Acute effects of different doses of malathion on the rat liver

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Abstract

Aim of the study: Our study was designed to evaluate the acute effects of malathion on rat liver tissues.

Material and methods: The animals were divided into 4 groups of 6 animals/each. Group 1 (control group) received corn oil, while groups 2, 3, and 4 were given malathion dissolved in corn oil at a dose of 100, 200 and 400 mg/kg, respectively. 24 hours after malathion administration, animals were sacrificed and liver tissues were collected. The liver tissues were then analysed biochemically and histopathologically.

Results: Butyrylcholinesterase levels in groups 2, 3 and 4 were significantly lower than that of group 1. Total oxidant status and tumour necrosis factor alpha level were significantly increased in group 4 compared to group 1. Catalase activities of groups 3 and 4 were significantly higher than that of group 1. Arylesterase activity was significantly decreased in groups 3 and 4 compared to group 1. In groups 3 and 4, some vacuoles in hepatocytes were revealed and hydropic degeneration was observed in group 4.

Conclusions: Acute administrations of malathion results in hepatotoxicity in a dose-dependent manner.

Key words: inflammation, oxidative stress, liver, malathion, histopathological examination.

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Introduction

Organophosphates are highly toxic pesticides with a high chemical mortality ratio. According to a World Health Organization (WHO) report, approximately 3 million organophosphate poisoning cases occur per year, either accidentally or intentionally including suicide attempts. Especially in agricultural countries, organophosphates, mostly preferred pesticides due to their low price and high yield, are one of the common causes of hospital admission [1]. Organophosphates inhibit acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) in the body. BChE is synthesized in the liver and released into the blood [2].

Malathion [O,O-dimethyl-S-(1,2-dicarbethoxyethyl) phosphorodithioate], the most common pesticide among the organophosphates, causes toxicity to the liver, kidneys, testicles and brain of both humans and animals. Malathion is rapidly metabolized in the body to its bioactive analogue malaoxon. It is soluble in lipids and is stored in the liver, causing a significant increase in reactive oxygen species (ROS) [3].

Epidemiological, clinical and experimental evidence indicate the hepatoprotective effects of antioxidants. In addition, some antioxidants inhibit the inflammatory process during hepatosteatosis [4].

Paraoxonase-1 (PON1) is an enzyme synthesized by the liver and has the capacity to hydrolyse aromatic
carboxylic acid esters and organophosphates in the plasma. PON1 has two main forms, paraoxonase and arylesterase. Both of them are used in clinical and experimental studies [5]. Paraoxonase is an antioxidant enzyme used in the detoxification of lipid peroxidation. Paraoxonase plays an active role in reducing the toxic effects of organophosphate compounds and nerve gases by hydrolyzing them [6]. Arylesterase catalyzes the hydrolysis of 1-phenyl acetate and it is also reported that arylesterase is a protective enzyme against oxidative stress along with paraoxonase [7].

It is reported that organophosphates cause increased levels of inflammatory cytokines such as tumour necrosis factor α (TNF-α) and interleukin 6 (IL-6), as observed in rat studies [8].

Chronic administration of malathion leads to liver damage, causing enlargement of sinusoids and vacuole formation in hepatocytes, leukocytic infiltrations, dilation and congestion of blood vessels with hemorrhage [9].

We planned to study the effects of acute malathion using various doses in the causation of oxidative stress, inflammation and histopathological changes in rat livers.

**Material and methods**

This study was accepted by Gazi University Board of Local Ethics under code number G.Ü. ET. 14.015. All chemicals used in this study were purchased from SIGMA.

