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A comparison of propofol and alfaxalone in a continuous rate infusion in dogs with mitral valve insufficiency

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Abstract: The aim of this study was to compare alfaxalone and propofol in balanced anaesthesia using midazolam 0.5 mg/kg, xylazine 0.125 mg/kg, butorphanol 0.2 mg/kg intravenously as premedication and the ultrashort acting anaesthetics alfaxalone or propofol for inducing and maintaining in dogs with medically stabilised mitral valve regurgitation. Seven client-owned dogs with a second stage cardiac insufficiency were used in this study. All the dogs suffered from class II cardiac insufficiency according to the classification by the International Small Animal Cardiac Health Council (ISACH). All the dogs were treated with angiotensin converting enzyme inhibitors (enalapril) and diuretics (furosemide), which eliminated the clinical signs of mitral valve regurgitation in all the dogs included in the study. This was a prospective controlled clinical study, 12 months in duration, when the dogs included in the study underwent regular dental prophylaxis. The dogs were monitored electrocardiographically throughout the anaesthesia for the presence of arrhythmias, % oxygen saturation of haemoglobin (%SpO_2) measured by pulse oximetry, heart rate, respiratory rate and body temperature. The dogs underwent two anaesthesia procedures with an interval of one year due to the prophylaxis of periodontitis, with the first anaesthesia maintained by propofol and second one by alfaxalone. The respiratory rate was mostly significantly higher in the individuals undergoing alfaxalone anaesthesia ($P < 0.05$), but neither the slower respiratory frequency in the propofol anaesthesia had any negative impact on the % oxygen saturation of the haemoglobin (%SpO_2). The heart frequency was significantly higher in the alfaxalone group ($P < 0.005$). The arterial blood pressures were comparable, but, on the contrary, the two dogs from propofol group had significantly higher blood pressure. The cardiovascular values in both types of anaesthesia had a tendency to progressively decrease within the physiological range. The level of the analgesia was significantly higher in the case of the propofol anaesthesia ($P < 0.01$) and the recovery period was also significantly shorter ($P < 0.005$). It can be concluded that the investigated ultra short acting anaesthetics used in balanced anaesthesia containing subanaesthetic doses of xylazine can be used over one hour of surgical procedures in dogs stabilised for mitral valve regurgitation without a significantly increased risk from the anaesthesia.

Keywords: ultrashort anaesthetics; intravenous anaesthesia; cardiac disease; small animal

Balanced anaesthesia using a combination of different sedatives, anaesthetic, analgesics provides muscle relaxation, analgesia and hypnosis with minimal adverse effects from the used individual drugs. The synergistic effect of the preanesthetic medications presents an important role in balanced

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anaesthesia. Alfaxalone, highly soluble in water, is a synthetic neuroactive steroid that may be used for the induction and maintenance of an anaesthesia in small animals. Alfaxalone as a short acting, non-cumulative aesthetic has a high therapeutic index. It has a good pharmacological profile and, in healthy dogs, has a minimal cardio-pulmonal depressive effect (Ferre et al. 2006). When used in clinically recommended doses, the effect on the cardiovascular system is similar as propofol (Ambros et al. 2008). The literature describes the use of alfaxalone with a variety of pre-anaesthetic medications including opioid analgesics, benzodiazepine derivates, α-2 adrenergic agonists, phenothiazines. In non-premedicated healthy dogs, supra-clinical doses of alfaxalone produce an increased heart rate and a dose-dependent decrease in the blood pressure, systemic vascular resistance and cardiac output (Muir et al. 2008).

Propofol is an ultrashort acting nonbarbiturate intravenous anaesthetic which is relatively non-cumulative. In comparison with alfaxalone, it produces minimal analgesia at sub-hypnotic doses. The short action of propofol is a result of the extensive metabolism producing inactive metabolites following rapid redistribution. In humans, the plasma clearance rate of propofol exceeds the hepatic blood flow (Kay et al. 1985).

