EFFECT OF DEXAMETHASONE ON LIVER FUNCTION IN MALE RATS EXPOSED TO PARAQUAT

Rana A. Asim Man S. Kalo Soulaf J. Kakel

Department of Physiology, Biochemistry and Pharmacology ,College of Veterinary Medicine, University of Mosul,Mosul, IRAQ.

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ABSTRACT

This study was conducted to evaluate the usage of dexamethasone (Dx) in the treatment of liver function tests in experimental paraquat (PQ)- induced oxidative stress in male albino rats. Three groups of rats were subjected to this trial, control, PQ group (50 mg/ kg orally) and PQ with Dx (50 mg/ kg orally, 4 mg/ kg ip. Respectively)daily throughout the 15 days. Results revealed that treatment with PQ caused a mortality rate in a ratio of 30%,significantly increased *($p \leq 0.05$)* of glucose, cholesterol, bilirubin concentrations and alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase and amylase activities but the concentrations of both triglycerides and serum proteins were reduced compared with control whereas the treatment of PQ- treated rats with Dx decreased mortality rate (30%) and corrected the activity of serum transaminases, alkaline phosphatase enzymes whereas Dx treatment induced an elevation in amylase activityin addition to the elevation of concentrations of total cholesterol, total protein and albumin in comparison with values of PQ- treated rats, Dx did not affect the concentration of glucose. In conclusion, the treatment of PQ- induced toxicity with Dx in rats was efficient in correction of most liver function tests.

INTRODUCTION

Paraquat (PQ) [1,1- dimethyl 4,4- bipiridillium] is widely spread non-selective contact herbicide. However, PQ is highly toxic for human and animals, in Asia and Africa since 1960, mortality in human due to paraquat intoxication was about 300000 cases/ year (1). A ratio of 40- 60% of acute poisoning occur within 24-72 hours while sub acute cases die throughout a few weeks with oral mean lethal dose(LD50) in rats is 157 mg/ kg (1,2).Oral intoxication with PQ is the most common route in mammals resulting in acute inflammation in throat and gut, liver and kidney necrosis in addition to the fibrosis of lung pneumocytes that considered the target organ (3) depending on PQ ability to promote redox reactions and create a heavy pool of reactive oxygen species (ROS) (4) which is the cause of oxidative stress and lipid peroxidation (5). Some reports of PQ poisoning observed a case of hepatotoxicity including degeneration and necrosis of hepatocytes (6).

Dexamethasone (Dx) is well established drug used as immunosuppressant, it is an artificial drug affiliates to the glucocorticoides hormones, it's activity is about 20-30 folds more than cortisol. Dx used as anti- inflammatory and anti allergic drug as well as the treatment of odema (7). Studies referred to that Dx has some antioxidant properties based on reduction of malondialdehyed (MDA) and elevation of superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GSH-PX) during treatment with Dx in both plasma and tissues (7). Because of the fatal impact of PQ on human and animals, and loss of respective treatment (8) also there was no studies on the advantages of the use of Dx to treatment of PQ poisoning (5), this study aimed to evaluate the hazardous effects of PQ on liver function and the effect of Dx in correction of disturbed liver functions indices resulted from the treatment with acute dose of PQ in male albino rats.

MATERIALS AND METHODS

Animals: Thirty adult albino male rats were subjected to the treatment with age ranged 70-90 days and weight 210 -245 g and they were divided into three equal groups (10 rats/ group) and brought in rat cages in controlled circumstances including ambient temperature (22 ±3 Cº) and light:dark cycle (12:12 hours).

Study was carried out in November / 2011in college of veterinary medicine/university of Mousl. Animals supplied with diet and drinking water *ad libitum*, diet ingredients were got from market and mixed in order to match the nutritional requirements of rats.

Study design:

1- Control group: Treated with distilled water by oral intubation and injected with normal saline (0.9 % NaCl) ip. daily for 15 days.
2- PQ group: Treated with PQ (Syngenta Crop Protection Co., USA) by oral intubation (50 mg/ kg) (9) daily for 15 days, dilution was formulated to be equal to 1 ml/kg BW.
3- PQ +Dx group: Treated with PQ by oral intubation (50 mg/ kg) and injected with Dx (Swiss Pharma Pvt Ltd Switzerland) (4 mg / kg) (10) ip daily for 15 days, dilution was formulated to be equal to 1 ml/kg BW.