Twenty-four female Wistar albino rats with an average weight of 230 g were used in this study. The animals were randomly assigned to four groups of 6 animals each. Group 1 (control group) was given corn oil; group 2, group 3 and group 4 were given malathion at 100, 200 and 400 mg/kg doses, respectively. These doses of malathion were chosen due to its acute toxic effects at 100 mg/kg, which is known as a toxic dose, the 400 mg/kg plateau level (70% inhibition of cholinesterase) and 200 mg/kg, which is considered as an intermediate value [10]. 24 hours later, the animals were sacrificed under ketamine/xylazine anaesthesia and liver tissues were collected by dissecting the liver diagonally and vertically into 4 pieces. Parts of the liver tissues were suspended in neutral buffered formalin for histopathological analysis. The remaining liver tissues were kept at −80°C then taken out and homogenized in 50 mM Tris-HCl buffer at a 1/10 ratio (500 mg liver tissue + 4500 ml Tris-HCL). Supernatants were centrifuged at 3500 rpm for 1 hour and preserved at −80°C until use. The liver samples were analyzed using standard methods to determine the amount of protein in liver tissue [11], BCHE activity (Roche Diagnostics brand Cobas E411 model AutoAnalyzer), malondialdehyde (MDA) level [12], advanced oxidation protein products (AOPP) levels [13], total oxidant status (TOS) level (Rel Assay Diagnostics Kit, catalogue no: RL0024), superoxide dismutase (SOD) activity [14], catalase activity [15], arylesterase activity [16] and TNF-α level (YH Bio search brand; catalogue no: YHB1098Ra).

For histopathological examinations, liver tissues were cut into 4 μm thickness and stained with hematoxylin and eosin. Histopathologic examination and photographing of the tissue damage were done with an Olympus brand model Cx30 binocular light microscope.

SPSS version 20 was used to evaluate the data. The Kruskal-Wallis test was used to determine whether there was a significance differences among the 4 groups. A p value ≤ 0.05 was accepted as statistically significant and the Mann-Whitney U test with Bonferroni correction was used to determine statistical differences between two groups. Since there were 6 pairwise comparisons for 4 groups, the p value (0.05) was divided by 6 according to Bonferroni correction (0.05/6 = 0.0083). Differences between two groups were considered significant when p ≤ 0.008. Correlation analysis was performed using Spearman’s correlation test.

**Results**

A significant decrease in liver BCHE activities was observed in groups 2, 3 and 4 compared to group 1 (p ≤ 0.008). There were no significant differences in liver SOD activities or MDA levels among the groups. There was a significant increase in liver AOPP levels of groups 3 and 4 compared to group 2 (p ≤ 0.008). Liver TOS levels were significantly raised in group 4 compared to groups 1 and 2 (p ≤ 0.008). Moreover, a significant increase in TOs level was also seen in group 3 compared to group 2 (p ≤ 0.008). Liver catalase activity showed a significant increase in groups 3 and 4 compared to group 1 (p ≤ 0.008). A significant increase in liver arylesterase enzyme activities was observed in groups 3 and 4 in comparison with group 1 (p ≤ 0.008). Liver TNF-α level was significantly increased in group 4 compared to group 1 (p ≤ 0.008). The results of biochemical analyses mentioned above are presented in Table 1.

The results of correlation analysis revealed a strong and significant positive correlation between liver AOPP and TOS, TOS and catalase, AOPP and catalase, BCHE and arylesterase as well as TNF-α and catalase (p ≤ 0.01). On the other hand, negative correlations were observed between liver TOS and arylesterase activity (p ≤ 0.01) liver arylesterase and catalase (p ≤ 0.05), as shown in Table 2.
The results of histopathological observations showed that there was no liver tissue damage in group 1 or 2 (Figs. 1 and 2) while some vacuoles in hepatocytes were seen in groups 3 and 4, and hydropic degeneration was detected in group 4 (Figs. 3 and 4).

