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Research Article | SOJ Anesthesiology and Pain Management | Open Access

Special Issue: Anesthesia & Critical Care

A Comparison of the Hemodynamic Effects of Alfaxalone and Propofol in Pigs

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Received: July 03, 2015; Accepted: August 07, 2015, Published: August 20, 2015

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Abstract

Objective: The hemodynamic effects of alfaxalone and propofol on the cardiovascular system during anesthetic maintenance in experimental medicine were investigated in pigs using a Pulse Contour-Derived Cardiac Output (Picco) thermodilution monitoring device.

Animals: In this prospective experimental study, six (alfaxalone) and seven (propofol) female Landrace pigs weighing 32.5±3.7 kg each were examined.

Procedures: Sedation was induced by administering ketamine, azaperone and atropine intramuscularly, and anesthesia was induced and maintained IV by treatment with either alfaxalone or propofol. Analgesia was achieved via pre-emptive metamizole in combination with transient remifentanil for vascular catheterization. For 2.5 hours, the following parameters were recorded every 15 min: heart rate, arterial oxygen saturation, end-tidal CO_2, rectal body temperature and central venous pressure. In addition, blood pressure, cardiac output, contractility, preload and afterload volumetric variables and extravascular lung water were recorded every 15 minutes by the PiCCO system. After these measurements were acquired, the pigs were allowed to awaken; each pig's recovery period was recorded until the animal could stand.

Results: Overall, blood pressure and cardiac output were higher in the alfaxalone group than in the propofol group. However no significant differences between the groups were detected. Recovery was smoother and less variable with propofol than with alfaxalone, which produce either excitation with a rapid recovery or persistent muscle relaxation followed by a prolonged and variable recovery period.

Conclusions and clinical relevance – This study indicates that alfaxalone (at the dosages studied) tends to produce higher hemodynamic stability than propofol for anesthesia maintenance in pigs but recovery from alfaxalone may be rougher than recovery from propofol.

Abbreviations

CO: Cardiac Output; CRI: Continuous Rate Infusion; CVP: Central Venous Pressure; ELWI: Extravascular Lung Water Index; GEDI: Global End-Diastolic Volume Index; GEF: Global Ejection Fraction; HR: Heart Rate; IM: Intramuscularly; IV: Intravenously; MAP: Mean Arterial Pressure; P_{ETCO_2}: End-Tidal CO_2; PiCCO: Pulse Contour-Derived Cardiac Output; Spo_2: Peripheral Capillary Oxygen Saturation; SV: Stroke Volume; SVRI: Systemic Vascular Resistance Index; SVV; Stroke Volume Variation

Introduction

Propofol (2,6-diisopropylphenol) and alfaxalone (3α-hydroxy-5α-pregnane-11,20-dione) are hypnotic agents used to induce general anesthesia. Due to their short half-lives, these drugs are also administered to maintain anesthesia; under these circumstances, drug treatment is followed by a controlled recovery period.

Anesthetics produce not only desirable effects such as hypnosis and relaxation but also develop various side effects, including depression of the respiratory and cardiovascular systems. These depressive effects can be associated with decrease in blood pressure and heart contractility that leads to pathophysiological conditions such as hypoxia and acidosis and results in organ hypoperfusion and tissue damage. These issues must be considered, particularly in cases involving long-term anesthesia and/or high-risk patients with decreased cardiac compensatory mechanisms.

Pigs were chosen for this study to enable the use of a human-sized PiCCO hemodynamic monitoring system. Investigative data are particularly interesting for anesthesia in the context of experimental medicine, which requires standardized and stable cardiovascular system conditions. For instance, anesthetic-induced depression of the circulatory system would affect the validity of pharmacokinetic and pharmacodynamic studies by only allowing parameters to be recorded under suboptimal blood pressure

conditions. Inhalational anesthetics may cause problems in pigs with unknown genetic backgrounds due to a potential predisposition for malignant hyperthermia. Therefore, propofol and other well-controlled and relatively non-cumulative injectable agents are often preferred for use in porcine studies [1]. Propofol is already used in pigs in experimental medicine; however, comparative studies in dogs and cats [2-5], have indicated that alfaxalone produce similar cardiovascular conditions compared to propofol. Particularly in the study from Ambrose et al. [3] alfaxalone produced excellent induction of anesthesia, maintenance and recovery in dogs similar to propofol. Therefore, in the current study, the question of whether this effect would also be observed in pigs was tested.

