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Study the Effect of Ketamine, Xylazine and Their Combination on Liver and Kidney Features in Rabbits

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Abstract

The current study aimed to evaluate effects of Ketamine, Xylazine and their combination on liver and kidney features parameters in male rabbits (age 4-5 months) were divided in to three groups (6 rabbits / group). Group 1 (control): six adult males' rabbit's injection distal water (1 ml), Group 2 (K+Z/M): six adult male rabbit's injection ketamine (35 ml) combination with xylazine (5 ml) intramuscular (I/M).Group 3 (K+Z/V): six adult male rabbit's injection ketamine (6 ml) combination with xylazine (0.6 ml) intravenously (I/V). Group 4 (Z- after 10 min given K): six adult male rabbit's injection xylazine (5 ml) and then after 10 min injection ketamine (35 ml) intramuscular (I/M). At end of treatment. Body weight (BW) of animals, as initial and final of administration were recorded. Plasma biochemical and liver enzymes are taken for analysis at the end of treatment. Results appeared ALT and AST concentrations increased in G4 (Z- after 10min given K) while significantly decreased in G2 but ALP concentrations significantly increased in G2 and G4 as compared to other treated groups. The data of ureaand concentrations of BUNand creatinine increment in group G4 but decreased in G2 than other groups in experiment, all groups showed significantly differences in TP. In this study; the results showed that combinations of ketamine and xylazine could be used in anesthesia practice in laboratory animals.

Key words: rabbits,Ketamine, Xylazine, liver and kidney functions

INTRODUCTION

Ketamine is classified as an *N*-methyl-D-aspartate (NMDA) receptor antagonist producing a dissociative anesthetic state (1). Ketamine 2-(2-chlorophenyl)- 2-(metthylamino), an arylcycloalkylamine which is structurally similar to cyclidine, like phencyclidine, eticyclidine, rolicyclidine and tenocyclidine (6).Ketamine usually stimulates cardiovascular function in normal animals causing increase in the heart rate and mean arterial pressure(2). Itis rarely used alone because of its association with poor muscle relaxation, tachycardia and catalepsy ormuscle rigidity and it is therefore commonly used in combination with xylazine, diazepam and acepromazine to minimize the untoward effects (3).

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Xylazine is a dose-dependent alpha2 adrenergic agonist that causes bradycardia, hypertension followed by hypotension. It has sedative, analgesic, and muscle relaxant effects (4,7).Ketamine and xylazine are metabolized mainly by liver cytochromes P450 enzymes and excreted by the kidney (5).Xylazine appears to reduce sensitivity to insulin and glucose uptake in humans (8).The application of different anesthetic combinations and methods provides new, hitherto unpublished, information for this species, thus facilitating the choice of chemical an aesthesia and method involving the lowest risk for both humans and animals (9).

This study aimed to detection the duration of anesthesia by ketamine with or without xylazine and its effect on the biochemical measurements.

METHODOLOGY

Experimental design:

The experimental animals were in this study included: thirty six adult males of rabbits were randomly divided into four groups as the following:

Group 1 (control): six adult males' rabbit's injection distal water(1 ml)

Group 2 (K+Z/M): six adult male rabbit's injection ketamine (35 ml) combination with xylazine (5ml) intramuscular (I/M).

Group 3 (K+Z/V): six adult male rabbit's injection ketamine (6 ml) combination with xylazine (0.6 ml) intravenously (I/V).

Group 4 (Z- after 10min given K): six adult male rabbit's injection xylazine (5 ml) and then after 5 min injection ketamine (35 ml) intramuscular (I/M)

Collection of blood samples were collected via the puncture of the heart of anesthesia animals using sterile syringe (5cc) putting in tubes without anticoagulant and serum were isolated from blood by centrifugation at (3000rpm for 15 min.) and then separation in eppendroff tubes, stored the tubes at -20°C for till uses for biochemical and hormonal examination.

Biochemical measurements: Some biochemical measurements were done on the serum after the separation by using special enzymatic kits as follow:

Aspartate Aminotransferase (AST) and Alanine Aminotransferase (ALT) estimations (U/I): Aspartate and alanine aminotransferase is measured by monitoring the concentration of oxaloacetate hydrazone formed with 2,4-dinitrophenyl-hydrazine (Schumann & Klauke, 2003).

Alkaline Phosphatase (ALP) estimation (U/I): This done by using the colorimetric determination of alkaline phosphatase activity (Biomeriexu, France). Tietiz (1999) who was described this method

Total protein measurement: The total protein was estimated by using a special chemical kit

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prepared by BIOLABO, SA, Maizy/ France). Colorimetric method is described by Young (1995) and Tietz (2006).

Urea measurement: The serum urea concentration was measured by using a special chemical kit (SPECTRUM-Egyptian Company for Biotechnology). The urea is hydrolyzed in the presence of water and urease to produce ammonia and carbon dioxide (Tietz, 1996).

