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### Bazı Kemoterapötik İlaçların İnsan Serum Paraoksonaz-1 (PON1) Üzerindeki İnhibisyon Etkisinin Araştırılması

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**ÖZET:** Kemoterapötik tedavide sıklıkla kullanılan iki ilacın (kladribin ve mitoksantron) insan serum paraoksanaz1 (PON1) enzim aktivitesi üzerindeki etkilerini *in vitro* inceledik. Kemoterapötik kullanılan bu ilaçlar *in vitro* PON1 aktivitesini azalttı. Kladribin ve mitoksantron inhibisyon mekanizması yarışmasızdır. Kladribin ve mitoksantron için IC<sub>50</sub> değerleri sırasıyla 0.077 mM, ve 0.099 mM, olarak hesaplandı ve K<sub>i</sub> sabitleri sırasıyla 0.057 ± 0.016 mM ve 0.067 ± 0.027 mM, olarak hesaplandı. IC<sub>50</sub> ve K<sub>i</sub> değerleri, kladribin'in daha güçlü inhibisyona sahip olduğunu gösterdi. Bulduğumuz sonuçlar kemoterapötik tedavide sıklıkla kullanılan bu ilaçların düşük dozlarda aynı inhibisyon mekanizmaları ile enzim aktivitesini inhibe ettiğini göstermiştir.

**Anahtar Kelimeler:** Paraoksonaz, inhibisyon, kladribin, mitoksantron.

#### Investigation of Inhibition Effect of Some Chemotherapeutic Drugs on Human Serum Paraoxonase-1 (PON1)

**ABSTRACT:** We examined the effects of two different drugs (cladribine and mitoxantrone), which are frequently used in chemotherapeutic treatment, on human serum paraoxanase1 (PON1) enzyme activity *in vitro*. Chemotherapeutic drugs decreased *in vitro* PON1 activity. Cladribine and mitoxantrone inhibition mechanism were not competitive inhibitors. IC<sub>50</sub> values for cladribine and mitoxantrone were calculated as 0.077 mM and 0.099 mM, respectively, and K<sub>i</sub> constants were calculated as 0.057 ± 0.016 mM and 0.067 ± 0.027 mM, respectively. IC<sub>50</sub> and K<sub>i</sub> values showed that cladribine has a stronger inhibition. The results we found showed that these drugs, which are frequently used in chemotherapeutic treatment, inhibit enzyme activity with the same inhibition mechanisms at low doses.

**Keywords:** Paraoxonase, inhibition, cladribine, mitoxantrone.

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## INTRODUCTION

Paraoxonase (PON1) (arylesterase, [EC 3.1.8.1]) is a serum lactonase containing calcium ( $\text{Ca}^{2+}$ ) in its structure.  $\text{Ca}^{2+}$  is necessary for both the enzyme activity and enzyme stability.  $\text{Ca}^{2+}$  shows its effect by directly participating in catalytic reactions and by providing the appropriate three dimensional structure of the enzyme active site (Harel et al., 2004). The enzyme, first discovered by Abraham Mazur in 1946, was purified from human serum in 1961. It is physically linked to high-density lipoprotein (HDL), which is synthesized in the liver and released into the human blood (Draganov et al., 2008). PON1 constitutes a very small part of HDL and shows activity dependent on Apo A1. The enzyme is named paraoxonase because it has a high affinity for paraoxon and the paraoxon substrate was first used to measure its activity. While the paraoxonase enzyme shows broad substrate specificity, its physiological substrate has not yet been determined (Marsillach et al., 2008). In addition, it was found to have arylesterase, organophosphatase, peroxidase and lactonase activities. The human serum paraoxonase enzyme is the esterase responsible for the hydrolysis of the O-P ester bond in paraoxon, which is the metabolic product of parathion and is a pesticide harmful to the organism. Paraoxonase enzyme hydrolyzes the paraoxon formed in metabolism by oxidative modification of parathion. It forms p-nitrophenol and diethyl phosphate compounds, which are relatively less harmful than paraoxon (Aviram et al., 1998). In the structural activity studies conducted in recent years, it has been reported that the natural activity of the PON1 enzyme is lactonase and the enzyme has been defined as  $\text{Ca}^{2+}$  dependent lipophilic lactonase. It has been reported that hydrolysis of oxidized lipids by PON1 results from the lactonase activities of this enzyme (Khersonsky and Tawfik, 2005). In other words, the fact that PON1 enzyme prevents the oxidation of LDL and HDL lipids and provides protection against atherosclerosis by metabolizing lipid peroxides is explained by its lactonase activity. The free cysteine amino acid at residue 284 is very important for the lactonase activity of the PON1 enzyme. Serum PON1 enzyme activity in newborn and premature infants is half of the adult level. The adult level is reached one year after birth. However, in most of the studies, it has been determined that PON1 activity decreases in advanced age. The level and activity of PON1 in serum vary among individuals (Teiber et al., 2003). The antioxidant role of PON1 is related to its peroxidase activity. This role of the enzyme leads to neutralization of fatty acids hydroperoxides, cholesteryl ester hydroperoxides and hydrogen peroxide ( $\text{H}_2\text{O}_2$ ) (Ferretti et al., 2010).

