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# A Study of Hepatotoxic Effect of Tiaprofenic Acid and Piroxicam in Normal and Adjuvant-Induced Arthritic Rats

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## Abstract

Hepatotoxicity is now a recognized adverse effect of NSAIDs therapy in any patient especially individuals suspected to be at risk as elderly patients or those suffering from rheumatic or arthritic conditions. So this study was performed to investigate the hepatic effect of chronic administration of two members of NSAIDs namely, tiaprofenic acid and piroxicam in normal and adjuvant induced arthritic rats. The animals received the tested drugs in doses of 10 mg/kg & 1 mg/kg respectively orally for 21 days. Serum levels of GPT, GOT and alkaline phosphatase were measured & also histopathological examination of the liver was done after 10,12 days of administration and one month later after drugs withdrawal to study the reversibility of their hepatic effect. It was observed that serum transaminases in normal rats receiving tiaprofenic acid were elevated 1 time normal whereas in case of piroxicam, the elevation was more and reached about 1.5 times normal. Histopathological changes revealed vascular changes and fatty degeneration of the liver cells. This effect was reversed and healing occurred after one month from cessation of the drugs. Meanwhile, in arthritic rats, there was a marked elevation in serum tranasminases, 2 times normal in tiaprofenic acid and 3 times normal in case of piroxicam. Moreover, the histopathological examination revealed more damage of the liver with areas of necrosis and fibrosis which more prominant with piroxicam. Some of these changes persist after the drugs were withdrawn for one month.

## Introduction

THE non-steroidal anti-inflammatory drugs (NSAIDs) are the major pharmacological tools in the treatment of rheumatic and arthritic disorders and as such enjoy an expanding global utilization and popularity. They share certain therapeutic side effects as well as benifits [1]. Hepatotoxicity is an increasingly recognized laboratory and a rare clinical side effect of administration of these drugs. It was reported in literature that NSAIDs therapy produced a symptomatic elevation of serum transaminases (transaminitis) which indicate a mild form of hepatitis [2,3]. Biopsy revealed histopathological lesions in the liver with mononuclear cells infiltration and the electron microscopy has also shown ultrastructural changes in the hepatocytes [4]. Zimmerman [5] reported that high doses of salicylates especially in Juvenile rheumatoid arthritis induced reversible hepatocellular injury. Also hepatotoxicity was noted with indomethacin [6], naproxen [7] and sulindac [8]. Furthermore, hepato cellular and cholestatic liver disease have been reported in association with phenylbutazone - induced hepatitis [9]. Moreover, benoxaprofen was withdrawn from the market because of a relatively high incidence of chlolestatic jaundice [10].

The pathogenesis of NSAIDs - induced hepatotoxicity remain unclear. Many reports suggested a hypersensitivity response, idiosyncracy due to accumulation of reactive cytotoxic metabolites formed during hepatic breakdown of NSAIDs or a direct toxic effect from drug accumulation.

Prostaglandins have been reported to prevent the hepatic damage caused by many agents including NSAD. Hepatic cytoprotection by PG was apparent not only in isolated hepatocytes but also in vivo and this property of PG extended to other tissues than liver including stomach, heart, kidney and pancreas. So this property of PG has been now described as organo-protection [11].

Therefore, the present work was carried out to study the hepatic effect of other members of NSAIDs namely tiaprofenic acid and piroxicam in normal male albino rats. These tested drugs are potent reversible PG synthesis inhibitors [12,13]. Moreover, it was found in literature an apparent "selectional phenomenon" among those individuals who may be susceptible to hepatic injury following treatment with NSAIDs including patients treated from a rheumatic, rheumutoid, arthritic or systemic lupus erythematosus [1, 14, 15]. Therefore, this study was extended to investigate the hepatic effect of the tested NSAIDs on an experimental model of rheumatiod arthritis which is the adjuvant-induced arthritic rats [16].

## Material and Methods

*Drugs and Chemicals:*

I. Anti inflammatory drugs used:

1. Piroxicam powder (Pfizer, Incorp, USA). [14 hydroxy - 2- Methyl - N - (2 Pyridyl) - 2H- 1,2- benzothiazine - 3 carboxamide - 1 - 1 dioxide]
2. Tiaprofenic acid powder (Les Laboratories, Roussel, France). [5 benzol - a methyl - 2- tiophene acetic acid].

