Comparative Study of Butorphanol-Ketamin HCl and Xylazine-Ketamin HCl Combinations for Their Clinical and Cardiovascular/Respiratory Effects in Healthy Dogs

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Abstract: The cardiovascular/respiratory and clinical effects of a xylazine-ketamine combination or a butorphanol-ketamine combination for the induction of anaesthesia in dogs were compared. A total of 12 dogs (two groups 6 dogs each) were premedicated with either xylazine (group I) or butorphanol (group II) and anaesthetized with ketamine HCl and monitored at 0, 5, 15, 30 and 60 min after induction. Sedative effects in both groups started within 15 min. Respiratory rate was significantly decreased in group I ($P < 0.05$). Body temperature was significantly altered after 15 min in group I ($P < 0.05$ and $P < 0.001$). Haematological analyses indicated that there were no differences in pH values between the groups. It was concluded that butorphanol followed by ketamine was comparable with xylazine plus ketamine for the induction of anaesthesia in healthy dogs.

Key Words: Butorphanol, Ketamine, Xylazine, Dog, Anaesthesia, ECG.

Köpekler de Butorphanol–Ketamin HCl Kombinasyonunun Ksilazin-Ketamin HCl Kombinasyonuyla Klinik ve Kardiyovasküler/Pulmoner Etkileri Yönünden Karşılaştırılması

Özet: Sağlıklı köpeklerde anestezi indüksiyonu için butorphanol-ketamine kombinasyonu ile xylazine-ketamine kombinasyonu kardiyovasküler/pulmoner etkileri ve klinik belirtileri yönünden karşılaştırıldı. Toplam 12 köpek (iki grup, her grup 6 köpekten oluştu) xylazine (grup I) veya butorphanol (grup II) ile premedike edildi. İndüksiyonu takiben 0, 5, 15, 30 ve 60. dakikalar da çeşitli kardiyovasküler/pulmoner parametreler kayıt edildi. Sedatif etki her iki grupta da 15. dakika da başladı. Solunum sayısı grup I'de önemli derece de azaldı ($P < 0.05$). Vücut ısısında, 15. dakikadan sonra, grup I'de, önemli derece de değişme oldu ($P < 0.05$ ve $P < 0.001$). Hematolojik analizler gruplar arasında fark olmadığını gösterdi. Sağlıklı köpeklerin anestezisinde butorphanol-ketamine kombinasyonunun xylazine-ketamine kombinasyonuna tercih edilebileceği sonucuna varıldı.

Anahtar Sözcükler: Butorphanol, Ketamine, Ksilazin, Köpek, Anestezi, EKG.

Introduction

In the unique world of veterinary medicine, the relief or prevention of suffering in the animal kingdom is one of the primary objectives of surgeons. Industrial efforts in the development of anaesthetic agents are greatly appreciated. However, there is no available anaesthetic drug which can provide proper anaesthesia alone at present. Therefore, combinations of sedatives and other anaesthetics have been widely used in animal practice.

One example is an α_2-adrenoceptor agonist such as xylazine and an anaesthetic, i.e. a ketamine combination (1).

Xylazine (Rompun, Bayer) is an α_2-adrenoceptor agonist (2,3). For the induction of general anaesthesia, it is used as a premedicant and has a favourable myorelaxant effect (4). Using the recommended label intravenous dosage (1.1 mg/kg of body weight), xylazine can provide adequate chemical restraint/analgesia for

most procedures not requiring general anaesthesia. However, xylazine causes notable haemodynamic disturbances which have been suggested to be dose related (5-8). Recommended doses of xylazine in dogs are 0.1-0.5 mg/kg by intravenous route and 0.4-0.9 mg/kg by intramuscular injection (1). The range of these doses provide analgesia for 15-30 min, but the sedative effect may continue for 1-2 h (4).

Butorphanol (Torbugesic, Fort Dodge Animal Health, Southampton, United Kingdom) is a parenteral synthetic opioid agonist-antagonist analgesic of the nalorphane-cyclozocine class. Its chemical structure is similar to morphine. Butorphanol is a potent analgesic agent with a favourable side effect profile (9). It acts on opioid receptor sites. There are three types of opioid receptors: mu, kappa and sigma (10,11). Mu receptors are associated with respiratory depression, supraspinal analgesia, euphoria and physical dependance. The drugs affecting mu receptors are opioid agonists. Kappa receptors cause spinal analgesia, miosis and sedation. Sigma receptors cause dysphoria, hallucinations and respiratory and vasomotor stimulation. Butorphanol has said to have no mu activity but induces a "walking" response in horses, which is said to be a mu effect (12).

