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ochemical Changes In Some Serum Constituents In Rats Exposed To Some Carcinogenic Compounds

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ABSTRACT

Two carcinogenic compounds thioacetamide ($CH_3 - \overset{S}{\overset{||}{C}}-NH_2$) and 2,4,6 - trimethyl aniline were tested for their effects on liver and kidney functions .

The first compound is used as food preservative, while the second used in dye stuff (aniline dyes) . They are chosen to study their effects on some blood biochemical constituents in albino rats and study the histopathological changes on the affected organs.

The result of liver function tests showed that the oral administration of 20 and 30 mg / kg thioacetamide and 2,4, 6 - trimethyl aniline to rats, produced significant elevation in serum aminotransferase , alkaline phosphatase activity , blood glucose level , total proteins concentration , the mean values of serum cholesterol level, total bilirubin concentration and both direct and indrect bilirubin concentration in thioacetamide and trimethyl aniline groups .

Regarding kidney function tests, a significant elevation in serum creatinine, urea and uric acid concentrations of experimental rats dosed with thioacetamide and 2,4,6 - trimethyl aniline .

Histopathological examination of the liver and kidney of intoxicated rats revealed that thioacetamide and trimethyl aniline produce marked alterations in these organs.

INTRODUCTION

Food safety is a complex subject. It does not take an expert to note that there is widespread public concern about carcinogenes in food. This is too is a bad news / good news issue, but the former is often emphasized to neglect of the later . The bad news is that exposure to dietary carcinogens is an unavoidable fact of life . Given the large number of naturally occuring carcinogens in the environment, it is now impossible to eat a meal devoid of traces of these substances *(1 , 2)*

It is apparent, however, that a constant toxicologic surveillance of food additives must be maintained as new evaluation techniques are developed *(2)* .

The possible carcinogenicity, mutagenicity and teratogenicity of a wide variety of food additive compounds are major problems in the field of toxicology for which there is no quick or easy answer *(3)* .

In the intervening years many classes and types of chemicals were found to be carcinogenic *(5 - 9)* . Some were discovered after they were suspected of being involved in the development of cancer in man as dye stuffs, aromatic hydrocarbon , N-2 fluorenylacetamide and diethylnitrosamine *(10)* .

MATERIALS AND METHODS

Materials

Experimental animals

Ninty apparantly healthy white mature albino rats 6 month old and weighted 150 - 170 gm. were used . Animals were kept under hygenic and environmental conditions and on a well balanced ration , water was supplied ad - libitum.

The experimental animals were classified into three equal groups .

The first group

Comprised 30 rats orally administered

thioacetamide in a dose level of 20 mg / kg b.wt. *(11)* .

The second group

Consisted of 30 rats, and orally administered 2, 4, 6 - trimethy aniline in dose level of 30 mg/kgb. wt. *(12)*. .

The third group

Included 30 rats and were considered as control group .

Sampling

Five rats from each group were sacrificed and blood samples were collected at the morning after 12 hours fasting and periodically every 2 weeks for 12 weeks .

Serum was collected and kept in deep feeze at - 20 °C till the biochemical analyses . The following parameters were determined .

Alanine aminotransferase (ALT), aspartate aminotransferse (AST)*(13)*, alkaline phosphatase (ALP) *(14)* , glucose *(15)*, total proteins *(16)*, total cholesterol *(17)*, total bilirubin *(18)*, creatinine *(19)*, blood urea nitrogen (B. U. N.) *(20)* and uric acid *(21)* .

Histopathological examination was carried out *(22)* .

Data were analysed Statistically *(23)* .

RESULTS AND DISCUSSION

In this study some trials were adopted to show the side effect and biochemical changes in some constituent in serum of experimental rats treated with two compounds which were commonly used in the field of food additives and dye stuffs (thioacetamide and trimethyl aniline).

Our result revealed that, the mean values of serum alanine aminotransferease (ALT) in control rats ranged from 30.90 ± 1.72 to 37.95 ± 2.82m/l . While in aspartate aminotransferase (AST) ranged from 77.16 ± 3.08 to 91.40 ± 3.48 m/l. (Table 1).

