

SOME HAEMATOLOGICAL AND SERUM BIOCHEMICAL CHANGES IN DOGS GIVEN DAILY ORAL DOSES OF KETAMINE HYDROCHLORIDE

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SUMMARY

Two groups of dogs were given 40 mg/kg ketamine and normal saline respectively orally for 28 days. The treatments were discontinued on day 28 and the dogs allowed recovering for a period of two weeks after which the study was terminated. To determine the effect of daily intake of ketamine and normal saline on the haemogram, blood samples were collected on days 0, 7, 21, 28 for the assessment of the packed cell volume (PCV), red blood cell counts (RBC), total and differential white cell counts. The serum levels of alanine aminotransferase (ALT) and creatinine were assayed on days 0, 7, 21, 28. On days 35 and 42 (post treatment), the haematologic variables, serum ALT and creatinine levels were re-determined. The RBC and PCV of the ketamine treated group were significantly ($P < 0.05$) lower than those of the control group on days 21, 28 and 35. Also on days 21 and 28, the WBC, absolute lymphocyte counts and absolute neutrophil counts of the ketamine group were significantly ($P < 0.05$) lower. On day 42 (post treatment), the WBC and absolute neutrophil counts of the ketamine group were significantly higher compared to those of the control group. The serum levels of ALT and creatinine of the ketamine group were significantly ($P < 0.05$) higher than control values by day 21 and 28 of the study. It was concluded that prolonged oral ingestion of ketamine led to mild anaemia. Continues use of ketamine may also cause reduction of lymphocytes and neutrophils thus increasing an individual's susceptibility to viral and bacterial diseases. Mild hepatocellular damage and decreased renal function may also characterize prolonged use of ketamine. The experimental findings highlight the need to discourage prolonged use of ketamine either for recreation or as a psychedelic.

KEYWORDS: Haematology, serum enzymes, oral, ketamine, dogs.

INTRODUCTION

Ketamine hydrochloride is a short acting anaesthetic agent used in veterinary and human anaesthesia (Bergman, 1999; Bonanno, 2002; Hijazi *et al.*, 2003). It is often described as a unique anaesthetic due to its hypnotic, analgesic and amnesic properties (Tomilson, 1994). It induces a state referred to as "dissociative anaesthesia" (Bergman, 1999). It is mainly used for induction of anaesthesia in patients in the intensive care unit and for short surgical procedures (White *et al.*, 1982; Kolenda *et al.*, 1996). In humans, it is

occasionally used for its sedative and analgesic properties (Clements *et al.*, 1982; Kolenda *et al.*, 1996). Extra medically, ketamine is used as a recreational drug due to its dissociative effects (Dotson *et al.*, 1995). It is also used in psychedelic therapy in the treatment of alcohol dependence and neuroses (Krystal *et al.*, 2006).

Ketamine is currently a controlled drug in the United States, United Kingdom, Canada, Hong Kong and Singapore due to its recreational / non-medical use (Dalgamo and Schewan, 1996; Lim, 2003). It is used recreationally in powder or liquid form. Recreationally used powders are

prepared by heating liquid ketamine stolen from veterinary and pharmaceutical shops (Anon, 1994). These powders are then insufflated, smoked or orally ingested on daily basis (Kent, 1996; Rebozo and Gonzalez, 1999).

The systemic side effects of daily recreational or psychedelic use of ketamine have not been reported. However, the mean red blood cell count, haemoglobin concentration and packed cell volumes were reported to decrease slightly following ketamine anaesthesia in sheep (Nowrouzian *et al.*, 1981). These parameters returned to baseline when the animals recovered from anaesthesia. The use of ketamine for infusion has been reported to moderately increase the serum concentration of some liver enzymes (Dundee *et al.*, 1980). Daily injection of ketamine for 6 weeks has also been reported to cause a transient increase in some liver enzyme of dogs (Corssen *et al.*, 1968). The use of ketamine for recreation or psychedelic therapy might cause more significant changes in the haemogram and biochemical variables of its prolonged users. Thus using dogs as experimental models, this work was carried out to establish possible systemic side effects of prolonged recreational use of ketamine in humans.