These drugs were administered orally as a freshly prepared aqueous suspension in a volume of 0.5 ml/100g. body weight in the dose of 10mg/kg for tiaprofenic acid & 1 mg/kg for piroxicam. It was found that these doses produced 62.4% and 65% mean inhibition of rat paw swelling, respectively in arthritic rats as measured by air displacement method [17].

II. Freund's complete adjuvant (F. C. A): (Behringwerk Ag, Marburg. Germany). It is emulsion of heat killed mycobacteria in oil.

III. G P T and G O T kits (Bio Mérieux, Laboratory reagents and instruments, France): Colorimetric determination of G O T & G P T activity according to Reitman and Frankel method [18].

IV. Alkaline phosphatase kit: (Bio Mérieux, Laboratory reagents and instruments, France): Colorimetric determination of alkaline phosphatase activity [19].

*Animals used:*

This study was conducted on 72 male albino rats weighing 150-200 grams. Animals were allowed food and water ad libitum.

Experimental design:

The animals were divided into the following groups:

Group (1): 12 normal rats served as control "N".

Group (2): 12 normal rats received tiaprofenic acid (10mg/kg) orally daily for 21 days (N+T).

Group (3): 12 normal rats received piroxicam (1mg/kg) orally daily for 21 days (N+P).

Group (4): 12 rats injected with 0.1ml of F. C. A. intradermal in the left hind paw (A). Severe systemic inflammation and characteristic rheumatoid arthritic manifestation appeared 2-3 weeks later [16]. The paw volumes were measured before injection and 21 days later by air displacement method.

Group (5): 12 arthritic rats received tiaprofenic acid (10mg/kg) orally daily for 21 days (A+T).

Table (1): The Serum Levels of GPT , GOT & Alkaline Phosphatase in Normal Untreated & Arthritic Rats.

| Animal Group | Serum GPT Level (U/L) | | | Serum GOT Level (U/L) | | | Serum alkaline phosphatas level (U/L) | | |
|---|---|---|---|---|---|---|---|---|---|
| | After 10 days | After 21 days | One month later | After 10 days | After 21 days | One month later | After 10 days | After 21 days | One month later |
| Group (1) "N" | 32.25 | 32.17 | 32.83 | 94.75 | 94.33 | 93.17 | 163.24 | 164.10 | 163.77 |
| Normal Untreated | ± 1.016 | ± 1.029 | ± 1.302 | ± 2.283 | ± 2.317 | ± 1.851 | ± 3.440 | ± 3.763 | ± 2.051 |
| Group (4) "A" | 33.75 | 32.08 | 33.67 | 94.83 | 95.92 | 94.0 | 166.78 | 168.22 | 168.58 |
| Arthritic Untreated | ± 1.207 | ± 1.276 | ± 1.606 | ± 2.602 | ± 2.421 | ± 1.983 | ± 4.780 | ± 4.051 | ± 2.020 |
| Student -t- test | | N.S. | N.S. | N.S. | N.S. | N.S. | N.S. | N.S. | N.S. |
| n. | 12 | 12 | 6 | 12 | 12 | 6 | 12 | 12 | 6 |

N.S. Non significant ($p > 0.05$)

n. Number of animals in each group.

Group (6): 12 normal rats received piroxicam (1m/kg) orally daily for 21 days (A+P).

On day 10 & 21 blood samples were obtained from the rats in all groups by means of capillary glass tubing from the retro-orbital plexus by the procedure described by Schermer [20]. Then 6 rats from each group were sacrificed, livers were removed and fixed in a buffered formaline. Paraffin sections (5 μ m thick) were stained with haematoxyline & eosin (H & E) and examined for any histopathological changes.

In groups 2, 3, 5, 6, the tested HSAID, were withdrown suddenly on day 22. Six rats in each group were allowed to live ad libitum for one month without any medication. After that, blood samples were obtained, the rats were sacrificed and the livers were removed.

In the serum samples, the levels of SGPT, SGOT and alkaline phosphatase-as parameters of liver functions - were measured.

*Statistical analysis of data:*

The results were given as the mean (±SE) and analysed by One-Way ANOVA test and paired Student -t- test. Differnces were considered significant at $p < 0.05$.

## Results

No significant changes in the serum transaminases levels were observed between normal (Group 1) and arthritic rats (group 4), table (1).

