

## **EFFECT OF PENTOXIFYLLINE ON ACETAMINOPHEN-INDUCED HEPATOTOXICITY IN ALBINO MICE**

BY

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### **ABSTRACT**

The present work was conducted to evaluate the possible protective effect of pentoxifylline (PTX) in comparison to N-acetyl- cysteine (NAC) on the hepatotoxicity- induced by acetaminophen (AP) in mice. Furthermore, this study aimed at declaring the effect of PTX on oxidative stress and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) in this model. The current work was carried out on 36 healthy male mice weighing (25-30 grams), the animals were divided into 6 equal groups; Group (I), received intra-peritoneal (IP) single dose of normal saline (0.5ml), group (II), received NAC in a single dose of 150mg/kg, IP, Group (III), received PTX in a single dose of 100 mg/kg, IP. Group (IV), received AP in a single dose of 900 mg/kg, IP; group (V) received once administration of NAC (150 mg/kg, 30 minutes before once injection of 900 mg/kg AP, IP), group (VI), received once administration of PTX in a dose of 100mg/kg, IP, 30 minutes before IP once injection of 900 mg/kg AP). Serum alanine aminotransferase (ALT), serum TNF- $\alpha$ , hepatic tissue malondialdehyde (MDA) and hepatic tissue calcium were significantly elevated after 4 hours of AP administration in comparison to control groups. These changes were nearly reversed by pre-treatment with either NAC or PTX. This improvement of the results may be due to high efficacy of NAC and PTX as antioxidant and anti-TNF- $\alpha$ .

### **INTRODUCTION**

Acetaminophen is a commonly used analgesic and antipyretic drug, however, when used in high doses, it causes fulminant hepatic necrosis and nephrotoxic effects in humans and experimental animals (Sener et al., 2003). The biochemical mechanism by which AP- induced liver injury has been elucidated in details and is believed to be the result of meta-

bolic conversion of AP to a highly reactive intermediate, namely; N-acetyl-P-benzoquinonimine (NAPQI) by cytochrome P<sub>450</sub> mediated mixed function oxidases; this metabolite is known to be detoxified by glutathione (Dambach et al., 2006).

Lipid peroxidation mediated by oxygen free radicals is believed to be an important cause of destruction and damage to cell

membranes and attention has been focused on the role of reactive oxygen species in mediating the micro-vascular disturbances that precede tissue damage induced by various chemicals (Mah et al., 1993 and Krahauser, 2000).

Pentoxifylline (PTX) has been used in the treatment of peripheral vascular diseases because of its potent effect on flexibility of erythrocytes and reduction of platelet aggregation (Gomez-Cambronero et al., 2000). Subsequently, PTX was found to have anti-inflammatory properties mediated via inhibition of phosphodiesterase (Semmler et al., 1993). In vitro data suggest that PTX may possess anti- (TNF- $\alpha$ ) properties (Maksymowych et al., 1995). Furthermore, PTX inhibits lipopolysaccharide-induced production of TNF- $\alpha$  by monocytes (Gomez-Cambronero et al., 2000).

N-acetyl cysteine (NAC) is a well known antioxidant prevented AP-induced depletion of glutathione and superoxide dismutase as well as hepatotoxicity. NAC also abrogated transcription factors including nuclear factor Kappa-B (NF-kB) which regulate the production of inflammatory mediators implicated in hepatotoxicity (Dambach et al., 2006).

In large doses, AP is hepatotoxic causing oxidative stress and lipid peroxidation therefore; antioxidants such as NAC

have been used against the hepatic toxicity of AP. The present study aimed at declaring the possible protective effect of PTX (being antioxidant and anti-TNF- $\alpha$ ) on AP-induced hepatotoxicity in mice and to examine the effect of PTX on TNF- $\alpha$  and lipid peroxidation in this specific situation.

## MATERIALS AND METHODS

### Drugs used:

- \* Pentoxifylline (PTX) powder was purchased from Sigma CO.; it was dissolved in sterile isotonic saline solution.
- \* Paracetamol powder (N-acetyl-4 aminophenol; acetaminophen; AP) also was purchased from Sigma chemicals CO., USA. It was dissolved in sterile isotonic saline.
- \* N-acetyl cysteine (NAC) was purchased from Sigma CO.

