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A Comparative Study on the Use of Acepromazine/Ketamine Combination and Propofol as Induction Agents for Enflurane Anesthesia in Dogs

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개에서 Enflurane에 대한 도입마취제로서 Acepromazine/Ketamine 병용 투여와 Propofol 단독 투여에 관한 비교 연구

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요 약 : 흡입마취에서 마취를 유지하기 위해서는 도입 마취가 필수적이다. 도입 마취제는 작용시간이 짧고 기관 튜브를 용이하게 삽입할 수 있으며, 투여로 인한 생리적 영향이 적어야 한다. Acepromazine/ketamine(Group-AK) 병용 투여와 propofol(Group-P) 단독 투여로 마취 유도한 후 Enflurane으로 마취를 유지하였을 때 나타나는 생리적 변화를 비교하였다. 체온, 호흡수, 평균 동맥압, $PaCO_2$, PaO_2, pH, toe-wep pinch reflex 및 jaw tone reflex는 두 군간에서 유의성 있는 차이가 나타나지 않았다. Group-P은 group-AK 보다 회복 시간이 유의성 있게 짧았다. 심박수는 group-AK군이 마취 후 5분에서 group-P보다 유의성 있게 증가하였다. 동성 빈맥은 group-AK군에서는 5 및 10분에 각각 2마리에서 관찰되었고 group-P에서는 5분에 2마리, 10분에 1마리가 관찰되었다. Acepromazine/ketamine과 propofol은 모두 enflurane 마취를 위한 도입마취제로서 양호한 효과를 나타내었다.

Key words **:** dog, enflurane, acepromazine, ketamine, anesthesia, induction

Introduction

Intravenous administration of anesthetic drugs is one of the principle methods for induction of short-term anesthesia prior to general anesthesia with inhalant anesthetics[10].

Propofol is an intravenous anesthetic agent chemically unrelated to barbiturates or other anesthetic agents. Propofol, 2,6-diisopropylphenol, is a member of the alkyl phenol family. It is available as a white, ready-to-use, oil-in-water emulsion containing 10% soya bean oil, 2.25% glycerol, 1.2% purified egg phosphatide, and 1% propofol sealed in ampules. It has a neutral pH, is isotonic, and because of its formulation it is effective only when administered by intravenous injection. It does not contain a preservative. Propofol has been used in premedicated and nonpremedicated dogs and cats[2,12].

The pharmacokinetics of propofol in dogs fits a two-compartment open model. Rapid onset of action is caused by rapid uptake into the central nervous system(CNS). The short duration of action and rapid smooth emergence results from rapid redistribution from the brain to other tissues and efficient elimination from plasma by metabolism[13].

Propofol anesthesia in dogs is characterized by rapid onset; short duration; rapid metabolism; lack of cumulation on repeated administration; some respiratory depression; and rapid, smooth recovery from anesthesia[10].

Ketamine, a dissociative anesthetic, is a rapid acting general anesthetic that also has significant analgesic

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activity and a lack of cardiopulmonary depressant effects. It is thought to induce both anesthesia and amnesia by functionally disrupting the CNS through over stimulating the CNS or inducing a cataleptic state[9].

Used alone, it tends to cause hypertonus, poor muscle relaxation, persistent pain reflex responses[8]; in addition, recovery from anesthesia can be violent[11].

Various drugs have, therefore, been used in combination with ketamine to contract these undesirable effects: phenothiazines such as acepromazine[7].

Acepromazine, phenothiazine neuroleptic agent, blocks post-synaptic dopamine receptors in the CNS and may also inhibit the release of and increase the turnover rate of dopamine. They are thought to depress portions of the reticular activating system which assists in the control of body temperature, basal metabolic rate, emesis, vasomotor tone, hormonal balance, and alertness.

Acepromazine cause an increase in central venous pressure, a vagally induced bradycardic effect[5].

Enflurane, 2-chloro-1,1,2-trifluoroethyl difluoromethyl ether, increases CNS irritability similarly to ketamine and nitrous oxide. It induces anesthesia and amnesia by a functional disruption of the CNS through marked CNS stimulation or induction of a cataleptoid state. Occurrence of seizures during enflurane anesthesia in dogs may be minimized by avoiding hypocapnia and enflurane concentrations exceeding 1.5 minimum alveolar concentration(MAC)[3].

