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THE EFFECT OF OLANZAPINE TREATMENT ON SOME LIVER ENZYMES (AST, ALT & ALP) ON EXPERIMENTAL WISTER ALBINO RATS' MODELS.

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ABSTRACT
Many of atypical antipsychotic drugs are associated with adverse metabolic effects, including obesity and obesity related liver diseases. Olanzapine is one of the atypical antipsychotic drugs used to treat schizophrenia, acute manic episodes and recurrence of bipolar disorders. This study aimed to evaluate the effect of olanzapine treatment on some liver enzymes (AST, ALT & ALP) On Wister Albino rats' models. This study has been conducted at AlAhfad University, Omdurman, Khartoum state, Sudan from April to June 2016. A total of 24 Albino rats were divided into four groups: GroupI served as untreated control group while the other three groups were divided corresponding to different human doses, GroupII olanzapine-treated with oral dose of 0.5mg\kg\day group, GroupIII olanzapine-treated with oral dose of 1mg\kg\day and GroupIV olanzapine-treated at a dose of 2mg\kg\day orally, six rats in each group. Baseline, intermediate and terminal serum ALT, AST and ALP were assessed in all four groups. The means of ALT & AST levels demonstrated notable increase in GroupIII and GroupIV when compared with control group after four weeks as well as their respective base line values from four weeks within their groups. At GroupII, the lowest olanzapine dose, there was a significant increase if ALT but no significant changes in AST level till the end of the experiment. There were no significant changes in the mean levels of ALP throughout the experiment in the four groups. Olanzapine induced liver ALT and AST in experimental Wister Albino rats at different human doses.

KEYWORDS: Olanzapine, Atypical antipsychotic drug, NAFLD, NASH.

INTRODUCTION
The liver has a central and critical role in the metabolism, digestion, detoxification and elimination of substances such as drugs from the body.[1]

NAFLD is a spectrum of liver diseases ranging from the relatively benign steatosis to the most severe form as liver cancer.[2] Non alcoholic fatty liver disease(NAFLD) is also defined as accumulation of fats to greater than 5-10% of liver mass that recognized histologically by increasing of cytoplasmic fat.[1]

Olanzapine(OLZ), a theinobenzodiazepine derivative also known Zyprexa as its brand name is used Effectively to treat schizophrenia, acute manic episodes and the recurrence of bipolar disorders.[3] It's a serotonin and dopamine antagonist with antimuscarinic activity and also blocks histamine.[1]

Unfortunately, several atypical drugs including olanzapine are associated with various metabolic disturbances, such as weight gain and obesity. Along the numerous adverse effects of those metabolic disturbances is the obesity-related liver disease such as NAFLD and nonalcoholic steatohepatitis(NASH). It has been suggested that antipsychotics interact with the complex systems of neurotransmitters, neuropeptides and other modulators in brain neuronal circuits to aggravate disturbances in energy homeostasis and body weight.[5,6]

MATERIALS AND METHODS
This experimental study has been conducted at AlAhfad University, Omdurman, Khartoum state, Sudan at a period of two months from April to June 2016. A total of Twenty four adult healthy Wister albino rats (6 months age, weight of 150-250 g) from Alahfad university animal house, Sudan were selected to participate throughout the study. Rats were subjected to a controlled condition of temperature, diet and water intake. Rats was divided into four groups, each group contained six rats with Group I served as the untreated control rats while the three other groups were divided corresponding to different human doses.

Group II included rats that were treated with olanzapine at a dose of (0.5 mg/kg/day), Group III were received (1

mg/kg/day) and Group IV were subjected to (2mg/kg/day), each 5mg, 10 mg and 20mg dissolved in 5,10 and 20 ml of normal saline respectively. Rats received 1 ml\kg\day via nasogastric tube to ensure that no drug loss occurred.

Permissions were obtained to perform this study from University of Khartoum, Faculty of Medical Laboratory sciences, Khartoum, Sudan and AlAhfad University animal house, AlAhfad Unversity, Khartoum, Sudan.

