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Effect of combination of Ziprasidone with Carbamazepine on liver of Wistar albino rats

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ABSTRACT

The present study was designed to explore hepatotoxic effects and pharmacodynamic profile of Ziprasidone when given in combination with Carbamazepine. In this study Wistar albino rats (150-200 gm) were subjected to two week treatment. Animals were divided into four groups (n=6). Group I (Control), Group II (Ziprasidone 10 mg/kg p.o alone), Group IIIa Ziprasidone with Carbamazepine (20 mg/kg p.o), Group IIIb Ziprasidone with Carbamazepine. In group IIIA animals were treated with carbamazepine for first four days followed by ziprasidone from day 5^{th} to 14^{th} day, in group IIIB animals were treated with placebo for first four days followed by ziprasidone from day 5^{th} to 12^{th} day and on 13^{th} and 14^{th} day carbamazepine was administered in a dose of (20 mg/kg p.o). Thus the changes in hepatic function was assessed by determining serum levels of biochemical parameters like alkaline phosphate, alanine transaminase, aspartate transaminase, other parameters such as atherogeic index, lipid profile and ECG analysis were also determined. The serum biochemical estimation revealed that there was significant elevation of ALT, AST and ALP level only in Ziprasone treated group. Carbamazepine when given along with the ziprasidone do not potentiate the liver damaging effect. The findings of our study indicate that there was not significant liver damage when Ziprasidone was given in combination with Carbamazepine.

Keywords: Cytochrome3A4, Ziprasidone, Carbamazepine, Liver

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INTRODUCTION

Bipolar disorder, also known as manic-depressive illness, is a brain disorder that causes unusual shift in a person's mood, energy and ability to function. It is a leading problem in the world where there is a swing of mood between mania and depression in patients. [1] These patients are receiving atypical antipsychotics such as olanzepine, respiridone and ziprasidone with mood stabilizers to treat maniac disorders. Mood stabilizers such as carbamazepine, oxcarbamazepine, valproate and lithium are used in chronic treatment. Maintenance therapy of atypical antipsychotics together with mood stabilizer is required for effective treatment of bipolar disorder. [2-6] Atypical antipsychotics are involved in asymptomatic increase in liver enzyme. [7, 8, 9] Antipsychotics may differ in their tolerability, especially in the risk of including weight gain, extrapyramidal side effects and QTc prolongation. [10, 11] Obesity and metabolic syndrome with increased risk of cardiovascular disease and type II diabetes are significant problems for patients receiving antipsychotics. [12-16] Ziprasidone induced metabolic disturbance alone and with combination of carbamazepine is one of the greatest concerns of current study. Liver is an important organ for metabolism of all xenobiotics. Ziprasidone is metabolized by cytochrome CYP3A4 enzyme in liver and carbamzepine is also metabolized by same. [17] Carbamazepine is potent inducer of CYP3A4. [18-20] Literature review revealed that co-administration of carbamazepine and ziprasidone has greater pharmacokinetic interaction and carbamazepine has increased ziprasidone metabolism reducing 33% of plasma ziprasidone concentration. [20] These antipsychotic drugs when co-prescribed with other CNS acting drugs which are either inducers or inhibitors of CYP3A4 may lead to hepatotoxicity. [21] In this paper we have evaluated the pharmacodynamic and CYP3A4 interaction of ziprasidone and carbamazepine.

MATERIALS AND METHODS:

Animals:

Wistar albino rat weighing between 150 to 220 gm of either sex were selected for the experiment. Animals were procured from Animal house, Smt Kashibai Navale College of Pharmacy, Pune, India. They were housed in polypropylene cages with not more than six animals per cage and maintained under standard conditions (12 h light/12 h dark cycle; 25 ± 3˚C; 35–60% humidity). Animals were allowed free access to standard dry pellet diet and water ad libitum. The rats were acclimatized to laboratory condition for 7 days before commencement of experiment. The study was approved by Institutional Animal Ethical Committee (IAEC).