Since little clinical information exists on the use of propofol and acepromazine/ketamine combination without premedication for anesthetic induction followed by maintenance with inhalants, this study was designed to compare the properties of acepromazine/ketamine combination and propofol as an anesthetic induction for enflurane maintenance in the dog.

Materials and Methods

Dogs

Six healthy sexually-intact mixed-breed dogs, weighing 16.2 ± 2.6 kg (mean ± SD) and 1 to 2.5 years old, were examined. The animals were kept in kennels appropriate size, fed a commercial diet. They had continuous access to water and received routine health care. Food, but not water, was withheld for at least 12 hours prior to induction of anesthesia. Metabolic and hematological profiles were determined 24 hours prior to anesthesia. Dogs were assigned to be administered with either acepromazine-ketamine combination or propofol on separate groups, with a minimum of 7 days between drug trials.

Drug trial

Propofol or acepromazine/ketamine combination was administered to each dog in a crossover design. Propofol (Pofol®, Dongkook), at the dose of 8 mg/kg (group-P), or acepromazine maleate (Sedaject®, Samwoo)/Ketamine HCL (Yuhan ketamine 50®, Yuhan), at the dose of 0.03/5 mg/kg (group-AK), was continuously administered intravenously over 60 seconds. Immediately after each anesthetic induction, the dogs were positioned in left lateral recumbency on the table and the intubations were done. The endotracheal tube was connected to a small-animal, semiclosed-circle system (Anesthesia machine, Royal medical, Seoul, Korea) with an oxygen (O_2) flow of 3 L per minute. Vaporizer settings were 2.0% enflurane (Gerolan®, Joungwoi). Spontaneous ventilation was maintained in all dogs. Anesthesia was maintained with enflurane for 60 minutes.

Observations

Heart rate (HR), systolic blood pressure (SAP), diastolic blood pressure (DAP), mean arterial blood pressure (MAP), respiratory rate (RR), blood gas tensions (pHa, PaO_2 and $PaCO_2$), toe web pinch, palpebral response, and jaw tone were measured before drug administration (time 0), and every 5 minutes for the first 15 minutes, then at 30, 45, and 60 minutes after drug administration of the bolus dose of propofol or acepromazine/ketamine combination. Heart rate and heart rhythm were recorded by the ECG (Patient monitor, Sein, Korea), using lead II at a paper speed of 25 mm/s. Sinus tachycardia was defined as HR exceeding 160 beats/min. Respiratory rate was measured as number of spontaneous breaths per minute. Blood pressures (i.e., systolic, diastolic and mean) were determined using a non-invasive system (Blood pressure monitor model 6000, Sensor devices INC, U.S.A) with a cuff placed on the front leg over the metacarpal artery. Blood gas analysis

were determined at time 0 and 5, 15, 30, and 60 minutes from the femoral artery. Arterial blood was collected in heparinized syringes and stored on ice for measurement of blood gas analysis and acid-base balance. The pH (pHa), PaO_2, and $PaCO_2$ were measured by the blood gas analyzer (Blood Gas Analyzer OPTI 1, AVL Scientific Corporation, U.S.A).

Rectal temperature was monitored throughout the trial with no attempt to maintain preanaesthetic values (Patient monitor, Sain Inc, Korea).

Toe web pinch reflex was assessed by pinching the interdigital skin of a hind foot and evaluating limb flexion; to ensure consistency, this was done by the same person for all dogs. Palpebral reflex was assessed by touching the medial corner of the upper eyelid and evaluating eyelid closure. Jaw tone was assessed by opening the mouth and evaluating the dog's ability to close its mouth. A scale of 0 to 3 was used to quantify the response, with 3 being normal awake response, 2 being moderate response, 1 being slight response, and 0 being no response.

The anesthetic vaporizer was turned off after 60 minutes of anesthesia. The rebreathing bag was compressed and emptied into the scavenger system, and refilled with O_2 to reduce the reservoir of anesthetic vapor. The endotracheal tube was left in place until adequate reflexes to protect the airway were observed. Endotracheal extubation time, sternal recumbency time, standing time and walking time were recorded for all trials. Subjective evaluation of the recovery period was made for each dog.

Statistical analysis.

Statistical analysis was performed with a 5.0 Excel program (5.0 Excel; Microsoft Corporation, Redmond, WA). A paired Student's t-test was used to compare the recorded measurements with premedication values. The differences were considered to be significant ($P<0.05$) and very significant ($P<0.01$).

