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The *In vivo* Effect of Anesthetic Drugs on Some Enzyme Activity and Biological Parametres

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ABSTRACT
Some studies have shown that anesthetic drugs cause various changes in the antioxidant system. The aim of our study has investigated the effects of propofol, thiopental, propofol+midazolam, and thiopental+midazolam anesthesia on oxidative stress and antioxidant enzyme activity in serum of surgical patients anesthetized with anesthetic drugs. Patients were divided into four equal groups with a computer-assisted randomization list. The first group for induction was propofol 2 mg kg^{-1}, the second group 4 mg kg^{-1} thiopental sodium, the third group 1 mg kg^{-1} propofol and 0.1 mg kg^{-1} midazolam, the fourth group 2 mg kg^{-1} thiopental and 0.1 mg kg^{-1} midazolam in combination. There are 60 patients (20-40 years old, male) in total, 15 in each group. In this study, combined anesthetic drugs (thiopental-midazolam and propofol-midazolam) caused an increase in TSH and GSH levels. Propofol, thiopental, propofol-midazolam, and thiopental-midazolam decreased PON1 and GST enzyme activity. The results show different effects on oxidative stress and antioxidant system according to the use of propofol, thiopental, propofol-midazolam, and thiopental-midazolam drugs in groups. These results suggest that this study provides information about the change of antioxidant systems with the use of this anesthetic drugs. Therefore, these drugs should be used with caution in order to reduce the side effects that may occur in patients.
Keywords : *Oxidative Stress, Anesthetic Drugs, Inhibition, Antioxidant Enzyme*

Anestezik İlaçların Bazı Enzim Aktivitesi ve Biyolojik Parametreler Üzerindeki *İn vivo* Etkisi

ÖZET
Bazı çalışmalar anestezik ilaçların antioksidan sistemde çeşitli değişikliklere neden olduğunu göstermiştir. Çalışmamızın amacı, anestezik ilaçlarla anestezi uygulanan cerrahi hastaların serumundaki propofol, tiyopental, propofol + midazolam ve tiyopental + midazolam anestezisinin oksidatif stres ve antioksidan enzim aktivitesi üzerine etkilerini araştırmaktır. Hastalar bilgisayar destekli randomizasyon listesi ile dört eşit gruba ayrıldı. İndüksiyon için ilk grup propofol 2 mg kg^{-1}, ikinci grup 4 mg kg^{-1} tiyopental sodyum, üçüncü grup 1 mg kg^{-1} propofol ve 0.1 mg kg^{-1} midazolam, dördüncü grup 2 mg kg^{-1} tiyopental ve 0.1 mg kg^{-1} midazolam kombinasyonu oluşturuldu. Her grupta toplam 15 hasta olmak üzere toplam 60 hasta (20-40 yaş, erkek) vardır. Bu çalışmada kombine anestezik ilaçlar (tiyopental-midazolam ve propofol-midazolam) TSH ve GSH düzeylerinde artışa neden olmuştur. Propofol, tiyopental, propofol-midazolam ve tiyopental-midazolam PON1 ve GST enzim aktivitesini azaltmıştır. Sonuçlar, gruplarda propofol, tiyopental, propofol-midazolam ve tiopental-midazolam ilaçlarının kullanımına göre oksidatif stres ve antioksidan sistem üzerinde farklı etkiler göstermektedir. Bu sonuçlar, anestezik ilaçların kullanımı ile antioksidan sistemlerin değişimi hakkında bilgi sağladığını göstermektedir. Bu nedenle, bu ilaçlar hastalarda ortaya çıkabilecek yan etkileri azaltmak için dikkatle kullanılmalıdır.
Anahtar Kelimeler: *Oksidatif Stres, Anestezik Ilaçlar, Inhibisyon, Antioksidan Enzim*