The objective of this study in pigs was to determine the most stable and gentle hypnotic agent with respect to the cardiovascular system; ideally, this agent should also be relatively non-cumulative. This investigation was followed by using previous studies that investigated the direct short-term cardiovascular effects of alfaxalone and propofol on porcine hemodynamic function [6,7].

Materials and Methods

Animal husbandry

The propofol and alfaxalone groups of this study consisted of seven and six female Landrace pigs, respectively, with body weights (expressed as means±SD) of 31.3±3.5 kg and 34.9±3.3 kg, respectively.

The pigs were obtained from an experimental breeding colony[a] and were group-housed (3m^2 per 2 animals) under conventional hygienic conditions at a temperature of 19±2°C and a relative humidity level of 50% to 60%. A cycle of 12 hours of light followed by 12 hours of dark was maintained. The animals were free from recognized pathogens. Accordingly, the pathogen status of the animals was regularly checked according to the German Guidelines about Hygienic Conditions for Keeping Pigs (Schweinehaltungshygieneverordnung [SchHaltHygV]). The pigs were fed a commercial pelleted diet[b] twice daily and received water ad libitum. All animals were made acclimatized to their new environment for at least 7 days. The animals were supplied with plastic balls, empty plastic bottles, plastic shoes, and other enrichment items. Prior to anesthesia, the pigs were starved for 12 hours but allowed free access to water.

The study protocol was approved by the local animal care committee and performed in accordance with the German Animal Welfare Act (Deutsches Tierschutzgesetz).

Anesthesia

On the day of the experiment, each pig was weighed and visually examined. Experiments were conducted between 8 AM and noon. Sedation was induced by administrating 10 mg/kg ketamine[c], 2 mg/kg azaperone[d] and 0.029mg/kg atropine[e] Intramuscularly (IM) in a single syringe. An intravenous catheter[f] was inserted into the lateral auricular vein. Anesthesia was induced intravenously by treatment with the supposed half dose of either alfaxalone[g] or propofol[h]. After this, the anesthetics were injected to effect aiming a good muscle relaxation and the loss of the swallowing reflex. To reach this, a total dose of either 1.6±0.7 mg/kg alfaxalone or 3.5±0.7 mg/kg propofol was injected intravenously for induction of anesthesia in the pigs. After the swallowing reflex was no longer evident, the trachea was intubated (tube size: 7 to 7.5mm). For the intubation, pigs were dorsally positioned and the glottis was visualized using a long, straight laryngoscope. For pre-emptive analgesia, a single bolus of 40mg/kg metamizole[i] (which is also known as dipyrone) diluted in 20 ml of saline was administered slowly and intravenously (IV) after the induction of anesthesia. Each pig was ventilated[j] with at least 40% oxygen at 12 - 17 breaths/min and with a peak ventilation pressure of 10–20 mbar. Pulse rate and SpO_2 were monitored using a pulse oximeter[k], and end-tidal CO_2. Monitoring rectal body temperature by Ventilator[i] was also included.

Anesthesia was maintained IV with a Continuous Rate Infusion (CRI) of either 13.4±0.8 mg/kg/h alfaxalone[g] or 11.9±0.4mg/kg/h propofol[l]. At these doses, a stable level of hypnosis was maintained, as evidenced by good muscle relaxation and highly stable values of the monitored variables (heart rate, blood pressure, Spo_2 and $PETCO_2$). For the choice of the anesthetic dose range, similar studies on the cardiopulmonary effects of continuous rate infusions of propofol and alfaxalone in dogs [3,8] were used for orientation. Fluids were provided by a CRI of Ringer's solution at a maintenance dose of 10mL/kg/h. To avoid circulatory overload in the tested pigs, all quantities of additional fluids infused for PiCCO measurements[m] were subtracted from the baseline infusion rate.

