BIOCHEMICAL CHANGES IN THE BLOOD SERUM OF DOGS TREATED WITH PHENOBARBITAL

ANDRIĆ N*, POPOVIĆ N*, STEPANOVIĆ P*, FRANCUSKI JELENA* and ĐURĐEVIĆ D**

*University of Belgrade, Faculty of veterinary medicine, Serbia
**Military Medical Academy, Institute for medical research, Belgrade, Serbia

Despite being described as the safest antiepileptic drug of first choice the presented literature data are much varied as far as dog blood serum biochemical parameters are considered. The aim of this study was to investigate the effect of phenobarbitone at different per os doses on the values of selected blood serum biochemical parameters in dogs during both short and long term application. The study was conducted on 30 dogs of different races, both sexes, ranging from 2 to 8 years of age. A total of 15 healthy and 15 dogs suffering from idiophatic epilepsy were observed. During the short term per os application of phenobarbitone (given at 3 week intervals) to the healty population in varied doseses a statistically significant increase in ALT and AP was recorded. Application of 16 mg/kg/day of phenobarbitone to the healthy population during 14 days resulted in a significant increase of ALT ans AP. This increase was dependant on the duration of the treatment. During chronic application of phenobarbitone to dogs suffering from idiopathic epilepsy a significant increase in values of AP and ALT depending on the given dose was recorded. In two of the studied epileptic dogs treated with high therapeutic doses of phenobarbitone clinical signs of hepatotoxicity were recorded. Hepatotoxicity resulted in decreased albumin and total protein concentrations, as well as increased blood serum total bilirubin, AST, ALP and AP.

The obtained results indicate that a long term application of phenobarbitone at high therapeutic doses can cause hepatotoxicity. However, there was no relationship between phenobarbitone dosage and duration of therapy and blood glucose, urea, creatinine, total proteins, albumins, total bilirubin, triglycerides and cholesterol.

Key words: blood serum, dogs, epilepsy, hepatotoxicity, phenobarbitone

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INTRODUCTION

Epilepsy is the most common neurological disorder in dogs. Irrespective of the cause epilepsy is treated with antiepileptic drugs. Despite being often described as an "old fashioned" drug phenobarbitone is still the drug of first choice in the treatment of epilepsy in dogs (Lane and Bunch. 1990; McNamara, 1996; Rambeck, 2001; Berendt, 2002). The anticonvulsive effect of this drug is achieved when its blood serum concentration reaches 15 μg/mL - 45 μg/mL (65 mmol/L - 193 mmol/L) (Farnbach, 1984; Lane and Bunch, 1990; Sisson, 1990; Boothe, 1996). Some authors report the best therapeutic results when blood serum phenobarbitone concentration is 20 μg/mL - 40 μg/mL (Frey, 1989; LeCouter, 1995; Podell, 1996).

Despite the fact of being a safe drug the data published up to now report that therapy with phenobarbitone can cause a number of changes in the biochemical blood serum profile. A number of studies carried out on dogs (Dayrell-Hart *et al*., 1991; Chauvet *et al*., 1995; Foster *et al*., 2000; Müller *et al*., 2000; Aitken *et al*., 2003; Gaskill *et al*., 2004; Gaskill *et al*., 2005) report increased activities of alanine transaminase (ALT) and alkaline phosphatase (AP). Increased ALT and AP activities were mainly recorded in patients who did not display clinical signs of hepatopaties. Similar results were reported for humans, however this was not an indication for changing the drug or its dose (Lippi *et al*., 2008). Contrary to these findings are those reported by Daryell and Hart (2008) who recorded increased AP and ALT activities accompanied by signs of hepatotoxicity as the result of phenobarbitone treatment. Dogs suffering from phenobarbitone iatrogenic hepatotoxicity displayed clinical signs such as disorientation, confusion, anorexy, icterus and ascites.

There are some controversies if phenobarbitone treatment can cause increased AST activity as a consequence of enzyme induction. AST can increase as a result of phenobarbitone treatment in humans (Verma and Haidukewych, 1994) and rats (Attia and Aref, 1991). Despite the fact that increased AST activity caused by increased enzyme induction in dogs is possible (center, 1995) a study on Beagle dogs treated with high phenobarbitone doses for over 3 weeks (Tettenborn *et al.*, 1973) and a study on 12 dogs of different breeds treated with 5 mg/kg/day for 27 weeks did not confirm this hypothesis (Müller *et al*., 2000).