**Discussion**

Malathion, a commonly used organophosphate, exerts its effects by inhibiting the serum enzymes AChE and BChE [17]. In this study, acute toxic effects were

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**Table 1. Results and significant differences of liver parameters**

| Parameters          | Group 1 (n = 6) | Group 2 (n = 6) | Group 3 (n = 6) | Group 4 (n = 6) |
|---------------------|-----------------|-----------------|-----------------|-----------------|
|                     | Mean ±SD        | Mean ±SD        | Mean ±SD        | Mean ±SD        |
| BChE (U/mg prot.)   | 382±10^1 ±111±10^1 | 179±10^1 ±333±10^4 | 219±10^3 ±52±10^6 | 189±10^1 ±38±10^4 |
| MDA (mmol/g tissue) | 252.5±56.55     | 303.33±139.34   | 314.17±92.33    | 255±80.99       |
| AOPP (mmol/mg prot.)| 85.73±25.55     | 75.53±16.37     | 120.98±40.72^1  | 133.27±42.51^1  |
| TOS (umol/l)        | 84.80±8.98      | 79.13±10.52     | 97.61±7.78^1    | 117.97±17.20^2^ |
| Catalase (U/mg prot.)| 1.65±0.29      | 2.08±0.47       | 2.59±0.58^1     | 2.67±0.44^1     |
| SOD (U/mg prot.)    | 0.96±0.29       | 0.92±0.21       | 1.18±0.28       | 1.33±0.35       |
| Arylesterase (U/mg prot.)| 60.40±12.26   | 47.41±10.18     | 40.26±5.14^6    | 36.88±8.25^5    |
| TNF-α (ng/l)        | 277.76±60.80    | 333.69±32.16    | 353.78±50.62    | 406.19±85.74^1  |

n – number of animals, *significance p < 0.008 (difference between group 1 and group 2), **significance p < 0.008 (difference between group 1 and group 3), ***significance p < 0.008 (difference between group 1 and group 4), ^significance p < 0.008 (difference between group 2 and group 3), ^significance p < 0.008 (difference between group 2 and group 4), ^significance p < 0.008 (difference between group 3 and group 4)  
BChE – butyrylcholinesterase, MDA – malondialdehyde, AOPP – advanced oxidation protein products, TOS – total oxidant status, SOD – superoxide dismutase, TNF-α – tumor necrosis factor α

**Table 2. Correlation analysis among liver parameters**

|          | BChE  | AOPP  | TOS     | Catalase | Arylesterase | TNF-α     |
|----------|-------|-------|---------|----------|--------------|-----------|
| BChE     | r 1   | 0.21  | -0.2    | -0.15    | 0.66**       | -0.25     |
| p        | 0.32  | 0.36  | 0.49    | 0.00     | 0.23         |
| n        | 24    | 24    | 24      | 24       | 24           |
| AOPP     | r 0.21| 1     | 0.52*** | 0.76***  | -0.24        | 0.32      |
| p        | 0.32  | 0.01  | 0.01    | 0.25     | 0.13         |
| n        | 24    | 24    | 24      | 24       | 24           |
| TOS      | r -0.2| 0.52**| 1       | 0.57***  | -0.58**      | 0.31      |
| p        | 0.36  | 0.01  | 0.01    | 0.04     | 0.01         |
| n        | 24    | 24    | 24      | 24       | 24           |
| Catalase | r -0.15| 0.76**| 0.57*** | 1        | -0.43*       | 0.53**    |
| p        | 0.49  | 0.00  | 0.00    | 0.04     | 0.01         |
| n        | 24    | 24    | 24      | 24       | 24           |
| Arylesterase | r 0.66**| -0.24| -0.58**| -0.43*| 1| -0.28 |
| p | 0.000 | 0.25 | 0.00 | 0.04 | 0.19 |
| n | 24 | 24 | 24 | 24 | 24 |
| TNF-α    | r -0.25| 0.32 | 0.31 | 0.53** | -0.28 | 1 |
| p | 0.23 | 0.13 | 0.14 | 0.01 | 0.19 |
| n | 24 | 24 | 24 | 24 | 24 |

*significant correlation at the 0.05 level, **significant correlation at the 0.01 level, r – correlation coefficient, p – significance, n – number of individuals  
BChE – butyrylcholinesterase, AOPP – advanced oxidation protein products, TOS – total oxidant status, TNF-α – tumor necrosis factor α
selected as 100 mg/kg as an acute effect, 400 mg/kg as the plateau level (70% AChE inhibition) and 200 mg/kg as a medial dose [10]. Studies showed that sub-chronic and chronic administration of malathion inhibits liver BChE activity [18, 19].