Experimental protocol

Further vascular catheters were inserted into the left external jugular vein[n] and a superficial branch of the left iliac artery[o]. During this procedure, anesthesia was maintained IV with a continuous rate infusion (CRI) of either 13.4±0.8 mg/kg/h alfaxalone[g] or 11.9±0.4mg/kg/h propofol[l] and sufficient analgesia was achieved by a CRI of 0.0065±0.001 mg/kg/h of remifentanil[p]. Immediately after the completion of invasive procedures, this CRI of remifentanil was stopped, and a wash-out period of at least 10 minutes was observed. All surgical procedures (insertion of vascular catheters) were completed in a sterile fashion; in addition, after the induction of anesthesia, each pig received 750 mg of the antibiotic cefuroxime[q].

After catheter insertion, central venous pressure could be recorded[r]. The 2.5-hour experimental period began after the remifentanil wash-out period. During this time, PiCCO hemodynamic monitoring findings were recorded every 15 minutes, with concurrent monitoring of each animal's anesthetic state.

After the end of the anesthetic experimental period, all catheters were removed under sterile conditions, the CRI of the hypnotic was stopped, and each pig received 4 mg/kg carprofen[s] per day for 48 hours for postoperative analgesia.

The recovery phase was observed until each animal could stand and move normally. During this recovery period after the infusion of the hypnotic had stopped, the following parameters and behaviors were recorded: the return of reflexes (e.g., the ear pinch reflex, the eyelid reflex and the righting reflex); muscle, jaw and tongue tone; swallowing; extubation; head lifting; the first

attempts to stand up and to stand alone; and negative side effects such as excitation.

The study was conducted as a randomized (random allocation to the anesthetic group [either propofol or alfaxalone] was performed in a one to one ratio) single-blinded study. Therefore people were blinded to drug administration and the parameter recording.

PiCCO technique

This technique for evaluating hemodynamic parameters involves a combination of two methods: a continuous method based on pulse-contour analysis and a discontinuous method based on transcardiopulmonary thermodilution. The sensor catheter placed in the superficial branch of the left iliac artery[o] can directly measure blood pressure and blood temperature. The PiCCO technique provides not only the information that can be obtained using pressure-based methods of hemodynamic measurement but also volumetric variable data. Index parameters are normalized to body surface or body weight. After an initial calibration by transcardiopulmonary thermodilution, cardiac output can be recorded in real-time by pulse-contour analysis. The PiCCO technique already has been used in pigs; particularly in cardiovascular and pulmonary research [9-11].

Transcardiopulmonary thermodilution measurements were performed every 15 minutes by 3 successive bolus injections of cold saline (10 ml each, <8°C) into the left jugular vein via a PiCCO injection pin. Each defined saline bolus arrived in diluted form at the arterial sensor catheter, allowing a thermodilution curve to be recorded. The PiCCO technique includes two different measuring methods – a discontinuous method based on transcardiopulmonary thermodilution and a continuous method based on pulse contour analysis [12,13,14]. This curve is dependent on cardiac output (blood volume/time) [15], the quantity of fluid within vessels and extravascular compounds. Cardiac Output (CO) is dependent on Stroke Volume (SV) and Heart Rate (HR) and thus varies based on the preload, afterload, and contractility, as specified by the Frank-Starling mechanism. The preload can be determined by the Global End-Diastolic Volume Index (GEDI), and the Extravascular Lung Water Index (ELWI) is an indicator of potential lung edema. The Systemic Vascular Resistance Index (SVRI) is a parameter that defines the afterload. The contractility of the heart is indicated by the dPmax (left ventricle) and Global Ejection Fraction (GEF) parameters [14,16]. High variability of the arterial pressure curve under mechanical ventilation and of preload parameters such as GEDI can also explain the positive volume reaction, which refers to the effects of infused fluid on circulation. However, baseline volume deficiencies prior to anesthesia were unknown. Therefore, there may have been individual variance in PiCCO preload data. A stroke volume variation (SVV) of >10% in a patient under controlled ventilation suggests a volume deficiency [16,17].

