

A STUDY ON THE EFFECT OF MIRAZID ON SOME OF THE INTERNAL ORGANS AND ITS POSSIBLE PRENATAL EFFECT IN ALBINO RAT

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ABSTRACT

30 adult albino rats were used in this study. They were divided into 3 groups (10 rats each): Adult male, female and pregnant rats. Each group was subdivided into control and treated ones. The treated rats were given 10% Mirazid emulsion (new natural schistosomicidal drug obtained from Myrrh), provided from Pharco Pharmaceuticals, Alexandria, Egypt. It was given orally in a dose 200 mg/ Kg body weight, one hour before breakfast, for six successive days. The pregnant rats were given the same dose starting day 6 to day 11 of pregnancy and were observed for abortions, numbers of newly born fetuses which examined for any congenital abnormalities. No abortions were noted in the treated pregnant rats. The

number of pups for each treated ones was higher than those of control mothers. Also, the pups of treated mothers were similar in weight to the control and no congenital anomalies were seen.

The rats were sacrificed at one and seven days after administration of the last dose with Mirazid. They were thoroughly dissected for the liver, pancreas, kidney and testis or ovaries, which then fixed in 10% formaldehyde. Sections were prepared and stained by haematoxylin and eosin. Haematoxylin and eosin stained sections of the liver, one day after the administration of the last dose of the drug, showed little infiltration with lymphocytes, slight dilatation of liver sinusoids with scanty vacuolation of its cells. However,

sections of the liver seven days after treatment showed minor lymphocytic infiltration with normal architecture. The sections of treated kidney one day after the last dose showed mild dilatation of its renal tubules with vacuolation of its lining cells, few R. B. Cs and intact glomeruli. These changes returned to normal in sections examined at seven days after the last dose. No detectable changes were seen in sections of the pancreas, the testis and or the ovary at one and seven days after the treatment.

So, Mirazid proved to be safe for liver, kidneys, pancreas and gonads.

INTRODUCTION

No doubt that schistosomiasis tops all endemic parasitic diseases world wide particularly in Egypt (Wilson, 1991 and WHO, 1995)^{43, 41}. There are many antibilharzial drugs belonging to different groups. The most recent drug used is belonging to praziquantel (Ismail et al., 1994 and 1996)^{17, 18}. Many side effects were reported after its use. Such side effects may restrict its use, especially during pregnancy and lactation. How-

ever, the reported side effects after treatment with praziquantel may be much less than the previously used antibilharzial drugs (El-Gammal et al., 1992, Hardman et al., 1996 and Redman et al., 1996)^{13, 15, 37}. Searching for new antibilharzial drug with lesser or even minute side effects was looked for.

Mirazid, is the most recently used antibilharzial drug in Egypt (Massoud, 1999a, 1999b, El-Maaty, 2002)^{21, 22, 14}. It is a new schistosomicidal, fasciolicidal and molluscicidal agent (Perrett and Whitefield, 1996; Allam et al., 2001; Massoud et al., 2001b; Hegab and Hassan; 2003)^{35, 3, 26, 16}. This agent is derived from Myrrh (the oleo gum resin of *Commiphora molmol*, family *Burseraceae*), all extracted from the stem of crude plant (Massoud et al., 2002 and Soliman et al., 2004)^{27, 39}. The drug is chiefly collected in Somalia and Arabian Peninsula (Chevallier, 1996)⁹.

The studies proved that it is effective anticarcinogenic (Al-Harbi et al., 1994)¹ and antiulcers of the stomach (Cleason et al., 1991; Al-Harbi et al., 1997; Borrelli and Izzo, 2000)^{10, 2, 7}. Also, it treats sore throat, bleeding gums and amenorrhea (Moran et al.,

1992 and Olajide, 1999)^{29, 31}. It is proved to be effective in controlling snails (Massoud and Labib, 2000; Massoud et al., 2001a; Allam et al., 2001)^{23, 25, 3}.

It is proposed to be of any side effects when given by therapeutic dose (15mg/Kg body weight, for six successive days, one hour before breakfast).

