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The Influence of Vitamin C or Selenium on Paraquat-induced Toxicity in Guinea Pigs

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Abstract: Paraquat, PO (1,1'-dimethyle-4,4'-bipyridylium dichloride) is widely used herbicide known to cause fatal intoxication in both human and animals. This study was carried out to investigate additional information about the deleterious haematological, hepatic, renal and neurotoxicities of this herbicide on male guinea pigs. Animals were injected intraperitoneally with sublethal dose (1 mg kg^{-1} b.wt.). The tested parameters were determined after 7 days of PG injections. The data presented in this work showed that PO administration induced elevations in haematocrit values, while the number of blood platelets were decreased. The number of red blood cells, haemoglobin contents and total bilirubin concentrations showed no significant changes. It provoked sever perturbations in liver functions as indicated by inhibition of aspartate and alanine aminotransferase (AST), (ALT) activities. Paraquat administration resulted in marked impairment in the renal function as indicated by elevations in serum urea levels. The hepatic and renal dysfunctions lead to increases in serum total lipid and triglyceride concentrations. On the other hand, hypocholesterolaemia as well as hypoglycaemia were prominent. Also, significant decreases were demonstrated in serum total protein and albumin concentrations, while the serum globulins were significantly increased with unique declines in the measured serum cation concentrations (Fe^{3+}, Na^{+} and K^{+}) and the water content of blood, liver, kidney and lung. Serum uric acid concentrations and the water content of muscle are still at their normal levels. Paraquat administration revealed consipecious disturbances in acetyl cholinesterase (Ach El and creatin kinase (CK) activities. Also, this work was planned to evaluate the ability of either vitamin C (vit. C) or selenium (Se) to prevent or reduce its toxic effects. The results show that i.p. injection of vit. C (100 mg kg^{-1} b.wt.) was highly effective than Se (20 μ mol/kg b.wt.) in the protection against paraquat induced toxicity. The mode of toxic action of PG and the effect of either vit. C or Se in preventing or reducing these toxic effects were discussed in details. It is concluded that vit. C might be an important participant in the treatment of PO toxicity. Also, the treatment with vit. C should include a suitable hyperglycaemic drug.

Key words: Paraduat-induced toxicity, vitamin C, selenium, Guinea pigs

Introduction

Paraquat (1,1'-dimethy1-4,4'-bipyridylium dichloride; PQ) is a member of bipyridylium herbicides which was discovered in 1955 and placed on market in 1962 (Sagar, 1989). Its toxic effects in the rat were first described by Clark *et al*. (1966). This relatively non selective foliage-applied contact herbicide is widely used in over 130 countries (Sagar, 1989). PQ is toxic to various mammalian species and its toxicity affects lungs, liver, brain, kidneys, and other organs (Smith and Health, 1976; Corasaniti *et al*., 1992). Also, PQ has been reported to be a neurotoxicant in humans (Grant *et al*., 1980; Hughes, 1988), rat (De Gori *et al*., 1988; Iannone *et al*., 1988; Dey *et al*., 1990) and mouse (Woolley *et al*., 1989).

The herbicide PQ is an example of a compound that can raise the level of reactive oxygen species in that it can undergo redox cycling and produce reactive oxygen species such as hydroxal radical and superoxide anion (Sies, 1988). Conditions of oxidative stress have been associated with major clinical conditions like rheumatoid arthritis, myocardial infarction, emphysema, and parkinson's disease (Halliwell, 1987).

There have been numerous fatalities caused by accidental or deliberate ingestion throughout the world. However, its fatal dose is not yet established in man (Ameno *et al*., 1994). After the initial acute symptoms the patients is characteristically free from symptoms for first two or three days and this period of well-being is misleeding. Symptoms then appear and rapidly progress to death at a time when the amount of PQ. in the body should be negligible. It is reasonable to presume that the damage occurs during this period of apparent well-being. Treatment to be effective would be applied during this latent period. As there is no known antidote to PQ (Soyannwo *et al*., 1968).

Many different therapeutic measures to treat PQ intoxication have been investigated, including the administration of antioxidants, such as reduced glutathione, vitamin E (Shahar *et al*., 1980), superoxide dismutase (Patterson and Rhodes, 1982), catalase and metal chelators such as deferoxamine (Van der Wal *et al*., 1990). The results, however, have not been satisfactory. Non of these agents was able to suppress or interfere with the formation of the PC radical and more effective therapy for PQ intoxication is needed.

It is assumed that reduction of oxidative damage is possible by increasing the antioxidant capacity of tissues and cells. There is increasing evidence that vitamin C (vit. C) and selenium (Se) have antioxidant properties (Barja *et al*., 1994; Stajn, 1997, respectively).

Vitamin C (ascorbic acid) is a water soluble vitamin. It is one of the biologic parameters involved in cell defence against oxygen free radicals. It is an ideal antioxidant to increase tissue protection from oxidative stress in human due to its easy, effective and safe dietary administration in large range of concentrations without harmful side effects. Altered antioxidant/prooxidant balance (Ogilvie *et al*., 1991) and strong plasma ascorbate depletion (Galley *et al*., 1996) have been recently observed in sepsis patients whereas therapy with antioxidants in animals (Goode and Webster, 1993) or with vitamin C in humans (Sawyer *et al*., 1989) increased survival during sepsis (Goode and Webster, 1993) or respiratory distress syndrome by as much as 50% (Sawyer *et al*., 1989). Selenium is an essential element and its role in normal metabolism has been well established. It exists in biological fluids bound to specific Se-binding proteins and largely as a constituent of various selenoproteins (Bansal *et al*., 1990; Burk and Hill, 1993).

