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The Pathogenic Impacts Of The Ant-Ulcer Drug Omeprazole On Some Morphological And Histological Aspects Of The Fetuses Of The Albino Mice

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Abstract

Introduction:- The anti-ulcer drug omeprazole with the trade name "Losec" is considered as one of the most important and widely used drug in the medical area in Egypt. It is used for the promotion of healing of the gastric peptic ulcers, duodenal ulcers and reflux oesophagitis as well as cases of Zollinger Elison syndrome. These cases are originating from the hypersecretion of HCl by the gastric parietal cells.

In spite of such important role of this drug, yet some medical clarification incriminating it for producing certain adverse consequnes following its usage.

Material And Methods: - Hence, the present study aims to assess and evaluate any possible expected anomalies following the usage of the therapeutic dose of the anti-ulcer drug omeprazole (0.03mg/kg body weight) on materally treated fetuses of albino mice. This study was concentrated on the morphological, skeletal and histological follow up of dose such drug and the target organs chosen in this survey were the liver and the kidney.

The present study was carried out on a group of pregnant females of albino mice and their fetuses, they were sub-divided into six sub-groups (10 mice each). The first three sub-groups are considered as control. Females of the first sub-group are injected intraperitoneally with the drug solvent (distilled water) for seven days (from day 7 till day 13 of pregnancy). The second sub-group is injected similarly with the drug solvent for14 days before pregnancy. Animals of the third sub-group are injected intraperitoneally with the drug solvent for 21 days (14 days before pregnancy and 7 days during gestation). Females of the last three sub-groups (4, 5 & 6) are injected with 0.03mg/kg body weight of the anti-ulcer drug in a manner similar to those performed in the first three sub-groups.

Results :-The morphological results showed that treatment with the drug doses revealed conspicuous decrease in the body weight and body length of maternally treated fetuses in all experimental groups. But, these fetuses did not show any external morphological malformations in all experimental groups. However, while these fetuses appeared smaller in size as compared with those of the control groups. The skeleton of the maternally treated fetuses exhibited growth retardation of the skeletal elements.

The histopathological results revealed marked changes in the foetal liver and kidney of all treated groups. The liver cells exhibited cytoplasmic vacuolar and fatty degeneration, beside noticeable nuclear pyknosis and karyolysis. The hepatic vasculatures (central veins & blood sinusoids) displayed conspicuous dilatation and congestion with marked deterioration of the portal veins as well as inflammatory cellular infiltration. Moreover, the hepatic tissue showed focal areas of haemorrhagic edema.

Kidney cortex showed variable degrees of devastation symptoms formed principally of erosion of the epithelial cells of Bowman's capsule followed by disruption of the glomerular capillaries and mesangial proliferation in some cases and hypoplasia in other cases. Proximal and distal convoluted tubules are detached from each other allowing wider intertubular spaces which become invaded with necro- inflammatory leucocytes and extravasated blood from the damaged capillaries allowing edema formation. The lining epithelial cells of these tubular structures manifested variable degrees of vacuolar degeneration and coagulative necrosis. Their nuclei showed pyknosis and karyolysis.

In conclusion: The use of the anti-ulcer drug omeprazole in the present investigation had exerted noticeable consequences in the morphological, skeletal and histological parameters of the fetuses of albino mice and the severity of such lesions are correlated with the period of drug administration before and during the gestation periods.

Key word: Anti-ulcer drug (Omeprazole) – Fetuses of albino mice – Morphology – Skeleton – Histopathology – Liver- Kidney.

Introduction

The anti-ulcer drugs are useful agents used for the prophylaxis of many cases of reflux and erosive oesophigitis, gastric ulcers, duodenal ulcers, and Zollinger Elison syndrome (Okabe *et al.*, 1992; Inaba *et al.*, 1995 and Pelacios *et al.*, 1995). Many authors mentioned the positive role of these drugs for the eradication of peptic ulcer disease produced by *Helicobacter pyroli* (Ogoshi *et al.*, 1995; Sugiyama *et al.*, 1995 and Sasaki *et al.*, 1999).

These drugs are classified according to their mode of action (Kagoshima *et al.*, 1995 and Takahashi & Okabe, 1995). They showed that these drugs caused inhibition of secretion of hydrochloric acid by the gastric parietal cells, while Ohashi *et al.* (1995), Sugiyama *et al.* (1995), Zimmermann and Katona (1997), Sasaki *et al.* (1999) and Gisbert *et al.* (2002) mentioned that these drugs decrease parietal cells HCL secretion by their powerful inhibition of H^+/K^+- ATPase enzyme system (proton pump) at the secretory surfaces of these cells.

Gilman *et al.* (2005) illustrated that these drugs are classified into two categories. The first category was the histamine H_2-receptor antagonist drugs like cimetidine, ranitidine, famotidine and gastrozopin. The second category was the proton pump inhibitors like gastrazole, lansoprazole and omeprazole.

In spite of the beneficial role of these forementioned drugs, they were largely manifested certain degrees of pathogenic lesions on some body organs either on adult and fetuses of mammalian animals.

According to Hashimoto *et al.* (1994), Imamura *et al.* (1994) and Pearce *et al.* (1996), liver of treated animals with the histamine H2-receptor antagonist drugs showed obvious cirrhosis as well as cholestasis. Also, Ratra *et al.* (1998) postulated marked features of hepatotoxicity of adult rats subjected to treatment with these drugs.

Burdan *et al.* (2000) and Okajima *et al.* (2002) showed noticeable lesions in the rats organs including the pancreatic and liver tissues subjected to treatment with certain doses of omeprazole and ranitidine in respective manner.

According to Ramadan *et al.* (2005) treatment of mice with oral high doses of lansoprazole (1.2 mg/kg body weight) for 4 weeks displayed conspicuous hepatic vacuolar degeneration as well as coagulative necrosis, besides marked pathogenecity in the hepatic vasculatures.

In a report forwarded by Montseny and Meyrier (1998), they regarded that the administration of the anti-ulcer drug omeprazole to 69 years old man caused severe damage in the renal tissues including: obvious granulomatous, interstitialnephritis, tubular injury and fibrosis leading to certain degrees of impairment of the renal function.

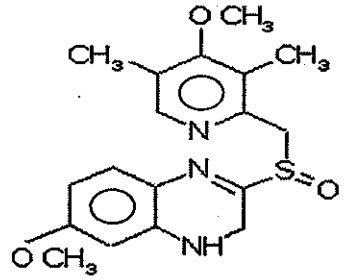
From the foregoing investigations, it was collectively felt worthy to make certain clarification, assess of one of widely used drugs in the Egyptian market namely omeprazole whose trade name is " Losec " on the albino mice fetuses from the morphological, skeletal and histological points of view taking into consideration that the main target organs in this survey are the liver and kidney.

Material And Methods

The drug used

The anti-ulcer drug used in the present investigation is omeprazole which known commercially as Losec.

The structural formula of omeprazole:



Omeprazole is available in the form of tablets or vials. The last-type is more common and is used for intravenous infusion, being manufactured by the Swedish Astra Zeneca pharmaceutical company.

The drug is supplied in packages enclosing vials, each containing 40mg of

the active ingredient omeprazole sodium lyophilized powder to be reconstituted or dissolved in 1ml distilled water.

Dosages and route of administration of the drug:-

The chosen dose of the anti-ulcer drug omeprazole was nearly comparable to the human cumulative effective therapeutic dose (ETD). It was calculated according to the table suggested by Paget and Barnes (1964). Accordingly, the resulting ETD of the drug for mice was estimated to be 0.03mg/Kg body weight.

Experimental animals:

The present investigation was carried out on mature albino mice of pure CD-1 strain with an average body weight of 20-30g obtained from the breeding unit of Theodor Bilharz Research Institute (TBRI), Imbaba, Giza. Mice were fed on cubes consisting of crude proteins, minerals and fibres. The animals were provided with milk and tap water *ad libitum*.