Furthermore, no experimental evidence of embryopathic or teratogenic effects were reported. It was also reported that the liver and kidney function tests as well as the blood pictures showed insignificant changes during therapy (Massoud, 1999a & b; Massoud and Labib, 2000; El-Baz et al., 2003)^{21, 22, 23, 12}. Sheir et al. (2001)³⁸ mentioned that the drug was well tolerated and side effects were mild and transient. These advantages of the drug were reported in few literature, and were mentioned only in the pamphlet of the drug.

So, it is decided to plane a research work for evaluating the possible side effects of Mirazid. The study includes the prenatal effect of the drug as well as the histopathologic changes in some of the body organs

after therapeutic dose of the drug.

MATERIAL AND METHODS

Animals :

30 adult rats were used in this study. They were divided into three groups: pregnant female rats, adult male rats and adult female rats (10 rats each). Each group was subdivided into control and experimental subgroups.

Pregnant rats :

Vaginal smears were taken from the female rats and the presence of spermatozoa was taken as an index of day one of pregnancy. The pregnant rats were followed up for time and number of abortions. Their newly born fetuses were examined for anomalies.

Drug used :

Mirazid aqueous emulsion (10% aqueous emulsion, in a bottle of 120 ml by Pharco Pharmaceutical, Alexandria, Egypt) was given to all experimental rats in an oral dose of 200 mg/Kg as reported in Paget and Barnes (1964)³³, using a stomach tube, on an empty stomach one hour before breakfast, for six successive days. The pregnant rats were given the

same dose starting from the day 6 to day 11 of pregnancy. Food and water were provided ad libitum for all rats.

Histological examination :

The rats were sacrificed one and seven days after treatment with Mirazid for adult male and female groups. After through dissection of rats, specimens from liver, pancreas, kidney, testis and ovary were taken. Then prepared for paraffin sections and stained with haematoxylin and eosin stain.

RESULTS

I - Morphological changes of adult rats :

The treated rats showed no signs or symptoms on their general conditions and looking like the control rats.

II -The effect of the drug on pregnant rats and offsprings :

- No abortions were reported.
- The pups from treated mothers showed the following:
 - a) The average number varied from 9 to 11 pups in comparison with the number of those from control as it was about 6-8 pups (Fig.1).

b) The average weight was almost similar to that of the control ones.

c) No congenital anomalies were noticed.

III - Histological Examination of Internal Organs of adult rats:

1. Liver :

a) Control liver :

Haematoxylin and eosin stained sections showed closely packed liver lobules, separated by scarce amount of connective tissue. The liver cells were arranged in cords radiating from the central vein to the periphery and separated from each other by blood sinusoids (Figs. 2, 3).

b) One day after the last dose of Mirazid :

Sections of the liver showed patches of few lymphocytic infiltration in few areas beside the central vein, mild dilatation of liver sinusoids and mild vacuolation of liver cells (figs. 4, 5).

c) Seven days after the last dose of Mirazid :

Sections of the liver showed multiple areas of focal necrosis near the central vein. However, the portal tract and liver architec-

ture, looked similar to the control (figs. 6, 7).

2. Kidney :

a) *Control kidney :*

Haematoxylin and eosin stained sections showed an outer densely eosinophilic cortex and an inner pale staining medulla. The cortex contained the glomeruli and the major projections of the proximal and distal convoluted tubules, loops of Henle and upper portions of the collecting tubules. The medulla contained the collecting ducts and the major projections of loops of Henle (figs. 8, 9).

b) *One day after the last dose of Mirazid :*

The sections of the kidney showed congested cortex, numerous dilated tubules and extravasated R. B. Cs. Some tubules showed swollen cells and others showed cells with vacuolated cytoplasm. The glomeruli, however, showed no noticeable changes (figs. 10, 11).

c) *Seven days after the last dose of Mirazid:*

The tubular ducts, the convoluted tubules and the glomeruli looked like the control ones (fig. 12).

3. Ovary :

a) *Control ovary :*

Sections of the ovary showed that it was covered by dense layer of connective tissue. The cortex contained ovarian follicles at different stages of growth. The mature follicle showed an oocyte surrounded by zona pellucida, corona radiata, cumulus oopharous and membrana granulosa. The theca interna and theca externa surrounded by fibrous connective tissue layer (fig. 13).

b) *One day after the last dose of Mirazid :*

The ovarian sections were almost similar to that of the control ones (fig. 14).

c) *Seven days after the last dose of Mirazid :*

The ovarian sections showed many growing follicles. However, the primary and mature follicles and corpus luteum appeared like the control ones (fig. 15).

