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PHARMACODYNAMICS OF XYLAZINE, ACEPROMAZINE AND DIAZEPAM ON VARIOUS PHYSIOLOGICAL PARAMETER IN EXPERIMENTAL RABBITS

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Abstract

The aim of the present study was to explore the effect of three selective sedative drugs i.e. Xylazine (XZ), Acepromazine (AC), and Diazepam (DZ) on normal physiological parameters such as pulse, respiration, body temperature and serum glucose. All the three drugs i.e. Xylazine, Acepromazine, and Diazepam were used at the dose rate of 8mg/kg, 0.5 mg/kgand diazepam1mg/kg respectively through intramuscular route (I.M.) in six healthy rabbits of non-descriptive breed. Before administration of drugs all physiological parameters were recorded Pulse, respiration and body temperature shows significant (0.05) decrease after administration of these drugs. Maximum decrease in the pulse rate was recorded at 60, 30 and 45 minutes and were returned to its normal at 150, 135 and 135 minutes with XZ, AC and DZ respectively. Low respiratory rate was noted at 45, 30 and 75 minutes and were returned to the non-significant level at 105, 90 and 135 minutes with XZ, AC and DZ respectively. Bodytemperature decreased to its maximum at 45, 30 and 60 minutes and returned to its normal at 120, 120 and 135 minutes after administration of XZ, AC and DZ, respectively. Onset of sedation started at 2.83±0.30, 6.16±0.47 and 3.83±0.30 minutes with XZ, AC and DZ respectively. Significant difference were found in XZ and AC, DZ and AC at 0.05 but there was no significant difference between XZ and DZ. Total duration of sedation was 101.17±1.07, 69.00±1.87 and 90.00±1.29 with XZ, AC and DZ, respectively. The XZ and DZ significantly (P< 0.05) increased serum glucose level while AC had no significant effect on serum glucose level. Overall, all the three drugs were found safe for rabbits but XZ shows the best results.

Keywords: *Acepromazine, Diazepam, Pulse, Rabbits, Respiration, Temperature, Xylazine,*

INTRODUCTION

An interest in rearing of rabbits as a pet animal has been developed in U.K. and some other countries of the world from last half century. Due to an interest in rearing of rabbits, UK has a maximum number of rabbits that made 3rd popular furry Pet County of the world. Similarly in Pakistan, a struggle has been started to increase the number of rabbits to fulfill the need of meat while in some countries rear the rabbit as a micro livestock because rabbits can rear in a limited space. There are different breeds of the rabbit are available in Pakistan and other world. In Pakistan the most important breed of rabbit is white black commonly found in Khyber Pakhtunkhwa province (1). Recently an increased interest has been observed for rearing of domestic rabbits instead of livestock spp., because backyard rearing system is well adopted by rabbits. Similarly one can rear the domestic rabbits in a limited space and no need of extra expenses necessary for their rapid growth and normal reproduction. Rabbits are also used as laboratory animals for different therapeutic trials (2). Xylazine is an Alpha2-adrenoceptor agonists has a good sedative and analgesic effects reported in most of the small and large animals (3).

Xylazine was used with different doses such as 6, 8 and 10 mg/kg body weight in rabbit and as result significant decrease was recorded for pulse, respiration and body temperature. Furthermore moderate to deep sedation with skin analgesia was also reported. (4). No life threatening complications were observed when Xylazine was used at the dose rate of 0.8mg/kg body weight along with other anesthetics in native cross breed ponies (5).

Acepromazine is most commonly used as tranquilizers for different animals. Acepromazine is responsible for decreases anxiety, depression of central nervous system, drop in blood pressure (B.P.) and heart rate. The suggested dosage for Acepromazine is 0.25mg to1mg per pound of body weight (6). A significant reduction was recorded production of tear in the rabbits when treated with Acepromazine while no significant change was seen in tear production by the rabbits when treated with diazepam (7).

