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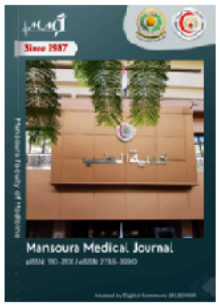

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STUDY OF THE EFFECT OF PENTOXIFYLLINE IN HEPATIC ISCHEMIA-REPERFUSION INJURY IN ALBINO RATS

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ABSTRACT

Hepatic ischemia reperfusion injury (IRI) is a common pathological process of traumatic surgical disease in the liver, liver transplantation, shock and infection. Inflammatory mediators are implicated in the pathogenesis of IRI. Pentoxifylline (PTX) is a derivative of methylxanthines, acts as a phosphodiesterase inhibitor and thereby elevates the levels of cAMP. Interest in PTX has been recently reawakened because of its reported suppressive action on immune functions, particularly on cytokine production. It has been shown to be beneficial in organ transplantation. Pentoxifylline probably acts primarily by inhibiting tumor necrosis factor-α (TNF-α). We hypothesized that PTX treatment would attenuate hypoxic ischemic liver injury.

Thirty-six male albino rats were used throughout this experiment. Animals were divided into 2 main groups; each comprised 18 rats (sham-operated & IRI groups). Group (1): sham-operated (exposed to anesthesia & laparotomy), this group is subdivided into 3 equal subgroups. Subgroup 1A: Sham- operated received daily intra-gastric saline, subgroup IB: sham-operated +PTX (8mg/kg/day) for 6 successive weeks before exposure to anesthesia& laparotomy, subgroup IC: as IB but received PTX (16mg/kg/day). Group (II): IRI group, divided into 3 equal subgroups, subgroup IIA,received intra-gastric saline for 6 weeks before the induction of IRI ,subgroup IIB, received 8mg/kg/day PTX intra-gastrically for 6 weeks before induction of IRI, subgroup IIC,

received PTX (16 mg/kg/day) before induction of IRI.

It was found that IRI produced significant increase in plasma alanine-transaminase (ALT), malondialdehyde (MDA), TNF-α and hepatic tissue calcium content as compared to sham-operated animal groups. Intra-gastric administration of PTX in the small or large doses for 6 weeks before induction of IRI produced non-significant change in the hepatic tissue calcium, plasma MDA, ALT and plasma TNF-α as compared to sham-control group, but it produced significant decrease as compared to IRI control group.

On the light of the present study, these preliminary results with PTX are encouraging to recommend further human studies in hepatic patients especially whom are given PTX for associated cardiovascular problems.

INTRODUCTION

IRI may be involved in hepatic dysfunction, liver transplantation, hemorrhagic and septic shock [1]. The pathogenesis of IRI has been extensively examined by using experimental rat models. Many interrelated mechanisms including calcium accumulation, lipid peroxidation and free radical generation may play a role in the evolution of IRI [2]. In addition inflammatory mediators; cytokines (e.g. TNF-α) are implicated in the pathogenesis of hepatic IRI [3].

Molecular oxygen behaves in a biological system as electron acceptor and produces a superoxide radical. It is further reduced into hydrogen peroxide and hydroxyl radical [4]. The reactive oxygen species are highly active atoms or molecules that mediate oxidation of biological molecules, membrane & tissues associated with a variety of pathological conditions [5]