MATERIALS AND METHODS

Animals

Ten adult local dogs of mean (SD) weight 6.8 (0.4) kg aging between 10 to 14 months were used for the study. They were confined in cages and fed with rice and meat twice daily. Water was provided *ad libitum*. The dogs were acclimatized for a period of two weeks prior to the study after which they were divided into two treatment groups group 1 (normal saline treated) and group 2 (ketamine treated).

Drug preparation and administration

A dose of 40mg/kg was used to calculate the volume of liquid Ketamine (kotamin*, Biofil chem. and Pharm. Indonesia) to be prepared for dogs in the ketamine treated group. On each day of the study, the volumes of ketamine to be prepared

were calculated. The required volumes for evaporation were aspirated and expired into different stainless steel dishes (A-E) placed over water baths. The water baths were heated gently until whitish powders were left in the dishes. These powders were scraped off the dishes and weighed. They were then prepared as 1% solutions using normal saline. These solutions were administered per os daily to the dogs for a period of 28 days. Dogs in the control group were given normal saline for the same number of days as ketamine. Subsequently, the animals were allowed to recover from days 29 to 42 of the study. After day 42, the study was terminated.

Haematology

Blood samples were collected from the jugular vein of dogs into ethylene diamine tetra acetic (EDTA) bottles on day 0 prior ketamine administration to determine the baseline haematologic values. The packed cell volumes (PCV), red blood cell counts (RBC), white blood cell counts (WBC), absolute lymphocyte counts (ALC) and absolute neutrophil counts were determined as described by Tvedten (1994) and Simpson (1996). On days 7, 21 and 28 blood samples were collected to re assess the haematologic variables. Ketamine administration was stopped on day 28 after which the dogs were kept for another two weeks without any treatment administered to them. Blood samples were collected again from the dogs for haematology on days 35 and 42.

Serology

Blood samples collected on day 0 were transferred into plain sample bottles. The sera were separated from the blood clots and then centrifuged to clarify them. These sera were used for the determination of serum ALT and creatinine of the dogs. Serum ALT was determined by the Reitman- Franknel colometric method for *in vitro* determination of ALT in serum (Reitman and Franknel, 1957). Creatinine was determined by the modified Jaffe method for *in vitro* determination of creatinine in serum (Blass *et al.*, 1974). On days

7, 21, 28 and 42 the serum ALT and creatinine levels were re assayed.

Statistical analysis

The data obtained were expressed as mean (SEM). The students T- test was to compare the mean haematologic and biochemical variables obtained in the two groups. Least significance difference (LSD) was used for post-hoc comparison of significant effects by the treatments. Values of P less than 0.05 were considered significant

RESULTS

The RBC (Fig. 1) and PCV (Fig. 2) of the ketamine treated group were significantly ($P < 0.05$) lower than those of the control group on days 21, 28 and 35. Also on days 21 and 28, the WBC (Fig. 3), absolute lymphocyte counts (Fig. 4) and absolute neutrophil counts (Fig. 5) of the ketamine group were significantly ($P < 0.05$) lower compare to those of the control group. On day 42 (post treatment), the WBC and absolute neutrophil counts of the ketamine group were significantly higher than those of the control group. The serum levels of ALT (Fig. 6) and creatinine (Fig. 7) of the ketamine group were significantly ($P < 0.05$) higher than the control values by day 21 and 28 of the study.

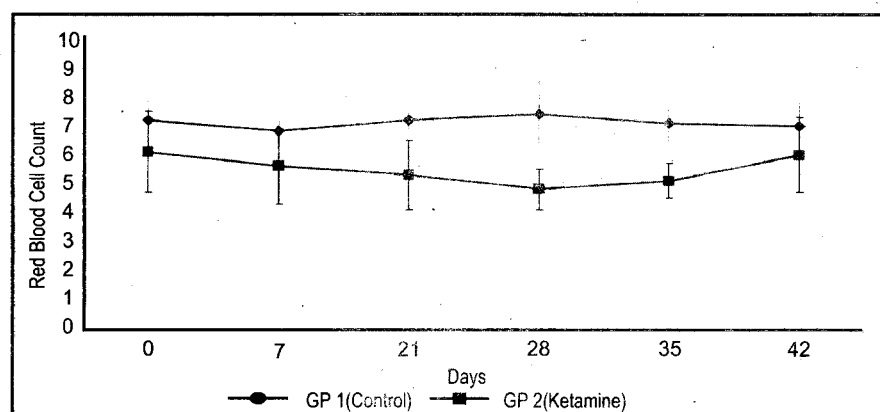


Fig 1: Red blood cell counts ($10^6/\mu\text{l}$) of dogs given normal saline and ketamine daily.