Results

Effects on body temperature

Group-AK had increased rectal temperature at 5-, 10- and 15-minute after administration and decreased at 30-, 45- and 60-minute after administration, compared with that of before administration.

Group-P had significantly decreased rectal temperature at 5-, 10-, 15-, 30-, 45- and 60-minute after administration, compared with that of before administration.

There were no significant differences in rectal temperatures between Group-AK and Group-P.

Effects on heart rate

Heart rate tended to increase immediately after administration of acepromazine/ketamine combination and propofol and decrease later.

Group-AK had significantly increased heart rate at 5 minute after administration, compared with group-P and significantly decreased at 30-, 45- and 60-minute after administration, compared with that of before administration.

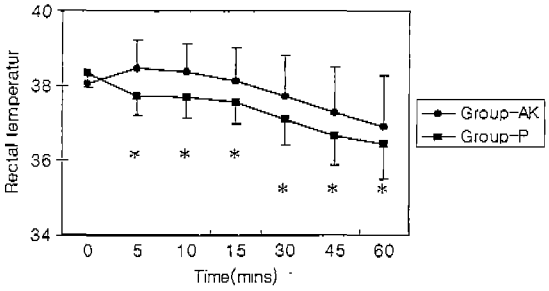

Fig 1. Changes of body temperature after administration of acepromazine/ketamine(●Group-AK) and propofol(■ Group-P). *Significant ($P<0.05$) difference from baseline.

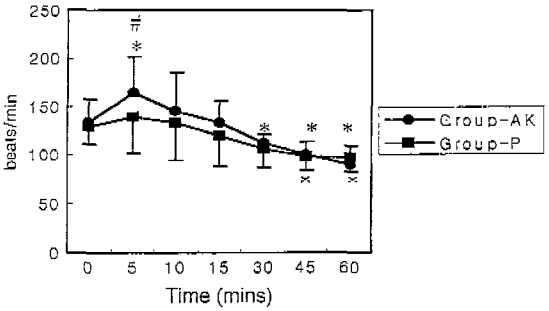

Fig 2. Changes of heart rate after administration of acepromazine/ketamine(●Group-AK) and propofol(■Group-P). *Significant ($P<0.05$) difference from baseline; #Significant ($P<0.05$) difference between acepromazine/ketamine combination and propofol treatments.

Group-P had increased heart rate at 5- and 10-minute after administration, but not significantly and decreased at 15- and 30-minute after administration and significantly decreased at 45- and 60-minute after administration, compared with that of before administration.

Effects on respiratory rate

Group-AK had decreased respiratory rate at 5-, 10-, 15- and 30-minute after administration, but not significantly and significantly decreased at 45- and 60-minute after administration, compared with that of before administration.

Group-P had decreased respiratory rate at 5- and 60-minute after administration, but not significantly and significantly decreased at 10-, 15-, 30- and 45-minute after administration.

There were no significant differences in respiratory rate between both groups.

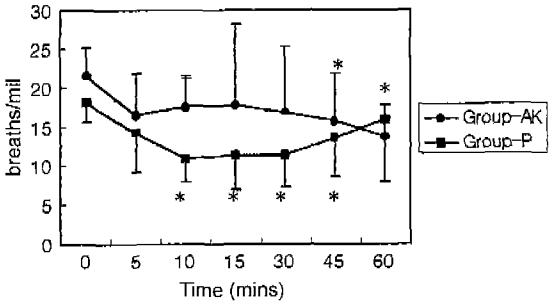

Fig 3. Changes of respiratory rate after administration of acepromazine/ketamine(●Group-AK) and propofol(■Group-P). *Significant (P<0.05) difference from baseline.

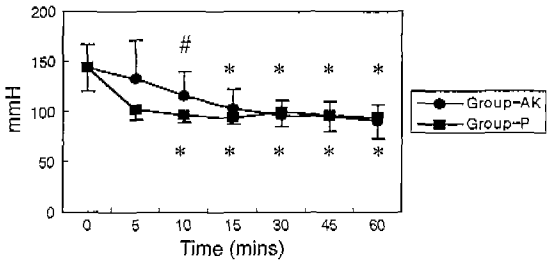

Fig 4. Changes of systolic blood pressure after administration of acepromazine/ketamine(●Group-AK) and propofol (■Group-P). *Significant (P<0.05) difference from baseline; #Significant (P<0.05) difference between acepromazine/ketamine combination and propofol treatments.