Pentoxifylline (PTX) is widely used in the treatment of peripheral vascular disorders and is claimed to improve microcirculation and tissue oxygenation by increasing the flexibility of erythrocytes and by reducing platelet aggregation. Interest in PTX has been reawakened because of its reported suppressive action on immune functions [6], particularly on cytokine production [7]. It has been shown to

be beneficial in the treatment of endotoxaemia [8], tumor induced cachexia [9], inflammatory bowel disease [9] and AIDs [10], as well as organ transplantation [11&12]. Pentoxifylline probably acts primarily by inhibiting tumor necrosis factor-α [7&13], but other cytokines, such as IL-IB, IL-2, IL-8, IL-10 and transforming growth factor are also implicated [14,15,16,17]. This agent additionally reduces leucocytosis and neutrophilia and inhibits the phagocytic activities of monocytes, macrophages and neutrophils [9 &18] as well as degranulation in the later [5]. It also modulates fibrinolytic activity, both in vitro and in vivo [19]. PTX has been shown in human and animal studies to have a variety of physiological effects at cellular and vascular levels. PTX may either up or down regulates circulating adhesion molecules [20 &21]. Interestingly, low doses of methyl -xanthines have been associated with suppression of neuotrophil function such as chemotaxis, superoxide anion production, hydrogen peroxide production, deformability, phagocytosis and degranulation [22]. Therefore these numerous potential beneficial effects make PTX an interesting modality in treatment of hepatic IRI. Thus we explored the role which PTX may play as an anticytokine therapy in alleviation of hepatic IRI in male albino rats with experimentally induced IRI.

MATERIALS & METHODS

This experiment was carried on 36 male albino rats, weighing 200-240 grams/rat. Animals were having free access to water and food. They were exposed to similar housing conditions of light, heat and humidity.

Drugs used :

Pentoxifylline (Sigma) dissolved in sterile isotonic saline.

Animal grouping :

Animals were divided into 2 groups, each comprised 18 rats (sham-operated & IRI groups). Then each of the two groups subdivided into 3 equal subgroups each consisted of 6 rats as the following:

I- Sham-operated groups :

- Sub-group IA : received intra-gastric saline 0.5ml/day for 6 weeks before anesthesia & laparotomy.
- Subgroup IB : received PTX, intragastric in a dose of 8mg/kg/day for

6 successive weeks before the operative procedure. This dose is similar to the usual dose in rats [3].

- Subgroup IC: received PTX intragastrically in a dose of 16 mg/kg for the previous duration before the operative procedure [3].

II - Ischemia- reperfusion groups:

This group further divided into 3 equal sub-groups as the following :

- Subgroup IIA: control IRI rats received intra-gastric saline (0.5ml/ day) for successive 6 weeks before induction of IRI.
- Subgroup IIB: consisted of rats received intra-gastric PTX in a dose of 8 mg/kg/day for successive 6 weeks before induction of IRI.
- Subgroup IIC: received PTX in a dose of 16 mg/kg/day intra-gastric for 6 successive weeks before induction of IRI.

Surgical procedure :

Hepatic ischemia was performed half an hour after the last dose of PTX under thiopental sodiuml anesthetic[23]. Thiopental Sodium was given intra-peritoneally (IP) in a dose of 30 mg/kg body weight for induction of anesthesia and repeated when needed in a dose of 10mg/kg, IP. Liver ischemia was induced for 90 minutes by clamping of the hepatic vascular pedicle by using bulldog clamp. Reperfusion was established by removal of the clamp for 30 minutes after which animals were killed by decapitation and their blood was collected on heparin to obtain plasma for assessment of (TNF-α), ALT and (MDA). Furthermore, liver tissues were dissected for assessment of hepatic tissue calcium content. Plasma ALT activity was determined according to Schmidt and Schmidt [24] using Biotic laboratories kits. The activity was expressed as units/liter. MDA which is an index for lipid peroxidation was determined according to Draper & Hadley [25], using thiobarbituric acid method. Its value was expressed as nmol/ml. Plasma TNF-α was determined according to Carti et al. [26], using kits from immunotech (Acloulter Co) by enzyme linked immunosorbent assay method. Its value was expressed as pg/ml. Hepatic tissue calcium was measured according to Sparrow and Johnstone [27], by using Perkin-Elmer 22380 atomic absorption spectrophotometer with

air acetylene flame. Its value was expressed in mg/gram of hepatic tissue.