Doses:

Dose of ziprasidone and carbamazepine for animal was selected on the basis of previous literature review. Thus, Ziprasidone (10 mg/kg p.o) and carbamazepine (20 mg/kg p.o) was given once a day.

Treatments:

Animals were divided into four groups (n=6). Each group was subjected for two week treatment with respective drug.

Group I served as normal control received saline (1ml/kg p.o) for two weeks.
Group II served as ziprasidone group was administered ziprasidone (10 mg/kg p.o) for 14 days.
Group III was divided into two part for placebo controlled parallel study.
Group IIIA Z+C (1) received carbamazepine (20 mg/kg p.o) for first four days, then from day 5^{th} to 14^{th} ziprasidone was administered 10 mg/kg p.o.
Group IIIB Z+C (2) received placebo 1ml/kg p.o for first four days, then from day 5^{th} to 12^{th} ziprasidone was administered (10 mg/kg p.o) and from day 13^{th} -day 14^{th} carbamazepine was administered (20 mg/kg p.o). [21]

Rats were subjected to ECG analysis after two weeks treatment for determination of QT prolongation. After 14 days of treatment, rats were anaesthetized and blood was collected from the retro-orbital sinus, and the serum was separated for assessment of different enzyme activities. The rats were then sacrificed by cervical dislocation the liver was carefully dissected, cleaned of extraneous tissue. Liver tissue samples were fixed in 10 % formalin for pathological examination.

Estimation of liver marker enzymes and Lipid Profile:

AST, ALT and ALP were estimated for hepatic damage. [22, 23] Serum total cholesterol, Serum triglycerides, HDL-C, LDL-C and VLDL-C were estimated for their metabolic influence by this drug-drug interaction.

Estimation of QT and QTc prolongation:

Lead II ECG analysis was performed on animals for determination of their influence on QT prolongation.

Estimation of Liver weight, Liver volume, Liver Index and Atherogenic Index:

After 2 week treatment animals were sacrificed and liver was isolated and scar tissues were removed and cleaned properly. They were weighed and volume was measured by volume displacement method. The liver index was calculated according to the formula: (Rats liver weight/Rats weight) *100%. Atherogenic Index was calculated according to the formula: Log (Serum triglyceride/ HDL-C).

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Histopathology of liver:

Portions of liver were preserved in 10% neutral buffered formalin for 24 hr. Specimens were dehydrated and embedded in paraffin, sectioned at 6µm and stained with hematoxylin and eosin (H&E) for histopathological examination. [24]

Statistical analysis:

Data were analyzed statistically by one-way ANOVA, followed by Dunnet test against control. The results were considered statistically significant for $p < 0.05$.

RESULTS

Effect on liver biomarker enzymes:

Significant ($p<0.001$) increase in AST, ALT and ALP was observed in ziprasidone treated group when compared with control. While rise in these levels was not significant in group IIIA and group IIIB when compared against ziprasidone treated group. (Table 1)

TABLE 1: Effect on AST, ALT and ALP enzymes in Ziprasidone and Z+C (1) and Z+C (2) treated rat.

Groups	AST	ALT	ALP
Control	48.83 ± 0.5426	6.000 ± 0.9661	128.3 ± 9.408
Ziprasidone Group	274.5 ± 23.24***	65.17 ± 16.74***	170.2 ± 6.750
Z+C (1) Group	231.5 ± 23.47**	65.83 ± 2.762***	241.3 ± 30.45**
Z+C (2) Group	281.2 ± 24.37***	75.17 ± 6.290***	176.3 ± 19.61

Values are mean ± SEM; n=6. Values are statistically significant at *P<0.05 as compared with control

TABLE 2: Effect on Total cholesterol, Serum triglycerides, HDL-C, LDL-C and VLDL-C level in Ziprasidone and Z+C (1) and Z+C (2) treated rat.

