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TOXICOLOGICAL PROFILE OF THE INTERACTION OF INDOMETHACIN WITH HEPATIC SCHISTOSOMIASIS MANSONI

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ABSTRACT

The toxicity of the antiinflammatory drug indomethacin in normal healthy , S. mansoni infected mice as well as mice cured the initial infection was assessed. The data showed augmented toxicity in both groups of bilharzial infected animals relative to the normal uninfected controls with steep dose-mortality curve for the bilharzial infected group.

Further exploration of hepatotoxicity potentiation in bilharzial infected and bilharzial cured mice, indomethacin was daily administered at three dose regimens; 1 x 50 mg / kg (single dose), 5 mg / kg / day x 15 and 0.5 mg / kg / day x 15. Serum γ -glutamyl transpeptidase (GGTP) and ornithine carbamoyl transferase (OCT) as well as granuloma measurements were considered as criteria for the assessment of the extent of hepatic damage.

Indomethacin caused elevation of serum activities of both enzymes in bilharzial infected mice at all dose regimens with less but still pronounced effect in bilharzial cured animals with no change in the enzyme activities at the lowest dose (0.5 mg / kg). Granuloma measurements showed augmentation in the size of the lesions only in infected animals at doses of 5 mg / kg. While such effect was not recorded in cured mice. The role of indomethacin in the development of bilharzial hepatic lesions was discussed.

INTRODUCTION

Indomethacin is a nonsteroid antiinflammatory drug. It was introduced in the early 1960s for the treatment of rheumatoid arthritis and related disorders including gouthy arthritis, ankylosing spondylitis and degenerative joint disease (Kaarela et al.,1989) . It is also effective in extra-articular inflammatory conditions such as pericarditis and pleurisy (Katzung, 1982 and Rao and Rao., 1982). Besides, it

has a pronunced antipyretic and analgesic effect (Kaarela et al., 1989). Recently, attempts were made to investigate the use of indomethacin, alone (Furuta et al.,1988)or combined with sulfhydryl compounds (Kozubik et al., 1990) as a pharmacological mean in radiotherapy of tumours based on its supressive effect on prostaglandins via cyclooxygenase inhibition.

Virtually, various arachidonic acid metabolites are known to regulate the immune cell functions and dictate the progression of both acute and chronic inflammatory reactions. (Kunkel et al., 1984). Current trends explored the contribution of arachidonic acid metabolic pathways to the formation of chronic hypersensitivity granulomas and evaluated the differential inhibitory effects of the antiinflammatory drugs on arachidonic acid metabolism via the cyclooxygenase and lipoxygenase pathways and their role in the modulation of the murine pulmonary granuloma formation (Kunkel et al., 1984 and Remick et al., 1988). In fact, it is well- established that heparic involvements caused by *Schistosama mansoni* is due to the host immune reaction to ova deposited by the parasite and carried by the blood to the liver where egg antigens released by the continuously disseminated parasite ova evoke a T lymphocyte-mediated granulomatous response in the tissues of infected mice (Warren et al ., 1967). Moreover, arachidonic acid derivatives have been also reported to occur at the inflammatory foci (Kunkel et al.,1984).

Though indomethacin, however, is considered as one of the most antiinflammatory drug available now, it is more toxic than any other related antiinflammatory agents (Katzung, 1982). Its toxicity has been proven in humans (Johnson and Mcfarlane, 1989) and experimental animals (Van Eeken et al.,1976). But uptill now no trials have been encountered to evaluate the toxicity of the drug on *S. mansoni* infected targets.

For this reason a series of investigations were intended to be performed to explore the interaction of indomethacin with murine schistosomaiasis mansoni. Hence the aim of the present paper is initially to provide a background insight on its toxicity to *S. mansoni* infected mice before and after curation from infection.

MATERIALS AND METHODS

Biological drugs:

1 - **Indomethacin,** [1 - (4 - chlorobenzyl) - 5 - methoxy - 2 - methylindol - 3 -yl] acetic acid with emperical formula $C_{14}H_{16}ClNO_4$ was used in the present study. The drug was dissolved in isotonic phosphate buffer (pH 7.4) and administered intraperitoneally at three dose regimens; 1 x 50 mg / kg, 15 x 5mg / kg and 15 x 0.5 mg / kg as presented later.