4. Testis :

a) *Control testis :*

Haematoxylin and eosin stained sections showed that the seminiferous lobules were separated by

interstitial connective tissues that contained blood vessels and Leyding cells. The seminiferous tubules were surrounded by basement membrane which formed of 4 layers of cells. Spermatogenic cells were seen followed by layers of cells at different stages of maturation: primary spermatocytes, secondary spermatocytes, elongated spermatids and sperms near the lumen (figs. 16, 17).

b) One day and seven days after the last dose of Mirazid :

The seminiferous tubules were almost normal in size and their constituent cells looked like the control. They showed cells in different stages of maturation from spermatogonia up to sperms. The interstitial tissues were

similar to the control (figs. 18,19).

5. Pancreas :

a) Control pancreas of albino rat :

Haematoxylin and eosin stained sections showed connective tissue septa dividing it into lobules. There were acini of different sizes and shapes (fig. 20). The acini consisted of a single layer of pyramidal cells rested on the basement membrane with rounded nuclei located towards the bases of the cells (fig. 21).

b) One day and seven days after the last dose of Mirazid :

The sections showed normal architecture of the lobules, interlobular tissue spaces and acini. The interlobular ducts were lined by normal columnar epithelial cells (figs. 22, 23).

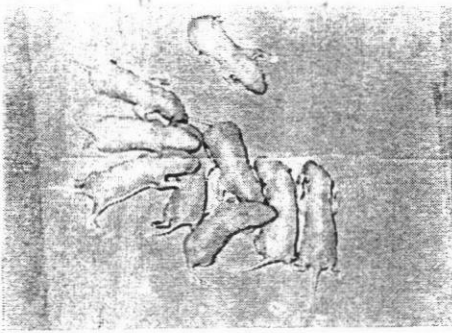


Fig. (1) : A photograph of pups from a pregnant rat treated with Mirazid one day after delivery. Notice, there are 9 normal pups with average size and no congenital abnormalities.

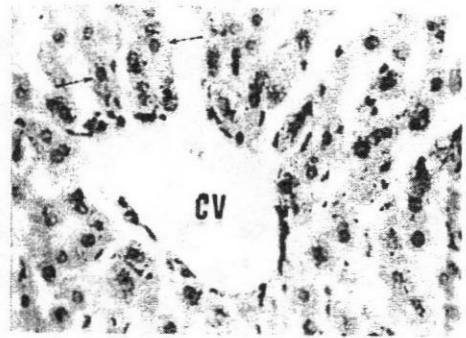


Fig. (3) : A higher magnification of Fig. (2) showing, the central vein (CV) and liver cells (arrows) forming cords radiating from the central vein and separated by liver sinusoids (S). (HX. & E.; X 400)

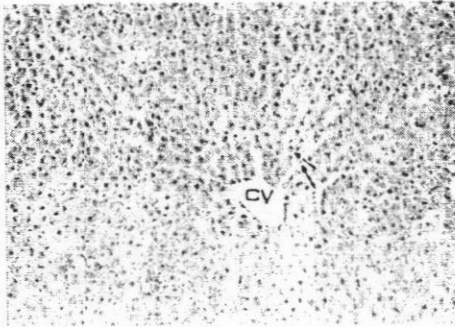


Fig. (2) : A photomicrograph of a section in the liver of control albino rat. Note the central vein (CV) and radiating cords of liver cells (arrows). (HX. & E.; X 100)

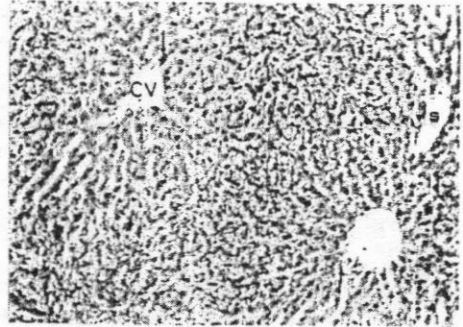


Fig. (4) : A photomicrograph of a section in the liver of albino rat one day after the last dose of Mirazid, showing slight dilatation of liver sinusoids (S), with few pyknotic nuclei (arrows) and central vein (CV) that appeared normal. (HX. & E.; X 100)