Experimental design:

The present investigation was carried out on a group of 60 adult female mice which were being sub-divided into six experimental sub-groups (10 mice each). The first three sub-groups are considered as the control sub-groups (C_1, C_2 & C_3) and the last three sub-groups (G1, G2 and G3) are the drug treated sub-groups and treatment of these six sub-groups was achieved in the following manner:

Sub-group (C_1): Each pregnant female was injected intraperitoneally with 0.1ml distilled water (the solvent of the drug) daily for 7 days during pregnancy from day 7 till day 13 of gestation.

Sub-group (C_2): Each female was injected intraperitoneally with 0.1ml distilled water daily for 14 days before pregnancy.

Sub-group (C_3): Each female was injected intraperitoneally with 0.1ml distilled water daily for 21 days (14 days before gestation and 7 days during pregnancy from day 7 till day 13 of gestation).

Sub-group (G1): Each pregnant female was treated intraperitoneally with 0.03mg/kg body weight of the anti-ulcer drug omeprazole daily for 7 days during pregnancy (from day 7 till day 13 of gestation).

Sub-group (G2): Each female was intraperitoneally injected with 0.03mg/kg body weight of the anti-ulcer drug omeprazole daily for 14 days before gestation.

Sub-group (G3): Each female was intraperitoneally injected with 0.03mg/kg body weight of the anti-ulcer drug omeprazole daily for 21 days (14 days before gestation and 7 days during pregnancy from day 7 till day 13 of gestation).

- Morphological examination of the fetuses:-

After 19 days of pregnancy, females of both control and experimental groups were sacrificed, dissected and their uteri were removed, placed in normal saline solution and the fetuses were taken out for morphological and histological studies. Living fetuses were distinguished from dead ones by their spontaneous movement. The average number, average body weight and average body length of fetuses were recorded and statistically analysed by using Student *t*-test.

The fetuses were carefully examined externally for any morphological malformations including their head, eyes, ears, jaws, palate, limbs and digits using a binocular microscope.

All fetuses were divided into two groups for the purpose of preparation of their skeleton and for histological examination.

Preparation of the skeleton:- For skeletal studies, fetuses of control and experimental groups were fixed in 95% ethanol for 7 days then placed in acetone for 7 days and they were double stained for cartilage and bone using alcian blue and alizarin red-S according to the method described by McLeod (1980). After staining, the specimens were transferred to 1% aqueous solution of KOH for 24 hours then to ascending series of glycerol in 1% aqueous KOH solution (20%, 50%, 80% glycerine). Finally the specimens were preserved in 100% glycerine. The stained preparations of the skeleton were carefully examined under the dissecting binocular

microscope. Photographs were made for skeletal systems of control and maternally treated fetuses.

Histological preparations:- After 19 days, the pregnant females of all groups were sacrificed and their foetuses were taken. The foetuses were then dissected and samples of their livers and kidneys were removed. The liver and kidney samples from both control and treated groups were fixed in 10% formalin and aqueous Bouin's solution for 24 hours. They were dehydrated in alcohol, cleared in terpineol and embedded in paraffin wax. Sections of 5µm thickness were stained with haematoxylim and eosin (Bancroft and Gamble,2002).

Results

Morphological studies

On the 19th day of gestation, the pregnant mice of control groups (C_1, C_2 & C_3) and their corresponding treated groups (G_1, G_2 & G_3) were sacrificed and the percentage of alive fetuses, mean body weight and mean body length were recorded (Table 1 and Figs. 1& 2). The data showed that treatment with 0.03mg/kg body weight of the anti-ulcer drug omeprazole caused marked growth retardation of mice fetuses indicated by the reduction of both fetal body weight and fetal body length. Fetuses of the three experimental groups (G_1, G_2 & G_3) showed non-significant decrease of mean fetal body weight compared with the control groups as illustrated in table 1 and figure 1.

The results displayed in table (1) and figure 2 showed pronounced decrease in the mean body length of the fetuses of the three experimental groups treated with 0.03 mg/kg body weight of the anti-ulcer drug omeprazole, as compared with those obtained in the control groups.

No mortality was recorded either in the control fetuses or in fetuses of G_2 experimental group (maternally treated for 14 days before pregnancy). On the other hand, only two dead fetuses were recorded among fetuses of the first and third experimental groups (maternally treated during gestation for 7 days and maternally treated before and during gestation); one dead fetus in each of the forementioned treated groups.

II- Skeletal studies

I- Control group:

At day 19 of gestation, the cleared cartilage and bone preparations of control mice fetuses are shown in Figs.(3 & 7).

II- Fetuses maternally treated with 0.03mg/kg body weight of the anti-ulcer drug omeprazole.

Fetuses taken from mothers treated with 0.03mg/kg body weight of the anti-ulcer drug omeprazole exhibited marked alternation in several parts of the skeleton as compared with control one. Bones of the skull of these fetuses show incomplete, or lack of ossification of some bones. The most affected bones of the skull are represented by the dermal bones, which show extreme retardation in individuals of maternally treated groups (Figs. 4 & 6). Severe consequences of the skeleton is noticed in fetuses of groups G_1 and G_3. These fetuses show retardation of the growth or formation of dermal bones while most of the replacing bones are completely non-ossified (Figs. 4 & 6). The lower jaw of maternally treated fetuses of groups G_1 and G_3 shows marked reduction of the formation of dermal bones as seen in figures 4 & 6 compared with the control groups.

In the treated groups G_1 and G_3, the thoracic and lumbar vertebrae show incomplete ossification of their centra (Figs. 4, 6, 8& 10). In addition to incomplete ossification of sacral and caudal vertebrae which appear absolutely non-ossified in all treated groups (G_1, G_2 & G_3) as illustrated in figures (8 – 10). The ribs of fetuses of all treated groups (G_1, G_2 & G_3) are of the same number as those seen in the control ones. The ribs of fetuses of group G_2 show normal ossification (Fig. 5), while those of fetuses of groups G_1 and G_3 show reduction in length of the ossified parts of the vertebral portions of their ribs (Figs. 4 & 6).

The skeletal elements of the pectoral girdle and fore limbs exhibit certain changes following treatment with 0.03 mg/kg body weight of the anti-ulcer drug omeprazole specially in groups $G_1$and G_3 which show reduction in the ossified parts as well as retardation of ossification of

scapulae in comparison with the control group as illustrated in figures (4 & 6). The humerus, radius and ulna, metacarpals and phalanges of the fore limbs of maternally treated fetuses are considerably shorter and less ossified than those of control (Figs. 4 & 6). The ilium, ischium and pubis of maternally treated fetuses specially in groups G_1 and G_3 show conspicuous reduction in their sizes and retardation of their ossification as represented in figures (8 & 10) compared with those illustrated in control groups. The bones of the hind limbs of all maternally treated fetuses are shorter than those of the control ones (Figs. 8 & 10). Such bones show reduction in their ossified parts with marked retardation in the ossification process, specially in groups $G_1$and G_3 as seen in figures (8 & 10), compared with the corresponding bones of the control group. The metatarsals and phalanges of toes are completely non-ossified in most fetuses maternally treated with 0.03mg/kg body weight of the anti-ulcer drug omeprazole as illustrated in figures (8 – 10).

III- Histological and Histopathological Histology of the liver of control fetuses

The liver of 19-days old mice fetuses is shown in Fig. (11).The liver of such fetuses appears to act as a hemopoietic organ, where groups of darkly stained cells are observed in the hepatic tissue; they represent the different types of blood forming cells or hemopoietic cells.