Diazepam can be used a good muscle relaxant and for anxiety. One can also use Diazepam as a pre-anesthetic for induction of sedation. It is extremely lipid-soluble and rapidly distributed in the body within short time after administration. Diazepam can also cross the blood-brain barrier and the placenta. It is mainly excreted into breast milk. After absorption, it is redistributed into muscle and adipose tissue. Diazepam is widely used for different purposes such as sedative, anxiolytic and analgesic effect in horses, cow, sheep, buffalo calves and dogs (8-12) Gracia et al., 1991; Kramer, 1991; Marais et al., 1991; Al-sharaet al., 2000; Kalhoroet al., 2000) while limited information is available in rabbit for their use.

MATERIIALS AND METHODS

ANIMALS

Six healthy (non-descriptive breed) male rabbits of the same age and weight were selected for the recent study. All the rabbits were placed under same environmental condition and fed on same diet. All the rabbits were physically normal and free of any infection. Three different sedative/tranquilizer i.e. xylazine (XZ), acepromazine (AC) and diazepam (DZ) with different dose rate such as 8mg/kg, 0.5mg/kg and 1mg/kg body weight were used respectively with interval of one week to each animal. The following physical parameters were recorded before and after administration of three different drugs.

PULSE RATE, RESPIRATION RATE AND BODY TEMPERATURE

Pulse rate, respiration rate and body temperature were recorded before and after administration of three different selected sedative/ tranquilizer drugs. These parameters were recorded at 0, 05, 15, 30, 45, 60, 75, 90, 105, 120, 135 and 150 minutes. Pulse rate was recorded with the help of stethoscope; respiration rate was counted through nostrils movement while the body temperature was taken directly from the rectum with the help of clinical thermometer.

SEDATION

Onset and total duration of sedation were recorded after administration of three sedative/ tranquilizer drugs.

DETERMINATION OF SERUM GULOCOSE

Blood samples were directly collected from the ear vein of the rabbit with the help of Syringe containing EDTA before administration of XZ, AC and DZ as control group. After administration of sedative drugs, blood samples were collected at different intervals such as 10, 30, 60 90, 120 and 1440 minutes. After collection, blood samples were placed in centrifuge machine and run at 4000rpm/ 5minutes. After centrifugation serum was collected for examination of serum glucose. Serum glucose level was determined with the help of U-1800 spectrophotometer (Hitachi, Japan) by using the enzymatic colorimetric test without depolarization (Glucose Liquicolor GOD-PAP Method kit, Human, Germany).

RESULTS

Pulse Rate: Different control values of pulse rate recorded before administration of three drugs i.e. XZ, AC and DZ, were 208.33±0.42, 208.67±0.49 and 208.17±0.70 respectively as shown in Table I. After of

administration of drugs at interval of 5 mints, recorded low pulse rate and statistically significant difference (P<0.05) was recorded. Similarly maximum decrease in pulse rate was observed at interval of 60, 30 and 45 minutes and was last for 135, 120 and 120 minutes with XZ, AC and DZ respectively. So it was concluded from the present experiment that XZ, AC and DZ exert maximum effect on pulse rate and statistically significant difference (P<0.05) was recorded while no side effect was observed on recommended doses. Among three sedative drugs, the efficacy of XZ was more for low pulse rate.

Table I. Effect of Xylazine, Acepromazine and Diazepam on pulse rate in rabbits

Interval (minutes)	Xylazine	Acepromazine	Diazepam
0	208.33±0.42^{a}	208.67±0.49^{a}	208.17±0.70^{a}
05	200.00±0.57^{b}	199.33±0.33^{ef}	203.17±0.83^{d}
15	189.67±16.41^{c}	194.83±0.60^{g}	198.83±0.47^{e}
30	177.33±1.35^{e}	**183.67±1.11^{i}**	191.67±0.55^{g}
45	166.67±2.24^{g}	189.50±0.61^{h}	**183.17±0.47^{i}**
60	**158.33±1.05^{h}**	193.33±0.88^{g}	186.00±1.06^{h}
75	165.33±2.47^{g}	197.50±0.88^{f}	195.83±1.30^{f}
90	172.33±1.42^{f}	201.50±0.88^{df}	202.33±0.76^{d}
105	183.67±1.56^{d}	203.83±0.54^{cd}	203.83±0.70^{cd}
120	192.83±1.64^{c}	206.17±0.60^{bc}	205.83±0.60^{bc}
135	200.33±1.3333^{b}	**207.17±0.4773^{ab}**	**207.83±0.4014^{ab}**
150	**208.17±0.7032^{a}**	208.17±0.3073^{ab}	208.17±0.3073^{a}

