

## EFFECTS OF SOME ANTIPSYCHOTIC DRUGS ON SOME LIVER ENZYMES IN RATS

Bello, B.A. and Labaran, I.

Department of Biochemistry, Kano University of Science and Technology Wudil, P.M.B 3244, Kano - Nigeria.

\*Corresponding author: [belloaminub@yahoo.com](mailto:belloaminub@yahoo.com), +2348065283248

### ABSTRACT

*This work investigated the effects of some antipsychotic drugs (Amitriptyline, Largatil and Regretol) on some liver enzymes; Aspartate aminotransferase (AST), Alanine amino transferase (ALT) and Alkaline Phosphatase (ALP) activities and weight of albino rats. During this study, forty (40) laboratory albino rats used were divided into four 4 groups of ten rats each. Group one served as control, Group two were given amitriptyline (35mg/kg/day), ten (10) were given largactil (500µg/kg/6hrs) while the Group four were given tegretol (35mg/kg/day), the drugs were administered for thirty (30) days. The mean serum, AST, ALT and ALP activities in rats treated with the three (3) drugs were found to be greater compared to that of control. The results showed significant increases ( $P < 0.05$ ) in the activities of enzymes in the rats administered with the three (3) drugs when compared with control. Weight gain was observed across all the groups which are less pronounced in the control.*

**KEYWORDS:** Antipsychotic drugs, liver enzymes, schizophrenia.

### INTRODUCTION

Antipsychotic drugs (APDs) are the first line pharmacotherapeutics for the treatment of schizophrenia. They are also widely used for the treatment of bipolar disorder and other Psychotic disorders. These drugs are important for treatment as well as prevention of relapse, suggesting that they may not only interfere with mechanisms that are responsible for the acute manifestation of the disease, but that they also normalize brain functions, through complex mechanisms that will eventually lead to patient stabilization (Raffaella *et al.*, 2009).

APDs are generally divided into two groups: First generation APDs (FGAs, also known as conventional or typical) and second generation APDs (SGAs, also known as non conventional or atypical). SGAs includes; Aripiprazole, Clozapine, Olanzapine, Quetiapine, Risperidone, Paliperidone, Ziprasidone and more recently iloperidone (Grunder *et al.*, 2009). While FGAs and SGAs appear to be equally effective for the treatment of positive symptoms, which are primarily produced by an excessive tone of the mesolimbic dopaminergic system, they are different with respect to the occurrence of neurological side effects. Moreover SGAs seem to be more effective on negative symptoms and cognitive deterioration, although this notion has been recently challenged (Keefe *et al.*, 2007).

Neurotransmitter receptors are the primary molecular targets of APDs and their interaction is thought to be important for the 'normalization' of neurotransmitter imbalances that are associated with specific symptoms and acute manifestation of schizophrenia (and bipolar disorder). However, although a potential relationship between pharmacodynamic and therapeutic properties of APDs can be established, the picture is complicated by the observation that most drugs show very complex receptor profiles. It is feasible to hypothesize

that the functional outcome of these complex mechanisms is not the pure 'algebraic' summation of single mechanisms, but is rather the consequence of their down-stream interactions with second messengers, signaling proteins and transcriptional molecules (Raffaella *et al.*, 2009). The understanding of neurotransmitter dysfunction is critical for delineating how APDs may be effective in controlling disease symptomatology, such alterations may be intimately linked to structural and circuitual abnormalities.

Recent studies showed that liver enzymes abnormalities were not only seen with typical antipsychotics drugs but also with atypical antipsychotics (Gaertner *et al.*, 2001; Mouradian Stamatiadis *et al.*, 2002; Garcia-Unzueta *et al.*, 2003; Erdogan *et al.*, 2004). Asymptomatic elevation of liver enzymes has been observed in approximately 50% of patients treated with atypical antipsychotics (Kumra *et al.*, 1997). However, serious hepatotoxicity with these agents has been rarely reported (Dumotier *et al.*, 2002; Ozeanli *et al.*, 2006).

The liver is a vital organ present in vertebrates and some other animals, it has a wide range of functions, including detoxification, protein synthesis, and production of biochemicals necessary for digestion. The liver is necessary for survival, there is currently no way to compensate for the absence of liver function. Therefore there is strong need to evaluate the function of this vital organ on administration of some antipsychotic drugs.

### MATERIALS AND METHODS

#### ANIMALS

Forty(40) albino rats wister strain, body weight ranging from 160-200g were purchased from Department of Biological Science, Bayero University, Kano- Nigeria.

The rats were kept in clean and tidy cages under 12/12 hours normal light/dark cycle and allowed. The rats were allowed to acclimatize to the laboratory environment for a period of two weeks prior to the commencement of the experiment. They were allowed free access to water and normal feed (Growers Palletized Feeds Agrovet, Ikeja- Lagos).

