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Original Research Paper

RETINOIC ACID AS A THERAPY FOR CUSHING'S DISEASE IN DOGS: EVALUATION OF LIVER ENZYMES DURING TREATMENT

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Summary: Recent studies have demonstrated that retinoic acid is capable to control the Pituitary-Dependent Hyperadrenocorticism by its action on the ACTH-secreting pituitary tumour. Because the hepatotoxic effects of retinoic acid have been reported, the hepatograms of dogs with Cushing's Syndrome treated with this medicine were analysed during 180 days of therapy and compared with dogs which received Ketoconazole as an alternative treatment. No animal showed hepatoxicity signs with both treatments. Dogs treated with retinoic acid showed a decrease (not significant) of the alkaline phosphatise (AP), without any changes in the other group. Alanine amine transferase (ALT) was reduced after 180 days vs. 0 days (P = 0.04) in the retinoic group. On the other hand, this enzyme increased in the Ketoconazole group (P<0.02). Alanine aspartic transferase (AST) did not show any variations in the retinoic group, remaining within the baseline values. In the Ketoconazole group a significant increase (P<0.03) was seen after 180 days vs. 0 day. The reduction of ALT and AP in the retinoic group is related to the decrease of ACTH (r=0.41, P=0.026 and r=0.37; P=0.035, respectively), there are also correlation between ALT and urine cortisol: urine creatinine ratio (r=0.40, P=0.028) in this group. These variables do not correlate in the Ketoconazole group. In conclusion, retinoic acid shows no risk of hepatoxicity after180 days of treatment in dogs with PDH.

Key words: cushing syndrome–physiopathology–therapy; pituitary ACTH hypersecretion; tretionin–therapeutic use; liver–drug effects; dogs

Introduction

Pituitary-Dependent Hyperadrenocorticism (PDH), is caused by the corticotroph adenoma of the pituitary (1). Medical treatments are the most frequently used and are based on the drugs that exercise their effects over the adrenal gland. These drugs have either cytostatic action, such as the o,p'-DDD, or are enzyme inhibitors that act in different steps of the corticosteroid synthesis , such as aminoglutemide, ketoconazole (Ktz), and trilostane (2, 3, 4, 5). Ketoconazole is routinely used in Argentina for the treatment of PDH because the other mentioned drugs are not available. It has been reported that Ktz has hepatotoxic effects which are demonstrated by the increase of transaminases and clinical signs of hepatic insufficiency, such as anorexia, vomiting and jaundice (6).

It is known that retinoic acid (RA) acts through its receptors at genomic level, regulating the expression of genes for transcription factors involved in the synthesis of the proopiomelanocortin-peptide (POMC), precursor of adrenocorticotrophin hormone (ACTH) (7, 8). It also interacts with factors that intervene in cell development and mitosis, particularly the bone morphogenetic protein 4 (BMP-4), as recently described (9). Paéz-Pereda and colleagues (10) reported that RA inhibited the function (synthesis of POMC and ACTH) and growth (inhibition of

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the cell mitosis) of the tumoral cell, inducing its apoptosis in experimental rats. Based on this report, the therapeutic action of RA was studied in dogs with PDH and proven presence of corticotrophinoma, resulting in the control of the disease (11).

It is known that dogs with PDH present hepatomegaly with an increase of alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (AP) due to an increase in their enzymatic activity (12). This is caused by an effect of the glucocorticoids on different functions of the hepatocytes, especially on gluconeogenesis and the glycerogenesis (13, 14).

As RA has been described as having a hepatotoxic effect (15), the aim of the present study was to determine if the aforementioned drugs in the effective dose for the treatment of PDH can provoke change on the liver enzyme activity (as indicators of possible liver damage) compared with Ktz. Furthermore, we aimed to determine if the control of hypercortisolism has a relationship to the changes in the hepatic enzymogram according to the treatment received.

Material and methods

Study population.

40 dogs with PDH were studied (11 male and 29 intact female). Average age of the animals at the time of the diagnosis was 9 years (range 3–14 years old), there were no significant differences between males and females. Dogs included in the study showed the following clinical signs, characteristics and consistent with PDH (12): polyuria–polydipsia, urinary density less than 1010, polyphagia, dermatologic problems, pendulous abdomen and anoestrus. Routine biochemical analysis was indicated as a control of the general status of the dogs. PDH was confirmed with specific endocrine test (ACTH stimulation test, urine cortisol:urine creatinine ratio and high-doses of dexamethasone suppression test). Besides that, the presence of the pituitary tumour has been visualised by Magnetic Nuclear Resonance Imaging (MNRI).