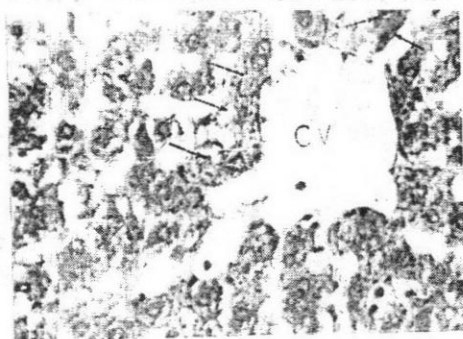


Fig. (5) : A higher magnification of Fig. (4), showing intact central vein (CV), few necrotic liver cells with vacuolated cytoplasm (arrows) and few of lymphocytic infiltration (crossed arrows). (HX. & E.; X 400)

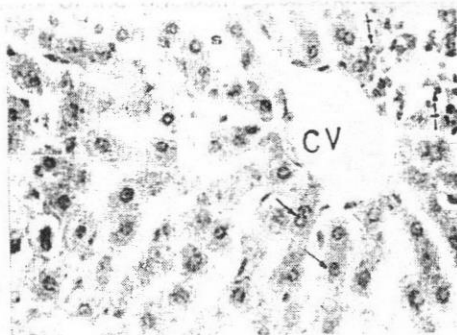


Fig. (7) : A higher magnification of Fig. (6). The liver sinusoids (S), the central vein (CV) and the liver cells are intact (arrows). Presence of rounded cells infiltration in area of focal necrosis (crossed arrows). (HX. & E.; X 400)

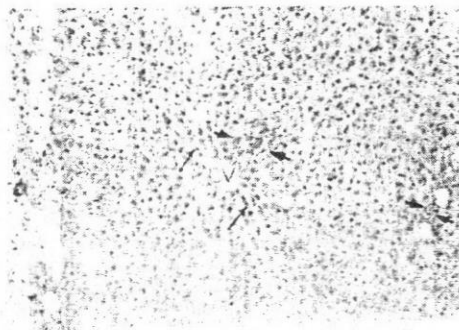


Fig. (6) : A photomicrograph of a section in the liver of albino rat seven days after the last dose of Mirazid. Notice: the central vein (CV) appeared normal, liver cells like control and the radiating cords (arrows). Rounded cells of infiltration are seen in two areas of focal necrosis (head arrows). (HX. & E.; X 100)

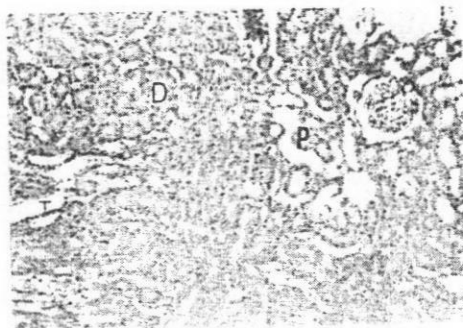


Fig. (8) : A photomicrograph of a section in the kidney of control albino, showing the glomerulus (G), proximal convoluted tubule (P), distal convoluted tubules (D) and collecting tubules (T). (HX. & E.; X 100)

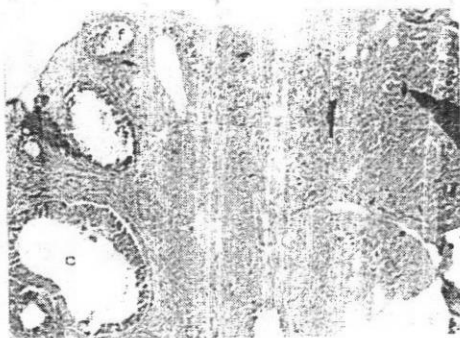


Fig. (13) : A photomicrograph of a section in the control ovary of albino rat ,showing the presence of primary follicle (p), growing follicle (F), and corpus luteum (C) . (HX. & E.; X 100)