A transient statistically significant increase in albumin and total protein concentration during epilepsy treatment with phenobarbitone in a dose of 10 mg/kg/day for 27 weeks was reported by Müller *et al*. (2000). Similar results were obtained in a study on 95 dogs treated with phenobarbitone doses in a range from less than 2 mg/kg/day up to over 10 mg/kg/day (Aitken *et al*., 2003). However, in a trial carried out on 10 dogs receiving phenobarbitone 6 mg/kg/day during 12 weeks there was no statistically significant change in total protein and albumin blood concentrations compared to the untreated control (Foster *et al*., 2000). Statistically significant differences in albumin and total protein concentrations were not recorded in a study on 10 dogs treated with phenobarbitone in doses from 3.9 mg/kg/day to 14.4 mg/kg/day (Foster *et al*., 2000).

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Literature data on the effects of phenobarbitone on serum bilirubin concentration indicate that the concentration of bilirubin does not change depending on phenobarbitone concentration (Foster *et al*., 2000) or duration of treatment (Chauvet, 1995). However, an increased bilirubin concentration above referent values was recorded in dogs suffering from hepatotoxicity as a consequence of phenobarbitone treatment (Dayrell-Hart *et al*., 1991).

The aim of this research was to study the effects of different *per os* therapeutic phenobarbitone doses on biochemical blood parameters in order to establish if the duration of the treatment affects enzyme activities in treated dogs.

MATERIAL AND METHODS

Animals: The experiment was carried out on 30 dogs allotted into two experimental groups. The first group of 15 healthy dogs was treated with *per os* phenobarbitone at different therapeutic doses and the second group consisted of dogs suffering idiopathic epilepsy treated with phenobarbitone.

The first experimental group: The first group consisted of 15 male healthy experimental mongrels, 2-8 years of age and body weight $10.3 - 25$ kg. At the start of the experiment the dogs were clinically examined and treated twice with antihelmintic Cestal plus (CEVA / Phylaxia). The accomodation period was 21 days, during which the dogs were vaccinated against infective diseases with Duramune $DA_2LP + P_i$ (Fort Dodge Laboratories, Iowa, USA) and Rabicel (Veterinarski zavod A. D., Zemun). The experiment was set in such a way that dogs received phenobarbitone at doses which were changed at three week intervals. Blood samples were taken each time the dose was changed and blood cell count, serum biochemistry and phenobarbitone concentration were determined. The experiment took place for 9 weeks and the *pr os* applied doses were 2 mg/kg/12h, 5 mg/kg/12h and 8 mg/kg/12h. Thereon, phenobarbitone was applied to the same dogs in an average dose of 8 mg/kg/12h for 11 weeks (a total of 14 weeks with this dose). During this period, starting from week four, blood samples were taken weekly and blood cell count, serum biochemistry and phenobarbitone concentration were determined.

The second experimental group: The second experimental group consisted of 15 mixed breed dogs of both sexes (4 females and 11 males), body mass $3.5 - 49$ kg and 2 to 4.5 years of age, all of which were diagnosed idiopathic epilepsy. The dogs were treated with phenobarbitone from one to five years. The females were ovariohysterectomized and the males were left intact. The starting phenobarbitone dose for this group was 2 mg/kg/12h *per os*. As long as phenobarbitone serum concentration was smaller than adviced the *per os* dose was not changed until sezures developed, and this was so three weeks after the start of the treatment. During the trial the dose of the drug was increased only if the frequency of the sezures was unacceptable. Prior to each dose change a thorough clinical and biochemical examination of the dog was carried out.

Blood samples. Blood samples were taken by sterile venepunction of the *v. cephalicae antebrachi* with a 0.9 gauge needle. The prepared plasma and serum blood samples were analyzed on the same day on which they were taken with the

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exeption of serum samples from the first group of dogs. These samples were frozen at -20ºC and phenobarbitone determination was done at monthly intervals. Serum samples taken from the second group of animals (dogs suffering from idiopathic epilepsy) phenobarbitone concentration was determined in fresh samples with no previous freezing. The tested biochemical parameters were: glucose, urea, creatinine, triglycerides, cholesterol, total proteins, albumin, total bilirubin concentrations, and AST, AP, ALT enzyme activities. The biochemical panel was determined on an automatic analyzer Basic - Sekomam (France) with J.T. Baker (Holland) reagents. The serum phenobarbitone concentration was measured at the Deparment of Toxicological Chemistry, Center for Poison Control at the Military Medical Academy (Belgrade) by HPLC at 254 nm.

