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Original Article

THE EFFECT OF TIME INFLUENCE ON PHYSIOLOGICAL PARAMETERS FOLLOWING KETAMINE AND DIAZEPAM ADMINISTERATION IN CATS

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ABSTRACT

Objective: The present study aims to determine the effect of time influence on rectal temperature, respiratory and pulse rate, onset and duration of action, duration of recumbency and recovery following ketamine and diazepam administration in cats.

Methods: Experimental study design was used on 20 cats (males and females) randomly divided into two equal groups (A and B). Ketamine (10 mg/kg i. m.) was administered to group A in the morning. The same procedure was repeated using different dosages (15 mg/kg and 20 mg/kg i.m.) at intervals of 3 days each. A similar procedure was applied to group B in the evening. A week after, diazepam (1.5 mg/kg, 2.5 mg/kg and 3.5 mg/kg i. v.) were administered to group A and B using the same procedure used in ketamine administration. All baseline measurements were recorded after each drug administration and were repeated at 15, 30, 45, 60, 75, 90, 105, and 120 min intervals after induction of anesthesia with ketamine and diazepam.

Results: It was found that the onset of action of ketamine following i. m. administration was slightly longer at evening (2-5 mins) while that of diazepam was instant after i. v. administration. The duration of recumbency was shorter in the morning using ketamine while longer following diazepam (7-19 mins) administration. The rectal temperature, respiratory and pulse rate were lower in the morning following ketamine and diazepam administration even though, the respiratory and pulse rate decreases as the dose was increased but not statistically significant. The duration of action and recovery was significantly longer in the morning after ketamine and diazepam administration.

Conclusion: According to this study, there was not much difference between morning and evening administration using both drugs. However, it should be noted that influence of time of administration was evident in some of the parameters measured especially with diazepam.

Keywords: Anesthesia, Cats, Diazepam, Ketamine, and Physiological parameters.

INTRODUCTION

Anesthesia has been defined as a reversible condition of comfort, quiescence, and physiological stability in a patient before, during, and after performance of a procedure that would otherwise be painful, frightening or hazardous [1]. General anesthetic is used to produce a state of insensibility to avoid pain of the surgical procedure. A compound like ether, chloroform and nitrous oxide has been used since 1850s to produce general anesthesia [2]. Some examples of general anesthesia are thiopentone sodium, ketamine, halothane, nitrous oxide[3].

Ketamine is approved for use in humans, primates, and cats, but has extricable uses in various species of animals, including dogs, horses, birds, small ruminants and reptiles [4]. No human study has been performed to demonstrate a circadian rhythm for ketamine effects. Nevertheless, numerous animal studies have shown the existence of a circadian dynamic in the expression of N-methyl-D-aspartate receptor in the brain [5]. Ketamine in combination with midazolam administered IM produces light anesthesia in cats with good muscle relaxation [6]. The side-effects of ketamine are an increased heart rate, cardiac output, and blood pressure. Ketamine also has been shown to exert a direct negative inotropic effect on the myocardium, an effect that is overridden by the ketamine-induced sympathetic tone and to cause minimal respiratory depression [7]. Ketamine is the most frequently used injectable anesthesia and it may also be used as a pre-anesthetic medication [8].

Benzodiazepines, such as midazolam, do not have any intrinsic analgesic properties, but are suggested to be particularly useful as a component of the premedication of cats with cardiovascular or respiratory disease [9]. Diazepam is the most widely used benzodiazepine derivative. The principle site of CNS depression produced by diazepam is the brain stem reticular formation and is 20 times more potent than chlordiazepoxide in blocking decelerate rigidity in animals [10]. However, the principal used of diazepam in canine epilepsy is the emergency treatment of status epilepticus. For this purpose, it has the advantages of minimal depressant actions on the respiration and the cardiovascular system and more rapid penetration of the CNS than other antiepileptic drugs or its own metabolites [11].

In veterinary medicine, diazepam has been employed as premedication for many surgical procedures. It increases the length of action or anesthesia, and also facilitates smooth induction [12].

Sedatives are generally used to render animals easier to handle, and widely used in dogs, cats, horses, farms, animals and livestock They are also used as a pre-anesthetic medication and chemical restrain of wild and zoo animals; also used to induce epidural analgesia and as a general anesthetic in combination with ketamine [3].

The influence of time of day on sedative or anesthetic properties of benzodiazepines has yet to be well explored. In mice, intra peritoneal diazepam is more toxic during the light phase of the cycle than during the dark phase [13]. The main clinical uses of diazepam are calming of wild or intractable animals, sedation, skeletal muscle relaxation, and as an anticonvulsant in status epilepticus. It is use combination with ketamine or with opioids for anesthesia rather than sedation [3].

