Possible Histological Changes Induced by Therapeutic Doses of Ciprofloxacin in Liver and Kidney of Juvenile Rats

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Abstract: Background: Fluoroquinolones (FQs), group of antibacterial agents are widely used in treating adults infected with Gram-negative bacteria. The drugs were contraindicated in children, growing adolescents and during pregnancy due to their joint toxicity potential. Their toxicity concerning other organs needs to be clarified. Objective: This study was designed to study the possible hepatic and kidney damage induced by two therapeutic doses of a drug belongs to FQs group, ciprofloxacin in juvenile rats. Materials and methods: Four week healthy rats were utilized in this study and divided into three groups of 6 rats each. Group I 25 IU i.p. saline solution two times daily for one week (control); Group II- 25 mg kg⁻¹ ciprofloxacin injected i.p. two times daily for one week and Group III-50 mg kg⁻¹ ciprofloxacin injected i.p. two times daily for one week. After euthanization of animals by anesthetic ether, histological examinations were performed using gross sections of liver and kidney tissues under ordinary light microscope haematoxyline/eosin stain and 450 magnification power. Results: Histological examination of the liver’s gross sections obtained from this work demonstrated the degeneration and necrosis in the liver of juvenile rats treated with doses of ciprofloxacin (25 and 50 mg kg⁻¹) compared to control animals. Moreover, there were nephrosis, cell swelling of the epithelial lining tubules in group of animals treated with 25 mg kg⁻¹ ciprofloxacin; and coagulative necrosis of epithelial lining cells of renal tubules were observed in animals treated with 50 mg kg⁻¹ ciprofloxacin compared to control groups. Conclusion: The results of this study showed that the selected therapeutic doses of ciprofloxacin utilized in this study caused changes in the histopathology of the liver and kidney of juvenile rats.

Key words: Fluoroquinolones, healthy rodent, hepato-renal injury

INTRODUCTION

Ciprofloxacin possesses excellent in vitro and in vivo antibacterial activities against most aerobic and facultative anaerobic bacteria, including Enterobacteriaceae (Shah et al., 1987; Davis et al., 1996). They target bacterial DNA gyrase and topoisomerase IV (Laurence and Parker, 2008).

In pediatric patients, growing adolescents and during pregnancy, ciprofloxacin is contraindicated due to its joint toxicity but it has limited therapeutic indications, it is active against P. aeruginosa-induced respiratory infections in children with cystic fibrosis, chronic suppurative otitis media or malignant otitis externa; acute or chronic osteomyelitis or osteochondritis; multidrug-resistant Gram-negative bacterial infections especially in immuno compromised hosts, bacterial septicemia or meningitis cases for which the causative organism is resistant to other approved agents; exposure to aerosolized Bacillus anthracis; serious infections in the children with life-threatening allergy to alternative antibacterial agents and multidrug-resistant mycobacterial infections (Saracoglu et al., 2009).

It’s toxicity concerning other organs needs to be clarified. Thus, this study was designed to study the possible histological changes induced by two therapeutic doses of ciprofloxacin in liver and kidney of juvenile rats.

MATERIALS AND METHODS

Animals: Eighteenth (4-week) healthy albino rats of both sexes weighing approximately 30 g were utilized in the study. They were obtained from the Animal Laboratory House of the College of Pharmacy, University of Baghdad. The animals were fed standard diet ad libitum and were free access to tap water. They were divided into three groups of 6 animals each as follows: group-I Juvenile rats were received 25 IU i.p. saline solution two times daily at twelve-hour intervals for one week, this group served as control; group II- Juvenile rats were injected intraperitoneally (IP or i.p.) with 25 mg kg⁻¹ ciprofloxacin two times daily at twelve-hour intervals for one week and group III-Juvenile rats injected i.p. with 50 mg kg⁻¹ ciprofloxacin two times daily at twelve-hour intervals for one week.
At the end of the treatment period, the livers and kidneys were dissected and stored in formaldehyde 10% until they were utilized for histological examination under light microscope utilizing haematoxyline/eosin stain and 450 magnification power (Junqueira et al., 1995).

RESULTS

Examination of histological sections of juvenile rats' livers received 25 mg kg⁻¹ ciprofloxacin (Fig. 2), the results showed the presence of vacuolar degeneration and multiple hepatocytes undergoing single-cell necrosis. In juvenile rats treated with 50 mg kg⁻¹ ciprofloxacin, the results showed that there were coagulative necrosis of the centrilobular hepatocytes, sinusoidal dilation and many of the hepatocytes undergoing atrophy (Fig. 3) compared to control juvenile liver sections (Fig. 1).

The histological sections of juvenile kidneys' rats received 25 mg kg⁻¹ ciprofloxacin (Fig. 5), the results showed that there were cell swelling of the epithelial lining of renal tubules. There were coagulative necrosis were observed in groups of juvenile rats kidneys received 50 mg kg⁻¹ ciprofloxacin (Fig. 6) compared to kidneys of juvenile rats (Fig. 4).

Fig. 1: Section showing normal hepatocyte of juvenile rats

Fig. 2: Hepatocytes of rats aged 37 days, administered 25 mg kg⁻¹ ciprofloxacin i.p. for 7 days, demonstrates vacuolar degeneration (blue arrow) and single cell necrosis (red arrow) (H and E/450 X)

Fig. 3: Rat's hepatocytes aged 37 days, administered 50 mg kg⁻¹ ciprofloxacin i.p. for 7 days, demonstrates coagulative necrosis of centrilobular hepatocytes (violet arrow), sinusoidal dilation (green arrow) and hepatocytes atrophy (black arrow) (H and E/450 X)

Fig. 4: Section showing normal kidney tissue cells of juvenile rats
inhibitory effects in ethanol and carbon tetrachloride-induced models of hepatic injury (Minuk et al., 1995; Zhang et al., 1996).

The results obtained from the present study showed that administration of the therapeutic doses (25 mg and 50 mg kg^{-1} ciprofloxacin) induced various changes in liver of juvenile rats. These changes varied from vascular degeneration, multiple hepatocytes undergoing single-cell necrosis, coagulative necrosis with many of the hepatocytes undergoing atrophy (Fig. 2, 3).

In addition, the kidney of the juvenile rats showed cell swelling of the epithelial lining of renal tubules and coagulative necrosis (Fig. 5, 6).

The quinolones are very important antimicrobials because they cover a wide variety of aerobic organisms.

Although ciprofloxacin was generally considered nontoxic by several authors (Baykal et al., 2005) but the results obtained from this work were consistent with those performed by Ismail (2006), where, the drug caused histopathological alteration in different body organs of rats.

Liver damage was previously observed by several studies following ciprofloxacin treatment (Bataille et al., 2002; Goetz et al., 2003; Zimpfer et al., 2004), such cases revealed extensive hepatocellular necrosis and mixed inflammatory infiltrate in livers of patients.

The pathomechanisms of ciprofloxacin-related liver and kidney injury are still unclear as reported by Zimpfer et al. (2004).

Formation of free radicals by ciprofloxacin in the microsomal system might provide an explanation to the mechanisms of adverse effects observed after administration of this drug (Xie et al., 2003).

CONCLUSION

According to the results obtained from this study that clearly demonstrated changes in the histopathological pattern of liver and kidney of juvenile rats treated with therapeutic doses of IP injection of ciprofloxacin. Thus, another limitation for the use of this drug in pediatric patients and further studies are required to support these findings.

REFERENCES


