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The Anesthetic Effects of Xylazine/Fentanyl/Azaperone and Ketamine Combination in Dogs

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개에서 Xylazine/Fentanyl/Azaperone 합제와 Ketamine의 병용마취

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요 약 : 임상적으로 널리 쓰이는 xylazine에 fentanyl과 azaperone이 첨가된 합제가 개발되어 사슴에서 쓰이기 시작하였다. 개에서 이 마취제와 ketamine을 병용하였을 때의 마취효과를 검토하였다. XFA와 ketamine의 병용마취하였을 때에는 혈청학적으로는 일시적인 과혈당증을 보인 외의 유의적인 변화는 없었다. XFA 1.1 (Xylazine: 1.1 mg/kg, Fentanyl: 8 μg/kg, Azaperone: 64 μg/kg)을 투여하였을 때는 ketamine의 농도가 증가함에 따라 진정시간과 회복시간이 길어지지 않았으며, 반사반응이 증가하고 근강직이 나타나며 신음소리와 함께 머리를 흔드는 ketamine의 부작용이 많이 나타났다. 그러나 XFA 2.2 (Xylazine: 2.2 mg/kg, Fentanyl: 16 μg/kg, Azaperone: 128 μg/kg)를 투여하였을 때는 농도가 증가함에 따라 마취시간이 길어지고 부작용도 적게 나타났다. 이상의 결과로 보아, XFA 2.2로 진정시킨 후, 병용투여하는 ketamine의 양으로 마취시간을 조절하는 것이 부작용을 줄이고 안전한 마취를 할 수 있는 유용한 방법이라고 사료된다.

Key words : ketamine, xylazine/fentanyl/azaperone(XFA), 마취, 개

Introduction

The search for drug combinations suitable for immobilization of deer, particularly for capture, lead to the evaluation of a fentanyl/azaperone combination which has subsequently achieved widespread use. The undesirable side effects of the fentanyl/azaperone combination were reduced by mixing it with xylazine[57,58].

Xylazine is an effective and relatively safe anesthetic agent and strongly potentiates the effects of all tranquilizers. So, it has been used in combination with other tranquilizers and anesthetics for short-term anesthesia in most domestic animals and many wild species[19,36].

Xylazine causes bradycardia, arrhythmia, first- or second-degree heart block, an initial increase in total peripheral resistance with increased blood pressure followed by a longer period of lowered blood pressures, respiratory depression, skeletal muscle relaxation, emesis, diuresis, hyperglycemia, abdominal distention, and so on[22,41].

Analgesic effect of fentanyl is approximately 100~250 times more potent than that of morphine. Its onset of action is rapid following intravenous or intramuscular injection, with analgesia, sedation, ataxia, respiratory depression and exaggerated response to loud noises developing in 3 to 8 minutes. It has a short duration of action, with the peak effect lasting less than 30 minutes. The actions of fentanyl can be reversed by an opioid antagonist[3,49].

Azaperone is a neuroleptic agent belonging to the butyrophenone derivatives, which have antiemetic activity, reduced motor activity, and inhibition of CNS catecholamines (dopamine, norepinephrine)[41]. It has

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been used for nearly two decades in European countries for swine practice[49].

Ketamine, a dissociative anesthetic, is a rapid acting general anesthetic that also has significant analgesic activity and less 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[10,14,41,42,56,59].

When ketamine is used as the sole anesthetic agent, it tends to cause hypertonus, poor muscle relaxation, persistent pain reflex responses and a violent recovery from anesthesia[31,34,53]. Ketamine does not abolish pedal and pinnal reflexes; photic and corneal reflexes persist in the cat as well as laryngeal and pharyngeal reflexes[44]. Skeletal muscle tone is also increased[4].

To counteract these undesirable side effects, various drugs, such as xylazine, an α_2-adrenergic agonist compound, have been used in combination with ketamine. Xylazine-ketamine anesthetic regimens have been used in dogs[24,34,45] and cats[1,9].

Xylazine/fentanyl/azaperone combination is developed and used in deer[57,58]. However, its anesthetic properties are not evaluated in dogs and other animals.

This study were performed to assess the sedative and physiologic effects of xylazine/fentanyl/azaperone combination, and to compare the anesthetic effects of xylazine/fentanyl/azaperone and ketamine in dogs.

