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The Effects of Melatonin on Brain Injury in Acute Organophosphate Toxicity

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1. Introduction

Organophosphates (OP) are potent toxic substances used in agriculture as insecticide and pesticides, and in warfare. Over 200,000 cases of accidental toxic exposure to OPs are reported annually (Jyaratnam, 1999).

OPs inhibit acetylcholine esterase (ACE), an enzyme which breaks down acetylcholine in cholinergic synapses in the peripheral nervous system (PNS) and central nervous system (CNS). Thus OP intoxication is characterized by findings related to hyperstimulation of cholinergic synapses in the PNS and CNS. Hyper-stimulation of cholinergic synapses in CNS may result in rapid blackout attacks and inhibition of respiratory center in medulla oblongata (Marrs, 2007). In animal studies of OPs used as chemical warfare agents, status epilepticus occurs rapidly due to severe brain damage, which is demonstrated on both electrophysiologic and histopathologic studies (McDonough et al, 1998). Pharmacological treatment of OP intoxication includes anticholinergic agents like atropine sulfate to block postsynaptic cholinergic receptors, oximes to reactivate inhibited enzymes, and antiepileptics to control seizure activity (Marrs, 2007).

In previous studies, oxidative stress caused by OPs was demonstrated in humans and rats. Lipid peroxidation in rat brain and human erythrocytes caused by OPs was confirmed as well (Abdollahi et al, 2004). Melatonin removes the potent hydroxyl radical secreted from pineal gland. Blood can easily pass the brain barrier and provides oxidative protection in the brain. At the same time, it also removes other reactive molecules such as hydrogen peroxide, singlet oxygen, peroxynitrite, and nitric oxide. Melatonin decreases oxidative stress by increasing the production of antioxidant enzymes like melatonin superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px), the most important protective substance in the brain (Hsu et al, 2002).

The aim of this study was to investigate the effects of melatonin on lipid peroxidation in erythrocytes and brain tissue in the setting of acute OP intoxication in rats and compare its effects with those of routine treatment (pralidoxime and atropine).

2. Materials and methods

2.1 Experimental methods

The study was carried out in the Experimental Medicine and Research Center at Selçuk University after being approved by the Ethical Board of the Experimental Medicine and

Research Center. Twenty (12 male, 8 female, weight range 2500-4000 g) New Zealand rabbits were used. The subjects were divided into three groups: a sham group (n=8), a pralidoxime (PAM) plus atropine group (n=6), and a melatonin plus PAM plus atropine group (n=6). Subjects were anaesthetized with 50 mg/kg IM ketamine and 15 mg/kg IM xylazine HCL. The central ear artery and marginal ear vein were catheterized. Blood was drawn in EDTA tubes to measure baseline plasma ACE, nitric oxide (NO), and plasma and erythrocyte malondialdehyde (MDA).

Orogastric feeding tubes were inserted and 50 mg/kg ($LD_{50}=50$ mg/kg) dichlorvos was administered. One hour later, when signs of toxicity (hypersalivation, bronchospasm, fasciculations, convulsions) appeared, venous blood samples were taken again in order to measure plasma ACE, nitric oxide (NO), and plasma and erythrocyte MDA.

In the sham group, no treatment was given. Venous blood samples were taken at 12 hours after OP administration hour to measure plasma ACE, nitric oxide (NO), and plasma and erythrocyte MDA. In the PAM+atropine group, 0.05 mg/kg IV atropine was given and this dose was administered again as needed. In addition, a 30 mg/kg IV bolus of PAM was given, then 15 mg/kg IV PAM was given every 4 hours. In the melatonin plus PAM-atropine group, 10 mg/kg IV melatonin was administered, as well as PAM and atropine as in the PAM-atropine group. Blood samples were taken from the subjects in PAM-atropine and melatonin-PAM-atropine groups at 12 and 24 hours after intoxication in order to measure plasma ACE, nitric oxide (NO), and plasma and erythrocyte MDA.

At 24 hours post-intoxication, craniotomy was performed and liver samples were taken after laparotomy to evaluate ACE, NO and MDA levels. At the end of the study, subjects were sacrificed by administering a high dose of ketamine.