Mitral valve regurgitation represents a common cardiac disease in dogs, accounting for approximately 75–80% of all cardiac diseases. Generally, it is diagnosed in geriatric dogs, however, a breed predisposition has been also described in Chihuahuas, Cavalier King Charles Spaniels, Poodles and Papillons (Buchanan 1999; Sisson and Kvart 1999). According to the severity of the disease, three stages are distinguished (Steinbacher and Dorfelt 2012). Stage I includes asymptomatic animals. This group is further divided into IA with no evidence of radiographic cardiomegaly and IB with radiographic evidence of cardiomegaly. Stage II represents mild to moderate cardiac insufficiency accompanied by reduced exercise tolerance, a mildly increased respiratory rate at rest, dyspnoea and coughing on physical exertion (Hagstrom et al. 2005). Severe cardiac insufficiency is classified as stage III. Clinical signs are dyspnoea and coughing at rest, oedema.

In literature, inhalation anaesthetics are mostly recommended to maintain general anaesthesia in dogs with mitral valve regurgitation. Propofol and alfaxalone are often used for the induction into inhalation anaesthesia. α-2 adrenergic agonist xylazine is not suitable for cardiac patients in commonly recommended doses due to the cardio-depressive effect. Based on the experience with the use of xylazine, benzodiazepines, opioid analgesics and ultra-short acting non-barbiturate anaesthetics in the healthy patients with minimal depressive effects and recovery, we suppose a similar pattern of general anaesthesia in patients with stabilised mitral valve insufficiency.

The aim of this study was to compare the clinical efficacy, cardiovascular and respiratory effects of alfaxalone and propofol under totally intravenous anaesthesia with premedication containing subanaesthetic doses of xylazine in medically stabilised dogs with mitral valve insufficiency.

MATERIAL AND METHODS

The study included seven client-owned dogs (two males and five females), the breed of a Chihuahua, aged from 9 to 14 years (a mean of 11.85 ± 1.95 SD) with second stage cardiac insufficiency. The weight of the dogs ranged from 2 kg to 2.7 kg (a mean of 2.35 ± 0.26 SD). All the dogs suffered from class II cardiac insufficiency according to the classification by the International Small Animal Cardiac Health Council (ISACH). All the dogs were treated with an application of angiotensin converting enzyme inhibitors (enalapril 0.5 mg/kg BID) and diuretics (furosemide 1 mg/kg BID), which eliminated the clinical signs of mitral valve regurgitation in all the dogs included in the study. This was a prospective, controlled clinical study, 12 months in duration, when the dogs included in the study underwent regular dental prophylaxis. The study was approved by the Animal Use and Care Committee at the University of Veterinary Medicine and Pharmacy in Košice. The dog owners were informed about the anaesthesia and agreed to the procedure by their signature on the patient's treatment form. The dogs were premedicated in both cases using 0.5 mg/kg of midazolam (Chiesi Pharmaceuticals, Vienna, Austria), 0.2 mg/kg of butorphanol (Richter Pharma AG, Wels, Austria) and 0.125 mg/kg of xylazine (Bioveta, Ivanovice na Hané, Czech Republic) *i.v.* mixed in one syringe. The monitored variables were noted immediately before the induction into the general anaesthesia. Induction into the general anaesthesia was conducted for three minutes follow-

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ing the premedication in the first stage of the study with 2 mg/kg of propofol (Fresenius Kabi GmbH, Graz, Austria) *i.v.* and maintained with a continuous infusion rate of 0.25 mg/kg/min of propofol. The induction dose of the anaesthetic was administered for 20 seconds. Following the induction of the anaesthesia, the dogs were immediately intubated to provide airway patency. The syringe with propofol also contained Ringer's lactate in the dose of 7 ml/kg/hr with the aim to provide hydration during the anaesthesia. Constant Rate Infusion (CRI) anaesthesia was conducted for one hour. The dogs were monitored electrocardiographically throughout the anaesthesia for the presence of arrhythmias, % oxygen saturation of haemoglobin (%SpO_2) measured by pulse oximetry, heart rate, respiratory rate and body temperature. An EDAN iM8 VET patient monitor served for this purpose. The electrical pad set to 38 °C kept the body temperature at the physiological values during the anaesthesia.