Statistical evaluation

Descriptive statistics (expressed as means ± SD) are reported for all data. Statistics were compared in the context of an exploratory data analysis; thus, no corrections for type I errors were considered. All statistical tests were two-sided, and p values of less than 0.05 were regarded as statistically significant.

To evaluate the overall time trends of response variable of interest, Linear Mixed Regression Models (Lmms) with monotonic (linear), transient (quadratic) and cubic time effects were fitted to the data. The linear mixed regression modeling approach appropriately reflects the structure of repeated data and accounts for correlations between measurements for the same subject. A first-order autoregressive correlation structure and random effects for each pig were considered in the regression analyses. Time effects were first specified by graphic assessment and then verified by stepwise model derivation. When a specific time effect was detected in the global trend analysis, a post hoc Student's *t*-test for paired samples was used to assess differences between values at each time point during the 2.5-hour examination period and the baseline value (the value at the first time point). Furthermore, to separately compare equivalent time points for the two medication groups, a global Kruskal-Wallis test was utilized as a non-parametric test that did not require normally distributed data. All statistical analyses were conducted using commercially available software[t].

Results

PiCCO hemodynamic monitoring

The main results of the statistical data analysis are summarized in tables 1, 2 and 3. The measuring period consisted of 11 time points (presented as means±SD) spaced at 15-minute intervals over the 2.5-hour experimental period.

Heart rate (HR) significantly increased over time. However, due to considerable data dispersion, post hoc comparisons to the baseline did not produce statistically significant results in either group. There was no statistically significant difference between the two groups with respect to mean HR level.

Mean Arterial Pressure (MAP) increased significantly over time. In the propofol group, this increase was significant in post hoc tests (for time points 2–6). In the alfaxalone group, higher standard deviations were observed; thus, comparisons to the baseline resulted in no statistically significant differences. In addition, MAP increases over time in the two medication groups did not significantly differ; however, significantly different mean MAP levels were observed in the propofol and alfaxalone groups (mean difference: 14.1±5.1 mmHg; *p=0.018*); in particular, MAP was at higher levels in the alfaxalone group than in the propofol group.

Cardiac output (CO) also tended to be higher for the alfaxalone group relative to the propofol group (mean difference: 0.50±0.45 L/min; *p=0.29*). In the propofol group, minor time effects that were not statistically significant in post hoc tests were observed.

Blood temperature increased significantly by 0.149±0.006°C over time in both medication groups (significant at all time points), but the two medication groups exhibited no significant

Table 1: Heart rate and MAP in propofol-anesthetized (P) and alfaxalone-anesthetized (A) pigs, as recorded every 15 minutes by PiCCO.

	Mean±standard deviation			
Time (min)	**(P)HR (bpm)**	**(A)HR (bpm)**	**(P)MAP (mmHg)**	**(A)MAP (mmHg)**
Baseline	98±20	103±21	71±11	86±9
15	99±20	104±19	**74±10**	88±11
30	99±18	104±17	**76±10**	90±16
45	99±16	103±16	**78±8**	91±13
60	98±15	103±15	**79±6**	92±12
75	100±14	104±16	**80±6**	92±11
90	99±12	106±16	79±7	92±10
105	100±11	107±17	79±6	93±11
120	101±12	107±16	79±6	94±11
135	105±13	111±17	79±6	92±12
150	107±12	113±16	78±4	92±14
[a] LMM:				
Intercept	**96.977**	103.683	**67.826**	83.436
Time (linear)	1.505	-0.644	**3.102**	2.380
Time (quadratic)	**-0.368**	0.131	**-0.196**	-0.147
Time (cubic)	**0.029**	***	***	***