The duration of treatment (15 days) was based on a preliminary study which revealed that 15 days was the more suitable period with minimum mortality rate.

Blood samples: Animals were fastened for 12- hours ,blood samples collected from rats from retro- orbital vein using capillary tubes at times, 0, 7 and 15 days. Blood obtained in centrifuge test tubes, permitted for complete coagulation then centrifuged at 1500 rpm for 20 minutes using Wagtech, UK centrifuge, serum aspirated by Pasteur pipettes and put at -18 Cº.

Liver function tests: Transaminases and alkaline phosphatase (ALP) activity were estimated using commercial kits (Bio MERIEUX, France) whereas glucose, total cholesterol (TC), triglycerides (TG), total bilirubin and albumin estimated using kits (Fabricant Biolabo SA, France). Absorbance was detected using spectrophotometer UV/VIS Biotech 2601, UK.Amylase activity was estimated using Reflotron® plus

chemistry analyzer, Roche, USA. Total protein (TP) was estimated using Biuret method whereas globulin concentration calculated according to (11).

Statistical analysis: The result were expressed as mean ±SE .our data were analyzed statistically using two ways analysis of variance(ANOVA) .Group differences were determined using Duncan multiple range test.Differences were considered significant when($p \leq 0.05$)(12,13)

RESULTS

Treatment with Dx overcame on the fatal effect of PQ which was seen in PQ–treated group and caused 30% mortality in rats since 5th day of treatment.

Table (1): Effect of Dx on serum glucose and lipids in male rats exposed to paraquat .

Glucose (mg/ 100 ml)			
Time / Treatments	Zero	7 days	15 days
Control	77.71 ±3.82 *c*	79.37 ± 2.93 *c*	77.71 ± 3.82 *c*
PQ	77.64 ± 5.26 *c*	108.13 ± 6.58 *b*	123.73 ± 2.49 *a*
PQ+ Dx	73.27 ± 6.25 *c*	103.66 ± 5.71 *b*	119 .34 ± 3.45 *a*
TC (mg/ 100 ml)			
Time / Treatments	Zero	7 days	15 days
Control	91.78± 1.28 *d*	90.20± 2.67 *d*	90.06± 0.72 *d*
PQ	91.06± 2.34 *d*	104.65± 1.80 *c*	140.13± 1.13 *b*
PQ+ Dx	90.74± 0.55 *d*	106.27± 1.55 *c*	202.50± 3.12 *a*
TG (mg/ 100 ml)			
Control	75.24± 0.80 *cd*	77.34± 1.30 *c*	81.32± 0.63 *bc*
PQ	71.55± 1.56 *d*	69.12± 0.88 *d*	71.46± 3.03 *d*
PQ+ Dx	71.08± 0.95 *d*	85.88± 0.89 *b*	93.22± 1.85 *a*

Values expressed as mean ± SE.

- Different letters in a row or column refers to significance ($p \leq 0.05$)
- n = 10

A significant ($p \leq 0.05$) elevation in serum glucose in PQ- treated group at 7th day was observed compared to either control and zero value, this value elevated at 15th day however the with Dx did not revealed a significant in glucose compaired with PQ- group (table 1).

An elevation in TC resulted from the treatment with PQ at 7th day compared to both control and zero day, TC elevated significantly in the same group at 15th day compared to values of zero, 7th day and control. No significance observed in TC of PQ+ Dx- treated group at 7th day compared to PQ– treated group whereas this group showed an elevation in TC concentration at 15th day compared to PQ- treated group to represent the higher TC value among the three groups throughout 15 days (table 1).

The concentration of TG started to significantly decrease since the 7th day in PQ group and continued in the same manner till the end of treatment in comparison with control however the injection of PQ- treated group with Dx in the PQ+ Dx group lead to a gradual elevation of TG since 7th day compared to either control or zero day, this value showed significant elevation at 15th day compared to zero, PQ- treated group, control and 7th day values.

