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Ameliorative role of misoprostol on hematological and biochemical parameters of male rats' treated with ciprofloxacin

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Abstract

Ciprofloxacin (CPX) is one of the most frequently used fluoroquinolone drugs used in treatment of infections caused by gram negative microbes. The currant aim of this study to ensure the defense action of misoprostol (MP) against undesirable effect induced by ciprofloxacin. Thirty white male rats were divided into three equal groups (first group: control group, second group: Ciprofloxacin group, which given ciprofloxacin at a dose 100mg/kg/day orally for 14 days, and third group: ciprofloxacin and misoprostol group, which given combination of ciprofloxacin at a dose 100mg/kg/day orally and misoprostol at a dose 200µg/kg/day orally for 14 days. After 14 day of treated, the rats were scarified, blood taken for measured RBC count, HB concentration, platelet number. WBC count and liver enzymes (ALT, AST, ALP). The results indicated a significant decrease ($p < 0.05$) of RBC, Hb, platelets and WBC in male rats treated with CPX compared with control group, also liver enzymes were increased significantly ($p < 0.05$) in CPX group compared with control group, while co-administration of misoprostol with CPX administration produce improving effects on hematological parameters and liver enzymes when compared with first and second group.

Conclusion: ciprofloxacin induced oxidative effect that can be removed by misoprostol.

I. Introduction

Ciprofloxacin (CPX) is an antibacterial agent; it was synthetized by Bayer at the end of 1982. Ciprofloxacin is considering as a second generation of fluoroquinolons group which has highly effective against gram negative bacteria (Sub and Lorber, 1995). It was widely used in the treatment of urinary, bone and soft tissue, skin, respiratory tract, reproductive tract, gastro-intestinal infections (Hooper and wolfson, 1985). It can be given orally and it well tissue penetration and induced its antibacterial action (Liu and Wong, 1999). Ciprofloxacin like other quinolones contains ciprofloxacin hydrochloride which responsible for induces many disturbances like hepatotoxicity, cholestatic jaundice, bilirubenemia, with increase of ALP, AST, ALT and prolonged time of prothrombin (Hirch and Lundquist, 2009). Wayers *et al.* (2002) found increased in lipid hydroperioxide (COOH) in the liver of mice treated with ciprofloaxacin, this indicate that the ciprofloxacin induced stress in the liver.

Misoprostol (MP) is a synthetic analogue to endogenous hormone prostaglandin E1 (PGE1), used mainly in the treatment of peptic ulcer that related with administration of NSAIDs (Park *et al*., 2009). The effect of MP in scavenger of ROS has gained highly interest within the past few years (Salam *et al*., 2009). In addition, MP has been used as antiapoptotic and cytoprotective effects (Yang *et al*., 2002; Sostres *et al*., 2010). Ozer *et al*., (2011), investigate the effect of MP on kidney disturbance induced by CP, which enhanced lipid peroxidation and induced decrease in the antioxidant enzymes of the kidney.

The present study was aimed to investigate the ameliorative role of misoprostol on hematological and biochemical parameter of male rats' treated with ciprofloxacin

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II. Material and Methods

Thirty albino wistar male rats weighing between 175- 200g were kept in wooden cages under standard conditions (28°C ambient temperature with 12 hours light-dark cycle). The first group was considered as control group, the second group was administered only with ciprofloxacin of 100mg/kg/day (AL-Rikaby et al., 2016) for 14 days orally and the third group was administered orally with ciprofloxacin of 100mg/kg/BW/day plus misoprostol of 200µg/kg/BW/day after one hour (Nasr, 2013) for 14 days orally. On the last day of administration, feeds were withdrawn from the rats twelve hours to the time of sacrifice. The rats were euthanized with chloroform, cardiac punctured by 10 ml disposable syringe of 22G needles (Parasuraman *et al*., 2010) and one ml of blood collected into sample tubes containing heparin for hematological analysis and the remaining volume the blood putting into plain tube without EDTA and centrifuged at 3000 rpm for 15 minutes to obtain the serum which then transferred into Eppendorf tubes and stored at -20ºC till used for measurement of biochemical parameters like liver enzymes (Gray *et al*., 2003).

