



Effects of Diazepam and Xylazine on Changes of Blood Oxygen and Glucose Levels in Mice

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Abstract | The present study aimed to explore the changes of body temperature, heart rate, blood partial pressure of oxygen (PO₂) and glucose levels upon diazepam and/or xylazine administration in mice. Sixty male albino mice (33.89 ± 0.41 g body weight; BW) were distributed randomly into five groups given intraperitoneal (IP) injection: control group given physiological saline; diazepam group (D) given 13.3 mg/kg BW; xylazine group (X) given 26.6 mg/kg BW; DX group given both 13.3 mg/kg BW diazepam and 26.6 mg/kg BW xylazine; DXvas group given DX dose for vasectomy surgical operation. The values of body temperature, PO₂, heart rate and blood glucose were recorded of groups at 0, 20 min, 40 min, 1h, 2h, 3h, 4h, 8h of diazepam and/or xylazine injection. The results indicated a significant (P < 0.05) transient negative side effect of diazepam and/or xylazine dosages on body temperature, PO₂, heart rate and blood glucose, which were the highest at 1-2 h post-drug administration. The transient negative side effects decreased gradually thereafter at 2h, 3h, 4h and 8h of drugs' injection. The transient negative side effects were more significantly pronounced in xylazine, DX and DXvas groups compared to diazepam and control groups and extended to 8h of injection. In conclusion, the given dosage of diazepam and/or xylazine resulted in transient negative side effects in body temperature, PO₂, heart rate and blood glucose, which returned approximately close to normal levels at 8h of injection. The DX anesthesia dose is sufficient and safe for performing minor and major surgeries in mice.

Keywords | Diazepam, Xylazine, Analgesia, Anesthesia, Oxygen, Glucose

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INTRODUCTION

Diazepam is a medication of the benzodiazepine family. Diazepam produces in human a calming effect and is commonly used to treat a range of conditions as anxiety, muscle spasms, and trouble sleeping (Calcaterra et al., 2014). Xylazine is a clonidine analogue used for sedation, analgesia and anesthesia in animals (Mohammed et al., 2011; Mohammed et al., 2012) and the overdose of xylazine is usually fatal in humans (Greene and Thurmon, 1988).

Mice and rats were used in scientific research for different studies (Mohammed et al., 2008; Mohammed, 2009; Mohammed et al., 2010; Mohammed and Al-Suwaiegh, 2016;

Mohammed, 2017; Mohammed, 2018). Mice and rats used in scientific research must be sedated or anaesthetized for surgical operation (Mohammed and Al-Hozab 2016; Mohammed, 2018). The proper use of analgesics and/or anesthetics in research animals is imperative for an ethical and scientific perspective. The use of analgesics and/or anesthetics for samples' collection and minor/major surgeries is more frequent for general scientific applications. Some of these drugs can cause serious reversible/irreversible disruption to pulmonary and cardiovascular organs (Flecknell et al., 1983; Peeters et al., 1988; Borkowski et al., 1990). Diazepam and xylazine were used for induction of sedation in research animals but the drugs caused reversible/irreversible side effects (Ghurashi et al., 2009; Mohammed et al., 2012; Karcz and Papadakis, 2013). Analgesics diaze-

pam and xylazine drugs were reported to cause respiratory, cardiovascular and hematological complications (Mohammed et al., 2012; Yadav et al., 2008). Changes of blood parameters were found upon diazepam or xylazine injection (Fani et al., 2004; Mohammed et al., 2012).

Maintenance of body temperature and blood glucose during anesthesia is the most important metabolic reactions in addition to blood oxygen level (Ljungqvist et al., 2012; Mohammed et al., 2012; Behdad et al., 2014). Hypothermia in addition to hyperglycemia is expected in the post-anesthesia period due to inflammatory mediators and stress hormones such as cortisol and epinephrine. In addition, respiratory complications such as hypoxemia (hemoglobin oxygen saturation <90%) is expected due to hypoventilation (Karcz et al., 2013) in the post-anesthesia period as well. Turina et al. (2006) reported that short-term hyperglycemia causes immunosuppression and significant increase of infectious conditions. During surgery, acute hyperglycemia worsens prognosis even in patients had normal glucose level (Bochicchio et al., 2005; Puskas et al., 2007). Muir and Mason (1993) found that diazepam and/or xylazine drugs have a dose-dependent effect in mice. In rodent research, the effects of analgesic and anesthetic dose of diazepam and xylazine drugs were evaluated on the glucose, hemoglobin, and urea levels in rats at 120 min post-anesthesia (Mohammed et al., 2012). Therefore, the aim of the present study was to investigate the time-dependent analgesic and anesthetic dose of diazepam (13.3 mg/kg) and/or xylazine (26.6 mg/kg) on body temperature, blood oxygen and glucose level in mice to improve recovery relevant to surgical practice.