Materials and Methods

Animals

Eighteen clinically healthy mixed breed dogs were used without distinction of sex. They weighed between 1.5 and 20 kg and a vermicide was medicated two weeks before. The water and food were supplied ad libitum.

The animals were divided into six groups (Table 1). Each dog was used repeatedly at intervals of 2 weeks.

Table 1. Design of experiment

Groups		Ketamine (mg/kg)	No. of Dogs
XFA 1.1	K 5	5	6
	K 10	10	6
	K 20	20	6
XFA 2.2	K 5	5	6
	K 10	10	6
	K 20	20	6

Anesthetics

A mixture containing 116.6 mg of xylazine HCl, 0.8 mg of fentanyl and 6.4 mg of azaperone per ml (XFA) (Fentazin-10®, Parnell Laboratories Ltd., New Zealand) and ketamine HCl (Ketamine®, Yu-Han Co., Korea) were used.

Observations

All baseline measurements were made in relaxed, nonsedated dogs. Ketamine HCl was followed 10 minutes after administration of XFA, intramuscularly. All measurements were determined at intervals of 10 minutes until 120 minutes after administration.

The temperature was recorded by digital thermometer (Electrotherm Model TC100A, Cooper Instrument Co., USA) at rectum. The heart rate was recorded by ultrasonic doppler flow detector (Model 811-B, Parks Medical Electronics Inc., USA) at metacarpal artery of forelimb. The respiratory rate was determined by stethoscope. The systolic blood pressure was recorded by ultrasonic doppler flow detector, cuff and sphygmomanometer (CAS Medical System Inc., USA) at metacarpal artery of forelimb. The pinprick reflex was tested by introducing an 18 G needle point into the skin of body. The pedal withdrawal reflex was tested by clamping an interdigit of a toe with an Allis tissue forceps for approximately five seconds. The pinnal reflex was tested by clamping a pinna of ear with an Allis tissue forceps for approximately five seconds. The palpebral reflex was tested by touching a medial canthus of eye with index finger. The corneal reflex was tested by touching a cornea with a soft hair.

The degree of muscle relaxation was always evaluated as excellent, good, fair or poor for the forelegs and hindlegs.

All visible side effects were recorded and used to assess the quality of induction and recovery as good, fair or poor.

Appraisal of anesthesia

The duration and quality of anesthesia were evaluated by recording the following time intervals: the time from injection to the moment when the animal was not able to stand and fall down head (induction time); to raise up head and posture sternal recumbency (recovery time).

The duration of sedation, analgesia were calculated as the recovery time minus induction time, absence of pin-prick, pedal and pinnal reflex responses.

Serum chemistry

Blood was collected at jugular vein before and at 30, 60, 120 minutes and 24 hours after injection, then centrifuged at 2,500 rpm for 15 minutes and stored in refrigerator at -20℃ until they were analysed.

Serum chemistry include total protein (TP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), creatinine and glucose.

Statistical analysis

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 of serum chemistry

There were no changes in total protein (TP) (Fig 1), alanine aminotransferase (ALT) (Fig 2), aspartate aminotransferase (AST) (Fig 3), blood urea nitrogen (BUN) (Fig 4) and creatinine (Fig 5).

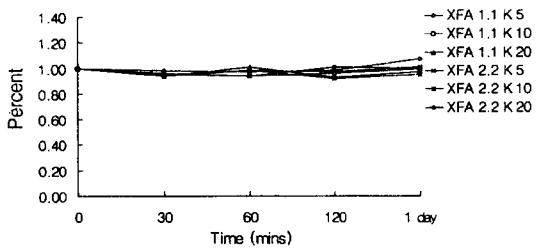

Fig 1. Changes of total protein (TP) after administration of combinations of xylazine/fentanyl/azaperone (XFA) and ketamine.

But in all six combinations of XFA and ketamine, glucose concentration increased for two hours after

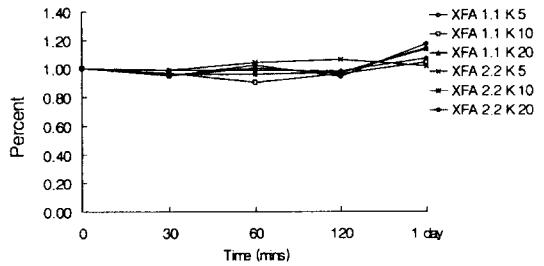

Fig 2. Changes of alanine aminotransferase (ALT) after administration of combinations of xylazine/fentanyl/azaperone (XFA) and ketamine.