It has been proved, scientifically, that selenium is a constituent of the human enzymes. It acts as a prosthestic group in the enzyme glutathione peroxidase. This enzyme is a natural antioxidant found in many tissues dependent upon a supply of $NADPH_2$.

Reduced activity of glutathione peroxidase contributes greatly to peroxidative damage (Zachara *et al*., 1990; Wang *et al*., 1994). It is reported that its protective effect is related to improvement of antioxidant defence system (Lane *et al*., 1991).

Paraquat toxicity was significantly enhanced in mice deficient in Se (Bus *et al*., 1975). Similarly, Omaye *et al*. (1978) reported the phenomenon of increased lethality of PQ in rats fed a selenium-deficient diet. Also, Glass *et al*. (1985)

demonstrated that enhanced lipid peroxidation is a major mechanism of lung injury in selenium-deficient rat lungs.
The present study was planned to evaluate additional information about deleterious haematological, hepatic, renal and neuro-toxicities of PQ on guinea pigs as well as the protective effect of either vit. C or Se administration against its toxicities. Guinea pigs are ideal laboratory animals for this kind of studies since they simultaneously lack, like humans, the capacity to endogenously synthesize vit. C due to lack of expression of the L. gulono-gamma-lactone oxidase gene (Yagi, 1996).

Materials and Methods

Experimental animals and treatment: Male adult guinea pigs, weighing about (600 to 700 g) were used in this present experiments. They were purchased from Abees farm and were acclimated under standard conditions. Animals were housed in groups in stainless steel cages in a room at a temperature of 22-24°C and with a 12 h light/12 h dark cycle. Commercial diet and water were given *ad libitum,* twice daily.
Paraquat (1,1'-dimethyl-4,4'-dipyridiliurn dichloride) was purchased from Sigma Chemical Co. (St. Louis, Mo, Sigma No. D-3506). Preliminary experiments were conducted to determine an intraperitoneally sublethal dose. It was found to be 1 mg kg^{-1} b.wt.
Vitamin C (L-ascorbic acid), was obtained as cebion ampoules from Merk, Germany. It was given to guinea pigs with a concentration of 100 mg kg^{-1} b.wt. intraperitoneally as it was described by (Spittle, 1971). My preliminary experiments proved that this dose was more effective on preventing adverse side effects of PQ when divided into five consecutive days.
Selenium as sodium selenite (Na_2Se0_3) was obtained from BDH England and was given intraperitoneally at a dose of 20 μ mol/kg b.wt. It was proved to be non toxic and more effective antioxidant when this dose was divided into 5 consecutive days (Araya *et al.*, 1990; El-Soian, 1998; Mohamed, 1998).

Animal Groups: The animals were divided into six groups, ten animals each as follows:

Group (1) (Normal control group): The animals did not receive any treatment.

Group (2) (Vitamin C-treated group): The animals received 100 mg of vit. C/Kg b.wt. divided into 5 consecutive days.

Group (3) (Selenium-treated group): The animals received 20 μ mol of Se/Kg b.wt. divided into 5 consecutive days.

Group (4) (Paraquat-vit. C-treated group): The animals were given a single intraperitoneal sublethal dose of PQ (1 mg kg^{-1} b.wt.).

Group (5) (Paraquat-vlt. C-treated group): The animals were given PG (1 mg kg^{-1} b.wt.) and vit. C (20 mg kg^{-1} b.wt.) simultaneously followed by additional 4 doses of vit. C (20 mg kg^{-1} b.wt.) for 4 days.

Group (6) (Paraquat-Se-treated group): The animals were treated similarly as group 4 using Se (4 μ mol/Kg b.wt.) instead of vit. C.
Animals were killed by sudden decapitation at day 7 post paraquat dosing. Blood was collected in heparinized tubes for cellular determinations and non-heparinized tubes for serum preparation.

Physiological and biochemical determinations: Erythrocytic counts (ABCs), haemoglobin contents (Hb), haematocrit values (Hct)and blood platelets counts (PLt) were determined by using the Coulter Counler Plus II.
Serum was prepared by centrifugation of the blood at 8000 r.p.m. for 15 minutes. The activities of transaminases [aspartate aminotransferase (AST or GOT) and alanine aminotransferase (ALT or OPT)], acetyle cholinesterase (AchE) and creatin kinase (CK) in the serum, as well as total lipids, triglycerides, cholesterol, blood sugar, total bilirubin, urea, total protein and albumin concentrations in the serum were estimated by using BM/Hitachi system 717 Automatic Analyzer.
Levels of iron in the serum were measured by atomic absorption spectrophotometer equipped with an HGA-400 graphite furance (Perkin-Elmer-Germany). While the levels of Sodium and Potassium in the serum were estimated using flame photometry (Beckman Labyte 800).
For the determination of water contents in organs (blood, liver, muscles, kidney and lung), the samples were preweighed in glass bottles. Tissue water contents were measured as weight loss on drying to constant weight at 105°C.