At the time of the diagnosis, none of the animals showed signs of concurrent diseases except for the hepatomegaly and the corresponding increase of ALT, AST and AP

A simple blind study was performed and dogs were randomly distributed into two groups according to the drugs they received over 180 days: A) Retinoic Group (RG): 20 dogs (5 male and 15 female). They were administered RA as isotretinoin 9-cis (2 mg/kg/once a day) because this is the form that binds to both isoforms of the recipient (8, 16). B) Ketoconazole Group (Ktz): 20 dogs (6 male and 14 female): They were administered ketoconazole 20 mg/kg/once a day.

Evaluation of the hepatic enzymogram

Hepatic enzymes AP (normal up to 250 UI/L), AST and ALT (both normal up to 80 UI/L) were evaluated in time "0" (at the time of the diagnosis) and 180 days after start of treatment. Basal and day 180 values were compared. Enzymatic determinations were performed by means of the automated kinetic method (ByoSystems®, Metrolab Autoanalizer Merck, Germany). The inter and intra-assay coefficients of variation were 1.1% and 4.5% for AP, 1.8% and 5.3% for ALT and 1.4% and 5.9% for AST.

Criteria for suspension of treatment

It was decided to separate any animal from the study protocol in case of: a) observing at least three of the following signs indicating hepatic insufficiency: jaundice, vomiting, anorexia, ascites, cachexia, hypocholia or acholia, increase of urobilinogen and/or bile pigments in urine. Presence of petechiae or echimosis and alterations of the coagulation tests (Quick time, Activated partial thromboplastin time, Altered bleeding time), b) 3-time increase of the AP and ALT, and 2-fold increase of AST during the treatment period, over the value found at the time of diagnosis (with presence or absence of the aforementioned signs).

Measurement of plasmatic ACTH, urine cortisol / urine creatinine ratio (C/C) and ACTH stimulation test

Basal plasma ACTH (22-250 pmol/L) and C/C (10-65, data from Laboratory of Nuclear Medicine, School Animal Hospital, Faculty of Vet. Sci.-U. Buenos Aires) determinations were carried out as was previously described (11, 17). Both were evaluated at day 0 (time of diagnosis) and day 180. ACTH (Nichols Advantage ACTH Assay, Nichols Institute Diagnostics, Bad Vilbel, Germany), and urinary cortisol (DPC Corporation, San Diego, California, USA) were measured by immune-radiometric assay and radioimmuno-assay respectively. The intra-assay variation coefficient of ACTH was 3%, with an inter-assay variation coefficient of 6.8%. The inter- and intra-assay coefficient of the cortisol was 8% and 5%, respectively. Creatinine (meas-

ured by automated kinetic method, ByoSystems®, Metrolab Autoanalizer Merck, Germany) inter and intra-assay coefficient of variation was 1.5% and 5.3% respectively.

High-doses of dexamethasone suppression test were performed in accordance with the method described by Rijnberk (17) and Galac (18). The urine samples (an aliquot of 2 ml for each) from each dogs were home collected in a non stressed environment into 2 flasks as follows: Flask 1 (as diagnostic of hypercortisolism and previous dexametasone intake), the second voided urine in the morning, the last one at night and the first urine of the following day (all mixed in the same flask). After collection of the last sample of urine on the second day, 0.1 mg/kg/w PO each 8 hours of dexametasone were given during one day. Flask 2: the first morning urine on the third day after dexametasone intake was obtained. It was consider suppression when the C/C of the flask 2 is less than 50% than C/C of flask 1.

ACTH stimulation test was performed as described previously (3) in order to confirmed the C/C result obtained from flask 1. Both ACTH stimulation test and high-doses of dexamethasone suppression test (data not shown) were carried out only at diagnosis time.

Statistical Analysis

Results are expressed as median and range. The comparisons between intra- and inter-group were made by Wilcoxon signed rank test (time "0" vs. 180 days), being significant $P<0.05$.

AP, ALT and AST values prior and post-treatment were correlated with the ACTH and C/C in each group, and also correlation between ACTH and C/C were performed (Spearman's correlation test).

The statistical program used was GraphPad Prism, version 3 (GraphPad Software, Inc.).