Initial weight and AST, ALT and ALP were measured at the beginning of the experiment. Serial blood samples were drowning two weeks and four weeks apart from the initial samples. AST, ALT & ALP were measured using reagents from Spinreact Kitts reagents spectrophotometrically.

Statistical analysis was performed using the Microsoft Office Excel (Microsoft Office Excel for windows; 2007) and SPSS (SPSS for windows version 22).

RESULTS

The result showed that AST levels were significantly begin to rise after two weeks of 10mg/kg/day and 20mg/kg/day with levels being more increased four weeks from the initiation of the experiment. There was no significant increased of AST at a dose of 5mg/kg/day neither after two weeks nor after four weeks as shown in table (1).

The levels of ALT were significantly increased after two weeks of all Olanzapine treated rats with more notably went higher after four weeks as represented in table (2).

No statistically significant changes were observed in ALP levels in OLZ-treated groups when compared with their corresponding levels after two and four weeks of the experiment as revealed in table (3).

Table (1): Shows the mean values of AST in baseline with week-two and week-four in groupI, II, III and IV.

Groups	Mean of AST in Baseline	Mean ofAST at week two	Mean of AST at Week four
GroupI	128.6±42.5U\L	127.3±38.9U\L	127.8±46.2U\L
GroupII	114.8±12.8	123.5±14.7	164.8±26.5
GroupIII	118.2±20.2	128.9±16.7	186.3±17.6 *
GroupIV	136.3±14.8	148.9±16.7	212.4±14.8 *

* P < 0.05 indicates its significance.

Table (2): signifies the mean values of ALT in baseline, week-two & week-four in each group.

Groups	Mean of ALT in Baseline	Mean ofALT at week two	Mean of ALT at Week four
GroupI	25.5±8.1U\L	25.5±8.8U\L	25.0±11.3U\L
GroupII	34.3±17.4	39.7±14.7	49±2.15 *
GroupIII	26.6±7.7	29.4±6.6	58.7±13.0 *
GroupIV	38.7±10.7	42.5±10.5	62.1±4.4 *

* P < 0.05 indicates its significance.

Table (3): represents the mean values of ALP in baseline, week-two & week-four in the four groups.

Groups	Mean of ALP in Baseline	Mean ofALP at week two	Mean of ALP at Week four
GroupI	27.7±9.4U\L	26.8±10.2U\L	28.3±12.3U\L
GroupII	32.7±11.4U\L	33.5±13.8U\L	31.3±9.0U\L
GroupIII	38.5±17.3U\L	40.7±17.5U\L	40.5±24.7U\L
GroupIV	33.2±14.4U\L	33.8±16.4U\L	33.7±15.9U\L

DISCUSSION

The result showed that ALT and AST were significantly higher in groups treated with olanzapine when compared with control group (P<0.05). No statistically significant difference (P>0.05) was observed in ALP in OLZ-treated groups when compared with control group.

Interestingly there was a significant increase in both AST and ALT levels after four weeks of olanzapine treatment within the treated groups when compared with their initial corresponding levels except for Group II that show no significant increase of AST until the end of our experiment.

Also a notable rate of increase of both AST and ALT observed with the increase of olanzapine dose.

A study conducted in India by Parama Sengupta et al,2010, reported that serum ALT & AST were significantly higher in olanzapine-treated rats when compared with control group (AST, $P = 0.045$ and ALT, $P = 0.000$) which is agree with our results.

Another study was done in Louisville, KY by Robin H. Schmidt, 2013, found that there were a significant rise in AST and ALT levels in rats models after treatment with OLZ($P<0.05$) that was an agreement with our findings.

A study was done in Saudi Arabia by Rehmat Shah et al, showed no significant change in ALT and AST levels ($P> 0.05$) that disagreed with our results. That may be due to the differences in conditions that rats were subjected to. A restricted diet and the procedures followed on the administration of the drug might lead to different findings.

CONCLUSION

The study revealed that olanzapine induced liver enzymes particularly tramsaminases ALT & AST in experimental Wister albino rats models which might be similar to changes in human and the rate of their induction may increase corresponding to the increase of OLZ dose. Hence monitoring of liver function tests is highly recommended to patients who taking olanzapine and more attention should be paid in prescribing this drug.

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