Statistical analysis: Measured values are presented as the arthmetic of ten experiments ± the standard error (S.E.). Results were analyzed using student's t-test. Differences were considered significant at $p < 0.05$.

The test significant of differences were calculated between:

a. Means of control group and the means of either of these treated groups: PQ group, vit. C group, Se group, PC) + vit. C group or PQ + Se group and they were reffered by letter (a).
B. Means of PQ group and either of PG + vit. C-treated group or PQ + Se-treated group. They were reffered by letter (b).

Results

Intraperitoneal administration of sublethal dose of PQ (1 mg kg^{-1} b.wt.) produced significant changes in some haematological parameters of guinea pigs after 7 days. Table 1 depicts significant increases in haematocrit values, while numbers of blood platelets were significantly decreased. At the same time red cell counts as well as haemoglobin concentrations showed unsignificant alterations.
Table 1 also shows that the simultaneous i.p. injection of a single dose of PQ and 20 mg vit. C/kg b.wt. followed by additional 4 doses of vit. C (20 mg kg^{-1} b.wt.) for 4 days partially reduced the increases in haematocrit values and succeeded completely in preventing the decreases in the number of blood platelets that were induced by PQ.
The results depicated in Table 2 show that PQ administration resulted in marked decreases in liver transaminases (AST and ALT) and AchE activities, while CK activities were increased. The activities of both AST and ALT did not show any significant changes in the group injected with both PQ plus vit. C, while the activities of both AchE and CK were partially improved, since there still significant differences between their values (group 5) and those of both control and PQ-treated groups.
The data in Table 3 indicate that blood sugar levels and serum cholesterol concentrations were decreased, while serum total lipid and serum triglyceride concentrations were increase. The total bilirubin concentrations did not show significant changes as compared to control.
Table 3 also indicates that administration of PQ caused increases in serum urea levels. The serum total protein and albumin concentrations were significantly decreased, while serum globulins concentrations were increased. There were no significant alterations in serum uric acid levels. The total lipid, triglyceride and cholesterol concentrations were unchanged in the group treated with both PQ and vit. C, while the blood

Table 1: The effect of i.p. administration of a sublethal dose of PQ (1 mg kg^{-1} b.wt.) with or without the i.p. injection of the antidote (100 mg of vit. C/kg b.wt. or 20 μ mol of Sod.selenite/kg b.wt.) as well as the antidote alone on some haematological parameters

Group number	Studied groups	R.BC's (x 10^6/μl)	Hb (g/dl)	Hct (%)	Plt (m/mm^3)
1	Normal control	5.16 ± 0.020	13.92 ± 0.020	43.92 ± 0.002	273,0 ± 2.30
2	Vit. C	5.14 ± 0.060	13.91 ± 0.040	43.94 ± 0,103	269.0 ± 1.90
3	Se	5.15 ± 0.050	13.90 ± 0.090	43.97 ± 0.180	274.0 ± 2.70
4	PQ	5.17 ± 0.090	13.89 ± 0.102	57.37 ± 0.080[a]	153.0 ± 3.09[8]
5	PO + vit.C	5.18 ± 0.080	13.94 ± 0.081	47.03 ± 0.193[a,b]	265.0 ± 4.82[b]
6	PQ + Se	5.15 ± 0.070	13.96 ± 0.108	57.01 ± 0.102[a]	220.0 ± 3.20[a,b]

Each value represents the mean of 10 experiments ± S. E.
a, b = Statistically significant ($p < 0.05$) when compared with values of the control group or PQ - treated group, respectively

Table 2: The effect of i.p. administration of a sublethal dose of PQ (1 mg kg^{-1} b.wt.) with or without the i.p. injection vit. C/kg b.wt. or 20 μ mol of sod.selenite/kg b.wt.) as well as the antidote alone on some serum enzymes activities

Group number	Studied groups	AST (GOT) (Iu/L)	ALT (GPT) (Iu/L)	AchE (Iu/L)	CK (Iu/L)
1	Normal control	85.06 ± 2.030	55.03 ± 0.901	5057 ± 20.50	76.60 ± 1.801
2	Vit. C	84.01 ± 1.986	54.09 ± 0.821	5060 ± 18.90	75.91 ± 1.302
3	Se	86.02 ± 1.899	55.07 ± 0.392	5050 ± 15.60	76.80 ± 1.200
4	PO	53.62 ± 0.908a	40.53 ± 0.123a	2647 ± 19.90a	132.10 ± 1.93a
5	PO + vit.0	86.01 ± 2.201b	56.03 ± 1.981b	3651 ± 16.20ab	88.40 ± 1.895a,b
6	PO + Se	99.58 ± 2.703a,b	61.90 ± 0.606a,b	2602 ± 20.90a	125.10 ± 1.086a

Each value represents the mean of 10 experiments ± S. E.
a, b = Statistically significant ($p < 0.05$) when compared with values of the control group or PQ - treated group, respectively

sugar levels were significantly decreased as compared to both control and PQ-treated group. Simultaneous administration of PQ plus vit. C partially reduced the changes in serum urea levels, as well as the serum total protein, albumin and globulins concentrations that were induced by PQ, since there were significant differences between the values of group (5) and those of either the control or the PQ group.