Similar levels in the activity of ALT was recorded *(24)* that the activity of ALT in serum of normal rats ranged from 35.1 ± 13.3 m/l . In case of AST *(24)* , the normal activity in serum of rats ranged from 42.9 to 0.0 m/l. The highly significant elevation in aminotransferases activities (AST and ALT) in rats dosed with thioacetamide were closely resemble with that previously reported *(25,26,27)* in rats .

The elevation of aminotransferases activities in serum may be due to tissue damage particularly in liver , kidney and heart *(28)* and increased permeability of cell membrane or increased synthesis or decreased catabolism of transaminases may be involved *(22)*. , the release of abnormally high levels of specific tissue enzymes into blood stream is dependent on both the degree and type of damage exerted by the toxic compound administered *(30)* .

Our results were supported by the histopathological finding in the affected liver by both compounds . There were scattered necrotic hepatocytes karyomegaly and nuclear damage Fig. 1,2.

Significant elevation of ALT activity was recorded *(31 , 32)* in rats . Our results regarding the significant elevation in ALT and AST in rats treated with trimethyl aniline was nearly similar to the results recorded by other investigators used aromatic hydrocarbon or aromatic amines in rats *(33 - 36)* .

The obtained results revealed that the mean values of serum alkaline phosphatase activity in control rats ranged from 81.99 ± 0.011 to 118.0 ± 5.15 m/l (Table 1) that agree those, *(37)*, who recorded that the mean value of serum alkaline phosphatase activity in control rats ranged from 81.27 ± 9.69 to 114.44 ± 8.17 μ/l .

The obtained data in table (1), revealed that both thioacetamide and trimethyl aniline induce significant elevation in serum alkaline phosphatase activity in the treated rats allover the experimental period except at 8th week of experiment. Our results were in accordance with that obtained by several investigators *(32,27)* , revealed a significant elevation in the serum alkaline phosphatase activity due to administeration of thioacetamide in rats dosed with different doses of thioacetamide for different periods .

The increased activity of serum alkaline phosphatase may be attributed to the hepatobiliary affection or due to the increased

Table (1) : Serum transaminases (AST and ALT) and Alkaline phosphatase (ALP) activities in sera of thioacetamide and trimethyl aniline treated rats (mean ± S. E.) .

paramter	ALT (u/l)			AST (u/1)			ALP (u/1)		
Time in weeks	Control group	thioacetamide group	Trimethyl aniline group	Control group	Thioacetamide group	Trimethyl aniline group	Control group	Thioacetamide group	Trimethyl aniline group
2	35.95 ± 2.68	76.57*** ± 6.72	57.10* ± 6.05	77.16 ± 3.08	128.95** ± 3.94	131.76*** ± 3.94	118.00 ± 5.15	174.98*** ± 5.79	155.12** ± 7.37
4	37.95 ± 2.82	101.95*** ± 4.71	101.73*** ± 5.84	83.73 ± 3.91	135.93*** ± 7.48	120.61*** ± 2.09	100.63 ± 3.48	139.02*** ± 4.17	156.15*** ± 3.10
6	32.24 ± 1.80	71.06** ± 7.71	70.61*** ± 5.53	91.40 ± 3.48	146.29*** ± 6.93	134.58*** ± 3.13	90.12 ± 2.03	105.78** ± 3.17	174.76*** ± 2.49
8	34.98 ± 1.81	70.02** ± 7.59	72.22*** ± 5.89	89.19 ± 4.90	182.31*** ± 6.38	181.03*** ± 6.30	81.99 ± 5.11	86.66 ± 3.92	88.64 ± 3.81
10	36.59 ± 2.81	74.96*** ± 5.44	70.91*** ± 5.54	79.07 ± 4.05	128.15*** ± 5.36	136.94*** ± 6.46	99.25 ± 3.46	133.78*** ± 4.81	162.31*** ± 7.65
12	30.90 ± 1.72	55.82*** ± 4.55	68.43*** ± 3.75	81.44 ± 3.66	124.55*** ± 2.91	140.27*** ± 7.22	88.02 ± 3.44	141.28*** ± 4.17	161.97*** ± 4.13

Significant ($P \leq 0.05$) ** Significant ($P \leq 0.01$)
*** Significant ($P \leq 0.001$)

synthesis and release of the enzyme by the damaged hepatic cells or decreased enzyme excretion through obstructed bile canaliculi and bile duct hyperplasia *(38)* . This explanation was supported by our histopathological examination of the liver which revealed sever and marked necrobiotic changes in the liver of treated rats Fig. 1,2.