Ketamine (Ketalar, Parke-Davis) is a dissociative anaesthetic agent which is licenced for use in dogs. It produces stable haemodynamics during anaesthesia as a result of its stimulatory effect on the sympathetic nervous system which counteracts the depressant effects of other drugs used during anaesthesia (13). Dose-dependent respiratory depression occurs but is usually minimal at clinically effective doses. Ketamine is also associated with reaction during recovery and it is not used as a sole anaesthetic agent in dogs owing to its tendency to potentiate seizures (14). It is therefore usually combined with other anaesthetic agents or adjuncts such as α_2-adrenoceptor agonists. Ketamine has been shown to have analgesic properties which are attributable to direct antagonism of the N-methyl-D-aspartate receptors (15). Ketamine inhibits ion-channels at the membrane levels; therefore, it is used for general anaesthesia (1) having anti-nociceptive effects (16). It has been recommended for attenuating postoperative hyperalgesia in human beings (17). To provide 30 min analgesia in dogs, ketamine at 1-2 mg/kg by intravenous and 2-4 mg/kg by intramuscular injection have been suggested (18). The

xylazine-butorphanol combination has been evaluated in horses (19), but it has not been widely investigated for use in dogs.

The purpose of the study reported here was to evaluate the cardiovascular/respiratory, haemodynamic and clinical effects of a butorphanol-ketamine combination and its comparison with a xylazine-ketamine combination in healthy dogs.

Materials and Methods

The study was conducted after the approval of the protocol by the Scientific Committee of the Department of Veterinary Surgery, Kafkas University.

Dogs: Twelve dogs kept in isolated rooms (kennels) at the veterinary teaching hospital were used in this study. They were periodically given antiparasite agents and fed once a day with water provided *ad libitum.* Occasionally, the animals were taken out for 2 km walks. Following a general check up (status of dehydration, body temperature, colour and nature of conjunctivas, physical appearance of urine, defecation and the quality of faeces), dogs were fasted for 12 h, but permitted to drink water, and then they were used in the study. The dogs were divided into two groups. Group I (*n* = 6; 3 females and 3 males) was nominated for the administration of xylazine and ketamine and their body weight varied from 8 to 14 kg with an average of 10.4 kg, and the age varied between 0.5 and 1.5 years (average 0.84 years). Group II (*n* = 6; 4 females and 2 males) was used for the administration of butorphanol and ketamine. In this group, the body weight of the dogs was between 7 and 15 kg (average 11.2 kg) and the age varied from 0.6 to 1.4 years (average 0.81 years). There were no detectable pathological abnormalities in the dogs during the study period.

Study design: Before applying any medication (at 0 min), pulse, respiratory rate, rectal body temperature, reflexes (pupilla, pedal, ear, tail), urination, defecation, and vomiting were recorded on a formatted paper. An indwelling catheter was applied into the *vena cephalica antebrachii* and *v. jugularis*. The *v. jugularis* was preferred for obtaining blood samples for haematological and biochemical analyses, while the *v. cephalica antebrachii* was selected for the administration of pre-anaesthetic and anaesthetic agents.

The dogs in group I were given 1 mg/kg of xylazine HCl by intravenous (iv) route and after 5 min 10 mg/kg of ketamine HCl was injected again via a similar route.

Group II was initially given 0.2 mg/kg of butorphanol. Five min later, 10 mg/kg of ketamine was administered by iv route.

Prior to placing the dogs on the table (when they were in a standing position), the parameters mentioned above were recorded. The dogs were positioned on the table at lateral recumbancy. The traces I, II and III of ECG, pulse, respiratory rate, and body temperature were all recorded premedication and postmedication at 0, 5, 15, 30 and 60 min. Five millilitres of blood samples were obtained from *v. jugularis*. Haematologic analyses consisted of counting the number of erythrocytes and leukocytes, packed cell volume (PCV) and measurement of haemoglobin concentration. In addition, the analyses included changes in pH, pO_2, $pHCO_3$ and pCO_2 of blood parameters.

An assistant observed the animals for signs of any physical discomfort (vomiting, defecation, urination, convulsions or delirium) throughout the study.

The sedative and anaesthetic effects of the drugs were scored in 4 degrees. The degrees were defined according to an animal's posture, and pedal, palpebral, pupillary and needle sticking reflexes. The myorelaxant effects of the drugs was determined by checking tail and ear movements (see Appendix).

Following the study, conscious animals were placed in their kennels and no food or water was given by oral route for 2 h.