Statistics :

Statistical analysis of the results was carried out by using the computer system SPSS (Statistical package for social science program; version 10). One-way analysis of variance (ANOVA) was done to compare between the studied groups, followed by Student's "t" test according to Pipkins (28) to compare between each two means. The quantitative data were presented in the form of Mean ± standard error of means. P value < 0.05 is considered to be significant.

RESULTS

There was non- significant change of all the parameters studied in between sham groups (treated or non-treated by PTX). Experimental induction of hepatic IRI produced a significant increase in the specific liver enzyme ALT and in hepatic calcium contents. Furthermore, plasma TNF-α and plasma MDA showed significant elevation as compared to control (sham-operated) groups. When induction of IRI was preceded by intragastric administration of PTX in the 2 different doses (8 & 16 mg/kg/day) for 6 weeks, the previously mentioned parameters showed non-significant change as compared to sham-operated groups, and significantly decreased as compared to IRI group (table1 & Fig. 1). However, when induction of IRI was preceded by intragastric administration of PTX in the 2 different doses (8 & 16 mg/kg/day) for 6 weeks, ALT showed significant increase as compared to sham groups and significant decrease as compared to IRI control group (tab.1 & Fig. 2)

Table (1): Effect of PTX (8mg & 16/kg/day) on hepatic biochemical changes in Sham and IRI groups. Mean ± SEMs. P< 0.05. (N=6).

Parameter	Sham			IRI		
	Saline	PTX (8mg/kg/d)	PTX (16mg/kg/d)	IRI + saline	PTX (8mg/kg/day)	PTX (16mg/kg/d)
Plasma ALT (IU/L)	11.8±0.06	11.3±0.03	11.5±0.04	37 ±2.1+	23±0.5 + *	21 ±0.3+ *
Plasma MDA (nmol/L)	1.31±0.01	1.24±0.01	1.22±0.01	3.2 ± 0.03+	1.2 ±0.01+ *	1.4±0.01+ *
PlasmaTNF-α (Pg/ml)	0.93 ± 0.02	0.91±0.01	0.92±0.01	3.91 ± 0.05+	1.1±0.11+ *	1.1±0.15+ *
Hepatic calcium (mg/gm liver tissue)	0.9 ± 0.01	0.9±0.01	0.88±0.01	1.99 ± 0.03+	0.89 ± 0.01+*	0.92±0.02+*

+=Significant difference between IRI and corresponding sham groups.

*=Significant difference between (IRI + PTX treated) and (IRI + saline) group.

PTX = pentoxifylline
IRI= ischemia-reperfusion injury (90 minutes transient ischemia followed by 30 minutes reperfusion)

SEMs = standard error of means

ALT = Alanine aminotransaminase.
MDA = Malondialdehyde
TNF-α = Tumor necrosis factor alpha.

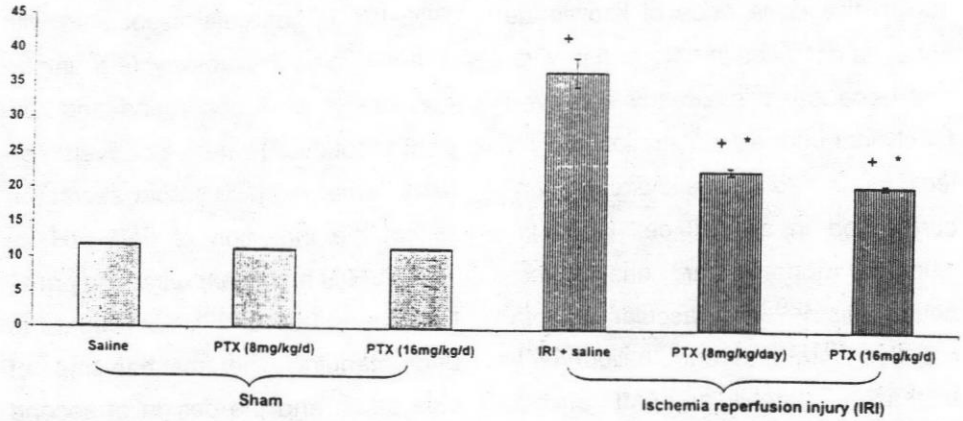

Fig (1): Effect of Pentoxifylline (PTX) (8mg & 16/kg/day) on Plasma alanine aminotransferase (IU/L) in Sham and IRI groups. Mean ± SEMs. P< 0.05 , (N=6/group)