Chronic administration of tiaprofenic acid in normal rats elevated significantly the serum levels of GPT, GOT & alkaline phosphatase by 1.26, 0.94 & 1.04 times normal respectively after 21 days of administration, table (2). In case of piroxicam a significant elevation by 1.82, 1.53 and 1.72 times normal in the serum levels of GPT, GOT and alkaline phosphatase, respectively, after 21 days of its chronic administration, table (2). One month after stoppage of medications, the serum level of transaminases improved and nearly returned to normal levels in rats that received tiaprofenic acid and piroxicam, but there was still significant elevation of serum levels of alkaline phosphatase in case of piroxicam.

As regard the arthritic treated rats. marked elevations of the serum levels of transminases were observed. Tiaprofenic acid produced a significant rise in SGPT, SGOT and alkaline phosphatase by 1.41, 1.05 and 0.76 times respectively after 10 days and by 2.17, 1.95 1.88 times normal, respectively, after 21 days from its oral administration, table (3).

Concerning the arthritic rats receiving piroxicam, it was obsereved that serum GPT, SGOT and alkaline phosphatase levels were raised by 1.75, 2.05 & 1.33 times respectively, after 10 days from its

Table (2): Effect of Chronic Oral Administration of Tiaprofenic Acid (10 mg/kg) and Piroxicam (1mg/kg) on the the Mean (± SE) Serum Levels of GPT , GOT and Phosphatase in Normal Rats.

| Animal Group | Serum GPT Level (U/L) | | | Serum GOT Level (U/L) | | | Serum Alkaline Phosphatase level (U/L) | | |
|---|---|---|---|---|---|---|---|---|---|
| | 10 days after starting tested drug | 21 days medication | One month after drug withdrawal | 10 days after starting tested drug | 21 days medication | One month after drug withdrawal | 10 days after starting tested drug | 21 days medication | One month after drug withdrawal |
| Group (1) Normal Untreated "N" | 32.25 ± 1.016 | 32.17 ± 1.029 | 32.83 ± 1.302 | 94.75 ± 2.283 | 94.33 ± 2.317 | 93.17 ± 1.851 | 163.24 ± 3.440 | 164.10 ± 3.763 | 163.77 ± 2.051 |
| Group (2) Normal + Tiaprofenic acid (10 mg/kg P.O) | 55.33* ± 1.671 | 72.92* ± 1.616 | 34.33 ± 1.308 | 133.50 ± 1.654 | 183.83 ± 1.646 | 93.83 ± 2.386 | 230.11* ± 2.717 | 335.76* ± 1.212 | 164.38 ± 2.884 |
| Group (3) Normal + Piroxicam (1mg/kg P.O) | 61.17* ± 1.408 | 90.83* ± 1.419 | 37.50 ± 1.258 | 165.5 ± 1.773 | 239.58 ± 1.873 | 100.83 ± 3.005 | 27472* ± 5.05 g | 447.95* ± 3.083 | 177.83* ± 2.218 |
| One - Way ANOVA test | 0.000 E + | .000 E + 00 | 0.0600 N.S. | 0.000 E + | .000 E + 00 | 0.0813 N.S. | 0.000 E + | .000 E + 00 | 1.094 E - 03 |
| n | 12 | 12 | 6 | 12 | 12 | 6 | 12 | 12 | 6 |

N.S. Non significant ($p > 0.05$)
* Significant ($p < 0.05$)
n. Number of animals in each group.

administration (table, 3). Marked rises of these transaminases were noted apparantly after 21 days of piroxicam administration in arthritic rats. The SGPT were elevated by 3.6 times normal. SGOT were raised by 2.99 times as well as serum alkaline phosphatase, table (3). Some improvements in these parameters were noted one month after withdrawal of both tested drugs but significant elevation was still observed in transaminases, table (3).

Fig. (1) represented graphically the changes in the serum levels of GPT, GOT and alkaline phosphatase in differnt groups.