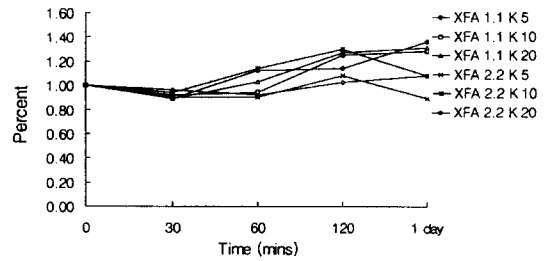

Fig 3. Changes of aspartate aminotransferase (AST)after administration of combinations of xylazine/fentanyl/azaperone (XFA) and ketamine.

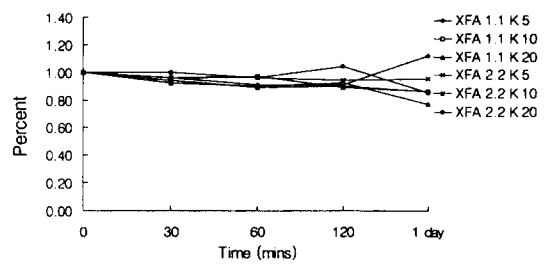

Fig 4. Changes of blood urea nitrogen (BUN) after administration of combinations of xylazine/fentanyl/azaperone (XFA) and ketamine.

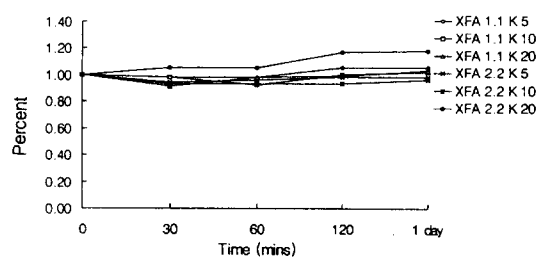

Fig 5. Changes of creatinine after administration of combinations of xylazine/fentanyl/azaperone (XFA) and ketamine.

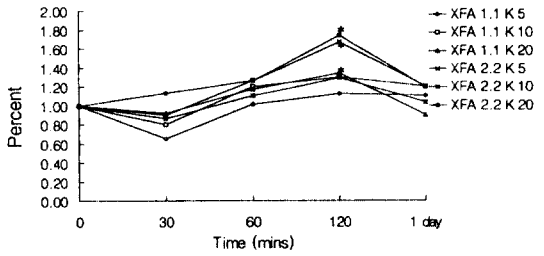

Fig 6. Changes in glucose after administration of combinations of xylazine/fentanyl/azaperone (XFA) and ketamine.
*: significant difference compared with premedication values ($p<0.05$).

administration and reached premedication values twenty four hours after administration (Fig 6).

Induction and recovery time

The induction time was shorter in XFA 2.2 than in XFA 1.1 with ketamine. The recovery time was increased with dosage of ketamine in XFA 2.2 with ketamine, but not in XFA 1.1 with ketamine.

There was no significant difference between the values of induction time and recovery time for the treatments XFA 1.1, 2.2 with ketamine 5, 10, 20 (Table 2).

Most dogs were able to walk 120 minutes after receiving the XFA 1.1 with ketamine and XFA 2.2 with ketamine.

Table 2. Induction and recovery time after administration of combinations of xylazine/fentanyl/azaperone (XFA) and ketamine (Mean±STD) (min)

Groups		Induction time	Recovery time
XFA 1.1	K 5	4.2±2.0 (6/6)	70.3±19.3 (6/6)
	K 10	4.4±2.8 (6/6)	57.0±18.8 (6/6)
	K 20	3.5±0.5 (6/6)	61.0±10.5 (6/6)
XFA 2.2	K 5	3.3±0.5 (6/6)	56.0± 4.5 (6/6)
	K 10	3.0±1.1 (6/6)	71.2±19.7 (6/6)
	K 20	2.8±0.4 (6/6)	89.5±25.8 (6/6)

Induction time, the time from injection to the moment when the animal was not able to stand and fall down head; Recovery time, the time to raise up head and posture sternal recumbency; (/), outbreak numbers/total numbers.

Effects on reflex

The pedal and pinnal reflex were not disappeared in 2 dogs of XFA 1.1 with ketamine 5 and one dog of XFA 1.1 with ketamine 10 (Table 3).