Mean±SD: HR: Heart Rate; MAP: Mean Arterial Pressure; PiCCO: Pulse Contour-Derived Cardiac Output
Measurements with p-values <0.05 relative to the baseline measurement are presented **in bold**.
[a] A Linear Mixed Model (LMM) with individual random effects and an autoregressive correlation structure. This model could be represented by the following equation: predicted value = intercept + (time × $coef_1$) + (time^2 × $coef_2$), where
$coef_1$ = the slope of the predicted value per minute increment of time;
$coef_2$ = the additive change in the predicted value that is dependent on time squared (minute^2)
** data assessment clearly revealed no quadratic time trends;
*** data assessment clearly revealed no cubic time trends.

Table 2: SVRI and CO in propofol-anesthetized (P) and alfaxalone-anesthetized (A) pigs, as recorded every 15 minutes by PiCCO.

	Mean±standard deviation			
Time (min)	**(P)SVRI (dyn*s*cm^{-5}*m^{-2})**	**(A)SVRI (dyn*s*cm^{-5}*m^{-2})**	**(P)CO (L/min)**	**(A)CO (L/min)**
Baseline	1138±208	1715±1212	4.62±0.93	5.25±0.71
15	1813±1642	1303±252	4.71±0.95	5.29±0.68
30	1186±282	1338±320	4.86±1.03	5.26±0.67
45	1258±174	1393±249	4.77±0.95	5.11±0.64
60	1271±133	1402±237	4.74±0.94	5.13±0.68
75	1289±126	1420±279	4.73±0.88	5.10±0.90
90	1300±117	1643±783	4.71±0.86	4.93±1.33
105	1292±154	1448±308	4.79±0.81	5.12±0.97
120	1296±177	1639±728	4.64±0.81	4.95±1.27
135	1299±163	1387±291	4.65±0.77	5.36±1.30
150	1234±210	1376±288	4.88±0.84	5.30±1.23
[a] LMM:				
Intercept	**1358.511**	1528.203	**4.404**	5.208
Time (linear)	-9.061	-9.878	**0.271**	0.004
Time (quadratic)	**	**	**-0.055**	**
Time (cubic)	***	***	**0.003**	***

SVRI: Systemic Vascular Resistance Index; CO: Cardiac Output; PiCCO: Pulse Contour-Derived Cardiac Output.
Measurements with p-values <0.05 relative to the baseline measurement are presented **in bold**.
[a] A Linear Mixed Model (LMM) with individual random effects and an autoregressive correlation structure. This model could be represented by the following equation: predicted value = intercept + (time × $coef_1$) + (time^2 × $coef_2$), where
$coef_1$ = the slope of the predicted value per minute increment of time and
$coef_2$ = the additive change in the predicted value that is dependent on time squared (minute^2);
** data assessment clearly revealed no quadratic time trends;
*** data assessment clearly revealed no cubic time trends.

Table 3: Blood temperature in propofol-anesthetized (P) and alfaxalone-anesthetized (A) pigs, as recorded every 15 minutes by PiCCO.

	Mean±standard deviation	
Time (min)	**(P)BT (°C)**	**(A)BT (°C)**
Baseline	37.5±0.6	37.7±1.0
15	**37.6±0.7**	**37.8±1.0**
30	**37.8±0.7**	**38.0±1.1**
45	**38.0±0.7**	**38.0±1.1**
60	**38.2±0.8**	**38.2±1.1**
75	**38.3±0.8**	**38.3±1.1**
90	**38.5±0.8**	**38.5±1.1**
105	**38.6±0.7**	**38.6±1.1**
120	**38.7±0.7**	**38.7±1.1**
135	**38.8±0.7**	**38.9±1.1**
150	**38.9±0.7**	**39.0±1.1**
[a] LMM:		
Intercept	**37.340**	**37.502**
Time (linear)	**0.146**	**0.173**
Time (quadratic)	**	**-0.009**
Time (cubic)	***	**0.001**

BT: Blood Temperature; PiCCO: Pulse Contour-Derived Cardiac Output. Measurements with p-values <0.05 relative to the baseline measurement are presented **in bold**.