Groups	TOTAL CHOLESTEROL	SERUM TRIGLYCERIDES	HDL	LDL	VLDL
Control	53.17 ± 4.400	61.67 ± 4.951	33.00 ± 2.221	7.833 ± 2.041	12.00 ± 1.015
Ziprasidone	45.83 ± 5.275	62.50 ± 3.845	16.50 ± 3.871***	16.83 ± 1.857	12.50 ± 0.7690
Z+C (1) Group	35.00 ± 3.266*	90.67 ± 7.641*$^{\#}$	7.200 ± 0.9592***	11.40 ± 2.566	16.40 ± 2.418
Z+C (2) Group	32.50 ± 3.334**	59.17 ± 5.205	13.33 ± 1.022***	7.333 ± 1.602	11.83 ± 1.041

Values are mean ± SEM; n=6. Values are statistically significant at *P<0.05 as compared with control, $^{\#}P$<0.05 as compared with ziprasidone

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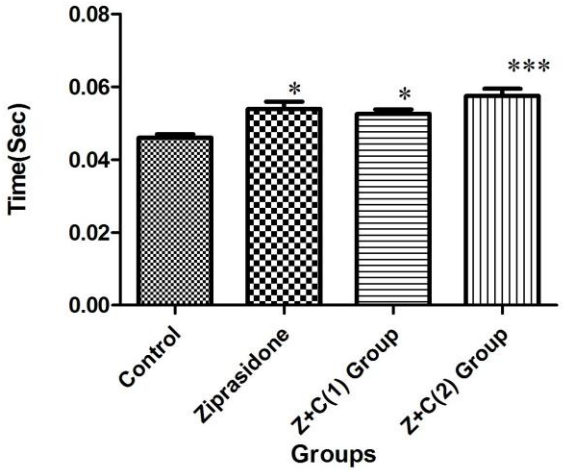
Effect on Lipid Profile:

Increased level of serum triglycerides, LDL-C and VLDL-C in ziprasidone treated group was found significant ($p<0.001$) when compared with control and significant ($p<0.05$) increase in serum triglycerides level in group IIIA was also observed. Level of HDL-C was significantly decreased ($p<0.001$) in group IIIA and group IIIB when compared with control. (Table 2)

Effect on QT and QTc interval changes:

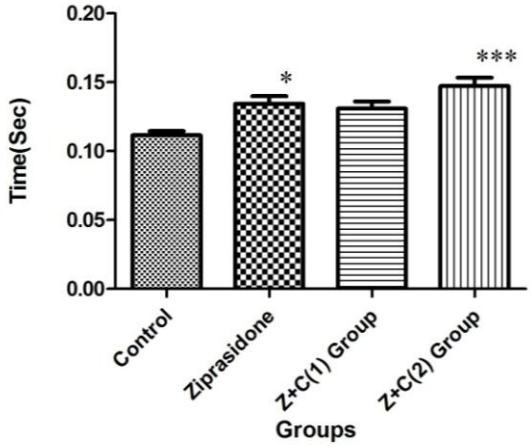
QT and QTc interval significantly increased ($p<0.05$) in ziprasidone treated group, group IIIA and group IIIB when compared with control. While no any significant increase was found in group IIIA and group IIIB when compared with ziprasidone treated group. (Figure 1 and 2)