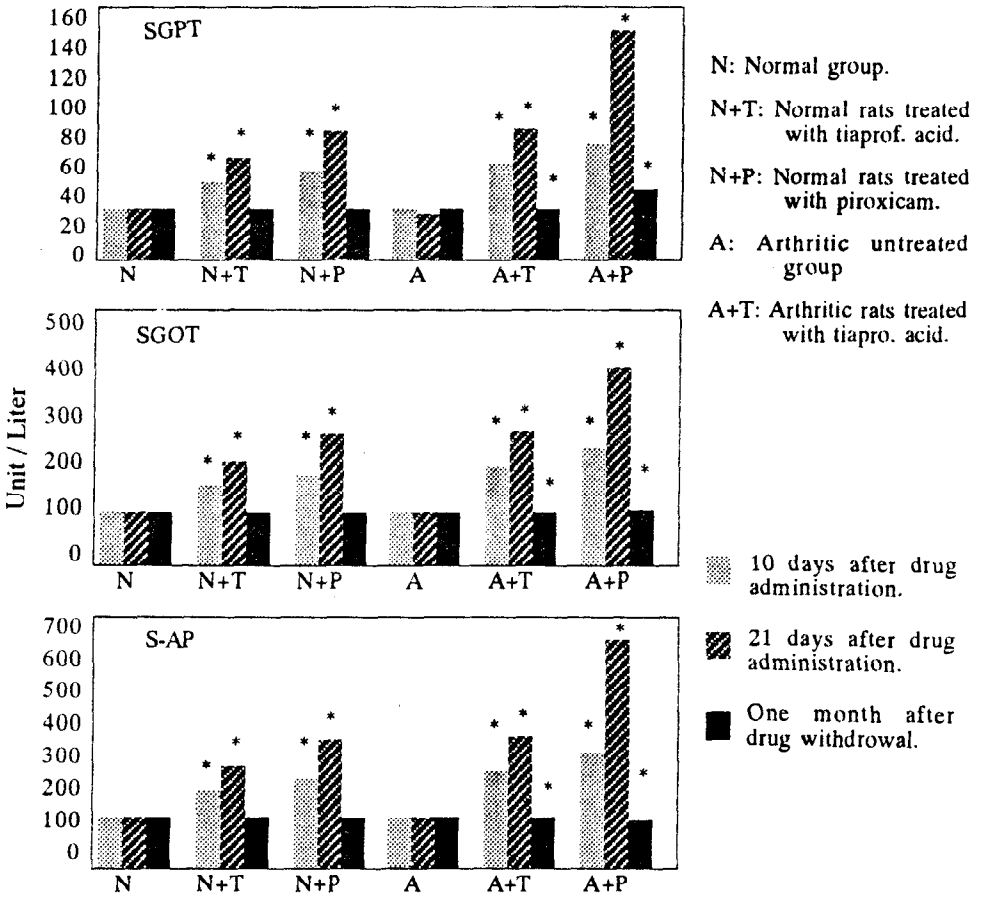


Fig. (1): Efect of administration and withdrawal of tiaprofenic acid (10 mg/kg) and piroxicam (1mg/kg) on serum levels of GPT,GOT & Alkaline phsophatase (AP) on normal & arthritic rats.

*Significant ($p < 0.05$) [one-way ANOVA test].

Table (3): Effect of Chronic Administration of Tiaprofenic Acid (10 mg/kg) and Piroxicam (1 mg/kg) on the Mean (± SE) Serum Levels of GPT , GOT and Alkaline Phosphatase in Adjuvant-Induced Arthritic Rats.

| Animal Group | Serum GPT Level (U/L) | | | Serum GOT Level (U/L) | | | Serum Alkaline Phosphatas level (U/L) | | |
|---|---|---|---|---|---|---|---|---|---|
| | 10 days after starting tested drug | 21 days medication | One month after drug withdrawal | 10 days after starting tested drug | 21 days medication | One month after drug withdrawal | 10 days after starting tested drug | 21 days medication | One month after drug withdrawal |
| Group (4) Arthritic Untreated "A" | 32.75 ± 1.207 | 32.08 ± 1.276 | 33.67 ± 1.606 | 94.83 ± 2.602 | 95.92 ± 2.421 | 94.0 ± 1.983 | 166.78 ± 4.780 | 168.22 ± 4.051 | 168.58 ± 2.020 |
| Group (5) A + Tiaprofenic acid (10 mg/kg P.O) | 81.417* ± 1.459 | 101.83* ± 1.604 | 40.33* ± .803 | 194.58* ± 2.054 | 283.50* ± 1.603 | 103.83* ± 2.892 | 294.65* ± 2.321 | 484.68* ± 2.383 | 179.79* ± 2.571 |
| Group (6) A + Piroxicam (lmg/kg P.O) | 93.167* ± 1.918 | 147.83* ± 0.796 | 57.167* ± 1.276 | 289.50* ± 2.366 | 383.0* ± 1.365 | 118.17* ± 2.023 | 390.15* ± 2.173 | 671.45* ± 1.429 | 203.68* ± 2.814 |
| One - Way ANOVA test | 0.000 E + | .000 E + 00 | 4.180 E-09 N.S. | 0.000 E + | .000 E + 00 | 1.062 E-05 | 0.000 E + | .000 E + 00 | 1.833 E - 07 |
| n | 12 | 12 | 6 | 12 | 12 | 6 | 12 | 12 | 6 |

* Significant ($p > 0.05$)

n. Number of animals in each group.