MATERIALS AND METHODS

The use of animals for this experiment met the requirements of the Animal Ethics Committee of College of Agriculture and Food Sciences, King Faisal University, Saudi Arabia.

SITE OF STUDY AND ANIMAL MANAGEMENT

The study was conducted during the period from January to February 2018 of Animal and Fish Production department. Sixty male albino mice of 33.89 ± 0.41 g body weight (BW) and six months of age were used for the study. The animals were bred in the animal lab of the department of Animal and Fish Production. Mice were fed commercial pellet diet (Arasco, KSA), which composed of 21.0% protein, 2.9% fat and 3.3% fiber, 1% mixture of vitamins and minerals, and 3300 kcal/kg energy. Animals had free access to food and water. Mice were kept controlled under 12h light and 12h dark cycle starting at 7 a.m. The controlled temperature and relative humidity during the experiment were $25.5 \pm 2.8^\circ\text{C}$ and $50 \pm 10\%$, respectively.

INJECTION OF DIAZEPAM AND XYLAZINE DOSAGES

The sixty male albino mice (33.89 ± 0.41 g BW) were distributed over five groups. Fasting males for six hours were given intraperitoneally (IP) the dosages of injection. The control group injected with 0.2 ml physiological saline. The diazepam group injected with 13.3 mg/kg BW of diazepam (Neuril 2.5 mg/ml; Memphis Co. Egypt). Xylazine group injected with 26.6 mg/kg BW of xylazine (Xylaject 10 mg/ml; Adwia Co. Egypt). Diazepam and xylazine group (DX) injected with both 13.3 mg/kg BW of diazepam and 26.6 mg/kg BW of xylazine. Diazepam and xylazine group used for vasectomy surgical operation (DXVas) The dosages of diazepam and xylazine used in this study were chosen according to the drugs' safety margin of our previous studies (Mohammed et al., 2012; Mohammed, 2012).

SURGICAL OPERATION OF VASECTOMY

Vasectomy surgical operation of males was carried out according to the method of Bermejo-Alvarez et al. (2014) using our general anesthesia dose (diazepam 13.3 mg/kg and xylazine 26.6 mg/kg) (Mohammed, 2018). Briefly, incision 1 cm of skin and muscle above the penis was done upon general anesthesia. Cauterization of the *vas deferens* in two points at once through flaming forceps followed by muscle and skin suture.

BODY TEMPERATURE MONITORING

Body temperatures were recorded using Digital LCD IR Infrared Thermometer Body Surface Temperature (Cofeo Portable Digital Termomete Infrared Thermometer Gun Non-contact IR LCD). The measurement time is less than 2 seconds, measurement range error is 0.1 – 0.3 degree Celsius and the measurement distance is 1-3 cm.

PULSE OXIMETER AND HEART RATE MONITORING

The pulse oximeter and heart rate monitor was used (CMS60D-VET Handheld Veterinary Pulse Oximeter) to measure partial pressure of oxygen (PO₂) and heart rate. The male mice were restrained in one hand and proper sensor put on the chest. The partial pressure of oxygen (PO₂) and heart rate were recorded since no shaving or hair removal is required.

BLOOD GLUCOSE MONITORING

Blood glucose monitoring recorded of male mice using blood glucose meter (iCare advanced Medical) (King 2012). Blood glucose levels were monitored at 0, 20 min, 40 min, 1h, 2h, 3h, 4h and 8h of injection. The tip of tail was punctured and the drop of blood put on strips for measuring blood levels.