The effect of PQ at TP and globulin revealed at table (2) . There was significant increased in TP after 7 days compared to either control, zero day or PQ+ Dx groups after 7 days of treatment however TP was turned to drop after 15 days significantly ($p \leq 0.05$) in relation to both control and zero values whereas the concentration of TP in the PQ+ Dx group revealed a statistical elevation to be the higher value in comparison with control and PQ- treated groups.

Table (2): Effect of Dx on serum proteins and bilirubin in male rats exposed to paraquat.

TP (g/ 100 ml)			
Time / Treatments	**Zero**	**7 days**	**15 days**
Control	**8.93± 0.07** ***c***	**8.89± 0.16** ***c***	**8.79± 0.06** ***c***
PQ	**8.98± 0.08** ***c***	**9.47± 0.06** ***b***	**7.02± 0.03** ***d***
PQ+ Dx	**8.90± 0.11** ***c***	**7.72± 0.14** ***cd***	**12.51± 0.59** ***a***
Albumin (g/ 100 ml)			
Control	**5.21± 0.08** ***b***	**5.16± 0.08** ***b***	**5.08± 0.15** ***b***
PQ	**5.23± 0.11** ***b***	**4.46± 0.06** ***c***	**4.39± 0.13** ***c***
PQ+ Dx	**5.17± 0.12** ***b***	**5.06± 0.07** ***b***	**7.63± 0.06** ***a***
Globulin (g/ 100 ml)			
Control	**3.72± 0.02** ***c***	**3.73± 0.03** ***c***	**3.71± 0.05** ***c***
PQ	**3.75± 0.03** ***c***	**5.01± 0.04** ***a***	**2.63± 0.36** ***d***
PQ+ Dx	**3.73± 0.01** ***c***	**2.66± 0.03** ***d***	**4.88± 0.05** ***b***
Total bilirubin (mg/ 100 ml)			
Control	**0.21± 0.001** ***b***	**0.20± 0.011** ***b***	**0.21± 0.007** ***b***
PQ	**0.020± 0.006** ***b***	**0.31± 0.008** ***a***	**0.31± 0.009** ***a***
PQ+ Dx	**0.20± 0.008** ***b***	**0.20± 0.005** ***b***	**0.19± 0.004** ***b***

- Values expressed as mean ± SE.
- Different letters in a row or column refers to significance ($p \leq 0.05$)
- n = 10

On the other hand, albumin signifcantly decreased at 7th day of treatment in the PQ- treated group compared to control and zero group ,the treatment with both PQ and Dx did not showed any significant altrations at the 7th day of treatment however this value elevated over the other two groups at 15th day in the same manner of TP mentioned above, also the concentration of serum globulin observed in the current study was parallel to that of TP (table 2).

The treatment with PQ revealed significant increase ($p \leq 0.05$) in total bilirubin concentration since 7th day till the end of experiment relative to either control or zero values, in the same time, injecting of PQ- treated rats with Dx was efficient to correct bilirubin level to be around the value of control in both 7th and 15th days (table 2).

As considered with serum enzymes, the treatment with PQ caused an increase in the activities of ALT and ALP since 7th day till the end of experiment compared to either control or zero values with a significant increase ($p \leq 0.05$) of the value of 15th day compared with that of 7th day. In the same time, the activity of both ALT and ALP elevated in the group exposed to PQ+ Dx at the 7th day relative to zero day and at 15th day relative to both control group or zero time however both values of this group still significantly ($p \leq 0.05$) less than that of PQ- treated group (table 3). AST elevated only at 15th day as a result of treatment with PQ compared to control and zero time but the treatment of PQ- intoxicated rats with Dx was successful to correct the elevated activity AST to be statistically decrease than the value of PQ- treated group and around those of control and zero time. Amylase activity elevated in the PQ-treated group at 7th day compared to control and zero time to keep on same manner till the end of experiment while amylase activity observed in the group treated with both PQ and Dx declined at 7th day significantly ($p \leq 0.05$) beyond those of control and zero time however this value inturned to elevate to represent the higher activity compared with control throughout the duration of experiment (table 3).