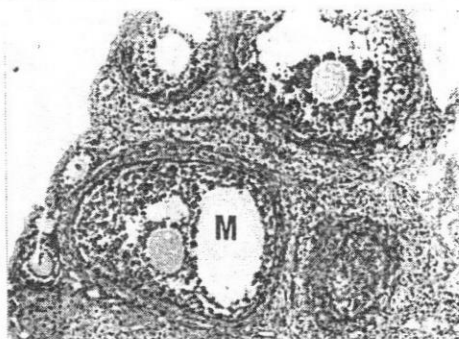


Fig. (15) : A photomicrograph of a section in the ovary of albino rat seven days after the last dose of Mirazid, showing intact primary follicles (f), and mature follicles (M). (HX. & E.; X 100)

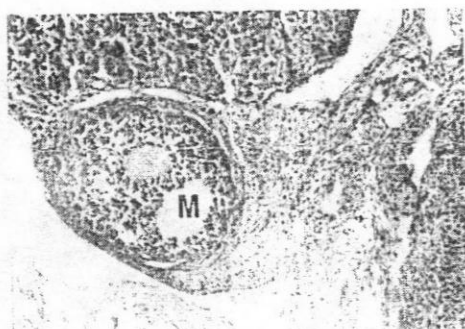


Fig. (14) : A photomicrograph of a section in the ovary of albino rat one day after the last dose of Mirazid, showing normal mature graffian follicle (M). (HX. & E.; X 100)



Fig. (16) : A photomicrograph of a section in the testis of control albino rat, showing multiple seminiferous tubules separated by interstitial tissue containing normal Leyding cells (L) and blood vessels (b). (HX. & E.; X 100)

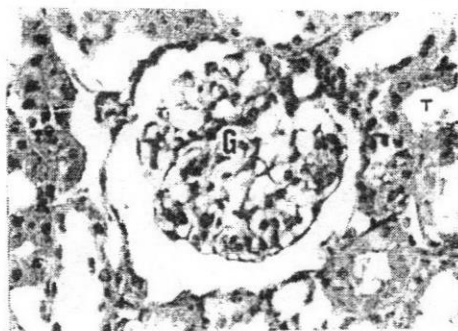


Fig. (9) : A higher magnification of Fig. (8), showing normal glomerulus (G) and normal tubules (T).
(HX. & E.; X 400)



Fig. (11) : A higher magnification of Fig. (10), showing extravasated R.B.Cs (crossed arrows), intact tubules (t) among dilated ones with degenerated vacuolated epithelial cells (arrows) and intact glomerulus (G).
(HX. & E.; X 400)

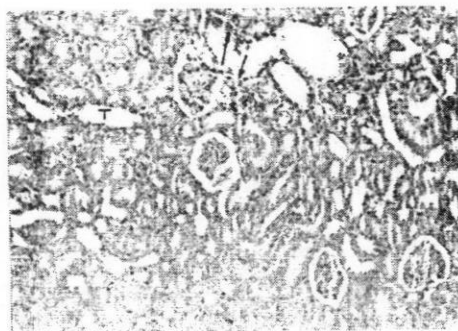


Fig. (10) : A photomicrograph of a section in the kidney of albino rat one day after the last dose of Mirazid. Notice the cortical congestion (arrows) and the dilated tubules (T).
(HX. & E.; X 100)

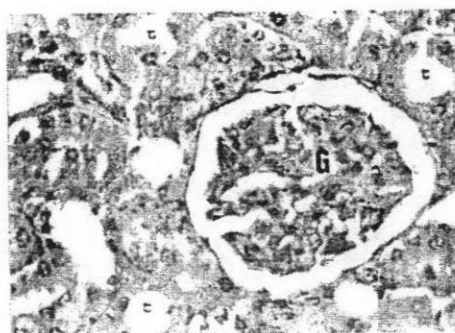


Fig. (12) : A photomicrograph of a section in the kidney of albino rat seven days after the last dose of Mirazid, showing glomerulus (G) with extravasated R.B.Cs and intact convoluted tubules (t).
(HX. & E.; X 400)

