Comparison of the Effects of Melatonin and Pentoxifylline on the Serum Lipids of Mice with Carbon Tetrachloride-Induced Liver Toxicity

KARBON TETRAKLORÜR İLE KARACİĞER TOKSİSİTESİ OLUŞTURULAN FARELERDE MELATONİN VE PENTOKSİFİLİNİN SERUM LİPİDLERİ ÜZERİNE ETKİLERİNİN KARŞILAŞTIRILMASI

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Abstract

Objective: The aim of this study was to investigate the effects of melatonin (MLT) and pentoxifylline (PTX) on the serum lipids of mice with liver injury induced by carbon tetrachloride (CCl_4).

Material and Methods: Total 60 animals were divided into six equal groups as; control, olive oil, toxicity, MLT, PTX and PTX + MLT. MLT 10 mg/kg/day, PTX 50 mg/kg/day, and the same individual doses in MLT + PTX combination were given intraperitoneally (i.p.) to mice for 7 day. 0.8 mg/kg/day CCl_4 was administered on the 4th, 5th, and 6th days of therapy in all groups except the control and olive oil groups.

Results: Triglycerides (TG) levels increased significantly in toxicity group as compared to control group ($p< 0.05$). Both MLT and PTX + MLT administration caused to significant increases in the TG levels as compared to control and olive oil groups ($p< 0.05$). Compared to toxicity, PTX and PTX + MLT groups, TG levels were also increased significantly in MLT group ($p< 0.05$). In addition, total cholesterol (TC) level increased significantly in PTX and PTX + MLT groups as compared to control groups ($p< 0.05$), and also TC level increased significantly in PTX + MLT group as compared to toxicity group ($p< 0.05$). High-density lipoprotein cholesterol levels did not change significantly among the groups.

Conclusion: These results indicate that administration of PTX and MLT alone and in combination before onset of liver toxicity did not reduce the increased triglycerides and cholesterol levels, in addition, MLT administration might cause to increase on the triglycerides levels.

Key Words: Liver cirrhosis; melatonin; pentoxifylline; triglycerides

Özet

Amaç: Bu çalışmada karbon tetraklorür ile (CCl_4) toksisite oluşturulan farelerde melatonin (MLT) ve pentoksifilinin (PTX) serum lipitleri üzerine etkilerinin araştırılması amaçlanmıştır.

Gereç ve Yöntemler: Toplam 60 hayvan kontrol, zeytinyağı, toksisite, MLT, PTX ve MLT + PTX grubu olarak eşit olarak 6 gruba ayrılmıştır. MLT 10 mg/kg/gün, PTX 50 mg/kg/gün ve aynı doz kombine MLT + PTX tedavisi 7 gün süreyle intraperitoneal (i.p.) olarak uygulanmıştır. Kontrol ve zeytinyağı grubu hariç diğer gruplara 0.8 mg/kg/gün CCl_4 çalışmanın 4., 5, ve 6. günleri uygulanmıştır.

Bulgular: Kontrol grubuyla karşılaştırıldığında, toksite grubunda trigliserit (TG) düzeyleri anlamlı olarak artış göstermiştir ($p< 0.05$). Kontrol ve zeytinyağı gruplarıyla karşılaştırıldığında, hem MLT hem de PTX + MLT uygulaması TG düzeylerinde anlamlı artışa neden olmuştur ($p< 0.05$). Toksisite grubu, PTX ve PTX + MLT gruplarıyla da karşılaştırıldığında, MLT grubunda TG düzeyleri anlamlı olarak artmıştır ($p< 0.05$). Bununla birlikte, kontrol grubuyla karşılaştırıldığında, total kolesterol (TC) düzeyi PTX ve PTX + MLT grubunda anlamlı olarak artmış ($p< 0.05$), yine toksisite grubuyla karşılaştırıldığında TC düzeyi PTX + MLT grubunda anlamlı olarak artış göstermiştir ($p< 0.05$). Yüksek dansiteli kolesterol düzeyi açısından gruplar arasında farklılık tespit edilememiştir.

Sonuç: Bu sonuçlar, karaciğer toksisitesi oluşmadan önce uygulanan hem tek başına hem de kombine PTX ve MLT tedavilerinin artmış TG ve TC düzeylerini azaltmadığını, bununla birlikte, MLT uygulamasının TG düzeylerini artırabileceğini göstermektedir.