+=Significant difference between IRI and corresponding sham groups.

*=Significant difference between (IRI + PTX treated) and (IRI + saline) group.

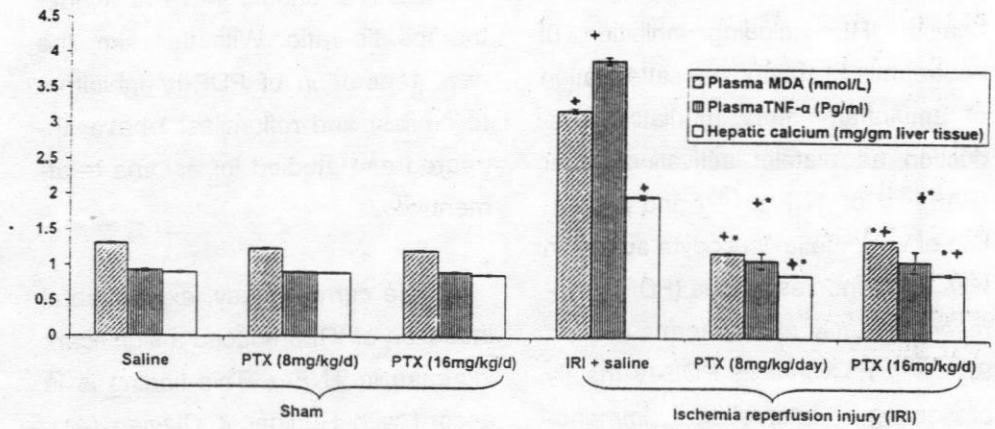

Fig (2): Effect of Pentoxifylline (PTX) (8mg & 16/kg/day) on plasma malondialdehyde (MDA), Tumor necrosis factor (TNF-α) and hepatic calcium content in Sham and IRI groups. Mean ± SEMs. P< 0.05 , (N=6/group)

+=Significant difference between IRI and corresponding sham groups.

*=Significant difference between (IRI + PTX treated) and (IRI + saline) group.

DISCUSSION

The present study evaluates PTX due to the large body of knowledge about its activities in vitro and in vivo, and because it is already approved for clinical use. Administration of PTX led o increased intracellular cAMP accumulation in several cell types including mononuclear phagocytes, neutrophils [29,30], vascular smooth muscles [31], and endothelium [32]. Increased intracellular cAMP affects gene transcription through several transcription factors, such as cAMP response element binding protein [33]. Multiple complementary anti-inflammatory effects of PTX could be responsible for its protective effect against IRI, including inhibition of neutrophils or monocytes, attenuation of anti-inflammatory mediators production as platelet activating factor (PAF)[34] or TNF-α [35] and prevention of endothelial leucocyte adhesion [36]. Phosphodiesterases (PDEs) represent a family of 9 isoforms (PDE1-9)[37,38]. PTX inhibits PDE-IV mainly presenting interesting immunomodulatory properties. PDE-IV is abundant and the major regulator of cAMP metabolism in almost every pro-inflammatory and immune cell [39]. There are 2 types of PDE-IV, PDE-IVH and PDE-IVL. Inhibition of PDE-IVL is generally associated with anti-inflammatory activity (e.g. inhibition of cytokine generation and oxidant production) where as adverse effects (emesis, gastric acid secretion) reflect the inhibition of PDE-IVH as PDE-IVH is highly expressed in parietal cells and CNS [40]. With regard to understanding the mechanisms of side effect and the design of second generation inhibitors with improved therapeutic ratios [40], an extension of this idea was that PDE-IV inhibitors that have lower affinity at PDE-IVH but the same or an improved affinity at PDE-IVL should have a higher therapeutic ratio. With this aim, the new generation of PDE-IV inhibitors (cilomilast and roflumilast) have appeared and studied for asthma treatment [40].

