ijvm.2019.274033.1004958

Iranian Journal of Veterinary Medicine
Volume 14- Issue 02

Original Article
Online ISSN : 2252-0554

Evaluation of Prophylactic and Therapeutic Effects of Silymarin on Phenobarbital-Induced Hepatotoxicity in Cats

Bahman Mosallanejad[1]*, Mohammad Razi Jalali[1], Reza Avizeh[1], Mahdi Pourmahdi[2]

[1]*Department of Clinical Sciences, Faculty of Veterinary Medicine, Shahid Chamran University of Ahvaz , Ahvaz, Iran*
[2]*Department of Food Hygiene, Faculty of Veterinary Medicine, Shahid Chamran University of Ahvaz , Ahvaz, Iran*

Abstract

BACKGROUND: Phenobarbital is one of the most commonly used drugs to treat epilepsy and other seizure disorders in dogs and cats. Hepatotoxicity following phenobarbital administration is dose-dependent.

OBJECTIVES: The present study aimed to evaluate the protective action of silymarin on phenobarbital-induced hepatotoxicity in cats.

METHODS: For this purpose, twenty-four healthy adult cats were randomly allotted to four equal groups. Cats in group A were given phenobarbital with dosage 16 mg/kg orally for 28 days; group B received silymarin (30 mg/kg/day for twenty-eight days) orally concurrent with phenobarbital; groups C and D were treated like group B, but silymarin was administered 3 and 48 h after administration of phenobarbital, respectively, and continued up to twenty-eight days. The serum concentrations of alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, lactate dehydrogenase, total and direct bilirubin, blood urea nitrogen and creatinine were measured before administration of phenobarbital and after 24 h, 72 h and 28 days.

RESULTS: Phenobarbital elevated significantly serum concentrations of liver enzymes (in all cases), and total and direct bilirubin in two cats of group A, after 24 h (P <0.001). In groups, B and C, levels of serum enzyme activities and total and direct bilirubin remained within the normal range up to 28 days (P>0.05), while in group D, levels of serum enzyme activities (in 4 cases) were higher than the normal values (P<0.001).

CONCLUSIONS: The results showed that silymarin can protect liver tissue against oxidative stress in cats with phenobarbital intoxication especially in the first 3 h post-exposure.

KEYWORDS: Cat, Hepatotoxicity, Phenobarbital, Silymarin, Therapeutic

Correspondence
Bahman Mosallanejad, Department of Clinical Sciences, Faculty of Veterinary Medicine, Shahid Chamran University of Ahvaz , Ahvaz, Iran Tel: +98 9166078287, Fax: +98 (611) 3360807, Email: bmosallanejad@scu.ac.ir
Received: 2019-11-09
Accepted: 2020-02-24

How to Cite This Article
Mosallanejad, B., Razi Jalali, M., Avizeh, R., and Pourmahdi, M . (2020). Evaluation of Prophylactic and Therapeutic Effects of Silymarin on Phenobarbital-Induced Hepatotoxicity in Cats. Iranian Journal of Veterinary Medicine, 14(2):205-214

Introduction

The liver is the main detoxifying organ in the body. Continuous exposure to drugs, toxins, and different infections can trigger liver injury and eventually lead to various liver diseases (Stephens et al., 2014). Susceptibility of the liver to injury is much higher than any other organ because it biotransforms most xenobiotics and receives blood directly from the gastrointestinal tract (Kumar et al., 2015). Phenobarbital is one of the most popular anticonvulsant medications used in the veterinary field today. It is highly effective for the treatment of epilepsy in small animals. Phenobarbital is primarily metabolized by the liver and induces the cytochrome P_{450} enzyme activity, which can lead to progressive shortening of the elimination half-life of barbiturates with chronic administration (Munana et al., 2015).

The elimination half-life of phenobarbital is approximately 40 hours in cats, although significant variability may be noted among them. Typically, the starting dosage for cats is 2 to 4 mg per kg of body weight (B.W.) This can be increased up to 16 mg per kg of B.W. per day based on the animal's response (Podell, 2013).