Anahtar Kelimeler: Karaciğer sirozu, melatonin, pentoksifilin ve trigliserit

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Carbon tetrachloride (CCl_4) is widely used as a hepatotoxic compound for screening the anti-hepatotoxic/hepatoprotective activity of drugs in experimental model systems, because CCl_4-induced hepatotoxicity is regarded as

an analogue of liver injury caused by a variety of hepatotoxins in man. According to general belief, CCl_4 hepatotoxicity mainly depends on the reductive bio-activation to trichloromethyl free radical (CCl_3) by cytochromes P450. $CCl_3^{\cdot}$ itself is highly toxic and may form many additional reactive intermediates in vivo.[1-3]

It is well known that triglycerides (TG) accumulate in the liver of rats intoxicated once with CCl_4 through enhancement of its synthesis in the liver and impairment of its secretion into the blood.[4] The regulation of serum free fatty acids (FFA) and TG in healthy subjects involves tissue TG lipases operating on serum lipoproteins and tissue TG in adipose tissue, intestine, muscle and liver. FFA absorbed in the intestine are re-esterified into TG and as chylomicrons and very low-density lipoprotein (VLDL), are transported through the portal circulation to the liver. There, depending on the metabolic state (*i.e.,* levels of insulin, glucagon, epinephrine, somatotropin and the insulin-like growth factors), they are oxidized or repackaged and transported to adipose tissue in VLDL or low-density lipoprotein (LDL) for storage as TG. Metabolism of serum TG occurs by heparin-sensitive lipoprotein lipase, which allows release and uptake of FFA into adipose tissue and muscle, followed by re-esterification into TG in fat or oxidation in muscle.[5]

In the search for novel drugs that can alleviate hepatocyte injury and reduce fibrosis, pentoxifylline (PTX) has received considerable interest.[6-8] PTX [3,7-dimethyl-1- (5-oxohexyl) xanthine] is a methyl-xanthine derivative that has been used for its regulator effects on the blood flow for the treatment of peripheral vascular disease, cerebrovascular disease and a number of other conditions involving a defective regional microcirculation.[9] In different studies, PTX, however, showed variable effects on hepatocyte injury from failure to alter indices of cell necrosis and cholestasis to prevention of liver cell damage.[10,11]

Melatonin (MLT), [N-acetyl-5-methoxytryptamine], is an indole amine synthesized during the night in the pineal gland.[12] Its biological antioxidant activity is well known and it stands out as a powerful neutralizer of hydroxyl free radical.[13] It has been suggested that MLT treatment results in decreases in plasma total-and LDL-cholesterol levels,[14,15] in fatty infiltration in the liver[16] and in the susceptibility of LDL to lipid peroxidation[17] in hypercholesterolemic humans and animals. In the present study, it was investigated that effects of PTX and MLT on the serum lipids in mice model of acute intoxication with CCl_4.

Material and Methods

Sixty healthy male Mus musculus Swiss albino specie mice weighing between 38-52 g were used in this study. Mice were kept under standardized conditions for food, water, light and temperature. The approval of Yüzüncü Yıl University, School of Medicine Animal Ethics Committee was obtained and "Guide for the Care and Use of the Laboratory Animals" was accepted in the present study. The study took seven days. Animals were randomly separated into six groups as shown below that include 10 mice in each group.

Group 1 (control): Animals were sham-treated with 0.8ml/kg/day serum physiologic via i.p during seven days.

Group 2 (olive oil): Animals were treated with 0.8 ml/kg/day olive oil via i.p starting from the 4^{th} day of the study during 3 days.

Group 3 (CCl_4): Nothing was applied to animals except than CCl_4.

Group 4 (MLT): The toxicity was formed as mentioned below and animals were treated with 10 mg/kg/day MLT via i.p for 7 days.

Group 5 (PTX): The toxicity was formed as mentioned below and animals were treated with 50 mg/kg/day PTX through i.p for seven days.

Group 6 (PTX + MLT): The toxicity was formed as mentioned below and animals were treated with 10 mg/kg/day MLT plus 50 mg/kg/day PTX via i.p during seven days.

To induce the hepatic toxicity, 0.8 mg/kg/day CCl_4 diluted 1:3 in olive oil was injected daily via intraperitoneally (i.p) on the 4^{th}, 5^{th} and 6^{th} days of the therapy in all groups except the control and olive oil group. To avoid possible interactions of

the chemicals all treatments were administrated at the same time and by different injectors. At the end of the study, after an overnight fasting, animals were sacrificed at 09:00 am by exsanguinations under anaesthesia. Blood samples was collected and centrifuged for obtain serum samples. Roche-Hitachi PP Modular analyser with Roche original reagents was used to perform the biochemical measurements.

Statistical Analysis

The data are expressed as mean ± standard deviation (SD). Student's t test for first and last day body weight was used to determine differences among all groups. Kolmogorov-Smirnov Goodness of Fit Test was used to control whether the distribution of characteristics was normal or not. Then groups of data were compared with an analysis of variance (One-way ANOVA) followed by Tukey's multiple comparison tests.