The following variables were recorded at ten-minute intervals: the respiratory rate (RR), the heart rate (HR), the systolic, diastolic and mean arterial blood pressure (SAP, DAP, MAP), the elevation of the heart rate by a pain stimulus. The blood pressure was measured indirectly at the base of the tail using a VET HDO Monitor MD PRO. The pain during procedure was triggered by the haemostat pressure applied at the second digital phalanx for 30 sec and the changes in the heart rate were noted. During the recovery period (from the end of the anaesthetic administration to the spontaneous walking without external stimuli), the times of picking up the head (extubation), the sternal position and the spontaneous unstable walking were noted. The same premedication was used one year later in the same dogs. The induction and maintenance of the anaesthesia was achieved using alfaxalone (Jurox Pty Limited, Kansas City, USA) in the induction dose of 2 mg/kg and maintenance dose of 0.1 mg/kg/min *i.v.* The statistical analysis of the data was performed by use of the Student´s paired *t*-test. A probability value of < 0.05 was considered statistically significant.

RESULTS

Premedication containing the calculated doses of midazolam, butorphanol and propofol in one syringe was allowed to act for three minutes. The premedication induced recumbency, poor response to auditory stimuli, but it was not possible to intubate the animals. Induction of the anaesthesia with propofol or alfaxalone was consistently rapid and smooth. None of the dogs from either group exhibited apnoea. The respiratory rate in the individual patients is shown in Table 1. The dogs breathed the ambient air without being hypoxic during the anaesthesia. The respiratory rate did not drop under eight breaths per minute in a few periods of anaesthesia. Figure 1 shows the average respiratory rate in the individual dogs. The mean respiratory rate between the studied types of anaesthesia was mostly higher in the alfaxalone group, but not significantly. When we compare the individual dogs, there was a significant difference in respiratory rate in four of them ($P < 0.05$) and a non-significant difference in three dogs between the compared anaesthetics. The % SpO_2 ranged from 96% to 98% (mean 97.35 ± 0.61 SD) in the propofol group and from 97% to 98% (mean 97.47 ± 0.55 SD) in the alfaxalone group.

Table 1. The range of the respiratory rate and mean values during the anaesthesia

Time		Alfaxalone	Propofol
3 min after premedication		12–16 (12)	10–16 (12)
10 min	after induction	8–16 (10)	8–16 (14)
30 min	after induction	8–16 (13)	10–12 (11)
60 min	after induction	12–16 (14)	10–12 (11)

The heart rate, three minutes after premedication, ranged in the physiological values in the propofol group and in most dogs in the alfaxalone group. One dog in the alfaxalone group remained tachycardic despite premedication (Table 2, Figure 2A).

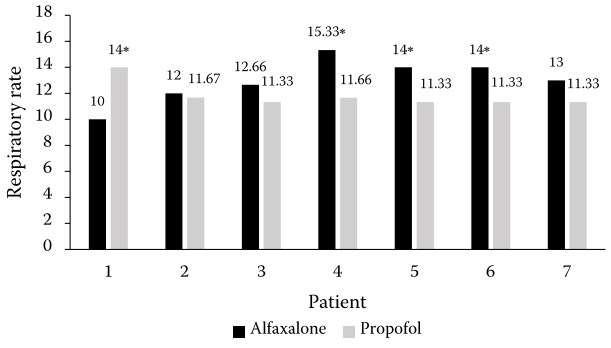

Figure 1. The mean respiratory rate in the alfaxalone and propofol groups in the individuals

*significant difference ($P < 0.05$)

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Table 2. The range of the heart rate and mean values in the groups during the anaesthesia

Time	Alfaxalone	Propofol
3 min after premedication	106–172 (129)	92–140 (111)
10 min after induction	96–174 (118)	78–128 (96)
30 min after induction	64–160 (100)	62–122 (88)
60 min after induction	64–132 (90)	68–80 (76)

At the end of the anaesthesia, the heart rate in both groups decreased, but not to bradycardic values (Table 2). The heart rhythm was regular without episodes of arrhythmias in both groups. The mean heart rate in the individuals with the alfaxalone or propofol anaesthesia was non-significantly higher in the alfaxalone group (Table 3). The mean heart rate in the propofol group ranged from 76 to 88 and from 79 to 93 in the alfaxalone group. Figure 2 compares the course of the heart rate in the dogs in both types of anaesthesia. The heart frequency compared between the alfaxalone and propofol anaesthesia in the individual dogs, confirmed a significantly higher heart frequency ($P < 0.005$) in five of the seven dogs with the alfaxalone anaesthesia. No dog showed any bradycardia indicated for the medical treatment. One dog was extensively excited before both types of anaesthesia (a heart rate of 172/140), the alfaxalone minimally decreased heart rate (from 170 to 132 at the end of the anaesthesia with a mean heart rate of 153) and the dog showed the most superficial plane of anaesthesia. The same dog with the propofol anaesthesia showed a marked decrease in the heart rate after ten minutes (from 140 to 88 and 76 at the end of the anaesthesia with a mean heart rate of 84) with no reaction to the pain stimuli (dog No. 3).