STATISTICAL ANALYSIS

Statistical analysis was done according to general linear model (GLM) of SAS program (2008). Differences be-

tween control and diazepam, xylazine, DX and DXVas treated groups were evaluated in body temperature, PO₂, heart rate and glucose level by one-way ANOVA. Duncan Multiple Range Test (Steel and Torrie, 1980) was used to test the effect of treatments. The data were presented as mean ± S.E.M. Level of significance was set at P<0.05. Statistical model as follow:

$$Y_{ij} = \mu + T_i + E_{ij}$$

Where: Y_{ij}= the experimental observation ij, μ =the overall mean, T_i = the effect due to treatment i., E_{ij} = the experimental error.

RESULTS

BODY TEMPERATURE

Body temperature of male mice is shown in (Table 1) at 0, 20 min, 40 min, 1h, 2h, 3h, 4h and 8h over injection of diazepam (D; 13.3 mg/kg), xylazine (X; 26.6 mg/kg), DX (DX; D 13.3 mg/kg & X; 26.6 mg/kg) and both DX used for vasectomy surgical operation (DXVas). Mean of body temperature before drugs' injection did not have significant differences between the five groups, but starting from 20 minutes of diazepam and/or xylazine dosage injection, body temperature values were significantly lower than control one. The amount of body temperature at 20, 40, 1h and 2h of diazepam and/or xylazine decreased significantly (P<0.05) compared to control group. The significant decrease (P<0.05) of body temperature was more pronounced in DX and DXVas groups followed by xylazine and diazepam groups, respectively. The lowest amount of body temperature recorded at 2h of drugs' injection in all groups. Thereafter, the values of body temperature started to increase in diazepam and/or xylazine groups. The significant return (P<0.05) of body temperature thereafter was more pronounced in diazepam followed by xylazine, DX and DXVas groups, respectively, but it was still lower significantly than control group.

PARTIAL PRESSURE OF OXYGEN IN BLOOD

Partial pressure of oxygen (PO₂) reflects the amount of oxygen gas dissolved in the blood. Amount of oxygen in the blood measured of male mice at 0, 20 min, 40 min, 1h, 2h, 3h, 4h and 8h over injection of diazepam (D; 13.3 mg/kg), xylazine (X; 26.6 mg/kg), both DX (D 13.3 mg/kg & X 26.6 mg/kg), and both DX used for vasectomy surgical operation (DXVas) is shown (Table 2). Mean of PO₂ before drugs' injection did not have significant differences between the five groups, but starting from 20 minutes of diazepam and/or xylazine dosage injection, PO₂ values were significantly decreased than control group. The amount of oxygen in the blood at 20 and 40 min of diazepam and/or xylazine decreased significantly (P<0.05) com-

pared to control group. The lowest amount of oxygen in the blood recorded at 1h of injection in all injected groups. The amount of oxygen in the blood started to increase in diazepam and/or xylazine groups thereafter. The increase of PO₂ was more pronounced in diazepam group where it was not differed than control group at 3h, 4h and 8h of injection.

HEART RATE

Pulse rate of male mice at 0, 20 min, 40 min, 1h, 2h, 3h, 4h and 8h over injection of diazepam (D; 13.3 mg/kg), xylazine (X; 26.6 mg/kg), both DX (D 13.3 mg/kg & X 26.6 mg/kg), and both DX used for vasectomy surgical operation (DXVas) is shown (Table 3). Mean of heart rate before drugs' injection did not have significant differences between the five groups, but starting from 20 minutes of diazepam and/or xylazine dosage injection, heart rate values of diazepam and/or xylazine groups was significantly lower than control group. Heart rate at 20 and 40 min of diazepam and/or xylazine groups decreased significantly (P<0.05) compared to control group. The decrease of pulse rate was significantly more pronounced in xylazine, DX and DXVas groups compared to diazepam and control ones. The lowest pulse rate recorded at 1h of diazepam and/or xylazine injection. The pulse rate started to increase in diazepam and/or xylazine groups thereafter. The increase of pulse rate was more pronounced in diazepam group where it was not differed significantly than control group at 3h, 4h and 8h of injection. The values of heart rate at 3h, 4h and 8h of xylazine, DX and DXV as groups was still significantly lower than those of diazepam and control ones.