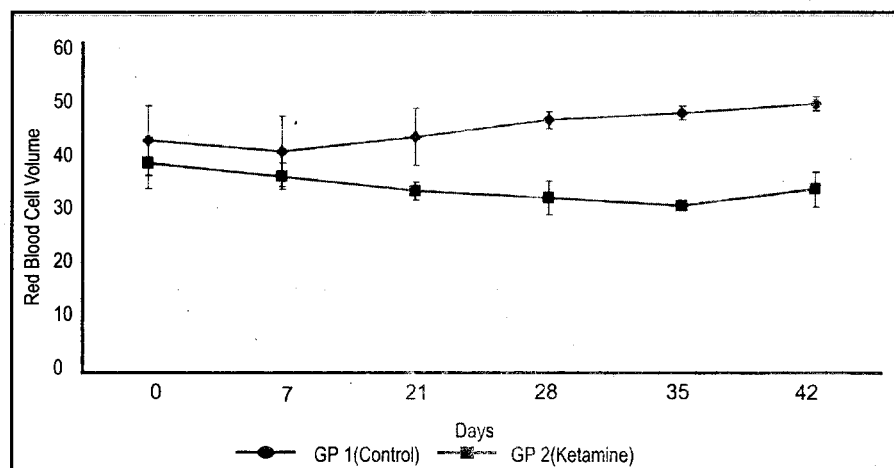


Fig 2: Packed cell volumes (%) of dogs given normal saline and ketamine daily

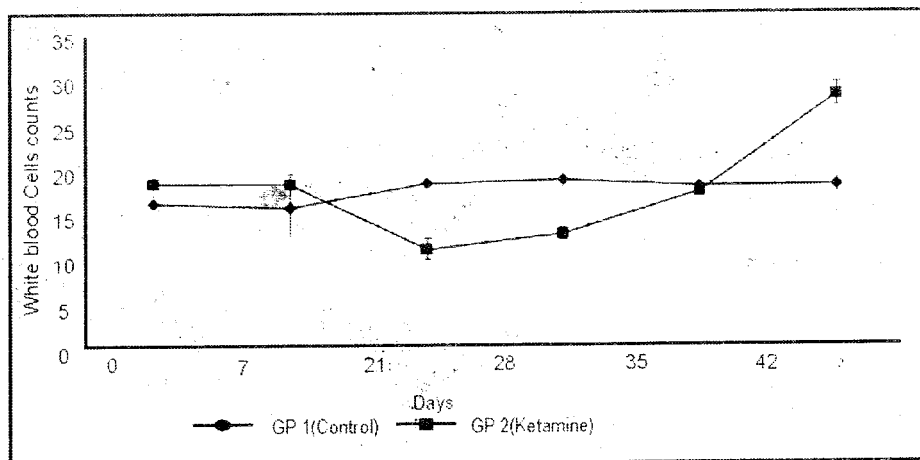


Fig.3: White blood cell counts ($10^3/\mu\text{l}$) of dogs given normal saline and ketamine daily