*Histopathological findings:*

Haematoxylin and eosin ( H and E) sections of liver of control animals showed normal polygonal hepatocytes with rounded nuclei. Blood sinusoids with kupffer cells were detected in between the plates of parenchymal liver cells. The limiting plate was respected and did not show inflammatory infiltrates (Fig. 2).

Section of the liver of arthritic rats showed ectatic vascular changes in the form of dilation of the vascular sinusoids as well as pelosis hepatis. The latter were dilated vascular spaces without an endothelial lining and were noticed in the periportal areas (Fig. 3).

Animals that received tiaprofenic acid only showed rounded cell infiltration in the portal tracts formed mainly of lymphocytes and plasma cells (Fig. 4). Congestion of the blood sinusoids, hyperplastic kupffer cells and mild ectatic changes were detected. The hepatocytes showed cloudy swelling. These changes were aggravated in the arthritic animals. The liver lobules showed diffuse fatty change. The fat is microvesicular in appearance (Fig. 6). Only an occasional scattered few hepatocytes had darkly eosinophilic cytoplasm with nuclear pyknosis and karyolysis (Liver necrosis). The lymphocytic infiltration is increased in the portal tracts. Although the limiting plate is infiltrated by lymphocytes and showed minimal erosion, no periportal hepatocytic necrosis could be detected. These reactions were similar to those observed with chronic persistant hepatitis (Fig. 5).

Examination of the rat hepatocytes which administrated piroxicam in normal rats revealed a picture similar to those received tiaprofenic acid alone. Moreover, patchy lymphocytic infiltrations within the lobules were also observed (Fig. 8).

Following administration of piroxicam in arthritic rats, the lobular hepatocytes disclosed serious findings. Diffuse marked micro and macro vesicular fatty changes were encountered (Fig. 10). The degenerative changes progressed to discrete necrotic areas in the hepatic lobules (Fi.g 12). The sinusoids, the central and protal veins were abnormally dilated. A significant widening of the protal tracts with increase in the fibrous connective tissue, proliferation of the bile ductules and excessive lymphocytic infiltrations were noticed (Fig. 9). The limiting plate was not respected as there was destruction of liver cells at an interface between parenchyma and connective tissue (Fig. 11), together with lymphocytic infiltrations (piecemeal necrosis). There were bridging necrosis with deposition of the fibrous tissue in the periportal region and the bridging is porto-portal or porto-central (Fig. 10). These histopathological findings were consistent with the picture of chronic active hepatitis.

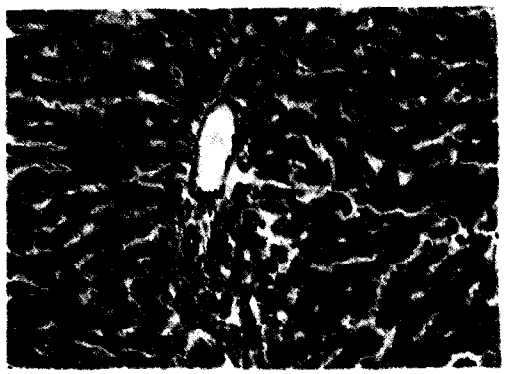

Fig. (2): Section in the liver of a control rat showing portal tracts and trabeculae of normal hepatocytes separated by blood sinusoids (H & E x 200).

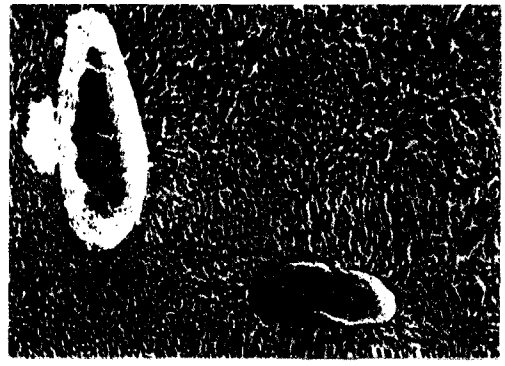

Fig. (3): Section in the liver of a rat receiving adjuvant only showing pelosis hepatis and dilated sinusoids (H & E x 100).