[a] A Linear Mixed Model (LMM) with individual random effects and an autoregressive correlation structure. This model could be represented by the following equation: predicted value = intercept + (time × $coef_1$) + (time^2 × $coef_2$), where

$coef_1$ = the slope of the predicted value per minute increment of time and

$coef_2$ = the additive change in the predicted value that is dependent on time squared (minute^2);

** data assessment clearly revealed no quadratic time trends;

*** data assessment clearly revealed no cubic time trends.

differences in mean blood temperature.

SVRI, GEDI, CFI, SVV and ELWI did not significantly differ between the two medication groups. In the propofol group, CFI was significantly higher at time points 4-6 than at baseline, but only minor time effects on CFI were detected in the alfaxalone group. For dPmax, a significant increase of 13.563±3.501 was observed as global trend over time for both graphs. However, no significant differences in means between medication groups were found in the post hoc Student's *t*-test for paired samples. GEF exhibited a significant decrease of 0.439±0.137 over time in the propofol group.

Anesthetic monitoring parameters

These variables were recorded simultaneously during the 2.5-hour measuring period. $PETCO_2$ values were held constant by mechanical ventilation and SpO_2 did not significantly change.

Recovery phase

The recovery phase data are summarized in table 4. Behavioral data were recorded after the CRI of the hypnotic was stopped. There were no statistically significant differences in central tendency over time. However, the alfaxalone group demonstrated significantly higher variability than the propofol group for the assessed activities. In the alfaxalone group, two different types of recoveries could be clinically observed:

a) A relaxed recuperation with a prolonged recovery caused by the late return of muscle tone (2 animals)

b) An excitatory recuperation with a short but rough recovery period (4 animals).

Although mean values for the propofol and alfaxalone groups were comparable, the standard deviations for these groups significantly differed.

Discussion

The reports regarding the direct, short-term cardiovascular effects of the hypnotics propofol and alfaxalone on hemodynamic function have already been published [6,7], the objective of the current study was to determine the hemodynamic and cumulative effects of these hypnotics during anaesthesia of 2.5 h in pigs.

Similar studies on the cardiopulmonary effects of continuous rate infusions have been performed in dogs [3,8], after premedication with the Neuroleptanalgesia acepromazine and opioids. In these studies, researchers used either propofol or alfaxalone to induce and maintain anesthesia in the examined dogs; they concluded that similar mild hemodynamic changes were observed for both anesthetics. In our study, it was evident that all important hemodynamic metrics, such as HR, MAP, SVRI and CO, began at a higher level in the alfaxalone group than in the propofol group at the initial baseline PiCCO measurement. In particular, MAP and CO subsequently exhibited superior values in the alfaxalone group than in the propofol group. However, MAP values in the propofol group remained in the normal physiological range, and no associated changes in HR were detected in this group. This phenomenon can be explained by the constant rate of hypnotic infusion that occurred in the absence of a bolus injection,

Table 4: Recovery in pigs anesthetized with propofol or alfaxalone.

	Mean ± standard deviation				
Time (min)	**Positive ear pinch reflex**	**Extubation**	**Head lifting**	**First standing attempt**	**Standing alone**
Propofol	34±7 Δ	46±14 Δ	68±28	100±25 Δ	137±30 Δ
Alfaxalone	38±33	57±52	96±48	122±63	139±68