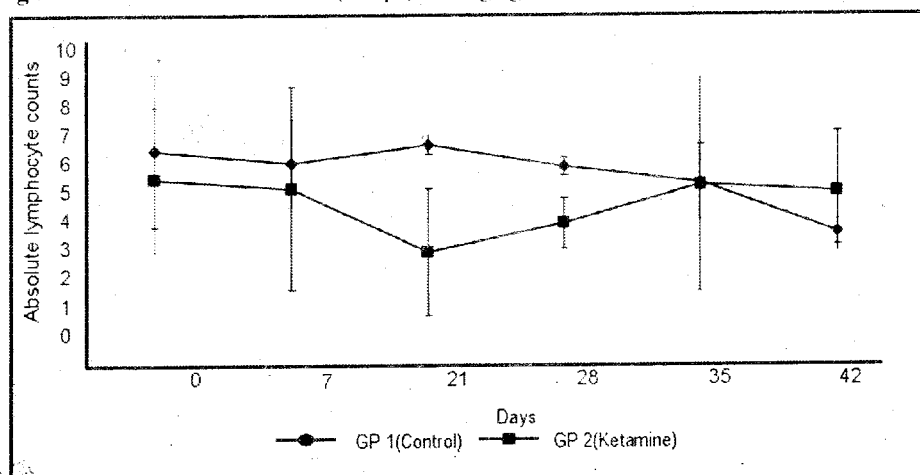


Fig.4: Absolute lymphocyte counts ($10^3/\mu\text{l}$) of dogs given normal saline and ketamine daily

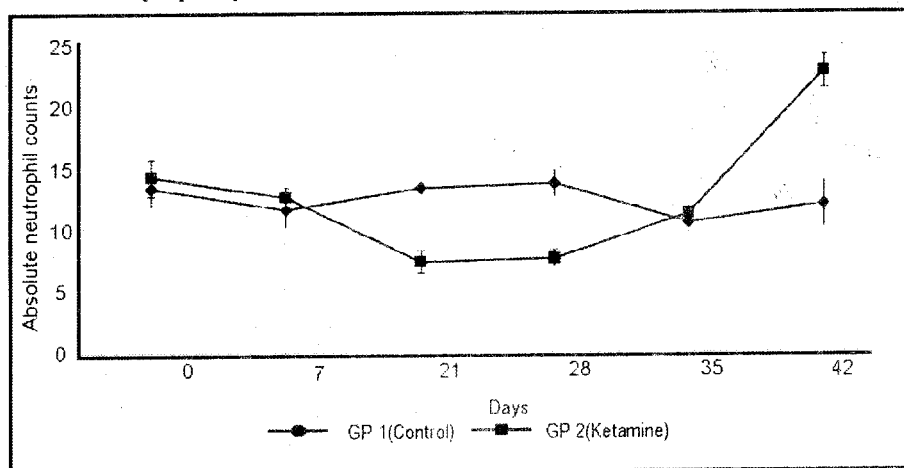


Fig.5: Absolute neutrophil counts ($10^3/\mu\text{l}$) of dogs given normal saline and ketamine daily

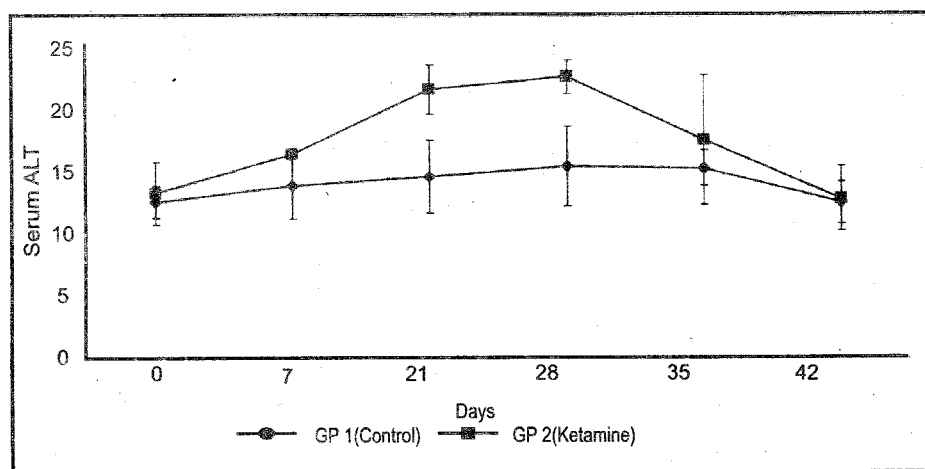


Fig. 6: Serum Alanine aminotransferase (IU/L) levels of dogs given normal saline and ketamine daily

