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# EFFECT OF SOME BENZO-1,3,2-DIOXAPHOSPHOLENES AND ACYCLIC PHOSPHORAMIDATES ON AMINOTRANSFERASES AND GLUTATHIONE ENZYMES IN RATS

[23]

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## ABSTRACT

The effects of two benzo-1,3,2- dioxaphospholenes and two acyclic phosphoramidates on serum and liver aminotransferases (AST and ALT), and liver glutathione enzymes (GST, Gpx and Grd) were examined in rats. Generally, the dioxaphospholenes had less effects on elevating the serum and liver AST and ALT activities. The highest effect of the cyclic phosphoramidates on elevating serum AST and ALT activities were 185 and 246% respectively after 8 days of treatment, while the highest effects on liver enzymes were 163 and 164% respectively after 4 days of treatment. Fenitrothion caused an increase of AST and ALT activities to 258 and 267% in serum after 6 h and to 151 and 148% in liver after 24 h respectively. All examined compounds were also reactive towards the glutathione enzymes (GST, Gpx, Grd) that posses detoxifying effect. The dioxaphospholenes were generally more reactive towards the detoxifying enzyme GST.

**Keywords:** Phosphoramidates, Dioxaphospholenes, Transferases, Glutathione enzymes

## INTRODUCTION

Hepatocellular damage by certain chemicals could lead to leakage of liver aspartate aminotransferases (AST, EC 2.6.1.1) and alanine aminotransferases (ALT, EC 2.6.1.2) into plasma; therefore, monitoring these enzymes in blood is widely used to assess liver toxicity or diseases (**Varley *et al* 1991**). Many investigators reported the elevation of AST and/or ALT activities upon treatment with organophosphorus compounds (**Reena *et al* 1989; Ceron *et al* 1995 and Tomar *et al* 1995**). However, **Gomes *et al* (1999)** observed a significant decrease in serum aminotransferases in animals given weekly a mixture of organophosphorus pesticides.

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Glutathione enzymes are an important family of enzymes involved in the detoxification of endogenous and exogenous toxicants. In addition, resistance of some species towards various toxicants is attributed to the elevated activities of this class of enzymes compared to their activities in the sensitive biotypes (**Hemingway *et al* 1985; Fournier *et al* 1992 and Lagadic *et al* 1993**). Glutathione peroxidases, Gpx (EC 1.11.1.9), catalyze the reduction of some harmful species produced endogenously during the metabolism e.g. hydrogen peroxide and organic and lipid hydroperoxides using glutathione (GSH) as a reducing agent. Glutathione reductases, Grd (EC 1.6.4.2) regenerates GSH by reducing the oxidized from (GSSG) using NADPH as cofactor. Grd also help to keep vitamin C in the reduced from (**Bayoumi *et al* 2000**).

Glutathione S-transferases, GST (EC 2.5.1.18), are divided into several groups from which are glutathione-S-alkyl or S-aryl transferases responsible for the detoxification of several organophosphorus pesticides by conjugating GSH with the pesticide alkyl or aryl groups respectively (**Motoyama and Dauterman 1980; Mannervik and Danielson 1988; Hassall 1990 and Kostaropoulos *et al* 2001**). In this process, lipophilic compounds are converted into less reactive hydrophilic products that may readily be excreted (**Habig *et al* 1974**).

In the search for new organophosphorus pesticides with low adverse effects on non-target organisms, a group of benzo-1,3,2-dioxaphospholenes and acyclic phosphoramidates were reported to have good pesticidal activities with less neurotoxicity and biochemical effects on mammals than fenitrothion, a moderately toxic pesticide (***Ali 1999; Ali and Ali 2000; Ali and Zidan 2000 and Ali et al 2003***). The present study reports the effects of these compounds on liver function enzymes (AST and ALT) and the detoxifying glutathione enzymes (GST, Gpx and Grd).

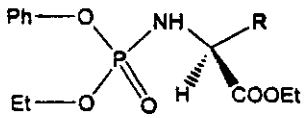
## MATERIAL AND METHODS

### Chemicals and Instruments

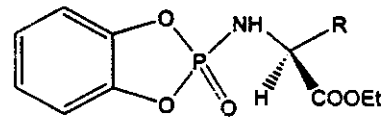
The phosphoramidates **1**, **2**, *N*-ethoxyphenoxyphosphinyl) glycine ethyl ester and L-glutamic acid diethyl ester respectively, and **3**, **4**, *N*-(2-oxido-1,3,2-benzodioxa-phosphol-2-yl) glycine ethyl ester and L-glutamic acid diethyl ester respectively (Fig. 1) were synthesized as previously published (**Ali 1999 and Ali and Zidan 2000**). Fenitrothion (95%), *O*, *O*-dimethyl-*O*-(3-methyl-4- nitrophenyl) phosphorothioate, was obtained from Sumitomo Chemical Co., LTD (under commercial name Sumithion). Absorbance in biological determinations was recorded on a Shimatzu 160A dual-beam UV-VIS spectrophotometer.