Results

The final and initial body weights of mice are presented in Table 1. The final body weights of animals in groups 3, 4, 5 and 6 were decreased significantly compared that in their initial values ($p< 0.05$). However, there were no significant differences between initial and final weights in-group 1 and 2.

The serum AST, ALT and LDH enzyme activities and lipid levels are presented in Table 2 and Figures 1 and 2. AST, ALT and LDH enzymes activities, indicator of liver function, were significantly increased in-group 3 as compared to all other groups ($p< 0.05$). The highest TG levels were found in-group 4 as compared to group 1, 2, and 3 ($p< 0.05$). TG levels were also significantly decreased in-group 5 and 6 as compared to group 4 ($p< 0.05$). However, total cholesterol (TC) level was found increased significantly in-group 5 and 6 as compared to group 1 ($p< 0.05$), and also TC level was found significantly increased in-group 6 as compared to group 3 ($p< 0.05$). High-density lipoprotein cholesterol (HDL-C) levels did not change significantly among the groups.

Discussion

In the present study, MLT and PTX therapies caused to decrease the body weight of mice. Effects of MLT are well known on body mass, adiposity, and both energy intake and expenditure.[18] These effects of MLT may vary according to the species. Thus, Wade et al[19] and Bartness et al[20]

Table 1. The comparison of mice's body weights included the study dependent on time (mean±SD)

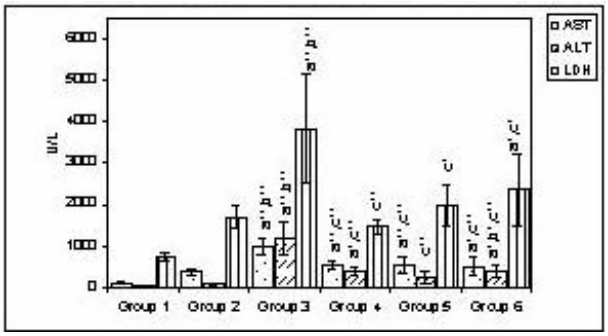
Parameter	Days	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6
Body weight (g)	0	44.8 ± 4.8	39.2 ± 2.8	46.8 ± 4.1	41.9 ± 3.4	44.2 ± 2.2	42.6 ± 2.8
Body weight (g)	7	45.7 ± 4.5	39.9 ± 2.1	44.4 ± 3.9**	39.7 ± 3.3*	40.2 ± 1.9**	41.4 ± 2.8**

$^{*}p< 0.05$, $^{**}p< 0.01$.

Table 2. Effect of MLT (10 mg/kg/day), PTX (50 mg/kg/day) and MLT+PTX administration on serum liver enzymes activities and lipid levels in mice CCl_4- induced liver toxicity.

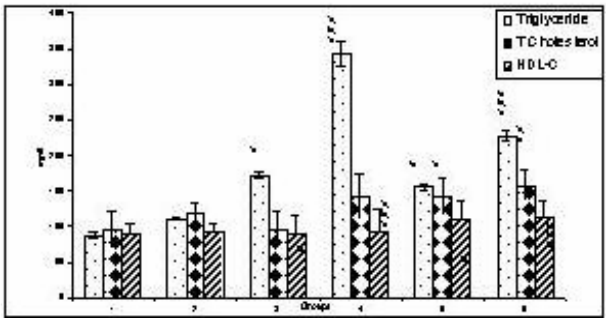
Parameters	Group 1 X ± SD	Group 2 X ± SD	Group 3 X ± SD	Group 4 X ± SD	Group 5 X ± SD	Group 6 X ± SD
AST (U/L)	123.5 ± 35.5	390.4 ± 78.4	1001.5 ± 192.1^{a**,b**}	547.1 ± 103^{a**,c**}	561.6 ± 198.2^{a**,c**}	510.8 ± 223.4^{a,*c**}
ALT (U/L)	31.7 ± 9.6	98.1 ± 29.3	1181.6 ± 401.9^{a**,b**}	383.8 ± 92.4^{a*,c**}	246.7 ± 125.1^{c**}	411.7 ± 148.7^{a,*,b*,c**}
LDH (U/L)	762.3 ± 100.9	1703.2 ± 255.4	3816.6 ± 1309.3^{a**,b**}	1466.5 ± 192.2^{c**}	1986.5 ± 506.8^{c*}	2361.5 ± 867.3^{a,c*}
TG (mg/dL)	87.4 ± 13.6	111 ± 10.6	172.80 ± 26.2^{a*}	343.7 ± 69.1^{a*,b*,c*}	155.4 ± 18.4^{d*}	227.5 ± 63.9^{a*,b*,d*}
TC (mg/dL)	95.6 ± 26.2	119.2 ± 15	96.4 ± 26.2	141.7 ± 30.8	141.1 ± 26.3^{a*}	158 ± 21.6^{a*,c*}
HDL-C (mg/dL)	89.5 ± 25.3	93 ± 19.7	89.8 ± 24.2	92.6 ± 18.9	108.8 ± 17.1	113.3 ± 25.8

^{a}compared to group 1, ^{b}compared to group 2, ^{c}compared to group 3, ^{d}compared to group 4, $^{*}p< 0.05$, $^{**}p< 0.01$.