Duration of sedation and analgesia

The durations of sedation and analgesia were calculated by recovery time minus induction time, and duration of abscence of pedal reflex (Table 4).

The duration of sedation of XFA 1.1 and ketamine groups were similar, but those of XFA 2.2 and ketamine groups were increased with ketamine dose dependent manner. The duration of analgesia was increased with dose dependent manner in XFA 2.2 with ketamine groups, but not in XFA 1.1 and ketamine groups.

Side effects

The side effects of treatment were injection pain, moan, head movement, anterioventral rotation of eyeball (AVR), loosing of anal sphincter muscle (LAS) as shown in Table 5.

Injection pain, moan, head movement were observed with ketamine dose dependent in many dogs with XFA 1.1. And anterioventral rotation of eyeball

Table 3. Disappearance and reappearance time of reflex after administration of combinations of xylazine/fentanyl azaperone (XFA) and ketamine (Mean±STD) (min)

Groups		Pedal reflex		Pinnal reflex	
		DTR	RTR	DTR	RTR
XFA 1.1	K 5	12.5±2.9 (4/6)	37.5± 9.6 (4/6)	12.5± 5.0 (4/6)	37.5± 5.0 (4/6)
	K 10	18.0±4.5 (5/6)	42.0± 4.5 (5/6)	18.3± 8.2 (6/6)	38.3± 4.1 (6/6)
	K 20	16.7±5.2 (6/6)	53.3± 5.2 (6/6)	17.5± 8.8 (6/6)	50.0± 8.9 (6/6)
XFA 2.2	K 5	14.2±9.2 (6/6)	51.7± 9.8 (6/6)	17.5±12.5 (6/6)	53.3±10.3 (6/6)
	K 10	14.2±6.7 (6/6)	61.7± 7.5 (6/6)	10.0± 5.5 (6/6)	56.7±16.3 (6/6)
	K 20	8.3±5.0 (6/6)	68.3±13.5 (6/6)	7.5± 5.4 (6/6)	68.3±13.5 (6/6)

DTR, disappearance time of reflex; RTR, reappearance time of reflex, (/), outbreak numbers/total numbers.

Table 4. Duration of sedation, analgesia after administration of xylazine/fentanyl/azaperone (XFA) and ketamine combinations (Mean±STD) (min)

Groups		Sedation	Analgesia
XFA 1.1	K 5	50.8±17.9 (6/6)	25.0± 9.1 (4/6)
	K 10	45.2±14.0 (6/6)	24.0± 5.9 (5/6)
	K 20	49.0± 9.7 (6/6)	36.7± 8.2 (6/6)
XFA 2.2	K 5	47.2± 5.4 (6/6)	37.5±15.4 (6/6)
	K 10	63.3±17.5 (6/6)	47.5± 6.1 (6/6)
	K 20	77.8±25.4 (6/6)	60.0±10.3 (6/6)

(AVR), loosing of anal sphincter muscle (LAS) were observed in most dogs.

Discussion

Xylazine has good visceral analgesia, muscle relaxation, not somatic analgesia. Ketamine has good somatic analgesia, not visceral analgesia and muscle relaxation. Xylazine and ketamine combination has been used in dogs[7,9,11,24,33,45] and cats[9].

In dogs and cats anesthetized with ketamine, mean arterial pressure, heart rate, and cardiac output increases while peripheral vascular resistance remains unchanged[25], xylazine-induced decrease in heart rate and cardiac output may be reversed with ketamine. Ketamine partially counteracts the bradycardiac effects of xylazine in a dose responsive manner. In the dog (and perhaps other species), ketamine and xylazine combination can adverse cardiopulmonary changes of xylazine[37].

The decrease in heart rate became less pronounced as the dose of ketamine was increased. The changes of heart rate among the groups receiving the combinations of xylazine/fentanyl/azaperone and ketamine were less pronounced two hours after the administration than 10 or 20 minutes after the administration.

In dogs anesthetized with ketamine, respiratory rate and minute volume decrease initially, but both return to baseline values within 15 minutes[23]. Both xylazine/ketamine and medetomidine/ketamine combinations induce significant decreases in heart rate and respiration rate, but the decrease is more profound and longer lasting with medetomidine/ketamine[39].

There were no changes in total protein (TP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN) and creatinine after administration of combinations of XFA and ketamine, but an increase in glucose concentration was shown, temporarily.