2.2 Biochemical methods

2.2.1 Measurement of plasma ACE activity

Plasma was separated from erythrocytes by centrifuging for 15 minutes at 3000 rpm. The following were placed into a 10 mL test tube: 3 mL of distilled water, 0.2 mL of plasma, and 3 mL of barbital phosphate (pH 8.1). The pH (pH_1) of the mixture was measured with a glass electrode pH meter. Then, 0.1 ml of 7.5% acetylcholine iodide solution was added to the reaction mixture and incubated for 20 min at 37° C. At the end of incubation period, the pH of the reaction mixture was measured (pH_2). ACE activity was calculated using the following formula:

ACE activity ($\Delta pH/20$ minutes) = $pH_1 - pH_2 - (\Delta pH \text{ of the blank})$

2.2.2 Measurement of ACE activity in brain tissue

To measure brain ACE activity, a brain tissue sample was homogenized (at 25% of the maximum speed) in barbital phosphate (pH 8.1) to weigh 3 ml/100 mg when wet. Homogenization was performed in an ice bath and brain homogenate was preserved in ice before cholinesterase determination. For determining brain ACE activity, 0.2 mL of tissue homogenate was used. ACE activity was calculated using the same formula as shown above.

2.2.3 Measurement of NO in plasma and brain tissue

To measure NO in plasma and brain tissue homogenate, the Nitric Oxide Synthase Assay Kit (Colorimetric) (Merck Chemicals, Darmstadt, Germany) was used.

2.2.4 Measurement of MDA in brain tissue

A brain tissue sample (0.5 g) was taken and preserved at -80° C. Using a cold 150 mM KCL solution, the tissue sample was homogenized to make a 10% homogenate, and was then centrifuged at 10,000 rpm for 10 minutes. The following substances were mixed: 0.1 ml of the homogenate, 0.2 mL of 8.1% sodium dodecyl sulfate (SDS) solution, 1.5 mL of 20% acetic acid solution (sodium hydroxide was added to this mixture for adjust pH>3), and 1.5 ml of 0.8% thiobarbituric acid liquid; this mixture was then stirred with a vortex. The mixture was then boiled in distilled water at 95° C for 60 minutes. Then it was cooled, and the following were added to the mixture: 1 mL of distilled water, 5 mL of n-butanol and pyridine (15:1, v/v) were added, and the mixture was rinsed. The resulting mixture was spun at 4,000 rpm for 10 minutes. A sample was from the upper layer of the mixture was taken, and absorbance at 532 nm was measured spectrophotometrically. MDA concentrations were derived with the following formula:

$$C = \text{Measured absorbance} \times 320.5 \times \text{dilution factor} / \text{microprotein of homogenate} = \text{nmol/mg tissue}$$

2.2.4 Measurement of MDA in erythrocytes

Blood was centrifuged and the plasma was separated. After being washed with normal saline solution once, 1.5 mL was taken from the erythrocyte plug and 1.5 mL of buffered sodium azide was added. 50 mL was taken from this hemolizate and 12.5 mL of Drabkin solution was added and the Hb was measured. 5 mL was taken from this mixture and 5 mL of 35% H₂O₂ was added and this mixture was incubated for 2 hours at 37° C with tubes open. After this was cooled, 3 mL was taken and 2 mL of trichloroacetic acid-arsenide solution was added and the mixture was then centrifuged at 2,500 rpm. 3 mL was taken from this supernatant and 1 mL of thiobarbituric acid was added and then the mixture was boiled for 15 min. After it cooled, absorbance at 532 nm was measured spectrophotometrically and the results were calculated for each gram of hemoglobin.

2.3 Statistical methods

Statistical analyses were performed using SPSS for Windows 13.0 (SPSS, Inc., Chicago, USA). Between group comparisons were made by repeated measurements with variance analysis (ANOVA). For significant values, Bonferroni one-way variance analysis as a post hoc test, and then the Tukey HSD test was applied. Comparisons with a P value of less than 0.05 were regarded as statistically significant. When comparing intra-group repeated measurements, the student t test was used. Means of each group's values were calculated and reported as a table. To compare tissue ACE and tissue MDA values, one-way ANOVA and then Tukey HSD tests were performed.

3. Results

All sham group animals died before 24 hours after intoxication, therefore no blood sample was collected from those subjects at 24 hours.