### Animal Experiment

Adult male albino Wistar rats (4 - 6 months old) weighting 100 ± 15 g were housed in six groups of 20 - 22 animals; one group served as the control, one group for each of the four phosphoramidates, and one group for fenitrothion. Animals fed on standard laboratory diet for a week for acclimation before introducing the compounds orally by a gavage with olive oil as a vehicle. Treated animals received a single dose of 85 mg / kg body weight which is ~ 1 / 3 of the $LD_{50}$ of fenitrothion (250 mg / kg) while




R = H (1)
R = $CH_2CH_2COOEt$ (2)




R = H (3)
R = $CH_2CH_2COOEt$ (4)

Fig. 1. Phosphoramidate structures

control group received olive oil only. At each interval i.e. 1,4,8 and 12 day for groups treated by the phosphoramidates 1-4 and 0.25, 1 and 2 day for group treated by fenitrothion, three animals from each group were sacrificed without the use of anesthesia. Blood samples were extracted by intracardiac puncture then centrifuged to obtain the serum for enzyme assays. Liver organs (2 g) were homogenized immediately after sacrificing the animals with 5 mL cold phosphate buffer (pH 7.2, 0.1M) containing 0.5 % triton X-100 and 0.25 M sucrose then centrifuged for 10 minutes at 10,000 rpm in an Eppendorf centrifuge.

### Enzyme Assays

Aminotransferases (AST and ALT) activities were determined according to the methods of **Reitman and Frankel** (1957) by using kits purchased from Randox Laboratories Ltd.

Glutathione S-transferase activity was determined by the method of **Habig *et al*** (1974). The reaction mixture consisted of 800 µl of phosphate buffer (0.2 M, pH 6.5), 50 µl of 20 mM 1-chloro-2,4-dinitrobenzene (CDNB) in 95% ethanol, 50 µl of reduced glutathione (20 mM in buffer solution), and 100 µl of enzyme extract. After the suitable agitation, the change in absorbance during 3 min was recorded at 340 nm. GST specific activity is expressed in U/mg protein where the enzyme unit (U) is the amount of enzyme that conjugates 1.0 µmol of CDNB with GSH.

Glutathione peroxidase activity was assayed by the method described by **Wendel, (1981)**. The reaction mixture composed of the following solutions: 500 µl of phosphate buffer (0.25 M, pH 7), 100 µl glutathione reductase, (activity per ml: 6 µmole/min at 25°C), 100 µl of reduced glutathione (10 mM in buffer solution), 100 µl of β-NADPH (2.5 mM in 0.1% $NaHCO_3$ solution) and 100 µl of enzyme extract. After 10 min of incubation period at 37°C, 100 µl of tert-butyl hydroperoxide (12 mM) were added. The change in the absorbance at 366 nm was monitored for 3 min.

Glutathione reductase activity was determined according to the method of **Carlberg and Mannervik, (1985)** by mixing 500 µl of phosphate buffer (0.2 M pH 7), 50 µl of β-NADPH (2 mM in 10 mM Tris-HCl buffer, pH 7), 50 µl of

oxidized glutathione (20 mM), 300 µl of redistilled water, and 100 µl of enzyme extract. The reaction mixture was incubated for 3 min at 30°C, then the change in absorbance was measured at 340 nm during 3 min.

Total soluble protein was determined by the method of **Bradford, (1976)** using Coomassie brilliant blue G-250 dye and bovine serum albumin as a standard. Absorbance was recorded at 595 nm.

### Statistical analysis

Statistical analysis was carried out to test the differences between the enzyme activities of the treated and control groups by using Student *t*-test (Sigma Plot for Windows, version 2.0).