Serum creatinine measurement: The particular feature of metabolism processes of muscle contraction is creatine and phosphocreatine; it is converted to a waste product creatinine. The amount of creatinine produced/day is related to a muscle mass, body weight, sex, age, diet and exercise. Creatinine is endogenously produced and released to body fluids at a stable rate and its plasma and serum levels are maintained within narrow limits, it can be measured as an indicator of glomerular filtration rate (GFR) (Bartels *et al*., 1971).

RESULTS

Effect of ketamine and xylazine on serum hepato- enzymes:

The effect ketamine and xylazine on serum concentrations of ALT, AST and ALP are showed in table (1). The data that indicated to there were a significantly ($p< 0.05$) increased in ALT concentration in G4 (Z- after 5min given K) compared to other treated groups and group of control, while significant ($p< 0.05$) decreased in group G2 injection combination of ketamine and xylazine (I/M) more than other groups of experiment.Concentrations of AST increased significantly ($p\leq0.05$) in G4 (Z- after 5min given K) more than other groups and control but not significant differences between group control and G3. The results of ALP concentrations significantly ($p\leq0.05$) increased in G2 and G4 as compared to the control and G3

Table (1) Effect of ketamine and xylazine on serum ALT, AST and ALP levels in adult male rats:

Parameters / Groups (n=10)	ALT (U/l)	AST (U/l)	ALP (U/l)
G1 (Control)	76.06± 0.31^{b}	44.62± 0.11^{c}	36.00± 0.81^{c}
G2 (K+Z/M)	63.37± 0.32^{c}	48.41± 0.52 ^{b}	55.62± 0.47^{a}
G3 (K+Z/V)	75.97± 0.91^{a}	46.34± 0.48^{c}	48.81± 0.23^{b}
G4 (Z- after 10min given K)	133.35± 4.60 ^{a}	105.02± 0.61^{a}	57.66± 0.47^{a}
LSD	19.59	1.71	2.04

Values expressed in small letters mean significant differences at ($p< 0.05$) levels (M±SD).

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Effect of ketamine and xylazine on serum total protein, urea, UBN and creatinine concentrations in adult male rats:

Ketamine and xylazine (I/M) injection group showed a significant decrease ($p<0.05$) in concentration of urea as compared with control and other groups (Table 2). While significantly ($p<0.05$) increment in group G4 than other groups in experiment, all groups showed significantly differences in TP between all these groups. While the serum urea concentration increase significantly ($p<0.05$) in group injectionXylazine and after 5min given Ketamine compared with control and other groups but decrement significantly ($p<0.05$) in G2 given combination of Ketamine and xylazine (I/M) injection. Concentrations of BUN increase significantly($p<0.05$) in group G4 but decrement ($p<0.05$) in G2 as compared to control and G3 injection the combination intravenously (I/V).Also table 2 documented significant increased in creatinine concentration in G4 but significant decrease in this concentration in G2 as compared to the other treated group and control group

Table (2) Effect of Ketamine and xylazine on serum total protein, urea BUN, and creatinine concentrations in adult male rats:

Parameters / Groups (n=10)	Total protein gm/L	Urea mg/L	UBN mg/dl	Creatinine mg/dl
G1 (Control)	45.15± 0.21^{c}	23.86± 0.68^{b}	76.06± 0.31^{b}	0.57± 0.014^{b}
G2 (K+Z/M)	22.67± 0.46 ^{d}	12.17± 0.46^{c}	36.37± 0.32^{c}	0.52±0.032^{b}
G3 (K+Z/V)	78.08± 1.38^{b}	25.37± 0.45^{b}	75.97± 0.91^{b}	0.63± 0.008^{bc}
G4 (Z- after 10min given K)	84.50± 0.40^{a}	31.52± 2.50^{a}	133.35± 4.60 ^{a}	0.95± 0.036^{a}
LSD	6.41	5.87	2.28	0.167

Values expressed in small letters mean significant differences at ($p< 0.05$) levels (M±SD).

DISCUSSION

Anesthetic agents are commonly applied to laboratory animals to prevent the pain or stress caused by experimental procedures or to facilitate zootechnical handling by means of chemical restraint (10).

Ismail *et al*. (2010) that investigate effects of ketamin-xylazin-diazepam anesthesia on plasma

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biochemical values in sheep and goats. The result of the study show that there were no significant difference between before and during ketaminexylazin anesthesia in AST, ALT, GGT, Creatinin, ALB, Urea in sheep but there were statically significant an increase Glucose during the anesthesia than the baseline values in goats (11). In this study there were no significant changes when the results comped the baseline values in AST, ALT, ALP, GGT, LDH, creatinine, ALB, GLB, Cholesterol, Urea, Uric acid, TBİL, DBİL, Na, K and Cl (12).

Aspartate aminotransferase (U/L) activity showed decreased in level of enzyme assay through induction and maintenance of anesthesia and increased after recovery but still below the base line of the study. Results of ALT showed no significant difference between donkeys, the enzyme level within normal range in all-time of experiment. ALP values of this study showed no significant difference (13).