In the current study, experimental induction of IRI produced a significant increase in TNF-α. This finding is in accord with Rudiger & Clavien (41), as they incriminated TNF-α in the pathogenesis of hepatic ischemia and reperfusion injury. They demonstrated increased serum TNF-α levels af-

ter reperfusion in a rat model of hepatic ischemia, and the levels correlated with the duration of ischemia. Further studies have shown that TNF-α mediates remote organ injury after prolonged ischemia injury to the liver (42&43). The present study demonstrated that PTX effectively inhibited the production of TNF-α in rats with induced hepatic IRI. These findings are consistent with Raetsch et al. (3) as he reported that inhibition of these cytokines by PTX evidently occurs at transcriptional level and can last for 5 days after the final PTX dose. In addition, Van Furth et al. (13), reported that PTX decreased bacterial- stimulated production of TNF-α by human leukocytes. Moreover, PTX blocks nuclear factor kappa B (NFK_B) activation in stimulated kupffer cells which explains its activity in suppressing NFK_B- dependent synthesis and release of tumor necrosis factor alpha (42&43).

In the present study, induction of hepatic IRI produced a significant increase in hepatic tissue calcium content, plasma MDA (index of lipid peroxidation), these findings are in agreement with previous studies as they proved that alteration of calcium homeostasis play a major role in cell necrosis (1). It has been demonstrated that increased intracellular concentration of calcium causes damage to hepatocytes (44). Furthermore, from experimental and clinical studies, it has become apparent that oxidative stress induced from increased free radical production plays a role in the pathogenesis of ischemic tissue injury (29). Among the underlying mechanisms through which increased calcium causes damage is the enhanced production and accumulation of toxic free radicals (33, 39). In the present study PTX pretreatment before induction of IRI prevent the increase in MDA. These findings were supported by previous studies (45, 46). They reported that low dose of methylxanthines have been associated with suppression of neutrophils function such as chemotaxis, superoxide anion production, hydrogen peroxide production, deformability, phagocytosis and degranulation. In addition, it has been documented that with the use of hepatitis A or B running a moderate course, PTX produced a positive action on lipid peroxidation; liver size and Jaundice

duration and hospital stay of the patients were reduced [47]. Korber et al. (48) demonstrated that PTX inhibited the secretion of superoxide anion and TNF-α by alveolar macrophages of patients with sarcoidosis in vitro in a dose dependent manner via a prostaglandin synthesis dependent mechanism that was independent of the glucocorticoid receptor.

These preliminary results with PTX are encouraging and they indicate that post ischemia reperfusion cytokine cascade interventions may alleviate some effects of IRI. PTX in the higher dose (16mg/kg/day) had no advantage in hepatoprotection as compared to effects PTX small dose (8mg/kg/day). Since PTX is an inexpensive drug, it presents very low toxicity and minimal side effects associated with chronic use (dizziness; headache; nausea or vomiting; stomach discomfort), further studies of the effects of PTX on hepatic patients are recommended. More selective inhibitors that preferentially block PDE-III&-IV are desirable as they could potentially exert more specific protective effect on IRI. Also further studies using PDE inhibitors with improved therapeutic ratio are needed.