Today, it has been found that the paraoxonase (PON) family consists of three genes. These are the genes encoding PON1, PON2 and PON3. Human PON is encoded by chromosome 7. In mammalian species, PON gene sequences are similar with a rate of 79-95% at the amino acid level and 81-95% at the nucleotide level (Furlong et al., 2016). PON1 is primarily expressed in the liver and is associated with high-density lipoprotein (HDL). Human PON2 is expressed in different tissues such as heart, liver, lung, testis, lung, placenta, stomach, small intestine, spleen, kidney, vascular endothelial cells, vascular smooth muscle cells and macrophages. PON2 is localized in the plasma membrane, endoplasmic reticulum, and inner mitochondrial membrane, which is essential for the correct functioning of the electron transport chain. In addition to the liver, PON3 expression has been detected in the kidney. Previous studies have reported that, similar to PON1, human PON3 is also localized on the HDL surface. The physiological effects of PON1 are very important. The physiological effects of the enzyme have been proven by many studies in the literature. Studies have shown that serum PON1 enzyme is important in protecting LDL phospholipids against oxidation in the first phase of the atherosclerosis process. It has been determined that the PON1 enzyme protects HDL as well as LDL from oxidation, increases cholesterol output from macrophages, and thus slows foam cell formation and the development of

atherosclerosis. It was observed that the development of atherosclerosis was accelerated and oxidative stress was increased in mice lacking PON1 enzyme. It was observed that oxidative stress decreased and the number of lesions decreased in mice into which a PON1 enzyme was injected (Rozenberg et al., 2005). In a study, it was observed that HDL decreased lipid peroxide accumulation on LDL by an enzymatic mechanism when kept under oxidizing conditions. Another study showed that the paraoxonase enzyme is one of the factors related to this feature of HDL. In addition, the PON1 enzyme limits the accumulation of oxidized LDL and HDL particles, prevents the conversion of LDL into proatherogenic particles, and reverses the biological effects of oxidized LDL particles; thus, it has been observed that it prevents the formation and progression of atherosclerosis lesions (Jaouad et al., 2003). In another study, oxidation of LDL by reactive oxygen species (ROS) or cellular enzymes is considered an atherogenic modification involved in the initial stage of atherogenesis. PON1-deficient mice showed a higher susceptibility to lipoprotein oxidation and inflammation. Mice overexpressing PON1 are more resistant to inflammation and atherosclerosis. A low PON1 activity in serum exposes subjects to a higher oxidative stress (Deakin et al., 2011). PON1 activity is significantly lower in the serum of patients affected by different types of cancer, such as lung cancer, gastrointestinal cancer, breast and gynecological cancer, prostate, bladder cancer, central nervous system tumors, non-hodgkin lymphoma and acute lymphoblastic lymphoma (ALL). Chemotherapeutic drugs used in the treatment of cancer types may further increase this risk. Because these drugs affect various enzymes after they are taken into the body. Some enzymes' being affected by drugs may prove to be fatal. One of these enzymes is PON1 enzyme. A decrease in the activity of this enzyme causes an increase in atherosclerosis and oxidative stress, as mentioned above. In this case, it may increase the risk of cardiovascular disease (Barrera, 2012). It is clear from the above statements that PON1 has important effects on living organisms. Therefore, more studies on the PON-drug interaction are needed. Enzyme-drug interactions have been done in previous studies. In vitro and in vivo inhibitory effects of ibuprofen, meloxicam, and methotrexate on PON1 activity were determined. They inhibited the enzyme at low concentrations ( Dilek and Polat, 2016).