In conclusion, no anesthetic drug alone has excellent properties. On the basis of our findings, we conclude that there were significant differences between groups of experiment of anesthesia in liver enzymes and kidney profiles effects of xylazine-ketamine anesthesia in male rabbits. The combination of ketamine and xylazine could be used for laboratory and other animals as anesthesia safety. This combination thus be recommended for premedication in healthy patients. However, the use of medetomidine should be carefully controlled because of the rapid decrease in heart rate

REFERENCES

1. Folts JD, Afonso S and Rowe GG. Systemic and coronary hemodynamic effects of ketamine in intact anaesthetized and unanaesthetized dogs. Br. J. Anaesth. 1975; 47:686–694.
2. Muir WW, Lerche P, Robertson JT, Hubbell JA and Beard W. Comparison of four drug combinations for total intra venous anesthesia of horse undergoing surgical removal of an abdominal testis. .J. AM. Vet. Med. Assoc.2000; 217: 869- 873.
3. Azizpour A and Hassani Y. Clinical evaluation of general an aesthesia with a combination of Ketamine HCL and Diazepam in pigeons. Journal of Agriculture.2012; 7: 101-105.
4. Tranquilli, WJ, Thurmon, JC and Grimm KA. Lumb and Jones' Veterinary Anesthesia and Cardiorespiratory effects in dogs. Veteriner Cerrahi Dergisi, 2007; 8: 35- 40.
5. Hijazi Y and Boulieu R. Contribution of CYP3A4, CYP2C9, and CYP2B6 in N-demethylation of ketamine in human liver microsomes. Drug Metab Dispos. 2002; 30:853–858.
6. Gianni AJ, Underwood RH, Gianni MC, *et al*. Phencyclidine and the dissociative. Psychiatric Medicine. 1985;3(3):197–217.
7. Baniadam A, Afshar SF and Ahmadifard Y. The effect of xylazine–ketamine on temperature, heart and respiratory rate, arterial blood pressure and blood gases, in sheep. Journal of Veterinary Research. 2004; 59(3):265– 270.

8. Xiao YF, Wang B, Wang X, Du F, Benzinou M, Wang YX "Xylazine-induced reduction of tissue sensitivity to insulin leads to acute hyperglycemia in diabetic and normoglycemic monkeys". *BMC Anesthesiology*. October 2013; **13** (1): 33. doi:10.1186/1471-2253-13-33. PMC 4016475. PMID 24138083
9. Encarna Casas-Díaz & Ignasi Marco & Jorge R. López-Olvera & Gregorio Mentaberre & Santiago Lavín Eur J Wildl Res Comparison of xylazine–ketamine and medetomidine–ketamine anaesthesia in the Iberian ibex (Capra pyrenaica). 2011, 57:887–893.3 DOI 10.1007/s10344-011-0500-7.
10. Chen Y, Ono F, Yoshida T, Yoshikawa Y. Relationship between body weight and hematological and serum biochemical parameters in female cynomolgus monkeys (*Macaca mfascicularis)* . *Exp Anim*. 2002;51:125-131.
11. Ismail ZB, Jawasreh K, and Al-Majali A, 2010: Effects of xylazine–ketamine–diazepam anesthesia on Blood cell counts and plasma biochemical values in sheep and goats. Comp Clin Pathol, 19, 571-574.
12. İlker Ç.; Nihat Ş.; Güzin Ö.; Hüdai İ.; , Halil S. B. and Tekin Ş. Effect of Ketamine-Xylazine Anesthesia on Some Hematological and Serum Biochemical Values of Bozova Greyhounds.Harran Üniv Vet Fak Derg. 2013;.2(1) 27-31.
13. Amin A.A.; Ali A.F. and Al-Mutheffer, E.A. Biochemical changes induced by general anesthesia with romifidine as a premedication, midazolam and ketamine induction and maintenance by infusion in donkeys. *raqi Journal of Veterinary Sciences, 2012,* 26 (Issue Suppl.II), Pp.: 19-22. 10.33899/ijvs.2020.167130.
14. Qasim MT, Al-Mayali HK. Investigate the relation between Baicalin effect and Gene expression of LH, FSH, Testosterone in male rats treated with Gemcitabine drug. Research Journal of Pharmacy and Technology. 2019 Sep 30;12(9):4135-41.
15. Qasim MT, Al-Mayali HK. The immunological and protective role of Baicalin in male rats treated with chemotherapy (Gemcitabine). InJournal of Physics: Conference Series 2019 Jul 1 (Vol. 1234, No. 1, p. 012065). IOP Publishing.
16. Ahmed Jassem AL-Naely, Maytham T. Qasim, Hussein Abbas Al-Hamadawi. Transfusion of Blood Components in the Newborn Service of the Hospital. Annals of RSCB [Internet]. 2021Apr.7 [cited 2021Apr.14];:952-8. Available from: http://annalsofrscb.ro/index.php/journal/article/view/2525.
17. Zainab I. Mohammed, Maytham T. Qasim. Correlation of AMH and LH Levels in PCOS Patients with Pregnancy Rate. Annals of RSCB [Internet]. 2021Apr.7 [cited 2021Apr.14];:945-51. Available from: http://annalsofrscb.ro/index.php/journal/article/view/2524