### Animals used :

The present work was conducted on mice because of its greater susceptibility to the toxic effects of AP as compared to rats (Kuralay et al., 1998). The present study was carried out on 36 healthy male mice weighing 25-30 grams. All animals were kept under similar housing conditions. They were divided into 6 equal groups as follows:

**Group (I)** : received intraperitoneally (IP) 0.5ml of normal saline (single dose).

**Group (II)** : received NAC in a single dose of 150 mg/kg IP, (Sener et al., 2003).

**Group (III)** : received PTX in a single dose of 100mg/kg IP, (Reuter & Wallace, 1999).

**Group (IV)**: received AP in a single dose of 900 mg/kg IP, (Sener et al., 2003).

**Group (V)**: received NAC (in a single dose of 150 mg/kg, IP), 30 minutes before IP injection of 900 mg/kg AP.

**Group (VI)**: received PTX (in a single dose of 100 mg/kg, IP), 30 minutes before IP injection of 900 mg/kg AP.

All the administered agents are given as a single dose. After 4 hours of administration knifing decapitated all the animals. Blood was collected and the serum samples were stored at -70°C. Liver tissues were carefully excised, and also stored at -70°C. Tissue samples were homogenized with ice-cold 150mM KCl for determination of MDA levels. The following parameters were estimated:

\* Serum alanine aminotransferase (ALT), utilizing Randox laboratories kits, UK (Schmidt and Schmidt, 1973).

\* Serum TNF- $\alpha$  according to (Carti et al., 1992).

\* Hepatic tissue malondialdehyde (MDA) was measured spectrophotometrically using the method of Beuge and Aust, (1978).

\* Hepatic tissue calcium content was measured according to the method of Sparaw and Johnstone (1964).

#### Statistical analysis:

Statistical analysis was done using the computer system SPSS (statistical package for social science program; version 10). Student "t" test according to Pipkins, (1984), was used to compare between each two means. A value of  $p < 0.05$  was considered statistically significant.

### RESULTS

Serum ALT and TNF- $\alpha$  levels were increased significantly following treatment with AP in comparison to control group (Tab. 1, Figs. 1 & 2). Intraperitoneal pre-treatment with either NAC or PTX decreased significantly ALT and TNF- $\alpha$  levels but the levels were still higher than the control (Table, 1 and Figs. 1&2). Liver tis-

sue MDA (the end product of lipid peroxidation) and hepatic tissue calcium contents were significantly increased after IP administration of AP to the mice. Administration of either NAC or PTX intraperitoneally to mice, 30 minutes before injection of AP induced significant decrease of hepatic tissue MDA and calcium contents but the levels were still higher than the control (Table 2 & Fig. 2).

### DISCUSSION

In the present study, serum ALT and serum TNF- $\alpha$  significantly increased following AP treatment (Table 1 & Figs. 1&2). This rise in serum ALT demonstrates deterioration of liver function. Furthermore, in this model of AP-induced hepatic injury, we observed a significant increase in hepatic tissue MDA and calcium levels (Table 2 & Fig. 3). These findings are in accord with Kernna et al., (2006). As they reported that oxidative stress plays an important role in AP-induced hepatotoxicity. In addition to inducing direct cellular damage, oxidants can activate transcription of factors including nuclear factor-kappa B (NF-KB), which regulates the production of many inflammatory mediators implicated in pathogenesis of hepatotoxicity. In the current study NAC as well as PTX pretreatment reduced AP-induced hepatotoxicity as documented from significantly decreased serum ALT. Furthermore, hepatic