The blood pressure was comparable in both groups, but two dogs had significantly higher values

Table 3. The mean heart rate in the individuals with the alfaxalone and propofol anaesthesia

Dog	Alfaxalone	Propofol
1	78.6	76.3
2	153	84
3	92.66	88.33
4	94	84.33
5	92.66	88
6	89	78.33
7	93	83

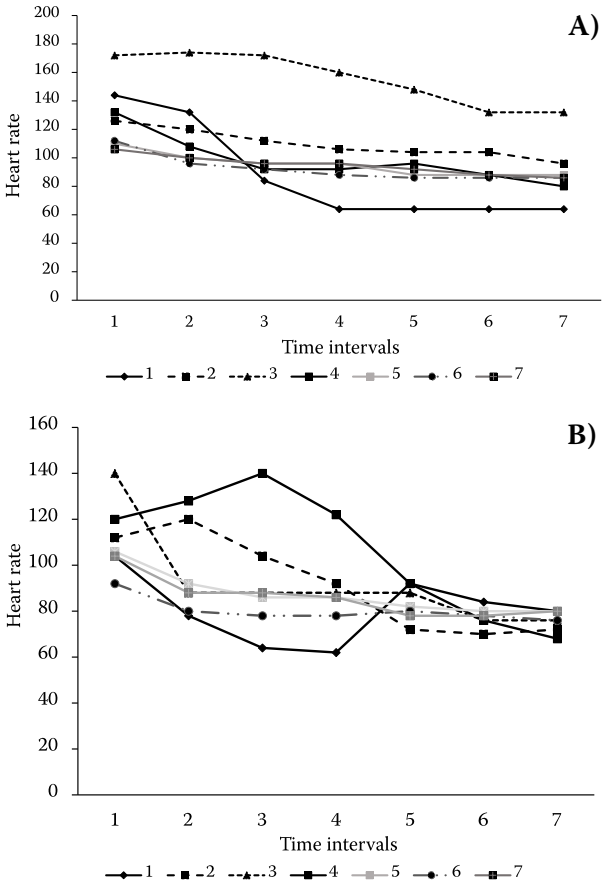

Figure 2. The heart rate in the individual patients. (**A**) Alfaxalone. (**B**) Propofol

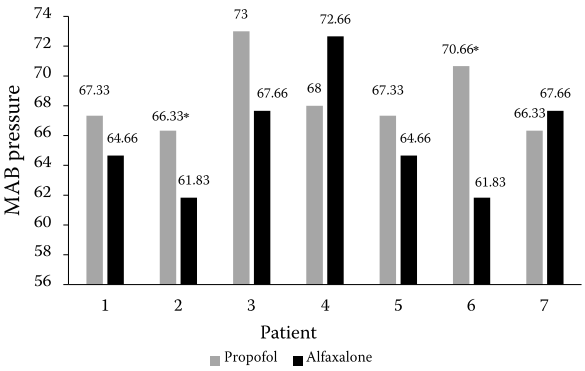

Figure 3. The mean arterial blood pressure (MAB) in the individual dogs

*significant difference ($P < 0.01$)