Chronopharmacology is the study variation of drug effect with regard to time of administration and endogenous periodicity. This influence on drug action may be any of the following mechanisms: change in absorption, change in an elimination, change in the metabolism, change in receptor affinity or efficacy and change in the susceptibility. It involves administration of drug to animals at the different time of the day and observation of the effort of the drug on the animals and recording any differences in the effect [14]. The

daily variations in biological functions such as the secretions of glands and the synthesis of RNA and protein are suggested to be an additional variable influencing the susceptibility to a drug. In other words, the variation in efficiency or toxicity of many drugs, at least in part, is due to the time of administration [15].

Cats are challenging to anesthetize because of their size, behavior and unique metabolism of anesthetic/analgesic medications. Choice of pre-anesthetic medications, induction agents, drugs used for maintenance of anesthesia, and analgesics for cats depends upon patient temperament, presence of underlying disease, expected intensity of pain, and duration of the procedure [16].

Generally cats are at risk of developing hypotension, hypothermia, hypoventilation and hypoxemia in the perianesthetic time period. Regardless of drug choice, close monitoring the patient's vital signs and response to anesthesia cannot be overemphasized. The presence of a dedicated, knowledgeable anesthetist aids in prompt recognition and treatment of complications that arise [16].

The aim of this study was to determine the influence of time of administration on the sedative effect of diazepam and ketamine in cats and to evaluate the effects of ketamine and diazepam on physiological parameters in cats using three different doses.

MATERIALS AND METHODS

Ethical approval

The ethical clearance was received from the Faculty of Veterinary Medicine Ethical Review Committee of Usmanu Danfodiyo University Sokoto.

Experimental animals

Twenty domestic cats (8 males and 12 females) weighing 2.1 kg to 3.7 kg were used in this study. They were divided randomly into groups (A and B) that each had four males and six females. They were housed in cages in asmall animal unit of Veterinary Teaching Hospital at Usmanu Danfodio University Sokoto, Nigeria. The cats were fed on leftover foods from restaurants, fish and tap water *ad libitum*and they were allowed to acclimate for two weeks prior to commencement of the experiment. They were also examined for external parasites or other external lesions. The blood samples and fecal samples from each cat were taken to the Parasitology laboratory for identification of blood and fecal parasites. Laboratory results showed absent of any clinical diseases and all physiological parameters were within normal range; the cats were certified healthy for the experiment. The experiment was conducted in conformity with standard ethics regarding the care and use of laboratory animals.

Experimental design

Ketamine (10 mg/kg intramuscularly through aquadriceps muscle) was administered to group A in the morning (7:00am). The same procedure was repeated using different dosages (15 mg/kg and 20 mg/kg i.m.) at intervals of 3 days each. A Similar procedure was applied to group B in the evening. A week after, diazepam (1.5 mg/kg, 2.5 mg/kg and 3.5 mg/kg intravenously through acephalic vein) was administered to group A and B using the same procedures used in ketamine administration. All baseline measurements were taken after each drug administration among the groups and were repeated at 15, 30, 45, 60, 75, 90, 105, and 120 minute intervals after induction of anesthesia with ketamine and diazepam.

The onset of action, duration of recumbency and recovery was measured according to the method described by [17]. For each group of animals, the rectal temperature was measured using a digital thermometer through the rectum while the respiratory rate was measured with a stethoscope between 5th and 6th rib of the right lateral aspect of the thorax and pulse rate at the femoral artery of the thigh.

Statistical Analysis

The data were tested for normality using the Kolmogorov Smirnov test in which histogram, box plot, Q-Q plot and p-value for a Kolmogorov Smirnov test statistic were significant (*p>0.05). The time influence (morning and evening) on physiological parameters and sedative effects of ketamine and diazepam was compared using Wilcoxon signed matched pair-rank test using SPSS version 17.0.

RESULTS

The mean time of manifestation of sedation at 10 mg/kg of ketamine was 4 min (morning) and 5 min (evening) which was significantly (*p<0.05) longer in the evening administration. At 15 mg/kg the mean time onset of action was 1.8 min (morning) and 2.6 min (evening) which was significantly (*p<0.05) longer in the evening administration. However, at 20 mg/kg the onset of action was 1.8 min (morning) and 2.4 min (evening) administration, which was significantly lower in the morning (*p<0.05). The duration of recumbency was also higher in the evening while the duration of action and recovery was significantly (*p<0.05) higher in the morning (table 1).