[a]compared to group 1, [b]compared to group 2 [c]compared to group 3, 'p< 0.05, "p< 0.01

Şekil 1. Effect of MLT(10 mg/kg/day), PTX (50 mg/kg/day) and MLT + PTX therapies on CCl_4 induced elevation of serum AST, ALT and LDH enzyme activities in mice.



[a]Compared to group 1, [b]compared togroup 2, [c]compared to group 3, [d]compared to group 4, 'p< 0.05.

Şekil 2. Effect of MLT (10 mg/kg/day), PTX (50 mg/kg/day) and MLT + PTX administration on serum lipid levels in mice CCl_4 induced liver toxicity.

reported that these opposite results were observed in Siberian and Syrian hamsters, in which MLT decreases or increases body fat mass, respectively. Furthermore, a MLT agonist and antagonist stimulate or reduce seasonal obesity in the garden dormouse.[21] The exact mechanism of action has not been understood fully. Both the direct effect[22] and indirect effect of MLT via the sympathetic nervous system[23] on brown adipocytes have been demonstrated. Effect of PTX on body weight may be associated with various mechanisms such as inhibition of TNF production by PTX. Thus, it has been reported that PTX inhibit TNF-α production[24] and also, TNF-α is elevated in obesity.[25] However, the present result is not definitive since these factors were not investigated in this study.

It is well known that CCl_4 inhibit the secretion of lipoproteins in the liver and alter the metabolism of fatty acids and resulted in fatty livers.[26] Plasma TG, the major lipid component of dietary fat circulating after a meal, also appears to be influenced by both the circadian clock and sleep time with higher levels during biological night (defined as the time between the onset and offset of MLT secretion) despite identical hourly nutrient intake.[27] There have been various studies of the diurnal variation in circulating lipid levels and the factors, which might influence them.[28-30] Diurnal changes in plasma TG not under constant routine conditions have been shown[29] the magnitude of these changes correlates with fasting TG levels.[30] Previous studies[31-33] reported that MLT causes a reduction in TC and TG levels whereas it increases HDL-C levels. But, reverse effects of MLT on TG and TC levels were found in this study. Recent study is similar to our study. Darul et al[34] reported that MLT causes a significant increase in the levels of TC and TG. Also, Ohta et al[4] reported that CCl_4 causes to increase in liver TG content and decrease in serum TG concentration, and MLT administration at 24 hr after CCl_4 injection did not ameliorate changes in serum TG, and liver TG content. Satapathy et al[35] reported that TG and TC levels did not change in the patients with non-alcoholic steatohepatitis after 6 months of PTX therapy. According to our knowledge, results of this study are the first report that investigation the effect of PTX on lipid levels in CCl_4 induced liver toxicity. PTX and MLT therapies did not indicate the decreasing effect on the TC levels as compared to toxicity group, and also PTX caused to decrease on TG level as compared to MLT therapy in the present study. However, both MLT and PTX administrations did not reverse to increasing TG levels caused by CCl_4. Effect of PTX might be associated with inhibition of phosphodiesterase and increase on cAMP and cGMP levels. As known, PTX is a methylxanthine derivative and a phosphodiesterase inhibitor.[9] The adenylate cyclase activation results in increasing cAMP-dependent protein kinase (PKA) and hormone-sensitive lipase (HSL) activities. As a result, TG in the fatty tissue is hydrolysed.[36] In the pre-

sent study, administration of PTX and MLT alone and in combination before onset of liver toxicity did not reverse the CCl_4 effects on serum TG levels. Possible causes of these results might be arise from various reasons which one of them is short time period of the study. The present study had a seven-day period, which may be insufficient to occur these changes. In addition, these treatment doses of PTX and MLT may be insufficient to prevent the change of lipid levels. Thus, this study might encourage with further studies that should be prolonged longer period and administrated by different dose of MLT and PTX.

In conclusion, MLT therapy caused to increase on serum TG levels in CCl_4 induced liver toxicity. Contrary, PTX therapy decreased serum TG level as compared to MLT therapy. But, administration of PTX and MLT alone and in combination before onset of liver toxicity did not reverse the CCl_4 effects on serum TG levels. Further studies are necessary to explain the preventive effects of MLT and PTX on serum lipid levels in liver toxicity induced by CCl_4.

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