Cladribine (2-chloro-2'-deoxyadenosine) is an immunosuppressive purine nucleoside analogue primarily used for the treatment of certain lymphoid malignancies and also used in recurrent Langerhans cell histiocytosis. It is used therapeutically for leukemia and multiple sclerosis. Cladribine has also been reported to induce cell death in blood monocytes and, to a lesser extent, B cells and dendritic cells (DC) (Kraus et al., 2014). Mitoxantrone is a symmetric drug consisting of a tricyclic planar chromophore and two main side chains. It is an important antineoplastic drug belonging to the anthracycline group. Mitoxantrone is used in the treatment of different types of cancer, such as myeloid leukemia, breast cancer, lung cancer and prostate cancer. Mitoxantrone is considered a chemotherapeutic drug of the anthracycline family of drugs with potent cytotoxicity and lower side effects against cardiotoxicity. Anthracycline drugs are known to cause cytotoxic effects through interaction with DNA, causing modification of DNA and thus inhibition of replication. Mitoxantrone is an inhibitor of topoisomerase II (Al-Otaibi et al., 2018). The aim of this study is to investigate the in vitro effects of cladribine and mitoxantrone on enzyme activity.

## **MATERIALS AND METHODS**

### **Material**

DEAE-Sephadex A50, Sepharose 4B, 1-naphthylamine, paraoxone, protein reagents and chemicals used for electrophoresis were obtained from Sigma Chemical Co. All other chemicals are

sourced from Sigma-Aldrich or Merck. Cladribine and mitoxantrone were obtained from Bursa Uludağ University Faculty of Medicine Oncology Department.

### Paraoxonase activity measurement

Human serum samples were obtained from Erzincan Mengücekgazi Research Hospital. PON1 activity was determined with paraoxone (diethyl p-nitrophenyl phosphate) (1 mM) in 50 mM glycine / NaOH (pH 10.5) containing 1 mM CaCl<sub>2</sub> at 25 °C. PON1 activity measurement was based on the estimation of p-nitrophenol at 412 nm. The molar extinction coefficient of p-nitrophenol ( $\epsilon = 18.290 \text{ M}^{-1} \text{ cm}^{-1}$  at pH 10.5) was used to calculate PON1 activity. An enzyme unit was defined as the amount of enzyme that catalyzes 1  $\mu\text{mol}$  of substrate hydrolysis at 25 °C. Activity measurement was performed using a spectrophotometer (CHEBIOS UV-VIS).

### *In vitro* studies for chemotherapeutic drugs

We examined the inhibitory effects of cladribine and mitoxantrone. Drugs were tested in triplicate for each concentration used. PON1 activities were measured in the presence of different drug concentrations. Control activity was assumed to be 100% in the absence of an inhibitor. For cladribine and mitoxantrone, % Activity-[Concentration] plots were plotted and IC<sub>50</sub> and K<sub>i</sub> values were calculated from the equation of the curve.