Table 4. The mean values of the mean arterial blood pressure in both groups

Time	Alfaxalone	Propofol
10 min	71.71	67.85
30 min	62.57	66
60 min	62.71	66.42

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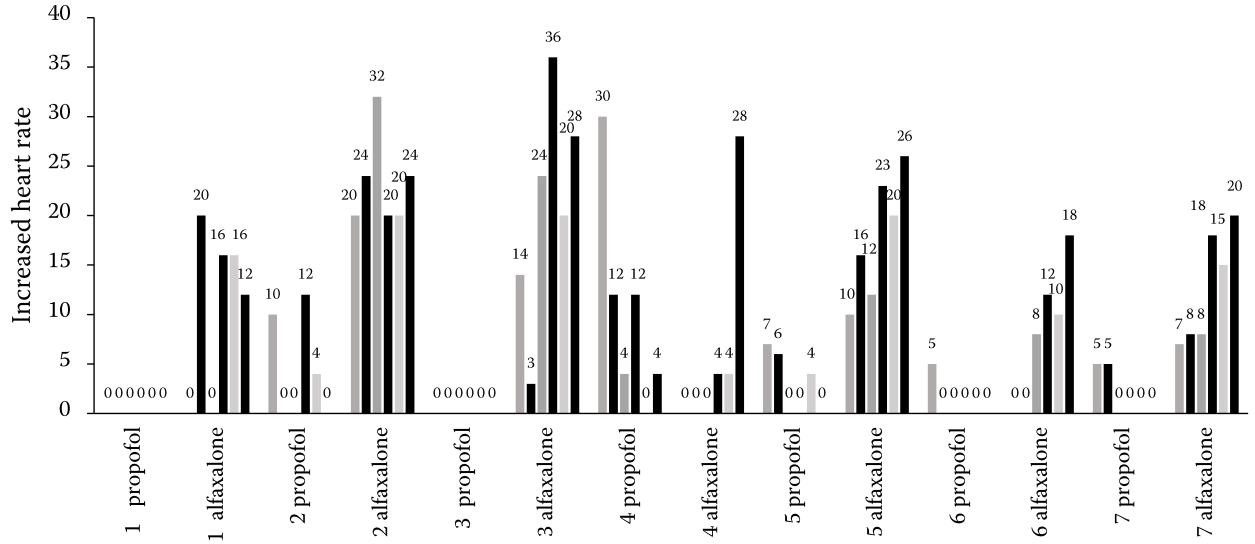

Figure 4. The heart rate increase during the elicited pain in the individual dogs in ten-minute intervals. The digits in the figure express the elevation of a minute's respiratory rate during the pain elicitation

with the propofol anaesthesia (Figure 3). The mean values of the mean arterial blood pressure during anaesthesia are expressed in Table 4.

The results related to the analgesia showed a deeper analgesic-anaesthetic effect in the propofol group. Two dogs in this group did not react to the painful stimulus and another two showed a minimal heart rate increase within the first twenty minutes of the anaesthesia (Figure 4). Pain perception was significantly higher in the alfaxalone group ($P < 0.01$). In one of the dogs undergoing the alfaxalone anaesthesia pain stimulation, it also elicited movement of the eye from the ventral to the central position. The head lift time related to the extubation in the dogs with the propofol anaesthesia ranged from 8 to 16 min and from 11 to 18 min with the alfaxalone anaesthesia. The recovery time, i.e., when the patient was able to stand up and walk ranged from 32 to 50 min in the alfaxalone group. The recovery time was significantly shorter in the propofol group ($P < 0.005$). In Figure 5, the recovery times in the individual dogs are compared.

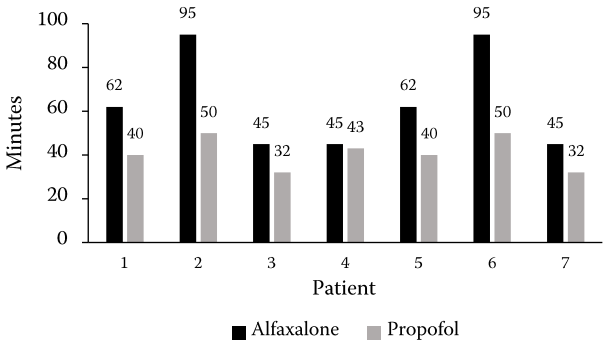

Figure 5. The recovery times in the individuals

DISCUSSION

Some articles describe propofol as an anaesthetic moderately decreasing myocardial contractility while other studies did not confirm any negative inotropic effect (Park and Lynch 1992; Cook and Housmans 1994; Mouren et al. 1994; Gelisen et al. 1996). The results in this study confirmed the cardiovascular depression of propofol compared with alfaxalone. The premedication of the patients was provided using midazolam, the shortest acting benzodiazepine derivate, xylazine with the shortest action among the α2-adrenoceptor agonists, and butorphanol, a synthetic agonist-antagonist opioid. Xylazine has good analgesic properties and sedative effects (Hall et al. 2001). The analgesic effect of xylazine is a result of the stimulation of the alpha adrenoreceptors at the central nervous system and spinal cord. In this way, it inhibits the release of neurotransmitters, substance P and norepinephrine (Kolahian 2014). Xylazine has been used in a subanaesthetic dose to prevent its cardio depressive effect and provide a synergic analgesic effect with butorphanol. No profound cardio depressive effect of xylazine at the administered dose was confirmed. In both groups of dogs, three min-