Histopathology

The liver of 19-days old fetus maternally treated with 0.03mg/kg body weight of the anti-ulcer drug omeprazole from day 7 to day 13 of the pregnancy illustrates marked deleterious consequences. The hepatocytes showed vacuolar and fatty degeneration with marginal chromatin in the nuclei. Their nuclei show noticeable symptoms of pyknosis and karyolysis as designated in figure (12). The central veins appear extensively dilated and congested and their lumina are engorged with blood.Their endothelial lining cells are conspicuously eroded (Fig. 12). Many inflammatory cells are observed infiltrating the hepatic tissues in some focal areas and around the dilated central veins as represented in figure (12).

The liver of 19-days old fetuses maternally treated with 0.03mg/kg body weight of the anti-ulcer drug omeprazole for 14 days before pregnancy displayed severe histological changes in hepatocytes and vasculatures. The hepatocytes manifest obvious vacuolar and fatty degenerations and their nuclei display noticeable pyknosis and karyorrhexis as revealed in figure (13). Some hepatocytes appear free from the cytoplasmic organoids.

The hepatic central veins are conspicuously dilated and show marked features of erosion of their lining epithelia. Also, pronounced feature of congestion in the central veins and lots of haemorrhagic areas are observed (Fig. 13). Severe haemorrhagic edema is also seen in the hepatic sinusoids which show aggregation of haemolysed blood cells in their lumina as illustrated in figure (13). Necro-inflammatory cells invade large areas in most of the hepatic tissues (Fig 13).

The liver of 19-days old fetuses maternally treated with 0.03mg/kg body weight of the anti-ulcer drug omeprazole for 14 days before gestation and 7 days during pregnancy illustrates the same pathogenic lesions displayed in the previous cases. The hepatocytes show clear features of fatty degeneration in their cytoplasm. Their nuclei display symptoms of pyknosis and karyolysis as represented in figure (14).

The hepatic vasculatures manifest highly congested and dilated central veins, crowded with haemolysed red blood corpuscles. Dilated sinusoids are also observed in the present cases (Fig. 14). also features of invasion of the hepatic tissues with inflammatory cells mainly of lymphocytes and plasma cells are observed in focal areas and around the deteriorated central veins with ruputre of their endothelial lining and blood haemolysis.

The kidney

Histology of the kidney of control fetuses

The kidney of 19-days old control fetus is shown in Fig. (15).

Histopathology

The kidney of 19-days old fetus maternally treated with 0.03mg/kg body

weight of the anti-ulcer drug omeprazole for 7 days during pregnancy shows marked histopathological consequences in the renal cortical tissue. Some glomeruli show proliferation of their mesangial cells filling almost large part of the urinary space that allow conspicuous narrowing of its lumen or space. In addition the lining epithelial cells of the Bowman's capsule manifests marked erosion (Fig. 16). Vacuolar degeneration is evident in the cytoplasm of the epithelial cells lining the proximal and distal convoluted tubules especially the distal ones.Their nuclei are markedly pyknotized and karyolyzed. Moreover, numerous debris are accumulated in the lumina of both the proximal and distal convoluted tubules. In addition, the intertubular capillaries are dilated and congested. Mild haemorrhagic edema as well as inflammatory cellular infiltration are noticed in Fig. (16).

The kidney tissues of 19-days old mice fetuses maternally treated with omeprazole for 14 days before gestation exhibit marked devastations in the cortical region. The renal corpuscles show obvious degeneration of their epithelial cells with marked hypoplasia of their mesangial cells (Fig. 17). The epithelial lining cells of some proximal and distal convoluted tubules exhibited vacuolated cytoplasm and pyknotized or karyolized nuclei but distal ones appear more sensitive. Also, debris are observed in the lumina of these devastated tubules. In addition, these tubules are detached from each other allowing wide intertubular spaces with marked aggregation of extravasated blood from the damaged cortical capillaries forming rather hemorrhagic edema as illustrated in Fig. (17).

The kidney of 19-days old mice fetuses maternally treated with omeprazole for 21 days (14 days before gestation and 7 days during pregnancy) shows several pathological lesions. The renal corpuscles manifest clear features of damage represented by congestion and dilatation of their capillaries which are packed with blood. Also, hypertrophid glomeruli with highly reduced Bowman's space (Fig.18). The epithelial cells of the glomerular tuft exhibit marked features of necrosis, besides the marked hypercellularity of their mesangial cells (Fig. 18). The proximal and distal convoluted tubules are severely detached from each other but distal ones appear more sensitive. Their epithelial lining cells display conspicuous degeneration and vacuolation in their cytoplasm. Their nuclei are pyknotized or karyolyzed. The intertubular spaces are infiltrated with numerous inflammatory cells as illustrated in Fig. (18).

Table 1: Designating the percentages of alive and dead fetuses, the mean body weight (g) and the mean body length (cm) of mice fetuses of the experimental groups (G1, G2 & G3) and their corresponding controls (C1, C2& C3).

Animal groups	Developing fetuses			
	A live %	Dead %	Mean body weight (±SE)	Mean body lengths (±SE)
C_1	100%	-	1.35 ±0.02	3.10 ±0.03
G_1	97.23%	2.77%	1.22 ±0.05	2.95 ±0.06
C_2	100%	-	1.36 ±0.02	3.11 ±0.03
G_2	100%	-	1.16 ±0.04	2.85 ±0.03
C_3	100%	-	1.36 ±0.02	3.10 ±0.03
G_3	97.56%	2.44%	1.07 ±0.02	2.67 ±0.03

C_1, C_2 and C_3: Fetuses of control groups.
G_1: Females treated for 7 days during gestation.
G_2: Females treated for 14 days before gestation.
G_3: Females treated for 21 days (14 days before gestation and 7 days during pregnancy from day 7 till day 13 of pregnancy).
$P>0.05$ =not significant, $P\leq0.05$ =significant (*), $P<0.01$ =high significant (**), $P<0.001$ or 0.005 = highly significant (***)

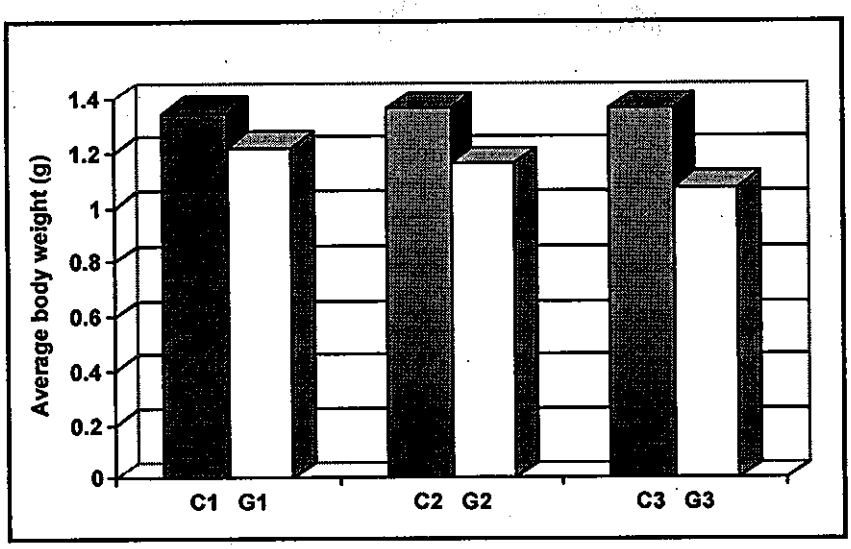


Fig. (1): Illustrating the average body weight of mice fetuses of the experimental groups (G_1, G_2 & G_3) and their corresponding controls (C1, C2 & C3).