The data concerning with the changes in the serum Fe^{3+}, Na^+ and K^+ concentration are depicated in Table 4. According to this table, PQ evoked marked decreases in concentrations of all measured cations as compared to controls. There is no significant differences between Fe^{3+} values of control and those of animals received both PQ and vit. C treatments, on the other hand, the changes in the Na^+ and K^+ levels were partially improved in animals of group (5).

Table 5 illustrates the results of the analysis of the water content of selected organs. According to this table, significant decreases were observed in the water contents of blood, liver, kidney and lung, while those of muscle were still at normal levels.

Simultaneous administration of PQ plus vit. C reduced partially the PQ-mediated dehydration of blood, liver, kidney and lung (group 5).

Table 1 to 5 indicate that the co-administration of PQ plus Se provided partial protection against the perturbations in the number of blood platelets, transaminases activities, total lipids, triglycerides, cholesterol and Fe^{3+} concentrations which were caused by PQ administration. At the same time PQ plus Se failed to improve PQ-induced disturbances in the other tested parameters.

The results obtained in this study showed that the administration of either vit. C or Se did not have any statistically significant effect on the studied parameters as compared to control.

Discussion

It has been observed that the intraperitoneal administration of a sublethal dose of PQ (1 mg kg^{-1} b.wt.) evocked marked changes in some haematological parameters of guinea pigs after 7 days of injection. Significant increases were observed in the haematocrit values while numbers of blood platelets were significantly decreased. On the other hand, red cell counts and haemoglobin concentrations remained in the normal range. Also, no significant changes were reported for the total bilirubin concentrations.

The present results confirm the previous observations of other investigators on man as well as on experimental animals. Soyannwo *et al*. (1968) measured the haemoglobin concentration of a farmer (patient) after 4 days of ingestion of a mouthful of gramaxone (paraquat). He found that it was 14.1 g/100 ml.

Increased haematocrit values have been observed after dosing rat with PQ (Fisher *et al*., 1975).

Lock (1979) found that the great vessel haematocrit in rat was significantly increased after oral PQ administration. On the other hand, he observed no significant differences in total red cell volumes.

Paraquat produced haemoconcentration in the rat (Fisher *et al*., 1975; Crabtree *et al*., 1977; Lock, 1979), the increase in haematocrit being due to a reduced plasma volume. The reduction of plasma volume is a consequence of a large fluid shift from the tissues into the lumen of the gastrointestinal tract seen after oral administration of PQ and diuresis following PQ s.c. or p.o. Thrombocytopenia can result from decreased platelet production, increased platelet destruction or sequestration of platelets in the spleen. Decreased platelet production can result from a reduced number of megakaryocytes in the bone marrow and/or the lungs or from ineffective platelet production from normal numbers of megakaryocytes (Bell *et al*., 1976; Campbell *et al*., 1984). Paraquat is known as a pulmonary toxicant. Regardless of the route of administration, it produces lung injury due to its selective accumulation. Therefore, the observed decreases in the number of blood platelets may be due to PQ-induced lung damage.

The present results show that the administration of PQ decreased the activities of serum transaminases significantly. Transaminases (aminotransf erases) can function both in amino acid catabolism and biosynthesis. Pyridoxal phosphate resides at the catalytic site of all transaminases. Increased serum transaminase activity in liver disease is assumed to reflect leaking from injured cells. Conversely, initially elevated serum transaminase activities may fall as the clinical course of massive hepatic necrosis deteriorates, suggesting that the liver is so severely damaged that little enzyme activity remains (Zakim and Boyer, 1982).

Table 3: The effect of i.p. administration of a sublethal dose of PQ (1 mg kg^{-1} b.wt.) with or without the i.p. injection of the antidote (100 mg of vit. C/kg b.wt. or 20 μ mol of sod. selenite/kg b.wt.) as well as the antidote alone on some biochemical indices

Studiesd Groups	1	2	3	4	5	6	7	8	9	10
Normal control	212.0±3.514	102.0±1.010	29.0±0.811	90.0±1.001	0.201 ±0.001	34.09±0.104	2.10±0.001	6.0±0.129	3.6±0.031	2.1±0.021
Vit.0	210.0±3.509	103.0±1.950	29.0±0.905	91.0±1.231	0.202±0.001	34.11±1.201	2.10±0.002	6.0±0.093	3.6±0.042	2.1±0.032
Se	214.0±2.509	100.0±2.001	29.0±0.790	90.0±0.990	0.200±0.001	34.13±0.812	2.20±0.001	6.1±0.103	3.7±0.021	2.2±0.021
PG	236.0±3.320[a]	124.0±1.121[a]	22.0±0.326[a]	76.0±0.702[a]	0.201±0.002	39.4±0.812[a]	2.20±0.002	4.1±0.002[a]	1.3±0.001[a]	2.7±0.006[a]
PQ + vit.0	209.0±3.210[b]	100.0±2.101[b]	28.0±0.991[b]	60.0±0.891[a]	0.200±0.001	36.0±0.401[a,b]	2.20±0.001	5.5±0.009[a,b]	3.0±0.006[a,b]	2.4±0.003[ab]
PQ + Se	225.0±2.910[a,b]	112.0±1.980[a,b]	25.0±0.319[a,b]	58.0±0.609[a]	0.201±0.001	40.0±1.009[a]	2.20±0.002	4.2±0.090[a]	1.4±0.009[a]	2.6±0.010[a]

