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Original Article *Pharmacology*

Adverse effects of moxifloxacin and flunixin meglumine and their combination on pregnant rats

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ABSTRACT

Objective: To detail an easy approach to identify the changes that moxifloxacin and flunixin meglumine have caused in the dam of female rats.

Design: Randomized controlled experimental study.

Animals: This study was conducted on thirty-five female (170-200 gm) mature white rats (170-200 gm) and clinically intact, 20 mature male albino rats for the purpose of mating.

Procedures: Once mating has occurred, this is considered the first day of pregnancy. Rats were randomly divided into seven groups 1) a control group 2) The moxifloxacin group 6 days 3) the moxifloxacin group 13 days 4) the flunixin meglumine group 6 days 5) the flunixin meglumine group 13 days 6) the moxifloxacin and flunixin meglumine mg group 6 days 7) the moxifloxacin and flunixin meglumine mg group on day 13. Rats were killed on the days specified for the sixth day and the thirteenth day. Blood and liver samples were collected for biochemical analysis of blood and tissue for pathological examination.

Results: Moxifloxacin and flunixin meglumine and their combination have been shown to have some negative effects in mothers of rats, so we recommend that caution be exercised when using moxifloxacin and flunixin meglumine during pregnancy. It was found that the tested drugs had caused a significant decrease in superoxide dismutase and glutathione levels compared to the control group. The histopathological examination of mothers, who were given moxifloxacin and flunixin meglumine and their mixtures, showed variable alterations in kidney, liver and placenta.

Conclusion and clinical relevance: From the above it is clear that moxifloxacin and flunixin meglumine and their combination have caused some negative effects for pregnant rats, so we recommend that you use caution when using moxifloxacin and flunixin meglumine during pregnancy.

Keywords: Liver, Antioxidants, Moxifloxacin, Flunixin meglumine

1. INTRODUCTION

Many drugs may be used during pregnancy for treatment of some diseases [1]. Such drugs may cause some adverse effects on pregnant females and can induce teratogenic effect [2]. Some drugs can cross the placental barrier and enter fetal circulation during pregnancy, so they may produce some sort of fetal abnormalities [3]. Fluoroquinolones are group of antibacterial agents which affect G +Ve and G –Ve bacteria. They are used for curing variety diseases (especially of the G.I.T, respiratory and urinary systems). They may be used during pregnancy intentionally or unintentionally [4].

Newer fluoroquinolones are extensively used in veterinary field as they have good efficacy and safety. Moxifloxacin is a new 4th Generation, 8-Methoxy Quinolone with a broad spectrum of activity and bactericidal action by inactivation of bacterial DNA Gyrase. It has in vitro activity against a wide range of Gram-positive and Gram-negative organisms [5]. Many NSAIDs can be joined the antimicrobial agent therapy for treatment of veterinary bacterial diseases for decreasing fever, pain and inflammation. Flunixin meglumine is one of the nonsteroidal anti-inflammatory drugs that are extensively used in veterinary field. It acts by the inhibition of cyclooxygenase, which synthesizes prostaglandin from arachidonic acid [6].

2. MATERIALS AND METHODS

2.1. Animals, housing and feeding

Thirty-five female albino rats (aging 3 -4 months and weighing 170-200 gm) and twenty male albino rats (4–5-month-old and weighing 200-230 gm for mating) were obtained from Laboratory Animals Colony, Helwan, Egypt. The rats were kept under hygienic condition, housed in metal cages and bedded with wood shavings, fed on a balanced ration composed of breed, milk, barely and carrots and watered *ad-libitum*. They were accommodated to the laboratory conditions for two weeks before being experimented**.**

2.2. Drugs

Moxifloxacin hydrochloride [Avelox]®

AVELOX Injection is available in ready-to-use 250 mL flexi bags as a sterile, preservative free, 0.8% sodium chloride aqueous solution of moxifloxacin hydrochloride (containing 400 mg moxifloxacin) with pH ranging from 4.1 to 4.6.

Dose: The recommended dose of moxifloxacin for rats is 5 mg/kg intramuscularly [7].

Flunixin meglumine [Flunixin]®

A vial contains 50ml of Flunixin meglumine (Norbrook Company, UK). Each milliliter of Flunixin Injection contains flunixin meglumine equivalent to 50 mg flunixin, 0.1 mg edetate disodium, 2.5 mg sodium formaldehyde sulphoxylate, 4.0 mg diethanolamine, 207.2 mg propylene glycol, 5.0 mg phenol as preservative, hydrochloric acid, water for injection q.s.

Dose: The recommended dose of flunixin meglumine for rats is 2.5 mg/kg by S.C [8].

