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Comparison of the effects of different anaesthetics on rabbit plasma biochemical parameters

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Abstract

The aim of the present study is to investigate the possible effects of different anaesthetics on selected biochemical parameters in rabbits. Twenty rabbits divided to five treatment groups; control (1 ml IV saline), Ketamine (10 mg/kg IV) with xylazine (3 mg/kg IV) or diazepam (2 mg/kg IV), Propofol (8 mg/kg IV) and pentobarbitone (30 mg/kg IV). Blood samples were obtained at: before injection, and at 15, 30, 60, 120 min and 24 hour post injection. Plasma ALT, AST, ALP, GGT, BUN, creatinine and potassium concentrations were measured. There was an increase ($P<0.05$) in plasma ALT levels in the ketamine-xylazine and ketamine-diazepam groups, while plasma AST levels were elevated ($P<0.05$) in the ketamine-xylazine, ketamine-diazepam and pentobarbitone groups. Plasma ALP decreased ($P<0.05$) in the ketamine-diazepam injection. Plasma GGT increased ($P<0.05$) following pentobarbitone injection. An increase ($P<0.05$) in plasma BUN was observed in the ketamine-xylazine, ketamine-diazepam and pentobarbitone groups. Significant increase ($P<0.05$) in plasma creatinine levels was observed in ketamine-xylazine and ketamine-diazepam groups. There were no significant changes in any variables in propofol group. Based on the results of this study, ketamine-xylazine, ketamine-diazepam and pentobarbitone, may alter selected biochemical parameters, when using the recommended doses and if higher doses are use by mistake or by mismatching doses severe consequence may develop such as very long recovery period or expiration of the patient. But propofol could be a safe anesthetic with low effect on biochemical parameters.

Keywords: New Zealand White Rabbit, ALT, AST, ALP, GGT, Bun, Creatinine, Potassium

Introduction

The anaesthesia used in experimental research can modify biochemical parameters. It is important to know the effect of the mostly used anaesthetics on these parameters in rabbits to avoid erroneous interpretation of laboratory tests in anaesthetized rabbits (González Gil et al., 2004). Frequently, rabbits have to be anaesthetized for experimental and other purposes. Rabbit blood chemistry studies have received a considerable attention in the literature. However, few reports have investigated the effects of anaesthetics on various biochemical parameters and electrolytes in rabbits (Bito and Eakins, 1969; Collado et al., 1987). The activities of serum enzymes in many diseases of humans and animals have been investigated extensively. Observations of these changes have proved to be an important aid in diagnosing the selected diseases and in determining the patient's prognosis (Hoffmann et al., 1989). In order to evaluate potential biochemical parameter changes due to tranquillizer or anaesthetic administration, ALT (alanine amino-transferase), AST (aspartate aminotransferase), ALP (alkaline phosphatase), GGT (gamma glutamyl transferase), BUN (blood urea nitrogen), creatinine levels were measured. The purpose of the present study was to investigate the possible effects of different anaesthetics on selected biochemical parameters in rabbits.

Materials and Methods

Twenty healthy male New Zealand white rabbits, weighing 4.0±0.5 kg, were used. The rabbits were kept for two weeks to be adapted to environmental conditions. They were housed in individual cages in a room with controlled temperature 20±0.8°C, and a 12 hour light/dark cycle. The rabbits were fed standard diet and provided with fresh water *ad libitum*.

Animals were randomly divided to five treatment groups: control (1 ml IV saline solution), Ketamine (K) (10 mg/kg IV, Trittau, Germany) with xylazine (X) (3

mg/kg IV; Rompun Bayer AG, Germany) or diazepam (D) (2 mg/kg IV, Valium, Roche, Madrid, Spain), Propofol (P) (8 mg/kg IV, Diprivan, Astrazenca, Sweden) and Pentobarbitone (PB) (30 mg/kg IV, Nembutal, Abbott Laboratories, Spain). Animals were fasted for 12 hour prior to the experiment and water was removed 2 hour before initiating the experiments. Intravenous administration was performed using the lateral ear vein. Blood samples (2 ml) were obtained from the central ear artery using 22 G catheter as previously described (Illera et al., 1990) before anaesthetic injection, at 15, 30, 60, 120 min and 24 hour post anaesthetic (Saline) injection. Blood was collected into heparinized tubes, centrifuged at 1200 rpm 20 min. Plasma was separated and stored frozen until tested.