Mean values carrying different superscript within the same column are differ significantly at (P<0.05) while carrying same superscript are differ non-significant at (P>0.05)

RESPIRATORY RATE

Table II shows (at 0 times) the average control values for respiration rate in rabbits before administration of XZ, AC and DZ, which were 62.00±0.5774, 62.83±0.4773 and 63.33±o.5578 respectively. After administration of three selected drugs, respiratory rate was recorded at different minutes of interval. As a result low respiratory rate was observed up to 75 minutes while slight increase was reported at 75 to 150 minutes. Statistically significant difference (P<0.05) was reported in respiration rate at different duration of time while non- significant difference (P>0.05) was reported at different timings (minutes) such as 105, 120, 135 and 150 after administration of xylazine. After administration of acepromazine, increase in respiration rate was recorded at 0, 5, 90, 105, 120, 135 and 150 minute of interval and statistically non-significant (P>0.05) difference was observed while decrease in respiration rate was recorded at time (minutes) of 15, 30, 45, 60 and 75 and statistically significant difference (P<0.05) was recorded. When diazepam was administered, decrease in respiratory rate was reported at different timings (mints) such as 0, 5, 15, 30, 45, 60, 75) while increase in respiratory rate was recorded at different timings such as 90, 105,120, 135 and 150(mints) and statistically significant difference (P<0.05) was recorded among different timings.

Table II. Effect of xylazine, acepromazine and diazepam on Respiration rate in Rabbits

Interval (minutes)	Xylazine	Acepromazine	Diazepam
0	62.00±0.57^{a}	62.83±0.47^{a}	63.33±o.55^{a}
05	55.16±0.47^{c}	56.00±0.36^{a}	55.83±o.30^{c}
15	48.66±0.42^{d}	50.33±0.55^{e}	52.50±0.42^{d}
30	42.33±0.33^{f}	**43.33±0.49^{g}**	49.00±0.36^{e}
45	**35.50±0.42^{h}**	46.66±0.49^{f}	44.66±f0.42^{f}
60	38.33±0.33^{g}	53.66±0.66^{d}	38.50±0.76^{g}
75	47.00±0.57^{e}	58.16±0.47^{b}	**36.50±0.76^{h}**
90	57.33±0.49^{b}	**61.66±0.55^{a}**	43.83±0.70^{f}
105	**61.66±0.42^{a}**	62.00±0.25^{a}	51.66±0.66^{d}
120	62.00±0.44^{a}	62.66±0.33^{a}	57.83±0.47^{b}
135	62.00±0.36^{a}	62.67±0.33^{a}	**62.50±0.42^{a}**
150	62.16±0.30^{a}	62.83±0.47^{a}	63.33±0.42^{a}

Mean values carrying different superscript within the same column are differ significantly at (P<0.05) while carrying same superscript are differ non-significant at (P>0.05)

BODY TEMPRATURE

Table III indicates the average control values (at 0) for body temperature before administration of XZ, AC and DZ, which were 103.17±0.30, 103.50± 0.22 and 103.17± 0.30 respectively. Maximum decrease in body temperature recorded at 45, 30 and 60 minutes and returned to the normal (non-significant) at 120, 120 and 135 minutes after administration of XZ, AC and DZ respectively. Statistically significant difference (P<0.05) was reported for efficacy of three different drugs on body temperature at different recorded times.