## RESULTS

The effects of the phosphoramidates **1-4** and fenitrothion on liver function enzymes are presented in Table (1) and Fig. (2). Results showed that Serum AST activiy was increased to the maximum level by the acyclic phosphoramidates **1** and **2** up to 154 and 185% after 4 and 8 days of introducing the dose respectively; on the other hand, the enzyme activity decreased to the minimum by the dioxaphospholenes **3** and **4** to 48 and 54% of the enzyme control level respectively after 24 hours. Serum ALT activities increased by the four tested compounds (**1-4**) up to 230, 246, 124 and 180% after 1, 8, 16 and 1 days respectively. Both serum AST and ALT activities regained their normal levels before the end of the experimental period. Fenitrothion raised serum AST and ALT activities up to 258 and 267% of their normal levels in 6 hours, then their activities decreased to 160 and 91% respectively in 48 hours during which the rest of animals were died.

Activities of both liver enzymes were also elevated by the phosphoramidate treatments (**1-4**). Compound **1** showed the highest elevation in liver AST and ALT activities to 163 and 150% respectively after 4 days. Liver AST and ALT activities were also increased by fenitrothion up to 151 and 148% respectively after one day.

Table (2) and Fig. (3) present the effect of the tested compounds on liver glutathione enzymes (GST, Gpx and Grd). All tested compounds inhibited GST whereas the dioxaphospholenes showed the highest effect. On the other hand, Gpx and Grd activities were depressed significantly by treatment with fenitrothion and compounds **1** and **3**, while compounds **2** and **4** caused initial inhibition followed by increase in both enzyme activities.

There was no significant change in the enzyme activities in the control group during the experimental period; therefore, one set of the control data was listed to express the average activities during the whole period.

## DISCUSSION

The phosphoramidates used are selected from two groups, acyclic compounds (**1**, **2**) or compounds containing 1,3,2-dioxaphospholene ring (**3**, **4**). Compounds in each group contain either glycine or glutamic acid moiety. These compounds are expected to give relatively low toxic metabolites i.e. phenol, catechol and amino acid esters; they exhibited much less neurotoxicity and biochemical effects than the commercial pesticide fenitrothion, where they inhibited the

Table 1. Effects of the phosphoramidates 1-4 and fenitrothion on serum and liver AST and ALT activities in albino rats

| Time (day) | Serum AST | Serum ALT | Liver AST | Liver ALT |
|---|---|---|---|---|
| | | Control | | |
| 0.00 | 100.00 ± 7.67 | 100.00 ± 6.76 | 100.00 ± 8.93 | 100.00 ± 5.63 |
| | | Phosphoramidate (1) | | |
| 1.00 | 129.79 ± 1.34** | 229.61 ± 31.12** | 117.41 ± 2.98* | 138.44 ± 11.18** |
| 4.00 | 153.77 ± 8.05*** | 184.55 ± 23.81** | 163.39 ± 6.70*** | 149.69 ± 9.55** |
| 8.00 | 124.32 ± 1.75** | 167.38 ± 1.92*** | 110.27 ± 9.83 | 155.31 ± 15.02** |
| 12.00 | 109.59 ± 12.23 | 200.64 ± 6.43*** | 104.46 ± 11.81 | 164.06 ± 18.68** |
| 16.00 | 95.89 ± 2.64 | 119.10 ± 10.75 | 96.88 ± 3.30 | 86.25 ± 5.94* |
| | | Phosphoramidate (2) | | |
| 1.00 | 67.47 ± 5.24** | 127.68 ± 16.00* | 128.13 ± 8.80* | 124.37 ± 3.67** |
| 4.00 | 123.97 ± 3.49** | 162.02 ± 2.04*** | 119.20 ± 6.79* | 112.50 ± 4.81* |
| 8.00 | 184.93 ± 7.67*** | 245.71 ± 7.62*** | 121.88 ± 13.64 | 124.06 ± 7.76* |
| 12.00 | 105.14 ± 3.90 | 105.15 ± 11.37 | 129.46 ± 5.91** | 121.87 ± 7.81* |
| 16.00 | 78.77 ± 7.61* | 111.59 ± 15.43 | 132.59 ± 4.77** | 115.00 ± 2.75* |
| | | Phosphoramidate (3) | | |
| 1.00 | 47.95 ± 2.57*** | 99.68 ± 2.21 | 154.46 ± 13.90** | 135.94 ± 6.32** |
| 4.00 | 75.68 ± 8.60* | 120.17 ± 14.87** | 123.66 ± 18.29 | 117.19 ± 7.08* |
| 8.00 | 62.33 ± 5.55** | 111.59 ± 13.86 | 114.73 ± 9.38 | 115.94 ± 7.03* |
| 12.00 | 61.99 ± 6.21** | 123.39 ± 14.81 | 116.96 ± 10.83 | 111.56 ± 9.23 |
| 16.00 | 89.38 ± 5.92 | 124.46 ± 16.20 | 103.57 ± 9.90 | 98.44 ± 5.28 |
| | | Phosphoramidate (4) | | |
| 1.00 | 54.45 ± 2.23*** | 180.26 ± 22.01** | 112.50 ± 8.63 | 118.12 ± 4.73* |
| 4.00 | 70.21 ± 5.93** | 149.14 ± 21.57** | 145.09 ± 12.83** | 129.69 ± 5.31** |
| 8.00 | 67.81 ± 4.64** | 108.37 ± 10.92 | 140.18 ± 14.18** | 145.00 ± 7.03*** |
| 12.00 | 74.32 ± 5.79** | 131.97 ± 9.01** | 103.13 ± 9.46 | 112.50 ± 7.19 |
| 16.00 | 82.19 ± 3.49* | 100.11 ± 16.39 | 100.89 ± 7.73 | 97.50 ± 6.46 |
| | | Fenitrothion | | |
| 0.25 | 258.22 ± 21.58*** | 267.17 ± 20.55*** | 143.30 ± 11.81** | 126.56 ± 8.47** |
| 1.00 | 160.96 ± 15.99** | 126.61 ± 18.39 | 150.89 ± 10.58** | 148.44 ± 5.71*** |
| 4.00 | 159.59 ± 19.22** | 91.20 ± 9.55 | 92.86 ± 11.29 | 94.06 ± 8.75 |