Figure1: Effect on QT interval in ziprasidone, Z+C(1) and Z+C(2) group



Values expressed are mean ± SEM n=6 *P<0.05 as compared with control

Figure 2: Effect on QTc interval in ziprasidone, Z+C(1) and Z+C(2) group



Values expressed are mean ± SEM n=6 *P<0.05 as compared with control

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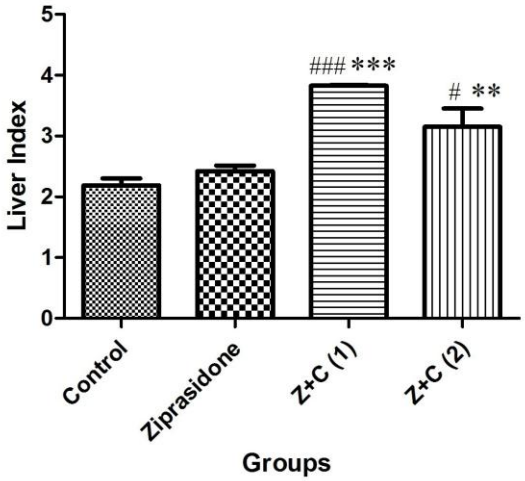
Effect of treatment on liver index and atherogenic index:

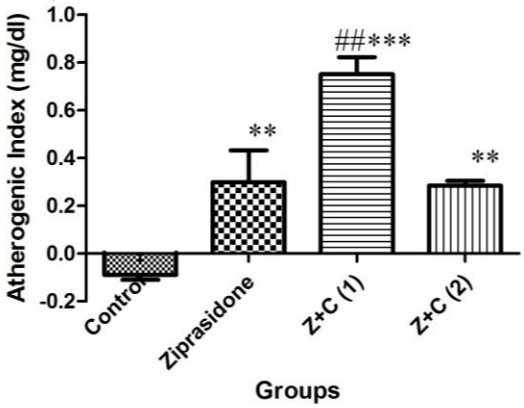
Liver weight and liver volume was increased in ziprasidone treated group, group IIIA and group IIIB. Liver index was significantly ($p<0.001$) increased in group IIIA and group IIIB as compared to ziprasidone treated group (Figure 3). Atherogenic index was significantly increased ($p<0.001$) in ziprasidone treated group, group IIIA and group IIIB as compared to control and significant rise in group IIIA when compared to ziprasidone treated group was observed (Figure 4).

Figure 3: Effect on Liver Index in Ziprasidone, Z+C(1), Z+C(2) treated group



Values expressed are mean ± SEM n=6 *P<0.05 as compared with control
#P<0.05 as compared with ziprasidone

Figere 4: Effect on Atherogenic Index in Ziprasidone, Z+C(1) and Z+C(2) treated Group



Values expressed are mean ± SEM n=6 *P<0.05 as compared with control
#P<0.05 as compared with ziprasidone

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DISCUSSION

Liver is an important organ for metabolism of various xenobiotics and toxins. Liver has majority of cytochrome enzymes in the endoplasmic reticulum which responsible of metabolism of exogenous compound. Among various cytochrome diverse families, CYP3A4 is an important enzyme involved in metabolism of many drugs. Different drugs which are metabolized by this enzyme can show clinically significant interaction. The present study aims to evaluate the possible clinical interaction between two drugs.viz ziprasidone and carbamazepine. Ziprasidone alone had increased levels of cytoplasmic enzymes (AST, ALT and ALP) when compared to control group which indicates the damage to the hepatocytes which is confirmed by histopathology. Increased serum triglyceride, LDL-C and VLDL-C was also found which supports the previous literature finding suggested increase in diabetes and obesity incidence.

Single and multiple treatment of carbamazepine in Ziprasidone pretreated animals do not produces any significant increase in serum ALT, AST and ALP levels. This indicates that the carbamazepine further does not potentiate the liver damaging effect of ziprasidone. The increased value of atherogenic index and level of triglycerides confirm the high risk of atherosclerosis in four day treated carbamazepine (Z+C (1)) group. Ziprasidone and carbamazepine have a property to prolong QT interval. The four day treatment of carbamazepine followed by eleven day treatment of ziprasidone does not prolong the QTc interval, thus no effect of carbamazepine on QTc interval was observed. As this study was conducted for short period of time the chronic treatment may worsen the drug metabolizing capacity of liver and electrical activity of heart. Our findings emphasis on prevention of ziprasidone treatment along with carbamazepine though this claim has to be confirm by carrying out human study.

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