Table (3): Effect of Dx on serum enzymes in male rats exposed to paraquat.

ALT (U/ L)			
Time / Treatments	**Zero**	**7 days**	**15 days**
Control	20.60± 0.81 **d**	21.80± 1.65 **d**	23.20± 1.46 **d**
PQ	20.80± 1.65 **d**	44.0± 0.63 **b**	58.60± 0.92 **a**
PQ+ Dx	22.60± 1.50 **d**	25.80± 0.73 **c**	45.40± 1.40 **b**
AST (U/ L)			
Control	48.49± 1.77 **ab**	46.91± 3.53 **a-c**	40.56± 1.66 **c**
PQ	42.02± 1.58 **bc**	48.77± 1.18 **ab**	50.24± 2.99 **a**
PQ+ Dx	45.39± 1.54 **a-c**	41.64± 2.78 **bc**	40.24± 2.99 **c**
ALP (U/ L)			
Control	113.20± 7.44 **dc**	114.60± 5.35 **dc**	113.0± 5.80 **dc**

PQ	113.20± 3.71 **dc**	171.0± 16.12 **a**	173.40± 4.44 **a**
PQ+ Dx	111.0± 7.54 **d**	118.0± 12.60 **c**	151.60± 9.55 **b**
Amylase (U/ L)			
Control	955± 17.96 **c**	930± 12.31 **c**	952± 8.02 **c**
PQ	958± 13.49 **c**	1037± 17.32 **b**	1049± 29.04 **b**
PQ+ Dx	938± 8.68 **c**	653± 16.22 **d**	1168± 29.09 **a**

- Values expressed as mean ± SE.
- Different letters in a row or column refers to significance ($p \leq 0.05$)
- n = 10

DISCUSSION

The decrease in mortality of Dx might be due to the anti- inflammatory effect particularly on target organ, lung which considered the main cause of death (7).

One of the results of PQ treatment and subsequent oxidative stress is hyperglycemia (5). PQ might be metabolized through enzymatic systems leading to formation of PQ^{+} which rapidly in turns to PQ^{2+} elaborating superoxide anion O_2^-. Oxygen acts as an electron receiver, the process responsible for formation of hydroxyl radical (OH^-). In this stage, nitric oxide NO^- binds with O_2^- resulting in peroxynitrite $ONOO^-$ (14). The state of oxidative stress plays a role in the creation of insulin resistance (15) which can be explained as a result of the inhibitory action of ROS on the gene of insulin receptors in addition to the destructive action of ROS on molecules that promotes insulin secretion (16). Also there will be an impeding in glucose entry to the cells (17).

The adverse effect of Dx on serum glucose was more pronounced in the cases of hyperglycemia irrespectively to the reasons, this effect of Dx may limit insulin secretion (18) also Dx exerts a negative effect on phosphatidyle inositol 3-kinase (19), it may be attributed to the administration of Dx in repetitive doses throughout the period of trial.So glucose will elevated

Results related to TC can be explained as a result of PQ– induced oxidative stress and subsequent LDL oxidation, apo- proteins in LDL oxidized leading to incompatibility of LDL to there receptors on the cells (20) on the other hand, Dx-induced hypercholesterolemia might be related to the interference of Dx with monocytes function in removing excess cholesterol as well as to the inhibition of cholesteryl esters hydrolysis and nitric oxide synthase (21). Related to TG, the high consumption of it will be an alternative source of energy in the states of stress (22). Regarding to the effect of Dx on TG, the elevation is due to the action of Dx in promoting TG- rich VLDL formation on one aspect and inhibiting lipoprotein lipase on the other aspect (23).

As considered with serum proteins, the decline might be attributed to the PQ-induced depletion of blood proteins and defective protein synthesis in the endoplasmic reticulum in addition to excessive loss of proteins through partially damaged renal

system (24). Dx injection elevated serum proteins which is in agreement with (25) who referred to the impact of Dx in correction of proteolysis.

