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Hepatobilliary Toxicity of Ciprofloxacin (An Antibiotic) In Albino Rats

[1]Agbafor K. N., [1]Offor C.E and [2]Obiudu I.K.
[1]*Department of Biochemistry, Ebonyi State University, Abakaliki, Nigeria.*
[2]*Department of Chemical Sciences, Godfrey Okoye University, Enugu, Nigeria.*

Abstract: *Various antibiotics are known to elicit side effects which may include toxicity to different body organs. Hence, the present study investigated the effect of ciprofloxacin (a wide-spectrum antibiotic) on hepatobilliary system in albino rats. Twenty (20) adult male albino rats were divided into five groups of four rats each. Groups A, B, C and D were treated orally with 3.57, 7.14, 14.28 and 21.42mg/kg body weights of ciprofloxacin solution respectively for seven consecutive days, while group E served as the control. The serum activity of Alanine aminotransferase (ALT), Aspartate aminotransferase (AST) and Alkaline phosphatase (ALP) were used to access the hepatotoxicity of the drug. There was a decrease in physical activities, feed and water intake in the treated groups, while the control showed no noticeable changes. The average body weight of the treated animals decreased, while that of the control increased. The total protein concentration of treated groups was not significantly different (P>0.05) from that of the control. The activities of the enzymes (AST, ALT and ALP) in the serum of the albino rats in the test groups were found to be significantly higher (P<0.05) from that of the control. This effect was found to vary among the doses. These findings are indicative that ciprofloxacin (an antibiotic) may be toxic to the cells of the hepatobilliary system.*

Keywords: *hepatobilliary, hepatotoxicity, ciprofloxacin and albino rats.*

I. Introduction

Antibiotics are substances derived from microorganisms that inhibits or destroy the growth of other micro-organisms. Antibiotics are used to treat infections caused by organisms that are sensitive to them, usually bacterial or fungi. They alter the normal microbial content of the body (example, in the lungs, bladder and intestine) by destroying one or more groups of harmless or beneficial organisms, which may result in infection (such as thrush in women) due to over growth of resistance organisms. These side effects are most likely to occur with broad-spectrum (those active against a wide variety of organisms) (Dorland, 2010).

Resistance may develop by the micro-organisms being treated; for example, through correct dosage or over prescription. Antibiotics should not be used to treat minor infections which will clear up unaided. Some antibiotics may cause allergic reactions (Dorland, 2010). With advances in the medicinal chemistry, most of today's antibacterial chemically is semi-synthetic modifications of various natural compounds (Von, 2006). These include the beta-lactamantibacterial, which include the penicillins. Compounds that are still isolated from living organisms are the aminoglycoside, whereas, other antibacterial, for example, the quinolones, the

oxazolidinones and the sulfonamides are produced solely by chemical synthesis (Lindblad, 2008).

Antibiotics are commonly classified based on their mechanisms of action, chemical structure or spectrum of activity. Most target bacterial functions or growth process. Those that target the bacterial cell wall (penicilins and cephalosporins) or the cell mernbrane(polymixins) or interfere with essential bacterial enzymes (quinolones and sulfonamides) have bacterial activities. Those that target protein synthesis (aminoglycosides, tetracyclins and macrolides) are usually bacteriostatic (Calderon and Sabundayo,2007).

Fluoroquinolones are synthetic antibacterial agents that are used in the treatment of a variety of bacterial infections. The first quinolone, nalidixic acid was introduced in 1962 (Oliphant and Green, 2002). Flouroquinolones induces their action by inhibiting DNA synthesis through promoting cleavage of bacterial DNA in the DNA-enzyme complexes of DNA gyrase and type IV topoisomerase, resulting in rapid bacterial death (Iannini *et al*., 2001).

Like other quinolones, ciprofloxacin which contains ciprofloxacin hydrochloride induces hepatotoxicity, cholestatic jaundice, elevated level of total bilirubin, direct bilirubin, alkaline phosphatase, aspartate aminotransferase and prolonged prothrombin time (Hirch and Lundquist (2009). Wayers *et al*. (2002) reported

increased in lipid hydroperioxide (COOH) in the liver of mice exposed to ciprofloaxacin. Increased in lipid hydroperioxide (COOH) is a marker of ciprofloxacin induced stress in the liver. On the contrary other researchers reported the safety of ciprofloxacin on the hepatic system. One of such reports is the ability of ciprofloxacin to reverse inhibitory effects of ethanol and carbon tetrachloride on hepatic injury (Minuk *et al.,* 2005).