## RESULTS AND DISCUSSION

Paraoxonase (PON1) is a calcium-dependent mammalian hydrolase that hydrolyzes esters such as lactone. It is a glycoprotein with a molecular weight of 43-45 kDa. It is synthesized in the liver. PON1 enzyme has anti-atherogenic and antioxidant effects in living metabolism. As the enzyme is associated with HDL, it hydrolyzes lipid peroxides in oxidized lipoproteins. The anti-atherogenic property of PON1 determines the protection of HDL, LDL and macrophages against oxidative stress. This property is inversely related to oxidative stress in macrophages and serum (Golmanesh et al., 2008). Oxidative stress can be defined as a deterioration in the prooxidant-antioxidant balance in favor of the former and leads to potential tissue and cellular damage (Gulcin, 2012). When oxidative stress occurs, excessive amounts of free oxygen radicals are produced (Adam-Vizi and Chinopoulos 2006). They have a very important role in carcinogenesis and show high mutagenic activity. There are antioxidant defense mechanisms such as PON, glutathione peroxidases, catalases and superoxide dismutases to protect mammalian cells from reactive oxygen species. The human body works to maintain its biological functions and balance its antioxidant-oxidant systems (Hofseth et al., 2003). Numerous studies have revealed that PON1 makes a significant contribution to the antioxidant capacity of HDL. With this antioxidant feature, PON1 prevents the oxidation of both HDL and LDL (Cipollone et al., 2007).

It is well known that enzymes are very important biocatalysts in metabolism. Therefore, all substances taken into the body can interact with enzymes. PON1 is important for its pharmacokinetic role and is worthy of future research. Recently, researchers reported a number of studies on different properties of PON1. Few studies have been conducted on the relationship between certain chemicals or drugs and PON1 activity, for example the effect of chemotherapeutic agents on PON1 enzyme activity. These drugs showed strong inhibition effect on PON1 enzyme. The effect of chemotherapeutic drugs on PON1 has not been extensively studied. For example, a decreased PON1 activity was observed *in vitro* during incubations with chemotherapeutic agents (cetuximab, paclitaxel, etoposide, docetaxel and ifosfamide) (Alim and Beydemir 2016). Oxidative stress and inflammation are considered important factors that play a role in the development of cancer and in determining the prognosis of chemotherapy. A decrease in PON1 activity in cancer patients resulted in an increase in oxidative stress markers. If any

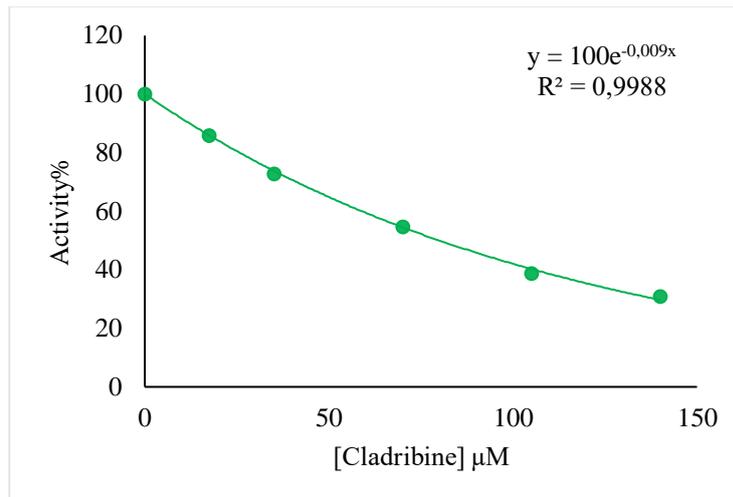
drug also causes a decrease in PON1 enzyme activity, many vascular diseases, including atherosclerosis, may occur due to increased oxidative stress (Ferretti et al., 2015). Statins generally appear beneficial for PON1. Pravastatin, simvastatin and atorvastatin have a positive effect on PON1 activity. (Malin et al., 2001; Kumar, 2010; Nagila et al., 2009). It was tested that aspirin may have beneficial effects on PON1 activity. Aspirin use significantly increased PON1 activity in patients with coronary artery disease (Bhattacharyya et al., 2008). Valsartan and barnidipine were found to have no effect on PON1 activity. (Saisho et al., 2006; Spirou et al., 2006). In another study, gentamicin sulfate and cefazolin sodium decreased PON1 activity. (Sinan et al., 2006). Işgör and Beydemir studied the effects of some cardiovascular drugs (digoxin, metoprolol tartrate, verapamil, diltiazem, amiodarone, dobutamine, and methylprednisolone) on human serum PON1 enzyme activity. The IC<sub>50</sub> values for these drugs were determined as 0.012 M, 0.621 M, 0.672 M, 1.462 M, 3.255 M, 4.495 M and 47.803 M, respectively (İşgör and Beydemir 2010). A similar study was carried out by Türkeş et al. They conducted some experiments on the *in vitro* effects of certain calcium channel blockers on PON1 purified from human serum. The IC<sub>50</sub> values for these drugs were determined as 0.121 mM, 0.130, 0.255 mM and 0.304 mM, respectively (Türkeş et al., 2014). In the study conducted by our study group, the *in vitro* effects of some anti-cancer drugs (1) palonosetron hydrochloride, (2) bevacizumab and (3) cyclophosphamide on PON1 were investigated. Compared with other anti-cancer drugs, palonosetron hydrochloride was found to inhibit enzyme activity significantly. The inhibition order of drugs was determined as 1 > 2 > 3 (Türkeş et al., 2016).