2.3. Experimental design

The pregnant rats were allocated randomly into 7 groups (10 dams each) as the following: The control group (G1) was administered saline subcutaneously 5mg/kg b.wt. The second group (G2): given moxifloxacin 5mg/kg b.wt intramuscular, once daily, at 6th day of gestation for 7 consecutive days. The third group (G3): given flunixin meglumine 2.5mg/kg b.wt. Subcutaneously, once day by day, at 6th day of gestation for 7 days. The fourth group (G4): given flunixin meglumine 2.5mg/kg b.wt. Subcutaneous, and moxifloxacin 5mg/kg b.wt intramuscular once day by day, at 6th day of gestation for 7 days. The fifth group (G5) given flunixin meglumine 2.5mg/kg b.wt. Subcutaneous, when every day, the thirteenth day of development for seven days. The sixth group (G6): given flunixin meglumine 2.5mg/kg b.wt. Subcutaneous, and moxifloxacin 5mg/kg b.wt intramuscular once day by day, The sixth day of incubation for seven days . The seventh group (G7): given flunixin meglumine 2.5mg/kg b.wt. Subcutaneous, and moxifloxacin 5mg/kg b.wt intramuscular once every day, the thirteenth day of incubation for seven days. The female rats were kept under daily observation until the 20th day of gestation.

2.4. Evaluation

2.4 .1. Blood samples

On 20th day of pregnancy, 5 rats from each group were subjected to anesthesia by using ketamine hydrochloride and fresh blood samples were immediately collected from eye plexus by syringes collected in centrifuge tubes, then put in refrigerator overnight and then centrifuged at 3000 r.p.m for 10 minutes and clear sera were separated carefully, collected and stored in Epindorff tubes at – 20 ºC until biochemical analysis [9].

2.4.2. Biochemical analysis

Effects of the tested drugs on oxidant and antioxidant activities:

2.4.2.1. Determination of catalase activity

Plasma and amniotic liquid catalase action were resolved by the strategy depicted by [10].

2.4.2.2. Determination of superoxide dismutase (SOD) activity

Superoxide dismutase (SOD) movement in both serum and amniotic liquid were distinguished by the strategy depicted by [11].

2.4.2.3. Determination of glutathione reduced (GSH)

Glutathione reduced (GSH) was measured spectrophotometrically by enzymatic colorimetric method by using ready-made Bio-diagnostic kits according to [12].

2.4.3. Histopathological studies

Specimens from liver, kidney and placenta from dams were collected on 20th day of pregnancy and preserved in 20% neutral buffered formalin for histopathological examination according to [13]**.** The slides were examined under a photomicroscope fitted with an Olympus DP25 digital camera.

2.5. Statistical analysis

The data was analyzed by using computerized SPSS program version 16. Results are presented as mean ± SE. The data were analyzed by one way ANOVA following by Duncan's test $p \leq .05$ were considered significant [14].

3. RESULTS

3.1. Effect of the tested drugs on the levels of catalase, glutathion and superoxide dismutase in serum tretated dams:

The effects of moxifloxacin (5 mg/kg B. Wt.), flunixin meglumine (2.5 mg/kg B. Wt.) and their combination on serum levels of catalse, glutathion and superoxide dismutase of treated groups compared with the control group were presented in Table (1) and illusterated in Figure (1).

3.2. Serum catalase levels

The recorded data reflected a non significant decrease ($P<0.05$) in serum catalase levels in moxifloxacin medicated group (1.31 ± 0.08) compared with the result of control group (1.67 ± 0.08). While a significant decrease in serum catalase levels were recoreded in seum of flunixin meglumine (1.28 ± 0.08) and moxifloxacin with flunixin meglumine (1.06 ± 0.04) treated groups in comparison with the control group (1.67 ± 0.08).

3.3.serum glutathione levels

The results revealed a significant decrease ($P<0.05$) in serum glutathione levels in groups treated with moxifluxacin (78.20 ± 1.87), flunixin meglumine (72.31 ± 2.50) and moxifloxacin with flunixin meglumine (56.66 ± 2.52) compared with the serum glutathion level of control group (91.20 ± 2.14).

3.4.Serum superoxide dismutase level

The serum levels of superoxide dismutase were significantly decreased ($P<0.05$) in all treated groups, where the levels were 45.61 ± 1.86 (with moxifloxacin), 43.31 ± 1.50 (with flunixin meglumine) and were 36.56 ± 1.13 (with

the combination of moxifluxacin flunixin meglumine) compared with that recorded in the control group (60.84 ± 2.19).