AIMS/OBJECTIVES

The aim of this research was to evaluate the hepatobilliary toxicity of ciprofloxacin (an antibiotic) in albino rats using Aspartate aminotransferase (AST), Alanine aminotransferase (ALT) and Alkaline phosphatase (ALP) activity as an indicator after treating the rats with the drug.

II. Materials And Methods

COLLECTION OF ALBINO RATS

Twenty adult male albino rats were collected from the Department of Veterinary, University of Nigeria, Nsukka, using steel cages and transferred to Ebonyi State University Animal House in Presco Campus, Abakaliki, Nigeria.

COLLECTION OF CIPROFLOXACIN TABLET

The ciprofloxacin tablets (500mg) were bought from Godal Pharmacy in Abakaliki, Ebonyi State.

PREPARATION OF CIPROFLOXACIN TABLET

Fourty tablets of ciprofloxacin weighing 2000mg were dissolved in 500ml of distilled water inside a beaker and stirred properly to form a solution. 40ml of the drug solution was measured and diluted with 400ml of distilled water, the concentration was obtained (4mg/ml). The drug solution was poured into a container and stored in refrigerator.

MEASUREMENT OF WEIGHT

The weight of the rats was measured daily, using a weighing balance and this was also used to determine the actual volume of the prepared solution of ciprofloxacin to be administered.

ANIMAL HANDLING AND TREATMENTS

The albino rats were divided into five groups of four rats each. The animals were fed with grower's mash and water on daily basis for seven days for acclimatization. The ciprofloxacin solution was administered to the animals using a 2ml syringe in accordance to their body weight. The animals in group E were the control and they were given distilled water while those in groups A, B, C and D were given 3.57, 7.14, 14.28, and 21.42mg/kg respectively for seven consecutive days.

COLLECTION OF BLOOD FROM ANIMALS

After seven days of administration, the animals were fasted overnight and blood samples were collected from them via cardiac puncture with mild anesthesia (diethylether). Blood sample was collected with a sterile bottle. The blood samples were taken to the laboratory where they were centrifuged and serum was removed for analysis.

DETERMINATION OF LIVER ENZYMES

Aspartate aminotransferase (AST), Alanine aminotransferase (ALT) and alkaline phosphatase (ALP) were determined by method described by Reitman and Frankel (1957).

III. Results

PHYSICAL OBSERVATIONS

There was a decrease in physical activities, feed and water intake in the animals treated with ciprofloxacin while the control group showed no noticeable changes.

AVERAGE WEIGHT (g) OF ANIMALS DURING SEVEN DAYS OF CIPROFLOXACIN SOLUTION ADMINISTRATION

There was a decrease in the average body weights of the treated groups (A, B, C and D) when compared with that of the control group E rats.

Table 1: CHANGES IN BODY WEIGHT

The average body weight of the groups

DOA	GROUP A	GROUP B	GROUP C	GROUP D	GROUP E
1	130.75±8.30	130.50±7.37	100.50±7.37	77.50±5.00	78.75±2.50
2	130.50±8.23	125.75±4.92	97.50±9.57	73.50±5.80	87.50±5.00
3	123.75±4.22	122.50±5.00	97.50±9.57	68.75±3.95	95.25±5.77
4	120.50±8.23	107.50±9.57	87.50±9.57	66.25±5.56	97.50±5.00
5	119.75±0.50	104.50±10.00	79.50±1.00	64.75±2.87	102.50±6.46
6	107.50±9.57	103.50±9.98	77.50±5.00	57.50±4.86	110.75±8.17
7	105.75±9.50	97.50±9.45	70.75±7.37	53.75±3.95	112.50±5.00

Values = Mean ± Standard Deviation

DOA = Day of Administration

AVERAGE PROTEIN CONCENTRATION, ENZYME ACTIVITY AND SPECIFIC ENZYME ACTIVITY FOR ALP

The protein concentration of the treated groups did not differ significantly (P>0.05), from that of the control. There was a significant increase (P<0.05) in the specific enzyme activity of the test groups when compared to the control.

Table 2: Changes in average enzyme activities, protein concentration and specific enzyme activity for ALP after seven days of drug administration.