In this study, inhibition effects of cladribine and mitoxantrone, which are chemotherapeutic drugs, on paraoxonase activity were studied. IC<sub>50</sub> values for cladribine and mitoxantrone were determined as 0.077 mM and 0.099 mM with the aid of %Activity-[I] graph (Table 1 and Figure 1-2). In our study, Lineweaver-Burk graphs were used to determine the K<sub>i</sub> constants for cladribine and mitoxantrone, which have inhibitory effects on human serum PON1 enzyme. K<sub>i</sub> constants were determined as 0.057 ± 0.016 mM and 0.067 ± 0.027 mM, respectively (Table 1 and Figure 3-4). For drugs, the type of inhibition is competitive.

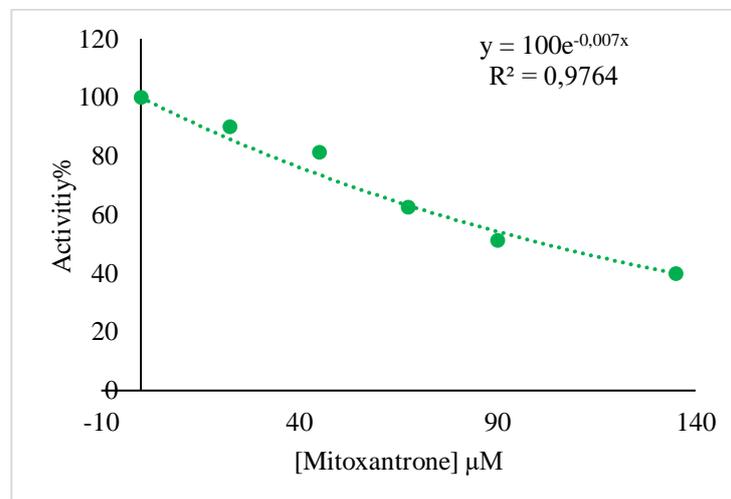
As a result of inhibition studies, it was observed that cladribine and mitoxantrone strongly inhibited the PON1 enzyme.