tissue MDA was restored to nearly control level (Table 1 & Figs. 1&3). This is because NAC is a known free radical Scavenger (Karbownik et al., 2001), the involvement of free radicals in the pathogenesis of AP-induced hepatotoxic effect is supported by previous studies done by Shibanuna et al., (1994), Rahman et al., (1998), Zhou et al., (2004), and Sullivan et al., (2005). They have been demonstrated that TNF- $\alpha$  exerts its effects via (NF-KB) in various types of cells. TNF- $\alpha$  induced NF-KB activation suggested to be mediated by reactive oxygen intermediates such as hydrogen peroxides. In addition, pretreatment with NAC for 0.5h inhibited TNF- $\alpha$ - induced generation of reactive oxygen species (ROS) as well as activation of NF-KB. NAC which is a sulfhydryl donor serving as a precursor of glutathione (GSH) synthesis and inhibiting formation of extra-cellular reactive oxygen intermediates (Dobrzynska et al., 2000). Moreover, it may directly react with electrophilic compounds such as NAPQI and free radicals. As AP metabolism is related to reduced GSH, at least part of the beneficial effects of NAC may be ascribed to the inhibition of lipo-peroxidative process. In addition, the antioxidant effect produced by PTX in this study is supported by the work of Kranse et al., (1991) and Ng et al., (2003), where they documented that PTX even in low doses (50mg/kg) has been associated with suppression of neutrophil function such as chemotaxis,

superoxide anion production, hydrogen peroxide production, phagocytosis and degranulation.

In the present study, AP-treated mice showed a significant increase in the hepatic tissue calcium (Table 2 & Fig. 3). This result is supported by the work of Ota et al., (1995) as they proposed that alteration in calcium homeostasis played a major role in cell necrosis- induced by a variety of chemical agents including AP. Pretreatment with either NAC or PTX significantly decreased hepatic tissue calcium as compared to control groups. This finding could be explained on the light of the work conducted by Beatric et al., (1989). They reported that the intrahepatocytes calcium concentration is controlled by active transport of these ions across the mitochondria, endoplasmic reticulum and plasma membrane. The liver mitochondria are protected against high cytosolic  $Ca^{+2}$  levels by the presence of glutathione, but became permeable to calcium when oxidative events convert GSH to oxidized glutathione (Li et al., 1995). In the present study NAC and PTX improved intrahepatocyte calcium homeostasis secondary to their antioxidant activity achieved by significant decrease of hepatic tissue MDA (Table 2 & Fig. ). These results also supported by the study of Anderson et al., (2005), where they demonstrated that oxidative stress provoked by alteration of hepatocyte calcium homeostasis played a

major role in cell necrosis occurs in ischemia reperfusion injury.

Furthermore, the current work showed that the level of TNF- $\alpha$  was significantly increased following AP dosing (Table 1 & Fig. 2), suggesting that TNF- $\alpha$  may be involved in liver injury elicited by AP overdose. These data corroborated by Blazka et al., (1995), they demonstrated that TNF- $\alpha$  played a role in AP-induced hepatotoxicity. In addition, Nagai et al., (2002), reported that reduced glutathione depletion causes necrosis and sensitization to tumor necrosis factor- $\alpha$ - induced apoptosis in cultured mouse hepatocytes. On the other hand, Boess et al., (1998) and Simpsn et al., (2000), have suggested that TNF- $\alpha$  is not involved in AP-induced liver injury because both TNF- $\alpha$ - knock out mice and wild type are equally susceptible to AP-induced toxicity. Also the inhibition of TNF- $\alpha$  activity fails to attenuate the liver injury elicited by AP.

On the light of the present study it could be concluded that PTX produced a prophylactic effect against acetaminophen-induced liver injury in mice. This is due to its antioxidant and anti- TNF- $\alpha$  effects. The action of PTX was comparable to the prophylactic effect of NAC in such condition. We are in need to further experimental studied on other different animal species and also human studies especially on those with normal liver functions.

**Table (1):** Changes in serum alanine aminotransferase (ALT) and tumor necrosis factor alpha (TNF- $\alpha$ ) in various groups. Mean  $\pm$  SEM. (n = 6 mice/group):

Parameter	Group (I) Control (0.5 ml saline, IP)	Group (II) NAC treated (150mg/kg /IP)	Group (III) PTX treated (100mg/kg IP)	Group (IV) AP treated (900mg/kg/IP)	Group (V) NAC (150 mg/kg, 30 minutes before IP 900 mg AP)	Group (VI) PTX (100 mg/kg, 30 minutes before IP 900 mg/kg AP)
Serum ALT (IU/ml)	11.5 $\pm$ 0.2	11.9 $\pm$ 0.4	11.8 $\pm$ 0.3	750 $\pm$ 8.6 <sup>•</sup>	75.3 $\pm$ 4.6 <sup>•+</sup>	98.8 $\pm$ 6.3 <sup>••</sup>
TNF- $\alpha$ (Pg/ml)	0.95 $\pm$ 0.02	0.97 $\pm$ 0.06	0.98 $\pm$ 0.03	4.5 $\pm$ 0.04 <sup>•</sup>	1.2 $\pm$ 0.01 <sup>*</sup>	1.8 $\pm$ 0.05 <sup>••+</sup>

SEM = Standard error of mean.