Table 1: Mean (SD) of time of sedation and recovery signs following intramuscular administration of ketamine in cats

	10 mg/kg		15 mg/kg		20 mg/kg	
	Morning	**Evening**	**Morning**	**Evening**	**Morning**	**Evening**
Onset of action	4(0.7)*	5.2±*2.9*	1.8±*0.5**	2.6±*0.5*	1.8±*0.5**	2.4±*0.6*
Duration of recumbency	21.6±*5.4**	32.2±*9*	27.8±*1.7**	37.0±*7.1*	47.6±*7.1**	53.2±*3.3*
Duration of action	128.8±*3.7**	114.3.9±*3.9*	177.6±*30.4**	142±*13.7*	281.4±*5.3* *	220.2±*6.6*
Duration of recovery	102.2±*2.9* *	82.2±*7.6*	159.6±*12.7**	107.6±*14.5*	233.2±*7.1**	165.4±*8.6*

Note: * Different between the group means in a row was significant at p<0.05.

The mean (SD) of rectal temperature, respiratory and pulse rate following morning and evening intramuscular administration of ketamine was also taken. The temperature was lower in the morning compared to evening administration even though was not statistically significant (*p>0.05). The respiratory rate was also lower in the morning compared to the evening, but statistically significant (*p>0.05) as it decreases as the dose increased. The pulse rate was lower in the morning after administration of ketamine but not significant (*p>0.05) as it decreases as the dose of ketamine was increased (table 2).

Table 2: Mean (SD) of rectal temperature, respiratory and pulse rate following ketamine administration at different dosages and time

Physiological parameters	Baseline		10 mg/kg		15 mg/kg		20 mg/kg	
	Morning	**Evening**	**Morning**	**Evening**	**Morning**	**Evening**	**Morning**	**Evening**
Rectal temperature	36±*0.4*	37±*0.2*	36±*0.6*	38±*1.1*	36±*0.8*	38±*0.5*	37±*0.3*	38±*0.6*
Respiratory rate	34±*0.5*	36±*0.2*	33±*0.5*	34±*0.2*	29±*0.9**	32±0.5	23±*2.1**	26±5.6
Pulse rate	130±*0.4**	134±*0.9*	138±*2.3**	132±*3.6*	123±*8.1**	120±*8.8*	114±*8.5**	112±*2.2*

Note: *Different between the group means in a row was significant at p<0.05.

The mean time of signs and manifestation of sedation and recovery sign at 1.5 mg/kg, 2.5 mg/kg, and 3.5 mg/kg following intravenous administration of diazepam was recorded. The onset of action following i. v. administration of diazepam was instant (0.0 min). The duration of recumbency was longer in the morning compared to evening administration. The duration of action was significantly (*p<0.05) longer in the morning compared to the evening. The duration of recovery was also significant (*p<0.05) longer following morning administration (table 3).

Table 3: mean (SD) of time of sedation and recovery signs following intravenous administration of diazepam in cats

Mean (SD)	1.5 mg/kg		2.5 mg/kg		3.5 mg/kg	
	Morning	Evening	Morning	Evening	Morning	Evening
Onset of action	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0
Duration of recumbency	7.8±0.2	7.6±3.8	7.0±1.22	8.4±1.14	19.4±0.89	17.4±2.4
Duration of action	113.6±5.6 *	96±1.8	173.2±2.1	160.2±24.5	357.8±26.8 *	330±15.7
Duration of recovery	101.6±0,2 *	88.8±4.2	166.4±3.1	154.2±25.9	327.8±10.6*	313±14.2

Note: * Different between the group means in a row was significant at p<0.05

The mean (SD) of rectal temperature, respiratory and pulse rate following morning and evening i. m. administration of diazepam was also measured (Table 4). The temperature was lower in the morning, even though was not statistically significant (*p>0.05). The respiratory rate was significant (*p<0.05) lower in the morning at 2.5 mg/kg and 3.5 mg/kg, which decreases as the dose was increased while the pulse rate was lower in the morning after administration of diazepam but not statistically significant (*p>0.05).

Table 4. Mean (SD) of rectal temperature, respiratory and pulse rate following diazepam administration at different dosages and time

Mean (SD)	Baseline		1.5 mg/kg		2.5 mg/kg		3.5 mg/kg	
	Morning	Evening	Morning	Evening	Morning	Evening	Morning	Evening
Rectal temperature	36±*0.4*	38±*.2*	37±*2.1*	39±*0.6*	38±*0.7*	39±*0.8*	37±*2.3*	38±*.4*
Respiratory rates	37±*5.7*	40±*10.1*	36±*2.4*	38±*3.9*	33±*11**	38±*8.4*	28±*0.7**	30±*.4*
Pulse rates	120±*9*	128±*8.7*	125±*2.5*	130±*10*	124±*5.5*	118±*10.5*	127±*.4*	121±*12*

Note: * Mean difference between groups in a row was significant at p<0.05.