Δ *p<0.05* for comparison of the standard deviations of propofol and alfaxalone

given that after a bolus injection, an extremely brief baroreceptor reflex response could be observed for both hypnotics directly after the bolus injections [6,7]. A primary decrease in heart rate due to propofol is typically not evident; instead, heart rate typically increases due to blood pressure depression [18]. Following fentanyl treatment, propofol exacerbates negative chronotropism, whereas alfaxalone maintains or increases heart rate [5]. Other studies have reported that propofol causes dose-dependent decreases in arterial blood pressure as a consequence of decreases in peripheral vascular resistance and the heart ejection fraction [19]. The extent of this blood pressure depression depends on plasma concentration. The impacts of sympathetic tone and of decreased cardiac output as a result of decreased preload have been discussed [20]. We could not observe this phenomenon in the current study. Other studies have assumed that propofol directly produces negative inotropic effects at the myocardium [19], leading to decreased cardiac ejection volume.

Reports have indicated that alfaxalone also decreases systolic arterial blood pressure in a dose-dependent manner due to reduced peripheral vascular resistance [21], although no direct negative inotropic effects have been observed [22]. In dogs and cats, the initial hypotonic effects of alfaxalone stabilize back to baseline values within 15 minutes [23,24].

Altogether, the collected hemodynamic data of the propofol and the alfaxalone study group must be carefully interpreted as the drugs used for sedation (ketamine and azaperone) and analgesia (metamizole, synonym: dipyrone, an antipyretic pyrazolone drug) might also have an impact on the cardiovascular function.

Heart rate and blood pressure increased slightly over the 2.5-hour measuring period in both groups. This phenomenon could indicate either a feeling of pain or a decreased level of hypnosis. With respect to the operating procedure prior to the measuring period, analgesia was regarded as sufficient when HR was not increasing and no reaction could be detected by pinching the well-innervated nose septum with fingernails. Neither propofol nor alfaxalone have notable analgesic properties; consequently, to perform surgical procedures (insertion of vascular catheters), these drugs must be combined with analgesics [25,26]. Remifentanil, a μ-receptor opioid agonist, was chosen for use in this study due to its extremely short duration of action (ca. 10 min [27]), which allows its effects to be more controllable than the effects of fentanyl. Because remifentanil is primarily inactivated by non-specific plasma and tissue esterases, its effects are largely independent of liver and kidney metabolism [28,29,30]. To avoid hemodynamic interaction caused by the presence of remifentanil, a wash-out period of at least 10 minutes was included in the study protocol During the non-painful measuring time, only metamizole continued to produce analgesic effects (for 6 - 8 hours in pigs [31]). Because the observed increases in blood pressure were rather slow and gradual, a decreasing level of hypnosis was the most likely explanation for these increase. In certain animals, spontaneous breaths and an elicitable eyelid reflex in conjunction with an increased HR could be observed at the end of the 2.5-hour measuring period. If the clinical monitoring parameters indicated a beginning lighter plane of hypnosis, a bolus should be avoided and only CRI was slightly adjusted by effect (increased in 2 ml/h steps) until the monitoring parameters stabilized again. Using this approach, a satisfactory level of hypnosis was once again achieved, allowing us to complete our measurements. At the end, the total dosage needed was calculated for the group. Because not all of the tested animals exhibited the aforementioned phenomenon, it was impossible to maintain the same CRI dose for all animals throughout the entire measuring period; the resulting differences in CRI doses could have influenced the recorded data and contributed to the individual variability during the recovery period. One explanation for this phenomenon could be that relative to adult pigs, young pigs have faster metabolisms, greater microsomal enzyme activity in the liver and less fat tissue[1]. Propofol is formulated in an oil-in-water emulsion containing glycerol, egg lecithin and soybean oil. Thus, propofol is rapidly distributed from blood into well-perfused tissue, such as the CNS, within 2–3 minutes; it is then redistributed into poorly perfused tissue (particularly fat) and slowly returns from this tissue into the blood. In dogs Nolan and Reid [32] described for the pharmacokinetic phase 3 a slow return of the drug from the poorly perfused tissue (especially fat) into blood up to 5h. However, plasma levels are clinically not effective. Furthermore, Banaszczyk et al. described the water-soluble propofol prodrug propofol phosphate as having an elimination half-life of 225±56 min in pigs [33]. However, the high elimination of propofol is caused by hepatic glucuronidation and sulphidation [25,34]. In contrast, alfaxalone is a neuroactive, highly lipophilic steroid molecule (progesterone derivative) that penetrates into the CNS extremely rapidly. Anesthesia duration is determined by hepatic cytochrome P-450 glucuronidation, with fully 70% of inactive metabolites eliminated within 3 hours [22].