In this study, a significant decrease in liver BChE activities was observed in groups 2, 3 and 4 in comparison with group 1 (p ≤ 0.008). The results of this study conducted by acute administration of malathion are in line with previous studies performed using chronic administration of malathion.

Various studies have indicated that chronic and sub-chronic applications of malathion in rats cause increased liver lipid peroxidation [18, 20-22]. Al-Othman et al. reported that acute administration of malathion at a dose of 27 mg/kg resulted in a significant increase in liver MDA level [23]. In contrast, Possamai et al. reported that there was no significant liver lipid peroxidation observed in rats treated with acute dosages of malathion at 100 and 150 mg/kg. Possamai et al. also reported that there was an increase in protein carbonyls indicating an increase in protein oxidation at 50 mg/kg acute dosage but there were no such effect at 100 and 150 mg/kg doses [22]. In this study, there were no statistically significant differences in liver MDA level among the groups. Thus, the results of this study are in line with those of Possamai et al. Liver AOPP levels of groups 3 and 4 were significantly higher than in group 2 (p ≤ 0.008) but were not significantly higher than in group 1.

It was also found that TOS levels were significantly increased in group 4 compared to groups 1 and 2. Liver TOS levels in group 3 were also significantly higher than in group 2 (p ≤ 0.008). Results of the Spearman correlation analysis revealed a strong and significant correlation between liver AOPP and TOS levels (p ≤ 0.01). This indicates that liver advanced protein and total oxidation levels increase in a complementary

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Fig. 1. Histopathologic observation of group 1. There was no degeneration

Fig. 2. Histopathologic observation of group 2. There was no degeneration

Fig. 3. Histopathologic observation of group 3. Some vacuoles in hepatocytes were seen

Fig. 4. Histopathologic observation of group 4. Vacuolar and hydropic degeneration in hepatocytes was seen
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way. Since there was no significant change in MDA levels, it is believed that protein oxidation is the main contributor to total oxidation observed in this study. The results of some previous studies showed that chronic applications of malathion resulted in a decrease in SOD activity and catalase in rat liver [20, 21]. Similarly, acute applications of malathion at a dose of 25 and 50 mg/kg also decreased rat liver SOD activity [22]. A study performed by Al-Othman et al. also gave similar results [23]. On the other hand, a study by Sharma et al. showed that acute application of dimethoate, an organophosphate, increased liver catalase and SOD activity [24].

In this study, an increase in SOD activity was observed in groups 3 and 4 but this increase was not statistically significant. There was a significant increase in catalase activity in groups 3 and 4 compared to group 1 ($p \leq 0.008$).

Sharma et al. reported that acute administration of organophosphates resulted in an increase in liver cytochrome P450 activity. Cytochrome P450 enzymes catalyze oxidation of oxygen molecules in organophosphate substrates and trigger the production of ROS [24]. Łukaszewicz-Hussain and Moniuszko-Jakoniuk reported that acute application of chlorfenvinphos, an organophosphate, contributed to an increase of ROS production by increasing hepatic $O_2^-$ and reducing the mitochondrial aconitase level [25]. It is also reported that 24 hours after chlorfenvinphos administration, liver SOD and catalase levels were increased in line with the increase in superoxide anion [26]. Łukaszewicz-Hussain and Moniuszko-Jakoniuk also reported that 48 hours after chlorfenvinphos application catalase activity was decreased. The increase in catalase and GSH-Px activity following organophosphate application was found to be sufficient to lower the toxic effects of $H_2O_2$. However, 48 hours after organophosphate administration, catalase activity was decreased to a very low level as GSH-Px activity is sufficient to decrease the level of $H_2O_2$ [27]. As a result, a conclusion can be made that 24 hours after organophosphate application, catalase, SOD and GSH-Px increase in reaction to the increasing liver ROS. It is thought that a continuous increase in ROS following sub-chronic administration of organophosphates may decrease activities of these antioxidant enzymes.