Plasma ALT, AST, ALP, GGT, BUN, creatinine and potassium concentrations were measured by auto analyser (BT-3000 Biotecnica, Italy).

Statistical analysis

The data were analysed by ANOVA, followed by the Turkey honestly significant difference (HSD) test and the level of significance was set to ($P<0.05$).

Results

There was an increase ($P<0.05$) in plasma ALT levels at 15, 60, 120 min and 24 hour in the K-X group and at 15 min and 24 hour in the K-D group (Table 1), while plasma AST levels were elevated ($P<0.05$) at 15, 60 and 120 min in the K-X group, at 15, 30, 60 and 120 min in the K-D group and 15 and 30 min in the PB group (Table 2) . No significant changes of plasma ALT and AST levels were observed in the P group (Table 1 and 2). Plasma ALP concentrations decreased ($P<0.05$) at 24 hour in the K-X group, 15, 30 min and 24 hour in the K-D injection (Table 3). Plasma GGT concentrations increased ($P<0.05$) at 24 hour in the K-X group and 30, 60 min after PB injection (Table 4)

An increase ($P<0.05$) in plasma BUN was observed at 15, 60 and 120 min in the K-X group, at 15, 30, 60 and 120 min in the K-D group and 120 min in the PB group (Table 5). Significant increase in plasma creatinine levels was observed at 15 and 120 min in K-X group and 15, 60 and 120 min in K-D group (Table 6). There were no significant changes in variables in propofol group.

Table 1: Plasma ALT concentrations (IU/litter) at six time points in the control (C), ketamine–xylazine (K-X), ketamine–diazepam (K-D), Propofol (P), and pentobarbitone (PB) groups

Anesthetic Time	C	K-X	K-D	P	PB
0	36.2 ± 1.2	35.5 ± 1.3	35.3 ± 1.5	38.3 ± 1.5	35.2 ± 1.5
15	32.4 ± 1.4	49.4 ± 1.8*	49.6 ± 1.9*	35.3 ± 1.2	38.1 ± 1.2
30	38.5 ± 1.6	34.8 ± 1.3	32.5 ± 1.2	32.5 ± 1.6	31.8 ± 1.1
60	35.8 ± 1.1	47.3 ± 1.5*	34.2 ± 0.8	32.8 ± 1.1	34.2 ± 1.3
120	33.1 ± 1.2	48.9 ± 1.8*	34.8 ± 1.1	31.1 ± 1.1	32.2 ± 1.2
24 h	37.7 ± 0.9	47.8 ± 1.4*	50.1 ± 1.8*	39.4 ± 1.3	37.6 ± 1.4

All values are expressed as mean ± S.E.M; *Significant difference compared to control values. $P<0.05$

Table 2: Plasma AST concentrations (IU/litter) at six time points in the control (C), ketamine–xylazine (K-X), ketamine–diazepam (K-D), Propofol (P), and pentobarbitone (PB) groups.

Anesthetic Time	C	K-X	K-D	P	PB
0	11.2 ± 3.2	13.2 ± 2.4	14.7 ± 1.8	13.2 ± 1.2	12.3 ± 1.4
15	13.1 ± 2.4	20.3 ± 2.4*	26.4 ± 2.6*	13.1 ± 2.5	7.5 ± 1.2*
30	12.5 ± 2.6	16.8 ± 2.1	21.7 ± 2.1*	12.5 ± 2.6	7.3 ± 1.1*
60	10.8 ± 1.7	25.7 ± 3.2*	24.1 ± 2.8*	12.8 ± 1.8	11.2 ± 1.4
120	14.3 ± 2.2	26.6 ± 3.6*	22.7 ± 1.9*	13.3 ± 2.2	13.2 ± 1.3
24 h	13.6 ± 3.1	15.5 ± 1.8	16.7 ± 2.3	14.6 ± 3.4	14.2 ± 2.2

All values are expressed as mean ± S.E.M; *Significant difference compared to control values. $P<0.05$

Table 3: Plasma ALP concentrations (IU/litter) at six time points in the control (C), ketamine–xylazine (K-X), ketamine–diazepam (K-D), Propofol (P), and pentobarbitone (PB) groups.