2-Praziquantel; 2 - cyclohexylcarbonyl - 1, 2, 3, 6, 7, 11, b -hexahydro- 4 H - pyrazino - (2, 1-a) isoquinoline -4 - one with emperical formula $C_{19}H_{24}N_2O_2$ is a schistosomicidal drug currently used by the national campaign in mass treatment of both types of schistosomiasis in Egypt. The drug was suspended in a mixture of glycerol and water and was administered as one oral dose of 685 mg / kg by gastric intubation.

Experimental animal and bilharzial infection

All studies were performed with albino mice weighing between 20 and 25 g at the begining of the experiments. The animals were fed on a standard food *ad libitum* with free access to water.

The experimental mice were exposed individually by tail immersion to single doses of 70 cercariae of *S. mansoni* shed by laboratory infected *Biomphalaria alexandrina.* The techniques used for the maintenance of the life cycle of this parasite in the laboratory and for collection of cercariae were as those described by Christensen et al ., (1984).

Experimental animal groups

In order to explore the toxicological profile of indomethacin in *S. mansoni* infected and *S. mansoni* cured mice, three experiments were undertaken :

1 - **Experiment I** for evaluation of the intraperitoneal LD_{50} s in both

normal and bilharzial as well as bilharzial cured mice. In this experiment, animals of an infection duration of 8 weeks were selected and divided into two groups; a group treated with the antibilharzial praziquantel as one oral dose of 685 mg / kg (i.e. cured group)and a group received no antibilharzial treatment (i. e .infected group). Besides, a healthy uninfected guoup was run along with the two previous groups. Each group was divided into 5 batches, each of 20 mice. The batches of each group were exposed to increasingly intraperitoneal doses of indomethacin and the number of animals died in each batch was recorded with the magnitude of the concentration which brought about that response. From the data recorded for each group, the logarithms of the concentration were plotted against the probability units of the observed percentage kill and the LD_{50}s were evaluated according to the method present by Finney (1952).

2 - **Experiment II** for primary evaluation of the toxic effects of acute and chronic administration of indomethacin on the bilharzial infected mice liver. In this experiment 3 groups, each of 5 infected mice were used. The schedule of indomethacin treatment was as follows, the first group received a single dose of 50 mg /kg; the second and third groups received respectively a daily dose of 5 mg / kg/ day and 0.5 mg / kg / day of indomethacin for 15 days.

3 - **Experiment III** aims at evaluation of the effect of indomethacin on *S. mansoni* cured mice. Three bilharzial infected groups of 8 week-old infection were received a therapeutic dose of praziquantel (685 mg / kg). These groups, each of 5 mice, were treated with indomethacin at the same dose regimens decribed in experiment II.

Biochemical assays:

In all groups, animals were sacrificed 24 hours after receiving the last indomethacin dose. Blood samples were taken and serum was separated by centrifugation at 3000 rpm and stored shortly in the refrigerator prior to the enzyme estimations. Serum gamma glutamyl transferase (GGTP) was estimated according to Rosalki et al . (1970). Ornithine carbamayl transferase determination was carried according to Brown and Cohn (1958).

Granuloma measurements :

Selected parts of liver of mice in all groups were removed, fixed in buffered saline, prepared for histologic sections and stained with haematoxylin and easin. The diameter of each liver granuloma was obtained by measuring two diameters of the lesion at right angles to each other (Fig. 1) using an ocular micrometer. A minimun of 50 granulomas were measured from each group. The volume of each granuloma was calculated, assuming a spherical shape, from its mean diameter using the formula : volume = R^3 x 22 / 7 x4 / 3.

Statistical analysis :

The "t" test was used to analyze the data from control and experimental groups throughout the studies. Values of $p > 0.05$ were not considered significant.

RESULTS AND DISCUSSION

The list of drugs and other chemicals that can cause liver damage increases year by year and is now very long indeed. In fact, most durgs and many other potentially toxic chemical are metabalised by the liver, partly because of its central role in this respect and because it is the organ that usually receives the largest initial dose of drugs and other foreign chemical taken orally, it is particularly susceptable to damage by chemical agents.