INTRODUCTION

Anesthesia has been a significant development in human history. It is considered safe with the development of technology and new drugs. However, anesthesia practices are still causing concern for the results they produce. Some anesthetics are often used without knowing the effects on specific diseases (Santamaria et al., 2010) Anesthesia with inhalation and non-volatile anesthetics affects all organ systems such as heart, lung, and kidney. The change in average redox balance in mammals can be attributed to increased plasma free radical concentrations and / or deterioration of protective mechanisms. Serious problems that can damage the cellular structure in the pathogenesis of human disorders can be observed in these situations (Mantle et al., 200). It is known that oxidative stress accumulation is beneficial in etiology in critical chronic diseases such as cancer, neurodegenerative, and cardiovascular diseases (Hussain et al., 2003; Alım et al., 2019) Studies have shown that anesthetic agents, such as remifentanil and propofol, are antioxidant-specific. Therefore, anesthetics such as propofol and remifentanil has suggested as an antioxidant in protecting the brain components from free radical-induced damage to lipid components of cell membranes (Naldan and Taghizadehghalehjoughi, 2019, Young et al.,, 1997). It has recently been suggested that anesthetic drugs may induce biomolecular exchange in different physiological and pathophysiological cellular functions such as apoptosis, angiogenesis, and proliferation (Mammoto et al., 2006, Kvolik et al., 2005). These studies and findings support the idea that the applications of anesthesia may affect physiological molecular and / or cellular processes with unknown mechanisms. However, how this process affects the development of anesthetic drugs and how it affects diseases is uncertain.

Propofol (2,6-di-isopropylphenol) is a short-acting intravenous anesthetic agent and is widely used as a general anesthetic in humans and veterinary medicine (Lejus et al., 2002, McDougall et al., 2008). Its structure contains a phenolic hydroxyl group and is similar to a natural antioxidant E vitamin (atocopherol) (Vasileiou et al., 2009). Sodium thiopental, more commonly known as thiopental, is an anesthetic agent with a barbiturate derivative. Thiopental is a lipid-soluble anesthetic that is both lipid peroxidation inhibiting and antioxidant (Yagmurdur et al., 2004). The midazolam, which acts on γaminobutyric acid (GABA) receptors by increasing neuronal permeability to chloride ions leading to cell hyperpolarization, is a commonly used benzodiazepine-derived anesthetic agent. It is known that midazolam binds to peripheral receptors on macrophages and inhibits certain aspects of immune function by regulating oxidative metabolic responses *in vitro* (Cruz et al., 2017). An antioxidant is a molecule capable of inhibiting the oxidation of other molecules. Antioxidants have a crucial role in the human body to reduce oxidative processes and harmful effects of reactive oxygen species (ROS) (Gülcin, 2020). Antioxidant enzyme activities and oxidative stress changes under the influence of anesthetic agents. These changes are known as essential factors in determining the variable effects of anesthetic agents (Godin and Garnett, 1994). The aim of this study, which was designed to clarify the complex interactions between anesthetic drugs and biomolecular pathways involved in oxidative stress is to investigate the effects of propofol, thiopental, propofol-midazolam and thiopental-midazolam anesthesia on oxidative stress and antioxidant enzyme activity in serum of surgical patients anesthetized with anesthetic drugs.