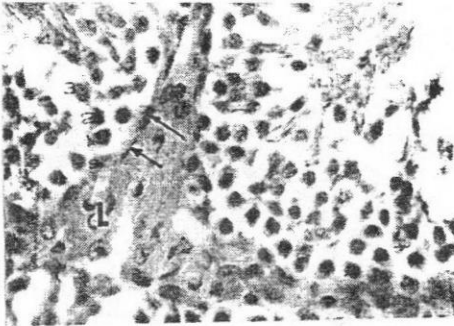


Fig. (17) : A higher magnification of previous Fig. (16). Notice: the nuclei of Sertoli cells (S) near the basement membrane (arrows), the Leyding cells (L). Spermatogonia (1), primary spermatocytes (2), spermatids (3) and sperms (4) are seen. (HX. & E.; X 400)



Fig. (19) : A higher magnification of Fig. (18), showing the intact layers of the germinal epithelium: (1) spermatogonia, (2) primary spermatocytes, (3) spermatids and (4) sperms. Note: the nuclei of Sertoli cells (S) near the basement membrane and intact Leyding cells (L). (HX. & E.; X 400)

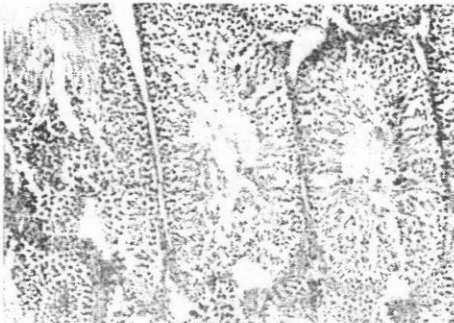


Fig. (18) : A photomicrograph of a section in the testis of albino rat one day after the last dose of Mirazid, showing intact tubular basement membrane, multiple seminiferous tubules separated by interstitial tissue containing normal Leyding cells (L). (HX. & E.; X 100)

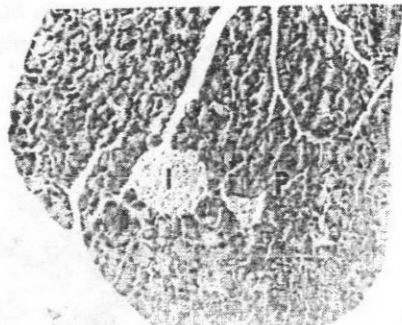


Fig. (20) : A photomicrograph of a section in the pancreas of control albino rat, showing scanty amount of connective tissue (arrows), the pancreatic acini (P) and Islet's of Langerhans (I). (HX. & E.; X 100)

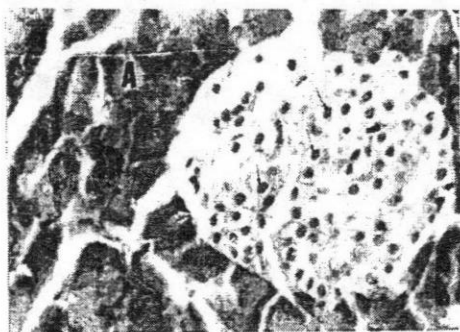


Fig. (21) : A higher magnification of Fig. (20). Notice: rounded basal nuclei (arrows) in the acinar cells (A) with basal basophilic and centrally acidophilic zones in the acinar cytoplasm. Centrally located rounded nuclei apparent in Islet cells (arrows). (HX. & E.; X 400)

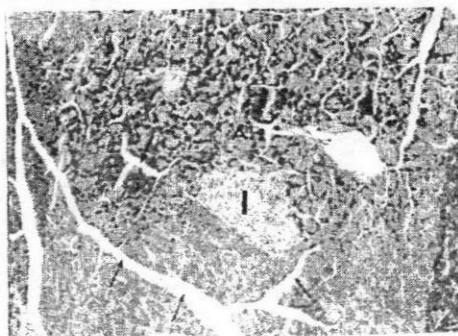


Fig. (22) : A photomicrograph of a section in the pancreas of albino rat seven days after the last dose of Mirazid, showing the pancreatic acini (A) and interlobular septa (arrows) and Islet's of Langerhans (I) looking like the control. (HX. & E.; X 100)



Fig. (23) : A higher magnification of Fig. (22). Notice : the pancreatic acini (A) and cells of Islet's of Langerhans (I) are looking like the control. (HX. & E.; X 400)

DISCUSSION

The present study is a trial to evaluate Mirazid safety regards histopathological changes to some of the most important internal organs of adult albino rats including the liver, kidney, pancreas and gonads. This study was also extended to include the possible embryotoxicity on pregnant rats.