Xylazine/fentanyl/azaperone (XFA) combination in dogs seems not to have enough analgesic effect. For analgesic effects of somatic tissues, combination of XFA and ketamine was considered in this experiment.

The results of these experiments show that xylazine/fentanyl/azaperone combination strongly potentiated the anesthetic effects of ketamine in dogs. A combination of ketamine with XFA 2.2 did not only produce a good anesthetic effect, but also produced better muscle relaxation. While 20 mg/kg of ketamine combined with XFA 2.2 resulted in a significant prolongation of recovery time, duration of anesthesia and muscle relaxation than XFA 1.1 and ketamine 20 mg/kg. In comparison with the xylazine/ketamine combination[39], XFA/ketamine anesthesia took longer recovery time but had fewer side effect.

Xylazine potentiates the anesthetic effects of ketamine in dogs. Furthermore, there is a clear dose/response relationship. In this experiment, an increase in the dose of ketamine combined with a fixed dose

Table 5. Side effects of administration of XFA and ketamine

Groups		Salivation	Injection pain	Moan	Head movement	AVR	LAS
XFA 1.1	K 5	0/6	1/6	1/6	0/6	4/6	4/6
	K 10	1/6	3/6	2/6	4/6	3/6	5/6
	K 20	0/6	2/6	6/6	5/6	6/6	3/6
XFA 2.2	K 5	0/6	1/6	3/6	2/6	6/6	4/6
	K 10	1/6	1/6	1/6	2/6	5/6	3/6
	K 20	0/6	1/6	2/6	2/6	6/6	6/6

AVR, anterioventral rotation of eyeball; LAS, loosing of anal sphincter muscle; (/), outbreak numbers/total numbers.

of XFA 2.2 lengthens both the duration of anesthesia and the period of good muscle relaxation but XFA 1.1 and ketamine did not.

Xylazine (1.1 mg/kg, IM) is often used with ketamine (11 mg/kg, IM) for short-term anesthesia of 25 to 40 minutes. The dose of ketamine can be adjusted (4~22 mg/kg) according to the duration for surgery[23].

Muscle rigidity and stereotypic lateral head movements were observed during recovery in most dogs which had received XFA 1.1 and ketamine 10 mg, 20 and in 2 dogs which had received the XFA 2.2 and ketamine 5 mg, 10, 20 combinations.

Muscle relaxation of fentanyl is caused by inhibition of intraneural transmission within the CNS[49].

The dogs treated with XFA/ketamine made a better smooth recovery than those given ketamine. The side effects observed with xylazine/ketamine were typical manifestations of the dissociative effects of ketamine which were not counterbalanced by the α_2-agonist. The prolonged period of recumbency which sometimes occurs with combinations of xylazine/ketamine, although not harmful, may be regarded as a practical disadvantage, but it can be quickly reversed by antagonist.

Responses to sharp auditory stimuli were observed after administration of xylazine[35] and fentanyl[49].

The corneal reflex was unsuitable for evaluating painful responses due to anterioventral rotation of eyeball after administration of XFA. And the pinprick reflex was unsuitable for evaluating the response to pain because it was often absent long after the pedal withdrawal reflex had reappeared.

Xylazine should be carefully considered when the complications exist[20]. So, XFA should be carefully used like xylazine too.

It was ascertained that a combination of XFA and ketamine might be alternative anesthesia to reduce undesirable effects of xylazine and ketamine in dogs.

Conclusion

The sedative and physiological effects of xylazine/fentanyl/azaperone (XFA) and anesthetic effects of combination of XFA with ketamine in dogs were evaluated.

The combination of XFA with ketamine induced hyperglycemia like XFA alone. Durations of sedation and analgesia were longer than xylazine and ketamine, and prolonged with increasing dosage of ketamine from 37.5 ± 15.4 to 60.0 ± 10.3 in XFA 2.2 and ketamine, but not in XFA 1.1 and ketamine. Injection pain, moan and head movement were observed in more dogs with XFA 1.1 than 2.2 adminstration. And anterioventral rotation of eyeball, loosing of anal sphincter muscle were observed in most dogs.

The combination of XFA 1.1 with ketamine was unsuitable to induce enough anesthesia for general surgery because of short duration of sedation and analgesia, muscle rigidity, and side effects. But combination of XFA 2.2 and ketamine induced longer anaesthetic state and less side effects.

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