Analysis. Statistical data analysis was completed with the Statistica 5.0 software. Results are given by descriptive statistical methods (mean value SV, standard deviation SD, and standard error SE). Comparison between groups was done with Student's t-test for a small sample and the multifactorial analysis by MANOVA (multifactorial variance analysis). Statistical significance was accepted at the level of $p < 0.05$.

RESULTS AND DISCUSSION

On analyses of the results in the first group of healthy dogs three weeks after the start of phenobarbitone therapy in a dose of 4 mg/kg/day (2 mg/kg/12h) a statistically significant increase was measured only for AP. Within the same group of experimental dogs, after the first three weeks of treatment with 10 mg/kg/day (5 mg/kg/12h) phenobarbitone, a statistically significant increase was measured both for AP and ALT. Studies on the effect of a 14 weeks phenobarbitone treatment on blood biochemical parameters of healthy dogs at an average *per os* dose of
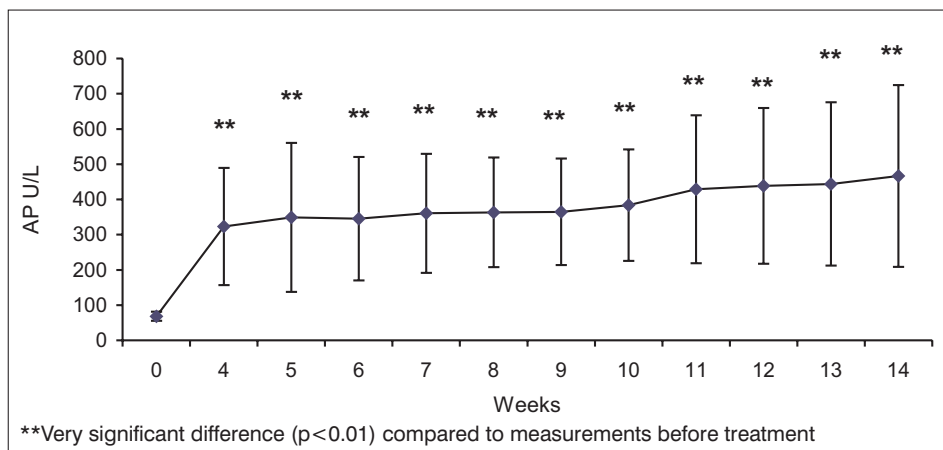

**Very significant difference ($p<0.01$) compared to measurements before treatment

Figure 1. Average AP activities ($X \pm SD$) in the first group of dogs treated with 16 mg/kg/day phenobarbitone *per os* for 14 weeks

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16 mg/kg/day (starting at 4 weeks, at weekly intervals) have shown a significant increase in AP (Figure 1) and ALT activities (Figure 2).

Results have shown ALT activities increased when the phenobarbitone dose reached 10 mg/kg/day and reached a high statistical significance ($p < 0.01$) at 16 mg/kg/day. During the 14 weeks of phenobarbitone treatment ALT activity increased throughout the trial which resulted with a statistically significant increase by the end of the trial (Figure 2).
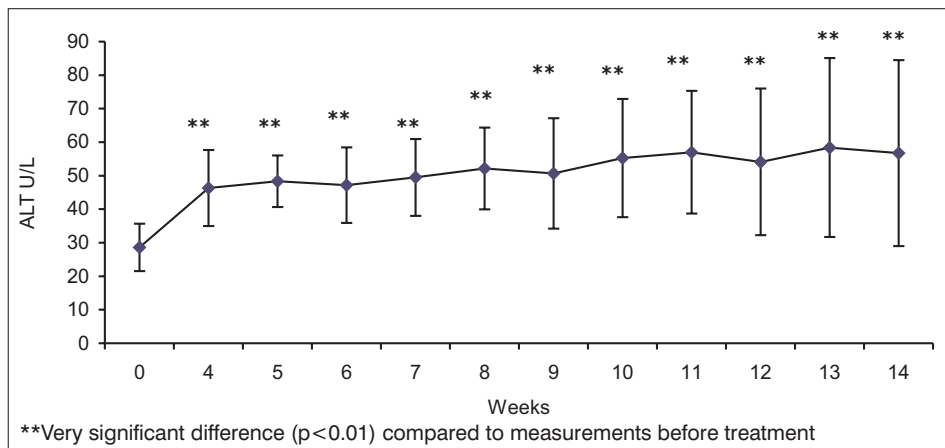