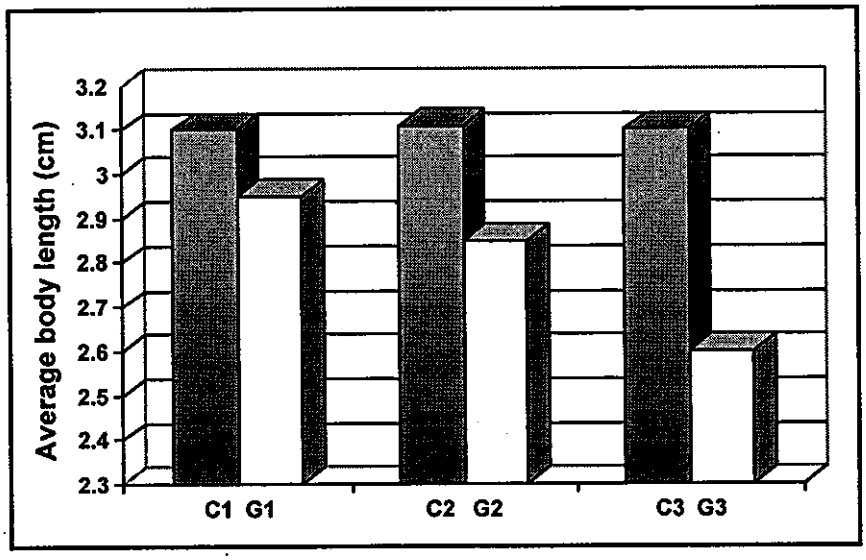


Fig. (2): Showing the average body length of mice fetuses of experimental groups (G_1, G_2 & G_3) and their corresponding controls (C1, C2 & C3).

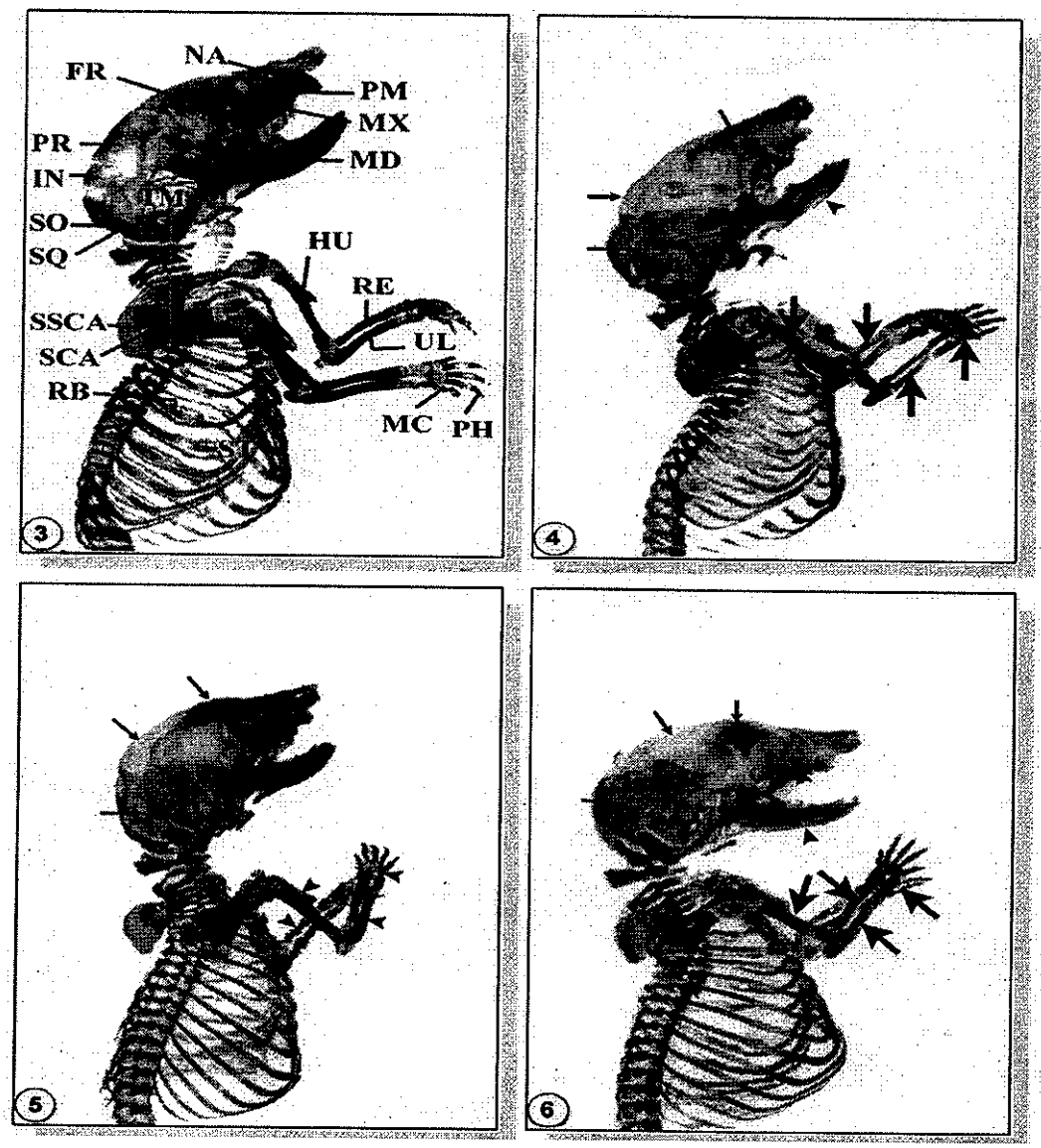


Fig. 3: Photograph of the anterior region of the skeleton of 19-days old fetus of a control group (C), manifesting conspicuous ossification of the dermal bones of the skull: nasal (NA), frontal (FR), parietal (PR), interparietal (IN); squamosal (SQ), supraoccipital (SO), temporal bones (TM). and bones of both upper and lower jaws; premaxilla (PM), maxilla (MX) and mandible (MD). Ribs (RB), thoracic vertebrae (THV) and sternum (ST). This figure also shows the ossification of scapula (Sca), humerus (HU), radius (RE), ulna (UL), metacarpals (MC) and phalanges (PH). **(X 34)**

Fig. 4: Photograph of the anterior region of the skeleton of 19-days old fetus maternally treated with 0.03mg/kg body weight of the anti-ulcer drug omeprazole for 7 days during gestation (G_1), manifesting incomplete ossification of the dermal bones of the skull (arrows) and bones of both upper and lower jaws (head-arrows). The figure also shows less degree of ossification and shortness of the skeletal elements of the fore limb (large arrows). **(X 34)**

Fig. 5: Photograph of the anterior region of the skeleton of 19-days old fetus maternally treated for 14 days before gestation (G_2), displaying incomplete ossification of the dermal bones of the skull (arrows) with less affected ossification of the skeletal elements of the fore limb (head arrows). **(X 34)**

Fig. 6: Photograph of the anterior region of the skeleton of 19-days old fetus maternally treated for 21 days before and during gestation (G_3), manifesting incomplete ossification of the bones of the skull (arrows) and bones of both upper and lower jaws (head-arrows).The figure also shows less degree of ossification of the skeletal elements of the fore limb (large arrows). **(X 34)**