Regarding the significant elevation in serum alkalin phosphatase activity induced by the aromatic amine timethyl aniline in rats, the obtained results , were in agreement with that recorded *(36)* .

The obtained data revealed that the mean value of serum glucose level in control rats ranged from 94.6 ± 11.0 to 114.00 . Similar level was recorded *(37)* , revealing that the mean value of serum glucose level in control rats ranged from 112.82 ± 3.79 to 125.12 ± 3.79 mg %.

The obtained data in table (2), revealed that both thioacetamide and trimethyl aniline have a significant and persistent hyperglycaemia in treated rats allover the experimental period . The hyperglycaemic effect in the treated rats may be attributed to the toxic effect of compounds on the thyroid and adrenal glands *(39)* .

Moreover, thioacetamide (100 mg/ kg) when administered to normal rats, caused a significant decrease in the activities of glucose - 6- phosphatase and significant decrease in the glucose content in the liver *(27)* .

In the present data indicated that the mean value of total proteins in control rats ranged from 5.82 ± 0.158 to 8.24 ± 0.533 g% . Similar range of total protein in control rats was recorded *(24)*, the level of total protein was 7.52 ± 2.7 g% . Similar result was recorded *(37)*, and revealed that the range of total protein was ranged from 5.97 ± 0.42 to 7.9 ± 0.23 g% .

The obtained results in table (2), revealed a significant increase in the serum total protein concentration in group I (thioacetamide) and group II (trimethyl aniline) at 6th and 8th week.

These results were similar to that previously recorded *(40)*, in that the administration of thioacetamide to rats increased the synthesis of total protein about 2.5 fold after 4 days of treatment . The increased concentration of serum total protein may be attributed to the increased level of globulin concentration *(41)* .

On the other hand , some aromatic hydrocarbon and aromatic amines induced similar effect on total protein concentration in rats. serum protein concentrations were elevated in rats dosed with clophen (polychlorinated biphenyl) at dose level of 50 mg/kg b. wt for six weeks *(42)*. Also it is *(43)*, stated that urinary proteins were elevated in rats treated i.p. with .8 - 1.2 g/ kg b. wt of the aromatic hydrocarbon (styrene).

The mean values of serum cholesterol level in serum of control rats ranged from 106.3 ± 7.65 to 110.00 ± 6.61 mg % (table 2) . In this respect our results nearly similar to those *(37)*, revealed that the level of cholesterol in serum of rats ranged from 55.28 ± 3.41 to 66.57 ± 2.0 mg %.

Regarding serum total cholesterol concentration, the obtained results (table 2), revealed a significant increase of serum total cholesterol in both groups treated with thioacetamide and trimethyl aniline . 2 , 4, 6 - trinitrotoluene induced elevation in serum total cholesterol concentration in dogs and rats *(34)* .

The increased level of serum total cholesterol concentration of the treated rats could be attributed to the compensatory or adaptive hyperatrophy and hyperplasia of hepatic cells as confirmed by histopathological examination.

Contrary to our results *(44,45,46)*, cholesterol - phospholipid , total lipid and triglyceride were not affected in rats and rabbits treated with different doses of thioacetamide *(17)* .

The mean value of total direct and indirect bilirubin concentrations in serum of control rats ranged from 0.171 ± 0.017 to 0.370 ± 0.023 mg % 0.069 ± 0.009 to 0.196 ± 0.029 mg % and 0.093 ± 0.024 to 0.181 ± 0.021 mg% respectively (table 3) *(24)* . The level of total bilirubin in rats was recorded to be 0.30 ± 0.14 mg / dl .