No significant differences between groups in erythrocyte ACE levels were found. At 12 hours after treatment, the mean erythrocyte ACE level of the melatonin+PAM+atropine group was not significantly different from that of the PAM+atropine group, but it was significantly higher than that of the sham group (p=0.023). The mean erythrocyte ACE level

in the melatonin+PAM+atropine group was significantly higher ($p=0.031$) than that of the PAM+atropine group (Table 1).

Treatment group	1 hour	12 hours	24 hours
Sham	1.75±1.0	1.45±1.1	
Pralidoxime + atropine	1.89±0.8	1.79±1.7	1.85±2.0
Melatonin+pralidoxime+atropine	2.10±1.2	2.31±1.3	2.95±1.8
p value	$p>0.05$	$p<0.01$	$p<0.05$

Table 1. Mean erythrocyte acetylcholine esterase levels (U/L) at various times after intoxication with dichlorvos in the three groups. Levels were compared using the Mann Whitney U test.

NO levels in the three groups were not significantly different from each other at 1 hour and 12 hours post-intoxication ($p>0.05$). The NO levels at 24 hours post-intoxication in the melatonin+PAM+atropine group were not significantly different from that of the PAM+atropine group ($p>0.05$, Table 2).

Treatment group	1 hour	12 hours	24 hours
Sham	5.36±1.89	5.92±3.65	
Pralidoxime + atropine	5.10±1.81	6.21±1.68	7.73±2.67
Melatonin+pralidoxime+atropine	5.41±2.10	5.81±1.89	7.05±2.71
p value	$p>0.05$	$p>0.05$	$p>0.05$

Table 2. Mean erythrocyte nitric oxide levels (mmol/gr Hb) at various times after intoxication with dichlorvos in the three groups. Levels were compared using the Mann Whitney U test.

At one hour post-intoxication, mean erythrocyte MDA levels were similar in all groups. At 12 hours, the mean erythrocyte MDA levels in the melatonin+PAM+atropine group were lower than those of both the sham group and the PAM+atropine group ($p=0.001$, $p=0.012$). At 24 hours, the mean erythrocyte MDA levels in the melatonin+PAM+atropine group were significantly lower than those of the PAM+atropine group ($p=0.002$, Table 3).

Mean brain tissue ACE levels in the melatonin+PAM+atropine group were significantly higher than those of the sham group and PAM+atropine group ($p=0.001$, $p=0.041$, Figure 1).

Mean brain tissue NO levels in the melatonin+PAM+atropine group were not significantly different from those of the sham group and PAM+atropine group ($p=0.28$, $p=0.65$, Figure 2).

The mean brain tissue MDA levels in the melatonin+PAM+atropine group were significantly lower than those of both the sham group and PAM+atropine group ($p=0.001$, $p=0.002$, Figure 3).

Treatment group	1 hour	12 hours	24 hours
Sham	5.40±0.45	9.05±0.66	
Pralidoxime + atropine	5.37±0.67	8.80±0.30	9.48±0.76
Melatonin+pralidoxime + atropine	5.12±0.53	5.93±0.37	6.14±0.42
p value	p>0.05	p<0.05	p<0.05

Table 3. Mean erythrocyte malondialdehyde levels (nmol/mL) at various times after intoxication with dichlorvos in the three groups. Levels were compared using the Mann Whitney U test.

Fig. 1.

Fig. 2.

Fig. 3.

4. Discussion

Reactive oxygen species play a key role in initiating secondary brain damage (Özdemir et al, 2005; Tyurin et al, 2000). The brain is prone to oxidative damage which results from high oxygen administration. High concentrations of metals like iron can catalyze reactive radicals, which leads to intense reactive radical production. Neural membranes are also rich in polyunsaturated fatty acids which also contribute to lipid peroxidation reactions (Reiter et al, 2000). Lipid peroxidation changes cell membrane permeability, increases the rate of protein degradation, and ultimately results in the destruction of cell membranes (Tyurin et al, 2000). Non-radical substances containing alkaline and carbonyl moieties produced during the last phases of lipid peroxidation can be measured by their reaction with thiobarbituric acid. Thiobarbituric acid reactive substances (TBARS), of which MDA is the most significant, reflect lipid peroxide production. Increased erythrocyte TBARS concentrations are correlated with severity of cerebral damage (Kasprzak et al, 2001).