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utes after premedication, none of the dogs showed any bradycardia or other arrhythmias. ECG (electrocardiogram) monitoring did not reveal any arrhythmias in the dogs. The results confirmed, on the one hand, that the dose of xylazine used in this study did not induce the commonly described cardio depressive effects and, on the other hand, it may contribute to the synergistic analgesic and sedative effects with the opiate as published by Chabot-Dore et al. (2015). Butorphanol is a morphine-type synthetic agonist-antagonist opioid analgesic. It exhibits partial agonist and antagonist activity at the κ-opioid receptors (Gear et al. 1999). Besides, the analgesia butorphanol also produces some sedative effect. The aim of combining these three drugs was to provide acceptable sedation and analgesia using minimal doses minimalising the side effects of the single drugs. The respiratory rate reduced significantly ($P < 0.05$) from the baseline in both groups from the time of the anaesthesia induction to the time of the termination of the anaesthesia. The peripheral oxygen saturation (SpO_2) was, in both groups, within the physiological range and oxygen support was not necessary in any of the patients. The results confirmed the higher depressive effect of propofol in comparison to alfaxalone, but not negatively influencing the peripheral oxygen saturation. This multimodal anaesthesia allowed us to use the lowest recommended doses of propofol minimalising the risk of possible hypercapnia as described in some literature sources (Kastner 2007). None of the dogs experienced apnoea during both types of anaesthesia, confirming the non-significant depressive effect of alfaxalone and propofol at the doses used. The mean heart rate of the dogs in both groups reduced significantly from the preanesthetic values. When the heart rates in individual dogs are compared, five of the seven dogs significantly differed with a higher frequency under the alfaxalone anaesthesia. In one dog that was extensively excited before both types of anaesthesia, the alfaxalone decreased the heart rate minimally and the dog showed the most superficial plane of anaesthesia. The same dog under the propofol anaesthesia showed a marked decrease in the heart rate after ten minutes with no reaction to the pain stimuli (dog No. 3). This result may indicate a lower effect of the alfaxalone in stressed patients with elevated catecholamine concentrations. The blood pressure in both groups was comparable, though in the second half of the alfaxalone anaesthesia, the dogs had a somewhat lowered mean arterial blood pressure than those under the propofol anaesthesia. In both groups, the blood pressure tended to gradually lower during the anaesthesia, but without dropping to critical values. In two dogs, the mean arterial blood pressures significantly differed between the alfaxalone and propofol while the difference was not significant in the other five dogs. The dogs under the propofol anaesthesia had generally higher mean arterial blood pressures. The pain perception in the dogs evaluated through the heart rate increase following the pain stimulation showed significantly better analgesia in the propofol group. This result points to a higher central nervous system depressive effect with the propofol in comparison with the alfaxalone in the studied doses. Alfaxalone most likely needs to be administered at higher doses to achieve a similar level of analgesia as described in some other studies (Muir et al. 2008; Maddern et al. 2010). Alfaxalone, in the used dose, also caused cardiovascular depression especially in relation to the blood pressure. The higher alfaxalone doses may be associated with the increased cardiovascular and respiratory depression. The recovery time in the patients undergoing propofol anaesthesia was significantly shorter in comparison with the alfaxalone anaesthesia. A longer recovery time may be related to the metabolism of alfaxalone mainly in the liver and lower blood flow to the liver in cardiac patients.

The comparison of alfaxalone and propofol in the dogs with medically treated mitral valve regurgitation confirmed the possibility to use both ultrashort acting injection anaesthetics in surgeries terminated within one hour without significantly increased risk to the anaesthesia procedure. Alfaxalone confirmed the better influence in the respiratory frequency and heart rate, though the mean arterial blood pressures were lower in comparison with the propofol anaesthesia. Propofol confirmed a higher central nervous system depressive effect resulting in a significantly higher level of analgesia and a significantly shorter recovery period.

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