BLOOD GLUCOSE LEVEL

Blood glucose levels of mice at 0, 20 min, 40 min, 1h, 2h, 3h, 4h and 8h over injection of diazepam (D; 13.3 mg/kg), xylazine (X; 26.6 mg/kg), both DX (D 13.3 mg/kg & X 26.6 mg/kg), and both DX used for vasectomy surgical operation (DXVas) is shown (Table 4). Blood glucose level increases significantly among groups due to diazepam and/or xylazine injection over time of injection. Mean of blood glucose levels before drugs' injection did not have significant differences between the five groups, but starting from 20 minutes of diazepam and/or xylazine dosage injection, blood glucose values of diazepam and/or xylazine groups was significantly higher than control group. Blood glucose levels at 20 and 40 min of diazepam and/or xylazine increased significantly (P<0.05) compared to control group. The highest glucose level recorded at 1h of diazepam and/or xylazine injection. The increase of blood glucose levels was significantly more pronounced in xylazine, DX and DXV as groups compared to diazepam and control ones. The highest blood glucose levels recorded at 1h of diazepam and/or xylazine injection. The blood glucose levels started to decrease in diazepam and/or xylazine groups

Table 1: Effect of diazepam (13.3 mg/kg) and/or xylazine (26.6 mg/kg) on body temperature (°C) in mice

PO2	Control	Diazepam (D)	Xylazine (X)	DX	DXVas
0 min	37.22 ± 0.061a	37.21 ± 0.06a	37.10 ± 0.10a	37.23 ± 0.12a	37.28 ± 0.12a
20 min	37.17 ± 0.07a	35.26 ± 0.01b	34.19 ± 0.02c	33.10 ± 0.02d	33.0 ± 0.10d
40 min	37.15 ± 0.07a	34.29 ± 0.02b	32.52 ± 0.06c	32.16 ± 0.04d	32.07 ± 0.07d
1 h	37.20 ± 0.06a	33.34 ± 0.02b	32.24 ± 0.05c	31.48 ± 0.02d	31.36 ± 0.13d
2 h	37.22 ± 0.07a	33.11 ± 0.03b	32.06 ± 0.07c	31.23 ± 0.07d	31.1 ± 0.14d
3 h	37.21 ± 0.07a	34.57 ± 0.12b	33.65 ± 0.20c	31.53 ± 0.10d	31.44 ± 0.17d
4 h	37.16 ± 0.06a	35.08 ± 0.13b	34.63 ± 0.23c	31.80 ± 0.05d	31.66 ± 0.17d
8 h	37.16 ± 0.05a	36.36 ± 0.04b	35.31 ± 0.37c	32.82 ± 0.21d	32.68 ± 0.26d

a,b, c; Values with different superscripts between groups of the same row differed significantly at P < 0.05.

Table 2: Effect of diazepam (13.3 mg/kg) and/or xylazine (26.6 mg/kg) on partial pressure of oxygen (PO2) in mice

PO2	Control	Diazepam (D)	Xylazine (X)	DX	DXVas
0 min	90.45 ± 2.13a	91.18 ± 1.21a	90.54 ± 2.17a	89.36 ± 2.21a	89.00 ± 2.13a
20 min	93.72 ± 1.67a	84.09 ± 2.10b	87.25 ± 1.44b	84.81 ± 1.61b	85.18 ± 1.58b
40 min	95.54 ± 1.35a	78.63 ± 1.79c	86.00 ± 1.62b	83.18 ± 1.82b	82.63 ± 1.88b
1 h	87.63 ± 2.37a	78.09 ± 1.80b	79.90 ± 3.53b	75.81 ± 1.78b	74.81 ± 1.92b
2 h	91.45 ± 1.82a	78.90 ± 1.01c	85.36 ± 2.05b	76.00 ± 2.98c	76.45 ± 3.32c
3 h	90.18 ± 1.62a	79.09 ± 2.71b	86.72 ± 0.66a	79.18 ± 3.71b	78.27 ± 3.64b
4 h	91.27 ± 1.82a	80.72 ± 1.82b	89.18 ± 1.85a	81.45 ± 2.23b	79.54 ± 2.97b
8 h	90.36 ± 1.46ab	86.36 ± 2.40bc	90.90 ± 0.93a	85.18 ± 0.52c	83.81 ± 1.46c

a,b, c; Values with different superscripts between groups of the same row differed significantly at P < 0.05.