Table III. Effect of Xylazine, Acepromazine and Diazepam on body temperature in rabbits

Interval (minutes)	Xylazine	Acepromazine	Diazepam
0	103.17±0.30^{a}	103.50± 0.22^{a}	103.17± 0.30^{ab}
05	101.83±0.30^{bc}	101.00±0.36^{c}	101.50±0.22^{c}
15	100.67±0.21^{de}	99.67±0.42^{d}	100.50±0.22^{d}
30	98.33±0.33^{f}	**98.17± 0.30^{e}**	99.33±0.33^{e}
45	**97.33±0.21^{g}**	98.83±0.30^{de}	98.17±0.30^{f}
60	99.83±0.30^{e}	100.67±0.21^{c}	**97.33±0.21^{g}**
75	101.00±0.36^{cd}	101.33±0.33^{c}	98.50±0.22^{f}
90	102.00±0.25^{b}	102.33±0.33^{b}	100.50±0.22^{d}
105	102.00±0.25^{b}	102.33±0.21^{b}	101.50±0.22^{c}
120	**103.50±0.22^{a}**	**103.50±0.22^{a}**	102.67±0.21^{b}
135	103.50±0.22^{a}	103.50±0.22^{a}	**103.33±0.21^{a}**
150	103.67±0.21^{a}	103.17±0.30^{ab}	103.50±0.22^{a}

Mean values carrying different superscript within the same column are differ significantly at (P<0.05) while carrying same superscript are differ non-significant at (P>0.05)

ONSET OF SEDATION

Average mean values for the onset of sedation was 2.83±0.30, 6.16±0.47 and 3.83±0.30 minutes for XZ, AC and DZ respectively (Table IV). This indicates that XZ produced quicker response in onset of sedation while AC produced slowest one. This also showed that there was significant difference (P<0.05) in onset of sedation of AC with XZ and DZ while there was non- significant difference was recorded between XZ and DZ.

TOTAL DURATION OF SEDATION

Average mean values for the total duration of sedation was recorded as 101.17±1.07, 69.00±1.87 and 90.00±1.29 minutes for XZ, AC and DZ respectively (Table IV). XZ has higher total duration of sedation than the AC and DZ. All the three drugs showed significant difference (0.05) in total duration of sedation from each other.

Table IV. Onset and total duration of sedation (minutes) in rabbits

Number of Animals	Drugs/ Parameters					
	Xylazine		Acepromazine		Diazepam	
	Onset of sedation	Total duration of sedation	Onset of sedation	Total duration of sedation	Onset of sedation	Total duration of sedation
1	3	105	5	75	4	90
2	2	100	6	70	3	95
3	4	102	5	65	5	88
4	3	98	8	73	4	86
5	2	103	6	68	4	92
6	3	99	7	63	3	89
Mean ±	2.83±0.30^{b}	101.17±1.07^{a}	6.16±0.47^{a}	69.00±1.87^{b}	3.83±0.30^{b}	90.00±1.29^{c}

Mean values carrying different superscript within the same row are differ significantly at (P<0.05) while carrying same superscript are differ non-significant at (P>0.05)

SERUM GLUCOSE LEVEL

Table V shows (at 0) the average control values for serum glucose in rabbits before administration of XZ, AC and DZ, which were 121.67±1.032, 120.83±0.408 and 120.00± 0.894 respectively. Serum glucose

level was significantly increased from 10 to 120 minutes with XZ. Significant difference at 30 and 60 minutes interval was found with DZ. The data on serum glucose with AC showed non-significant difference at (P>0.05).

Table V. Effect of xylazine, acepromazine and aiazepam on serum glucose(mg/dl) in rabbits

Time Intervals	Xylazine	Acepromazine	Diazepam
0 (Control)	121.67±1.032^{f}	120.83±0.408^{a}	120.00± 0.894^{bc}
10 (minutes)	127.17±2.562^{e}	121.67± 0.816^{a}	122.33±1.366^{b}
30 (minutes)	137.33±7.174^{d}	121.50±0.836^{a}	125.83±4.167^{a}
60 (minutes)	148.50±7.713^{c}	121.52±1.048^{a}	125.33±2.160^{a}
90 (minutes)	155.00±5.621^{b}	121.33±1.032^{a}	121.33±1.211^{b}
120(minutes)	161.17±3.600^{a}	121.33±0.516^{a}	118.67±1.366^{c}
24 (Hours)	119.50±1.048^{f}	121.33±0.516^{a}	120.17± 0.752^{bc}