In this study, two types of recovery from alfaxalone treatment were observed in the examined pigs: a relaxed recuperation involving a prolonged period of decreased muscle tone and psychomotor excitation consistent with descriptions in the literature [4]. The recommended approach for promoting a calm recovery after alfaxalone treatment involves administering this drug in conjunction with premedication, which all pigs in the current study received. Our results are similar to the findings in cats reported by Boesing et al. [35] and Mathis et al. [4], who described a smooth recovery for most cats after short-term anesthesia, although mild signs of hyperexcitability (muscle tremors, short-term opisthotonus and hyperacusis) occurred in individual animals. Recovery duration markedly varied among the observed cats; similarly, we also observed varying recovery durations among the pigs examined in the current study. In dog studies by Ambros et al [3] and Suarez et al. [8], animals exhibited good recovery quality, although median recovery times were approximately one-third shorter in the propofol group than in the alfaxalone group.

The PiCCO device generally worked well in the pigs as already described in other studies [9,10,11]. However, in one animal of each group an unexplainable high SVRI value (propofol at 15 min; alfaxalone at baseline) was observed at two time points. As it was not obvious if this was a measuring error for this parameter or not, data from these two animals were not excluded, resulting in higher standard deviations at the two time points.

In summary, this study indicates that relative to propofol, alfaxalone (at the dosages studied) may tend to promote higher blood pressure and cardiac output levels during anesthesia maintenance in pigs; however, recovery quality after alfaxalone treatment may exhibit large individual variance, with potential excitation during the recovery period.

Disclosures: The authors declare no conflicts of interest.

Footnotes

a. Versuchsstation Thalhausen, Germany

b. deuka Kornmast 130 gekoernt, Alleinfuttermittel für Mastschweine, Deutsche Tiernahrung Cremer GmbH and Co KG, Regensburg, Germany

c. Narketan 10, Vétoquinol, Ravensburg, Germany

d. Stresnil, Janssen Animal Health, Neuss, Germany

e. Atropin B. Braun, Melsungen, Germany

f. Vasofix, 0.9 X 25 mm, B. Braun, Melsungen, Germany

g. Alfaxan, Vétoquinol, Ravensburg, Germany

h. Propofol 1% MCT Fresenius, Fresenius Kabi Deutschland GmbH, Bad Homburg, Germany

i. Novaminsulfon-ratiopharm 2.5; Ratiopharm GmbH, Ulm, Germany

j. Cicero, Draeger Medizintechnik, Luebeck, Germany

k. 8600 V, Nonin Medical, Inc., Plymouth, USA

l. Propofol 2% MCT Fresenius, Fresenius Kabi Deutschland GmbH, Bad Homburg, Germany

m. PULSION Medical Systems SE, Feldkirchen, Germany

n. 50 cm CH08 tube/X-ray line; Unomedical, Birkerod, Denmark

o. PiCCO A. brachialis catheter 16cm 4F, PVPK2014L16-46N, Pulsion Medical Systems AG, Munich, Germany

p. Ultiva 5mg, GlaxoSmithKline, Munich, Germany

q. Cefuroxime, Fresenius Kabi, Graz, Austria

r. Datex Ohmeda S/5 Type F-CM1.00 pressure transducers, Hellige Type 4-327-I, Datex Ohmeda, Helsinki, Finland

s. Rimadyl, Pfizer, Karlsruhe, Germany

t. SPSS, version 19; IBM, Munich, Germany

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