Effects of Combination of p-Dimethylaminoazobenzene and Dioxin on Serum Lipid Profile

p-Dimetilaminoazobenzen ve Dioksin Kombinasyonunun Serum Lipid Profili Üzerine Etkileri

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ABSTRACT Objective: The liver cancer initiator p-dimethylaminoazobenzene and the potent liver promoter Dioxin are the environmental pollutants that people may be exposed to those in their daily lives. Butyrylcholinesterase is a natural detoxificant that hydrolyses some xenobiotics. The relation between butyrylcholinesterase activity and lipoprotein metabolism is well documented. In this study, we aimed to determine the effects of two chemicals that had potential of liver cancer by combined administration on butyrylchonlinesterase activity and serum lipid profile. **Material and Methods:** p-dimethylaminoazobenzene was administered with diet as 0.06% ratio for 15 weeks and dioxin was administered weekly as 70 ng/100 g body weight for 13 weeks. At the end of the study serum LDL Cholesterol, HDL Cholesterol, Triglyceride, and Total Cholesterol levels and Butyrylcholinesterase, Lecithin: Cholesterol Acyltransferase activities were measured. **Results:** Butyrylcholinesterase activity was increased ($p< 0.01$) while LDL Cholesterol ($p< 0.001$), HDL Cholesterol ($p< 0.01$) and Total Cholesterol ($p< 0.01$) levels were decreased significantly in p-dimethylaminoazobenzene and dioxin treated rats. There was no change in Lecithin: Cholesterol Acyltransferase activity. **Conclusion:** Carcinogens with lipophilic properties increases Butyrylcholinesterase activity when administered with p-dimethylaminoazobenzene and dioxin, and interacts with lipoproteins and causes lipid protein metabolism impairments.

Key Words: Tetrachlorodibenzodioxin; butyrylcholinesterase; lipids; dioxins

ÖZET Amaç: Karaciğer kanserinde inisiyatör etkili p-dimetilaminoazobenzen ile potent bir tümör promotörü olan dioksin insanların günlük yaşamlarında kolaylıkla maruz kalabildikleri çevresel kirleticilerdir. Bütirilkolinesteraz, bazı ksenobiyotikleri hidrolize edebilen doğal bir detoksifikanttır ve bütirilkolinesteraz aktivitesi ile lipoprotein metabolizması arasında ilişki olduğu bilinmektedir. Bu çalışmada karaciğer kanseri oluşturma potansiyeline sahip bu iki kimyasalın birlikte verilmesinin bütirilkolinesteraz aktivitesi ve serum lipid profiline etkilerinin değerlendirilmesi amaçlandı. **Gereç ve Yöntemler:** Sıçanlara p-dimetilaminoazobenzen 15 hafta boyunca yemleriyle beraber %0.06 oranında ve dioksin 13 hafta boyunca haftada bir 70 ng/100 g vücut ağ. oranında verildi. Çalışma sonunda serum LDL Kolesterol, HDL Kolesterol, Trigliserid, Total Kolesterol seviyeleri ve Bütirilkolinesteraz ile Lesitin: Kolesterol Açiltransferaz aktiviteleri ölçüldü. **Bulgular:** p-dimetilaminoazobenzen ve dioksin uygulanan sıçanlarda Bütirilkolinesteraz aktivitesi anlamlı derecede artarken ($p< 0.01$), LDL Kolesterol ($p< 0.001$), HDL Kolesterol ($p< 0.01$) ve Total Kolesterol ($p< 0.01$) anlamlı derecede azalmıştı. Lesitin: Kolesterol Açiltransferaz aktivitesi ise değişmedi. **Sonuç:** Lipofilik özellikteki karsinojenler, p-dimetilaminoazobenzen ve dioksin birlikte verildiğinde Bütirilkolinesteraz aktivitesini arttırırken lipoproteinlerle etkileşir, lipid ve kolesterol metabolizmasında bozukluklara neden olur.