Activities are means of three determinations ± SD and expressed as percentage of the control activities
* ($p \leq 0.05$), ** ($p \leq 0.01$) and *** ($p \leq 0.005$) are significant different from control values.

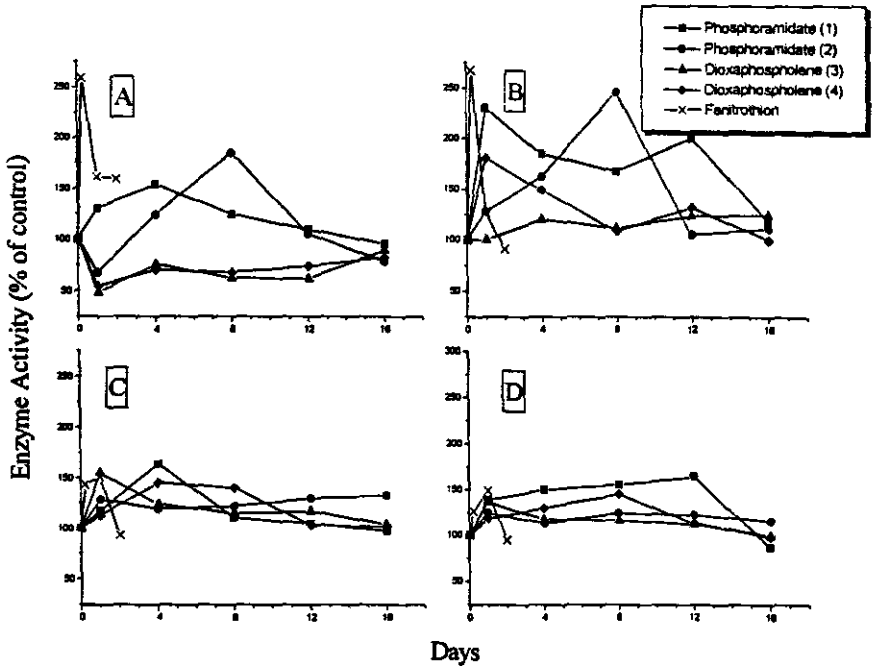



Figure 2. Effects of the phosphoramidates **1-4** and fenitrothion on AST and ALT in serum (A and B) and liver (C and D) in albino rats respectively

activities of both serum and liver alkaline phosphatase (ALP) to 27-65, 58-80% (**Ali *et al* 2003**) and acetyl-cholinesterase (AChE) to 56-69, 58-76% (**Ali *et al* 2004**) of the normal levels respectively after 24 hours of introducing the single dose mentioned in the material and methods section. On the other hand, fenitrothion during the same period showed strong neurotoxic effect and inhibited ALP in serum and liver to 13 and 8% and AChE to 16 and 5% of the control activities respectively leading to the death of 40% of the fenitrothion treated animals in 48 hours.

