kg) has also been used (11,12). However, the pentobarbital-fentanyl combination has not been widely investigated for long-term anaesthesia in pigs.

The aim of this study was to assess the outcome of a pentobarbital and fentanyl combination for maintenance of anaesthesia in pigs.

Materials and Methods

Animals: The study was performed in 9 clinical healthy pigs 3 months old with a mean body weight of 30 kg. The pigs were kept in a controlled environment (room temperature, 18-21 °C; humidity, 55-65%), fed a special diet (FK 128, Bayerische Kraftfutter GmbH, Vilsbiburg, Germany) twice a day and allowed ad libitum access to water. Food was withheld for about 12 h prior to anaesthesia. A standard clinical examination preceded general anaesthesia. Anaesthesia was induced for thoracotomy.

Anaesthetic protocol: In all pigs, the pre-anaesthetic medication was atropine (Atropinsulfat 0.5 mg – B. Braun Melsungen Pharmaceutica) at a dose of 0.05 mg/kg and azaperon (Stresnil-Janssen Pharmaceutica) at

a dose of 2 mg/kg given intramuscularly. Prior to the induction of anaesthesia a catheter (Venflon 2, Ohmeda, Helsingborg) was placed into the V. auricularis magna and secured in place. General anaesthesia was induced with an i.v. injection of thiopental sodium (Trapanal-Byk Gulden Pharmaceutica) at a dose of 3.3 mg/kg through the catheter. After the induction of anaesthesia, the pigs were intubated (Magill-Endotrachealtubus 26-28 Ch., Rüschi, Weiblingen) and put on an inhalation machine (Servo Ventilator 900 D, Siemens, Muenchen). The animals were supplied with oxygen during anaesthesia. The pigs were placed on a heated surface and observed during anaesthesia with regard to induction time. Anaesthesia was maintained with an i.v. infusion of pentobarbital-sodium (Narcofen-Rhone Merieux) at a dose of 45 mg/kg/h and fentanyl (Fentanyl-Janssen Pharmaceutica) at a dose of 0.026 mg/kg/h. The infusion was administered by syringe pump (Perfusor 20). The pentobarbital and fentanyl infusion was maintained for 4 h. Pentobarbital infusion was started 20 min after the induction of anaesthesia and was maintained throughout the anaesthetic period. At the end of the anaesthetic period, the infusions of pentobarbital and fentanyl were discontinued simultaneously. Baseline cardiovascular and pulmonary responses of each pig were determined immediately prior to the induction of anaesthesia. During anaesthesia the following variables were recorded: heart rate, rectal temperature, arterial blood pressure, and respiratory pattern.

Measurement of variables: After induction, the left carotid artery and jugular vein were exteriorised aseptically. Heparinised, saline-filled catheters (Opticat, Abbott, Wiesbaden) were implanted in the carotid artery and jugular vein. Arterial blood pressure was measured using a pressure transducer (TNF-R, Ohmeda, Helsingborg) on a monitor (Sirecust 401-1, Siemens, Erlangen). Arterial blood samples for the determination of PaCO₂, PaO₂, pH, bicarbonate concentration (HCO₃-), and base excess (ABE) were measured immediately by an automatic blood gas analyser (IL 306, Lexington, USA). Arterial haemoglobin saturation (SpO₂) and heart rate were recorded using a pulse oximeter (Capnomac Ultima SY, Hoyer Bremen, Bremen) with the probe attached to the pig's tongue. The end-tidal CO₂ concentration (ETCO₂) was recorded using a capnometer (Capnomac Ultima, Datex, Achim).

Statistical analysis: Data were recorded as mean \pm SD. The results obtained were statistically evaluated using Student's t-test. Values of $P < 0.05$ were considered statistically significant.

Results

Induction of anaesthesia: All pigs were in lateral recumbency before the administration of thiopental sodium. Induction of the anaesthesia with thiopental sodium was smooth. In all pigs, tracheal intubation was performed easily following induction; the jaw was relaxed, and the laryngeal reflexes were not evident. Five pigs were apnoeic for 1-2 min after induction.

Cardiopulmonary effects: End-tidal CO_2 concentrations (ETCO_2), arterial haemoglobin saturation (SpO_2), pH and blood gas values did not change significantly over time (Table 1). During anaesthesia, pH decreased, whereas bicarbonate concentration and acid-base excess increased.

The study results showed that while heart rates and systolic arterial pressure did not change significantly, diastolic arterial pressure remained high throughout the anaesthesia (Table 2).

Other effects: Rectal temperature was significantly below the baseline value after 65, 90 and 115 min, and then increased significantly 190 and 215 min after anaesthetic administration (Table 2).

Discussion

Barbiturates are the most commonly used intravenous anaesthetics in laboratory animals. However, barbiturates are a poor analgesic, and if used to maintain anaesthesia, they must be supplemented with an analgesic and a muscle relaxant (6,9,11). In this study, pentobarbital was combined with fentanyl.

The ultrashort barbiturates such as thiopental sodium or thiomylal sodium are used the most for the induction of anaesthesia in pigs. Five pigs were apnoeic for 1-2 min after induction in this study. Similar findings have been recorded in other studies in pigs (6,9,11).