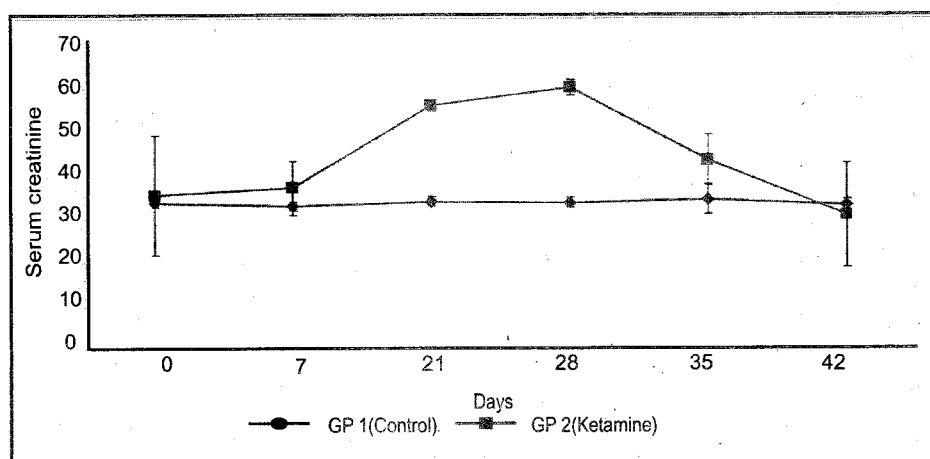


Fig.7: Serum creatinine levels (µmol/L) of dogs given normal saline and ketamine daily

DISCUSSION

Mild anaemia was observed in the ketamine treated dogs. Red blood cells are known to last in circulation for 100 to 120 days before being destroyed (Swenson, 1993). Thus the dogs may have become anaemic probably due to shortened life span or haemolysis of circulating red cells. This claim however needs to be substantiated by further studies. Chest pain, tachycardia, palpitation, increased blood pressure and dizziness have been observed in recreational users of ketamine (Anon., 2007). These reported side effects of prolonged ketamine usage may be due to anaemia since

injectable anaesthetics like thiopentone had been reported to suppress leucocyte transmigration (Horfbauer, 1999), phagocytosis (Salman *et al.*, 1998), immune system (Salo, 1992) and the bone marrow (Stover and Stocker, 1998), these findings of decreases in the number of neutrophils and lymphocytes in the ketamine group during this study suggests that ketamine similar to thiopentone may have decreased these white cells. Decrease in the number of cells may suggest that prolonged use of ketamine may increase an individual's susceptibility to viral and bacterial diseases. The cause of the leucocytosis and neutrophilia seen in the ketamine group following ketamine withdrawal is unknown.

However it may be suggested that there was increased mobilization of neutrophil into the blood stream. However, the recovery of favourable leukocytes response appears to suggest that permanent damage to the bone marrow had not occurred by the 28th day of ketamine administration.

Alanine aminotransferase is highly concentrated in the liver (Pratt and Kaplan, 2000). Its increased level in serum signals liver damage (Willard and Twedt, 1994; Pratt and Kaplan, 2000; Giannini *et al.*, 2005). When the liver cell membrane is damaged ALT is released into the blood (Pratt and Kaplan, 2000). Mild ketamine toxicity, hence mild membrane damage to hepatocytes may have partly contributed to the increased ALT observed during this study.

Creatinine is a by product of muscle creatinine phosphate, a compound predominant in the muscle (Blood *et al.*, 1994; Lipps, 2006; Silberberg, 2006). When produced, creatinine enters the blood and is filtered by the kidney (Silberberg, 2006). The remaining amount accumulates in the serum and plasma (Lipps, 2006). With normal glomerular filtration rate, serum creatinine level remains constant and normal (Silberberg, 2006). However, if glomerular filtration rate or renal blood flow was impaired more creatinine accumulates leading to a rise in serum/plasma creatinine level (Blood and Radositis, 1989; Lees *et al.*, 1994; Lipps, 2006). Thus it appears reasonable to summarize that the increased creatinine levels of the dogs given ketamine suggests some impairment of their kidney function.