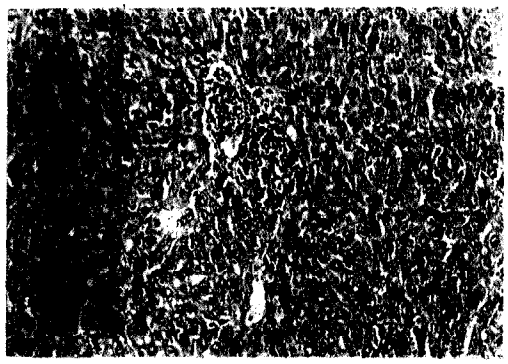

Fig. (4): Section in the liver from a rat treated with tiaprofenic acid showing lymphocytic infiltration in the portal tracts. Hepatocytes have diffuse cloudy swelling (H & E x 200).

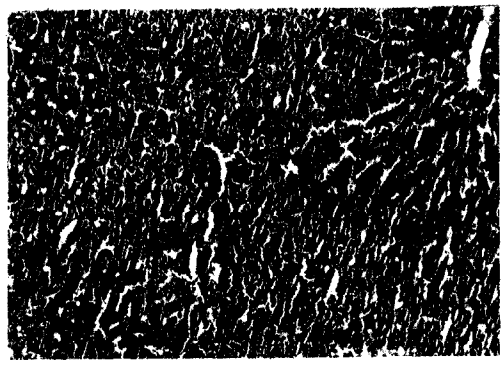

Fig. (5): Section in the liver of a rat treated with tiaprofenic acid and adjuvant having lymphocytic infiltration in the limiting plate (H & E x 100).

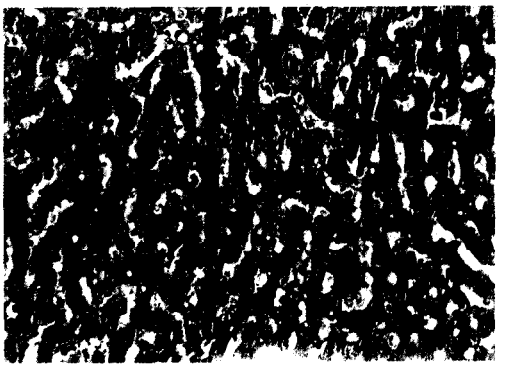

Fig. (6): Section in the liver of a rat treated with tiaprofenic acid and adjuvant showing diffuse microvesicular fatty changes. Some of the liver cells have pynnotic nuclei (H & E x 400).

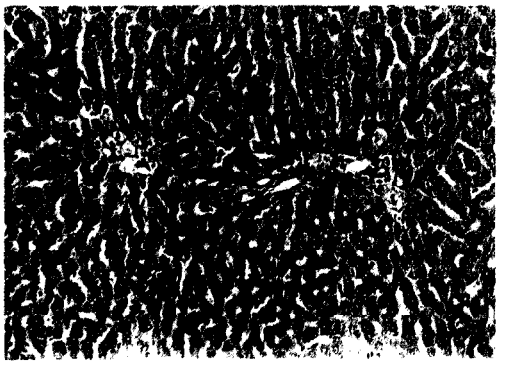

Fig. (7): Degenerative changes disappear in the liver of a rat after withdrawal of tiaprofenic acid and adjuvant. Few lymphocytic infiltration is still present in the portal tract (H & E x 200).

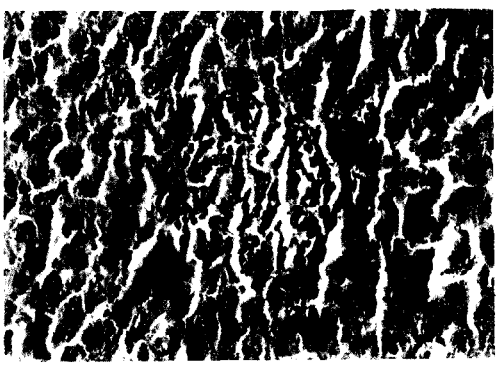

Fig. (8): Section in the liver of a rat received piroxicam showing intralobular lymphocytic infiltration (H & E x 400).