Effects of systolic arterial blood pressure.

Group-P had significantly decreased systolic blood pressure, compared with that of group-AK, at 10-minute after administration.

Group-AK had decreased systolic blood pressure at 5- and 10-minute after administration, but not significantly and significantly decreased at 15-, 30-, 45- and 60-minute after administration, compared with that of before administration.

Group-P had decreased systolic blood pressure at 5-minut after administration, but not significantly and significantly decreased at 10-, 15-, 30-, 45- and 60-minute after administration, compared with that of before administration.

Effects on mean arterial blood pressure

There were no significant differences in mean blood pressure between both groups.

Group-AK had significantly decreased mean blood pressure at 5-, 10-, 15-, 30-, 45- and 60-minute after administration, compared with that of before administration.

Group-P had decreased mean blood pressure at 5- and 10-minute after administration, but not significantly and significantly decreased at 15-, 30-, 45- and 60-minute after administration.

Toe-wep pinch reflex

Group-P had slightly greater toe-wep pinch replex than group-AK at 30-, 45- and 60-minute after administration.

Group-AK and group-P had significantly decreased toe-wep pinch at 5-, 10-, 15-, 30-, 45- and 60-minute after administration, compared with that of before

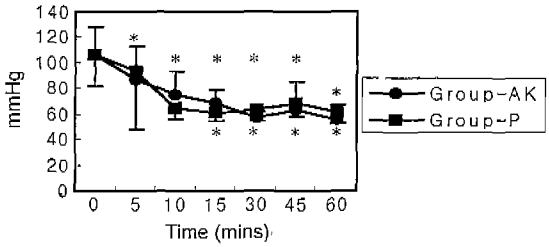

Fig 5. Changes of mean blood pressure after administration of acepromazine/ketamine(●Group-AK) and propofol (■Group-P). *Significant (P<0.05) difference from baseline.

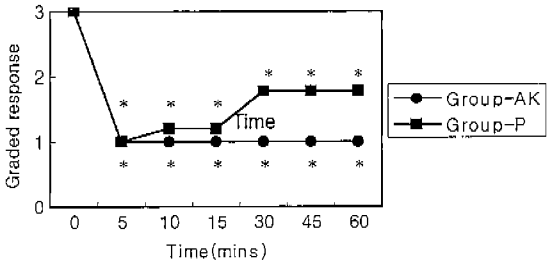

Fig 6. Changes of toe-wep pinch reflex after administration of acepromazine/ketamine(●Group-AK) and propofol (■Group-P). *Significant (P<0.05) difference from baseline.

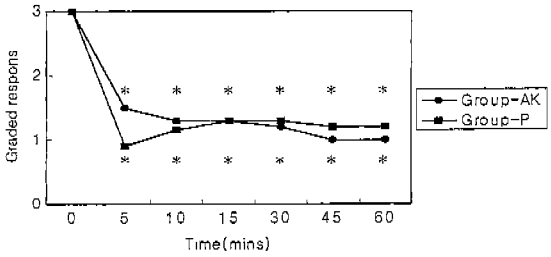

Fig 8. Changes of jaw tone reflex after administration of acepromazine/ketamine(●Group-AK) and propofol(■Group-P). *Significant (P<0.05) difference from baseline.

administration.

Palpebral reflex.

Group-AK had significantly greater palpebral reflex than group-P at 5-, 10- and 15-minute after administration.

Group-AK and group-P had significantly decreased palpebral reflex at 5-, 10-, 15-, 30-, 45- and 60-minute after administration, compared with that of before administration.

Jaw tone reflex

There were no significant differences in jaw tone reflex between both groups.

Group-AK and group-P had significantly decreased jaw tone at 5-, 10-, 15-, 30-, 45- and 60-minute after administration, compared with that of before administration.

Effects on $PaCO_2$

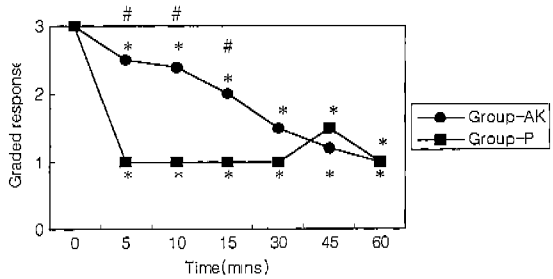

Fig 7. Changes of palpebral reflex after administration of acepromazine/ketamine(●Group-AK) and propofol(■Group-P). *Significant (P<0.05) difference from baseline; #Significant (P<0.05) difference between acepromazine/ketamine combination and propofol treatments.