ANIMAL GROUP	AVERAGE TOTAL PROTEIN (mg/I)	AVERAGE ACTIVITY (u/1)	SPECIFIC ENZYME ACTIVITY (u/I/mg/1)
A	0.48 ± 0.08^{c}	17.37 ± 0.88^{c}	286.71 ± 7.13^{b}
B	0.49 ± 0.07^{b}	22.41 ± 1.43^{b}	284.48 ± 7.55^{b}
C	0.44 ± 0.01^{a}	27.28 ± 2.08^{a}	408.86 ± 5.78^{a}
D	0.40 ± 0.06^{b}	34.31 ± 1.23^{a}	538.82 ± 9.02^{c}
E	0.63 ± 0.04^{a}	12.00 ± 1.20^{b}	164.04 ± 5.83^{a}

All values are mean ± standard deviation, n = 4

Values within the same column having different superscript varied significantly (P<0.05)

AVERAGE PROTEIN CONCENTRATION (mg/ml), ENZYME ACTIVITY (u/1 PROTEIN) FOR ALT

Table 3: Showed the result of protein concentration of enzyme activities of alkaline phosphatase (ALT). The protein concentration of the test groups did not differ significantly (P>0.05), from that of the control. There was a significant difference (P<0.05) between the specific enzyme activity of the test groups from the control.

Table 3: Changes in average enzyme activities, protein concentration and specific enzyme activity for ALT after seven days of drug administration.

ANIMAL GROUP	AVERAGE TOTAL PROTEIN (mg/1)	AVERAGE ACTIVITY (u/1)	SPECIFIC ENZYME ACTIVITY (u/I/mg/1)
A	0.48 ± 0.08^{c}	135.42 ± 3.09^{a}	37.12 ± 7.31^{c}
B	0.49 ± 0.07^{b}	161.76 ± 6.73^{b}	47.09 ± 10.01^{a}
C	0.44 ± 0.01^{a}	177.81 ± 3.29^{a}	62.70 ± 4.40^{b}
D	0.40 ± 0.06^{b}	206.20 ± 9.78^{c}	88.37 ± 11.10^{a}
E	$0.63\pm O.04^{a}$	103.04 ± 6.50^{b}	19.17 ± 2.56^{b}

All values are mean ± standard deviation, n = 4

Values within the same column having different superscript varied significantly (P<0.05)

AVERAGE PROTEIN CONCENTRATION (mg/ml), ENZYME ACTIVITY (u/I PROTEIN) FOR AST

Table 4: Showed the result of protein concentration of enzyme activities of aspartate aminotransferase (AST). The protein concentration of the test groups did not differ significantly (P>0.05), from that of the control. There was a significant difference (P<0.05) between the specific enzyme activity of the test groups from the control.

Table 4: Changes in average enzyme activities, protein concentration and specific enzyme activity for AST after seven days of drug administration.

ANIMAL GROUP	AVERAGE TOTAL PROTEIN (mg/1)	AVERAGE ACTIVITY (u/1)	SPECIFIC ENZYME ACTIVITY (u/l/mg/1)
A	0.48 ± 0.08^{c}	27.68 ± 1.62^{b}	59.19 ± 4.19^{a}
B	0.49 ± 0.07^{b}	31.19 ± 1.87^{b}	65.30 ± 5.10^{a}
C	0.44 ± 0.01^{a}	40.54 ± 0.87^{a}	93.20 ± 7.04^{b}
D	0.40 ± 0.06^{b}	49.91 ± 3.07^{c}	129.93 ± 9.93^{c}
E	$0.63\pm O.04^{a}$	21.23 ± 1.33^{b}	33.91 ± 3.84^{a}

AH values are mean ± standard deviation, n = 4

Values within the same column having different superscript varied significantly (P<0.05).

IV. Discussion

The actual biochemical mechanism, responsible for the observed decrease in physical activities, water intake and feed is not clear. However it may be due to some chemical constituents of the administered drug (ciprofloxacin). The work by James *et al.*, (2001), observed that some of the antibiotics influenced various body processes such as appetite and overall body metabolism of the animals. The influence may be as a result of the stimulation/inhibition of the cell metabolic enzymes.

The body weight of the animals treated with drug sample significantly decreased (P>0.05) while the control increased during the days of administration. The actual mechanism to support this loss of weight can be a suggestion for further studies (Young, 2007).

The protein analysis carried out on the serum revealed an insignificant difference (P>0.05) in protein concentration between the test groups and the control. This suggests that the chemical constituents of the drug at the doses administered may not influence the rate of protein synthesis and degradation. This report has also been presented by Douglas et al., (2010) when the albino rats were treated with ofloxacin, an antibiotic drug.

V. Conclusion

Based on the results of this research, the use of ciprofloxacin tablet may lead to hepatobilliary toxicity especially when taken at higher dose. This is indicated by the rising activities of the enzymes AST, ALT and ALP as a result of the malfunction of the sites of their production. However, more investigations are required to establish the actual mechanisms involved.

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