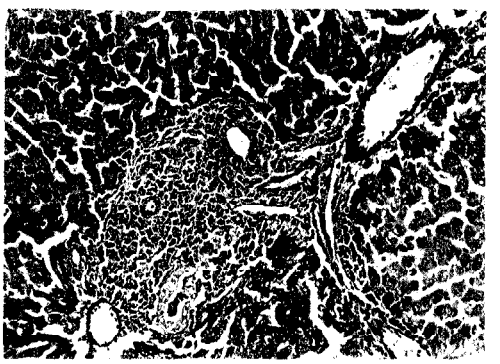

Fig. (9): Section in the liver of a rat received piroxicam and adjuvant showing widening of the portal tracts with marked lymphocytic infiltration and bile duct proliferations (H & E x 200).

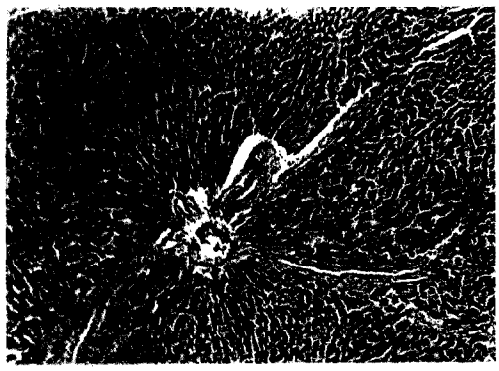

Fig. (10): Section in the liver from a rat treated piroxicam and adjuvant showing lymphocytic infiltration in the limiting plates with bridging necrosis and fibrosis porto-portal and porto-central (H & E x 100). Micro and macro vesicular fatty changes are also present.

Fig. (11): Section in the liver of a rat received piroxicam and adjuvant showing piece meal necrosis and fatty changes (H & E x 400).

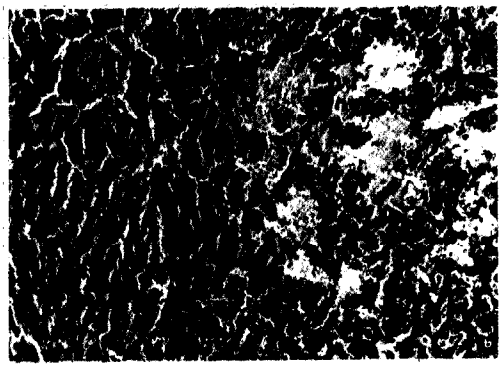

Fig. (12): Section in the liver of a rat received proxicam and adjuvant showing marked hepatic necrosis and fatty changes (H & E x 200).

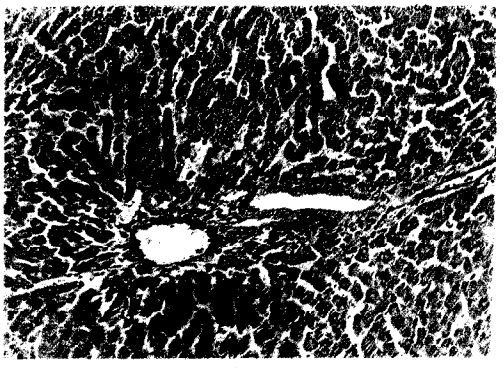

Fig. (13): Section in the liver of a rat showing scanty lymphocytic infiltration with minimal fibrosis in the portal tracts after withdrawal of piroxicam and adjuvant. Scattered hepatocytes still have fatty changes (H & E x 200).

Regenerative changes were initiated when the different drugs were stopped. However, the degree of regeneration was variable. Degenerative changes of the liver in normal animals that received tiaprofenic acid or piroxicam disappeared in the majority of hepatocytes. On the other hand, the process of healing was slow in the arthritic treated groups. Moreover, the histopathological examination revealed less regenrative responses in the arthritic rats treated with piroxicam if compared to those receiving tiaprofenic acid.

## Discussion

The results of the present work revealed that the serum levels of GPT, GOT and alkaline phosphatase were significantly elevated in normal rats that received the tested NSAIDs, tiaprofenic acid and piroxicam. Marked elevation in these parameters were observed in arthritic rats treated with the same drugs especially in case of piroxicam. These results were in agreement with other investigators [21, 22], who described acute hepatitis as an adverse reaction of piroxicam. Helfgot et al. [15], reported an elevation of serum transaminases with diclofenac $Na^+$ of 1.2 to 3 times in 15% of patients receiving the drug, > 3 times normal occurred in 4% and marked elevation > 8 times normal in 1%. Although these clinical cases were noted to be reversible on cessation of treatment with diclofenac $Na^+$, nontheless three reports of fulminant hepatitis leading to fatality have appeared.