The effect of oral administration of thioacetamide and trimethyl aniline on the concentration of total , direct and indirect

Table (2) : Serum glucose, total proteins and total cholesterol levels in sera of thioacetamide and trimethyl aniline treated rats (mean ± S. E.)

paramter	Glucose (mg/dl)			Total proteins (gm/dl)			Total cholesterol (mg/dl)		
time in weeks	Control group	Thioaceta mide group	Trimethyl aniline group	Control group	Thioaceta mide group	Trimethyl aniline group	Control group	Thioacet amid group	Trimethyl aniline group
2	94.6 ± 11.0	196.00*** ± 9.0	157.00*** ± 7.00	5.82 ± 0.158	6.25 ± 0.161	6.14 ± 0.238	107.97 ± 5.43	152.19*** ± 4.38	141.79** ± 4.16
4	99.3 ± 7.0	216.00*** ± 13.0	213.00*** ± 12.00	6.52 ± 0.170	6.14 ± 0.282	6.68 ± 0.20	107.88 ± 6.85	147.39** ± 7.67	139.77* ± 6.93
6	114.0 ± 7.0	250.00*** ± 11.0	235.00*** ± 15.00	7.87 ± 0.24	11.49** ± 0.650	11.04** ± 0.70	107.14 ± 7.13	195.40*** ± 11.63	199.3*** ± 9.74
8	104.0 ± 7.0	197.00*** ± 7.0	220.00*** ± 17.00	6.19 ± 0.224	8.77** ± 0.688	9.43** ± 0.73	10.00 ± 6.61	299.54 ± 13.79	268.98*** ± 8.76
10	111.0 ± 6.0	168.00*** ± 6.00	171.00*** ± 8.00	8.24 ± 0.533	7.78 ± 0.426	8.81 ± 0.55	106.30 ± 7.65	166.37** ± 11.50	177.25*** ± 4.81
12	114.0 ± 7.0	188.00** ± 13.0	162.00** ± 8.00	7.45 ± 0.19	8.17 ± 0.28	8.15 ± 0.21	107.84 ± 4.05	176.76*** ± 5.95	168.65*** ± 8.43

* Significant ($P \leq 0.05$) ** Significant ($P \leq 0.01$)
*** Significant ($P \leq 0.001$)

Table (3) : Serum total , direct and indirect bilirubin in sera of thioacetamide and trimethyl aniline treated rats (mean values ± S. E.)

paramter	Total bilirubin (mg / dl)			Direct bilirubin (mg / dl)			Indirect bilirubin (mg /dl)		
time in weeks	Control group	Thioaceta mide group	Trimethyl aniline group	Control group	Thioaceta mide group	Trimethyl aniline group	Control group	Thioacet amide group	Trimethyl aniline group
2	0.268 ± 0.026	0.716*** ± 0.036	0.840*** ± 0.028	0.087 ± 0.009	0.262*** ± 0.021	0.281*** ± 0.013	0.181 ± 0.021	0.451*** ± 0.035	0.560** ± 0.083
4	0.199 ± 0.095	0.555 ± 0.118	0.522* ± 0.106	0.071 ± 0.008	0.394 ± 0.144	0.161* ± 0.026	0.128 ± 0.027	0.332* ± 0.071	0.361* ± 0.083
6	0.242 ± 0.014	1.383** ± 0.275	0.568 ± 0.164	0.069 ± 0.009	0.558** ± 0.132	0.183 ± 0.055	0.173 ± 0.018	0.825** ± 0.145	0.380 ± 0.110
8	0.171 ± 0.017	0.452*** ± 0.25	0.573** ± 0.08	0.078 ± 0.009	0.205*** ± 0.011	0.157** ± 0.013	0.093 ± 0.024	0.247** ± 0.016	0.416** ± 0.078
10	0.257 ± 0.023	0.439** ± 0.033	0.479** ± 0.054	0.125 ± 0.117	0.130 ± 0.027	0.240 ± 0.041	0.152 ± 0.011	0.310 ± 0.081	0.239* ± 0.035
12	0.370 ± 0.023	0.894*** ± 0.051	1.091** ± 0.166	0.196 ± 0.029	0.347** ± 0.015	0.488* ± 0.109	0.174 ± 0.010	0.547*** ± 0.050	0.603** ± 0.085

*Significant ($P \leq 0.05$) ** Significant ($P \leq 0.01$)
*** Significant ($P \leq 0.001$)

Table (4) : Serum creatinine, urea nitrogen and uric acid concentration in sera of thioacetamide and trimethylaniline treated rats (mean values ± S. E.).