The present work declared that there was a minimal side effect on liver cells in the form of little lymphocytic infiltration, slight dilatation of liver sinusoids with scanty vacuolation of liver cells were noticed one day after the last dose. However, seven days after treatment the lymphocytic infiltration was still minor but the liver architecture looked similar to the control ones. This concomitant with Massoud et al (2003)²⁸ who found no hepatotoxicity to treated patients. This was also confirmed by Motawea et al (2001)³⁰.

Al-Harbi et al. (1994)¹ and Massoud et al. (1998, 2000)^{20, 23} on their studies on mice, found that Mirazid at all dose levels had no hazardous effect on liver functions except a slight increase after the treatment. They attributed this for many reasons: cell necrosis, impaired of increased syn-

thesis and alterations in the permeability of the enclosing cell membrane (Boyd, 1985 and Pennington, 1988)^{8, 34}. Massoud et al. (2000)²⁴ reported that, Mirazid given for a long period at high level dosing to rats is well tolerated with high margin of safety for liver. Also, Massoud et al. (2002)²⁷ found no hepatotoxic effect after treatment with Mirazid, since there were no significant changes in normal liver enzyme levels except minimal increase in serum bilirubin and serum alkaline phosphatase that returned to normal after treatment.

In contrary as compared to marketed schistosomicidal drug praziquantel, Ambroise and Goullier (1981)⁴ found many toxic effects and even necrosis of liver cells with fatty infiltration after treatment with it. Praziquantel has an etiological factor implicated in carcinogenesis associated with schistosomiasis by modulation of potential enzymes concerned with detoxification, protein and fat metabolism. It may be responsible for enhancement of metabolism of benzene to form muconaldehyde that cause enhancement of the effect (Au et al., 1990)⁵. Furthermore, Watt et al. (1988)⁴⁰ stated that, the side effects

of praziquantel are increased in the presence of liver diseases. Basseler and Schriver (1970)⁶ as well as Putter and Held (1979)³⁶ demonstrated that the direct toxic effect of praziquantel through interference with metabolism and excretion or both.

In this study minimal histopathological change in the kidney appeared one day after treatment in the form of dilated tubules and vacuolation in its cells, while the glomeruli were intact and the changes returned normal in specimens seven days after the last dose. This in agreement with results of Massoud et al. (2000)²⁴, Dixit et al. (1980)¹¹ and Lata et al. (1991)¹⁹ on rat studies using other species of Myrrh. They didn't notice any change of kidney functions (serum creatinine, serum urea and serum uric acid). Also, Massoud (1999a, b)^{21, 22} and Sheir et al. (2001)³⁸ reported that Mirazid is not nephrotoxic as it caused no significant changes in serum urea and serum creatinine levels in human. However, Wilson et al. (1990)⁴² found that praziquantel has a toxic effect to all segments of renal tubules due to both direct toxic action and a central mechanism. The proximal convoluted tubules were swollen and

their cells vacuolated and degenerated. Also, Ott et al. (1983)³² reported persistence of glomerulonephritis in patients treated with oxamniquine schistosomicidal drug.

No changes were noticed in the pancreas of treated rats one and seven days after the last dose of Mirazid. This is in agreement with studies of Massoud et al. (2000)²⁴ who found no significant changes in serum sugar and calcium levels of rats after Mirazid administration.

No detectable histopathological changes were noticed in the sections of testis nor ovary of rats at one and seven days after Mirazid administration. This in agreement with observations of Massoud et al. (2000)²⁴ who reported no hazardous effect of Mirazid on fertility of male rats and or on pregnant female rats. Moreover, Massoud et al. (2002)²⁷ mentioned that daily treatment of male rats with Mirazid had no significant effects on both matting and fertility rates and had no lethal mutation. It didn't alter weight of testis and didn't affect motility, sperm cell concentration and sperm head abnormalities. Also, Mirazid had no effect on testosterone level treated rats and the histology of

reproductive organs.