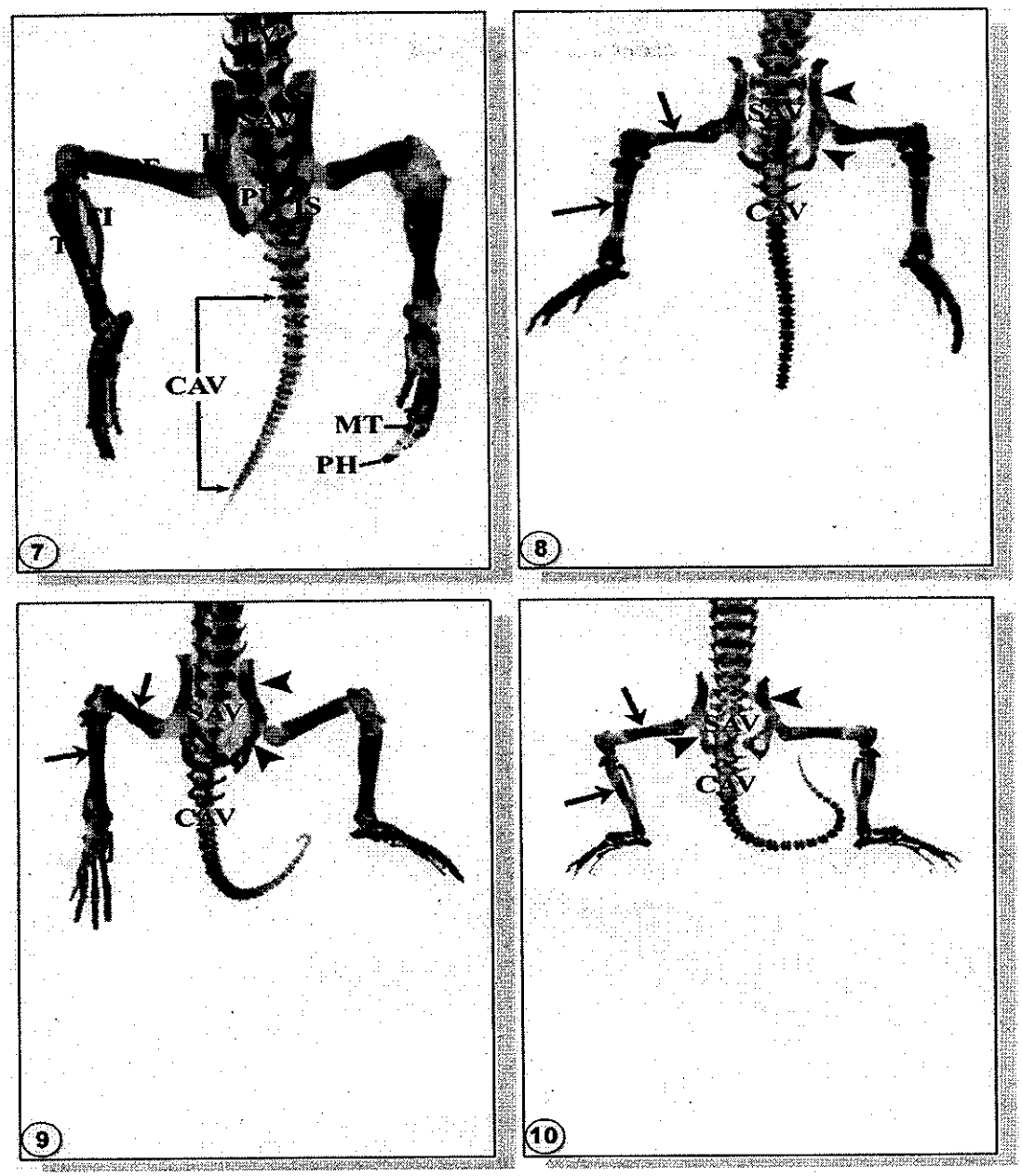


Fig. 7: Photograph of the posterior region of the skeleton of 19-days old fetus of a control group (C).The figure shows parts of the vertebral column consists of the lumbar vertebrae (LV), sacral vertebrae (SAV), caudal vertebrae (CAV) and parts of the pelvic girdle consisting of ischium (IS), ilium (IL) and pubis (PU). Also bones of the hind limb consisting of the femur (FE), tibia (TE), and fibula (FI) and bones of the feet showing metatarsals (MT) and phalanges (PH). **(X 34)**

Fig. 8: Photograph of the posterior region of the skeleton of 19-days old fetus (G_1), manifesting less ossification and shortness of the pelvic girdle (head arrows) and the hind limb (arrows). The figure also shows incomplete ossification of the sacral (SAV) and caudal (CAV) vertebrae. **(X 34)**

Fig. 9: Photograph of the posterior region of the skeleton of 19-days old fetus (G_2), showing less affected skeletal elements of the pelvic girdle (head arrows) and hind limb (arrows)as well as incomplete ossification of the sacral (SAV) and caudal (CAV) vertebrae. **(X 34)**

Fig. 10: Photograph of the posterior region of the skeleton of 19-days old fetus (G_3), displaying less ossification and shortness of the pelvic girdle (head arrows) and the hind limb (arrows).The figure also shows incomplete ossification of the sacral (SAV) and caudal (CAV) vertebrae. **(X 34)**

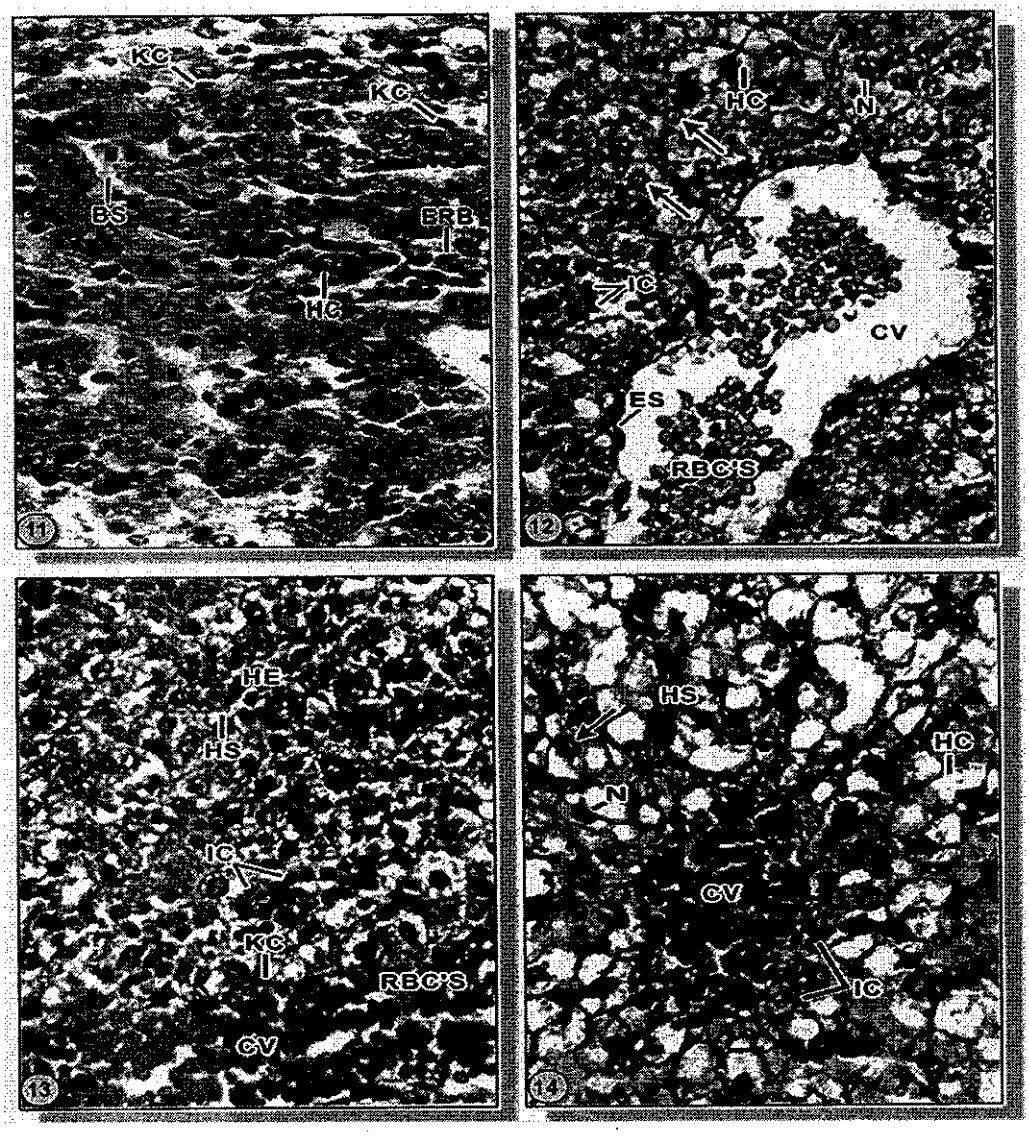


Fig. 11: Photomicrograph of a section of the liver of 19-days old control mouse fetus, showing strands of hepatocytes (HC), the blood sinusoids (BS), Küpffer cells (KC) and aggregations of haemopoietic erythroblast cells (ERB) **(X 400)**