**Table 1.** IC<sub>50</sub> and K<sub>i</sub> values

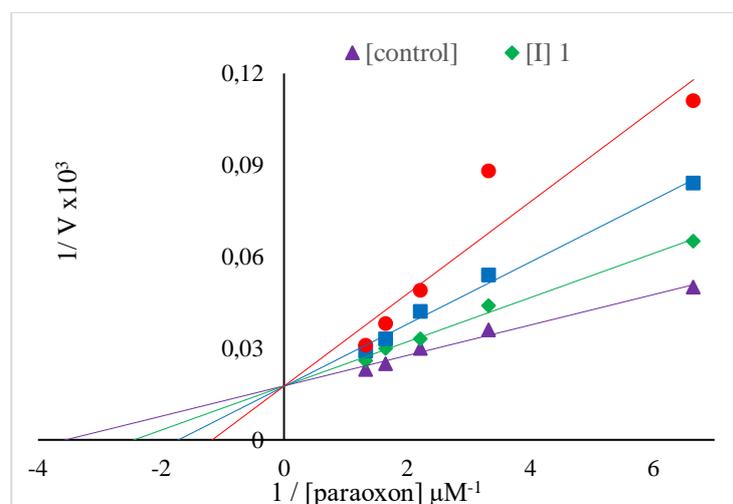
Inhibitor	IC <sub>50</sub> (mM)	K <sub>i</sub> (mM)	Type of inhibition
Cladribine	0.077	0.057 ± 0.016	Competitive
Mitoxantrone	0.099	0.067 ± 0.027	Competitive



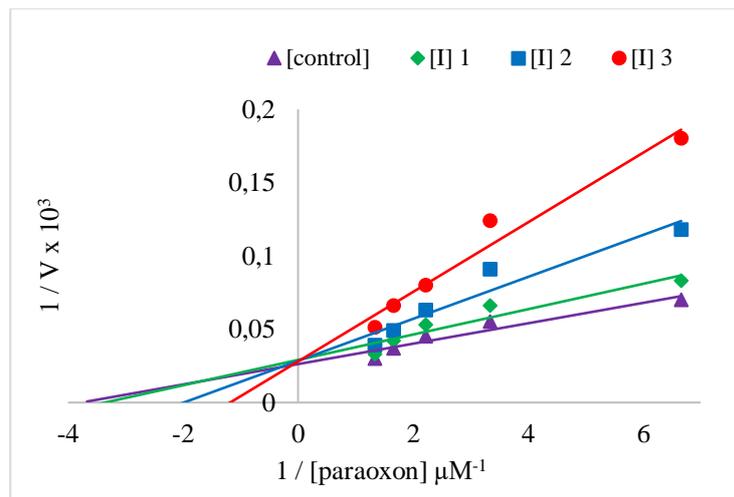
**Figure 1.** % Activity-[Concentration] graph showing the inhibitory effect of cladribine on PON1 enzyme activity and used to determine the  $\text{IC}_{50}$  value



**Figure 2.** % Activity-[Concentration] graph showing the inhibitory effect of mitoxantrone on PON1 enzyme activity and used to determine the  $\text{IC}_{50}$  value



**Figure 3.** Lineweaver-Burk graph showing the effect of cladribine on human serum PON1 enzyme activity and used to determine the  $K_i$  constant



**Figure 4.** Lineweaver-Burk plot showing the effect of mitoxantrone on human serum PON1 enzyme activity and used to determine the  $K_i$  constant

## CONCLUSION

In conclusion, we investigated the *in vitro* effects of cladribine and mitoxantrone on PON1. We did not encounter any literature on the relationship between PON1 and cladribine and mitoxantrone. However, it is known that the expression and activity of the paraoxonase enzyme is critical for cancer diseases. Many studies have shown a decrease in PON1 activities in different cancer patients. PON1 is a multifunctional enzyme involved in the regulation of antioxidant defense and cell behavior. In addition, PON1 activity provides protection against cardiovascular diseases. Cladribine and mitoxantrone are used as chemotherapeutic drugs in the treatment of cancer. When applied in cancer therapy, they may cause some metabolic disorders, especially in patients with atherosclerotic lesions. However, our results should be confirmed by some *in vivo* studies.

## Conflict of Interest

The article authors declare that there is no conflict of interest between them.

## Author's Contributions

The authors declare that they have contributed equally to the article.

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