paramter	creatinine (mg / dl)			urea nitrogen (mg / dl)			uric acid (mg /dl)		
time in weeks	Control group	Thioaceta mide group	Trimethyl aniline group	Control group	Thioaceta mide group	Trimethyl aniline group	Control group	Thioacet amide group	Trimethyl aniline group
2	0.900 ± 0.052	1.113 ± 0.098	1.282** ± 0.060	21.56 ± 1.75	42.71*** ± 1.65	29.39* ± 2.22	1.232 ± 0.233	1.803 ± 0.289	1.600 ± 0.270
4	0.294 ± 0.021	0.428** ± 0.030	0.636*** ± 0.028	21.39 ± 1.12	46.05*** ± 4.14	35.06*** ± 2.17	1.108 ± 0.112	1.846** ± 0.089	1.528** ± 0.046
6	0.362 ± 0.028	0.605* ± 0.100	0.651** ± 0.083	20.83 ± 1.08	37.48** ± 3.36	35.69*** ± 2.06	1.230 ± 0.162	3.986*** ± 0.127	2.788*** ± 0.137
8	1.260 ± 0.050	3.093*** ± 0.359	2.080*** ± 0.122	21.10 ± 1.61	39.44*** ± 0.83	34.45*** ± 1.27	1.450 ± 0.266	4.550*** ± 0.343	4.760*** ± 0.207
10	0.373 ± 0.018	0.755** ± 0.096	0.716*** ± 0.033	17.48 ± 0.76	30.79*** ± 1.53	36.53*** ± 1.52	1.752 ± 0.157	3.926*** ± 0.383	3.934*** ± 0.346
12	1.082 ± 0.101	2.562*** ± 0.171	2.845*** ± 0.122	16.07 ± 1.25	35.51*** ± 1.32	27.20*** ± 0.68	1.920 ± 0.175	0.906*** ± 0.271	3.760*** ± 0.256

* Significant ($P \leq 0.05$) ** Significant ($P \leq 0.01$)
*** Significant ($P < 0.001$)

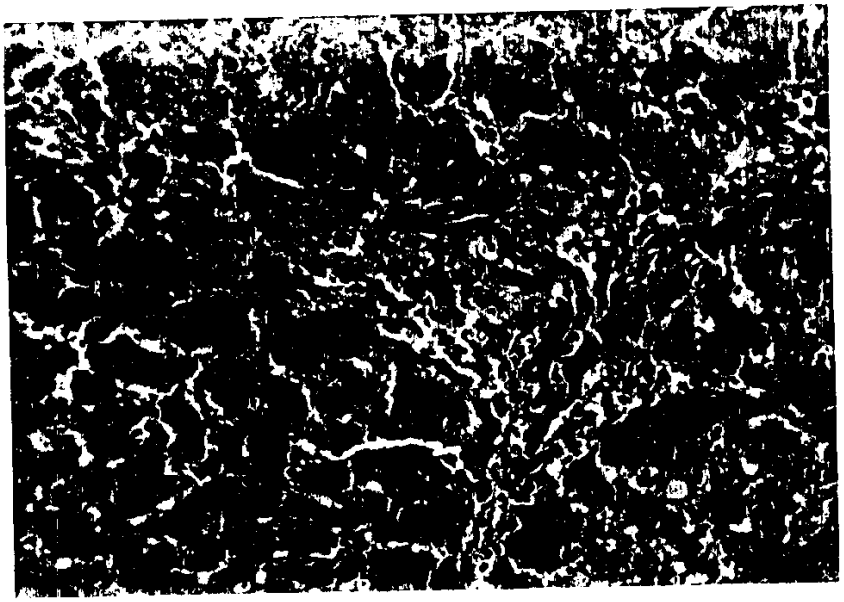

Fig. (1) : Liver of rat (trimethyl aniline group) notice fibroblastic , proliferation and mononuclear cell infilteration (H & E stain x 160).