**Very significant difference ($p < 0.01$) compared to measurements before treatment

Figure 2. Average ALT activities (X ± SD) in the first group of dogs treated with 16 mg/kg/day phenobarbitone *per os* for 14 weeks

The group of dogs suffering from idiopathic epilepsy (second group) and receiving phenobarbitone at doses of 4 mg/kg/day and 6 mg/kg/day a statistically significant increase of AP was measured. Per os treatment with 8 mg/kg/day phenobarbitone resulted in an even more dramatic increase in AP activity (Figure 3) accompanied with increased ALT activity (Figure 4). When the unadequate response to 10 mg/kg/day phenobarbitone antiepileptic therapy was observed the measured ALT and AP activities were significantly higher. At the average dose of 13 mg/kg/day a significant ($p < 0.05$) decrease in albumin and total protein concentrations was measured, as well as a significant ($p < 0.01$) increase in ALT and AP activities. At a higher therapeutic dose of 16 mg/kg/day when an unadequate effect was recorded a significant decrease ($p < 0.05$) of albumin and total proteins and increased values for total bilirubin (Figure 8) were measured. The same phenobarbitone dose induced a statistically significant increase in ALT and AP activities.

In the second group of dogs suffering from idiopathic epilepsy ALT activities increased depending on phenobarbitone dose. In this group significantly higher ($p < 0.05$) ALT activities were measured at phenobarbitone doses of 8 and 10 mg/kg/day and recorded values were even higher ($p < 0.01$) for

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phenobarbitone doses of 13 and 16 mg/kg/day compared to the start of the treatment (Figure 4). During phenobarbitone therapy at a dose of 16 mg/kg/day in a total of 8 dogs (53%) ALT was above referent values.
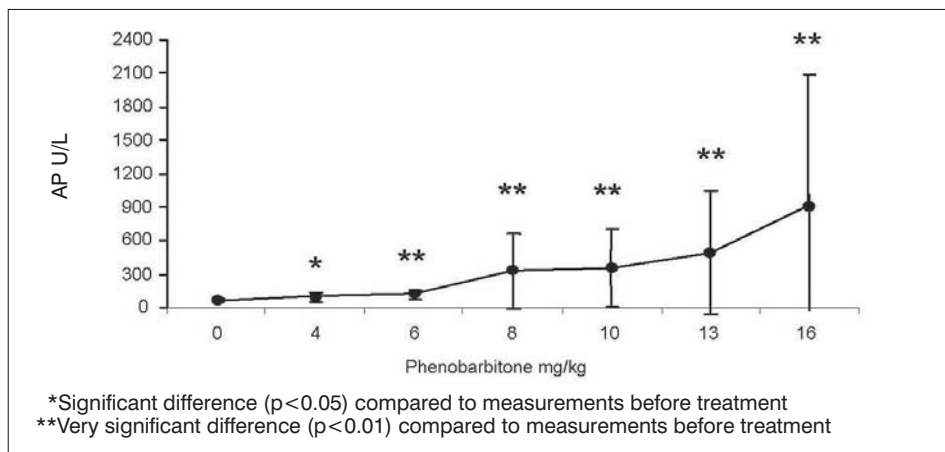

*Significant difference (p<0.05) compared to measurements before treatment
**Very significant difference (p<0.01) compared to measurements before treatment

Figure 3. Average blood serum AP activities (X ± SD) in the second group of dogs treated with different phenobarbitone doses