Analysis of data: Data were reported as mean ± standard error. Student's t-test was applied to unpaired data for comparisons within the group. Two-way analysis of variance (ANOVA) for repeated measures was used to detect differences in heart rate, respiratory rate, blood pressure and blood gases. Significance was set at P < 0.05.

Results

There were no significant differences with respect to the age of the dogs or the duration of anaesthesia, although the period of anaesthesia was longer in group II (60-80 min [average 68.3 min]) than in group I (50-60 min [average 54 min]). The difference in total recovery time from anaesthesia between the groups was statistically significant (P < 0.01).

Physical parameters: The behaviour of the animals was thoroughly observed when they entered the operating theatre. They were kept for approximately 30 min in the theatre in order for them to adapt to their environment. Then, pre-anaesthetic agent was administered. During this period, except for 1 dog, group I dogs displayed excitement and vomiting reflexes. No vomiting was noted in group II, but 2 dogs showed temporary groaning. Excitement and convulsions were noticable in group I, especially around 5 and 15 min, and took place for 2-4 min. Three dogs in group II showed slight excitation and sedation was influenced by outer physical impulses. In this group only 1 dog (number 1) defecated (solid and weighed approximately 250 g). Sedation began 2-3 min after the administration of premedicants in both groups. Evaluation of the degree of sedation and reflexes are summarized in Table 1 and in the Appendix. In group I, there was a degree 2 sedative effect in 2 dogs at 5 min, whereas in group II 4 dogs showed degree 2 sedation and 2 dogs showed degree 1. At 15 min, there was deep anaesthesia in 4 dogs in group I. Similarly, in group II deep anaesthesia was observed in 4 dogs whereas in the others degree 2 and 3 sedative effects were recorded. At 30 min, 4 dogs displayed a degree 2 score which denoted that the deep anaesthesia was disappearing and 2 dogs showed a degree 3 score in group I. Five dogs in group II showed findings of deep anaesthesia at 30 min and 1 dog had a degree 3 score. At 60 min, the findings were similar in the two groups, being a degree 1 score except for one dog in group I. The animals recovered after ca. 60 min.

Cardiovascular and pulmonary parameters: The ECG data from the pre-anaesthetic and anaesthetic period showed that there was no differences among P, Q, R, S and T waves. Therefore, these waves were not considered significant in this study. However, heart rate, bradycardia, and tachycardia in the ECG evaluation were used and these are summarized in Table 2. Normal preanaesthetic heart rate was altered 5 min after the anaesthetic agent was administered in both groups. In group I all dogs showed sinus bradycardia and arrhythmia and in group II only 3 dogs showed sinus arrhythmia while the others had a heart rate in the normal range. At 15 min, 4 dogs in group I and 2 dogs in group II showed sinus tachycardia or sinus arrhythmia. At 30 min, the

Table 1.   Comparisons of the sedative effects of anaesthetic agent combinations in groups I and II.

Dog	Group I						Group II					
	0 min	5 min	15 min	30 min	60 min	TRT	0 min	5 min	15 min	30 min	60 min	TRT
1	-	2	3	2	1	50	-	2	4	4	1	80
2	-	1	4	2	1	50	-	1	4	4	2	60
3	-	2	4	3	1	60	-	2	4	4	1	65
4	-	1	3	2	1	50	-	2	4	3	1	70
5	-	1	4	3	1	60	-	2	3	4	1	70
6	-	1	4	2	1	50	-	1	2	4	1	65

TRT = Total recovery time from anesthesia, min = minute
TRT in group I was 50-60 min (average 54 min), while in group II it was 60-80 min (average 68.3 min).

Table 2.   Results of ECG in groups I and II during anaesthesia.

Dog	Group I					Group II				
	0 min	5 min	15 min	30 min	60 min	0 min	5 min	15 min	30 min	60 min
1	N	SB	SB	N	N	N	SA	N	N	N
2	N	SB SA	SB SA	SB SA	SA	N	N	ST	ST	N
3	N	SB SA	SB SA	SB SA	SB	N	SA	SA	N	N
4	N	SB SA	N	N	ST	N	N	N	ST	ST
5	N	SB	SB SA	SB SA	SA	N	SA	N	ST	ST
6	N	SB	SB SA	SA	N	N	N	N	N	N

N = Normal ECG
SA = sinus arrhythmia
SB = sinus bradycardia
ST = sinus tachycardia

heart rate returned to normal ranges in 2 dogs, but there was sinus arrhythmia and sinus bradycardia in the other group I dogs. However, in group II there was sinus tachycardia in 3 dogs. Rhythym instability in group I (4 dogs) continued; however, there was slight sinus tachycardia in 2 dogs in group II. The pulse was decreased at 5, then increased at 15 and 30 min in group I. In group II there was a slight decrease at 5 and 15 min, but then it increased (Table 3). The repiratory rate was significantly decreased in group I ($P < 0.05$). Again in group I, during 15 and 30 min of the anaesthesia the respiration stopped for 5-15 s in 2 dogs, Cheyne-Stokes respiration. This was not recorded in group II. Body temperature was significantly altered after 15 min in group I ($P < 0.05$ and $P < 0.001$), whereas this was not the case for group II (Table 3).