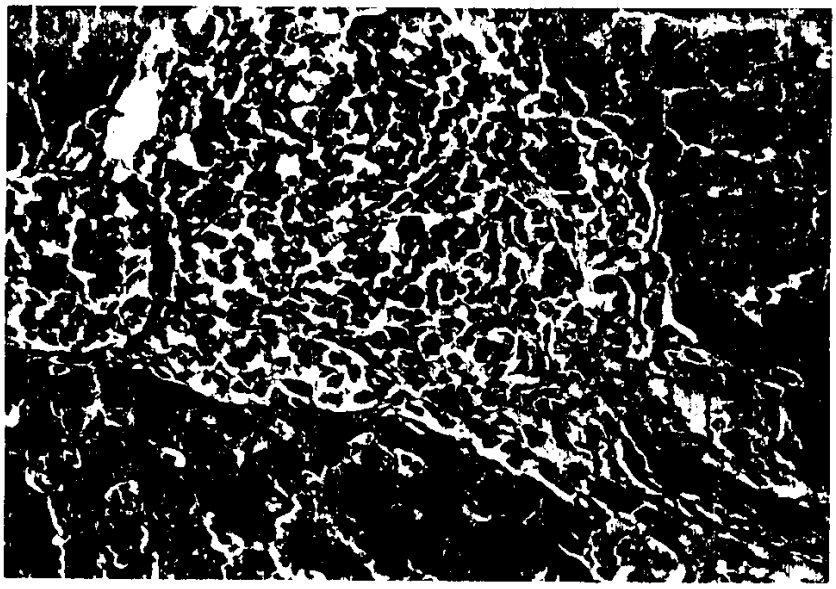

Fig. (2) : Liver of rat (thioacetamide group) notice mononuclear inflammatory cells and fibroblastic proliferation (H & E stain x 160).

Fig. (3) : Kidney of rat (trimethyl aniline group) showed granular cytoplasm and desquamation of many tubular epithelial cells (H & E stain x 250)

Fig. (4) : Kidney of rat (trimethyl aniline group) showing cystic like areas , oedema and disappearance of the renal tubular epithelium together with mononuclear inflammatory cells infilteration.

bilirubin in the treated rats revealed significant elevation of serum bilirubin level during the whole experimental period table 3.

The same results was reported *(27,48)*, in rats orally administered with thioacetamide for long term.

The significant elevation in total bilirubin levels in treated rats with thioacetamide may be attributed to hepatobiliary obstruction *(48)*, our attribution was supported by the histopathological findings in liver of treated rats Fig. 1 and 2.

Direct and indirect forms of the serum bilirubin are elevated in acute or chronic hepatitis , biliary tract obstruction. toxic reaction to many drugs , chemicals and toxins *(49)* .

Our results regarding the effect of trimethyl aniline on level of total bilirubin, similar to those previously reported *(35)* . Oral administration of thioacetamide and trimethyl aniline to rats in doses level of 20 and 30 mg/ kg b. w. for successive 12 weeks induced marked effect on kidney function.

Our results in (table 4) were similar to those *(24)*, indicating that the mean values of serum creatinine concentration in control rats ranged from 0.294 ± 0.021 to 1.260 ± 0.50 mg /dl .

The presented data in table (4), showed that there was a significant elevation in serum creatinine concentration in rats treated with both thioacetamide and trimethyl aniline during the whole experimental periods . Very low values of creatinine clearance indicated that there was some degree of kidney failure due to the effect of thioacetamide *(32 , 48)* .

The significant elevation of serum creatinine level of the treated rats may be attributed to the damage occured in liver and kidney of the toxicated rats as confirmed by our histopathological examination Fig. 3 and 4. Similar lesions in kidney of treated rats with thioacetamide was recorded *(31)* .

Our results revealed that there was a significant elevation in serum creatinine level in rats treated with trimethyl aniline. Similar results for the aniline was recorded *(43)* .

The mean value of blood urea nitrogen level in serum of control rats ranged from 16.07 ± 1.25 to 21.56 ± 1.75 mg / dl. *(24)*. The obtained results in table (4) denote that the oral administration of thioacetamide and trimethyl anline to rats induce marked and significant elevation in the concentration of urea nitrogen allover the experimental periods.

The significant elevation of serum urea concentration in thioacetamide and trimethyl aniline treated rats may be attributed to the toxic effect of the tested substances which lead to disorders of the the kidney function which reduced the glomerular filteration rate and consequently retention of urea in the blood *(50)* . Blood urea nitrogen was elevated in renal insufficiency , nephritis , acute and chronic renal failure (tubular necrosis) and urinary tract obstruction *(49)*. The obtained results were supported by what previously mentioned *(47)* .