III. Results

The results in table (1) showed a significant decreased (P≤0.05) in, RBC count, Hb level, platelets number and WBC count in the second group when compared with the first group. Administration of misoprostol with ciprofloxacin in the third group ameliorated the effects of ciprofloxacin on the above blood parameters but there were non-significant elevated in RBC count and plat. number, and a significant elevated (P≤0.05) in Hb level, and WBC count when compared with first group.

Table 1: Ameliorative role of misoprostol on heamatological parameters of male rats treated with ciprofloxacin

M ± SE

Groups	RBCs×10^6/µL	Hb(g/dL)	Plat.×10^3/µL	WBC
G-1	5.44±0.8 a	10.36 ± 0.07a	501.86±0.67a	4.69± 0.086 a
G-2	4.22±0.9 b	7.33± 0.06 c	363.34±12.3b	3.22±0.08 c
G-3	5.39 ±0.1 a	9.42 ± 0.12 b	519.54±7.58a	4.28±0.11 b
LSD	0.86	0.85	154.56	0.095

The obtained results in Table (2) revealed that the administration of CPX cause a significant increase (P<0.05) in serum ALT, AST and ALP levels when compared with the levels of normal rats. This elevation in serum level of the liver enzymes were reduced significantly (P<0.05) after administration of MP in dose of 200µg/kg/BW compared with control animals.

Table 2: Ameliorative role of misoprostol on biochemical parameters of male rats treated with ciprofloxacin

M ± SE

Groups	ALT(U/L)	AST(U/L)	ALP (IU/L)
G-1	8.62±0.19 c	23.81±0.16 c	32.22±0.23 c
G-2	16.16±0.25 a	42.5±0.20 a	49.96±1.48 a
G-3	8.94±0.23 b	26.92±0.25 b	39.54±0.7 b
LSD	0.53	0.44	9.21

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IV. Discussion

Ciprofloxacin is one of the fluoroquinolones class, which are mostly prescribed in both humans and animals. This class of antibiotics is the first line drug for several infections including infections of the reproductive and urinary system and respiratory infection (Liu and Mulholland, 2005; MacDougall *et al*., 2005).

CPX has been readily prescribed for treatment of gram negative bacteria in recent times with efficacy in respiratory, urinary tract, gastrointestinal and abdominal infections (Oliphant and Green, 2002; Kumar *et al*., 2011).

In the present study administration of ciprofloxacin result in a significant decreased in erythrocytes count, hemoglobin concentration, platelet number, and in leukocytes counts, these results are agreed with (Stiene-Martin *et al*., 1998; Oridupa *et al*., 2013; Priyadharshini, 2013; Edem *et al*., 2016). The reduction in red blood cell count and hemoglobin level may be due to suppression of bone marrow function which may result in anemia. Anemic condition which may be a consequence of iron deficiency (Palande, 2011) and unavailability (Gupta, 2014) may be as a result of coagulation of iron with ciprofloxacin thereby rendering the ion insufficient (Borcherding *et al*., 1996). The depletion of iron reduces the synthesis of hemoglobin in the bone marrow which in turn decreases the red blood cell counts. Also the significant decrease in red blood cell counts and hemoglobin was obtained by AL- Nahari (2014) who studied the physiological and hematological changes induced by the administration of ciprofloxacin in mice and found marked decline in RBC count and Hb concentration.

Packman, 2001, suggested other mechanisms that have been postulated for drug-mediated anemia. The first mechanism is the hapten-drug adsorption mechanism, means attachment of the drug with the membrane of RBC, and attachment of anti-drug antibody to the membrane-bound drug, which opsonizes the cells for destroyed by splenic macrophages. Second mechanism, is the a trimolecular complex may be formed which composes of the drug, RBC membrane antigen and an antibody which recognises the complex formed by the drug and RBC membrane. These two mechanisms require the presence of the drug, while the third mechanism does not require the drug for destruction of RBC. Some drugs directly stimulate formation of true autoantibodies which are same as those seen in autoimmune haemolytic anaemia, with increased synthesis of lymphocytes (Packman, 2001; Pierce and Nester, 2011).