1 = Serum total lipids (mg/dL) 2= Serum triglycerides (mg/dL), 3= Serum cholesterol (mg/dL), 4 = Blood sugar level (mg/dL), 5- Total bilirubin (mg/dL), 6= Serum urea (mg/c11-), 7 = Serum uric acid (mg/dL), 8= Serum total protein (g/dL), 9= Serum Albumin (g/dL) and 10= Serum Globulin (g/dL)
Each value represents the mean of 10 experiments±S.E.
a, b = Statistically significant ($p<0.05$) when compared with values of the control group or PQ - treated group, resepctively

Table 4: The effect of i.p. administration of a sublethal dose of PQ (1 mg kg^{-1} b.wt.) with or without the i.p. injection of the antidote (100 mg of vit. C/kg b.wt. or 20 μ mol of sod. selenite/kg b.wt.) as well as the antidote alone on some serum cations

Studied group	Serum iron (μg/dL)	Serum sodium (m mol/L)	Serum potassium (m mol/L)
Normal control	70.53±0.915	154.230±2.004	3.750±0.002
Vit. C	70.65±0.819	155.001±2.613	3.748±0.006
Se	70.72±0.718	153.919±2.680	3.751±0.003
PCL	18.43±0.102[a]	126.050±2.080'	2.676±0.001[a]
PQ +vit.C	72.31±0.899[b]	140.056±3.305[a,b]	3.103±0.009[a,b]
PQ + Se	55.97±0.302[a,b]	128.571±2.001[a]	2.691±0.001[a]

Each value represents the mean of 10 experiments±S.E.
a, b = Statistically significant ($p<0.05$) when compared with values of the control group or PQ - treated group, respectively

Thus, it appears that PQ administration depressed trnsaminases activities as a result of sever liver dysfunction. The data presented demonstrated that the administration of PQ caused impairment in the renal function as indicated by elevations in the serum urea concentrations. Uric acid concentrations remained at the normal levels.

Soyannwo *et al*. (1968) described a case of a farmer after taking a mouthful of gramaxone (paraquat), his blood urea levels were 178 mg/100 ml and 310 mg/100 ml after 4 and 6 days of PQ ingestion, respectively. Similarly, Shahar *et al.* (1980) found that the plasma urea concentration of a 3-yearold boy increased to 60 mg/100 ml after 4 days of swallowing of a mouthful of 20 % PQ solution, his initial plasma urea concentration was 12 rng/100 ml after 24 h of ingestion. In experimental animals, PQ induced similar effect, a reduction in renal function has been reported following PQ administration to mice (Ecker *et al*., 1975) and dog (Davis *et al*., 1977). Also, Lock (1979) recorded a rise in the plasma urea concentration of rat after 24 h of p.o. administration of a single dose of PQ (680 μ mol/kg. b.wt.).

Renal failure in dogs was observed at a plasma concentration of approximately 20 pM PQ (Pond *et al*., 1993). Also, Abdel-Magied (1994) stated that PQ causes pathogensis to the rat kidney tissues that could possibly lead to renal dysfunction. *In vitro,* the metabolism of proximal renal tubular cells was affected by a paraquat concentration of 500 pM (Molck and Friis, 1997).

Groves *et al*. (1995) studied the pathways responsible for the entrance of the polyvalent organic cation (PQ) into the renal cell. They measured the uptake of this compound in suspensions of rabbit renal proximal tubules. Their observations suggested that PQ is transported by a novel peritubular polyvalent organic cation transport system which may provide an additional mechanism by which the kidney can clear potentially harmful xenobiotics from the systemic circulation.

It is obvious from the results of the present study that the administration of a sublethal dose of PQ caused deleterious effects on the haematopoietic system as well as the hepatic and renal organs. It may also causes perturbations in the functions of other tissues or glands.

The present work demonstrated that PQ administration resulted in significant hyperlipidaemia, hyertriglyceridacmia and hypocholesterolaemia.

Hyperlipidaemia has long been recognized as a complication of some forms of parenchymal liver disease. Also, hyperlipidaemia is common in the nephrotic syndrome. The primary mechanism appears to be increased hepatic synthesis, but reduced catabolism of lipids (Wyngaarden and Smith, 1985).

Triglycerides concentration is elevated in cases of liver dysfunction, chronic uremia and dialysis and nephrotic syndrome. Also, diuretic agents may associated with small increases in triglyceride levels (Wyngaarden and Smith, 1985).

Cholesterol concentrations are determined by metabolic functions which are influenced by integrity of vital organs such as liver and kidney (Marcus and Milton, 1982).

El-Hennawy *et al*. (1980) reported that administration of a low dose of some herbicidal agents to rats resulted in a decrease of serum cholesterol probably as a hepatotoxic effect. similar results were also seen in rabbits (Ryhanen *et al*., 1984). Also, Shakoori *et al.* (1988) and Saleh (1990) have shown that different insecticides and herbicides produce decreases in cholesterol content.