CONCLUSION

In conclusion, prolonged oral ingestion of ketamine led to mild anaemia and a significant reduction in number of circulating neutrophils and lymphocytes. Prolonged users of ketamine may show signs of anaemia, such as dizziness. Continued use of ketamine may also cause reduction of lymphocytes and neutrophils thus

increasing an individual's susceptibility to viral and bacterial diseases. Mild hepatocellular damage and decreased renal function may also characterize prolonged use of ketamine. The experimental findings highlight the need to discourage prolonged use of ketamine either for recreation or as a psychedelic.

REFERENCES

- ANONYMOUS (1994): Psychoactive chemicals Ketamine FAQ. [Http://www.erowid.org/Chemical/ketamine/ketamine_fa.q.shtml#1](http://www.erowid.org/Chemical/ketamine/ketamine_fa.q.shtml#1) (Retrieved 23/5/2006).
- ANONYMOUS (2007): Drugs and human performance facts sheets. htmKetamine <http://www.yahoo.com> (Retrieved 23/5/2006).
- BERGMAN, S. (1999): "Ketamine: A review of its Pharmacology and its use in pediatric anaesthesia". *Anesth. Prog.* **46**(1):10-20.
- BLASS, K. G., THIERBERT, R. J. and LAM, L. K. (1974): 2. Clinical. chemistry, *Clinical Biochem.*, **12**: 336-343.
- BLOOD, D.C and RADOSITIS, O.M (1989): Diseases of musculoskeletal system. *Veterinary Medicine*. 6th Ed. Baillere Tindall; 450-474.
- BONANNO. F. (2002): Ketamine in war/tropical Surgery. A final tribute to the racemic mixture. *Injury*, **33**(4):323-327.
- CLEMENTS, J.A., NIMMO, W.S. and GRANT, I.S. (1982): Bioavailability, pharmacokinetics and analgesic activity of Ketamine in humans. *J. Pharm.Sci.*, **71**(5):539-541.

- CORSSEN, G., MLYASAKA, M. and DOMINO, E.F. (1968): Changing concepts in pain control during surgery: Dissociative anaesthesia with CI- 581. A progress report. *Anesth. Analg.*, **47**:746
- DALGAMO, P.J and SCHEWAN, D. (1996): Illicit use of ketamine in Scotland. *J. Psychoactive Drugs*, **28**(2):191-199
- DOTSON, J.W., ACKERMAN, D.L and WAST, L.J. (1995): Ketamine Abuse. *J. Drug Issues*, **25**(4):751-757.
- DUNDEE, J.W., FEE, J.P.H., MOORE, J., MCLLOY, P.D and WILSON, D.B (1980): Changes in serum enzyme levels following ketamine infusions. *Anaesthesia*, **35**:12-16.
- GIANNINI, E.G., TESTA, R and SAVARINO, V. (2005): Liver enzyme alteration. A guide for clinicians. *Canadian Med. Ass. J.*, **172** (3): 367-379.
- HIJAZI, Y., BODONIAN, C., BOLON, M., SALORD, F. and BOULIEU, R. (2003): Pharmacokinetics and haemodynamics of ketamine in intensive care patients with brain or spinal cord injury. *British J. Anaesthesia*, **90**(2): 155-160.
- HOFBAUER, R., KAYE, A.D., KAPIOTIS, S., WAGNER, O. and FRASS, M. (1999): The immune system and the effects of non-volatile anaesthetics on neutrophil transmigration through endothelial monolayer. *Curr. Pharm. Des.*, **5**(12):1015-1027.
- KENT, J. (1996): The ketamine Konundrum. http://www.crowid.org/chemicals/ketamine/ketamine_info.Shtml (modified by crowid in 2007). Retrieved 14/8/2007.
- KOLENDA, H., GREMMELT, A., RADING, S., BRAUN, U and MARKAKIS, E. (1996): Ketamine for analgosedative therapy in intensive care treatment of head injury patients. *Acta Neurochir.*, **138**:1193-1199.
- KRYSTAL, J., MADONICK, S., PERRY, E., GUEORGUEVA, R., BRUSH, L., WRAY, Y., BELGER, A and D'SOUZA, D. (2006): Potentiation of low dose ketamine effects by Naltrexone., potentiation. implications for the pharmacotherapy of alcoholism. *Neuropsychopharmacology*, **31**(8):1793-1800.
- LEES, G.E., WILLARD, M.D and GREEN, R.A (1994): Urinary disorders In : Small animal Clinical Diagnosis by Laboratory methods. 2nd Ed. (Willard, M. D., Tvedten, H., and Turnwald, G. H., Eds) W. B. Saunders Co. Philadelphia; 179-218.
- LIM, D.K. (2003): Ketamine associated psychedelic effects and dependence. *Singapore Med. J.* **44**(1):31-34.
- LIPPS, B. (2006): Serum creatinine and kidney disease. www.healthline.com (Retrieved 22 6-2007).
- NOWROUZIAN, I., SCHELS, H.F., GHODSIAN, I and KARIMI, H (1981): Evaluation of anaesthetic properties of ketamine and ketamine/xylazine/atropine combination in sheep. *Vet. Rec.*, **354**-356.
- PRATT, D.S and KAPLAN, M.M. (2000): Evaluation of abnormal liver enzyme results in asymptomatic patients. *N. Eng. J. Med.*, **342** (17):1266-1271.
- RADOSITIS, O.M., BLOOD, D.C. and GAY, C.C. (1994): Diseases of the