Among compounds **1-4**, the phosphoramidate **2** caused the highest elevation of AST and ALT activities (185 and 246% respectively) after 8 days while the dioxaphospholenes **3** and **4** had generally the least adverse effect on both serum enzymes. Fig. 2 (C and D) showed that the liver AST and ALT activities increased upon treatment with either fenitrothion or the tested phosphoramidates. However, the increased activities of liver enzymes were less than those observed by serum enzymes where the activities of liver AST and ALT enzymes did not exceed 164 and 155 % of the control levels

Table 2. Effects of the phosphoramidates 1-4 and fenitrothion on liver GST, Grd and Gpx activities in albino rats

| Time (days) | GST | Gpx | Grd |
|---|---|---|---|
| | | Control | |
| 0.00 | 100.00 ± 10.55 | 100.00 ± 10.39 | 100.00 ± 11.48 |
| | | Phosphoramidate (1) | |
| 1.00 | 83.88 ± 5.31 | 41.53 ± 7.55** | 46.48 ± 9.98* |
| 4.00 | 94.09 ± 29.33 | 71.73 ± 7.69* | 20.28 ± 2.92** |
| 8.00 | 4.13 ± 1.26*** | 73.49 ± 9.70* | 69.53 ± 5.60* |
| 12.00 | 6.94 ± 0.19** | 61.42 ± 7.22* | 40.27 ± 5.69* |
| | | Phosphoramidate (2) | |
| 1.00 | 4.76 ± 1.02** | 5.48 ± 0.69*** | 35.03 ± 4.91* |
| 4.00 | 2.96 ± 0.95*** | 74.73 ± 7.30 | 140.05 ± 8.98 |
| 8.00 | 4.95 ± 0.99** | 150.98 ± 25.43* | 177.63 ± 2.70* |
| 12.00 | 36.72 ± 3.09** | 258.03 ± 13.75*** | 144.53 ± 14.18 |
| | | Phosphoramidate (3) | |
| 1.00 | 5.37 ± 0.20** | 111.16 ± 31.83 | 97.50 ± 13.76 |
| 4.00 | 3.85 ± 0.72** | 14.88 ± 3.64*** | 11.16 ± 2.26** |
| 8.00 | 4.15 ± 0.07** | 16.97 ± 3.77*** | 12.99 ± 0.03** |
| 12.00 | 5.26 ± 0.30** | 128.02 ± 16.78 | 16.60 ± 3.00** |
| | | Phosphoramidate (4) | |
| 1.00 | 2.83 ± 0.26** | 4.60 ± 1.65** | 2.17 ± 0.41** |
| 4.00 | 6.85 ± 1.04** | 66.11 ± 21.38 | 139.67 ± 11.49 |
| 8.00 | 17.64 ± 3.60** | 207.99 ± 33.67** | 180.86 ± 8.03* |
| 12.00 | 6.85 ± 0.90** | 185.64 ± 9.34** | 355.00 ± 17.25** |
| | | Fenitrothion | |
| 0.25 | 11.46 ± 0.84** | 24.11 ± 3.09** | 13.41 ± 1.73** |
| 1.00 | 11.06 ± 2.21** | 28.11 ± 2.56** | 20.99 ± 2.99** |
| 2.00 | 4.69 ± 1.42** | 10.77 ± 1.02** | 9.17 ± 0.68** |

Activities are means of three determinations ± SD and expressed as percentage of the control activities

* ($p \leq 0.05$), ** ($p \leq 0.01$) and *** ($p \leq 0.005$) are significant different from control values.

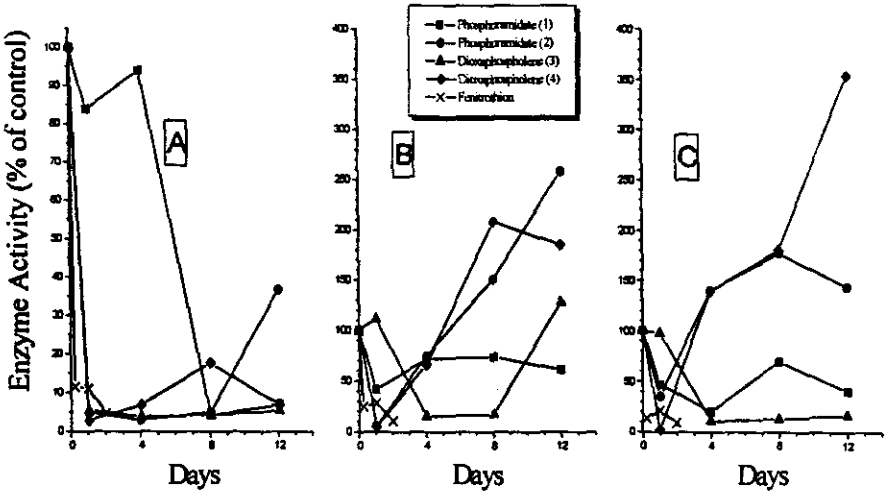



Fig. 3. Effects of the phosphoramidates 1-4 and fenitrothion on liver GST (A), Gpx (B) and Grd (C) in albino rats

respectively before returning to the normal activities. The narrower range of the increased enzyme activities in liver than in serum may result from the previously mentioned leakage of liver AST and ALT to the serum where they could accumulate.