*Significant difference (p<0.05) compared to measurements before treatment
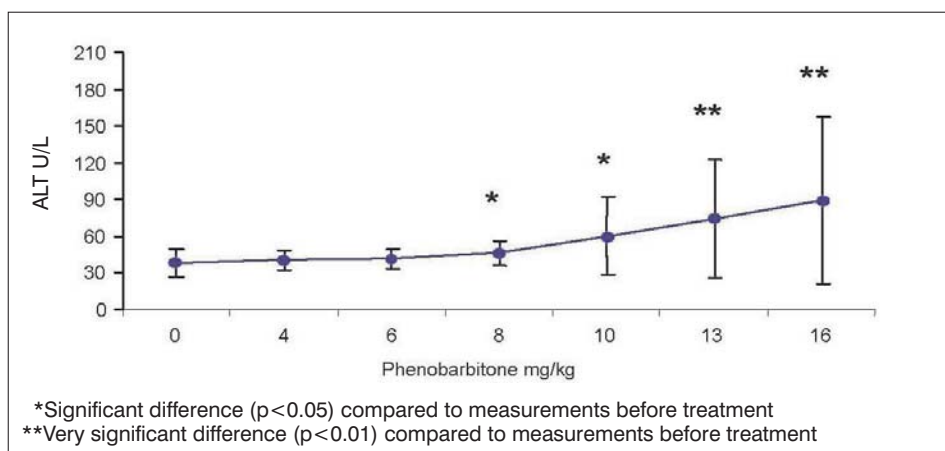**Very significant difference (p<0.01) compared to measurements before treatment

Figure 4. Average blood serum ALT activities (X ± SD) in the second group of dogs treated with different phenobarbitone doses

AP activities increased as phenobarbitone dose increased. Besides, the AP activity levels in the first group of dogs significantly increased (p<0.01) at 16 mg/kg/day phenobarbitone (Figure 1). Same as for the first group of dogs, the

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second group had an increasing trend in AP activities with increasing phenobarbitone doses. Two of the dogs from the second group with high AP values were lethargic, weak, disoriented and with poor appetite. One of these two dogs had an obviously enlarged abdomen.

The AP activity in the blood serum of dogs treated with phenobarbitone is highly individual which is clearly shown by the large differences between the activity levels. The obtained variations are in accordance to the existing published data (Foster *et al*., 2000).

A number of authors states that phenobarbitone application in dogs results in increased serum AP and ALT activities which are not accompanied by clinical signs of liver disease (Fanuel-Barret and Vivier, 1993; Chauvet *et al.*, 1995; Center, 1995; Booth, 1996; Dowling, 1999; Müller *et al*., 2000; Foster *et al*., 2001; Aitken *et al.*, 2003). In support of this finding are the results of our study with the difference that in the group of dogs suffering from idiopathic epilepsy after treatment with 16 mg/kg/day phenobarbitone two dogs had clinical symptoms of hepatotoxicity. AP activity in the dog number 11 was 1112 U/L and ALT activity was 292 U/L. For the dog number 14 AP and ALT activities were 745 U/L and 134 U/L, respectively. In these dogs a concurrent increase in AST values was registered, also (Figure 7).

The true reasons for such an increase in serum AP and ALT activities during phenobarbitone therapy are still unclear. Results of previous studies indicate that the explanation for such an increase may be the induction of enzymes which results in increased concentrations of izoenzymes L-AP and C-AP within the hepatocytes and their subsequent release in the general circulation (Solter and Hoffmann, 1995; Deng *et al*., 1996). In support of this theory is a paper (Gaskill *et al*., 2004) which claims that a significant increase in serum AP during phenobarbitone therapy is the result of increased activities of all three isoenzymes (C-AP, L-AP and B-AP).

The results published in this paper relative to AST activity in the first group of treated dogs support the hypothesis which claims that phenobarbitone does not induce enzymatically AST (Tettenborn *et al*., 1973; Müller *et al*., 2000). However, the second group of dogs during treatment with 16 mg/kg/day phenobarbitone a total of 5 dogs (33%) had increased AST activities which were above the starting physiological referent values (Figure 5).

Two of the dogs with the highest AST values (111 U/L and 78 U/L) developed clinical symptoms of liver disease. During liver disease AST increases paralell to the activity of ALT (Center, 1995) which is in accordance to our finding in dogs suffering from hepatotoxicity. Studies on the diagnostic value of different liver enzymes in dogs with diagnosed liver disease indicate that an increase in serum AST is a more sensitive diagnostic tool compared to serum ALT activity (Abdeldaker and Hauge, 1986).

