The effect of lansoprazole administration during pregnancy on the placenta

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Abstract

Introduction: Lansoprazole is one of the proton pump inhibitor drugs widely used in the treatment of gastro-duodenal ulcers and disorders. However, there is not enough data about unexplored adverse effects of lansoprazole on the integrity of the placental barrier. Therefore, the present study was conducted to determine whether placental structure could be affected by lansoprazole administration.

Materials and methods: A total of 24 pregnant Balb/C mice were randomly divided into one control and three experiment groups (n=6).The experimental animals were given 25, 50 and 100 mg/kg of lansoprazole intraperitoneally on days 6-16 of pregnancy. At the end point and on the day 17 of gestation all animals were sacrificed. Then, the placentas specimens were taken and processed for histological examinations. Histological sections were stained with hematoxylin-eosin and were examined under light microscopy.

Results: The histological examinations showed remarkable cellular changes in the placenta after treatment with lansoprazole. The placentas from drug administrated mice exhibited conspicuous decrease in the spongy layers size when compared with controls. Also, both polymorph and mononuclear cell infiltration into placental parenchyma were seen in the animals treated with 100 mg/kg lansoprazole. In addition, dilation of the intervillous space, massive vasculature congestion, increased giant cell population and fibroblastic proliferation were seen in the placental tissues from experimental groups.

Conclusion: The findings of the present study led us to investigate the effect of the lansoprazole administration on the mouse placenta. Taken together, this drug should not be prescribed during pregnancy.

Keywords: Histology, Placenta, Mouse, Lansoprazole, Health

Introduction

Lansoprazole is one of the most proton pump inhibitor drugs (PPIs) that widely prescribed for the treatment of gastro-duodenal ulcers and disorders. It acts as noncompetitive inhibitors of the H+/K+ ATPase enzyme in the parietal cell membrane of the stomach (1). In spite of most frequently prescription; lansoprazole has recently been suggested to induce some adverse effects in the laboratory animal studies. For example, the effects of PPIs administration on the lung, stomach and oro-pharyngeal microorganism contents have been criticized in the recently published studies (2). It has also been shown that taking 30 mg of lansoprazole could induce Kounis syndrome in a 52 year old man (3). Additionally, PPIs including lansoprazole may exert direct negative effects on the structure and function of the immune system (4). Furthermore, PPIs has been

considered as a potential causative agent for developing the acute interstitial nephritis (5) and as well as celiac disease (6).

As above mentioned, there are many literature investigations on the potential complications of the PPI including lansoprazole on the various organs in the body. On the other hands, in spite of common occurrence of gastro intestinal disorders during pregnancy, there is not enough data about probable adverse effects of lansoprazole administration on the placenta as a major endocrine organ during pregnancy. Since many subjects need to take PPI medicines for treatment of the gastro-duodenal disorders during pregnancy, therefore; the present study was conducted to determine whether placental structure could be affected by lansoprazole administration.

Materials and methods

In this study, the experimental protocols were approved by the institutional animal care and use ethics committee of Ilam University .

For this study a total of 24 pregnant Balb/C mice were randomly divided into one control and three experiment groups (n=6). The experimental animals were given 25, 50 and 100 mg/kg of lansoprazole intraperitoneally (i.p.) on days 6-16 of pregnancy. The control group was treated by intraperitoneal injection of distilled water in the same manner to the experimental animals. All animals were fed standard laboratory chow and tap water ad libitum throughout the study.

At the end point and on the day 17 of gestation, all animals were sacrificed. Then, the placentas specimens were taken and processed for histological examinations. For histological study, the specimens were fixed in the formalin10%; then sectioned by microtome at 6 microns and mounted on the glassy slides. The prepared slides were stained with hematoxylin-eosin and examined under a light microscope. The proportion of various placental areas was compared between various groups.

Results

The histological studies of the placentas from control and experiments group are shown in the figures 1 and 2. The histological examinations showed remarkable cellular changes in the placenta after treatment with lansoprazole (Figure 1). The placentas from drug administrated animals exhibited conspicuous decrease in the spongy layers size when compared with controls (Figure 1).

Also, both polymorph and mononuclear cell infiltration into placental parenchyma were seen in the animals treated with 100 mg/kg lansoprazole (Figures 1 and 2).

In addition, in the placental tissues from experimental groups; the intervillous spaces were more dilated (figure 1-d). Similarly, in the experimental groups the placental parenchyma was occupied with fibroblast cell proliferation than in the controls (Figure 2). Furthermore, in the experimental placental sections, the maternal and fetal blood vessels were relatively dilated and vessels massive vasculature congestion was remarkable (Figure 2). Finally, the number and the size of the trophoblastic giant cells were found to be increased in the treated animals (Figure 2).