Blood parameters: Haematological analyses indicated that there were no differences in pH values between the groups. However, at 5 min and onwards pCO_2 was observed to be high in group I ($P < 0.05$). There were significant changes in pCO_2 and $pHCO_3$ levels after 30 min in group II ($P < 0.05$ and $P < 0.001$) (Table 4). Only the packed cell volume (haematocrit) at 60 min (a decrease) and leukocyte number at 5 min (an increase) were recorded in group I. In group II, packed cell volume fell at 5 min, but there was a decrease in haemoglobin status at 15 min and onwards (Table 5). No differences were seen in the other parameters.

Following the experiments, all animals were placed under controlled observation until they were clinically normal. No side effects were recorded in the following days and the dogs were homed.

Discussion

Cardiovascular stability is a major goal during the maintenance of anaesthesia. Minimal depression is also desirable. In healthy dogs, anaesthesia is generally induced with intravenous agents which rapidly produce narcosis.

Table 3. Mean values of respiration, pulse and body temperature in dogs in groups I and II during anaesthesia.

Time (min)	Group I					Group II				
	0	15	30	60		0		15	30	60
Pulse (x ± sx)	113.3 (± 4.7)	60.6 (± 4.1) ***	77.3 (± 8.3) ***	86.6 (± 9.0) **	97.7 (± 10.0) *	99.3 (± 8.3)	97.3 (± 7.2) *	91.33 (± 5.9) **	125.3 (± 5.9) *	124.7 (± 10.8) *
Respiratory rate (x ± sx)	31.3 (± 3.2)	17.3 (± 1.3) ***	19.3 (± 1.2) **	25.3 (± 3.0) **	24 (± 1.0) **	34.3 (± 1.5)	31.5 ± 4.7 *	28.7 (± 3.2) **	32 (± 4.3) *	30 (± 2.5) *
Temperature (x ± sx)	39.3 (± 0.2)	39 (± 0.2) *	38.5 (± 0.3) **	38 (± 0.3) **	37.9 (± 0.3) ***	38.9 (± 1.3)	38.8 (± 0.1) *	38.9 (± 0.1) *	38.5 (± 0.2) *	38.1 (± 0.2) *

*** = P < 0.001 and ** = P < 0.05 statistically significant, * = P > 0.05 non-significant
x = mean
sx = standard error

Table 4. Mean values of blood gas in groups I and II during anaesthesia.

Time (min)	Group I					Group II				
	0	5	15	30	60	0	5	15	30	60
pH (x ± sx)	7.8 ± 0.01	7.3 ± 0.02	7.3 ± 0.01*	7.3 ± 0.01*	7.3 ± 0.02*	7.3 ± 0.01	7.3 ± 0.01*	7.3 ± 0.05*	7.3 ± 0.01*	7.3 ± 0.01*
pCO_2 (x ± sx)	37.5 ± 0.24	39.2 ± 1.05	37.9 ± 1.49*	36.4 ± 1.08*	34.0 ± 1.60*	35.2 ± 1.59	36.0 ± 1.48*	36.1 ± 1.50*	39.7 ± 2.01**	40.8 ± 1.39***
pO_2 (x ± sx)	54.8 ± 2.25	43.0 ± 2.72	47.8 ± 1.82*	51.6 ± 2.46*	48.2 ± 2.67**	46.2 ± 2.20	46.1 ± 2.21*	45.7 ± 2.29*	46.1 ± 2.53*	44.1 ± 2.34*
$pHCO_3$ (x ± sx)	20.1 ± 0.81	20.3 ± 0.74	20.0 ± 0.77*	20.1 ± 0.85*	20.0 ± 0.44*	19.1 ± 0.74	19.4 ± 0.75*	19.3 ± 0.84*	19.7 ± 0.71**	20.2 ± 0.73**

*** = P < 0.001 and ** = P < 0.05 statistically significant, * = P > 0.05 non-significant
x = mean
sx = standard error

Table 5. Mean values of haematocrit, haemoglobin, leukocyte and erythrocyte in groups I and II during anaesthesia.