•; P value is significant (<0.05) between AP treated and control group.

\*; P value is significant (<0.05) between (NAC + AP) group and (AP) group

+<sup>•</sup>; P value is significant (<0.05) between (NAC + AP) and (NAC) groups.

••; P value is significant (<0.05) between (PTX +AP) and (AP) groups.

+; P value is significant (<0.05) between (PTX +AP) and (PTX) groups.

NAC = N-acetylcysteine

PTX= Pentoxifylline

AP = acetaminophen.

**Table (2):** Changes in hepatic tissue calcium and malondialdehyde (MDA) in various groups.Mean  $\pm$ SEM. (n=6 mice/group):

Parameter	Group (I) Control (0.5 ml saline, IP)	Group (II) NAC (150mg/kg /IP)	Group (III) PTX (100mg/kg /IP)	Group (IV) AP (900mg/kg/IP)	Group (V) NAC (150 mg/kg, IP before AP (900 mg /kg IP)	Group (VI) PTX (100 mg/kg, IP, 30 minutes before AP (900 mg/kg IP)
Hepatic tissue MDA (nmol/gm tissue)	1.4 $\pm$ 0.001	1.5 $\pm$ 0.002	0.99 $\pm$ 0.001	3.7 $\pm$ 0.03•	1.99 $\pm$ 0.005*+ <sup>+</sup>	2.1 $\pm$ 0.01+••
Hepatic tissue Ca <sup>2+</sup> (mg/g m tissue)	0.99 $\pm$ 0.002	0.98 $\pm$ 0.001	0.88 $\pm$ 0.001	3.8 $\pm$ 0.01•	1.9 $\pm$ 0.03*+ <sup>+</sup>	2.1 $\pm$ 0.02+••

SEM = Standard error of mean.

•; P value is significant (&lt;0.05) between AP treated and control group.

\*; P value is significant (&lt;0.05) between (NAC + AP) group and (AP) group

+<sup>+</sup>; P value is significant (<0.05) between (NAC + AP) and (NAC) groups.

••; P value is significant (&lt;0.05) between (PTX +AP) and (AP) groups.

+; P value is significant (&lt;0.05) between (PTX +AP) and (PTX) groups.

NAC = N-acetylcysteine

PTX= Pentoxifylline

AP = acetaminophen.