The mean value of serum uric acid level in control rats ranged from 1.108 ± 0.112 to 1.920 ± 0.15 mg /dl . The mean value of serum uric acid concentration in control rats was 1.52 ± 0.30 mg/dl *(24)*.

Regarding the mean value of serum uric acid concentration in the treated rats, a significant elevation was recorded in both experimental groups during the whole experimental period (Table 4) . These results were in agreement with the results of *(48)* , who reported that thioacetamide was injected to rats for 3 weeks . The serum uric acid level was elevated at the end of experiment. Moreover, it is recorded *(51)* that a significant elevation in serum uric acid concentration in rats was observed after administration of mixture of 1 , 3, 5 - trinitrotoluene and hexa hydro - triazine.

The recorded significant increase in serum uric acid concentration could be attributed to renal insufficiency *(49)*, confirmed by the histopathological changes in kdiney of treated rats in both experimental groups .

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الملخص العربى

التغيرات البيوكيميائية في بعض مكونات المصل في الفئران المعرضة لبعض المركبات السرطانية

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فى هذه الدراسة تم استخدام (٩٠) فأر أبيض بالغ من كلا من الجنسين وقد تم تقسيم الفئران إلى ثلاث مجموعات متساوية .

المجموعة الأولى : أشتملت على عدد ٣٠ فأر وتم تجريعها عن طريق الفم بمركب الثيواستياميد لجرعة مقدارها ٢٠ مجم / كجم من وزن الحيوان الحي . أما المجموعة الثانية : وقد احتوت على عدد ٣٠ فأر وقد تم تجريعها بنفس الطريقة بمركب ٢ ، ٤، ٦ ثلاثى ميثيل الانيلين لجرعة مقدارها ٣٠ مجم / كجم من وزن الحيوان الحي. بالنسبة للمجموعة الثالثة : وقد اشتملت على عدد ٣٠ فأر وتم استخدامها كمجموعة ضابطة ولم تجرع بأى من المادتين . وقد استمرت التجربة ١٢ اسبوعاً متوالياً وكانت الجرعات يومية وقد تم الحصول على عينات الدم اللازمة لفصل المصل وكذا عينات الأنسجة كل اسبوعين من حيوانات كل مجموعة عمل وظائف الكبد والكلى وكذلك عينات من الأعضاء الداخلية مثل (الكبد – الكلى – الرئتين – القلب – الطحال) لدراسة التغيرات الهستوباثولوجية وقد أسفرت الدراسة على الآتى.

١ – وظائف الكبد :

وجد أن أعطاء جرعة مقدارها ٢٠ ، ٣٠ مجم /كجم من وزن الحيوان لكل من مركب الثواستياميد ، ٢، ٤، ٦ ثلاثى ميثل الاثيلين يؤدى رلى زيادة معنوية واضحة في نشاط خميرتى الاسبرتات أمينوترانس فيراز والالينين أمنيو ترانس فيراز كذلك خميرة الفوسفاتيز القلوية في مصل الفئران بالأضافة إلى الجلوكوز والبروتين الكلى والكوليسترول كما اسفرت النتائج أيضاً على زيادة تركيز البليروبين الكلى. أما في حالة البيليروبين المباشر الغير المباشر فقد زاد كلا منهم زيادة معنوية ملحوظة .

٢ – وظائف الكلى :

اسفرت النتائج أن كل من مركب الثيواسيتاميد ٢ ، ٤، ٦، ثلاثى مثيل الانيلين يحدث زيادة معنوية وملحوظة في تركيز كل من الكرياتينين ، اليوريا وحامض البوليك في مصل الفئران في المجموعتين الأولى والثانية .

٣ – التغيرات الهستوباثولوجية :

أسفرت الدراسة أن كل من الثيواسيتاميد ، ٢، ٤، ٦ ثلاثى مثيل الانيلين يحدث تغيرات هستوباثولوجية فى كل من الكبد والكلى واعضاء أخرى لفئران المجموعتين الأولى والثانية وان التغيرات كانت ملحوظة وواضحة في الكبد والكلى اكثر من أى عضو آخر. ولذلك ينصح بالحد من استخدام هذه المواد سواء كاضافات للعلائق أو في الصبغات ووضع اللوائح والقوانين التى تنظم استخدامها للحد من أضرارها البالغة على كل من الانسان والحيوان .