Anesthetic Time	C	K-X	K-D	P	PB
0	32.2 ± 2.4	30.5 ± 2.3	32.3 ± 2.5	35.2 ± 2.7	31.2 ± 2.7
15	34.4 ± 2.6	39.4 ± 3.2	26.6 ± 2.3*	33.4 ± 1.8	32.1 ± 2.2
30	33.5 ± 3.1	35.3 ± 2.6	19.2 ± 2.8*	32.5 ± 3.2	35.3 ± 2.5
60	35.1 ± 2.7	38.5 ± 3.1	34.2 ± 3.4	32.1 ± 2.4	36.6 ± 3.3
120	38.3 ± 3.2	37.3 ± 3.4	35.7 ± 3.1	34.5 ± 2.4	34.3 ± 3.6
24 h	37.7 ± 3.3	21.2 ± 3.1*	24.6 ± 2.7*	34.2 ± 2.2	33.5 ± 3.4

All values are expressed as mean ± S.E.M; *Significant difference compared to control values. $P<0.05$.

Table 4: Plasma GGT concentrations (IU/litter) at six time points in the control (C), ketamine–xylazine (K-X), ketamine–diazepam (K-D), Propofol (P), and pentobarbitone (PB) groups.

Anesthetic Time	C	K-X	K-D	P	PB
0	3.2 ± 0.4	3.8 ± 0.5	4.1 ± 0.4	3.6 ± 0.5	3.9 ± 0.6
15	2.8 ± 0.6	3.2 ± 0.8	3.6 ± 0.9	3.1 ± 0.8	3.7 ± 0.6
30	3.5 ± 0.5	3.6 ± 0.4	4.2 ± 0.5	3.2 ± 0.2	8.8 ± 1.2*
60	3.8 ± 0.7	3.4 ± 0.4	3.8 ± 0.6	3.2± 0.4	11.2 ± 1.3*
120	3.3 ± 0.6	4.0 ± 0.6	4.1 ± 0.8	3.3 ± 0.5	4.2 ± 0.7
24 h	4.2 ± 0.9	15.8 ± 2.4*	4.3 ± 0.9	3.7 ± 0.9	5.6 ± 0.8

All values are expressed as mean ± S.E.M; *Significant difference compared to control values. P<0.05

Table 5: Plasma BUN concentrations (mg/dl) at six time points in the control (C), ketamine–xylazine (K-X), ketamine–diazepam (K-D), Propofol (P), and pentobarbitone (PB) groups.

Anesthetic Time	C	K-X	K-D	P	PB
0	16.2 ± 0.5	16.5 ± 0.8	15.3 ± 0.9	15.3 ± 0.5	17.2 ± 1.3
15	17 ± 1.3	23.4 ± 2.9*	27.6 ± 3.2*	16 ± 1.7	17.2 ± 1.3
30	16.4 ± 1.7	20.8 ± 2.4	24.6 ± 1.7*	15.3 ± 1.4	18.4 ± 2.3
60	18 ± 1.5	26.4 ± 1.8*	27.6 ± 1.8*	16.2 ± 1.4	19.4 ± 2.5
120	17.5 ± 1.6	28.9 ± 1.8*	25.7 ± 1.6*	16.5 ± 1.7	24.8 ± 1.9*
24 h	17.8 ± 1.8	19.6 ± 1.8	20.4 ± 1.1	16.8 ± 1.5	18.6 ± 1.4

All values are expressed as mean ± S.E.M; *Significant difference compared to control values. P<0.05

Table 6: Plasma Creatinine concentrations (mg/dl) at six time points in the control (C), ketamine–xylazine (K-X), ketamine–diazepam (K-D), Propofol (P), and pentobarbitone (PB) groups.