There were no significant differences in $PaCO_2$ between both groups.

Group-AK and group-P had significantly increased $PaCO_2$ at 5-, 10-, 30- and 60-minute after administration, compared with that of before administration.

Effects on PaO_2

There were no significant differences in PaO_2 between both groups.

Group-AK and group-P had significantly increased PaO_2 at 5-, 10-, 30- and 60-minute after administration, compared with that of before administration.

Effects on pHa

There were no significant differences in $PaCO_2$ between both groups.

Group-AK and group-P had gradually decreased $PaCO_2$ at 5-, 10-, 30- and 60-minute after administration, compared with that of before administration.

Recovery time

The first signs of arousal from anesthesia were tail

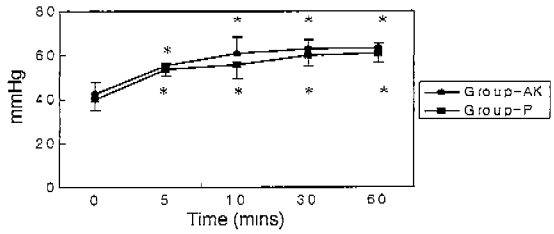

Fig 9. Changes of $PaCO_2$ after administration of acepromazine/ketamine (●Group-AK) and propofol (■ Group-P). *Significant (P<0.05) difference from baseline.

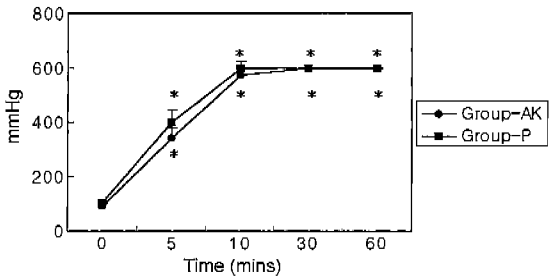

Fig 10. Changes of PaO_2 after administration of acepromazine/ketamine(●Group-AK) and propofol(■Group-P). *Significant ($P<0.05$) difference from baseline.

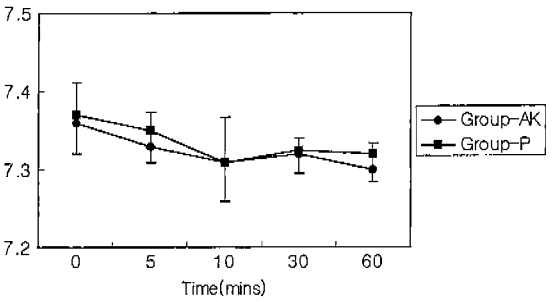

Fig 11. Changes of pHa after administration of acepromazine/ketamine(●Group-AK) and propofol(■Group-P).

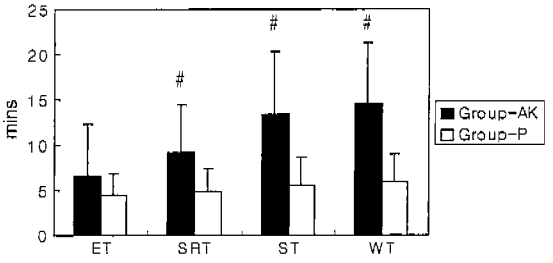

Fig 12. Recovery times for dogs given acepromazine/ketamine(■ Group-AK) and propofol(□Group-P). ET = extubation; SRT=sternal recumbency time; ST = standing time; WT = walking time. #Significant ($P<0.05$) difference between acepromazine/ketamine combination and propofol treatments.

movement and head lift. Sternal recumbency and recovery were not associated with any excitement or other complications. All dogs appeared friendly, curious, and interested in their surroundings immediately after standing.

There were no significant differences in time to extubate between group-AK and group-P.

Group-P dogs had a significantly shorter time to sternally, stand and to walk unaided, compared with group-AK. Group-AK had more struggling during recovery from anesthesia than group-P.

Discussion

The present study was designed to determine the physiological changes during anesthesia that was induced with either acepromazine/ketamine combination or propofol and maintained with enflurane.