Table 1. Effect of moxifloxacin (5 mg/kg, I.M), flunixin meglumine (2.5 mg/kg, S.C) and their combination on 13th day of gestation on serum catalase (CAT), glutathione (GSH) and superoxide dismutase (SOD) levels of treated dams.

Group	Catalase (U/ml)	GSH (µmol/ml)	SOD (U/ml)
Control	1.67 ± 0.08 a	91.20 ± 2.14 a	60.84 ± 2.19 a
Moxifloxacin	1.14 ± 0.13 a	68.10 ± 1.28 b	40.63 ± 2.07 b
Flunixin meglumine	1.12 ± 0.11 a	66.41 ± 3.31 bc	39.62 ± 0.89 b
Moxifloxacin + Flunixin	0.98 ± 0.11 a	50.03 ± 2.17 c	31.30 ± 1.31 b
Significance	0.2 N. S	0.0005	0.0012

P value consider significant when less than 0.05
Different letters at the same column consider significant at P < 0.05.

3.5. Histopathological findings

Specimens from liver, kidney, placenta from dams and liver,were collecting on 20th day of pregnancy were preserved in 20% neutral buffered formalin for 48 hours then washed over night by running water. Tissue samples were dehydrated by using ascending grades of ethyl alcohol starting with 50% ending with 3changes of absolute alcohol. The tissue samples were left for 12 hours in each grade. The samples were put in xylol for 3 hours for clearing. Specimens were transferred in methyl paraffin wax for 2 hr. Finally, the samples were blocked in hard paraffin and cut into sections of 5 microns thickness, stained by Hematoxyline and Eosin stain (H&E), then mounted by Canada balsam and covered by cover slides [15]. The slides were examined under a photomicroscope fitted with an Olympus DP25 digital camera.

Administration of moxifloxacin, flunixin meglumine and their combination on kidney, liver and placenta of pregnant rats showed the following results.

4. DISCUSSION

The exposure of animals to a considerable number of potential toxicants as drugs and chemicals is considered unsuitable to the process adverse effects [16].

A new fluoroquinolone antibacterial for the treatment of respiratory tract infections is known as moxifloxacin. Moxifloxacin as a 4th generation antibacterial agent has a bactericidal effect with broad spectrum activity against G – Ve and G +Ve activity [17]. Flunixin meglumine is a potent non-steroidal anti-inflammatory, that relief pain in painful procedures by inhibiting the production of PGE2 from arachidonic acid [18].

Superoxide Dismutase (SOD), Hydrogen Peroxide (H_2O_2), and Hydroxyl Radical (OH) as reactive oxygen species (ROS) are reactive oxidant species. They are by-products of intracellular metabolic processes that producing macromolecular damage. They are harmful to health and cause damage to DNA, RNA, proteins, and lipids. Superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPX) are 3 main antioxidant enzymes in animals. Glutathione is an important endogenous antioxidant with numerous cellular functions that protect against harmful effects of ROS and free radicals. SOD is the first enzyme in the antioxidative system and increases in inflammation and pain. GSH plays a role in the antioxidant defense system by eliminating the reactive oxygen species formed in the living organism, acts as non-enzymatic and SOD enzymatic antioxidant [19].

The results recorded a non significan decrease in the activity of catalase and a marked reduction in glutathione (GSH) and superoxide dismutase (SOD) activities in moxifloxacin treated tats after its s.c administration at 5 mg/kg at 6th day of pregnancy which may lead to increased oxidative stress and lipid peroxidation, as well as decreased activity of the detoxification enzyme.

The decreased activity of GSH and SOD in rats treated with the moxifloxacin is attributed to the response of organs to the elevated ROD production, as a result of exposure to the drug and its metabolites. Glutathione (GST) is a multifunctional enzyme and one of the key enzymes in drug metabolism, which is also known to play a vital role in redox balance in the cell [20]. The effect of quinolones as bactericidal initiates the production of the free radicals in both G -Ve and G +Ve bacteria as end product of drug biotransformation [21]. The GSH level in the liver is a measure of non-enzymatic anti-oxidant and cellular Redox Status of the cells [22]

The observed reduction in GSH levels are in accordance with the previously recorded data by many fluoroquinolones [23] . Also, quinolones have the capacity to produce free radicals and change the activity of antioxidant enzymes [24].Moreover, [25] said that, gatifloxacin significantly decreased the activity of superoxide dismutase and blood glutathione levels of treated rabbits. In addition [26]. mentioned that, moxifloxacin evoked a marked reduction in the activities of Superoxide Dismutase, and Glutathione in treated tats.