- muckuloskeletal system. Veterinary Medicine. W.B. Saunders, co. Ltd. London; 343-357.
- REBOSO, M.J and GONZALEZ, M.F. (1999): Ketamine". Rev Esp Anesthesiol Reanim, **46**(3): 111-122.
- REITMAN, D. and FRANKNEL, S. (1957): A Colorimetric method for determination of serum glutamic oxaloacetic and glutamic pyruvic transaminase J. Am. Clin. Pathol. **28**:56-62.
- SALMAN, H., BERGMAN, H., BESSLER, H., ALEXANDROVA, S., BEILIN, B. and DJALDETTI, M. (1998): Effect of sodium thiopentone anaesthesia on the phagocytic activity of peritoneal macrophages. Life. Sci., **63**: 2222-2226.
- SALO, M. (1992): Effects of anaesthesia and surgery on the immune response. Acta. Anaesthesiol. Scand., **36**:201-220.
- SILBERBERG, C (2006): Creatinine-serum. <http://www.umm.edu/ency/article/003475ris/htm>. (Retrieved 22-6-2007)
- SIMPSON, G. (1996): Laboratory techniques In: Practical Veterinary nursing . 3rd Ed. British small animal assoc. Kingsley house, Shuderyton; 116-169.
- STOVER, J.F and STOCKER, R. (1998): Barbiturate coma may promote reversible bone marrow suppression in patients with sever isolated traumatic brain injury. Eur. J. Clin. Pharmacol., **54**: 529-534.
- SWENSON, M.J. (1993): Physiological properties and cellular and chemical constituents of blood In: Dukes's physiology of domestic animals. 11 Ed. M.J. Swenson and W.O. Reece. Eds. Comstock Publishing Associates. Ithaca; 22-48.
- TOMILSON, A. (1994): Ketamine. Update in Anaesthesia, **4**(5):1-3.
- TVEDTEN, H. (1994): The complete blood count and bone marrow examination. General comments and selected techniques In: Small animal Clinical Diagnosis by Laboratory methods. 2nd Ed. (Willard, M. D., Tvedten, H., and Turnwald, G. H., Eds) W. B. Saunders Co. Philadelphia; 179-218.
- WHITE, P.F., WAY, W.L and TREVOR, A.J. (1982): Ketamine its pharmacology and therapeutic uses. Anesthesiology. **56**:119-136.
- WILLARD, M. D. and TWEDT, D.C. (1994): Gastrointestinal and hepatic disorders In: Small animal Clinical Diagnosis by Laboratory methods. 2nd Ed. (Willard, M. D., Tvedten, H., and Turnwald, G. H., Eds) W. B. Saunders Co. Philadelphia; 179-218.