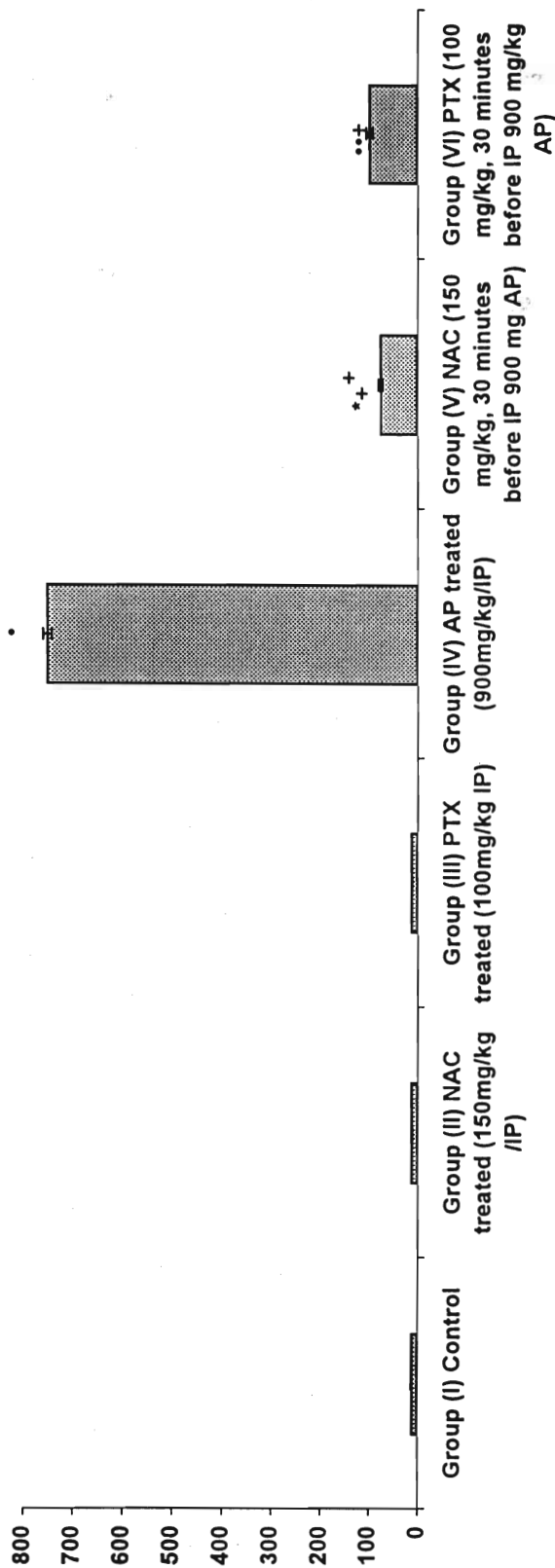


Fig (1): Changes in serum alanine aminotransferase (ALT) in various groups. Mean  $\pm$  SEM (n = 6 mice/group).

SEM = Standard error of mean.

- \*; P value is significant (<0.05) between AP treated and control group.
  - \*; P value is significant (<0.05) between (NAC + AP) group and (AP) group.
  - +; P value is significant (<0.05) between (NAC + AP) and (NAC) groups.
  - \*\*; P value is significant (<0.05) between (PTX +AP) and (AP) groups.
  - +; P value is significant (<0.05) between (PTX +AP) and (PTX) groups.
- NAC = N-acetylcysteine  
 PTX= Pentoxifylline