Ethical procedures in experimental animals

This study was approved by the Ethics Committee of the School of Veterinary Sciences and the Secretariat of Science and Techniques (UBACyT) of the University of Buenos Aires (project V045), adapting itself to the laws in force as to experimental animals and the recommendations of the WHO. Written consent was obtained from the owners of the dogs to participate in this project.

Hepatic biopsy was not performed because the owner and Ethical Committee did not authorise this procedure, considering it unnecessary risk.

Results

Clinical aspects

None of the animals treated with one of the drugs presented signs of hepatic insufficiency during the treatment. An increase of AP or transaminases 3 times greater than the PDH value at the time of the diagnosis was not observed in any of the dogs in both groups. No side effects with isotretinoin-9 cis or Ketoconazole during the time of therapy were observed. Eight dogs from Ktz group died during the experiment because of the poor control of hypercortisolism. Thus, 12 animals of Ktz group ended the study.

With respect to the evaluated clinical signs, dogs under treatment with retinoic acid showed an improvement in all clinical signs (normalization of the water intake resulting in normal diurises, normal food intake, diminution of the abdomen size, hair growth and return of the oestrus in 10 of 15 females). In Ktz group polydipsia-polyruria and polyfagia and hair loss were presented in 7 dogs, the oestrus did not return in any females and no change in the abdomen size of the 12 dogs was observed.

Hepatic enzymogram, plasmatic ACTH, C/C.

Dogs with PDH (both groups) had an increase of AP and ALT at the time of the diagnosis, while AST was found, except for 2 dogs in RG and 1 in Ktz, within the reference range for the method. There is an individual decrease of AP (time "0": 805 UI/L [156-2998]) after 180 days (620 UI/L [136-1970]) of treatment in the RG group (but not significant if comparing the median values of the group), reaching its lower serum concentration compared to the previous values (Fig. 1a). This was not observed in the Ktz group, where values practically do not change ("0" day: 683.5 UI/L [164-2990] vs 180 days: 960 UI/L [200-3000])

ALT (Fig 1b), shows a decrease in the RG group, which is significant when comparing the time 0 days vs. 180 day (106.5 UI/L [16-393] and 95.5 UI/L [27-283]; $P= 0.04$). In the Ktz group, comparing the same time a significant increase is observed ("0" day:144 UI/L [25-392] vs 180 days: 152 UI/L [25-284]; $P<0.02$). Comparing 180 days vs 180 days, ALT concentration is greater in Ktz group in comparison to the RG group ($P<0.02$)