Long-term administration of phenobarbital has been reported to cause hepatic injury (hepatotoxicity) (Dayrell-Hart et al., 1991). Some dogs and cats receiving phenobarbital develop increases in certain liver enzymes, especially alkaline phosphatase (ALP) and aspartate transaminase (AST). Phenobarbital should be administered with extreme caution in pets diagnosed with hypovolemia, kidney disease, anemia, and hypoadrenocorticism. The use of the medication should be avoided outright in pets with severe respiratory dysfunction, liver disease, or those with a known sensitivity to other anti-seizure medications (Muller et al., 2000). Treatment of seizures in cats is similar to dogs, with only a few limitations related to species-specific drug toxicities (Hazenfratz et al., 2018).

In many studies, silymarin has long been used in the treatment of liver disorders, including acute and chronic hepatitis, toxin/drug-induced hepatitis, and other liver diseases (Lappin, 2001; Lo et al., 2014). There are few reported adverse effects of silymarin in cats. Beneficial effects on minimizing the formation of free radicals associated with reperfusion of ischemic have been reported (Lappin, 2001; Sun et al., 2018). The cat has been used extensively as an experimental model for studying the pharmacology of drugs (Das and Vasudevan, 2006).

Cats are extremely sensitive to the toxic effects of different drugs. These animals form glucuronides with many compounds slowly, or not at all because they possess fewer isoforms of the enzymes that mediate the conjugation. Cats have a relative deficiency of a specific high-affinity glucuronyl transferase that conjugates drugs with glucuronic acid. The deficiency of the glucuronide conjugation pathway results in more drugs being conjugated to sulfates; however, the sulfation pathway has a finite capacity, which is also lower in cats than the other species (Lappin et al., 2001).

During prolonged treatment with different drugs, measurement of serum enzyme activities is necessary. Clinical signs and laboratory test results are nonspecific and do not differentiate drug-induced from other causes of hepatic diseases (Muller et al., 2000). Elevation in alanine aminotransferase (ALT) and AST activities are the most consistent findings. Serum ALP and lactate dehydrogenase (LDH) activities also may be increased.

Bilirubinuria and hyperbilirubinemia occur more commonly in cats than in dogs (Kayne and Jepson, 2004).

Silymarin was chosen because of the antioxidant properties. This drug may protect the liver against oxidative stress through direct reactions with free radicals. Silymarin most likely inhibits TNF-α production in the liver (Gabrielova et al., 2015; Singh et al., 2016). Based on the aforementioned background, the present study was conducted to evaluate the possible hepatoprotective effects (therapeutic and prophylactic) of silymarin against experimental phenobarbital-induced hepatotoxicity in cats.

Materials and methods

Animals

Twenty-four adult cats, DSH breed, 1-1.5 years old, and weighing 2.35-3.9 kg were randomly allotted to four equal groups. All cats appeared healthy, as determined by clinical examination, normal hemogram, and clinical biochemical profiles. The cats were kept in separate cages at 22-25˚C with 12-h light/12-h dark cycles, in a controlled environment. They were fed with a homemade diet containing chicken and fish. Water was provided ad libitum. This study was approved by the animal care program and research committee of Shahid Chamran University of Ahvaz. It was conducted based on the guidelines for small animal care and use (code of ethics: 1397.57202). Cats in group A were given phenobarbital (DarouPakhsh Pharmaceutical Co., Tehran, Iran) with dosage 16 mg/kg (as a toxic dose) orally for 28 days in gelatin capsules; group B received silymarin with dosage 30 mg/kg/day (Jalinous Pharmaceutical Co., Tehran, Iran) and continued for twenty-eight days orally concurrent with phenobarbital; groups C and D were treated like group B, but silymarin was administered 3 and 48 h after administration of phenobarbital and continued up to twenty-eight days. Blood samples were collected from the jugular vein under general anesthesia (a combination of ketamine with dosage 15 mg/kg and acepromazine 0.15 mg/kg) for all groups. After collecting blood in centrifuge tubes, the tubes were allowed to coagulate at room temperature and then placed in a water bath at 37˚C for 10 min. Centrifugation was performed at 1000 g for 20 min. The clear serum was separated and used for the analysis of biochemical parameters. The serum concentrations of ALP, ALT, AST, and LDH (as indices of liver injury), total and direct bilirubin, and kidney indices (BUN and creatinine) were measured before administration of phenobarbital and 24 h, 72 h and 28 days later. Serum concentrations of the above indices were measured in an automated chemical analyzer (BT 3000 Plus, Biotechnica, Milan, Italy) using diagnostic kits (Pars Azmoon Co., Tehran, Iran).