Table 3: Effect of diazepam (13.3 mg/kg) and/or xylazine (26.6 mg/kg) on pulse rate in mice

PR	Control	Diazepam (D)	Xylazine (X)	DX	DXVas
0 min	178.18 ± 6.39a	186.00 ± 5.32a	185.09 ± 3.86a	186.54 ± 5.09a	185.45 ± 5.07a
20 min	188.00 ± 4.53a	155.18 ± 11.03b	120.72 ± 5.98c	119.09 ± 8.39c	118.27 ± 8.05c
40 min	187.63 ± 10.55a	146.09 ± 9.94b	119.18 ± 5.83c	118.36 ± 7.27c	117.45 ± 6.99c
1 h	176.45 ± 8.5a	129.45 ± 4.68b	113.54 ± 5.61c	116.36 ± 7.39c	115.09 ± 7.22c
2 h	197.27 ± 8.40a	162.45 ± 6.15b	114.09 ± 5.33c	124.27 ± 9.10c	124.90 ± 8.73c
3 h	192.27 ± 6.76a	163.36 ± 14.49a	114.54 ± 8.41b	132.36 ± 13.69b	131.45 ± 13.2b
4 h	191.09 ± 6.62a	180.09 ± 8.37a	145.36 ± 2.47b	138.45 ± 9.53b	138.72 ± 9.16b
8 h	189.09 ± 6.45a	186.18 ± 4.40a	160.18 ± 5.71b	156.45 ± 6.16b	154.63 ± 6.14b

a,b, c; Values with different superscripts between groups of the same row differed significantly at P < 0.05.

Table 4: Effect of diazepam (13.3 mg/kg) and/or xylazine (26.6 mg/kg) on blood glucose levels in mice

Glucose	Control	Diazepam (D)	Xylazine (X)	DX	DXVas
0 min	115.63 ± 5.94a	118.63 ± 4.05a	122.36 ± 3.03a	123.27 ± 3.72a	122.54 ± 3.68a
20 min	123.27 ± 1.47c	168.54 ± 6.84b	238.54 ± 5.42a	239.00 ± 10.0a	237.18 ± 10.2a
40 min	121.00 ± 2.72c	163.36 ± 14.49b	261.54 ± 24.21a	259.27 ± 4.31a	258.36 ± 3.97a
1 h	136.09 ± 4.29c	176.27 ± 10.08b	263.25 ± 6.86a	277.54 ± 19.76a	275.72 ± 18.97a
2 h	114.72 ± 3.80b	141.09 ± 5.80b	226.54 ± 32.90a	253.18 ± 30.30a	255.0 ± 28.80a
3 h	111.18 ± 3.40c	128.00 ± 6.61c	187.81 ± 9.99b	227.90 ± 16.77a	228.81 ± 16.32a
4 h	107.54 ± 2.74b	127.18 ± 0.85b	172.54 ± 6.84a	176.63 ± 19.83a	177.54 ± 19.44a
8 h	102.00 ± 2.54c	126.54 ± 4.98b	154.00 ± 1.69a	152.54 ± 5.71a	150.72 ± 5.40a

a,b, c; Values with different superscripts between groups of the same row differed significantly at P < 0.05.

thereafter. The decrease of blood glucose levels was more pronounced in diazepam group where it was not differed significantly than control group at 3h and 4h of injection. The values of blood glucose at 3h, 4h and 8h of xylazine, DX and DXV as groups were still significantly higher than those of diazepam and control ones.