Propofol is a useful agent, either as an intravenous agent for the induction of anesthesia maintained by inhalation agents or for injectable anesthesia with or without premedicants[4]. The major advantage associated with propofol is that it has a rapid and coordinated recovery from anesthesia. The pharmacokinetics of propofol confirm a rapid distribution phase, rapid elimination, and lack of accumulation with repeated administration. As a result, the vaporizer should be administered to prevent arousal from propofol before adequate anesthesia is achieved.

Acepromazine/ketamine combination and propofol have been administered intravenously for induction anesthesia in dogs. Dose rates sufficient to allow tracheal intubation in nonsedated healthy dogs have been associated with propofol at a dosage between 2.9 and 8.6 mg/kg[2,12]. The suitable dosage of propofol necessary to inhibit laryngeal reflexes of nonsedated dogs has been reported as 8 mg/kg. The induction dose of acepromazine/ketamine (acepromazine 0.03 mg/kg and ketamine 5 mg/kg, IV) combination in dogs was determined in a preliminary study.

All anesthetics have potential adverse effects at relatively high doses or concentrations. Apnea is the most common adverse effect related to the administration of propofol. The incidence of apnea can be affected by the dose of propofol or speed of administration. Fast administration of propofol can cause apnea or vomiting[8]. However, too slow administration may not provide adequate induction of anesthesia due to rapid redistribution and metabolism. Propofol should be injected intravenously for 60 seconds with appropriated dose and speed of injection based on premedication. The injection can be administered as propofol alone or with concurrent electrolyte solution administration.

Propofol lacks vagolytic activity and may actually increase vagal activity. A central vagotonic or sympatholytic effect, or both, may be exerted. The mechanisms for parasympathetic control of heart rate may be stronger than the baroreflex-mediated enhancement of central sympathetic activity. Propofol has been reported to decrease nodal sinus activity, causing decreased blood pressure and heart rate in dogs.

Sinus tachycardia is not considered a life-threatening cardiac arrhythmia; however, it may increase ventricular work and predispose anesthetized animals to more severe arrhythmias.

Development of cardiac arrhythmias after propofol administration is rare. One dog was reported to have cardiac arrhythmia after being administered propofol, but the arrhythmia was not characterized. One dog also underwent cardiac arrest after propofol administration, but was successfully resuscitated[2].

Rectal temperature was decreased after propofol administration and throughout the anesthesia period. Decreases in body temperature associated with propofol anesthesia have been attributed to decreases in skeletal muscle tone and the shivering threshold, vasodilatation, and impairment of thermoregulatory control. We did not study the mechanisms responsible for the decreases in body temperature, but they might be attributed to the aforementioned decreases in the shivering threshold and impairment of thermoregulatory control.

Cardiorespiratory variables were similar to both groups. Respiratory depression can be associated with either agent. Prevalence of cardiac arrhythmias was also similar between both groups.

Controlled ventilation reduces the blood flow of venous return and lowers cardiac output. In contrast, high $PaCO_2$ induced by spontaneous ventilation stimulates sympathetic nerves and compensates for cardiovascular system depression[9]. In this study, we aimed to evaluate the physiological effects of acepromazine/ketamine combination, compared with those of propofol under conditions similar to those of clinical cases; thus, spontaneous ventilation was chosen.

The increase in HR was thought to be mainly caused by the baroreflex induced by the decrease in arterial blood pressure. The decrease in MAP was mainly caused by the systemic vasodilatation represented by the gradual decrease in systemic vascular resistance(SVR), because cardiac index(CI) remained constant at all anesthesia stages. A similar tendency was observed in this study; however, the exact action was unclear because hypercapnia induced by spontaneous ventilation might have reduced SVR as a result of its direct depressant action on smooth muscle of the peripheral blood vessels[9].

After an initial increase in heart rate, progressive drop below the baseline values was observed in both groups. Despite the greater decrease in arterial blood pressure and increase in $PaCO_2$, enflurane was not associated with a change in HR and greatly decreased stroke volume, indicating greater baroreflex and myocardial depressant effects of enflurane.

In a study in which dogs were administered with 6.6 mg/kg of propofol, DAP was significantly decreased (26 and 24%, respectively) 2 and 5 minutes later, respectively. In dogs with experimentally induced hypovolemia, propofol caused significant decreases in mean arterial pressure. In the present experiment, DAP was significantly decreased 15-, 30-, 45- and 60-minute after administration of propofol and 5-, 10-, 15-, 30-, 45- and 60-minute after administration of acepromazine/ketamine combination. There were no differences between group-P and group-AK.