Glutathione S-transferases are known to act on electrophilic xenobiotics such as organophosphorus compounds leading to their detoxification (Chasseaud 1979). Fenitrothion and the used phosphoramidates posses an electrophilic phosphorus atoms and hence they inhibited GST in the process of their detoxification. As indicated in Table 2 and Fig. 3A, the four phosphoramidates and fenitrothion were reactive towards GST, where they depressed the enzyme activity after 24 hours to 84, 5, 5, 3 and 11% of the control level respectively. Compound 1 was the least reactive and thus the least detoxified, which might explain its highest effect on raising serum AST and ALT activities, while the dioxaphospholenes 3 and 4 were the most reactive compounds toward GST and thus the most detoxified which might explain their lower neurotoxicity (Ali *et al* 2003) and lower effects on AST and ALT discussed above than the other tested phosphoramidates (1, 2) and fenitrothion. It was also reported that the in *vivo* inhibition of hepatic GST by organophosphorus compounds results from the formation of reactive oxygen species (ROS) that cause lipid

peroxidation and disruption in the hepatocyte cellular membranes leading to the enzyme depletion (**Siddiqui *et al* 1990, Bagchi *et al* 1995**).

The actions of glutathione peroxidases (Gpx) and reductases (Grd) are complementary; while Gpx catalyze the oxidation of glutathione (GSH) with the reduction of reactive oxygen species (ROS) induced by some xenobiotics, glutathione reductases regenerate glutathione by reduction of the oxidized form (GSSG). Results listed in Table 2 and presented in Fig.3 (B and C) showed that the examined phosphoramidates inhibited both enzymes significantly in the first 24 hours except compound **3** which inhibited the enzymes after 4 days. Afterwards, both enzymes showed elevation in their activities especially in animals treated with the phosphoramidates **2** and **4** reflecting the participation of Gpx and Grd in the natural defense system against the foreign phosphoramidates. On the other hand, fenitrothion did not stimulate the activities of both enzymes but reduced them after 48 hours to 11 and 9% of the control level respectively.

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# تأثير بعض مركبات البنزو ١، ٣ ، ٢ -دايوكسا فسفولين و الفوسفوراميدات غير الحلقية على أنزيمات نقل مجموعة الأمين وأنزيمات الجلوتاثيون فى الفئران

## [٢٣]

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تم دراسة تأثير اثنين من الفوسفوراميدات الحلقية (بنزو ١، ٣، ٢ -دايوكسا فسفولين) واثنين من الفوسفوراميدات غير الحلقية ومبيد الفينيتروثيون على انزيمات نقل مجموعة الامين (ALT, AST) بسيرم الدم والكبد وانزيمات الجلوتاثيون (GST, Gpx, Grd) بالكبد فى فئران الألبينو. وقد وجد أن الفوسفوراميدات الحلقية ذات تأثير أقل على زيادة نشاط انزيمات نقل مجموعة الامين بالسيرم والكبد. وقد وجد أن أعلى نشاط لانزيمات ALT, AST بالسيرم يصل الى ١٨٥، ٢٤٦ % على الترتيب بينما أعلى نشاط ملحوظ بانزيمات الكبد هو ١٦٣، ١٦٤% على الترتيب نتيجة المعاملة بالفوسفوراميدات غير الحلقية. كما أدى مبيد الفينيتروثيون الى زيادة نشاط انزيمات السيرم الى ٢٥٨ ، ٢٦٧% بعد ٦ ساعات وانزيمات الكبد الى ١٥١ ، ١٤٨ % بعد ٢٤ ساعة على الترتيب. وقد أظهرت كل المركبات المختبرة نشاط تجاه انزيمات الجلوتاثيون (GST, Gpx, Grd) التى تعمل على خفض سمية المبيدات, كما أظهرت مركبات الفسفوراميدات الحلقية تأثير أعلى على انزيم GST .

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