Toxicity after an acute intentional or accidental exposure to OP insecticides is largely a reflection of inhibition of ACE in the peripheral and central nervous systems. However, the toxic effects of OPs are not limited to ACE inhibition. In both acute and chronic OP toxicity, changes in antioxidant enzymes occur, and lipid peroxidation increases in many organs, especially the brain. In acute OP poisonings, a decrease in antioxidants occur, which upsets the critical balance between oxidants and antioxidants – thus accumulation of reactive oxygen species and cell destruction begins. In OP toxicity, oxidative stress is an important patho-physiological mechanism, especially for neurotoxicity and cerebral damage (Lukaszewicz-Hussain, 2008).

Atropine and oximes are the fundamental medicines used in the treatment of OP intoxications. Atropine blocks muscarinic receptors in the peripheral and central nervous systems, crosses the blood-brain barrier, and is widely used in OP poisonings. Pralidoxime is the most commonly used oxime in the management of OP poisonings. It reactivates ACE which has been inhibited by OPs (Eddleston et al, 2008). In OP acute poisoning, PAM's penetration into brain tissue may be enhanced by local inflammation. In sublethal OP

poisoning in rats, the group given oxime and atropine preserved cognitive functions compared to the atropine only group. The helpful effects of PAM on brain damage in OP intoxication may be partially explained by its peripheral effects which resolve any respiratory problems. Hypoxic brain damage is slight due to the peripheral effects of PAM (Shrot et al, 2009).

We found that in rabbit model of OP poisoning, melatonin added to PAM and atropine had more positive effects on erythrocytes and brain tissue than PAM and atropine alone. For example, erythrocyte ACE activity of the melatonin+PAM+atropine group was higher than the PAM+atropine group, a finding which can be attributed to lower lipid peroxidation in the group receiving melatonin. The activity of ACE localized in erythrocyte membranes is a significant indicator of OP poisoning severity (13). In previous studies (chronic and sub-chronic exposure) in rats and humans, acute OP poisoning erythrocyte ACE activity was not significantly different than levels in healthy controls (Tinoco & Halperine, 1998; Ögüt et al, 2011). On the contrary, in a rat study of subchronic OP exposure, erythrocyte ACE activity and TBARS levels were found to be significantly lower in the toxicity group compared to healthy controls (Lukaszewicz-Hussain & Moniuszko-Jakoniuk, 2005). In our acute toxicity study, we found that melatonin added to PAM-atropine was beneficial to erythrocyte and brain tissue, findings similar to those of Lukaszewicz-Hussein.

In an in vitro study by Durak D et al, the effect of C and E vitamins in human erythrocytes exposed to OPs on some anti-oxidant enzymes and MDA levels was measured (Durak et al, 2009). In their study, antioxidant enzyme levels in erythrocytes pre-treated with vitamin C and E were higher, and lipid peroxidation was slightly lower.

In our study, the addition of melatonin to 'routine' treatments for OP poisoning did not make a significant effect on erythrocyte NO levels compared to PAM+atropine. Casares et al. stated that OPs may spoil cell calcium homeostasis and change NO and NOS production, and thus decrease the effect of additional environmental negative factors. In our study, we did not find any result that supported Casares's hypothesis (Casares & Mantione, 2007).

In an in vitro OP toxicity study, levels of antioxidant enzymes like erythrocyte superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GSH-Px) decreased and erythrocyte MDA level increased (Karademir Çatalgöl et al, 2007). Ögüt et al. (Ögüt et al, 2011) reported that MDA levels in erythrocyte samples taken from agriculture workers who were chronically exposed to OP insecticides were significantly higher compared to levels in healthy controls. On the contrary, erythrocyte SOD, CAT and GSH-Px levels were significantly lower than healthy controls. In another in vitro study, in the group in which C and E vitamins were added before OP toxicity occurred, erythrocyte MDA levels were significantly lower compared to the group which was not treated with vitamins C and E.

In our study, erythrocyte MDA levels of the sham group were higher than those of other groups. Erythrocyte MDA levels of the melatonin+PAM+atropine group were lower than those of PAM+atropine group. This result is compatible with the results of the previous studies (Puntel et al, 2009). The intense oxidative tissue damage caused by OPs can be decreased with PAM+atropine. Puntel et al., who studied the antioxidant effects of oximes, reported that lipid peroxidation caused by various oxidizing substances was decreased with oximes. In our study, melatonin added to routine treatment decreased lipid peroxidation compared to routine PAM+atropine treatment. Thus, erythrocytes are better protected from oxidative stress when melatonin is added to the treatment regimen.