Bilirubin elevated as a net result of ROS and consequence liver fibrosis and proliferation of bile duct endothelium, these effects disturb resistance of sinusoids leading to cholestasis and hyperbilirubinemia (26). Zhang *et al* proposed that either the immunosuppressive activity of Dx, inhibition of ROS and cytokines, improvement of lysosomal membrane or inhibition of proteases induced by Dx may be responsible for bilirubin improvement (27), another trial demonstrated that Dx has a pronounced antioxidant activity through inhibiting NO formation (28) also Dx inhibit antifibrotic mediators secreted from Kuffer cells and sinusoidal epithelium in liver (29).

As considered with liver enzymes, Akinloye *et al* (22) reported that elevated activity of ALT, ALP and AST refers to hepatotoxicity resulted from ROS activity (6). The observations of current study related to increased amylase activity can be explained as a result of pancreatic dysfunction.

The results of Dx treatment on serum enzymes might be related to the anti-inflammatory properties and limiting of vasoactive substances (30) and aggregation of stimulated macrophages and α- tumor necrotic factor (7). Dropping of amylase might be due to secretion of amylase inhibiting factor accompanying hyperlipidemia. Furthermore, Kandil and his co- workers illustrated the reason of amylase decline as that Dx can elevates pancreatitis associated protein II & III mRNA leading to decline in amylase activity (31) however the detrimental effects of PQ might be overcame on the therapeutic potency of Dx in addition to that long term treatment with Dx stimulated the secretary function of pancreatic cells and enlarging secretary granules in rough endoplasmic reticulum raising the level of amylase biosynthesis in pancreas, so Dx might be a useful agent at least in partial correction of liver enzymes which they are a vital determinant in the metabolism and homeostasis of body systems.

The conclusion related to the outcomes of present study, authors suppose that the use of Dx in treating PQ intoxication is effective in some extent with some considerations related to the time of administration and doses which may need a further studies in order to adjust the effective dose with minimal side effects in different species.

تاثير الديكساميثازون في وظائف كبد ذكور الجرذان المعرضة للباراكوات

رنا عامر عاصم، معن سمير كلّو، سولاف جبار كاكل

فرع الفسلجة والكيمياء الحياتية والأدوية كلية الطب البيطري، جامعة الموصل ،الموصل، العراق

الخلاصة

اجريت الدراسة الحالية لتقييم تأثير الديكساميثازون في تصحيح بعض معايير وظائف الكبد المضطربة جرّاء التسمم التجريبي بالباراكوات والمحدث في ذكور الجرذان البيضاء. شملت التجربة استخدام ثلاث مجاميع

من ذكور الجرذان هي على التوالي، السيطرة، مجموعة الباراكوات (50 ملغم/ كغم عن طريق الفم)، مجموعة الباراكوات مع الديكساميثازون (50 ملغم/ كغم عن طريق الفم و 4 ملغم/ كغم في غشاء الخلب) اذ دامت فترة المعاملة 15 يوما. بينت نتائج التحليل الإحصائي أن المعاملة بالباراكوات قد أدت إلى نسبة هلاكات بلغت 30% فضلا عن زيادة معنوية في تراكيز الجلوكوز، الكوليستيرول والبيليروبين فضلا عن ارتفاع فعالية الإنزيمات الناقلة للأمين، الفوسفاتاز القاعدي والأمايليز مع انخفاض تراكيز الجليسيريدات الثلاثية وبروتينات مصل الدم معنويا *($p\leq0.05$)* عن مجموعة السيطرة بينما أدت معاملة الجرذان المعرضة للباراكوات بالديكساميثازون إلى الحد من نسبة الهلاكات فضلا عن خفض فعالية الإنزيمات الناقلة للأمين، الفوسفاتاز القاعدي وتركيز كل من الجليسيريدات الثلاثية والبيليروبين الكلّي في مصل الدم (*$p\leq0.05$*) بينما ارتفعت فعالية الأمايليز وتراكيز كل من الكوليستيرول الكلي، البروتين الكلّي، الألبومين والغلوبيولين في حين لم يظهر الجلوكوز أي تغير مقارنة بالمجموعة المعاملة بالباراكوات لوحده. يستنتج من الدراسة الحالية أن الديكساميثازون يمكن أن يحد من اضطراب مؤشرات وظائف الكبد الناتج عن المعاملة بالباراكوات.

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