Of the commonly used antiinflammatory drugs, many seem to be hepatotoxic to at least some extent, indomethacin, ibuprofen, dantrolene, naproxen, phenylbutazone and its derivatives; penicillamine and even gold all have been reported to cause cholestasis with variable degree of hepatocellular injury and the toxicity of benoxyprophen in the elderly patients is now well recognized. Phenylbutazone and oxyphenylbutazone in therapeutic doses can cause a hepatic illness in human targets. In overdose, phenylbutazon can produce a cholestatic hepatitis (Johnson and McFarlane, 1989). Meanwhile, hepatotoxic effects of indomethacin have been emphasized in experimental animals (rats) even at very low doses, 0.2 mg / kg (Klimniuk, 1989). In acute oral indomethacin toxicity studies in mice and rats considerable species differences as well as marked delayed

toxicity have been encountered. Indomethacin was found to be more toxic to rat than mice . The oral LD_{50} values were 2000 mg / kg for mice and 110 mg / kg for rats, however, these values were found to decerase as the observation period extended (Van Eeken et al., 1976) . In the present study, indomethacin, however, was found to show further toxicity to the already diseased animals. Table (1) shows the absolute values of the data obtained in acute intraperitoneal toxicity studies in both *S. mansoni* infected mice and mice cured the initial infection relative to healthy ones. Indomethacin showed augmented toxicity in mice whether infected or cured the infection with extreemly steep dose - lethality curve for bilharzial infected mice (Fig 1) suggesting the combined adverse effects of the ongoing infection and hepatotoxicity of the drug and or the inability of the diseased liver to metabolize the drug hence increased its toxicity.

Considering how extensively the nonsteroid antiinflammatory drugs are used, however, overt liver damage is quite rare. Nevertheless, a high proportions of patients receiving these and other antiinflammatory agents show persistent mild abnormalities of the liver function tests suggestive of some degree of chronic cholestasis (Johnson and McFarlane, 1989). In rats, even at very low doses, indomethacin was found to cause severe damage of the liver manifested by an increase of the serum activity of aminotransferases and alkaline phosphatases (Klimniuk, 1989). Generally , the biochemical abnormalities in common with nonsteroid antiinflammatory drugs, mainly comprise only slight elevation in alkaline phosphatase and γ - glutamyl transferase (GGTP) concentrations. Serum aminotransferase activities and bilirubin concentrations are usually normal but activities of another (less commonly used) serum maker of hepatocellular damage, ornithine carbamoyl transferase (OCT) have been found to be elevated up to 20 percent of rheumatoid patients on gold or phenylbutazone therapy (Johnson and McFarlane, 1989).

Table (2) shows both acute and chronic indomethacin administrations caused significant elevation in serum GGTP and OCT of *S. mansoni* infected mice particularly with repeated administration of the higher dose (5 mg / kg). Less, but still pronounced, elevations of both enzyme activities were recorded in bilharzial - cured mice, maintained on the same indomethacin administration

regimens. The repeated administration of the lowest dose (0.5 mg / kg / day) produced no appreciable change in the enzymatic activities. The elevation recorded in the serum activity of the OCT suggests the hepatotoxicity of indomethacin in both bilharzial and bilharzial-cured mice, since the enzyme is a sensitive indicator of the hepatotoxicity following administration of antiinflammatory drugs (Reichard et al, 1960), with the possibility of the involvement of hepatobilary tract as manifested by increased serum GGPT activity . Lipid peroxidation is thought to be an important feature of indomethacin toxicity where an increase of peroxidation of lipids of hepatocytic membrane besides a decrease of reserves of restored glutathione and a disturbance of the functional state of the liver of rats were recorded following indomethacin treatment (Klimniuk, 1989).