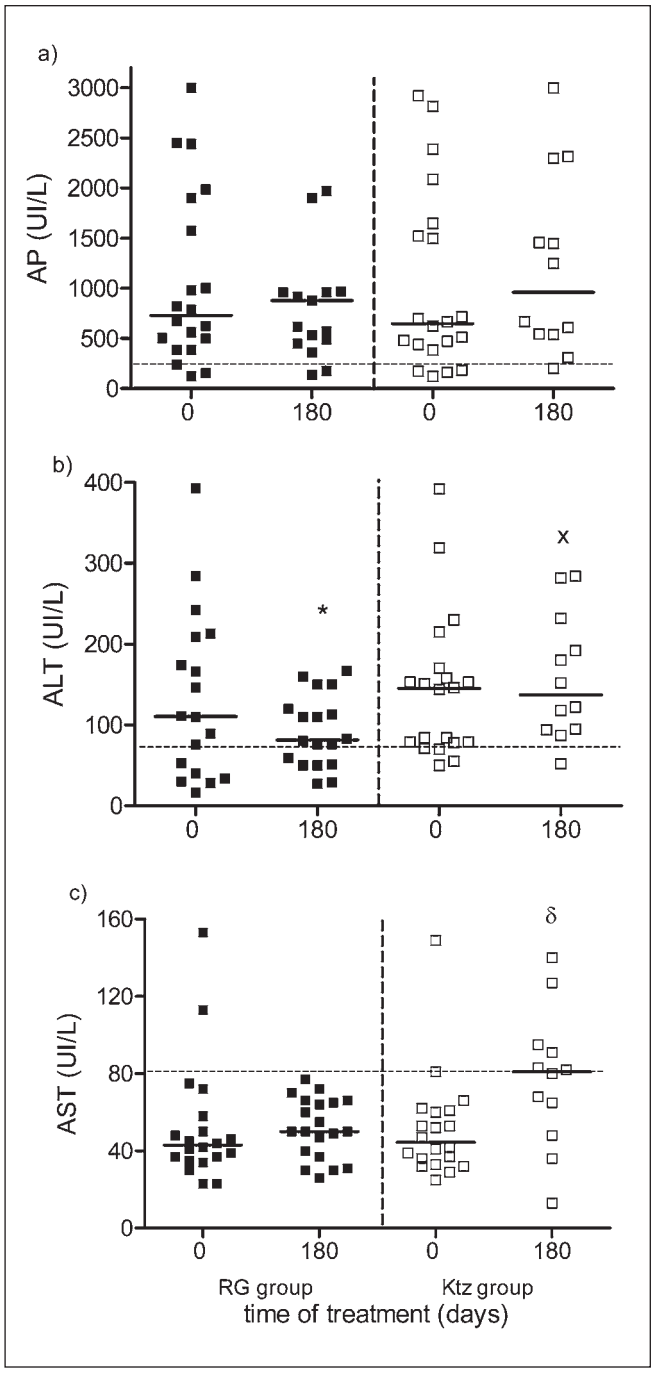

Figure 1: Variation in the plasma concentration of AP (a), ALT (b), and AST (c) in dogs treated with retinoic acid (full square) and ketoconazole (open square). In spite of individual decrease of AP in RG group (a), the difference is not significant. In (b), decrease of A LT (*P = 0.04) is evident after isotretinoin 9-cis therapy. On the other hand, in the Ktz group, there is a slight increase of ALT (xP< 0.02) in comparison to the RG group at the same time period. In (c), AST serum concentration is not changed in the RG group, but increased in the Ktz group(δ P<0.03). Doted lines indicate the upper limit of each enzyme

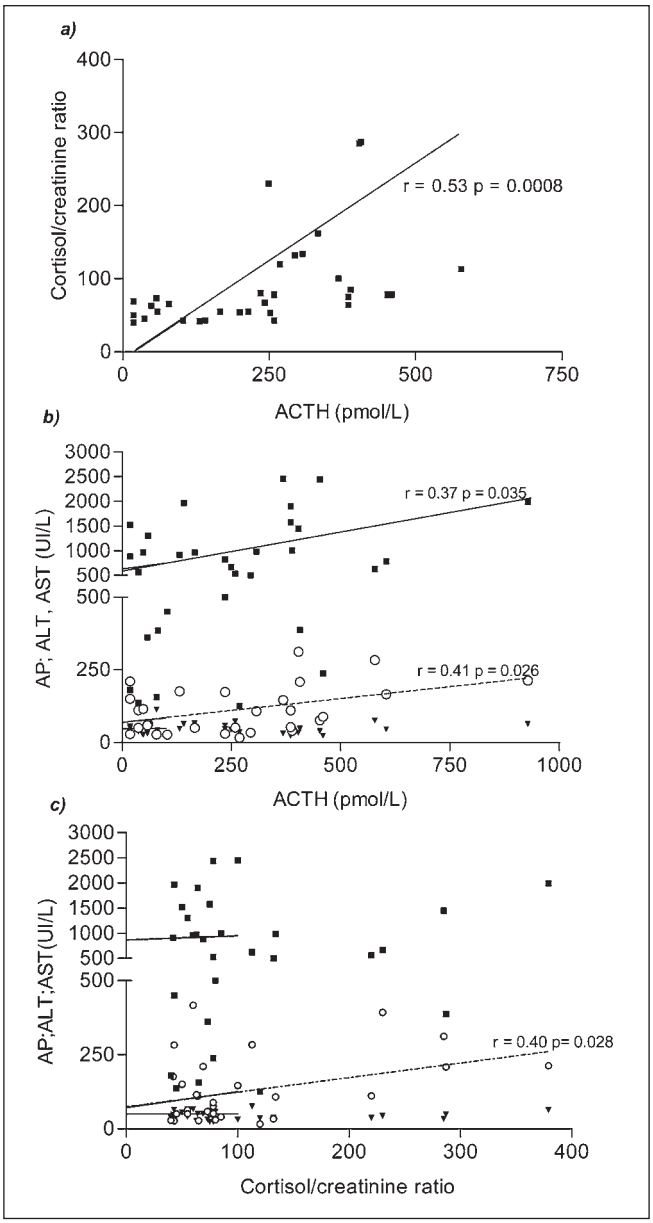

Figure 2: Correlation between ACTH vs. C/C (a), ACTH vs AP, ALT and AST (b) and C/C vs AP, ALT and AST in dogs treated with retinoic acid. Correlation between ACTH and C/C (a) demonstrated the effectiveness of RA to control PDH through its action on the corticotroph adenoma. As a result of this control, a positive correlation (b) between AP (full squares), ALT (open circles) and ACTH was observed, while there was no correlation between AST (full triangles) and ACTH