In the same direction, flunixin meglumine and its combination with moxifloxacin evoked a non-significant decrease in catalase level and a marked reduction in Superoxide Dismutase and glutathione of treated dams. These findings are in accordance with those recorded by [27].who mentioned that, Flunixin meglumine induced significant decrease in GSH and SOD levels. Moreover, [28]. stated that, ibuprofen and diclofenac showed a significant decrease in GSH level of treated fish. In addition, [28]. reported that, celecoxib as non-steroidal anti-inflammatory

induced a significant reduction in levels of SOD and GSH of tested rats.

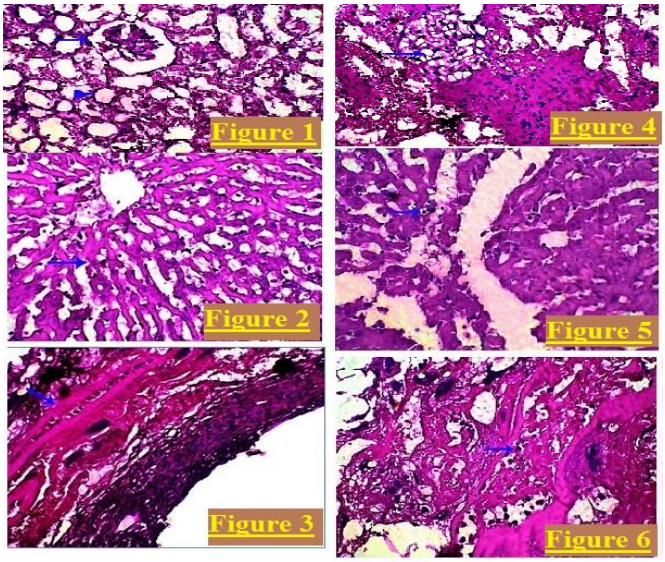

Figure 1. Kidney of dam displays normal renal glomeruli (arrow) and normal renal tubules (arrowhead). (H&E, 400X). ***Figurer 2.*** Liver of dam displays normal hepatocytes in normal radial arrangement around central vein (arrow). (H&E, 400X). ***Figure 3.*** Placenta of dam showing normal histological structure with normal blood vessels (arrow). (H&E, 400X). ***Figure 4.*** The kidney of dam given moxifloxacin displayed congestion of the renal glomeruli (arrow) and degenerative changes of the renal tubular epithelium. (H&E, 400X). ***Figure 5.*** The liver of dam given moxifloxacin displays lytic necrosis of hepatocytes and lymphocytic infiltrates (arrow). (H&E, 400X). ***Figure 6.*** The placenta of dam given moxifloxacin displays neutrophils infiltration (arrow). (H&E, 400X).

The recorded results regarding the histopathological study in this work revealed that, the given moxifloxacin to pregnant rats at 6th day of gestation period showed different alterations in liver (lytic necrosis of hepatocytes, lymphocytic infiltrates, dilatation of hepatic sinusoids and edema in sub-endothelial around central vein) and kidney (congestion of the renal glomeruli, degenerative changes of the renal tubular epithelium and hemorrhage in interstitial tissues) of treated dams. Moxifloxacin induced some changes in placenta of the treated Dams (neutrophilic infiltration and the blood vessels plugged with neutrophils).

The result regarding the effect of moxifloxacin on liver is similar to that obtained by many investigators [29]. found that, fluoroquinolones showed severe liver damage (extensive hepatocellular necrosis and a mixed inflammatory infiltrate with abundant eosinophil) [30]. reported that ciprofloxacin administration during gestation evoked severe liver damage in Westar albino rats. In addition [31]. said that oral administration of norfloxacin during pregnancy revealed congestion in central and portal vein associated with edema and inflammatory cells infiltration in liver. Moreover, [32]. revealed that ciprofloxacin caused histological changes in liver of pregnant rats (dilatation of central and portal vein, and appearance of macrophages and Kupffer cells in sinusoidal spaces with congested blood vessels. Further, [33]. mentioned that norfloxacin showed some histopathological alterations in liver, kidney, heart, spleen and intestine of treated dams. The accumulation of antimicrobials in the kidneys can induce sever damage (as tubular injury, interstitial inflammation, alterations in renal electrolyte levels and glomerular apparatus damage [34]. The results of moxifloxacin on kidney are in accordance with the findings of [35]. who reported mild interstitial nephritis associated with fluoroquinolones, norfloxacin, ciprofloxacin and nofloxacin. Also, [36-38]. reported that, norfloxacin showed glomerular olization in the lining epithelium of the renal tufts while the intertubular tissue showed focal hemorrhages in kidney after its oral administration.