MATERIAL and METHODS

Experimental Design and Sample Collection / Preperation

The study that conducted according to provisions of the Helsinki Declaration was approved by Erzurum Regional Training and Research Hospital Clinical Research Ethics Committee (Decision number 2015/04-25). Patients were divided into four equal groups with a computer-assisted randomization list. The first group for induction was propofol 2 mg kg^{-1}, the second group 4 mg kg^{-1} thiopental sodium, the third group 1 mg kg^{-1} propofol and 0.1 mg kg^{-1} midazolam, the fourth group 2 mg kg^{-1} thiopental and 0,1 mg kg^{-1} midazolam in combination. There are 60 patients (20-40 years old, male) in total, 15 in each group. There was no significant difference between the patient and control groups about gender or age ($p > 0.05$). Electrocardiography, automatic monitoring of blood pressure and pulse values were continuously monitored in all patients, recorded at three different times during the case: before anesthesia induction, 5 min after induction but before rocuronium bromide injection, and 60 min after induction. Blood samples were also taken at the same times. All blood was taken under sterile conditions from the 20G broth, which was opened onto the hand as standard and no medication was taken from the place where blood was taken. Aliquots of this serum were kept frozen at -20°C until assayed. The enzyme activities of PON1, and antioxidant defense, using glutathione S-transferase (GST), MDA, GSH, and total thiol levels were measured by spectrophotometric methods. Blood samples to be used for analysis were taken before surgery, after induction of anesthesia and 1 hour after the surgery. Patients were 20-40 years old, male, had elective surgery, had no additional disease, and had general anesthesia. Patients with cardiovascular disease, hyperthyroidism, chronic, rheumatoid arthritis, renal failure, and age-related macular degeneration were excluded from the study. Noninvasive arterial pressure, ECG, and pulse oximetry were monitored during the procedure. In all groups, tracheal intubation 5 minutes after the administration of these drugs rocuronium bromide. Sevoflurane anesthetic gas was given to all patients after intubation. Air / oxygen was administered continuously and additionally when rocuronium bromide was required. All anesthetic procedures were performed by the same experienced anesthesiologist.

Measurement of PON1 activity

hPON1 activity was measured using paraoxon (diethyl p-nitrophenyl phosphate) as substrat (1 mM) in 50 mM glycine/NaOH (pH 10.5) including 1 mM $CaCl_2$. hPON1 assay was based on the measurement of *p*-nitrophenol at 412 nm (Demir and Köksal, 2019; Demir, 2019)

Measurement of GST Activity

GST activity was measured at 25°C using 1-chloro-2,4-dinitrobenzene (CDNB) as a model substrate. The assay system included a phosphate buffer (pH 6.5), GSH (20 mM), and CDNB (25 mM). A spectrophotometer was used to estimate the changes in absorbance at 340 nm for 3 min. One unit of activity is defined as the formation of 1.0 μmol product per minute (Ceylan et al., 2019; Özaslan et al., 2019; Türkan et al., 2019;).

Measurement of Total Thiol Amount

Total thiols were estimated as per the method of Reddy and co-authors (Reddy et al., 2004a, Reddy et al., 2004b). Aliquots of 0.1 mL sample were mixed with 1.5 mL of 0.2M tris buffer, pH 8.2 and 0.1 mL of 0.01M DTNB. The mixture was made up to 10 mL with 7.9

mL of absolute methanol, and it was incubated for 30 min. The mixture was then centrifuged at 3000 rpm for 15 min, and the absorbance of the supernatant was read at 412 nm. Standard graphics were used to calculate total thiols.

Measurement of GSH Amount

GSH was measured according to the modified method of Reddy et al., (Reddy et al., 2004a) Twenty microliters of serum samples treated with 5% TCA were mixed with 660 µL of 67 mM phosphate buffer (pH 8.0) and 330 µL of 1 mM 5,5'-dithiobis-2-nitrobenzoate (DTNB). The samples were incubated in the dark at room temperature for 45 min, and the absorbance was read at 412 nm. The GSH concentration was determined as previously described (Veskoukis et al., 2008). The GSH content was calculated as nanomoles GSH mg/mL using a molar extinction coefficient of 13.6 $x10^3$ M^{-1} cm^{-1}.

Determination of Lipid Peroxidation

The lipid peroxidation was estimated by the measurement of TBARS, as malondialdehyde (MDA, at 532 nm) and by modifications of the method of Jentzsch et al., (Jentzsch et al., 1996). The results are expressed as nmol MDA/mL of serum.

Statistical Analysis

Results were statistically analyzed according to SPSS. Statistical comparison between different groups was performed using one-way ANOVA tests. LSD post hoc pairwise comparison tests were also performed. Statistical significance was defined as $P < 0.05$, $P < 0.01$ and $P < 0.001$.