Anesthetic Time	C	K-X	K-D	P	PB
0	1.2 ± 0.1	1.2 ± 0.2	1.1 ± 0.09	1.1 ± 0.1	1.2 ± 0.1
15	1.0 ± 0.09	1.7 ± 0.2*	1.8 ± 0.2*	1.1 ± 0.1	1.1 ± 0.2
30	1.1 ± 0.6	1.1 ± 0.1	1.2 ± 0.2	1.2 ± 0.4	1.2 ± 0.1
60	1.2 ± 0.1	1.2 ± 0.2	1.7 ± 0.2*	1.2 ± 0.2	1.2 ± 0.3
120	1.2 ± 0.2	1.8 ± 0.2*	1.9 ± 0.2*	1.2 ± 0.3	1.1 ± 0.2
24 h	1.0 ± 0.9	1.1 ± 0.1	1.2 ± 0.2	1.0 ± 0.9	1.2 ± 0.1

All values are expressed as mean ± S.E.M; *Significant difference compared to control values. P<0.05

Discussion

Anaesthetics may affect both the structure and function of organ and biological systems and these effects have been extensively studied. However, the effects of commonly used anaesthetics on biochemical parameters in rabbits are poorly understood. The result of this study showed an alteration in selected biochemical parameters after administration of four anaesthetic combinations. Increased plasma ALT and AST concentrations were observed after K-X administration. It is possible that hypotension in combination with hypoxemia (Wyatt et al., 1989 and Baumgartner et al., 2010) may be associated with the release of these enzymes from the heart muscle or liver. However, plasma ALT and AST concentrations were within normal range for this species. Significant increases in plasma ALT and AST were also observed in the K-D group, probably due to hypotension and profound hypoxemia observed after ketamine administration in rabbits (Wyatt et al., 1989, González Gil et al., 2003). Researchers have proved a toxic effect on liver cells by diazepam (Strombeck and Guildford., 1991), however longer post anaesthetic patient evaluation (e.g. 48 h, 72 h) are required to evaluate a possible hepatotoxicity effect of the drugs used. The increase in plasma BUN and creatinine concentrations above the control values observed after K-X administration might be related to a possible short-term effect of the anaesthetics on renal function, as the levels returned to normal value before 24 h. It has been shown in the dog that ketamine reduces renal cortical blood flow and urine output (Hirasawa and Yonezawa, 1975), and hence, decreases glomerular filtration rate and increases plasma BUN and creatinine concentrations. Moreover, some alterations in renal functions after xylazine anaesthesia in rabbits, rats and dogs have been demonstrated (Oh and Lee, 1984). A significant increase in plasma BUN and creatinine in the K-D group was also observed, probably due to hypotension and hypoxemia resulting from the anaesthetic mixture. Benzodiazepines reduce glomerular filtration rates and urine output in man. Burchardi and Kaczmarczyk (1994), and Zahir et al. (1995) have demonstrated

alterations in renal histology after K-D in rabbits. However, Mercatello (1990) summarizes that the effects of ketamine and diazepam on renal function in man are not clearly defined. Increased plasma ALP and GGT levels of the animals treated with pentobarbitone may be a feature of bile duct or duct obstruction (Strombeck and Guildford, 1991). After 24 hours post PB injection, ALP and GGT levels were reduced and showed similar values to those of control animals. Although, this effect was transient, it should be regarded when evaluating the experimental results in rabbits anesthetised with pentobarbitone. Other investigators have reported a cholestatic effect of PB in rats (Fukuyama et al., 1996). Also no significant changes could be observed on plasma BUN and creatinine concentrations in the PB group. Plasma BUN levels also were increased after ketamine–xylazine and ketamine–diazepam administration in rabbits (González Gil et al., 2002). On the basis of the results obtained in this study, we conclude that pentobarbitone can induce changes in plasma hepatic and renal biochemical parameters within a short period of time after administration of anaesthetics. There were no significant changes in any variables in Propofol group. Therefore propofol could be a safe anaesthetic in Veterinary Medicine with low effects on plasma biochemical parameters (Ypsilantis et al., 2007).

Based on the results of this study, we can conclude that K-X, K-D and PB, the three most widely used anaesthetics, may alter selected biochemical parameters concentrations, when using the recommended doses and if higher doses are used by mistake or by mismatching doses severe consequence may develop as a very long recovery period or expiration of the patient. But propofol could be a safe anesthetic with low effect on biochemical parameters.

References

González Gil, A., Silvan, G., Illera, M. and Illera, J.C. 2004. The Effects of Anesthesia on the Clinical Chemistry of New Zealand White Rabbits. *Contemporary Topics in Laboratory Animal Science*, 43:23-29.