In OP poisonings, the brain is one of the most damaged organs. Sub-acute poisonings are characterized by significant brain edema and corresponding clinic symptoms. Even with a

single high dose, heavy axonal degeneration can be seen (Read et al, 2010). Major side effects of OP poisoning are rapid loss of conscious resulting from hyperstimulation in central cholinergic synapses, and inhibition of the respiratory center in the medulla oblongata. In animal models, status epilepticus with profound brain damage occurs after significant OP intoxications. Oximes pass through the blood-brain barrier insubstantially and reactivate ACE enzymes which were previously inactivated by OPs. Although the concentrations of oximes in the brain are low, they are adequate to reactivate ACE enzymes and produce positive clinical responses. However, oximes' positive effects on brain tissue are not only dependent on reactivation of ACE enzymes, because studies to date have not found a significant correlation between ACE enzyme levels reactivated in the brain (Eddleston et al, 2008). On the other hand, studies have found that even a small amount of ACE reactivation can increase the rate of survival (Shrot et al, 2009).

In our study, brain tissue ACE activity of the melatonin+PAM+atropine group was higher than that of PAM+atropine group, which were only slightly higher than that of the sham group. This result suggests that the beneficial effects of melatonin are not only related to PAM's reactivation of inactivated ACE enzyme. Hsu et al. studied the effects of melatonin on antioxidant enzymes and MDA levels in the brain tissue of rats that they exposed to OPs in vivo and in vitro (Hsu et al, 2002). OPs lead to lipid peroxidation and DNA oxidation both in vivo and in vitro mediums. However, in the melatonin-treated groups, GSH-Px activity in the brain was significantly higher than non-treated groups; MDA levels were much lower after melatonin treatment. Our study results are compatible with theirs. Brain tissue MDA levels of the PAM+atropine group were close to those of the sham group. The MDA levels in the animals receiving melatonin were lower than the other two groups. This result indicates that a significant amount of peroxidation lipid develops in the brain after exposure to OPs. This lipid peroxidation and ensuing damage in brain tissue can be significantly decreased with melatonin.

Rats with untreated subchronic OP toxicity develop very high MDA levels in the hippocampus and low SOD levels (Chen et al, 2010). In another study, ACE activity in the hippocampus decreased after subchronic dermal exposure (Mitra et al, 2008). In chronic and subchronic exposures to OPs, the memory and learning functions of the brain are seriously affected due to damage in this area. Giving melatonin before and after acute OP poisoning in rats prevented an increase in brain tissue MDA levels. Brain tissue NO levels in groups treated with melatonin before and after toxicity were significantly higher than those of controls not given OP. In our study, lipid peroxidation in a particular region of the brain, localized ACE activity, NO levels, and oxidative damage were not researched. However, in our acute OP poisoning model, lipid peroxidation in brain tissue and oxidative damage decreased in general, and ACE activity decreased. In our study, melatonin did not show any beneficial effect on brain tissue NO levels. However, lipid peroxidation in brain tissue of the group in which melatonin was added to treatment and ACE levels were positively influenced. Our results suggest that brain damage may be decreased and memory and learning functions can be preserved with the addition of melatonin to routine OP poisoning treatment. Further studies should be performed to determine melatonin's effect in a variety of clinical processes.

Limitations of this study include its low number of subjects; but the ethics board did not allow us to use more subjects. In addition, histopathological examination of brain tissue samples was not performed.

5. Conclusion

Melatonin added to PAM and atropine in the treatment of acute OP poisoning increases ACE activity in brain tissue, and shows a beneficial effect on brain injury by decreasing lipid peroxidation and oxidative stress in brain tissue.

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The present two volume book "Brain Injury" is distinctive in its presentation and includes a wealth of updated information on many aspects in the field of brain injury. The Book is devoted to the pathogenesis of brain injury, concepts in cerebral blood flow and metabolism, investigative approaches and monitoring of brain injured, different protective mechanisms and recovery and management approach to these individuals, functional and endocrine aspects of brain injuries, approaches to rehabilitation of brain injured and preventive aspects of traumatic brain injuries. The collective contribution from experts in brain injury research area would be successfully conveyed to the readers and readers will find this book to be a valuable guide to further develop their understanding about brain injury.

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