DISCUSSION

Present study was carried out in six non-descriptive breed of rabbits to find out the sedative and other physiological effects of Xylazine (XZ), Acepromazine (AC) and Diazepam (DZ) at different doses. It was concluded from the present study that XZ, AC and DZ produced significant (P<0.05) effect on pulse, respiration, body temperature, onset of sedation and total duration of the sedation in all six rabbits with recommended doses. Furthermore it was also observed that all the rabbits recovered from sedation without showing any side effects. In the present study lowest pulse rate was recorded at 60 minutes followed at 30 minutes followed by at 45 minutes. Similarly the lowest respiration rate was recorded at (45, 30 and 75 minutes) while the lowest body temperature was recorded at (45, 30 and 60 minutes) by XZ, AC and DZ respectively. It was concluded that DZ has a longer effect on pulse rate, respiration rate and body temperature than XZ and AC while AC produced minimum effect on these parameter than the other two drugs. Our findings are close to other findings reported by different researchers globally either alone or in combination with other anesthetics. Our results are also similar to the findings reported by Sarwar *et al.,* (2014) where lowest pulse rate, respiration rate and body temperature was recorded in rabbits (4). Our results are also very close to Masoud and Moghaddassi (2010) where efficacy of diazepam and ketamine was studied in combination and recorded its anesthetic affect such as maximum depression effect on respiration and pulse rate than Acepromazine and ketamine combination in rabbits (13). Lipman *et al.,* (2006) also reported that Xylazine and ketamine anesthetic protocol in combination is more effective for the purpose of sedation and surgical anesthesia without anylife threatening effects on normal respiration rate and pulse rate (14). Eze and Nweke, (2004) also studied the sedative and anesthetic effect of Xylazine and ketamine in combination in white rabbit and it was concluded that these drugs produce reversible depression in pulse and respiration rate while the body temperature was remained normal in the whole duration of sedation and anesthesia (15). Mohammed *et al.,* (2011) also reported that diazepam and Xylazine produced significant depression on heart rate, respiration and body temperature in white New Zealand rabbits (16). Similar findings were also observed by other researchers such as Gonzalez *et al.,* (2002) in rabbits; Hodgson *et al.,* (2002) in cows; in rock partridges Gracia *et al.,* (1981), Sakamoto *et al.,* (1996) in goats and Ilbäck and Stalhandske (2003) in dogs (8, 17-19).

Presently it was concluded that XZ produce a rapid and prolong sedation as than AC and DZ in rabbits. Similarly KoJ C *et al.,* (1998) also studied the effect of these three drugs in ferret and concluded that Xylazine produced better chemical restrain as compared to diazepam and acepromazine (20).

According to Sarwar *et al.,* (2014), it was concluded that Xylazine produced dose dependent Sedation in rabbits with high margin of safety (4). Similar findings were also reported by Imtiaz *et al.,* (2014), who studied the sedation effect that Xylazine produce a prolonged and rapid sedation in ducks (21).

In the present the effect of anesthetic agents was also studied on serum glucose level, where increased level of serum glucose was recorded after analysis of blood serum while statistically significant (P<0.05) difference reported. Our results are in close with the findings reported by Wajid *et al.,* (2014) where increased level of glucose was reported after administration of Xylazine in dogs (22). Efficacy of Xylazine was studied in various species of animals where increase the serum glucose level in cattle was reported by Brockman (1981) and in rats by Gotoh *et al.,* (1988) depending upon its dosage (23, 24). In this study, it was

concluded that diazepam alters glucose level to high in rabbit but this was not for longer period. According to Dixi *et al.,* (2000), that Diazepam when used at the dose rate of 0.6 mg/kg body weight, will have no significant effect on glucose level in rabbits after one month treatment (25). Data from the present study on serum glucose are close in connection with Heithem Bougherara and Omar Bouaziz (2014) in which there is non-significant effect of acepromazine on serum glucose level in laboratory rat alone or in combination with other ketamine was observed (26).

CONCLUSION

From the present study it was recorded that all the three anesthetic drugs were found safe for rabbits but XZ shows the best results. No side effect was observed during anesthesia. XZ and DZ showed significantly ($p< 0.05$) increase in serum glucose level while ac should non- significant ($p>0.05$) effect on serum glucose level.

Conflict of interest:

The authors declare that there is no conflict of interests with regarding the publication of this article.

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