Based on the results of the correlation analysis, a strongly significant positive correlation was observed between liver TOS and catalase activity as well as AOPP and catalase activity ($p \leq 0.01$). This study revealed that an increase in ROS (increasing TOS and AOPP) induced catalase activity within 24 h of organophosphate administration.

The results of this study are in line with previous studies reported by Sharma et al. [24], Łukaszewicz-Hussain [26], Łukaszewicz-Hussain and Moniuszko-Jakoniuk [25], and Łukaszewicz-Hussain and Moniuszko-Jakoniuk [27], but our results contradict studies of Possamai et al. [22] and Al-Othman et al. [23]. This may be due to a low dose of malathion administered acutely during liver antioxidant activity studies. In this study, acute administration of malathion at a dose of 100 mg/kg did not show a significant difference in oxidative stress and antioxidant enzymes. Significant increases in liver oxidative stress and catalase activities were observed after acute administration of malathion at a dose of 200 and 400 mg/kg.

Łukaszewicz-Hussain demonstrated that rats’ paraoxonase activity was significantly decreased with an increase in serum lipid peroxidation after sub-chronic application of chlorpyrifos [28]. In this study, liver arylesterase activities in groups 3 and 4 were significantly decreased in comparison with that of group 1 ($p \leq 0.008$). Based on the results of correlation analysis, there was a strong significant negative correlation between TOS level and liver arylesterase activity ($p \leq 0.01$). The results of this study revealed that acute administration of malathion at a dose of 200 and 400 mg/kg resulted in a significant decrease in arylesterase activity with an increase in TOS. This demonstrated for the first time the relationship between liver arylesterase activity and TOS following acute administration of malathion in rats.

A study by Akgür et al. identified a significant correlation between paraoxonase activity and BChE in the sera of humans exposed to acute organophosphate poisoning [29]. Akgür et al. also reported that chronic administration of organophosphate did not reveal a significant correlation between paraoxonase activity and AChE [6]. It is reported that paraoxonase plays a more effective role in acute organophosphates poisoning than chronic organophosphate poisoning [29].

The results of this study also showed a strong positive correlation between liver arylesterase activity and BChE ($p \leq 0.01$). It is found that with increasing dose of malathion (acute administration) rats’ liver BChE and arylesterase activities decrease simultaneously.

Experimental studies showed that chronic administration of organophosphates resulted in an increase in serum TNF-α levels and inflammation in rats’ brain, Langerhans islets, and macrophages [6]. Gordon and Rowsey reported that acute administration of chlorpyrifos gave rise to an increased serum TNF-α level [30]. Mostafalou et al. [19] and Ince et al. [21] reported that chronic administration of malathion increases liver TNF-α level.
In this study, there was a significant increase in the liver TNF-α level of group 4 compared to that of group 1 ($p \leq 0.08$). Thus, this result indicated that acute administration of malathion at a dose of 400 mg/kg caused a significant increase in liver TNF-α level.

A study by Selmi et al. showed that chronic administration of malathion caused enlargement of sinusoids, mononuclear cell infiltration, dilatation, haemorrhage and necrosis of rats’ liver tissues [31]. Similar results were observed in studies by Al-Attar [9].

In this study, the results of histological examinations showed that acute administration of malathion at a dose of 200 mg/kg was seen some vacuoles, in addition to observing vacuolar and hydropic degeneration at a dose of 400 mg/kg in the liver tissues. However, acute administration of malathion at a dose of 100 mg/kg did not cause any significant histological changes.

Conclusions

We believe the results obtained from this study could provide comprehensive data regarding the effects of acute administration of malathion on the liver oxidant and antioxidant system, inflammatory indicators and histological parameters. We believe that this study will encourage new ideas about the acute dose of malathion which causes liver damage and has malign impacts on human health and the environment to be determined and prevented and also to make regulations for its dose for agricultural products in domestic and foreign markets.

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Disclosure

The authors report no conflict of interest.

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