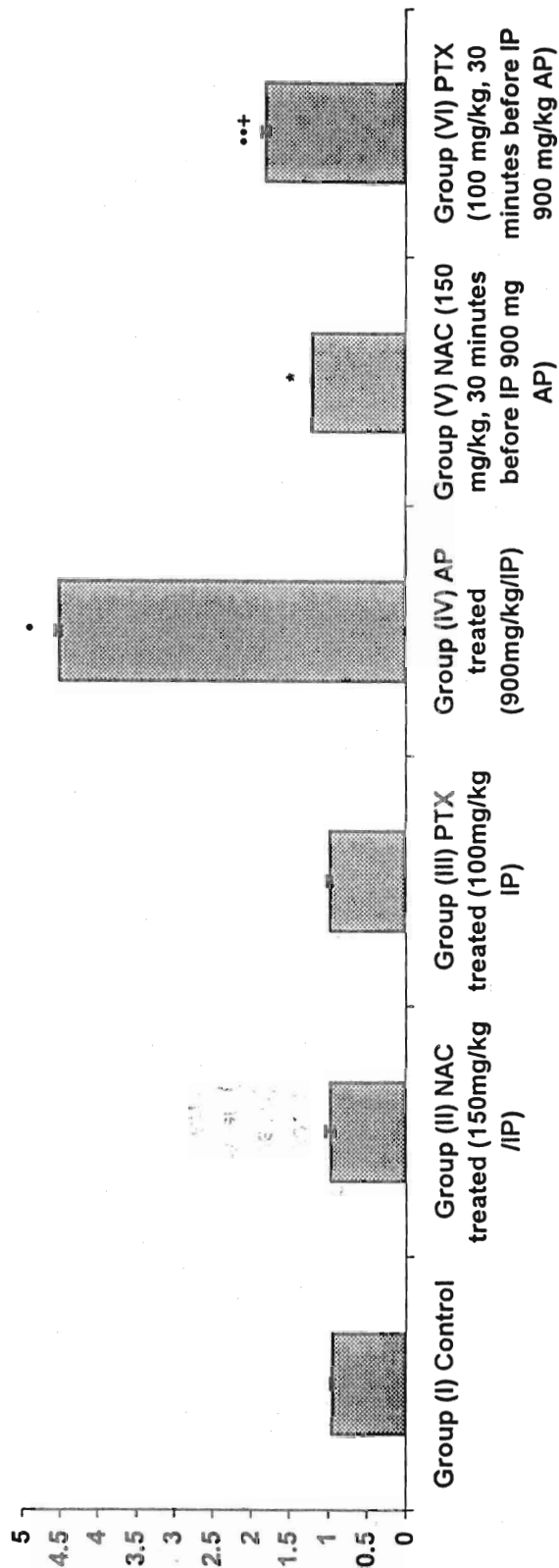


Fig.(2): Changes in serum tumor necrosis factor alpha (TNF-α) in various groups. Mean ± SEM (n = 6 mice/group).

SEM = Standard error of mean.

\*; P value is significant (<0.05) between AP treated and control group.

\*; P value is significant (<0.05) between (NAC + AP) group and (AP) group

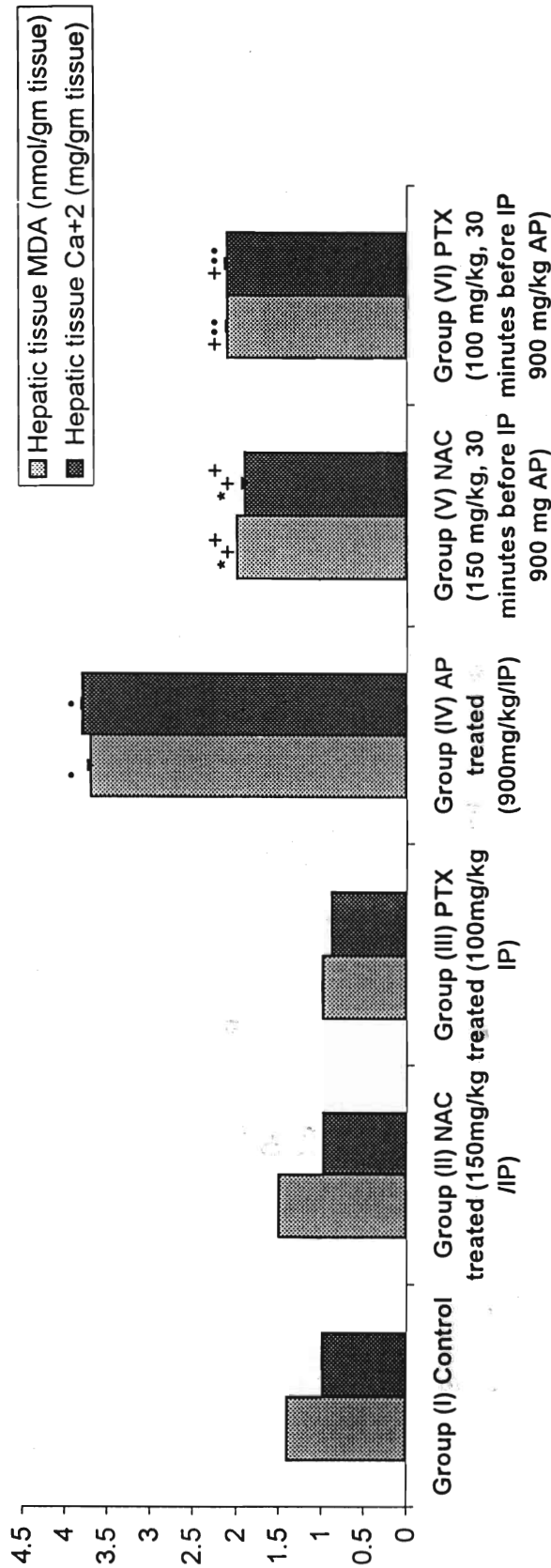
\*\*; P value is significant (<0.05) between (PTX +AP) and (AP) groups.

+; P value is significant (<0.05) between (PTX +AP) and (PTX) groups.

NAC = N-acetylcysteine

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AP = acetaminophen.



**Fig.(3): Changes in hepatic tissue calcium and malondialdehyde (MDA) in various groups. Mean ±SEM (N=6mice/group).**

SEM = Standard error of mean.

