Original Articles

# Effects of Ciprofloxacin on Foetal Hepatocytes

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## Introduction

Early clinical pharmacology studies of oral and parenteral form of ciprofloxacin were begun shortly after the drug was discovered in Germany in 1982. The clinical trials programme for the efficacy of intravenous ciprofloxacin began in the USA in late 1985 and expanded throughout 1986, 1987 and April 1988. A new drug application for intravenous ciprofloxacin was submitted to the United States Food and Drug Administration.1 Ciprofloxacin is a fluorinated quinolone that is broad spectrum antibacterial agent. It is recommended for the treatment of infections caused by susceptible bacteria in lower respiratory tract, skin, bone and joint, urinary tract infections, and infectious diarrhoea.2 Although ciprofloxacin is contra-indicated in pregnancy and children3 but the drug is used unchecked, which may be prohibited by the government under rules.
This study was done to evaluate the effects of ciprofloxacin administration during gestation on morphology of liver parenchyma in prenatal laboratory animals, i.e., foetuses of Wistar albino rats.

## Patients and Methods

Eighty rat foetuses were used in this study. They were obtained from 20 pregnant female Wistar albino rats, 16-18 weeks of age, weighing 140-200 grams, looking active and healthy, taken from the Animal House of BMSI, Jinnah Postgraduate Medical Centre, Karachi. These female Wistar albino rats were mated with fertile males of same strain allowing one male rat with two female rats in one cage.4 On next morning, the female rats were examined for sign of mating in the form of blood stained vagina or a vaginal plug (a mucoid greenish white material). Presence of any of these signs was considered as day-1 of pregnancy.5 The normal gestational duration in albino rat ranged between 21-23 days.6
Twenty pregnant rats were divided into two equal groups each comprising 10 animals. Group-A were given injection Ciprofloxacin (developed in Bayer Research Laboratories AG, Germany) at a dose of 20 mg/kg body weight7 intraperitoneally on day-8 of pregnancy (twice daily) from day-8 to day-18 of gestation, as organogenesis starts from day-8 of pregnancy. Group B were given normal saline at a dose of 3 ml/kg body weight intraperitoneally twice daily from day-8 to day-18 of gestation.8
Intact rat foetuses were obtained on day-18 of gestation by killing their mothers with cervical dislocation (the pregnant female rat in each group) from both experimental and control groups. Total 80 specimens were then randomly selected for study (40 each from group-A and B). The sex of these offspring was omitted.
All foetuses were then sacrificed on day-18 of gestation by giving deep ether anaesthesia and were operated to obtain their liver which were weighed, fixed in 10% non-buffered formalin, embedded in paraplast and 3µm thick sections were cut on rotary microtome. The sections were stained with H&E. The histomorphological features of liver in both groups were observed. Micrometry was done and the data was subjected to statistical analysis. Students 't' test was employed to see the significance of the results.9

## Results

The ciprofloxacin administered in 10 pregnant Wistar albino rats daily from gestational day-8 to day-18 of gestation after confirming pregnancy by staining vaginal smear with H&E, to observe the pressure of spermatozoa (Figure 1).

The mean value of liver weight of foetuses in groups-A and B was recorded 0.189 ± 0.003 G and 0.281 ± 0.002 G respectively as shown in Table. A highly significant decrease in liver weight in group-A was observed when difference of mean was compared with control group-B ($P<0.001$).

The histological structures in the liver of group-A animals demonstrated, the hepatocytes to be closely packed with intact bile canaliculi. The sinusoids appeared moderately dilated. The shape of hepatic lobules appeared almost hexagonal, the hepatocytes were mild to moderately large polyhedral in shape with small rounded nuclei. Many hepatocytes showed pyknotic nucleus while few showed distinctly visible nucleoli as shown in Figure 2, when compared with group-B. No change in liver parenchyma was demonstrated.

The lymphocytic infiltration and degenerating cells were observed to be markedly increased in zone-II and III in group-A, as shown in Figure 2. The control group-B showed normal appearance of lymphocytic infiltration and absence of degenerating cells, as shown in Figure 3.

Mean hepatocyte count, hepatic cell size and their nuclear size

The mean value of viable hepatocyte count per field in groups-A and B was recorded as 286.75±1.2 and 423.95±1.2 respectively, as shown in Table. A highly significant decrease in hepatocyte number was observed when difference of mean was compared with control group-B ($P<0.001$).

The mean value of hepatocyte size per field in groups A and B was recorded as 10.60±0.17µm and 9.012±0.31µm respectively, as shown in Table. A highly significant increase in size was observed when the difference of mean was compared with control group-B ($P<0.001$).

The mean value of hepatic nuclear size per field in groups A and B was recorded as 4.223±0.1µm and 5.068±0.12µm respectively, as shown in Table. A highly significant decrease in nuclear size was observed when the difference of mean was compared with control group-B ($P<0.001$).

## Discussion

In the present study, we observed the effects of ciprofloxacin when administered during gestation on morphology of liver parenchyma in Wistar albino rat foetuses.

The microscopic examination revealed a decrease hepatic cell count per unit area, increased hepatic cell size with decreased nuclear size. These changes are in accordance with the studies by Hooper et al10, Grassmick et al11 and George et al.12 In these studies the investigators found the common lesion in the liver, i.e., hepatic cellular necrosis on the basis of laboratory analysis. However, none of these workers has counted the cells per unit area, size of hepatocytes, and their nuclei. Therefore, our observations could not be compared with previous studies.

The absolute liver weight in group-A showed a highly significant decrease which could be attributed to the necrosis of cells and resorption of necrosed cells. Our results are in agreement with Minuk et al13 who found that the quinolone antibiotics inhibit eukaryotic as well as prokaryotic cell growth and protein synthesis by interfering with DNA and RNA replication.

Regarding number of hepatocytes, a marked decreased cell per unit area occurred while size of hepatic cells increased with decreased nuclear size which may be attributed to fat deposition and interference with RNA, DNA and protein synthesis in response to toxic effects of ciprofloxacin. The necrosed cells were found in zone-II and III accompanying marked infiltration of inflammatory cells.

Our observations correlate with the observations of George et al12 who found that in cipro-floxacin treated liver, there was marked congestion of sinusoids with same midzonal and centrolobular necrosis and leucocytic infiltration.

References

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