Fig. 12: Photomicrograph of a section of the liver of 19-days old fetus maternally treated with 0.03mg/kg body weight of anti-ulcer drug omeprazole for 7 days during pregnancy, displaying vacuolar degeneration of the hepatocytes (HC). The nuclei show symptoms of pyknosis (N) and karyolysis (arrow). The central vein (CV) shows rather eroded endothelium (ES) and appears dilated and congested with clear aggregation of red blood corpuscles (RBC's). Focal aggregation of inflammatory cells (IC) is also seen. **(X 400)**

Fig. 13: Photomicrograph of a liver section of 19-days old fetus maternally treated with 0.03mg/kg body weight of the anti-ulcer drug omeprazole for 14 days before gestation, showing congestion and dilation of the central vein (CV) and dilated hepatic sinusoids (HS) with conspicuous haemorrhagic appearance (HE). Activated Küpffer cells (KC) are also seen in the deteriorated sinusoids. Besides, focal aggregation of inflammatory cells (IC) is observed between the degenerated hepatocytes. **(X 400)**

Fig. 14: Photomicrograph of a liver section of 19-days old fetus maternally treated with 0.03 mg/kg body weight of the anti-ulcer drug omeprazole for 21 days (14 days before gestation and 7 days during pregnancy from day 7 till day 13 of pregnancy), showing that almost all the hepatocytes (HC) suffer from severe fatty degeneration in their cytoplasm with marginal chromatin in the nuclei (N) and show clear feature of pyknosis (arrow). Note also, congested central vein (CV) and rather deteriorated hepatic sinusoids (HS). Collections of inflammatory leucocytes (IC) are seen surrounding the devastated central vein. **(X 400)**

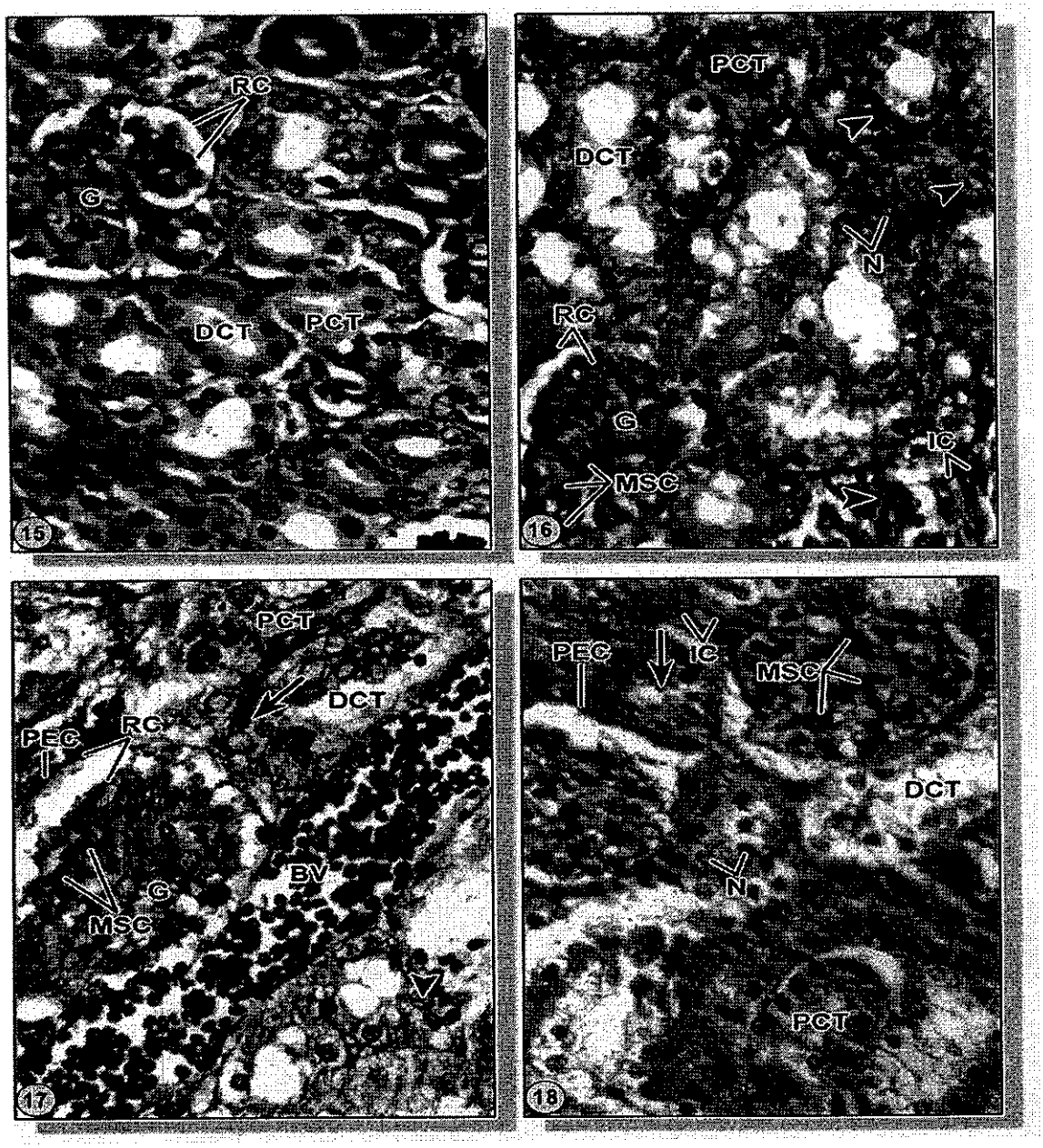


Fig. 15: Photomicrograph of a section of the kidney cortex of 19-days old control mouse fetus, showing the renal corpuscle (RC), the glomerulus (G) and the proximal (PCT) and the distal convoluted tubules (DCT). **(X 400)**

Fig. 16: Photomicrograph of a section of a kidney of 19-days old mouse fetus (G_1), manifesting marked erosion of the epithelial cells of Bowman's capsule of the renal corpuscle (RC), proliferation of the mesangial cells (MSC) of the glomerulus (G) allowing marked narrowing of the Bowman's space. The lining epithelial cells of the proximal (PCT) and distal (DCT) convoluted tubules show vacuolar degeneration of their cytoplasm. Their nuclei (N) manifest obvious pyknosis and karyolysis and their lumina contain cellular casts or debris. The intertubular spaces display mild haemorrhage or edema (head arrows) and inflammatory cellular infiltration (IC). **(X 400)**

Fig. 17: Photomicrograph of a section of a kidney of 19-days old mouse fetus (G_2), showing mild degeneration of the epithelial cells (PEC) of Bowman's capsule. The renal corpuscle (RC) shows hypoplasia of the mesangial cells (MSC) of the glomerulus (G). The proximal (PCT) and distal (DCT) convoluted tubules are detached from each other. The intertubular spaces capillaries are dilated and cognesed (BV). Their lining cells display vacuolar degeneration as well as nuclear pyknosis (arrow) and karyolysis (head arrow) **(X 400)**

Fig. 18: Photomicrograph of a section of a kidney of 19-days old mouse fetus (G_3), illustrating distinctly damaged renal corpuscles with demolished epithelial cells (PEC) and hypercellularity of the mesangial cells (MSC). The lining epithelial cells of the proximal (PCT) and distal (DCT) convoluted tubules show coagulative necrosis, pyknosis and karyolysis of their nuclei (N) and aggregation of cellular debris or casts in their lumina (arrow). The intertubular spaces show collection of inflammatory cells (IC). **(X 400)**

Discussion

The use of the anti-ulcer drugs was greatly extended in the medical area because they are very good agents useful for the prophylaxis of many cases of reflux oesophagitis, duodenal ulcers, gastric ulcers, as well as Zollinger Elison syndrome as reported by Okabe *et al.* (1992); Inaba *et al.* (1995) and Pelacios *et al.* (1995).