Thus, it appears that PQ administration caused disturbances in lipid metabolism as a result of hepatic and renal dysfunction. Hypoglycaemia has been reported in a wide variety of acquired hepatic diseases. It may be caused by excessive removal, by inadequate production of glucose or by a combination of both mechanisms. Excessive insulin secretion results in hypoglycaemia (Campbell *et al*., 1984). The hypoglycaemia of congestive heart failure, sepsis and Reye's syndrome is considered to be due to hepatic mechanism (Wyngaarden and Smith, 1985).

The liver cell, which is freely permeable to glucose, is a principal mean of regulating the blood glucose concentration. Defective enzymes of gluconeogenesis lead to hypoglycaemia. Because gluconeogenesis is dependent upon fatty acid oxidation, any impairment in fatty acid oxidation leads also to hypoglycaemia.

The data presented demonstrated that PQ induced significant decreases in serum total protein and albumin concentrations, while the serum globulins were significantly increased. Concentration of protein determines colloidal osmotic pressure of plasma. The concentration of protein in plasma is influenced by hepatic failure and renal function. It decreased in acute or chronic glomerulonephritis, nephrosis and acute or chronic hepatic insufficiency (Marcus and Milton, 1982).

Albumin is synthesized exclusively in the liver. The synthetic rate is influenced by systemic or liver disease, thyroid

Table 5: The effect of i.p. administration of a sublethal dose of PQ (1 mg kg^{-1} b.wt.) with or without the i.p. injection of the antidote (100 mg of vit. C/kg b.wt. or 20 μ mol of sod.selenite/kg b.wt,) as well as the antidote alone on the water content on some guinea pig organs (g H_2O/g dry wt.)

Studied groups	Tissue				
	Blood	Liver	Muscle	Kidney	Lung
Normal control	5.121 ± 0.001	2.754 ± 0.001	2.754 ± 0.001	2.571 ± 0.001	3.224 ± 0.002
Vit. C	5.112 ± 0.003	2.756 ± 0.002	2.753 ± 0.001	2.572 ± 0.002	3.225 ± 0.001
Se	5.122 ± 0.002	2.755 ± 0.002	2.755 ± 0.002	2.572 ± 0.001	3.226 ± 0.002
PQ	3.601 ± 0.001[a]	1.545 ± 0.001[a]	2.756 ± 0.003	1.655 ± 0.002[a]	2.010 ± 0.001[a]
PQ + vit.0	4.090 ± 0,622[a,b]	2.151 ± 0.001[a,b]	2.752 ± 0.002	2.097 ± 0.003[a,b]	2.688 ± 0.001[a,b]
PQ + Se	3.101 ± 0.009[b]	1.549 ± 0.001[a]	2.777 ± 0.004	1.661 ± 0.001[a]	2.019 ± 0.004[a]

Each value represents the mean of 10 experiments ± S.E.
a, b = Statistically significant ($p < 0.05$) when compared with values of the control group or PQ - treated group, respectively

hormone, glucocorticoids, plasma colloid osmotic pressure, and toxins. The rate of albumin degradation is increased in exfoliative dermatities, sever burns and nephrotic syndrome. Thus, albumin concentration, which reflects the balance between synthesis and degradation or loss, may be importantly influenced by factors other than the functional state of the liver (Wyngaarden and Smith, 1985). Badawy (1997) reported slight decrease in serum albumin of rats and sheep after administration of certain insecticides. He stated that the decrease of serum albumin may be due to an increase in the permeability of the walls of the blood vessels or/and the release of the kidney to albumin due to the insecticide. It can be suggested that the depression of serum total protein and albumin levels observed in the present investigation may be due to the suppressive action of PQ on the synthetic capacity of liver and/or the enhancement of renal tubular excretion of proteins lost in urine.

Albumin deficiency may share in the water loss from the blood and organs that was obtained in the results of this study. Gobulins include coagulation factors, immunoglobulins, the complement system, circulating enzymes, and proteins with specific transport functions. The concentration of serum globulins may be influenced by a wide variety of hepatic and extrahepatic factors and disease states. The mechanism for their increased serum concentration in liver disease may be due to release of antigenic material from injured liver cell (Wyngaarden and Smith, 1985).

The present study provides significant decreases in the serum Fe^{3+} as a result of PQ injection.

Iron concentration in the plasma is determined by several factors including: absorption from the intestine, storage in the intestine, liver, spleen and marrow, break down or loss of haemoglobin. Iron serum level decreased in iron deficiency with nephrosis and chronic renal insufficiency (Marcus and Milton, 1982). Also, it relatively common for the plasma iron level to fall as soon as iron stores are depleted but before the haemoglobin concentration has fallen producing a state of iron deficiency without anaemia (Campbell *et al.*, 1984).

The present study indicated that PG induced significant decreases in the serum Na^{2+} and K^{+} concentrations.

Badawy (1997) observed similar decreases in serum sodium and potassium contents as a result of administration of certain organophosphorous compounds (insecticides) to rats and sheep. Rattner *et al*. (1983) attributed the fluctuations of the serum sodium and potassium contents of the treated animals to the disturbances in the renal function.

Sodium with associated anions provides the bulk of osmotically active solute in the plasma, thus affecting the distribution of body water significantly. Shift of sodium into cells or a loss of sodium from the body results in a decrease of extracellular fluid volume, with consequent effect on circulation, renal function and nervous system function. Sodium concentration is decreased in adrenal insufficiency; renal insufficiency, especially with inadequate sodium intake; renal tubular acidosis and unusual losses via the gastrointestinal tract, as in a acute or chronic diarrhea.