In the first group of dogs the significant decrease in albumin and total protein concentrations was of a transient nature as it was recorded only in the third week of the trial at 16 mg/kg/day phenobarbitone. The measured concentrations of albumins and total proteins in the first group were within the reference values and were independent of the duration of the phenobarbitone treatment.
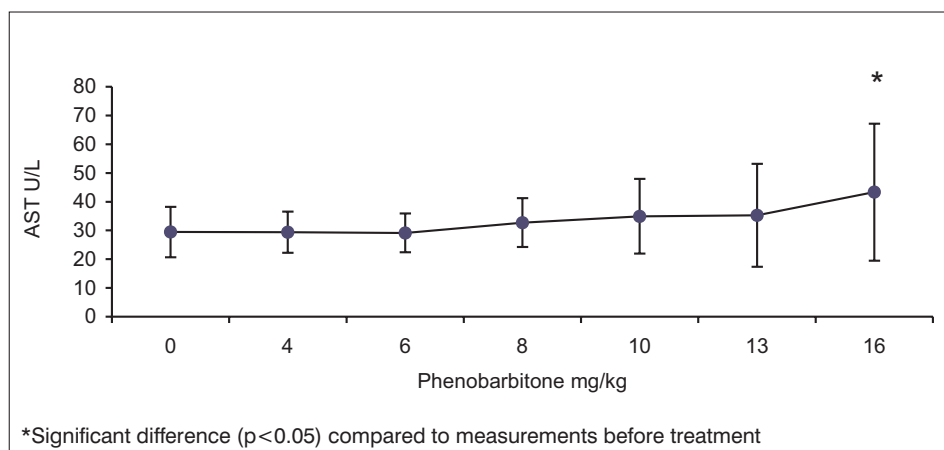
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*Significant difference (p<0.05) compared to measurements before treatment

Figure 5. Average blood serum AST activities (X ± SD) in the second group of dogs treated with different phenobarbitone doses

In the second group of dogs suffering from idiopathic epilepsy a decreasing trend in albumin (Figure 6) and total protein concentrations (Figure 7) dependant on phenobarbitone concentration was reported. This decrease was statistically significant for phenobarbitone doses of 13 and 16 mg/kg/day. Albumin concentrations lower than the reference values were measured in two dogs treated with 16 mg/kg/day and low protein concentrations were measured in two dogs treated with 13 mg/kg/day phenobarbitone and two dogs treated with 16 mg/kg/day of the same drug. The results obtained in our study are close to the
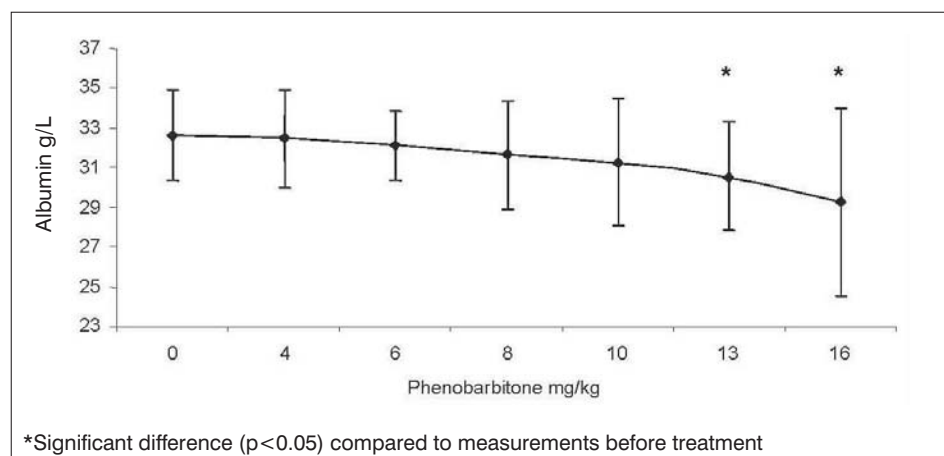

*Significant difference (p<0.05) compared to measurements before treatment

Figure 6. Average blood serum albumin concentrations (X ± SD) in the second group of dogs treated with different phenobarbitone doses