Regarding the respiratory parameters, few changes were observed. The level of ETCO_2 mirrors PaCO_2 in the blood, which reflects lung exchange of CO_2 based on sufficient lung ventilation and blood perfusion (9,11). Changes in ETCO_2 thus reflect lung ventilation together with cardiovascular apparatus function. Significant

Table 1. End-tidal CO_2 concentration (ETCO_2), arterial haemoglobin saturation (SpO_2), arterial pH, and arterial blood gas values for 9 pigs during 4 h of anaesthesia maintained by an infusion of pentobarbital sodium-fentanyl.

Variable	Baseline	Time after induction								
		20	40	65	90	115	140	165	190	215
ETCO_2 (mmHg)	34.4 ± 1.6	36.4 ± 1.5	35.5 ± 0.7	36.0 ± 1.1	36.5 ± 1.0	36.5 ± 0.8	36.4 ± 1.1	37.1 ± 0.9	36.7 ± 1.1	36.2 ± 0.8
SpO_2 (%)	97.7 ± 0.6	97.6 ± 0.7	97.3 ± 0.8	97.3 ± 0.6	96.8 ± 0.8	96.2 ± 0.7	96.8 ± 0.8	96.8 ± 0.8	96.6 ± 0.8	96.3 ± 0.8
pH	7.43 ± 0.03	7.42 ± 0.02	7.41 ± 0.01	7.41 ± 0.02	7.40 ± 0.04	7.39 ± 0.05	7.40 ± 0.06	7.40 ± 0.05	7.40 ± 0.04	7.39 ± 0.04
PaCO_2 (mmHg)	41.5 ± 3.8	44.6 ± 3.2	45.4 ± 2.5	44.0 ± 2.5	44.8 ± 2.8	46.2 ± 9.9	43.1 ± 9.1	43.8 ± 2.8	46.6 ± 8.8	48.2 ± 3.1
HCO_3^- (mmol/l)	27.1 ± 2.1	29.8 ± 2.7	29.1 ± 2.2	29.5 ± 3.2	29.6 ± 2.6	28.4 ± 2.7	29.1 ± 1.5	30.0 ± 3.2	30.0 ± 5.5	28.2 ± 1.1
ABE (mmol/l)	4.3 ± 2.8	4.5 ± 2.6	4.3 ± 2.8	4.4 ± 2.2	5.7 ± 2.3	5.8 ± 2.1	5.1 ± 1.5	5.7 ± 3.0	6.1 $\pm 4.2^*$	6.3 $\pm 2.1^*$

Values reported are mean \pm SEM (range). *Mean value differs significantly ($P < 0.05$) from baseline value ABE = Acid-base excess

Table 2. Rectal temperature (C), heart rate (HR), and arterial blood pressures for 9 pigs during 4 h of anaesthesia maintained by an infusion of pentobarbital sodium-fentanyl.

Variable	Baseline	Time after induction								
		20	40	65	90	115	140	165	190	215
Rectal Temperature (C)	35.9 ±0.2	35.8 ±0.2	35.4 ±0.1	35.1 ±0.4*	35.0 ±0.5*	35.2 ±0.1*	35.8 ±0.4	36.3 ±0.5	36.5 ±0.7*	36.9 ±0.6*
Heart rate (beats/min)	84.6 ±4.9	77.3 ±3.7	73.3 ±3.2	87.3 ±4.8	86.2 ±3.4	86.0 ±4.8	79.3 ±3.1	77.5 ±2.2	76.2 ±1.5	74.4 ±2.4
SAP (mmHg)	103 ±9.2	110 ±4.1	102 ±10.1	100 ±5.2	100 ±6.8	98 ±8.2	100 ±10.2	95 ±9.6	95 ±14.2	95 ±11.5
DAP (mmHg)	90 ±6.3	95 ±9.7	75 ±10.2*	70 ±11.2**	70 ±12.2**	60 ±9.4***	65 ±8.5**	60 ±9.2***	65 ±9.6**	65 ±11.2**

Values reported are mean ± SEM (range). *Mean value differs significantly (P<0.05) from baseline value. ** Mean value differs significantly (P<0.01) from baseline value. *** Mean value differs significantly (P < 0.001) from baseline value. SAP = Systolic arterial pressure. DAP = Diastolic arterial pressure.

differences in ETCO₂ and PaCO₂ were not observed in this study.

In the study reported here, blood pH decreased, and bicarbonate concentration increased over time. However, these values were still within reference ranges after 4 h of anaesthesia. It was reported that nonintubated pigs under thiopental anaesthesia showed respiratoric acidosis due to hypoxia and hypercarbia. Long-term hypoxia and hypercarbia will lead to acidosis as a result of anaerobic glycolysis with the production of lactic acid (13,14). In this study, all pigs were intubated.

The cardiovascular system of domestic swine is seen to differ in certain functional characteristics from those of

the dog and cat. The diastolic blood pressure is 30-45 mmHg lower than the systolic pressure (1-3). Decreases in arterial blood pressure have been reported for pentobarbital in pigs (4-6). The changes in arterial blood pressure and heart rate showed considerable variation in this study.

A significant decrease in rectal temperature was recorded until 90 min. Peripheral vasodilatation and heat loss may have resulted from the α-adrenergic blocking action of azaperon (15).

A combination of pentobarbital and fentanyl may prove suitable for long-term anaesthesia in pigs.

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