- ; P value is significant (<0.05) between AP treated and control group.
- \*; P value is significant (<0.05) between (NAC + AP) group and (AP) group
- +; P value is significant (<0.05) between (NAC + AP) and (NAC) groups.
- ; P value is significant (<0.05) between (PTX +AP) and (AP) groups.
- +; P value is significant (<0.05) between (PTX +AP) and (PTX) groups.

NAC = N-acetylcysteine

PTX= Pentoxifylline

AP = acetaminophen.

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## دراسة تأثير دواء البنثوكسيفلين على السمية الكبدية المحدثه عملياً بالاسيتامينوفين فى الجرذان البيضاء

المشركون فى البحث

د. سوميه عبداللطيف مقبل

قسم الفارماكولوجى - كلية الطب - جامعة المنصورة

أجرى هذا البحث لدراسة احتمال وجود أثر وقائى لدواء البنثوكسيفلين بالمقارنة بدواء إناستيل - سستين على السمية الكبدية المحدثه عملياً فى الجرذان البيضاء بواسطة دواء الاسيتامينوفين.

أستخدم لإجراء هذا البحث ٣٦ جرذاً أبيضاً وتم تقسيمهم إلى ٦ مجموعات متساوية كالتالى :

المجموعة الأولى : ضابطة عادية، حقنت مرة واحدة بـ ٢/١ ملل من محلول الملح المتعادل فى الغشاء البريتونى.

المجموعة الثانية : ضابطة أيضاً، حقنت مرة واحدة باناستيل - سستين فى الغشاء البريتونى بجرعة ١٥٠ مجم/كجم.

المجموعة الثالثة : ضابطة، حقنت مرة واحدة بدواء البنثوكسيفلين بجرعة ١٠٠ مجم / كجم فى الغشاء البريتونى أيضاً.

المجموعة الرابعة : حقنت مرة واحدة بدواء الاسيتامينوفين بجرعة ٩٠٠ مجم/كجم فى الغشاء البريتونى، وذلك لإحداث تلف حاد فى الخلايا الكبدية.

المجموعة الخامسة : حقنت مرة واحدة باناستيل - سستين بنفس الطريقة والجرعة السابقة وذلك قبل حقن ٩٠٠ مجم/كجم من الاسيتامينوفين بمدة ٣٠ دقيقة وذلك مرة واحدة.

المجموعة السادسة : حقنت مرة واحدة بدواء البنثوكسيفلين بجرعة ١٠٠ مجم/كجم قبل حقن ٩٠٠ مجم/كجم من الاسيتامينوفين فى الغشاء البريتونى بمدة ٣٠ دقيقة وذلك مرة واحدة بعد مرور ٤ ساعات من بداية التجربة ثم ذبح جميع الجرذان وتجميع المصل لقياس معدلات كلاً من إنزيم الألاتين أمينوترانسفيراز وأيضاً معامل تحلل الأورام - ألفا. كم تم تشريح الكبد لقياس كلاً من الكالسيوم والمالونديألدهيد فى النسيج الكبدى.

وكانت نتائج هذه الدراسة كالتالى :

- أحدث حقن دواء الاسيتامينوفين ارتفاعاً ذو دلالة إحصائية فى معدلات إنزيم الألاتين أمينوترانسفيراز ومعامل تحلل الأورام - ألفا فى المصل، كما أحدث أيضاً زيادة ذات دلالة إحصائية فى محتوى النسيج الكبدى من الكالسيوم والمالونديألدهيد وذلك بالمقارنة بالمجموعات الضابطة، حقن أى من دوائى الأناستيل - سستين أو البنثوكسيفلين قبل حقن الاسيتامينوفين بثلاثين دقيقة فى الغشاء البريتونى أحدث نقصاً ذو دلالة إحصائية فى المعدلات السابقة وعلى ضوء هذه الدراسة يمكن إستخلاص أن دواء البنثوكسيفلين بعمله كمضاد للأكسدة ومضاد لمعامل تحلل الأورام - ألفا أحدث تأثير وقائى فى حالات التسمم الكبدى المحدث بواسطة تأثير الاسيتامينوفين فى الجرذان البيضاء، وان هذا التأثير لا يقل عن تأثير الأناستيل - سستين وعليه يوصى بدراسات إكلينيكية مماثلة على الأشخاص المعرضون للتسمم بدواء الاسيتامينوفين كثير الاستخدام فى الصغار والكبار.