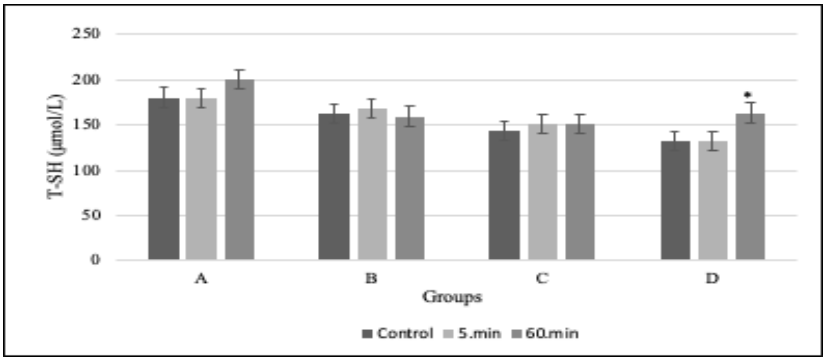
RESULTS and DISCUSSION

Endogenous antioxidant mechanisms function continuously against oxidative damage associated with normal metabolic functions (Gülçin, 2012). Increased ROS levels play a critical role in the reduction of the antioxidant defense system. This situation may be critical in the etiology of many chronic diseases such as cardiac vascular diseases, cancer, and neurodegenerative diseases (Lee et al., 2015; Demir et al., 2019; Demir, 2020). Oxidative stress originates from many causes such as age, metabolic disorders, toxic substances, or drugs (Işık et al., 2015; Durgun et al., 2020). Some previous studies have shown that anesthetic drugs cause various changes in the antioxidant system. In our study investigated the effects of propofol, thiopental, propofol-midazolam and thiopental-midazolam anesthesia on oxidative stress and antioxidant enzyme activity in serum of surgical patients anesthetized with anesthetic drugs. Propofol's structure contains a phenolic hydroxyl group is similar to a natural antioxidant E vitamin (a-tocopherol) which is a natural antioxidant. This antioxidant activity of propofol is partly dependent on this phenolic structure, as demonstrated in both *in vivo* and *in vitro* studies (Ansley et al., 1998). In experimental models, it has been shown that propofol protects the cells against oxidative stress by inhibiting lipid peroxidation and increases the antioxidant capacity of plasma (Manataki et al., 2001, Hans et al., 1997, Stratford and Murphy, 1998). Mathy- Hartert and co-authors have reported that propofol reacts with peroxynitrite leading to the formation of a propofol-derived phenoxyl radical and therefore it is a peroxynitrite scavenger (Mathy-Hartert et al., 2000). Sodium thiopental is a barbiturate derivative, which is both a lipid-soluble anesthetic agent and an antioxidant by inhibiting lipid peroxidation (Yagmurdur et al., 2004). Midazolam is widely used benzodiazepine-derived anesthetic. It increases neuronal permeability to chloride ions and is valid through γ -aminobutyric acid (GABA) receptors as it causes hyperpolarization in the cell. It is known that midazolam, which is bound to

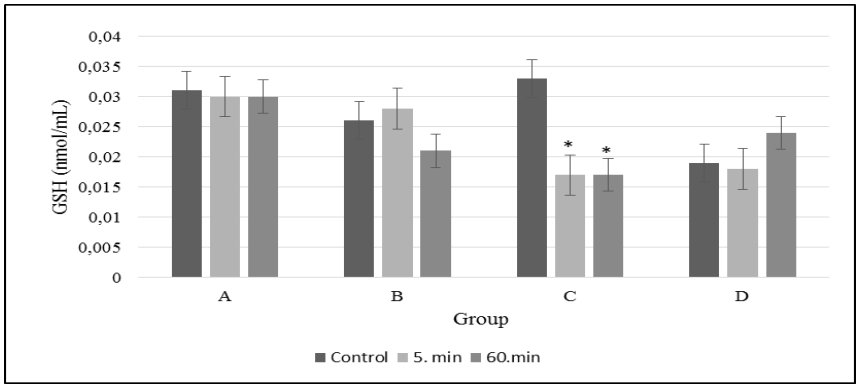
receptors on macrophages and is known to regulate oxidative responses in vitro, affects immune functions in various ways (Cruz et al., 2017).