On the other hand the study revealed that there was a slight decrease in white blood cell suggesting a disorder in the bone marrow which hampered the production of white blood cells. In this respect, the findings agreed with those obtained by Priyadharshini (2013) who reported the decrease in white blood cell count in rats during administration of ciprofloxacin. Reduced platelet count as seen in all the dosage administered may be caused by disorder in platelet production or conditions in which platelets are used up (consumed) or destroyed faster than normal and this may result to thrombocytopenia which could lead to impairment of the normal physiological activities of the system (Stiene-Martin *et al.*, 1998).

Also the results are showed a marked increase in AST, ALT and ALP in rats treated with ciprofloxacin. This is agreed with the finding by (Orman *et al*., 2001; Edem *et al*., 2016), showed that CPX induced hepatic dysfunction manifestation with marked elevated in liver enzymes (AST, ALT and ALP). Bhagirath, (2008) demonstrated that ciprofloxacin induced hepatotoxicity in most patient treated with therapeutic doses is characterized by elevated levels of AST, ALT and ALP. This is supported by Hirsch and Lundquist (2009), who found that ciprofloxacin, has a potential hepatotoxic agent.

The mechanism of hepatic injury that occurs by ciprofloxacin is not well understood. Some studies suggested that the ciprofloxacin generates free oxidative radical could cause oxidative stress in the liver, result in liver damage. This is supported by study by Weyers *et al*., 2002, who investigated that lipid hydroperoxide (LOOH) is increased by ciprofloxacin in mice liver, which is a marker of induced oxidative stress, this oxidative stress was decrease or inhibited released by ascorbic acid. The synthesis oxidative radicals due to administration of CPX may lead to

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decrease of protein content in the liver cell which results in decreased in nucleic acids and finally damage of DNA, as a result of this effect, the number of mitochondria is decreased due to degeneration of it, which is responsible for energy supply. (Pino *et al*., 1991). This supported that the antibacterial activity of CPX by marked inhibition of bacterial DNA topoisomerase (Gellert *et al*., 1981; Crumplin *et al*., 1984; Gilman *et al*., 1990).

The results show the benefit effect of MP on the liver enzymes. These results are agreed with Salam et al., 2009, who found that the treatment with misoprostol protects against hepatocellular necrosis induced by CCl_4, and agreed with Ozer *et al.*, 2011 and Nasr *et al*., 2013, who findings that the MP has antioxidant activity renal toxicity in rats induced by CP, it cause decreased MDA level with increased production of antioxidant enzymes as SOD and CAT in the kidney tissue when compared to the normal rats. Thus MP considerable as scavenger of ROS scavenger (Ozer *et al*., 2011).

A combination of two drugs misoprostol and ciprofloxacin in third treated group produced a significant decrease in liver enzymes when compared with the ciprofloxacin-treated rats. Treated with MP cause improvement of liver enzymes, which might be cause stabilizing effect on the hepatocyte cell membrane, result in prevents AST, ALT, and bilirubin leakage into the extracellular fluid (Ajith *et al*., 2007). MP enhance regenerating of the destroy liver cell **(**Salam *et al*., 2009).

It has been reported that, the antioxidant effect of misoprostol did not limit lipid peroxidation in vivo and did not protect against the oxidant injury of tert-butylhydroperoxide in vitro (Ozer *et al*., 2011). Conversely, the protective effect of MP might be due to hemodynamic factors, increased regenerative capacity of epithelial cells, or an inflammatory response through a cytoprotective effect and reduction of the immune-mediated liver damage. **(**Brunton *et al.,* 2006**;** Asci *et al*., 2011**).** Moreover, misoprostol was shown to block the apoptosis generated through the toxic D-galactosamine (Ranchal *et al*., 2006).

In conclusion, this experiment has shown that ciprofloxacin exert distrubance in hematological parameters and some liver enzymes in albino male rats, which can modulation by administration of misoprostol.

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