I-Morphological studies

The present investigation showed that mice treated with 0.03 mg/kg body weight of the anti-ulcer drug omeprazole for 7 days (during gestation), 14 days (before gestation) and 21 days (14 days before gestation and 7 days during gestation) displayed growth retardation in maternally treated fetuses. Growth retardation was indicated by the reduction of both fetal body weight and fetal body length. It was noticed that fetuses of the three experim-ental groups showed non-significant decrease of the mean fetal body weight and mean fetal body length as compared with the control groups. It is worthy to mention that the minimal increase in mean fetal body weight was recorded in fetuses maternally treated with omeprazole for 21 days (14 days before pregnancy and 7 days during gestation).

Such retarding effect of the anti-ulcer drug, omeprazole on fetal growth during gestation is consistent with the findings of Higashida *et al.* (1983) who reported that pregnant rats injected with oral doses of the histamine H2-receptor antagonist ranitidine hydrochloride displayed a significant decrease in the body weight of their developing fetuses.

EL-Shabaka (1992) showed similar results in mice fetuses maternally treated with 0.12 mg/g body weight of xylocaine after 8 days of pregnancy.

Oo *et al.* (1995) illustrated that the histamine H2-receptor antagonist cimetidine was transported into the breast milk by an active way via the blood stream resulting in a milk serum ratio 5.5 times higher than that expected with passive diffusion.

The decrease in the mean body weight of maternally treated fetuses, observed in the present investigation, may be probably due to an impairment of blood flow to the placenta and reduced uterine blood flow by the effect of the drug thus leading to reduced transfere of nutrients and oxygen to the fetal circulation. Along the same line, Gilman *et al.* (2005) reported that the marked morphological changes in the pregnant mice and their surviving fetuses may be correlated with disturbances in the metabolic rate of these experimental animals when subjected to treatment with the anti-ulcer drugs during pregnancy.

In the present study, fetuses maternally treated with the anti-ulcer drug omeprazole did not show any external morphological malformations for all groups. However, all the fetuses of the three experimental groups appeared smaller in size as compared with those of the control groups. These observations agree with those of Brunner *et al.* (1997) who reported that no congenital malformations were observed among fetuses of seven pregnant women treated with omeprazole. In this respect, Nikfar *et al.* (2002) reported that infants maternally exposed during the first trimester to proton pump inhibitors and omeprazole in particular did not possess an important teratogenic risk. Also, Diav-Citrin *et al.* (2005) showed that treatment with the proton pump inhibitor drugs during pregnancy did not display any recorded signs of teratogenic risk in the resulting infants of pregnant women. On the same line, Nava-Ocampo *et al.* (2006) reported that treatment with omeprazole did not induce teratogenic effects in infants of pregnant patients who had symptoms of peptic ulceration disease.

II-Skeletal studies

The present investigation illustrated that treatment with 0.03 mg/kg body weight of the anti-ulcer drug omeprazole for 7 days during gestation, 14 days before gestation and 21 days (14 days before gestation and 7 days during gestation) caused conspicuous growth retardation of the skeletal elements of maternally treated fetuses. Such retardation is represented by reduction in the length of some long bones and incomplete ossification of some others.

Such results may be correlated with the inhibition of osteoclastic activity (osteoclastic bone reabosrption), or it may

be due to the inhibition of the process of bone formation and calcium replacement or precipitation in the long bones.

Similar results were reported in rats treated with colchicine, molybdate ions and omeprazole (Zaidi, 1990), as well as in pregnant mice treated with 0.08 and 0.12 mg/g body weight of xylocaine after 8 and 9 days of pregnancy (EL-Shabaka, 1992). The latter author added that such treatment induced cleft palate malformation as well as marked retardation in the dermal bones of maternally treated fetuses.

Growth retardation and malformations of the skeletal elements were also observed in mice fetuses maternally treated with ethanol (Stuckey and Berry, 1984), ethanol and nicotine (Mohamed, 1996) and the insecticide methomyl (Ebied, 2002).

The present investigation illustrated marked delay of the ossification of some bones in the limbs and girdles of mice fetuses maternally treated with the anti-ulcer drug omeprazole for all groups. Such effects could be attributed to the inhibitory effect of the drug which may cause a decrease of calcium absorption in the treated mothers and their fetuses since the gastric acid HCl is thought to facilitate the intestinal absorption of the ingested calcium by mobilizing calcium from insoluble complexes in the diet. So the lack of acid due to treatment with the proton pump inhibitor, omeprazole may affect calcium absorption as well as bone formation.

In the present study, fetuses maternally treated with the anti-ulcer drug omeprazole did not show congenital malformations in their skeletal elements. Magee *et al.* (1996) reported that pregnant women received H_2-blockers during the first trimester did not show an excess risk of bone malformations among their offsprings. Along the same line, Ruigomez *et al.* (1999) noticed no increased risk of bone malformations in babies-live births and still births-whose mothers used acid-suppressing drugs during pregnancy.

III-Histopathology

Liver

The liver and kidney were used in the present investigation as an example of the body organs, to study and evaluate any possible pathological impacts of the drug. The liver was chosen as a drug metabolizing and detoxifying organ (Schmidt-Nielsen, 1988; Guyton and Hall, 2006) and the kidney as an organ of excretion and elimination of harmful waste products of the body (Tanagho and Mcaninch, 1992 and Jennette *et al.*, 1998).

The liver is considered as the most suitable organ for testing the possible adverse or toxic impacts of any chemical or physical factors in the body. This fact has been rather emphasized by Yamazuki and La-Russo (1989) and Guyton and Hall (2006) who confirmed that the liver is the most highly qualified organ of the detoxification and metabolism of a wide range of drugs and chemical compounds.

The present investigation showed marked impairments of the hepatic vasculatures of 19 days old fetuses maternally treated with 0.03 mg/kg body weight of the anti-ulcer drug omeprazole for all groups. These lesions include degeneration of the hepatocytes which showed vacuolar and fatty degeneration in their cytoplasm and focal collection of inflammatory cells. Congestion and dilatation of the central veins and the surrounding sinusoids as well as erosion of their endothelial lining cells with the activation of the phagocytic Küpffer cells.

Along the same line, such features were recorded by Zaidenstein *et al.* (1992) in patients with duodenal ulcers subjected to treatment with cimetidine. Also, the same authors showed dilated sinusoids and hyperplasia of the Küpffer cells. Moreover, Van-Bommel and Meyboom (1992) revealed serious hepatic injury including dilated sinusoids as well as periportal edema in the case of ranitidine administration.

From another angle, Lewis (1987) and Schneider *et al.* (1987) suggested that the lesions of the hepatocytes following the usage of cimetidine and oxmetidine drugs were attributed to the possible inhibition of the hepatocytes mixed function of oxidase system responsible for the metabolism of such drugs and other chemical compounds.

Also, Koury *et al.* (1998) displayed a unique case of acute hepatitis accompanied by deteriorated blood vessels secondary to the use of omeprazole that were resolved spontaneously with discontinuation of the drug.

Similar observations were obtained by Ramadan (2001) and Ramadan *et al.* (2005) in mice liver treatment with the anti-

ulcer drug ranitidine and lansoprazole respectively.