Anti-oxidants contain various chemical compounds and many enzymes including PON and GST. Also, many chemical substances, including drugs, affect enzyme activity in many ways, that is, many enzymes target drugs. Propofol affects the antioxidant system of glutathione (GSH) at doses used for anesthesia. Aartlar and co-authors demonstrated that glutathione inhibited lipid peroxidation by the action of propofol (Aarts et al., 1995). Propofol not only affects lipid peroxidation, but also increases the activity of the glutathione antioxidant system. The strong effect of propofol in the glutathione enzyme is essential for its antioxidant effect. Because propofol increases the cellular ability to recovery GSH from GSSG, through GSSGrd activity, and from other proteins with sulfhydryl groups, by the GSH activity (De La Cruz et al., 1999). For example, transform the glutathione to oxidized glutathione (GSSG) is an essential antioxidant defense mechanism. It is well known that the cells are protected from ROS by the antioxidant properties of the GSH molecule (Işık et al., 2017; Özaslan 2017). In our study, the effects of anesthetic drugs (A, B, C, D) on total thiol, MDA and GSH in the serum of the anesthetic patients were shown in Schema. 1-3.

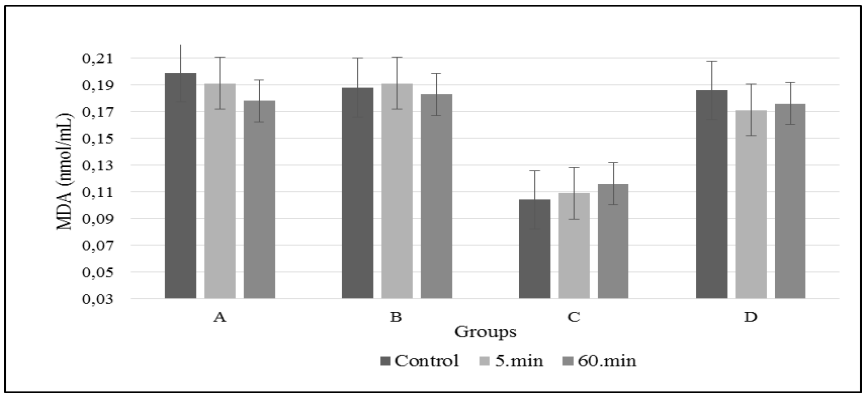
Schema 1. The *in vivo* effects of on total thiol level of A (propofol), B (thiopental), C (propofol-midazolam) and D (thiopental+midazolam)



Schema 2. The *in vivo* effects of on GSH level of A (propofol), B (thiopental), C (propofol-midazolam) and D (thiopental+midazolam)

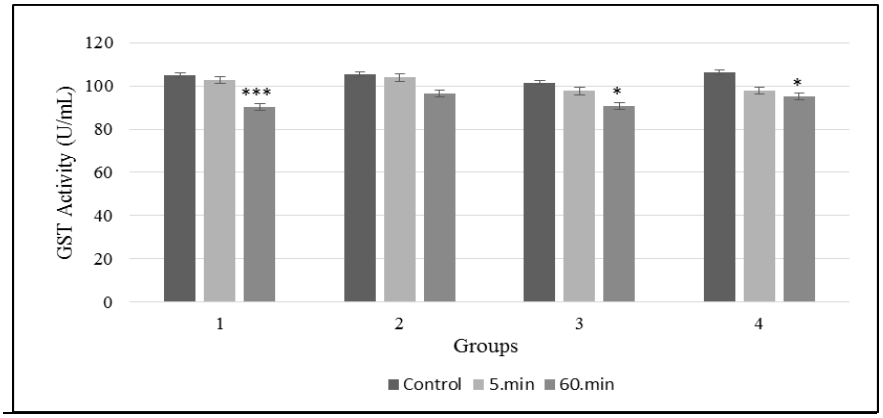


Schema 3. The *in vivo* effects of on MDA level of A (propofol), B (thiopental), C (propofol-midazolam) and D (thiopental+midazolam)