Bito, J.Z. and K.E. Eakins. 1969. The effect of general anesthesia on the chemical composition of blood plasma of normal rabbits. *Journal of Pharmacology and Experimental Therapeutics*,:169:277-285.

Collado, P. S., M. J. Pozo-Andrada, J. González, R. Jiménez, and A. Esteller. Effect of pentobarbital or urethane on bile secretion and chemical composition of blood in the rabbit. *Laboratory Animal*, 1987:21:11- 17.

Hoffmann, W.E., Kramer, J., Main, A.R. and Torres, J.L. 1989. Clinical enzymology. In: The Clinical Chemistry of Laboratory Animals. Loeb, W.F. and Quimby, F.W. (eds). New York: Pergamon Press, Pp: 237-78.

Bush, B.M. 1991. Plasma biochemistry (5. Nutrients and metabolites/ 6. Enzymes). In: Interpretation of Laboratory Results for Small Animal Clinicians. Oxford: Blackwell Scientific Publications. Pp: 221-347.

Fox, R.R. 1989. Clinical chemical studies applicable to laboratory animal species and their interpretation: the rabbit. In: The Clinical Chemistry of Laboratory Animals. Loeb, W.F. and Quimby, F.W. (eds). New York: Pergamon Press, Pp: 41-47.

Wyatt, J.D., Scott, R.A. and Richardson, M.E. 1989. The effects of prolonged ketamine-xylazine intravenous infusion on arterial blood pH, blood gases, mean arterial blood pressure, heart and respiratory rates, rectal temperature and reflexes in the rabbit. *Laboratory Animal Science*, 39: 411-16.

Baumgartner, C., Bollerhey, M., Ebner, J., Laacke-Singer, L., Schuster, T. and Erhardt, W. 2010. Effects of ketamine-xylazine intravenous bolus injection on cardiovascular function in rabbits. *Canadian J of Veterinary Research*, 74: 200-208.

González, Gil A., Illera, J.C., Silván, G. and Illera, M. 2003. Effects of the anaesthetic/tranquillizer treatments on selected plasma biochemical parameters in NZW rabbits. *Laboratory Animal*, 372: 155-161.

Strombeck, D.R. and Guildford, W.G. 1991. Hepatic necrosis and acute hepatic failure. In: Small Animal Gastroenterology. London: Wolfe Publishing, Pp: 574-592.

Hirasawa, H. and Yonezawa, T. 1975. The effects of ketamine and Innovar on the renal cortical and medullary blood flow of the dog. *Der Anaesthetist*, 24: 349-53.

Oh, K.S. and Lee, C.S. 1984. Histological observations of the parenchymal organs of the rats, rabbits and dogs injected with Rompun. *Korean Journal of Veterinary Research*, 24: 127-36.

Burchardi, H. and Kaczmarczyk, G. 1994. The effect of anaesthesia on renal function. *European Journal of Anaesthesiology*, 11: 163-168.

Zahir, F.T., Elzahwy, A.K., Ismail, Z.M. and Mohamed, S.A. 1995. Effects of ketamine and diazepam on the morphology of the kidney of rabbit: an electron microscopic study. *Assiut Veterinary Medical Journal*, 34: 1-12.

Mercatello, A. 1990. Changes in renal function induced by anesthesia. *Annals Francaises d 'Anaesthesia et de Reanimation*, 9: 507-524

Fukuyama, T., Yamaoka, K., Tabata, K. and T. Nakagawa. 1996. Inhibitory effect of pentobarbital on biliary excretion of diclofenac in a rat liver perfusion system. *Journal of Pharmacy and Pharmacology*, 48: 734-737.

González Gil, A., Illera, J.C., Silván, G., Lorenzo, P.L. and Illera, M. 2002. Changes in hepatic and renal enzyme concentrations and heart and respiratory rates in New Zealand White rabbits after anesthetic treatments. *Contemporary Topics in Laboratory Animal Science*, 41: 30-32.

Ypsilantis, P., Politou, M., Mikroulis, D., Pitiakoudis, M., Lambropoulou, M., Tsigalou, C., Didilis, V., Bougioukas, G., Papadopoulos, N., Manolas, C. and Simopoulos, M. 2007. Organ toxicity and mortality in propofol-sedated rabbits under prolonged mechanical ventilation. *Anaesthsia & Analgesia*,105:155–66.