Kidney

The kidney is considered as the second target organ useful for the elimination of the harmful waste products and metabolites produced by the body of the used drug doses. As illustrated by Andersson (1996), omeprazole drug is almost completely metabolized in the liver primary by the cytochrome P450 isoenzyme (CYP2C19) to form hydroxy-omeprazole and to a small extent by CYP3A to form omeprazole sulfone. These metabolites are inactive and are excreted mostly in the urine via the kidney.

The present investigation illustrated that the kidney tissues of maternally treated fetuses showed severe pathogenecity towards treatment of mothers with 0.03 mg/kg body weight of the anti-ulcer drug omeprazole before and during pregnancy. Such consequences included swollen of the glomerular capillaries accompanied with narrowing of the Bowman's spaces. The proximal and distal convoluted tubules are detached from each others and their lining epithelial cells are degenerated or vacuolated. Also, inflammatory cellular infiltration was observed in focal areas.

In confirmation with the present results previous studies which were carried out by D'Adamo *et al.* (1997) who stated that omeprazole treatment during pregnancy is not safety enough for patients suffering from peptic ulcer disease as well as for their infants. They also noticed acute interstitialnephritis and the drug must be discontinued during pregnancy and lactation.

Nonetheless, contradictory or conflicting results were noticed by Yio *et al.* (1997) who showed acute renal impairment secondary to interstitialnephritis which is a rare complication of the anti-ulcer drug omeprazole during pregnancy.

In order to give an explanation to such features, some authors including Kaloyanides and Ramsammy (1990) and Walker and Duggin (1992) stated that the proximal convoluted tubules represent the main site of transport and accumulation of drugs or chemicals. Also, Walker and Duggin (1992) added that even low concentrations of the drugs or other metabolites could lead to a certain degree of nephrotoxicity. However, Kaloyanides and Ramsammy (1990) stated that the pathogenesis of many drugs induced nephrotoxicity entails two main successive steps; firstly: the transport and accumulation of the drug by the proximal convoluted tubule cells and secondly: the adverse interaction between these substances and tubular intercellular process.

Rather recently, Fisher and Le-Couteur (2001) stated that treatment with the histamine H2-receptor antagonist cimetidine was noticed to cause nephrotoxicity accompanied with elevation of serum creatinine.

In a report issued by Ra and Tobe (2004), they showed conspicuous glomerularnephritis as well as marked tubular necrosis in an elderly women suffering from gastro-oesophageal reflux disease when subjected to treatment with the anti-ulcer drug pantaprazole.

Rather recently, Geevasnga et al. (2005) announced that treatment with the proton pump inhibitor drug rabeprazole during pregnancy was also not safe enough because of reported cases of acute interstitialnephritis which is an uncommon but important cause of acute renal failure among patients with duodenal ulcer using such drug.

Such marked effects of the anti-ulcer drug omeprazole on the kidney tissues of maternally treated fetuses obtained in the present investigation may be explained due to that the foetal kidney tissue are functionally immature enough to excrete the drug moved metabolites rapidly as adult so it will cause such pathological changes as illustrated by Guyton and Hall (2006).

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التأثيرات المرضية للعقار المضاد للقرحة أومبرازول على بعض النواحى المورفولوجية والهستولوجية لأجنة الفئران المهقاء

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قسم العلوم البيولوجية

يعتبر عقار أومبرازول المعروف تجاريا باسم "لوسيك" من أهم الأدوية التى تستخدم فى الساحة الطبية فى مصر على نطاق واسع فى علاج حالات إلتهاب المرئ الترجيعى والقرحة المعدية وقرحة الإثنى عشر وحالات زولينجر إليسون الناشئة عن الزيادة الإفرازية لحامض الهيدروكلوريك.

وبالرغم من هذه الإستخدامات المفيدة لهذا العقار إلا هناك بعض التقارير الطبية تشير الى دوره فى إحداث بعض الأثار الجانبية عند إستعماله ومن ثم فإن الدراسة الحالية قد صممت لتقييم وتوضيح أى أثار جانبية محتمله تنجم عن إستعمال الجرعات العلاجية لدواء الأومبرازول وهى 0.03 مليجرام لكل كيلو جرام من وزن الجسم على أجنة أمهات الفئران المهقاء الحوامل وذلك من النواحى المورفولوجية والهيكلية والهستولوجية.

وقد أجريت التجربة على مجموعة من إناث الفئران المهقاء الحوامل حيث قسمت إلى ست تحت مجموعات واعتبرت تحت المجموعات الثلاثة الأولى مجموعات ضابطه – وقد حقنت إناث تحت المجموعة الأولى عن طريق التجويف البريتونى بالمذيب لهذا الدواء وهو الماء المقطر وذلك لمدة سبعة أيام متتالية (من اليوم السابع إلى اليوم الثالث عشر من بداية الحمل). أما تحت المجموعة الثانية فقد حقنت بنفس الإسلوب السابق بالمذيب لمدة 14 يوماً قبل الحمل – وبالنسبة لحيوانات تحت المجموعة الثالثة فقد حقنت أيضا عن طريق التجويف البرتيونى بالمذيب (الماء المقطر) لمدة 21 يوماً (14 يوما قبل الحمل وسبعة أيام أثناء الحمل)– أما إناث تحت المجموعات الثلاثة الأخيرة (الرابعة والخامسة والسادسة) فقد حقنت بنفس الإسلوب السابق على الترتيب مثل الذى حدث فى تحت المجموعات الثلاثة الأولى وذلك بإستخدام الجرعة 0.03 مليجرام لكل كيلو جرام من وزن الجسم لعقار أومبرازول.

وقد أوضحت النتائج المورفولوجية بالنسبة للأجنة وجود تأخر فى النمو يظهر من خلال نقص أوزان وأطوال الأجنة مقارنة بالمجموعات الضابطة. وأن المعالجة بالعقار بجميع المراحل ليس لها تأثير على المظهر الخارجى لأجنة الامهات المعاملة حيث لم تظهر أية تشوهات خلقية. وتبين من فحص الهياكل العظمية لهذه الاجنة أن المعاملة سببت تأخرا فى نمو العظام يتمثل فى قصر عظام الأطراف والحزام الصدرى والحوضى وكذلك نقص فى تعظم عظام الجمجمة والفقرات الذيلية.

وأظهرت النتائج الهستوباثولوجيه للكبد فى أجنة الأمهات الحوامل المعالجة حدوث تهدم واضح فى الخلايا الكبدية والتى يظهر فيها التحلل الفجوى والدهنى للسيتوبلازم وكذلك حالات البكنزة النووية والتحلل النووى – وحدوث إحتقان وتمدد فى الأوردة المركزية و الجيوب الدموية المحيطه بها مع حدوث

غزو بالخلايا الالتهابية متزامنا مع حدوث نزف دموى مسببا حالات من الأوديماً في أماكن متفرقة. أما فى قشرة الكليه للأجنة فقد ظهرت درجات متفاوته من الهدم اشتملت على تحلل الخلايا الطلائية الجدارية لمحافظ بومان مع هدم واضح فى الأوعية الجُمعية وتزايد فى أعداد خلايا الميسنجيم أو قلة عددها فى حالات أخرى. وحدوث تباعد للأنيبيبات الملتفة القريبة والبعيده متبوعاً بإتساع فى الفراغات بين أنيبيبية وعانت الخلايا المبطنه لهذه الأنيبيبات من حالات التحلل الفجوى والتنكرز التجلطى مع ملاحظة وجود حالات البكنزة النووية والتحلل النووى ووجود تجمعات هياليئية من حطام الخلايا المتحللة وحدوث غزو بالخلايا الإلتهابية الدفاعية فى المناطق البين أنيبيبية مع حدوث تجمعات دموية من الأوعية الدموية المتهدمة مكونة حالات الأوديما البين أنيبيبية. وكانت هذه التغيرات جميعاً أكثر حدة فى أجنة الأمهات المعالجة لمدة 21 يوماً بالعقار أومبرازول.