Discussion

Lansoprazole is an effective proton pump inhibitor drug act by irreversibly blocking the hydrogen/potassium adenosine triphosphatase enzyme system in the parietal cell membrane of the stomach. It is used for the treatment of gastro-duodenal disorders and peptic ulcers especially during pregnancy (7). Since many subjects need to take lansoprazole medicines for treatment of the gastro-duodenal disorders during pregnancy; the present study aims to investigate its probable adverse effects on the mouse's placenta.

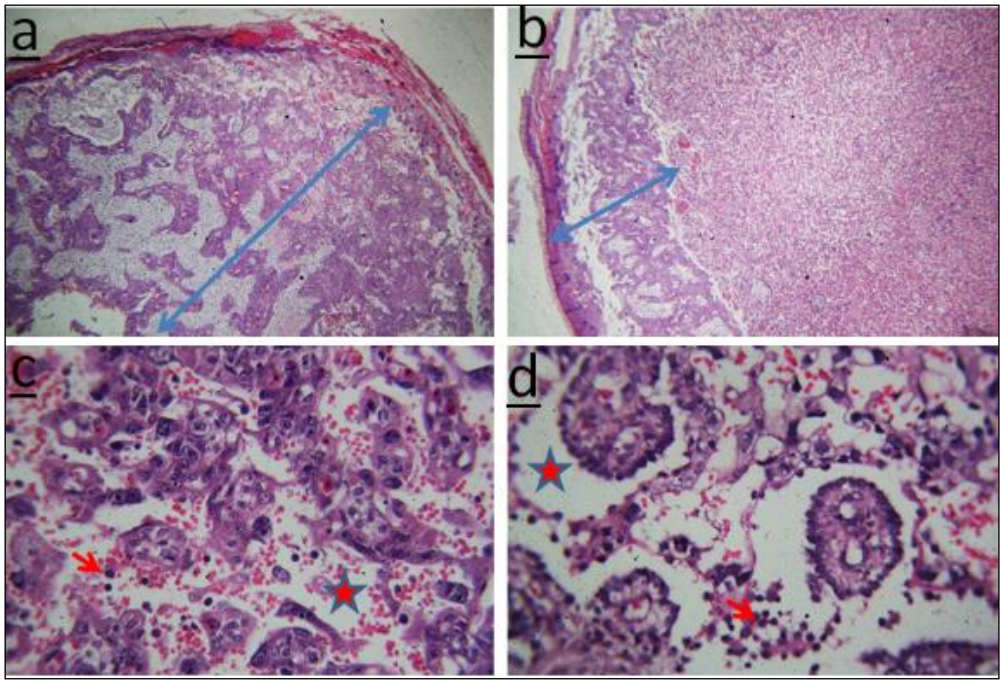

Figure 1. Placental histology of the control group. The double head arrow indicates the normal size of the spongy layer (a). Placental histology of the treated animals with lansoprazole at 100 mg/kg. This figure reveals the conspicuous decrease in the spongy layers s size (b). Placental histology of the control animals. The star represents the normal size of the inter-villous spaces(c). Placental histology of the treated animals with lansoprazole at 50 mg/kg. The arrow reveals the lymphoid cells infiltration in the placental parenchyma. As star reveals the intervillous spaces are more dilated (d). (Haematoxylin and Eosine) (Magnification: × 100 a, b. × 400 c, d).