No significant gross anomalies of all pups, except their number, was higher in the treated than in control ones. Consistently, El-Baz et al. (2003)¹² found no chromosomal aberrations or fetal anomalies after rat treatment with Mirazid. Also, Mas-soud et al. (2000)²⁴ reported that daily treatment of male rats with Mirazid had no significant effects on each of matting, fertility rates, mutation and testosterone level. Moreover, Mirazid in all dose levels had no hazardous effects on pregnant rats.

Inconclusion : Mirazid can be given for a long period at high dose levels. It is well-tolerated remedy, with high safety margin for liver, kidney, pancreas and reproductive organs and its use during pregnancy may be safe. It is a safe antischistosomal drug that can be used in community-based programs. Low toxicity of Mirazid, relative to any schistosom-icidal drug is a further merit and promise in favor of this newly emerging drug.

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دراسة عن تأثير عقار الميرازيد على بعض الأعضاء الداخلية وتأثيره المحتمل قبل الولادة في الجرذ الأبيض

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استخدم ثلاثون جرذا أبيضاً بالغة في هذه الدراسة ، التي قسمت إلى ثلاثة مجموعات في كل واحدة عشر جرذان : مجموعة ذكور بالغة ، ومجموعة إناث بالغة ، ومجموعة حوامل . وقسمت كل مجموعة إلى : مجموعة ضابطة ومجموعة تجريبية التي أعطيت ١٠% من مستحلب الميرازيد (وهو عقار طبيعي جديد يستخدم في علاج البلهارسيا وهو مستخلص من نبات المر) وهو معد خصيصاً من قبل شركة فاركو للأدوية بالإسكندرية بمصر . أعطى الدواء بالفم بجرعة مقدارها ٢٠٠ مجم / كجم من وزن الجسم باستعمال أنبوبة المعدة وذلك قبل الإفطار بساعة ولمدة ٦ أيام متتالية . وأعطيت الجرذان الحوامل نفس الجرعة اعتباراً من اليوم السادس إلى اليوم الحادي عشر للحمل وكانت تحت الملاحظة حتى يوم الولادة لملاحظة حدوث إجهاض لها وملاحظة عدد الجرذان المولودة وفحصهم لمعرفة أي تشوهات جنينية . لم تسجل أي حالة إجهاض للجرذان الحوامل التي أعطيت الميرازيد ، وكان عدد أولادها من الجرذان الصغيرة أكثر من عدد أولاد الفئران الحوامل من المجموعة الضابطة ، ولم يلحظ أي عيوب خلقية فيها .

وتم التضحية بالجرذان بعد يوم ، وسبعة أيام من آخر جرعة من الميرازيد ثم شربت بدقة وتم استخراج الكبد ، والبنكرياس ، والكلى ، والخصية والمبيض وثبتت في ١٠% فورمالدهيد وتم تجهيز الشرائح منها وصباغتها بالهيماتوكسيلين والأيوسين .

ولوحظ في شرائح الكبد بعد يوم من آخر جرعة وجود تمدد ضئيل في التجاويف الكبدية مع ظهور فراغات بخلاياه وظهور عدد قليل من الخلايا الليمفاوية . أما في الشرائح بعد السبعة أيام من انتهاء العلاج فلقد ظهر تغلل طفيف بخلايا ليمفاوية وكان شكل الكبد طبيعي .

أظهرت شرائح الكلى بعد يوم من آخر جرعة تمردا بسيطا فى الأنابيب الكلوية مع ظهور
تجاويف بالخلايا المبطنة لها ووجود بعض كرات الدم الحمراء بينما كانت الحويصلات البولية
طبيعية. ولم يلحظ أى تغيرات غير طبيعية فى شرائح غدة البنكرياس والخصية والمبيض بعد يوم
أو سبعة أيام من آخر جرعة .

لهذا فان عقار الميرازيد آمن على الكبد. والبنكرياس والكلى والغدد التناسلية .