### Drugs

The tablets of Amitriptylene(35mg), Largatil(500) and Tegretol (35mg) each, were obtained from Department of Pharmacy, Psychatric Hospital, Dawanau, Kano- Nigeria. Each tablet was dissolved in 100cm<sup>3</sup> of distilled water to obtain the desired concentration for administration to the rats.

### Experimental Design

A total of Fourty (40) Albino rats with weight ranges 160 - 200g were used in this research. They were divided into four groups on the basis of weight, each with ten rats of both sexes. Group one served as control, group two were administered with Amitriptyline (35mg/kg/day), group three were administered with Largatil (500µg/kg/6 hour) and group four were administered with Tegretol (35mg/kg/day).

### Drug Administration

Amitriptyline, Largatil and Tegretol drugs suspensions were administered orally using insulin syringe (1cm<sup>3</sup>) for thirty (30) days. The dosages depend on the animals' weight and the drug to be administered.

### Collection of Samples

After thirty (30) days of oral administration of the drugs, the rats were sacrificed and the blood samples were collected into centrifuge tubes. The blood samples were allowed to clot then centrifuged at 2,500rpm for 15 minutes.

A clean Pasteur pipette was used and serum was carefully collected and dispensed into a clean labelled sample tube. The sera samples were analyzed for activity of Alkaline phosphatase (ALP), Aspartate aminotransferase (AST) and Alanine aminotransferase (ALT).

### Methods

Alkaline phosphate activities were determined using King Armstrong method (Moss *et al.*, 1972) while Alanine aminotransferase and Aspartate aminotransferase activities were determined using Reitman and Frankel method (Wilkinson *et al.*, 1972).

### Statistical Analysis of the Results

Data were presented as mean±standard deviation in three (3) replicates. The significant difference between the means groups was assessed by the student T-test (Mukhtar, 2003).

### RESULTS

The results of the effect of some antipsychotic drugs in rats (Table 1) showed significant increases (P<0.05) in the activities of AST, ALT and ALP in the serum compared with the control after oral administration of the drugs; Amtriptyline (35mg/kg/day), Largatil (500µg/kg/6hrs) and Tegretol (35mg/kg/day) in all the three (3) groups respectively.

**Table 1:** Effects of some antipsychotic drugs on the serum activities of Liver enzymes in Albino Rats.

Group	AST (U/L)	ALT (U/L)	ALP (U/L)
Group 1 (n=10)	25.9±5.3	20.8±5.6	34.8±10.1
Group 2 (Amitriptyline) (n=10)	38.5±3.7*	32.5±4.5*	48.4±14.5*
Group 3 (Largatil) (n=10)	37.1±7.6*	37.6±4.1*	69.4±4.7*
Group 4 (Tegretol) (n=10)	40.9±8.2*	33.8±2.9*	49.3±8.1*

n = Number of rats

\*Statistically significant increases (P<0.05) in comparison with normal control.

### DISCUSSION

Results from this study showed that a typical antipsychotic drug commonly cause asymptomatic increases in the serum activities of Aspartate aminotransferase(AST), Alanine aminotransferase(ALT) and Alkaline phosphatase(ALP) and is inline with work reported by Atasoy *et al.*, (2007), that oral administration of antipsychotic drugs causes increase in activities of some liver enzymes.

The results reveals that, the activities of AST, ALT and ALP of Albino rats treated with Amitriptyline (35mg/Kg/day) (group2),Largatil (500µg/Kg/6hours)(group3) and Tegretol (35mg/Kg/day)(group 4) were found to be much greater than that of control (group1). This showed a significant increases (P<0.05) in the levels of liver enzymes (AST, ALT and ALP) which may be due to drug induced hepatotoxicity. The

result tallies with the work of Pae *et al.*, (2005) who had found that liver enzymes were elevated in 26.9% in patients treated with Olanzapine and 14.2% in patients treated with Reperidone respectively.

Increased activities of alkaline phosphatase, a maker enzyme for plasma membrane and endoplasmic recticulum (Wright and Plummer, 1974) observed after administration of the antipsychotic drugs can be employed to assess the integrity of the plasma membrane (alikanji *et al.*, 1993), since it is localize predominantly in the micrivilli of the bile Canaculli located in the plasma membrane.

The result of this research also reveals a significance increases (P<0.05) in the weight of the Albino rats treated with the antipsychotic drugs( Groups 2,3 and 4) compared with control rats (group1).

In conclusion it is clear that daily oral administration of antipsychotic drugs; Amitriptyline and Tegretol together with six (6)

hours oral administration of Largatil suspension induces Liver toxicity within thirty (30) days.

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