Anahtar Kelimeler: Tetraklorodibenzodioksin; bütirilkolinesteraz; lipidler; dioksinler

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Azocompounds are extensively used as dyes in different industries including cosmetics, food, and textile. Some azo compounds give rise to carcinogenicity by highly reactive metabolic intermediates which interact covalently with DNA and cause mutations. p-dimethylaminoazobenzene (p-DAB) is the basic structure of these azo-dyes. It has been used as a dye in food.[1] It was concluded as a Group-2B carcinogen by the IARC (International Agency for Research on Cancer).[2] Because of its carcinogenic activity use of p-DAB is prohibited in rodents.[1] p-DAB acts as an initiator of liver cancer when used chronically and is known to cause hazards to humans and animals.[3]

Dioxins are unwanted by-products of many industrial processes consist of industrial air emissions, waste incineration and fuel combustion.[4] It also occurs naturally in volcanic eruptions and forest fires.[5] 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD, Dioxin) is considered as one of the most potent member of dioxins. Hepatotoxicity, carcinogenicity, teratogenicity, interference with lipid metabolism, chloracne, endocrine disruption, wasting syndrome, developmental and reproductive toxicity are the main adverse effects of TCDD.[4] A common feature of TCDD is its tumor-promoting potency in rat liver, when the animals have been treated previously with a genotoxic (initiating) carcinogen.[6] The most potent tumor promoter in rodent liver is TCDD.[7] Exposure to TCCD in humans is largely by diet and dioxins are accumulates in dietary chain due to their lipophilicity, stability and resistance to biodegradation.[8]

After an oral intake TCDD is transported to the plasma by chylomicrons via lymphatics. TCDD is primarily found in adipose tissue and liver.[9] It has a high affinity of binding to lipoproteins and lipids.[10] In vitro human blood studies showed that TCDD is found in lipoprotein fraction (80%), proteins (15% primarily in serum albumin) and cellular components (5%).[11] According to Marinovich et al. maximal binding capacity for TCDD was exerted by VLDL, followed by LDL, and HDL.[12] Arehart et al. showed that at low molar ratios of TCDD/lipoproteins (3:1), both the structure and biological activity of apo CII (Apolipoprotein CII), LDL, and VLDL are affected. They also concluded that the amount of this alteration may cause cellular alteration.[13]

Polyakov et al. concluded that lipoproteins transport lipophilic carcinogens such as TCDD, 3-methylcholanthrene, and p-dimethylaminoazobenzene.[14] P-DAB is transported predominantly by LDL. Binding process to lipoproteins and transportation is aligned by the rule from high to low density such as LDL, HDL, and VLDL.[15]

Butyrylcholinesterase (BuChE, EC 3.1.1.8) is also known as "pseudo" cholinesterase. It is synthesized in liver and primarily found in serum.[16] BuChE acts on hydrophilic and hydrophobic Colin esters[17,18] and hydrolyses some xenobiotics.[19] BuChE is a biologic detoxificant for drugs, organophosphates, and carbamate insecticide.[20] Previous studies demonstrated correlation of serum BuChE activity with obesity, coronary artery disease, and triglyceride (TG), VLDL-C, LDL-C and apolipoprotein B with type II diabetes mellitus and hepatic lipid content.[21,22] Increase of BuChE activity in certain metabolic disorders is known for a long time. High BuChE activities are typical for patients with hypercholesterolemia, hypertension, obesity, and Type I or Type II diabetes. Bradamante et al. concluded that there is a relationship between BuChE activity, lipoprotein metabolism, and serum phospholipids levels. However, the mechanism of this interaction has not been demonstrated yet.[23] In the light of this data, this study was designed to evaluate the effects of p-DAB and dioxin combinations on BuChE activity and lipid profiles.

MATERIAL AND METHODS

The experiments described in this article were performed in adherence to National Institutes of Health Guidelines on the use of animals in experimental studies. The experimental protocol was accepted by the Ethical Committee of Eskisehir Osmangazi University. The study was performed at Eskisehir Osmangazi University, Faculty of Medicine, Department of Biochemistry. Sixteen Spraque Dawley male rats, 16 weeks of age were used. The rats were housed in 22-24^{0}C room temperature with a 12-hours period of light-dark cycle.

p-DAB (0.06%) was added to diet. Dioxin was resolved in corn oil (0.25 ml/100 g body weight) and administered (70 ng/100 g body weight once a week) by gavage. The animals were divided into two groups; group 1 (control, n= 8) and group 2 (study, n= 8). Group 1 was fed by the standard rat chow, corn oil by gavage, and tap water. Group 2 took tap water and p-DAB (Sigma-6760) with diet for 15 weeks; Dioxin (TCDD, Accustandard-D-404N) was administered by gavage for 13 weeks after the initiation of p-DAB in the second week. Two rats died in group 2 during the study. At the end of the study intracardiac blood samples were withdrawn under ether anesthesia and the rats were sacrificed by cervical dislocation. Serum TG, LDL-C, HDL-C, and Total cholesterol (TC) levels were measured by Roche autoanalyser. BuChE activity was measured by spectrophotometric method of Ellman and coworkers.[24] Lecithin cholesterol acyltransferase (LCAT) activity was measured by spectrophotometric method of Nagasaki and Akanuma.[25]

The data was analyzed by SPSS 15.0 packed program. Student t-test and Mann Whitney U tests were used for normal and abnormal distributed data, respectively. Data was expressed as the mean ± SD. $p< 0.05$ was concluded as statistically significant.