The induced pathological changes in placenta might be attributed to toxic of the drug as it pass easily through placenta due to its low molecular weight [33]. The result is supported by [39]. who stated that the given norfloxacin to pregnant rats showed necrosis in the placenta (giant cells figure with focal hemorrhages in labyrinth layer) and the uterus showed desquamation of endometrial epithelium.

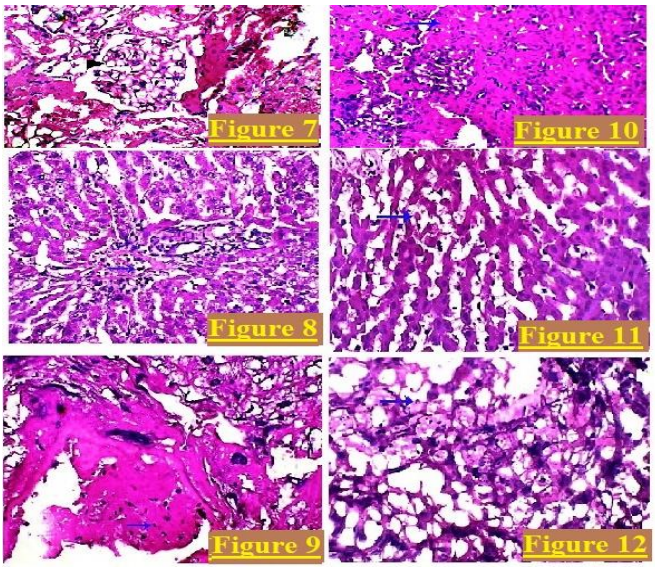

Figure 7. The kidney of dam given flunixin meglumine showing necrosis of renal tubular epithelium lining renal tubules (arrow) and slight congestion of the renal glomeruli (arrowhead). (H&E, 400X). ***Figure 8.*** The liver of dam given flunixin meglumine showing swollen endothelial cells and lymphocytic adherence to it (arrow). (H&E, 400X). ***Figure 9.*** The placenta of dam given flunixin meglumine showing polymorph nuclear cell infiltration (arrow). (H&E, 400X). ***Figure 10.*** The kidney of dam given moxifloxacin with flunixin meglumine showed degenerative change in the renal tubular epithelium (H&E, 400X). ***Figure 11.*** The liver of dam given moxifloxacin with flunixin meglumine showed dilation of hepatic sinusoids with dissociation and necrosis of hepatocyte. ***Figure 12.*** The placenta of dam given moxifloxacin with flunixin meglumine showing congestion and degenerated neutrophils (arrow). (H&E, 400X).

The effects of flunixin meglumine on liver, kidney and placenta of pregnant dams were recorded. The liver of dam given flunixin meglumine showed swollen endothelial cells and lymphocytic adherence to it and showed vacillation of hepatocytes. The kidney of dam given flunixin meglumine showed necrosis of renal tubular epithelium lining renal tubules and slight congestion of the renal glomeruli and showed proliferation of the renal glomeruli. The placenta **of** dam given flunixin meglumine showed polymorph nuclear cell infiltration and showed severe neutrophil infiltration. The mechanism by which NSAIDs as diclofenac and

ibuprofen induced hepatotoxicity [39]. who said that non-steroidal anti-inflammatory inducing liver injury. The obtained data are supported [40] who reported that, the use of mefenamic acid revealed variable histopathological alterations as mild hepato-cellular necrosis with increased liver weight. Moreover, [38]. noticed that liver sections of piroxicam treated mice showed inflammatory cellular infiltration, vacuolated hepatocytes, dilated sinusoids, and increased number of Kupffer cells. In addition, [41]. The effect of flunixin meglumine on kidney tissues is supported by [42] who recorded renal papillary necrosis in kidney of horse on by phenylbutazone. In addition. [3] mentioned that, piroxicam evoked some cellular inflammations, shrunken glomeruli, edema and vacuolation in the tubular cells of the kidney [3].stated that, meloxicam revealed swelling in the endothelial cells lining the tufts associated with degeneration and necrosis in the tubular lining epithelium of the glomeruli of kidney.

Conclusion

It could be concluded that, administration of moxifloxacin and flunixin meglumine to pregnant rats induced some adverse effects on dams. So, we recommend that neither moxifloxacin nor flunixin meglumine should be used together during pregnancy because of their negative effects.

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Conflict of interest statement

The authors declare that they have no conflict of interest.

Ethical approval

The current study complies with national and international guidelines. The current study was approved by the research ethics committee at Mansoura university Code No: R/78.

Authors' contribution

All authors are equally contributed.

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