Statistical analysis

The arithmetic mean of ALP, ALT, AST, LDH, bilirubin (total and direct), BUN and creatinine were compared among groups using repeated measures ANOVA, one way analysis of variance and LSD test (SPSS, version 10, SPSS Inc., Chicago, IL, USA). Differences were considered significant when $P \leq 0.05$.

Results

In the present study, there were significant differences in enzyme activities among the different treatment groups ($P < 0.001$). According to the results presented in Tables 1-4, phenobarbital elevated significantly serum concentrations of ALP, ALT, AST, LDH (in all cases), and total and direct bilirubin

in two cats of group A, after 24 h. Group, time, and the interaction of group and time had a significant effect on changes of liver enzymes (P<0.001). In groups, B and C, levels of serum enzyme activities and total and direct bilirubin remained within the normal range up to 28 days (P >0.05), but in the group D, levels of serum enzyme activities were higher than normal values (P<0.001) (in four cases) and total and direct bilirubin remained within the normal range. The variables were different according to the drug administration time in group D. Prophylactic (time zero) or therapeutic (3 h later) application of silymarin had a significantly beneficial effect and prevented the increase in serum enzyme activities, and total and direct bilirubin in both groups B and C. BUN (18-27 mg/dl) and creatinine (0.9-1.8 mg/dl) levels were normal in all groups. Clinical findings mainly included depression, sedation, and ptyalism, during the study period. None of the cats died during the experiment. The course of the enzymatic activities is shown in Tables 1 to 4 (mean ± SD).

Table 1. The mean ± SD of serum ALP concentration (IU/L) in experimental groups of cats based on group and time

Group	Time			
	Time zero	After 24 h	After 72 h	After 28 days
A	$^{C}28.17\pm11.81^{a}$	$^{B}140.83\pm23.08^{a}$	$^{B}156.67\pm27.53^{a}$	$^{A}242.83\pm17.86^{a}$
B	$^{A}40.83\pm19.92^{a}$	$^{A}50.83\pm27.72^{c}$	$^{A}67.17\pm16.29^{b}$	$^{A}63.83\pm21.83^{c}$
C	$^{A}64.33\pm18.39^{a}$	$^{A}67.83\pm11.79^{c}$	$^{A}55.33\pm8.43^{b}$	$^{A}60.50\pm14.77^{c}$
D	$^{C}47.50\pm20.28^{a}$	$^{B}109.17\pm36.31^{b}$	$^{AB}142.33\pm57.74^{a}$	$^{A}159.33\pm66.65^{b}$

Significant differences are presented by capital letters in each row and lower case letters in each column (P<0.05).

Table 2. The mean ± SD of serum ALT concentration (IU/L) in experimental groups of cats based on group and time

Group	Time			
	Time zero	After 24 h	After 72 h	After 28 days
A	$^{D}41.83\pm17.62^{a}$	$^{C}138.17\pm21.81^{a}$	$^{B}168.83\pm9.37^{a}$	$^{A}231.67\pm33.44^{a}$
B	$^{A}52.33\pm19.88^{a}$	$^{A}50.17\pm16.59^{b}$	$^{A}61.83\pm16.02^{b}$	$^{A}60.33\pm13.88^{c}$
C	$^{A}49.83\pm14.02^{a}$	$^{A}62.17\pm9.81^{b}$	$^{A}54.50\pm10.37^{b}$	$^{A}58.33\pm9.83^{c}$
D	$^{B}50.67\pm8.41^{a}$	$^{A}142.67\pm77.94^{a}$	$^{A}150.83\pm62.49^{a}$	$^{A}163.17\pm77.59^{b}$

Significant differences are presented by capital letters in each row and lower case letters in each column (P <0.05).