As concerns the granulomatous reactions, it is well established that the metabolism of arachidonic acid by inflammatory cells is known to involve a cascade of complex biochemical reactions that result in the production of numerous biologically active lipids including : thromboxanes, prostaglandins, hydroxyeicosatetraeonic acids, hydroperoxyeicosatetraenoic acids and leukotrienes (Samuolsson, 1982). These metabolites from both the cyclooxygenase (CO) and lipoxygenase (LO) pathways are known to influence the immune cell function (Bailey et al., 1982; Ford - Hutchinson et al., 1980 ; Gordon et al.,1976; Koren et al., 1981 and O'Flaherty et al., 1981) as well as modulate the progression of inflammatory reactions (Chensue et al., 1983, Kunkel et al., 1981 and Mertin and Stackpool, 1981).

As arachidonic acid derivatives can be found at inflammatory foci (Ohuchi et al, 1976) many investigators have focused on the biochemical manipulation of these metabolites in order to pharmacologically control inflammatory reactions (Higgs et al. 1979; Kemp et al. , 1980 ;Snyder et al., 1982 and Steeg, 1982). In various in vivo as well as in vitro models, arachidonic acid metabolic inhibitors, including indomethacin, have been shown to modulate both acute inflammatory cell functions (Higgs et. al, 1980; Needleman, 1977 and Smolen and Weissman, 1980) and T cell - mediated responses (Crout et al., 1975 Kelly et al., 1979 ; Leung et. al., 1982 and Panayi and Rix, 1974). Meanwhile, Kunkel et al (1984) have established the contribution of arachidonic acid metabolic pathways to the

formation of experimental murine hypersensitivity pulmonary granuloma by *S. mansoni* eggs and investigated the role of several antiinflammatory drugs that have differential inhibitory effects on arachidonic acid metabolism via cyclooxygenase and lipoxygenase pathways. Unlike other antiinflammatory agents used, chronic administration of the cyclooxygenase inhibitor indomethacin showed a trend of augmentation of the size of the pulmonary granulomas at a dose regimen comparable to that used in the present study and had no effect at a dose level of 2.5 mg / kg. The highest dose of indomethacin; 10 mg / kg, proved to be toxic but in surviving animals supression could be demonstrated. In addition, indomethacin showed no significant effect when administered postgranulomagenic challenge at a dose of 5 mg / kg. These results are in complete accord with the present findings where chronic administration of indomethacin induced pronounced increment in the hepatic granuloma volume at a dose level of 5 mg / kg while no effect was recorded whether with single acute dose or repeated adminsteratin of lower doses (Table 2) explaining its selective inhibitory effect on the cyclooxygenase pathway . Also, no significant change in the hepatic granuloma volume of bilharzial cured mice at any dose regimen used (Table 3) indicating that indomethacin induced its effect only on the ongoing hepatic granuloma formation where arachidonic acid metabolites were beeing released. This could be explained in the view of Kunkel et al. (1984) who pointed out that, in contrast to other antiinflammatory agents, indomethacin as a selective cyclooxygenase antagonist, had no effect on granuloma formation at nontoxic doses. But daily administration of indomethacin at higher doses (5 mg / kg) showed clear potentiation of granuloma macrophage Ia antigen expression via inhibition of cyclooxygenase products such as PGE_2 and thereby, indirectly, regulate T cell - macrophage interaction. This concept is supported by the report of Chensue et al. 1983 that described the suppression of granuloma size and granuloma macrophage Ia expression by parenterally administered PGE. It can also reflect the capacity of indomethacin to potentiate mixed lymphocyte reactions (Darrow and Tomar, 1980) which require the participation of Ia-positive macrophages.

In conclusion, the present study does not suggest the use of indomethacin in manipulating chronic hepatic granulomatous inflammation induced by *S. mansoni.*

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Table(1):Intraperitoneal toxicity of indomethacin in bilharzial mice .