The histopathological findings in this work revealed a viral hepatitis like picture. The severity of these reactions ranges from mild spotty hepatocellular necrosis to briding necrosis and fibrosis. Also ectatic vascular lesions in the form of congestion of the sinusoids and peloisis hepatitis were observed. Most findings were in agreement with other investigators [22, 23, 24].

The mechanism of hepatic injury which occurred with NSAIDs therapy is not known. It could be assumed that hepatotoxicity might be related to hypersensitivity reaction, but the typical features of drug hypersensitivity including fever, rash did not appear and no eosinophils could be detected in between the inflammatory infiltrates. These results were confirmed by the observations of Breen et al. [25] and Schapira et al. [23].

Other investigators suggested an idiosyncratic mechanism for hepatic injury (unusual vulnerability) due to aberrant metabolism and accumulation of reactive metabolites of free radical intermediates [26, 27]. The time interval between starting medication and the onset of the hepatitis & the recurrence of hepatitis on rechallenge with the drug seen to support the theory of idiosyncrasy [1]. Paterson et al. [22], reported that piroxicam produced submassive necrosis of the liver 6

weeks after beginning of its administration in patients with long term therapy with piroxicam, probably as an idiosyncratic reactions.

On the other hand, a direct toxic effect due to drug accumulation may be the cause of hepatitis especially in elderly patients, [3, 28]. Piroxicam is liable for accumulation because it has a long half life about 45 hours, highly bound to plasma proteins 90% but has a short half life (40 minutes -2 hours). It is excreted mainly unchanged via kidney and only 10% metabolized in liver [31]. Hosie and Hosie [32], observed no evidence of accumulation of the drug after a 4 week treatment period in elderly arthritic patients but with long term therapy, the possibility of accumulation was increased with age leading to a rise of the free fraction of the drug. This may explain that hepatotoxic effect of tiaprofenic acid in this work was less than that induced by piroxicam.

Moreover, Masaki et al. [33], suggested that $PG_2$ may have the ability to stabilize the plasma membrane of hepatocytes protecting them from various liver injuries in vivo. This suggestion may add an explanation for hepatocellular damage that occurred by the tested drugs which are potent reversible inhibitors of PG synthesis. The previous explanation was confirmed by other investigators. Gaurner et al., [34], demonstrated that PG synthesis inhibition by indomethacin led to an increase in hepatotoxicity of carbon tetrachloride. Furthermore, Nasseri - Sina et al. [11], found that paracetamol produced reduction in the percentage of viable isolated hepatocytes and the addition of aspirin or ibuprofen exacerbated the loss of viability indicating that endogenous PG may play a role in protecting hepatocytes from paracetamol toxicity.

In this work, the hepatotoxic effect of tiaprofenic acid and piroxicam in arthritic rats was more marked than that occurred in normal treated rats. Although, no elevation of serum transaminases was observed in arthritic untreated rats compared to normal, histopathological changes in the liver was seen in the form of ectatic vascular changes. The vascular dilatation may compress the near adjacent hepatocytes causing more anoxia and making them more susceptible to the toxic effect of the drugs. So the adjuvant induced arthritis act as a risk factor aggravating the hepatocellular damage observed in the arthritic treated rats. These results were comfirmed by the observation of Schwartz et al. [35], who noted liver damage disseminated intravascular coagulation in patients suffered from elapses of systemic juvenile rheumatoid arthritis who not under NSAIDs therapy. They suggested that hepatocellular damage was a direct manifestation of disease activity.

As regard, the reversibility of hepatotoxic effect after withdrawal of the tested

drugs, it was noted that transaminases serum levels in normal rats were returned to original levels and signs of healing were appeared in the liver. In arthritic rats, the process of healing was delayed especially in case of piroxicam withdrawal and there was a significant elevation of the serum transaminases. These results were confirmed by the findings of many investigators who reported that discontinuation of the use of NSAIDs did not always result in a return of normal liver functions **[15, 25, 36]**. Other investigators reported that most of NSAIDs may commonly induce hepatotoxicity which was reversible on discontinuation of these drugs and recure when the therapy started again **[1, 3, 14]**.

According to the findings of this work, the liver function tests should be monitored carefully and serially in any patients undergoing longterm therapy with NSAIDs.

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