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results published by Müller *et al*. (2000) and Aitken *et al*. (2003) contrary to the findings of Foster *et al*. (2000) who reported the lack of a significant influence of phenobarbitone dose on albumin and total protein concentrations. Serum albumin concentration is often used as a non specific marker for hepatic function (Center, 1995). Serum albumin concentrations below physiological values in phenobarbitone treated dogs are probably the result of its direct influence on albumin synthesis and/or its degradation (Mülleri *et al*., 2000). It is considered that albumin levels below physiological values are the result of induced hepatic dysfunction (Chauvet *et al*., 1995). This can be the rationale for our results as in the second group in two dogs hepatotoxicity was diagnosed. This is supported by the findings of Dayrell-Hart *et al*. (1991), as well. Transient falls in serum albumin concentrations during phenobarbitone therapy have no major clinical importance (Müller *et al*., 2000).
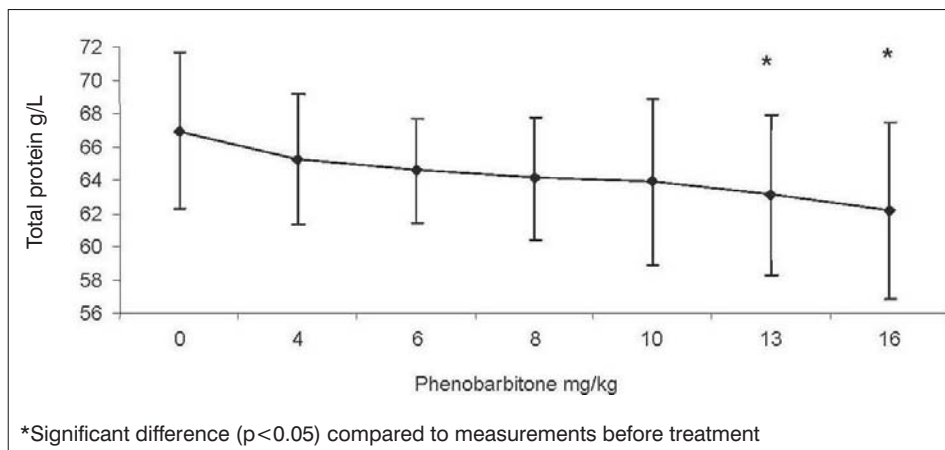

*Significant difference (p<0.05) compared to measurements before treatment

Figure 7. Average blood serum total protein concentrations (X ± SD) in the second group of dogs treated with different phenobarbitone doses

The short-lived statistically significant increase in triglyceride and cholesterol concentrations was determined in the first group of dogs during two measurements. However, no correlation between triglyceride and cholesterol concentrations and phenobarbitone dose and therapy duration was established. A cholesterol concentration below reference values was measured in one dog suffering from idiopathic epilepsy.

A cholesterol concentration below reference values was measured in one dog suffering from idiopathic epilepsy. This patient was treated with 16 mg/kg/day phenobarbitone and displayed clinical symptoms of idiopathic epilepsy. As cholesterol is synthetized in the liver the measured low concentration can be the result of the hepatic disfunction caused by phenobarbitone (Chauvet *et al*., 1995).

All measured serum total bilirubin concentrations in the first group were within the reference values and were not significantly different from the values

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measured before treatment. There was no link between the concentration of total bilirubin and time and dose of applied phenobarbitone. However, in the second experimental group a statistically significant increase in plasma total bilirubin was measured in dogs treated with 16 mg/kg/day phenobarbitone (Figure 8). The concentration of total bilirubin did not change depending on dose or duration of the treatment (Chauvet *et al*., 1995; Foster *et al*., 2000).

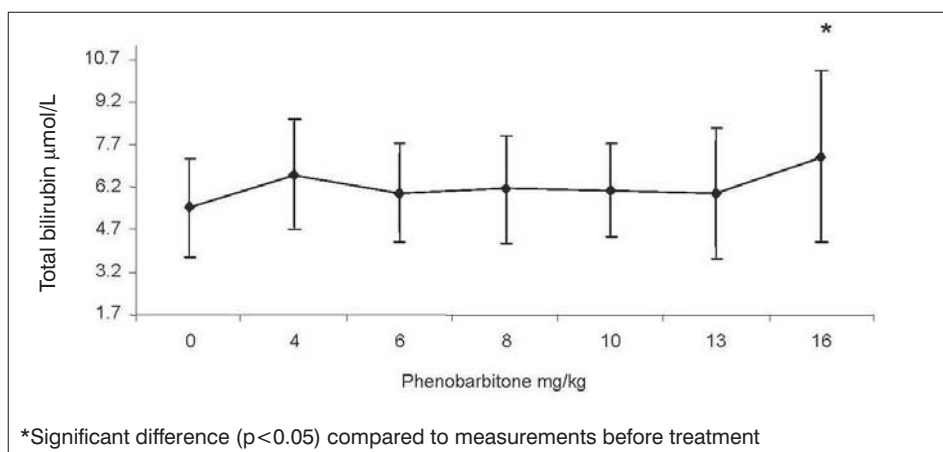*Significant difference ($p < 0.05$) compared to measurements before treatment