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دراسة تأثير اعطاء دواء البنتوكسيفيلين على الاصابة التى تحدث فى كبد الفئران نتيجة تعرضها لقصور فى الدورة الدموية بالكبد ثم إعادة ضخ الدم

د. سومية عبد اللطيف مقبل ، د. كروان محمد عبد الرحمن

قسم الفارماكولوجى - كلية الطب - جامعة المنصورة

يعتبر قصور الدورة الدموية بالكبد عامل مشترك فى العديد من الحالات التى تصيب الكبد. تلعب وسائط الالتهابات مثل معامل تحلل الأورام ألفا والشقوق الحره وكذلك زيادة معدل الكالسيوم فى خلايا الكبد دوراً هاماً فى الإصابة الناتجة عن قصور الدورة الدموية الكبدية.

لقد أجرى هذا البحث لدراسة احتمال وجود تأثير وقائى لعقار البنتوكسيفيلين على الإصابة المحدثة معملياً فى كبد الفئران البيضاء بسبب قصور الدورة الدموية به ثم استعادة وصول الدم بعد فترة.

تم إجراء هذا البحث على عدد ٣٦ فأراً أبيضاً من الذكور يتراوح وزنها بين ٢٠٠-٢٤٠ جرام، قسمت إلى مجموعتين أساسيتين تتكون كل منها من ١٨ فأراً، الأولى قياسية غير معرضة إلى قصور فى الدورة الدموية الكبدية، والثانية عرضت لقصور بالدورة الدموية لمدة ٩٠ دقيقة ثم استعادة وصول الدم لمدة ٣٠ دقيقة .

تم تقسيم كلاً من هاتين المجموعتين إلى ثلاث تحت مجموعات كل منها يتكون من ٦ فئران، الأولى غير معالجة دوائياً وعولجت بمحلول متعادل، والثانية معالجة بالبتنوكسيفيلين بجرعة ٨ مجم/كجم يومياً كما عولجت المجموعة الثالثة بجرعة أكبر من البنتوكسيفيلين ١٦ مجم/كجم يومياً وذلك عن طريق الفم لمدة ٦ أسابيع متتالية.

أحدث القصور الدموى الكبدى فى الفئران المخدرة بغلق الحزمة الوعائية الدموية الداخلة للكبد لمدة ٩٠ دقيقة متبوعة بفترة ٣٠ دقيقة استعادة للدورة الدموية وذلك برفع الغلق عن الحزمة.

وقد تم تقييم مدى اصابة الكبد بقياس معدل انزيم الألانين ترانزاميناز وكذلك قياس معدل كلاً من المالونديالديهيد ومعامل تحليل الأورام الفا فى البلازما وذلك بالإضافة إلى محتوى تراكم الكالسيوم فى النسيج الكبدى.

لقد لوحظ عند تعرض الكبد لقصور الدورة الدموية به ثم إستعادتها انه حدثت زيادة ذات دلالة احصائية فى انزيم الألانين ترانزاميناز وايضاً فى الشقوق الحرة فى البلازما وكذلك معدل الكالسيوم داخل انسجة الكبد وايضاً زيادة معدل معامل تحلل الأورام ألفا فى البلازما، فى الجانب الآخر عندما أعطى دواء البنتوكسيفيلين بجرعته ٨ أو ١٦مجم/كجم يومياً عن طريق الفم لمدة ٦ اسابيع متتالية للفئران قبل تعرضها لقصور الدورة الدموية بالكبد لم تحدث زيادة فى المعدلات السابقة.

وعلى ضوء هذه الدراسة يمكن استنتاج واستخلاص أن دواء البنتوكسيفيلين بجرعتيه الصغيرة والكبيرة له تأثير وقائى من الإصابة التى تحدث فى الكبد نتيجة لقصور الدورة الدموية وهذا يشجعنا إلى أن نوصى بتجربته خصوصاً بالجرعة الصغيرة (لأنها تحقق نفس الهدف وبأقل أعراض جانبية) على مرضى الكبد الذين يعانون من مشاكل فى الجهاز الدورى ويحتاجون إلى البنتوكسيفيلين .