The effect on Total thiol (TSH) amount of D (thiopental-midazolam) was showed significantly higher at the sixtieth min (P <0.05). Moreover, the effect on GSH amount of C (propofol-midazolam) was showed significantly higher at the fifth and sixtieth min (P <0.05). Except it did not find a significant change in others (Schema 1-3). Interestingly, these results indicate that our results are supported by the information given in the above literature. These anesthetic drugs are taken in single and combined form inhibit lipid peroxidation. It is well known that TSH and GSH has an antioxidant role in the oxidative stress defense mechanism (Esen et al., 2015). As a result of our study, the use of this combined drug (thiopental-midazolam and propofol-midazolam) may change TSH and GSH levels due to its antioxidant role. GST plays a vital role in detoxification of endogenously produced free radicals associated with glutathione peroxidase such as reactive oxygen and nitrogen derivatives (Hayes et al., 2005; Özaslan et al., 2018). Antioxidant enzymes and other oxidative defense mechanisms, including GST, play an essential role in the host defense mechanism of inflammation (Hayes et al., 2005, Sohail et al., 2007). In the study of Hans and colleagues, the plasma antioxidant capacity increase in patients anesthetized with propofol (Hans et al., 1997). Allaouchiche et al., worked that desflurane administration decreased GSH-Px activity and high TBARS levels and sevoflurane administration did not change GSH-Px activity and TBARS levels. In this study, the authors stated that desflurane has the lowest blood gas coefficient and may cause oxidative stress (Allaouchiche et al., 2001). Dikmen and colleagues evaluated the antioxidant effects of sevoflurane and desflurane on lipid peroxidation and histological effects. They showed that desflurane GST activity and TBARS levels were lower than sevoflurane but this was not statistically significant (Dikmen et al., 2007). Mantle and co-authors reported that inhibition of the release of superoxide radical from *in vitro* polymorphonuclear leukocytes might be by several compounds such as thiopentone (Mantle et al., 2000). In our study, Inhibition effect on GST of propofol, propofol-midazolam and thiopental-midazolam (1, 3 ve 4) was significantly higher at the sixtieth min (P<0.001, P <0.05) (Schema 4).

Schema 4. The *in vivo* effects of 1 (propofol), 2 (thiopental), 3 (propofol-midazolam) and 4 (thiopental+midazolam) on serum GST activity

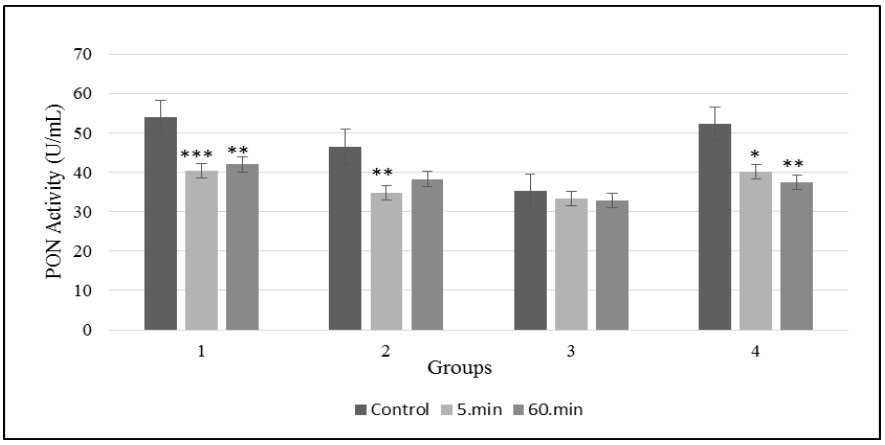


The results indicate that GST activity was reduced after the sixtieth min from the use of these anesthetic drugs. Therefore, the results of this study suggest that widely used anesthetic agents such as propofol, propofol-midazolam and thiopental-midazolam may cause changes in the enzymatic antioxidant defense system (La Du et al., 1999).