AST (Fig 1c) showed a significant increase (P< 0.03) after 180 days vs. 0 day (75 UI/L [13-127] vs 42 UI/L [18-149]) in the Ktz group and in comparison to values for 180 days (50 UI/L [26-77]) RG group (P< 0.03). There were no significant differences in the RG group ("0" day: 42 UI/L [23-153]. In this group 2 dogs normalized its previous elevated values.

Both plasma ACTH and C/C (Table 1) decreased after 180 days vs 0 day (P=0.0002 and P<0.0001 respectively) in RG group. In contrast, plasmatic ACTH augment at the end of treatment with KTZ vs 0 day (P=0.001) and C/C diminished at 180 day vs 0 day (P=0.0001). Nevertheless, the C/C in this group was significant higher (P=0.012) compared with RA group at 180 days.

In the RG group correlation was found between ACTH vs. C/C (r=0.53; P=0.0008) (Fig. 2a), with the decrease of the C/C accompanying the decrease of ACTH. In this group, a correlation (Fig. 2b and c) was also seen among ACTH vs. AP and ALT (r=0.37; P=0.035 and r=0.41; P=0.026 respectively) and between C/C vs. ALT (r=0.40; P=0.028). These correlations were not found in the Ktz group.

Table 1: Variation of ACTH and C/C in dogs treated with isotretinoin 9-cis vs ketoconazole

	RG		KTZ	
	0 day	180 days	0 day	180 days
ACTH (pmol/L)	375.7 (50-940.7)	100.5 [a] (18-258.4)	296.2 (52.1-904.2)	480 b (170-700)
C/C	126 (64-1200)	53 [c] (40-78)	114 (65-420)	77.5 d,e (52-120)

a) P=0.0002 (vs 0 day); b) P=0.001 (vs 0 day); c) P<0.0001 (vs 0 day); d) P=0.001 (vs 0 day), e) P=0.012 (vs 180 days of RG group)

Values are expressed as median and range. Wilcoxon signed rank test.

RG: retinoid group (N=20), Ktz: ketoconazole group (N=20 at 0 day and N=12 at 180 days). C/C: cortisol: creatinine ratio

Discussion

In the present study, we found that treatment with retinoic acid at the doses and in the studied time did not produce any significant alterations on the liver enzymes status.

Adverse effects of hypercortisolism in the organisms are well known. The same happens with the drugs prescribed for its control, especially due to their effect on the hepatic function (19, 20). These pharmacological products are inductors of the transaminases activity, and may cause damage in the hepatocytes (5). Taking into account that in PDH there is an increase of the hepatic enzymes activity, as well as in the size of the liver (1, 12), it is plausible to be concerned about the potential risk of the use of these drugs in dogs. It is known for AP, ALT and AST that their concentration in serum can be increased by corticosteroid induction (increase of enzymatic activity). On the one hand, the hepatic AP-isoenzyme is associated to the membrane of the hepatocytes and the bile epithelium, increasing its concentration in serum by induction and further release in the cholestatic liver disease (21, 22, 23).

In case of hepatopathy, the serum increase of ALT is related to the number of hepatocytes affected (cytoplasmic rupture), resulting also in an increase of AST (19, 22). The later enzyme is indicative of the hepatocellular damage and necroinflammation (22, 24). Corticoids also induce a greater activity of both enzymes (ALT and AST), due to their action on the neoglucogenesis and the glyceroneogenesis, metabolic pathways where both enzymes intervene (13, 14). The fact that ALT and AP were already high at the time of the diagnosis, while AST was within its normal range (except for three dogs, see Figure 1) could indicate that cortisol has a larger inducing effect on the ALT and AP than on AST.