Time (min)	Group I					Group II				
	0	5	15	30	60	0	5	15	30	60
Haematocrit (x ± sx)	39.6 ± 3.06	41.8 ± 3.41*	37.0 ± 3.01*	38.6 ± 3.67*	35.7 ± 3.0**	39.2 ± 3.18	37.1 ± 3.11*	37.5 ± 3.15**	39.0 ± 2.45*	38.6 ± 2.2*
Haemoglobin (x ± sx)	13.4 ± 0.81	12.9 ± 0.68*	12.9 ± 0.71*	13.2 ± 0.71*	13.0 ± 0.70*	12.3 ± 0.72	12.2 ± 0.80*	11.8 ± 0.81*	11.8 ± 0.64*	12.6 ± 0.77*
Leukocyte (x ± sx)	7.7 ± 0.36	8.3 ± 0.29**	8.1 ± 0.33*	8.0 ± 0.28*	7.7 ± 0.20*	7.2 ± 0.49	7.3 ± 0.43*	7.0 ± 0.41*	7.5 ± 0.50**	7.1 ± 0.55*
Erythrocyte (x ± sx)	6.9 ± 0,12	6.9 ± 0.25*	6.8 ± 0.17*	6.9 ± 0.21*	6.7 ± 0.23*	6.3 ± 0.38	6.2 ± 0.13*	6.8 ± 0.39***	6.3 ± 0.15*	6.2 ± 0.11*

*** = P < 0.001 and ** = P < 0.05 statistically significant, * = P > 0.05 non-significant
x = mean
sx = standard error

It was reported that xylazine induced sinus bradycardia and arrhythmogenic effects in a dog's heart (1). A similar result was also observed in this study, especially 1 mg/kg of xylazine and 10 mg/kg of ketamine inititated bradycardia at 30 min and they caused arrhythmia until 60 min. If xylazine is used alone, the decrease in the heart rate could reach serious levels ca. < 60 beat/minute.

Butorphanol, like other opioids, is a dose-related respiratory depressant. It may increase the heart rate for 1 h or keep it slightly higher than the normal range (20). However, in our study the quality of induction of the butorphanol-ketamine combination was satisfactory in all cases. It was shown that the animals initially displayed marked ataxia, salivation and piloerection, but less than 10 min later appeared alert and responsive to sound stimulation (21). This was not the case in the current study, but responsiveness to sound stimulation was observed. Limited respiratory depression may exist after the administration of butorphanol (9). We did not record any significant side effects. In this study, the administration of butorphanol did not significantly affect the degree of sedation, temperament or the values of physiologic variables (heart rate, respiratory rate, and rectal temperature). Butorphanol at dosages of 0.1, 0.2 and 0.4 mg/kg can be safely administered to dogs and its usage as a pre-anaesthetic does reduce the dosage requirements of other anaesthetic agents (11). Therefore, the combination of this drug with ketamine produces remarkable anaesthetic effects in dogs.

Haemodynamic effects aside, the chemical restraint provided by the combination (butorphanol-ketamine) was good. Therefore, the restraint/sedation/analgesia and anaesthesia effects of the butorphanol-ketamine combination is advised for use in healthy dogs.

The time taken for recovery differed between the groups, with it being longer in group II, but the quality of recovery was considered good in all cases; no dogs became excited, a behaviour sometimes reported after the administration of ketamine, probably owing to the delay between dispensing the ketamine and the recovery period. The quality of anaesthetic induction with butorphanol and ketamine was comparable with that obtained with the xylazine-ketamine combination. Ketamine may thus be a useful adjunct to butorphanol for anaesthetizing dogs and further studies to optimize the dose ratios are considered worthwhile.

Operator warning: Butorphanol has opioid-like activity; therefore, precautions should be taken to avoid accidental injection or self-injection with this potent drug.

Acknowledgements

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APPENDIX

Scoring systems used for assessing degree of analgesia and anaesthesia provided by administration of the drugs

Degree 1- Animals were relaxed, fully alert and responsive to outer impulses, effort to raise his or her head and all reflexes were present. No apparent sensory or motor deficit; appears similar to preanaesthetic state.

Degree 2- Faintly sedate, animals were relaxed, partially responsive to environment, dilated pupilla, palpebral and pedal reflexes were present, limited response to needle insertion.

Degree 3- Moderately sedate, muscle relaxation was complete, limited palpebral reflex and no other reflexes.

Degree 4- Very sedate, myorelaxation was perfect, no sign of reflexes and eyeball was ventrally dropped. Deep anaesthesia.