PON1 synthesized in the liver is prominent due to its antioxidant effects. Although the role of paraoxonase cannot be fully elucidated, PON1 plays an important protective role against toxic agents-induced damage, such as toxic organophosphates (Demir and Beydemir, 2015; Beydemir and Demir 2017; Kaya et al., 2019). PON1 is one of the endogenous antioxidants found in many lives. There are many antioxidant systems to clean free oxygen radicals synthesized in our body (Mackness et al., 1998; Caglayan et al., 2019a; Caglayan et al., 2019b). Many studies are showing the antioxidant effect of PON1. One of the essential effects of PON1 is the protection of HDL, LDL and macrophages by clearing free oxygen radicals (Aviram et al., 2004; Isık et al., 2020; Demir et al., 2020). Vascular and cardiovascular diseases are prevented by PON1, which prevents LDL oxidation (Ekinci and Beydemir 2009; Taslimi et al., 2019). Thus, the determination of anesthetic drugs, which are PON1 inhibitors and activators, is essential. Recently, several studies have performed on different types of PON1. However, the study of its interaction with drugs and chemicals is scarce. For example, Kumar investigated the effect of simvastatin on PON1 and found that simvastatin increased PON1 activity (Kumar, 2010). In a similar study, Nagilla and co-authors investigated the effect of atorvastatin on PON1. These researchers reported that atorvastatin increased PON1 activity (Nagila et al., 2009). The effects of different hypocholesterolemic drugs such as lovastatin, spironolactone, mevastatin, prulifloxacin and pravastatin on PON1 activity were studied. It was found that the drugs caused PON1 enzyme activity change (Malin et al., 2001, James, 2000, Tomas, 2000). In another study, the *in vitro* effects of gentamicin sulfate and cefazolin sodium on purified human serum PON1 were investigated, and gentamicin sulfate and cefazolin sodium were found to be potent inhibitors of human serum PON1 and the IC_{50} values of these drugs were 0.887 and 0.0084 mM, respectively (Sinan et al., 2006). Alici and co-authors examined the effects of etomidate, propofol and ketamine on human PON1 activity. The drugs were potent inhibitors of hPON1 activity at physiologically relevant doses, with IC_{50} values of etomidate, propofol, and ketamine of 0.021, 0.328, and 3.8 mM, respectively, for rank order of etomidate>propofol>ketamine (Alici et al., 2008). In our study, inhibition effect on PON1 of A (propofol) and D (thiopental-midazolam) was significantly higher at the fifth

and sixtieth min (P<0.001, P <0.01,P <0.05). B (thiopental) showed inhibition at the fifth minute on PON1(P <0.01), but did not show up at the sixtieth minute. Inhibition effect on PON1 of C (propofol-midazolam) was higher at the fifth and sixtieth min, but significant differences were not observed (Schema 5).

Schema 5. The *in vivo* effects of 1 (propofol), 2 (thiopental), 3 (propofol-midazolam) and 4 (thiopental+midazolam) on serum hPON1



Propofol, thiopental and thiopental-midazolam anesthetic drugs inhibit PON1 activity at physiological doses, If PON1 activity was decreased, it could be cause atherosclerotic lesions due to the LDL oxidation. Also, patients with low PON1 activity from chronic renal failure, cardiovascular diseases, diabetes mellitus and age-related macular degeneration could show significant side effects, especially after chronic treatment. Therefore, these studies are essential for clarifying the molecular mechanism of enzyme inhibition.

CONCLUSION

In conclusion, this study provides information about the change of antioxidant systems with the use of anesthetic drugs. Our results show that the use of this combined drug (thiopental-midazolam and propofol-midazolam) may cause an increase in TSH and GSH level with an antioxidant role. In another result of this study. Propofol, thiopental and midazolam anesthetic drugs inhibit PON1 and GST activity. While some use of anesthetic drugs increases the glutathione antioxidant system and decreases some cellular oxidative damage, some of them can cause oxidative damage by inhibiting antioxidant enzymes. Therefore, these drugs should be used with caution in order to reduce the side effects that may occur in patients.

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