The values obtained and the correlation analysis between ACTH and C/C in RG group shows that the isotretinoin 9-cis control PDH by inhibiting the secretion of ACTH and, consequently, cortisol. On the contrary, this does not occur in the Ktz group. Although there is a decrease of C/C, the ACTH remains high because the corticotroph adenoma is not targeted. As a result, the C/C is higher in the Ktz group than in RG. Similar effect has also been

observed before with o,p'-DDD and trilostane (26, 27). Thus, when the secretion of both hormones is controlled, this event will be reflected in the correlations observed with regards to the analyzed hepatic enzymes. The cortisol-induced effect on ALT is diminished with treatment, which is demonstrated in its significant decrease in the RG. With regard to AP, individual decrease is observed, with values remaining above 1,500 UI/L only in two dogs (see Figure 1). Considering the correlation between ACTH and AP, the cortisol action on the isoenzyme (23) is probably less important. This would explain the absence of correlation between AP and C/C. However, it is not known at the present if AP would decrease after longer time period than the one reported in the present study.

The lack of correlation between AST, ACTH and C/C would indicate that this enzyme is only marginally influenced by cortisol and that the isotretinoin 9-cis do not produce, at the indicated dose and time, hepatic damage. Therefore, when PDH is controlled as described in the RG group, the metabolic pathways where both enzymes interact are normalized and the activity of ALT and AST decrease in RG.

It is evident in the second group that the lack or loss of correlation between studied variables is due to the effects of ketoconazole. On one hand, as it does not completely normalize the synthesis of glucocorticoids, its inducing effect over these enzymes persists, adding to the choleostasis caused by hepatomegaly. On the other hand, this effects could be due to initial stages of liver damage after 180 days of treatment. The significant increase of ALT and AST in this group could be due to lesser control of the hypercortisolism, however, it could be also by necroinflammatory event with the consequent passage of the enzymes to the portal circulation (6, 24).

The behaviour of the studied enzymes and their relationship with the ACTH and C/C in the RG indicates that the isotretinoin 9-cis in the prescribed doses does not produce hepatocyte damage during the treatment period (180 days), being safe in PDH therapy. The elevated serum concentration of ALT and AP at the diagnosis time is not a contraindication for use of this drug. By contrast, Ketoconazole could imply a certain hepatoxicity risk according to the behaviour of ALT and AST, and therefore its use should be interrupted in case of a sustained increase in the activity of these two enzymes. Therefore, we conclude that AST enzyme must be closely monitored during PDH therapy as this enzyme could be a marker for hepatic damage in these patients.

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RETINOJSKA KISLINA KOT ZDRAVILO ZA CUSHINGOVO BOLEZEN PRI PSIH: OVREDNOTENJE JETRNIH ENCIMOV V ČASU ZDRAVLJENJA

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Povzetek: Nedavne študije so pokazale, da je možno z retinojsko kislino nadzorovati od hipofize odvisni hiperadenokorticizem (PDH), saj deluje na hipofizni tumor, ki izloča adenokortikotropni hormon (ACTH). Ker pa obstajajo poročila o hepatotoksičnosti retinojske kisline, smo se odločili analizirati hepatograme psov s Cushingovim sindromom. Primerjali smo pse, ki so 180 dni prejemali retinojsko kislino, s psi, ki so bili zdravljeni s ketokonazolom. Pri nobeni živali ni bila ugotovljena hepatotoksičnost. Pri psih, zdravljenih z retinojsko kislino, smo ugotovili (statistično neznačilen) padec alkalne fosfataze (AP), pri skupini, zdravljeni z ketokonazolom, pa ni bilo razlik. Pri retinojski skupini je bila po 180 dnevih (v primerjavi z dnem 0, P=0,04) znižana alanin amin transferaza (ALT). V ketokonazolni skupini je bil ta encim povišan (P<0,02). Alanin aspartanska transferaza (AST) se v retinojski skupini ni spreminjala, vrednost je ostala na osnovni ravni. V ketokonazolski skupini pa je AST po 180 dneh v primerjavi z dnevom 0 opazno narasla (P<0,03). Zmanjšanje vrednosti ALT in AP v retinojski skupini je povezano s padcem vrednosti ACTH (r=0,41, P=0,026 in r=0,37; P=0,035), obstaja pa tudi povezava med ALT in razmerjem urinskega kortizola in urinskega kreatinina (r=0,40, P=0,028). Te spremenljivke se v ketokonazolni skupini niso ujemale. Zaključimo lahko, da zdravljenje psov, obolelih s PHD, po 180 dnevih tretiranja z retinojsko kislino ne povzroča hepatotoksičnosti.

Ključne besede: cushingov sindrom–patofiziologija–zdravljenje; hipofizni ACTH, hipersekrecija; tretionin–terapevtska uporaba; jetra–učinki zdravil; psi