Animal group	LD_{50}
Healthy uninfected	1102 mg/kg
S.mansoni-infected	769 mg/kg
S.mansoni-cured	832 mg/kg

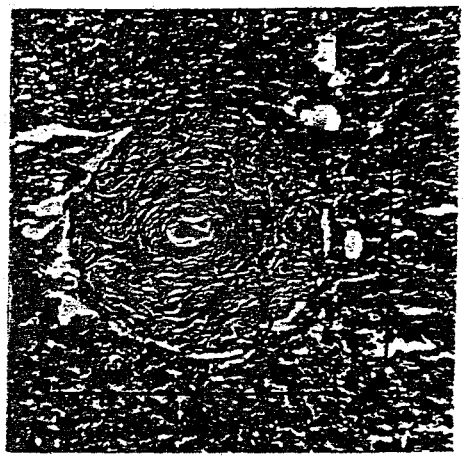
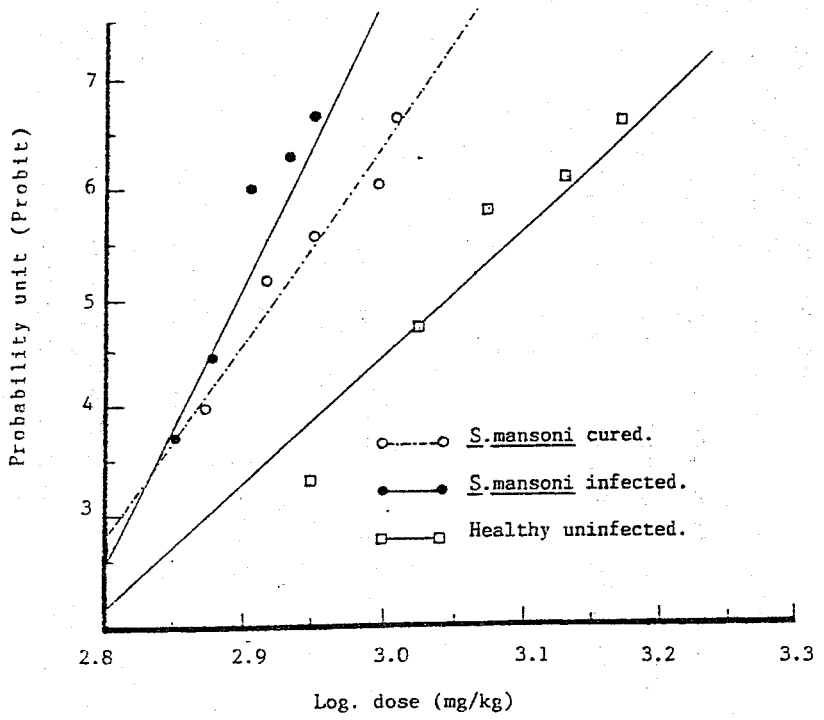


Fig.(1):A typical hepatic granuloma containing one egg in its center selected for mean diameter(d)measurements.



ig(2) Dose-Leathality curves of intraperitoneal administeration of indcmethacin to bilharzial mice .

Table (2) : Effect of indomethacin treatments on hepatic granuloma measurements and the serum γ - glutamyl transpeptidase (GGTP) and ornithine carbamoyl transferase (OCT) activities of *S. mensoni* - infected mice.

Animal group	Granuloma measurements		GGTP activity (Mean ± SD)	OCT activity (Mean ± SD)
	Mean diameter (um ± SD)	Mean volume ($mm^3 \times 10^{-4} \pm SD$)		
S. mansoni infected	329 ± 36	201 ± 51	08.93 ± 1.03	45.31 ± 3.39
S. mansoni infected + Indomethacin				
- 50 mg / kg (single dose)	338 ± 60	221 ± 69 (+ 9.95)	10.90 ± 0.91 (+ 22.06)*	53.51 ± 5.10 (+18.12)*
- 5 mg / kg / day x 15	369 ± 65	289 ± 113 (+ 43.78)***	12.92 ± 1.60 (+ 44.86)**	63.41 ± 6.6 (+ 39.95)**
- 0.5 mg / kg / day x 15	323 ± 49	180 ± 75 (- 10.45)	11.01 ± 1.20 (+ 23.29)*	52.67 ± 56 (+ 16.24)*

- Activity is expressed umol p- nitroaniline / min / l for GGTP and umole citrulline / min /l for OCT.
- Number inside parenthesis is the percentage change from control (infected - untreated).
- All animal groups were decapitated 24 hr post indomethacin treatments.
- Infection with 70 cercariae / head - (8 week - old infection).

* P < 0.05 ** P < 0.01 *** P < 0.001.