The potassium depletion has profound effects on neuromuscular, cardiac and renal function and acid-base status (Marcus and Milton, 1982).

It is obvious from Table 5 that PG injection resulted in significant dehydration of the blood, liver, kidney and lung, while the water contents of the muscle did not affected. Lock (1979) demonstrated similar dehydration in the blood and lung following s.c. administration of PQ to rats. He stated that the reduction in the plasma volume is a consequence of diuresis. He noticed that water loading bipyridyl-treated rats either p.o. or i.p. does not rehydrate them. The mechanism whereby bipyridyls (paraquat or diquat) alter water redistribution, causing fluid loss into the lumen of the gastrointestinal tract, is not known. Thus, the reduction in renal excretory function produced by bipyridyls is probably not direct effect of these chemicals on the kidney but is secondary to a reduction in plasma volume which alters renal haemodynamics.

The present data also indicated that PQ is a potent inhibitor of acetyl cholinesterase activity. Similar results were obtained by Di Marzio and Tortorelli (1994).

The normal function of acetyl cholinesterase is to terminate neurotransmissiton due to acetylcholine that has been liberated at cholinergic nerve endings in response to nervous stimuli. The enzyme activity in serum is reduced in poisoning by organophosphorous compounds (used as insecticides), ishock, anemia, cancer and malnutrition (Campbell *et al*., 1984).

The potency of PQ as a neurotoxic agent has been investigated to a limited extent only and the reports give ambiguous information. De Gori *et al*. (1988) reported that systemic and intracerebral administration of PQ to adult rat causes both behavioural and neurological disorders, including decreased locomotor activity.

Tanner (1989) indicated that the link between PQ and a possible induction of parkenson's diseases is constituted by paraquat's structural similarity to the 1-methyl-4-phenyldium ion, a metabolic of 1-methy1-4-pheny1-1,2,3,6-tetrahydropyridine.

The present results showed that PQ administration induced marked increase in creatine kinase activity.

The mitochondrial isoenzyme of creatin kinase functions in muscle cells to catalyze the transfere of a high-energy phosphate bond from ATP to creatin to form creatin phosphate. Creatin kinase activity increases in myocardial infarction, muscular dystrophy and in the disease of the central nervous system (Campbell *et al*., 1984). Since PQ induced disturbances in the nervous system as indicated by inhibition of acetyl cholinesterase activity, thus increased activity of creatin kinase may be due to neural toxicity. Also, it may be due to cardiac infarction.

Soyannwo *et al.* (1968) demonstrated the development of

cardiac arrest (ventricular asystole) of a farmer after eight days of ingestion of mouthful of gramoxone (paraquat).

Some investigators tried to interpret the biochemical mechanisms by which PQ causes cell damage. The damage may be related, in part, to biological reduction oxidation cycles of PQ which involves molecular oxygen and reduced flavoprotein. As a result of the reduction-oxidation cycles of PQ, oxygen radical generation, free radical-catalyzed lipid peroxidation, and membrane lysis presumably occur (Farrington *et al*., 1973; Winterbourne, 1981; Youngman and Elstner, 1981). *In vitro* experiments have demonstrated an enhancement of lipid peroxidation in lung, liver and brain microsomes following PQ administration (Talcott *et al*., 1979; Peter *et al*., 1996).

Another hypothesis concerning PQ toxicity assumes that herbicide-induced tissue damage may be not necessarily or totally dependent on peroxidation of membrane phospholipids in cells. It has been suggested that NADPH is oxidized by oxygen free radicals generated in the cyclic reduction and re-oxidation of PQ and that the resulted NADPH depletion may account for cell death by disturbing vital physiological and biochemical functions (Rose *et al*., 1976a; Brigelius *et al*., 1982). Because most oxidized glutathione is reduced rapidly by oxidized glutathione reductase with NADPH as a reductant, oxidized glutathione increases when the NADPH supply becomes rate-limiting. In the case of a direct induction of lipid peroxidation or after an indirect impairment of cellular oxidative defenses by reduced glutathione depletion, an involvement of oxygen free radical reactions due to PG toxicity is very probable (Melchiorri *et al*., 1996).

The result depicted in the present investigation clearly show that the simultaneous administration of a sublethal dose of PQ (1 mg kg^{-1} b.wt.) and 20 mg kg^{-1} b.wt. of vit. C followed by additional 4 doses of vit. C (20 mg kg^{-1} b.wt.) for 4 days reduced the serious toxic effects of PQ. It is evident from these results that the co-administration of vit. C with PG succeeded in preventing the decreases in the number of blood platelets. I mentioned before that thrornbocytopenia that was caused by PQ administration may be due to lung damage. Thus, the protective effect of vit. C is through the prevention of PQ mediated lung damage.

The co-administration of vit. C plus PQ also succeeded in returning the activities of AST and ALT back to their normal conditions since there were no significant difference between the control and group (5). In addition, the co-administration of vit. C with PQ succeeded in preventing the perturbations in the total lipids, triglycerides, cholesterol and Fe^{3+} concentrations which were caused by PQ alone.