Table 3. The mean ± SD of serum AST concentration (IU/L) in experimental groups of cats based on group and time

Group	Time			
	Time zero	After 24 h	After 72 h	After 28 days
A	$^{D}39.33\pm13.23^{a}$	$^{C}134.33\pm12.13^{a}$	$^{B}163.33\pm18.80^{a}$	$^{A}245.50\pm19.39^{a}$
B	$^{A}37.17\pm15.36^{a}$	$^{A}43.50\pm13.44^{c}$	$^{A}46.17\pm7.03^{b}$	$^{A}62.33\pm14.75^{c}$
C	$^{A}63.83\pm15.37^{a}$	$^{A}76.17\pm34.74^{b}$	$^{A}64.33\pm20.97^{b}$	$^{A}62.17\pm10.11^{c}$
D	$^{B}45.33\pm10.76^{a}$	$^{A}116.67\pm33.46^{a}$	$^{A}137.17\pm54.36^{a}$	$^{A}130.67\pm68.65^{b}$

Significant differences are presented by capital letters in each row and lower case letters in each column (P <0.05).

Table 4. The mean ± SD of serum LDH concentration (IU/L) in experimental groups of cats based on group and time

Group	Time			
	Time zero	After 24 h	After 72 h	After 28 days
A	$^{C}196.83\pm24.46^{a}$	$^{B}521.83\pm34.20^{a}$	$^{AB}551.83\pm22.16^{a}$	$^{A}569.83\pm30.42^{a}$
B	$^{A}201.83\pm29.26^{a}$	$^{A}203.83\pm18.58^{b}$	$^{A}200.33\pm21.68^{c}$	$^{A}196.33\pm17.84^{b}$
C	$^{A}218.33\pm32.12^{a}$	$^{A}268.67\pm146.21^{b}$	$^{A}277.50\pm146.21^{c}$	$^{A}281.17\pm148.39^{b}$
D	$^{B}193.83\pm13.64^{a}$	$^{A}429.83\pm62.41^{a}$	$^{A}440.17\pm176.59^{b}$	$^{A}461.67\pm183.42^{a}$

Significant differences are presented by capital letters in each row and lower case letters in each column ($P<0.05$).

Discussion

The results of the present study showed that silymarin had inhibitory effects on phenobarbital-induced hepatotoxicity in cats of groups B and C completely so that the parameters remained within the normal range. In group D, relatively similar to group A, the variables were different according to the time of drug intake. In the present study, the oral administration of phenobarbital (16 mg/kg) for 28 days caused chronic hepatotoxicity in cats as verified by clinical and biochemical investigations. Administration of phenobarbital increased serum concentrations of liver enzymes (in all cats) and total and direct bilirubin (in two cats) of group A. The result of the therapeutic dose of silymarin (up to 3 h after phenobarbital administration) was similar to prophylactic dose (co-administration of both the drugs) in the prevention of hepatotoxicity in our study, but administration of silymarin did not have preventative effects after 48 h.

Antioxidative and anti-inflammatory effects of silymarin (by a significant decrease in hepatic myeloperoxidase activity and nitric oxide production) are known in rat models (Kumar et al., 2015). Silymarin can prevent liver injury by the inhibition of free radical formation. The recommended dosage for silymarin is 20-50 mg/kg/day in dogs and cats (Hsu, 2013). It is reported that the beneficial effects of silymarin on phenobarbital-induced liver injury may be attributed to the effect of the former on aldehyde oxidase mediated metabolism of phenobarbital in the liver (Singh et al., 2016). Phenobarbital likely increases the effects of the inhibitory neurotransmitter gamma aminobutyric acid (GABA), and decreases the release of the excitatory neurotransmitter glutamate (Podell et al., 2016).

In the present study, we used silymarin for 28 days; nevertheless, the duration of administration depends on the condition being treated, response to the medication, and the development of any adverse effects. This medication is available in a variety of formulations, including oral tablets and injectable forms. Dosage is determined based on several different factors, including the pet's species, breed, size, and age. Phenobarbital hepatotoxicity can be managed with drug discontinuation or substantial dose reduction.