DISCUSSION

Results of the current study demonstrated the effects of diazepam (D; 13.3 mg/kg), xylazine (X; 26.6 mg/kg), both diazepam and xylazine (DX; D 13.3 mg/kg & X; 26.6 mg/kg), and both diazepam and xylazine used for vasectomy surgical operation (DXVas) at 0, 20 min, 40 min, 1h, 2h, 3h, 4h and 8h of injection on body temperature, PO₂, heart rate and blood oxygen level (Tables 1-4). Diazepam and/or xylazine drugs were used for sedation, analgesia and anesthesia in rabbit, mice and rats (Mohammed et al., 2011; Ljungqvist et al., 2012; Mohammed et al., 2012). Because of their transient negative side effects (Mohammed et al., 2012), the current study recorded the values of body temperature, PO₂, pulse rate and blood glucose at the previous aforementioned times to explore the time of recovery over diazepam and/or xylazine injection relevant to surgical practice.

The significant reduction of body temperature in this study over diazepam (13.3 mg/kg) and/or xylazine (26.6 mg/kg) presented in Table 1. The decrease was more pronounced in both X, DX and DXVas groups as previously indicated over 6.2 mg/kg diazepam and/or 13.3 mg/kg xylazine in rats at 2h after injection (Mohammed et al., 2012) as in other species [cattle (Yadav et al., 2008); male Mongolian gerbils (Sarnowska et al., 2009); rabbits (Mohammed et al., 2011)]. The changes of thermoregulatory control upon diazepam and/or xylazine administration might be due to the decrease of vital functions of cardiovascular and respiratory systems.

The significant reduction of blood oxygen and heart rate in this study due to diazepam (13.3 mg/kg) and/or xylazine (26.6 mg/kg) presented in tables (2-3). Diazepam caused minimal cardiovascular effects compared to xylazine. The appropriate use of analgesic and anesthetic drugs clearly influences pulmonary outcomes. The decrease of myocardial contractility and cardiac output is body of evidence of some studies (Kul et al., 2000; Ismail et al., 2010) due to xylazine injection. Decreased heart rate could be attributed to sinus carotid baroreceptor reflex in response to an initial hypertension due to vasoconstriction caused by peripheral postsynaptic adreno-receptors (Garner et al., 1971). Decreased heart rate due to xylazine administration was found in pregnant goats (Sakamoto et al., 1996), pregnant cows (Hodgson et al., 2002), dogs (Ilbäck and Stalhandske, 2003), and heifers (Araujo and Ginther, 2009).

The effects of diazepam cardiovascular and respiratory systems vary considerably among species (Rail, 2009). In general, diazepam may cause minimal cardiovascular and moderate respiratory effects (Booth, 1988) and known as minor tranquilizers (Goldberg et al., 2009). Increasing dosage of midazolam in swine resulted in a progressive decrease in heart rate (Smith et al., 1991). Similarly, heart rate decreased significantly upon diazepam in pre-weaned seal pups, particularly during the first 20 min. after administration (Lapierre et al., 2007). Dosage of both diazepam and xylazine (13.3 & 26.6 mg/kg BW, respectively) resulted in general anesthesia (Mohammed et al., 2011; Mohammed et al., 2012). It is indicated that general anesthesia resulted in decreased oxygenation in the post-anesthesia period (Karcz and Papadacos, 2013). Pulmonary atelectasis in combination with alveolar hypoventilation of anesthetized individuals has been shown that is a common finding occurred in 85% to 90% of healthy adults.

Blood glucose levels increased significantly among groups due to diazepam and/or xylazine injection over time of injection. Our previous study in rats using 6.2 mg/kg diazepam and/or 13.3 mg/kg xylazine (Mohammed et al., 2012) presented the insignificant increase of plasma glucose level at 2h of injection. Other studies in other species (cattle, buffaloes, camels and dogs) indicated hyperglycemia upon drugs' administration (Symonds, 1976; Custer et al., 1977; Dwivedi et al., 2004; Fani et al., 2004). Custer et al. (1977) found that the value of glucose was approximately twice in xylazine-induced restrain camels compared to the value of manually restrained camels. Hyperglycemia of anesthesia drugs might be due to the stress-induced gluconeogenesis and the probable suppression of insulin.

CONCLUSION

It could be concluded that administration of 13.3 mg/kg BW of diazepam and/or 26.6 mg/kg BW xylazine resulted in transient negative side effects in body temperature, heart rate and blood oxygen and glucose levels, which returned approximately close to normal levels at 8h of injection in mice.

CONFLICTS OF INTEREST

No conflict of interest of this article to declare.

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