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Histological and Biochemical Changes Associated with Blocking of Serotonin Receptor

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ABSTRACT

Schizophrenia is one of many psychotic disorders on a broad spectrum. The symptoms of psychosis resulting from schizophrenia and other spectrum disorders are treated with several medications, including aripiprazole, clozapine, risperidone, etc. However, these drugs are associated with adverse effects. This study was conducted to evaluate histological and biochemical changes linked to the blockage of serotonin receptors caused by risperidone and aripiprazole. Fifteen Sprague Dawley albino rats were divided into three groups of five rats each. Group 1 served as the control and received a placebo (normal saline), Group 2 received risperidone (20 mg/kg/day), and Group 3 was given aripiprazole (10 mg/kg/day). After three months of treatment, a biochemical analysis of liver enzymes was performed, followed by a histological examination. The results revealed that the architecture of the liver cells appeared normal in all three groups. However, when risperidone and aripiprazole treatment groups were compared to the control group, histology was slightly altered. The level of glutamic oxaloacetic transaminase (GOT) in the control group increased slightly from 70 to 75 U/L. GOT levels increased from 80 to 120 U/L and 130 to 140 U/L in the aripiprazole and risperidone groups, respectively. A similar observation was made for the levels of glutamate pyruvate transaminase (GPT) and alkaline phosphatase (ALP) compared to the control group. The findings of this study found the levels of the biochemical enzymes within safe limits with the administration of aripiprazole and risperidone. However, patients using these drugs should always have routine laboratory examinations for liver enzyme tests.

Keywords: ALP, Biochemical changes, GOT, GPT, Histological changes, Liver, Serotonin.

Introduction

Schizophrenia is a disorder on a spectrum that encompasses schizophreniform disorder, schizophrenia, delusional disorder, and other psychotic disorders.[1] All of these conditions are mainly characterized by defects in the following domains; hallucinations, delusions, cognitive defects, disorganized or abnormal motor behavior, and diminished intellectual functions.[1] Symptoms remain in an episodic fashion throughout life, depending on intensity. The symptoms are either domain-specific or broad.[2] Approximately 30% of all diagnosed schizophrenia patients are treatment-resistant schizophrenic (TRS), which means that symptoms persist even after two or more trials of optimum dose.[3] This raises major clinical concerns about the drug's pharmacologic treatment and management of schizophrenia. The dopaminergic hypothesis of schizophrenia increased the need for antipsychotics, which are broadly classified as typical (conventional) and atypical. Typical antipsychotics are dopamine receptor antagonists that exclusively treat the positive symptoms of schizophrenia while causing multiple side effects.[4]
As a result of the increasing extrapyramidal adverse effects of first-generation antipsychotics (e.g., chlorpromazine and haloperidol),[5] atypical antipsychotics or second-generation antipsychotics have become a better treatment option for schizophrenia and other treatment-resistant depressive disorders.[6]
Commonly used atypical antipsychotics include olanzapine, quetiapine, paliperidone, risperidone, sertindole, ziprasidone, aripiprazole, etc. Because atypical antipsychotics have a weak antagonistic effect on D2 receptors, they act beyond this domain and block serotonin 5-HT2 receptors. This allows antipsychotic effects with reduced extrapyramidal side effects such as dyskinesia and dystonic reactions, Parkinsonism, paranoia, slurred speech, and so on.[7]
Aripiprazole, an FDA-approved atypical antipsychotic, is primarily used to treat the symptoms of psychosis caused by schizophrenia and other spectrum disorders. It is also a preferred treatment for delirium and apraxia of eyelid opening in Parkinson's disease patients.[8,9]
Clozapine and risperidone have become the first-line treatments for a variety of psychotic diseases, including chronic and acute schizophrenia, autism-related irritability, and bipolar disorder.[10]
Adverse effects which are associated with the use of atypical antipsychotics include symptoms like accumulation of body fat, deregulation of insulin metabolism and glucose, dyslipidemia, etc.[11]
This study was aimed at investigating the liver toxicity of commonly prescribed antipsychotic drugs (risperidone and aripiprazole) in hospitals and private clinics.

Materials and Methods

Source of experimental animals
Fifteen Sprague Dawley male albino rats, weighing 200 to 300 g were obtained from the College of Veterinary Medicine, University of Mosul, Mosul, Iraq. The rats were divided into three groups of five rats each and kept in a controlled environment with a temperature of 23 ± 1°C, humidity level of 50 ± 5%, and 12-hour light and 12-hour

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dark cycle for three months. The animals had free access to food and tap water and were kept according to the procedure of the animal ethical committee.[12,13] The research was conducted in an animal home at the College of Veterinary Medicine, University of Mosul, Mosul, Iraq.