Based on the presumption that phenobarbital is a hepatotoxic drug, an increase in serum enzyme activities within 24 h after onset, indicates a need to suspend drug administration and to provide supportive care (Khoury et al., 2015). Reports of hepatotoxicity associated with phenobarbital administration in veterinary medicine are exclusively limited to dogs; however, vigilance for these

adverse effects in cats is warranted, and routine monitoring of serum chemistry profiles is recommended in feline patients receiving this drug. The most common adverse reactions of phenobarbital reported in dogs are sedation, weight gain, increased thirst (polydipsia), increased urination (polyuria), and increased appetite, most of which resolve within a few weeks of starting treatment. Less common but more serious adverse effects of phenobarbital administration include acute idiosyncratic liver or bone marrow toxicity. Additional rare adverse effects of phenobarbital specifically reported in cats include facial pruritus, limb edema, thrombocytopenia, and cutaneous and mucosal hypersensitivity reactions (Hazenfratz et al., 2018). In the present study, the most common clinical signs were depression, sedation, and ptyalism. All cats completed the study without mortality. We did not see signs of hypersensitivity reactions as observed in dogs.

The role of oxidative stress in phenobarbital-induced hepatotoxicity and the therapeutic effects of natural antioxidants have been evaluated in some studies. For example, Muller et al. (2000) suggested that increases in concentrations of ALP, ALT, and GGT may reflect enzyme induction rather than hepatic injury during phenobarbital treatment in dogs.

In another study, serum ALP isoenzyme activities were determined for 23 epileptic dogs before the start of phenobarbital and at three weeks, six months, and 12 months after the start of treatment. Median serum ALP was significantly increased at six months and 12 months compared with time zero (Gaskill et al., 2005).

Silymarin is a scavenger of radicals, such as hydroxyl, superoxide, and hydrogen peroxide (H2O2) (Ozkilic et al., 2006). This drug decreases lipid peroxidation. It protects liver cells directly by stabilizing the membrane permeability through inhibiting lipid peroxidation. Silymarin alone or in the form of supplements with other drugs can influence the treatment process in liver diseases in many species of animals. Many medicinal, nutraceutical, and botanic extracts such as S-adenosylmethionine, N-acetylcysteine, ursodeoxycholic acid, allopurinol, sitagliptin, and vitamin E have been used as cytoprotective agents in liver disease (Papich, 2016; Abo-Haded et al., 2017). Host factors such as age, sex, individual genetic constitution, malnutrition, especially protein deficiency, disease status, and concomitant use of other medications can affect the severity of drug-induced hepatic disease (Akbulut et al., 2015).

The prophylactic and treatment effects of silymarin administration and the role of serum enzyme activities in phenobarbital-induced hepatotoxicity in this study were relatively similar to the results of Avizeh et al. (2010). In their research, a single oral administration of acetaminophen in cats significantly elevated serum concentrations of ALT, AST, ALP, LDH, methemoglobin, and total and direct bilirubin. In both groups that received acetaminophen plus N-acetylcysteine or silymarin, the levels of serum enzyme activities, methemoglobin, and total and direct bilirubin remained within the normal range. They stated that the major activity of both the compounds is their antioxidant property, which makes them useful in the prevention of other organ-specific toxicities related to the induction of oxidative stress (Avizeh et al., 2010). As previously stated information about the toxicity of phenobarbital is relatively low in cats. Most cases of drug-induced hepatopathy are mild and present with vague signs of lethargy and depression with or without jaundice.

In conclusion, the results of this study

showed that silymarin has a protective effect in prophylaxis and treatment of phenobarbital-induced hepatotoxicity in cats and might be very useful at least in the first 3 h post-exposure. The activity of silymarin is due to the antioxidant property, which makes it suitable for the prevention of other organ-specific toxicities related to the induction of oxidative stress.

Acknowledgments

The authors wish to express their gratitude to the research council of Shahid Chamran University of Ahvaz for financial support.

Conflict of Interest

The authors declared that there is no conflict of interest.