Table (3) : Effect of indomethacin treatments on hepatic granuloma measurements and the serum γ- glutamyl transpeptidase (GGTP) and ornithine carbamoyl transferase (OCT) activities of mice cured *S. mensoni* - infection .

Animal group	Granuloma measurements		GGTP activity (Mean ± SD)	OCT activity (Mean ± SD)
	Mean diameter (um ± SD)	Mean volume ($mm^3 \times 10^{-4} \pm SD$)		
S. mansoni infected	222 ± 41	129 ± 39	4.61 ± 0.8	33.57 ± 3.1
S. mansoni cured + Indomethacin				
- 50 mg / kg (single dose)	221 ±70	111 ± 53 (-13.95)	5.45 ± 1.2 (18.22)	40.11 ± 3.2 (19.48)*
- 5 mg / kg / day x 15	237 ±53	142 ± 41 (+ 18.92)	5.95 ± 1.0 (29.07)*	42.88 ± 4.1(27.73)**
- 0.5 mg / kg / day x 15	207 ± 60	133 ± 39 (+ 3.1)	5.01 ± 0.7 (8.68)	38.12 ± 3.8 (13.55)

- Activity is expressed in umol p- nitroaniline / min / l for GGPT and umol citrulline / min /l for OCT.
- Number inside parenthesis is the percentage change from control (*S. mansoni* - cured).
- Animal groups were decapitated 24 hr post indomethacin treatments.
- Praziquantel was administered as a single oral dose (685 mg / kg).
- Infection with 70 cercarie / head - (8 week - old infection).

* $P < 0.05$ ** $P < 0.01$

تقدير السمية الناتجة من تفاعل عقار الإندوميثاسين مع الإصابة الكبدية بالبلهارسيا المانسونية

اسماعيل مصطفى الشرقاوى

قسم علم الحيوان - كلية العلوم - جامعة طنطا

تم فى هذه الدراسة تعيين سمية عقار الإندوميثاسين المضاد للإلتهابات بالنسبة لكل من الفئران المصابة بالبلهارسيا المانسونية وكذلك التى عولجت من الإصابة بالإضافة إلى الفئران الطبيعية غير المصابة . وقد أظهرت الدراسة سمية هذا العقار بالنسبة لكل من الحيوانات المصابة بالبلهارسيا وكذلك التى عولجت من الإصابة قياسا على الحيوانات الطبيعية مع ظهور انحدار شديد فى منحنى معدل الوفيات المرتبط بالجرعات بالنسبة للحيوانات المصابة بالبلهارسيا .

وتم كذلك استكشاف سمية هذا العقار على الكبد المصاب وكذلك الذى عولج من الإصابة عند ثلاث نظم من الجرعات وهى : ٥٠ مجم / كجم كجرعة واحدة ، ٥ مجم / كجم يوميا حتى ١٥ جرعة ، ٥ر٠ مجم / كجم يوميا حتى ١٥ جرعة . وقد اتخذ نشاطا كل من انزيمى الجاما جلوتاميل ترانس ببتيداز و الأورنيثين كارباموبل ترانسفيراز فى مصل دم الحيوانات بالإضافة إلى قياس حجم الإلتهاب المميز للإصابة كمعايير لتقدير حجم الضرر الناشيء فى الكبد نتيجة المعالجة .

وقد تسبب الإندوميثاسين فى زيادة نشاط الإنزيمين فى مصل الحيوانات المصابة بالبلهارسيا عند كل الجرعات . وكان هذا التأثير واضحا أيضا بالنسبة للحيوانات التى عولجت من الإصابة ولكن بدرجة أقل حيث لم يظهر أى تغيير عند الجرعة الأقل (٥ر٠ مجم / كجم). وأظهرت قياسات حجم الإلتهابات زيادة واضحة فى حجمها فى الحيوانات المصابة فقط وعند الجرعات ٥ مجم / كجم دون غيرها . ولم يلاحظ مثل هذه التغيرات فى الحيوانات المعالجة من الإصابة . هذا وقد تم مناقشة الدور الذى يقوم به الإندوميثاثين فى احداث هذه التغيرات .