RESULTS

Serum LDL-C, HDL-C and TC levels decreased in our study. TC ($p< 0.01^{**}$), LDL-C ($p< 0.001^{***}$) and HDL-C ($p< 0.01^{**}$) levels of the group 2 was statistically lower than group 1 (Table 1 and Table 2). It was observed weight loss at day 105th of group 2 ($p< 0.05^{*}$). Body weights alterations between the first and 105th days were shown in Table 3.

TG levels were higher in the group 2 than the group 1, but the difference was statistically not significant. There was no change in LCAT activity in p-DAB and dioxin treated rats, and there was no correlation between LCAT activity and lipid parameters. Serum BuChE activity was also significantly increased in p-DAB and dioxin treated rats ($p< 0.01^{**}$), (Table 2). There was no correlation between BuChE activity and lipid parameters.

TABLE 1: Serum TG, TC, LDL-C, LCAT levels of Group 1 (n: 8) and Group 2 (n: 6).

	Group 1 (Mean ± SD)	Group 2 (Mean ± SD)	t	S.D.	p
TG (mg/dL)	58 ± 16.41	68.16 ± 21.83	0.911	10	p= 0.384
TC (mg/dL)	68.66 ± 7.06	50.83 ± 7.41	4.266	10	p= 0.002
LDL-C (mg/dL)	13.66 ± 1.21	6 ± 2.75	6.237	10	p= 0.001
LCAT (µmol/mL/h)	2.56 ± 1.67	2.42 ± 1.65	0.146	10	p= 0.887

Note: Statistical analysis was by Student t-test in case of normal distribution.

TG: Triglyceride; TC: Total cholestrol; LDL-C: LDL cholesterol; LCAT: Lecithin cholesterol acyltransferase.

TABLE 2: Mean HDL-C, BuChE serum levels and 25th and 75th percentiles and p values.

	Group 1 Mean (25%-75%)	Group 2 Mean (25%-75%)	P
HDL-C (mg/dL)	51.5 (49-59.75)	42.5 (34.25-43.25)	p= 0.002
BuChE (µmol/mL/min)	0.017 (0.01-0.018)	0.025(0.023-0.028)	p= 0.002

Note: Statistical analysis was by Mann-Whitney test in case of nonnormal distribution.

HDL-C: HDL cholesterol; BuChE: Butyrylcholinesterase.

TABLE 3: Body weight alterations between first and 105th days.

	First day bw (g) (Mean ± SD)	105th day bw (g) (Mean ± SD)	t	S.D.	p
Group 1	302.3 ± 16.6	317.3 ± 24.2	0.672	10	p=0.519
Group 2	307.8 ± 11.2	282.0 ± 23.3	2.460	10	p=0.034

Note: Statistical analysis was by Student t-test in case of normal distribution.

bw: Body weight.

DISCUSSION

In this study BuChE activity increased in group 2. Yokoyama et al. showed an increase in BuChE activity in 3'-Methyl-4-dimethylaminoazobenzene induced hepatocellular carcinoma in rats.[26] There is no data about interaction between BuChE activity with p-DAB and dioxin in literature. It was known that BuChE may detoxify some xenobiotics. The increased activity of BuChE in this study may be due to the detoxification of p-DAB and dioxin.[19,20] BuChE interacts with lipid and lipoprotein metabolism.[27] Increased BuChE activity in certain metabolic disorders has been known for a long time. High BuChE activities are typical for patients with hypercholesterolemia, hypertension, obesity, and Type I or Type II diabetes. In such patients, BuChE activity shows a strong positive correlation with serum levels of LDL-C and triglycerides and inverse correlation with serum HDL-C. Similar changes were also observed in animals.[28] However, a correlation was not observed between BuChE activity and serum lipids in this study. Serum TC, LDL-C and HDL-C levels decreased in group 2. Fletcher et al. suggested that TCDD exposure markedly alters cholesterol metabolism and synthesis and transport of bile acids.[29] Some epidemiological studies of workers and community residents have reported that total cholesterol levels significantly increased among persons exposed to TCDD compared with controls. In a study of British workers, one year exposure to TCDD had ceased, total cholesterol levels compared significantly elevated compared with those of unexposed controls. Cholesterol did not elevate in most other studies.[30] It was known that TCDD decreases the synthesis of 3-hydroxy-3-methylglutaryl-CoA reductase (HMGR), which is a regulator in cholesterol biosynthesis.[31] Four week of exposure to 10μg/kg TCDD caused 60% inhibition of hepatic cholesterol synthesis without affecting the fatty acid synthesis either in liver or adipose tissue.[32] The reduction in serum TC levels may be due to the inhibition of hepatic cholesterol synthesis by TCDD,[32] which may be associated with lower serum LDL levels in this study.