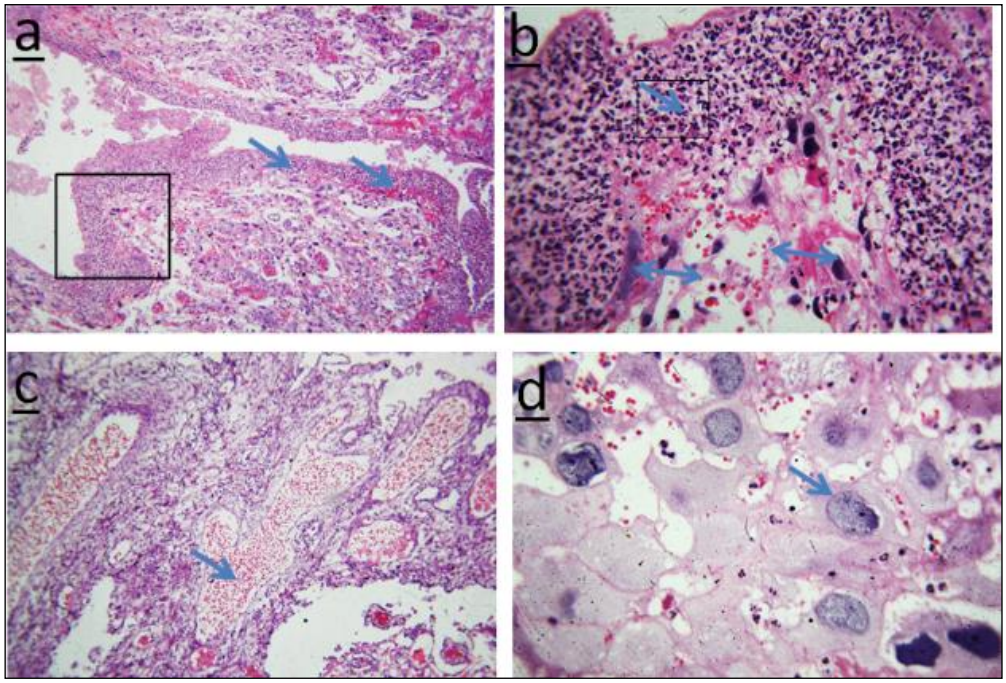

Figure 2. Placental histology of the treated animals with lansoprazole at 100 mg/kg. As arrows indicate the placental parenchyma are occupied with fibroblast cell proliferation (a). Higher magnification of the marked area in the figure 2-a (b). Placental histology of the treated animals with lansoprazole at 50 mg/kg. The arrow indicates remarkable vessels congestion(c). Placental histology of the treated animals with lansoprazole at 50 mg/kg. As arrow indicates the number and size of the trophoblastic giant cells are increased (d). (Haematoxylin

and Eosine) (Magnification: × 100 a, c. × 400 b, d).

Overall, the present histological results clearly demonstrated that lansoprazole administration at organogenesis period of the mouse placenta could exert remarkable harmful impacts. On the basis of the reproductive investigation which have been done in the pregnant rats; lansoprazole at concentrations of 50 and 300 mg/kg could cause a significant decrease in the fetal weight (8). Similarly, it has been suggested that higher incidence of birth defects and major congenital malformations were seen in the patient which exposed to lansoprazole before pregnancy (9). Because of placental dysfunction has been positively correlated with fetal weight retardation and can also restrict embryo growth by limiting nutrient exchange between mother and embryo(10), therefore, the above mentioned literatures are in keeping with the obtained data in the present research.

Although it is not known whether the administered lansoprazole to the pregnant mothers have the potential to cross the placenta, but its molecular weight is low enough that passage across the placenta and reach embryo (11). So, the present results on the placental histology can indicate readily diffuse of lansoprazole across the placental membrane and reach the fetus .

In the current work the polymorph and mononuclear lymphoid cells infiltration in the placental parenchyma after drug exposure is abnormal. Indeed, any elevation in the lymphoid cells infiltration seems to indicate the occurrence of inflammation in the placental tissue and related to experimental dosing.

Present findings provided the first experimental evidence that lansoprazole induces noticeable detrimental impacts on the murine placenta. There are not any investigations in the literature about the effects of the lansoprazole on placenta which compared with present findings .

In the current investigation the number and size of the trophoblastic giant cells were found to be increased after lansoprazole prescription. It has been demonstrated that trophoblastic giant cells are precursors of invasive trophoblasts that collaborates channels within the labyrinthine region of the murine placenta (12). Since feto-maternal interface occurs within the labyrinthine zone (13), therefore, the trophoblastic giant cells impairments suggests these critical nutrient transport site were compromised by lansoprazole exposure.

Although mechanism underlying placental toxicity in the case of lanzoprazole treatment is not clear; but it is likely multifactorial and maybe is due to this facts that trophoblastic cells might be vulnerable to the inhibition of proton extrusion and inhibition of the ATPase activity during drug exposure (14). In addition to this phenomenon, the immune-modulatory effects of PPIs (4) including lanzoprazole could be a major risk factor for placental insufficiency.

Further work is needed to elucidate the possible association between lansoprazole exposure and placental tissue alterations.

The limitation of the present study was the lack of electron microscopy research accompanying the histological alterations.

Conclusion

The findings of the present work led us to investigate the effect of the lansoprazole administration on the mouse placenta. Taken together, this drug should not be prescribed during pregnancy.

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