Figure 8. Average blood serum total bilirubin ($X \pm SD$) in the second group of dogs treated with different phenobarbitone doses

Measurements above referent values for total bilirubin can be the result of phenobarbitone hepatotoxicity (Dayrell -Hart et al., 1991) or as an artifact due to lipemic serum samples (Willard and Twedt, 1994; Burkhard and Meyer, 1995). This was registered in two dogs treated with 16 mg/kg/day phenobarbitone and suffering from hepatotoxicity had readings for plasma bilirubin above the reference values.

Glucose concentration did not significantly change depending on phenobarbitone dose or duration of treatment. All glucose measurements were well within the physiological range in both experimental groups.

No relationship between phenobarbitone treatment and blood urea and creatinine concentration was established. The transient statistically significant difference in urea and creatinine concentration during one sampling was of no clinical significance.

Address for correspondence:
Ass. Dr Andrić Nenad
Faculty of Veterinary Medicine
University of Belgrade
Bul. oslobodjenja 18
11000 Belgrade, Serbia
E-mail: nenad@vet.bg.ac.rs

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BIOHEMIJSKE PROMENE U KRVNOM SERUMU PASA TRETIRANIH FENOBARBITONOM

ANDRIĆ N, POPOVIĆ N, STEPANOVIĆ P, FRANCUSKI JELENA i ĐURĐEVIĆ D

SADRŽAJ

Iako označen kao antiepileptik prvog izbora i veoma bezbedan lek, u literaturi su prezentovani različiti podaci o uticaju fenobarbitona na vrednosti biohemijskih parametara krvnog seruma kod pasa. S obzirom na to, cilj ovog istraživanja bio je da se ispita uticaj fenobarbitona pri različitim *per os* dozama na vrednosti biohemijskih parametara krvnog seruma kod pasa, tokom kratkotrajne i dugotrajne aplikacije. Istraživanje je sprovedeno na 30 pasa različitih rasa, oba pola, starosne kategorije od dve do osam godina, od kojih su 15 bili zdravi psi a 15 psi oboleli od idiopatske epilepsije. Tokom kratkotrajne *per os* aplikacije fenobarbitona (intervali od po tri nedelje) zdravoj populaciji pasa pri različitim per os dozama, u krvnom serumu je registrovano značajno povećanje aktivnosti ALT i vrlo značajno povećanje aktivnosti AP u zavisnosti od doze leka. Aplikacija fenobarbitona u dozi od 16 mg/kg/dnevno tokom 14 nedelja zdravoj populaciji pasa ukazala je, na vrlo značajno povećanje aktivnosti ALT i AP u zavisnosti od dužine trajanja aplikacije. Tokom hronične aplikacije fenobarbitona psima obolelim od idiopatske epilepsije, ustanovljeno je statistički vrlo značajno povećanje aktivnosti AP i ALT u krvnom serumu u zavisnosti od doze leka. Kod dve jedinke u bolesnoj grupi pasa pri visokim terapeutskim dozama fenobarbitona registrovana je hepatotoksičnost, što je dovelo do statistički značajnog smanjenja koncentracije albumina i ukupnih proteina, statistički značajnog povećanja koncentracije ukupnog bilirubina, statistički značajnog povećanja aktivnosti AST i statistički vrlo značajnog povećanja aktivnosti ALT i AP u krvnom serumu Dobijeni rezultati ukazuju da dugotrajna aplikacija fenobarbitona, pri visokim terapeutskim dozama može izazvati hepatotoksičnost. Nije ustanovljeno postojanje veze između koncentracije glukoze, uree, kreatinina, ukupnih proteina, albumina, ukupnog bilirubina, triglicerida i holesterola u krvnom serumu pasa sa *per os* dozom fenobarbitona, niti sa dužinom trajanja terapije.