All dogs of this study were easily intubated after either agent was administered. We evaluated 3 reflex variables: palpebral response, toe web pinch response and jaw tone. All reflexes were depressed immediately after either drug was administered, but none of the reflexes were completely abolished in response to either drug.

One of the major advantages of propofol versus acepromazine/ketamine is the rapid recovery from anesthesia. Fast recoveries have been observed in dogs[2,12]. Rapid redistribution($t1/2\alpha = 7.7$ minutes) and elimination($t1/2\beta = 122$ minutes) suggest that recovery will be fast in this species[13]. Sternal recumbency time, standing time and walking time in group-P were more rapid than those of group-AK.

However, propofol is five times as expensive as acepromazine/ketamine. Propofol ampule should be used within 6 hours after opening because it does not contain preservatives. In this study, both acepromazine/ketamine and propofol revealed good effects as a induction agent

for enflurane anesthesia. Therefore, it was considered that acepromazine/ketamine could be used extensively as an induction agent for enflurane anesthesia, compared with propofol.

Conclusion

There were no significant differences in rectal temperature, respiratory rate, mean arterial blood pressure, $PaCO_2$, PaO_2, pHa, toe-wep pinch reflex and jaw tone reflex between acepromazine/ketamine group and propofol group.

Group-P dogs had a significantly shorter time to recover from anesthesia, compared with group-AK. Group-AK had significantly increased heart rate at 5 minute after administration, compared with group-P. Sinus tachycardia was observed at 5- and 10-minute after administration in 2 dogs of group-AK respectively, at 5-minute in 2 dogs and at 10-minute in 1 dog of group-P.

Both acepromazine/ketamine and propofol revealed good effects as induction agents for enflurane anesthesia.

In conclusion, acepromazine/ketamine was found to be a suitable and useful induction agent for enflurane anesthesia in dogs.

References

1. Allen DG, Dyson DH, Pascoe PJ and O'Grdy MR. Evaluation of a xylazine-ketamine hydrochloride combination in the cat. Can J Vet Res 1986; 50: 23-26.
2. Morgan DWJ, Legge K.. Clinical evaluation of propofol as an intravenous anesthetic agent in cats and dogs. Vet Rec 1989; 124: 31-33.
3. Nicholas HB, Leslie EM. Veterinary phamacology and therapeutics. 6th ed. Ames: Iowa state university press. 1988: 203-206
4. Nolan AM, Reid J, Grant S. The effects of halothane and nitrous oxide on the pharmacokinetics of propofol in dogs. J Vet Pharmacol Ther 1993; 16: 335-342.
5. Plumb DC. Veterinary drug handbook. 2nd ed. Ames: Iowa state university press. 1995: 1-3
6. Riech DL, Silvery G. Ketamine: An update on the first twenty-five years of clinical experience. Can J Anaesth, 1989; 36: 186.
7. Sanford TD and Colby ED. Feline anesthesia induced by ketamine/acepromazine and ketanine/xylazine. Feline Pract 1982; 12: 16-24.
8. Smith JA, Gaynor JS, Bednarski RM, Muir WW. Adverse effects of administration of propofol with verious preanesthetic regimens in dogs. J Am Vet Med Assoc 1993; 202: 1111-1115.
9. Steffey EP. Inhalation anesthetics. In: Thurmin JC, Tranquilli WJ, Benson GJ, eds. Lumb E Johns' veterinary anesthesia. 3rd ed. Baltimore: The Williams and Wilkins. 1996; 227-229.
10. Turner DM, Ilkiw JE. Cardiovascular and respiratory effects of three rapidly acting barbiturates in dogs. Am J Vet Res 1990; 51: 598-604
11. Wateramn AE. Influence of premedication with the xylazine on the distribution and metabolisme of intramusculary administered ketamine in cats. Res Vet Sci 1983; 35: 285-290.
12. Weaver BMQ, Raptopoulos D. Induction of anesthesia in dogs and cats with propofol. Vet Rec 1990; 126: 617-620.
13. Zoran DL, Riedesel DH, and Dyer DC. Pharmacokinetics of propofol in mixed breed dogs and greyhounds. Am J Vet Res 1993; 54: 755-760.