DISCUSSION

The results of this study suggest that the onset of action of ketamine in cats was 1.8-4 min and 2.4-5.2 min (dose dependent) following morning and evening administration respectively. Similarly, [18] showed almost similar results (1.83-2.5 min) to this study even though the dosages were higher (25 mg/kg, 50 mg/kg and 75 mg/kg) after i. m. administration of ketamine. However, there was an immediate onset of action after i. v. diazepam administration in cats. Even though [19] reported 15 min in canaries following i. m. administration while [18] showed a little variation of the onset of action between morning (3.67-6.17 min) and evening (2.67-7.67 min) in rabbits after i. m. administration of diazepam.

It was found out that the duration of action of ketamine in cat was higher in the morning which was in contrary to the results (15-60 min) obtained from[20] when ketamine was administered in cats. This variation was observed may be due to time influence dose dependent effect of ketamine. In contrast, diazepam administration in cats has a longer duration than ketamine and there was as light variation between the morning (113.6-330 min) and evening (96-330 min). According to the results of [18] there was slightly lower duration in goats in the morning (40.83-101.67) and evening (37.17-103.67 min). However, [21] reported the duration of action in goat was 23 min after diazepam administration.

In this study, there was statistically significant (p<0.05) difference of the duration of recumbency (21.6-47.6 min and 32.2-53.2 min) between morning and evening following ketamine administration in cats. However, diazepam i.v. administration showed a longer duration of recumbency in the morning. During this experiment, it was observed that immediately after administration of diazepam at 5 mg/kg the cat goes to lateral recumbency and after 5-20 min it begin to lick everything around it especially the site of injection. There was also voracious appetite displayed by the cats, indicating possible negative of the anesthesia.

The results showed a mild decreased in respiratory rate at different dosages of ketamine while the pulse rate and temperature were not affected. This was in line with [22] which reported mild respiratory depression after ketamine administration and it usually manifested by an increased rate which does not compensate for a decreased tidal volume. However, [23] reported increased in cardiac output mean aortic pressure, pulmonary arterial pressure, central venous pressure and heart rate. Almost similar effect was seen following i. v. administration of diazepam in cats resulting in decreased in respiratory rate but increased after a few min as the drugs was metabolized. It was also found that the higher dosages of diazepam the lower the respiratory rate in cats. In contrary [24] showed that, following diazepam administration in the same animals intravenously, but the dosages were lower (0.05, 0.1, 0.2 and 0.4 mg/kg) compared in this study. His results showed no any significant changes in heart rate, cardiac output, mean pulmonary arterial aortic and right arterial pressure and arterial pH or blood gas levels. According to [25] diazepam administration caused as light increase in the body temperature; it has been reported that administration of diazepam in healthy animals may cause excitation. This was evident in this study after 30-60 min the cats showed slight excitation in all 3 doses. Ruminants, especially sheep and goats, are highly sensitive to the effects of α2-adrenoceptor agonists requiring a reduction in dose of approximately 20 to 40 times when compared to species such as the cat, dog or horse [26]. The difference in drug effects and drug sensitivity between species may be responsible for variations in the physiological responses.

Additionally, [20] reported influence of time during recovery in cats after ketamine administration to be more than 10 hours; but most were able to stand within 2 h. However, this study showed a recovery period within 3 hrs.

CONCLUSION

The study has shown that ketamine and diazepam administration in cats results in respiratory depression, but does not cause any change in pulse rate and rectal temperature. The depression was slightly influenced by time of drug administration in cats and care should be taken to avoid long duration during surgery or any other procedure

using these drugs especially diazepam. There were also slight time influence following these drug administrations in cats with regard to onset of action, duration of action and recovery, duration of recumbency. However, there was no significant difference between time of administration either morning or evening with ketamine or diazepam. Based on these findings, it is recommended that ketamine and diazepam can be administered at morning or evening. The duration of effect of the drugs increases with an increase in the dose, therefore the dose of the drugs should be reduced when minor surgery is to be conducted. There is a need for further Chrono-pharmacological studies of this type with many other veterinary drugs since this has assisted greatly in optimization of drug therapy in veterinary and human medicine. The benefits derivable from the further studies will help clinicians determine the influence of time of administration of the effects of veterinary drugs and use that to decide the most appropriate time to administer of various drugs.

CONFLICT OF INTERESTS

Declared None.

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