Similar modulatory effect of vit. C on the genotoxicity of pesticides in Swiss albino mice was investigated (Khan and Sinha, 1994). Also, the protection afforded by vit. C against oxidative stress has been well documented in many studies. Sharaf *et al*. (1978) observed a decreased level of glutathione in ascorbic acid deficient animals. Vitamin C was singled out by Frei *et al.* (1988, 1989), Nandi *et al*. (1991), Ogilvie *et al*. (1991), Galley *et al.* (1996) and Regoli and Winston (1999) in its effectiveness to protect lipid from peroxidative damage and have shown that it is a potential scavenger of reactive oxygen species.

Most mammals synthesize ascorbic acid is apparently to protect the tissues from oxidant damage (Chatterjee *et al*., 1975; Chatterjee, 1978). However, humans, primated guinea pigs and flying mammals lack L-glulono-Lactone oxidase, the terminal enzyme in the pathway of ascorbic acid biosynthesis (Chatterjee, 1973). Accordingly these species are dependent on dietary sources of ascorbic acid and in case of ascorbic acid deficiency, these animals would be susceptible to lipid peroxidation (Othman and Moumena, 1998).

Recently, Cadenas *et al*. (1998) observed increases in superoxide dismutase and reduced glutathione in the vitamin C-supplemented guinea pigs. Also, Othman and Moumena (1998) demonstrated that the administration of vit. C caused marked stimulation of endogenous antioxidants (superoxide dismutase, glutathione reductase and glutathione) and reduction of lipid peroxidation in the liver of guinea pigs. Superoxide may act as an endogenous toxin. The occurrence of superoxide dismutases in nearly all aerobic creatures promoted the suggestion that O_2^- is an obligatory byproduct of a cellular metabolism in which oxygen serves as a recipient of electrons (Frank *et al*., 1980). According to this view superoxide dismutases have evolved to prevent the otherwise deleterious effects of O_2^- (Krall *et al*., 1988).

The co-administration of PQ plus vit. C succeeded partially in preventing the impairment in the renal function. There are significant differences in the serum concentrations of urea between group (5) and both control and PQ-treated group. It also, succeeded partially in preventing the disturbances in the serum total proteins, albumin, globulins. Na^+ and 10 concentrations, water contents of the selected organs (blood, liver, kidney and lung), haematocrit values and the activities of both AchE and CK that were caused by PQ alone. The kidney achieved high concentrations of PQ, greatly in excess of the concentration in plasma (Rose *et al*., 1976b). Paraquat is almost exclusively excreted by the kidney and it may suppress its own excretion causing its accumulation in this organ and may also in other organs (Ecker *et al*., 1975; Bismuth *et al*., 1987; Pond *et al*., 1993). Therefore, vit. C administration in this investigation provided partial protective effect in the previously mentioned parameters rather than complete protection against PQ-induced toxicities.

In this investigation, the effects of Se administration on PD-induced disturbances in some haematological, physiological and biochemical parameters were studied.

Although, there is an increasing evidence that Se has antioxidant properties and can provide protection from free harmful radicals, *in vivo* (Young, 1981) and the Se deficiency results in liver necrosis in rats (Johnson *et al*., 1981). Also, superoxide dismutase showed a moderate enhancement upon applying Se to Wistar rats (Newsholme and Leech, 1985) and Se is an integral component of glutathione peroxidase, an enzyme with an intracellular antioxidant role (Stadtman, 1990). In addition, Othman and Moumena (1998) observed that the administration of Se to guinea pigs caused marked stimulation of endogenous antioxidants and reduction of lipid peroxidation in liver. The present data revealed that the co-administration of Se with PQ succeeded partially in preventing the disturbances in the number of blood platelets, transaminases activities, total lipids, triglycerides, cholesterol and Fe^{3+} concentrations, while it failed in preventing the disturbances in serum urea, total proteins, albumin, globulins, Na + and K^+ concentrations, water contents of the tested organs, haematocrit values and activities of both AchE and CK that were caused by PQ injection. The accumulation of PQ in the kidney and some other organs, as previously mentioned, may cause the lack of protective effect of Se against PQ-induced perturbations in these parameters.

The results of the present work show that the administration of either vit. C or Se into normal guinea pigs did not affect blood glucose level. Similar results were obtained by Othman and Moumemna (1998). My results also revealed that the administration of either vit. C or Se with PQ induced hypoglycaemic effect than that caused by PQ alone. Othman and Moumena (1998) found that vit. C or Se administration to diazoxide hyperglycaemic guinea pigs resulted in lowering the

blood sugar level to normal values. The hypoglycaemic effect of vit. C in that case was interpreted to be due to an increase in insulin action (Paolisso *et al*., 1995) or an enhancement glucose uptake and utilization by peripheral tissues (Safinaz and Bakshwan, 1988).

It is important to note that the negative control has no effect on all the studied parameters i.e. the dose of either vit. C or Se alone is safe.

It is obvious from the present study that vit. C is superior to Se in the modulation of the toxic effects of PG administration in guinea pigs. It is concluded that vit. C might be an important participant in the treatment in cases of accidental or suicidal poisoning from PQ. Since vit. C has a serious hypoglycaemic effect, the treatment also should include a suitable hyperglycaemic drug. Further research is recommended to investigate the mechanism of protection offered by vit. C.

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