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ijvm.2019.274033.1004958

Iranian Journal of Veterinary Medicine
Abstracts in Persian Language

Online ISSN *2252-0554*

مجله طب دامی ایران، ۱۳۹۹، دوره ۱۴، شماره ۲، ۲۱۴-۲۰۵

ارزیابی اثرات درمانی و پیشگیرانه سیلیمارین بر مسمومیت کبدی القایی توسط فنوباربیتال در گربه‌ها

بهمن مصلی‌نژاد*[۱]، محمد راضی‌جلالی[۱]، رضا آویزه[۱]، مهدی پورمهدی[۲]

[۱] **گروه علوم درمانگاهی دانشکده دامپزشکی دانشگاه شهید چمران اهواز**

[۲] **گروه بهداشت مواد غذایی دانشکده دامپزشکی دانشگاه شهید چمران اهواز**

(دریافت مقاله: ۱۸ آبان ماه ۱۳۹۸، پذیرش نهایی: ۵ اسفند ماه ۱۳۹۸)

چکیده

زمینه مطالعه: فنوباربیتال یکی از شایع‌ترین داروهای مورد استفاده جهت درمان صرع و سایر اختلالات تشنجی در سگ‌ها و گربه‌ها است. مسمومیت کبدی متعاقب تجویز فنوباربیتال، وابسته به دوز می‌باشد.

هدف: هدف از انجام مطالعه حاضر، ارزیابی عملکرد محافظتی سیلیمارین بر اثرات مسمومیت کبدی ناشی از تجویز فنوباربیتال در گربه‌ها بود.

روش کار: بدین منظور ۲۴ قلاده گربه بالغ سالم به‌طور تصادفی به ۴ گروه مساوی تقسیم‌بندی شدند. گربه‌های گروه A، فنوباربیتال را با دوز ۱۶ میلی‌گرم/کیلوگرم به صورت خوراکی و برای مدت ۲۸ روز دریافت کردند. گربه‌های گروه B سیلیمارین را با دوز ۳۰ میلی‌گرم/کیلوگرم و به شکل همزمان با فنوباربیتال برای مدت ۲۸ روز دریافت کردند. گروه‌های C و D مشابه گروه B درمان شده بودند، اما سیلیمارین به‌ترتیب ۳ و ۴۸ ساعت بعد از تجویز فنوباربیتال، به آن‌ها خورانده شده بود و تا روز ۲۸ ادامه یافت. غلظت آنزیم‌های سرمی آلانین آمینوترانسفراز، آسپارتات آمینوترانسفراز، آلکالاین فسفاتاز، لاکتات دهیدروژناز، بیلی‌روبین تام و مستقیم، ازت اوره خون و کراتینین، قبل از تجویز فنوباربیتال، ۲۴ ساعت، ۷۲ ساعت و ۲۸ روز بعد، اندازه‌گیری شدند.

نتایج: در گربه‌های گروه A، فنوباربیتال به شکل معنی‌داری غلظت‌های سرمی آنزیم‌های کبدی را (در تمام موارد) و بیلی‌روبین تام و مستقیم را در دو قلاده گربه، بعد از ۲۴ ساعت افزایش داد ($p< ۰/۰۰۱$). در گربه‌های گروه B و C، میزان فعالیت آنزیم‌های سرمی و بیلی‌روبین تام و مستقیم، تا ۲۸ روز، در محدوده نرمال قرار گرفتند ($p< ۰/۰۵$)، اما در گروه D، میزان فعالیت آنزیم-های سرمی، در ۴ مورد افزایش پیدا کرد ($p< ۰/۰۰۱$).

نتیجه گیری نهایی: نتایج نشان داد که سیلیمارین می‌تواند بافت کبد را از استرس اکسیداتیو القایی توسط فنوباربیتال در گربه‌ها، بویژه در ۳ ساعت اول پس از در معرض قرار گرفتن دارو، محافظت نماید.

واژه‌های کلیدی:

گربه، مسمومیت کبدی، فنوباربیتال، سیلیمارین، درمانی

نویسندهٔ مسئول: بهمن مصلی‌نژاد، گروه علوم درمانگاهی دانشکده دامپزشکی دانشگاه شهید چمران اهواز، ایران. ایمیل: *bmosallanejad@scu.ac.ir*