Polyakov et al. demonstrated that TCDD, 3-methylcholanthrene and p-DAB are transported by lipoproteins. They concluded that lipophilicity of the carcinogen is important for ligand binding to lipoproteins.[14] According to Arehart et al. TCDD bounds primarily with of LDL and VLDL and disrupts the secondary and tertiary lipoprotein structure and decreases cellular uptake.[13] Hjelmborg et al. showed that TCDD congener Aroclor-PCB cause reduction in VLDL, LDL and HDL levels, and increase in cholesterol and triglyceride levels in pigeons.[33] Chen et al. reported that p-DAB was transported in plasma mainly by LDL and they concluded if LDL is the major transport vehicle for water-insoluble carcinogens in vivo, the ramifications may be profound. Specific receptor sites for LDL exist in a variety of normal cells such as human fibroblasts, lymphocytes, and arterial smooth muscle cells. The interaction of LDL with this specific receptor initiates a series of complex processes involving endocytosis and lysosomal degradation of the internalized LDL, with concomitant activation of acyl-coenzyme A: cholesterol acyltransferase (ACAT) and suppression of HMG-CoA reductase within cultured cells.[15] Low levels of LDL-C and HDL-C in this study are in accordance with Hjelmborg et al. low levels of LDL-C may be either due to dioxin induced inhibition of hepatic cholesterol synthesis or degradation of internalized LDL-C which is the primary transporter of p-DAB and dioxin in plasma. Dioxin decreases Lipoprotein Lipase (LPL) activity.[32] LPL activity regulates HDL-C levels and positively correlates with HDL-C levels.[34] Low levels of HDL-C in group 2 may due to decreased LPL activity by dioxin.

In this study HDL-C levels were decreased. In contrast LCAT activity was not changed. LCAT is a plasma enzyme that esterifies free cholesterol, primarily at the surface of the HDL particle, after the migration of cholesterol ester molecules to the inner core of HDL. Through this action, LCAT plays a key role in the maturation of HDL particles. It is also known that reduction of LCAT activity correlate with reduction of HDL levels.[35]

There was no difference in TG levels between groups in this study. There are few studies which reports elevated triglycerides levels among British trichlorophenol (TCP) workers that are highly ex-

posed to between chloracne and among subjects with higher TCDD levels from the US Ranch Hand Studies 1987 and 1992. Triglyceride levels did not elevate in other studies.[36,37] Even though the epidemiologic human studies have shown that there was an association between dioxin exposure and serum triglycerides levels. Lind et al. showed that serum triglycerides levels did not alter in rats treated with dioxin.[38] Our results are in accordance with Lind et al.

One of the toxic effects of dioxin is wasting syndrome[39] and body weight measurements of group 2 confirmed this data. Because of its high-lipid solubility, dioxin accumulates in adipose tissue,[39] and severely impairs carbohydrate and lipid metabolism in liver and adipose tissue.[40] The biochemical mechanism of body weight loss caused by dioxin exposure might be explained by strong inhibition of lipid synthesis in the adipose tissue, decreased flow of fatty acids into adipose tissue due to marked reduction in lipoprotein lipase activity and increased mobilization of adipose tissue.[32]

These environmental pollutants and lipophilic carcinogens are easily accessible in daily life. They can bind with the lipoprotein fractions in plasma and destruct their cellular uptake. They may cause disturbances in lipid cholesterol metabolisms by changing the activity of some enzymes of lipid cholesterol biosynthesis. They can also change in activity of different enzymes in liver

In conclusion it was observed in this study that p-DAB combinated with dioxin increased BuChE activity, and decreased serum lipoproteins.

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