Ethical approval

The study was approved by the Medical Research Ethics Committee at the University of Mosul, Mosul, Iraq with approval number UOM/COP/2021-2022 (3) issued on December 13, 2021.

Experimental groupings and treatment

A randomized double-blind experiment with 15 rats separated into three groups was conducted. Group 1 served as the control and received a placebo (normal saline), Group 2 received risperidone (20 mg/kg/day), and Group 3 was given aripiprazole (10 mg/kg/day).[13] The risperidone ($C_{23}H_{27}FN_4O_2$) and aripiprazole ($C_{23}H_{27}Cl_2N_3O_2$) were suspended in a 0.5% solution of CMC and administered intraperitoneally.

Histopathological examination

At the end of the experiment, the rats were euthanized, and blood specimens were collected for histological analysis. For 48-50 hours, liver tissue was fixed in 10% formalin solution and dehydrated in a graded alcohol series. It was then cleaned using xylene, embedded in paraffin, mounted on slides, and stained with hematoxylin and eosin. The slides were examined and photographed under an electron microscope.[12]

Biochemical analysis

After 3 months of treatment with either aripiprazole or risperidone, the blood sample was collected to evaluate the levels of glutamic oxaloacetic transaminase (GOT), serum glutamic pyruvic transaminase (GPT), and alkaline phosphate (ALP).[13] The serum ALP was quantified calorimetrically using a kit supplied by Giesse Diagnostics Srl (Italy, cat. No. 4096). The assay was predicated on the fact that ALP hydrolyzes 4-nitrophenyl phosphate (4-NPP) into two components: 4-nitrophenol and inorganic phosphate. Kinematically, the reaction is driven by capturing the phosphate group in the reaction's alkaline buffer medium. This reaction was then kinetically monitored at 405 nm as a directly proportional measure of the generated 4-nitrophenol. The serum GOT was quantified calorimetrically based on a kit provided by Giesse Diagnostics Srl (Italy, cat. No. 4191).[14] The principle of the assay is based on the formation of glutamate and oxaloacetate from aspartate and oxoglutarate after the amino group was transferred from aspartate to oxoglutarate. In the presence of decreased nicotinamide adenine dinucleotide (NADH), malate dehydrogenase reduces the generated oxaloacetate to maleate. This subsequent step consumes NADH and oxidizes it to NAD^+.[13] This redox reaction was evaluated kinetically at 340 nm, and the results were proportional to GOT levels in blood samples. The serum GPT was measured calorimetrically using a kit provided by Giesse Diagnostics Srl (Italy, cat. No. 4194). The assay was designed around GPT catalyzing the conversion of oxoglutarate to glutamate and pyruvate. Lactate dehydrogenase catalyzes the final reduction of the pyruvate conversion into lactate. This subsequent step consumes NADH and oxidizes it to NAD^+. The redox process was evaluated kinetically at 340 nm, and the results were proportional to GPT levels in serum samples.[13,14]

Statistical analysis

The data are presented as mean ± standard deviation (SD). Statistical analysis was performed using a two-way analysis of variance (ANOVA) followed by the Student's t-test and the Friedman test on IBM SPSS version 22. Statistical significance is based on $p \leq 0.05$.

Results and Discussion

The architecture of the liver cells was examined histologically, and the appearance of all three groups seemed normal, as shown in Figure 1. Hepatocytes with hexagonal-shaped lobules that were one or two cells thick and structurally separated by connective tissues were among the clear structures observed. The hepatic artery and a big portal vein, as well as the bile duct, could be seen in the hepatic portal areas. Other observed anatomical structures included Kupffer cells and hepatic sinusoids covered by sinusoidal lining cells (Figure 1a). Aripiprazole-related histological problems include modest cell swelling of some hepatocytes, mild necrosis of other cells, congestion of the central vein, slight vacuolar degeneration of hepatocytes, and necrosis (Figure 1b1). As observed in Figure 1b2, the histological problems associated with risperidone include hepatocyte cell enlargement, portal vein congestion, hepatocyte degeneration, bile duct epithelial cell hyperplasia, and inflammatory cell infiltration.

The biochemical analysis of the liver enzymes revealed that for three months, the level of GOT (U/L) in the control group increased from 85±14 to 100±14 U/L. In the aripiprazole treatment group, the mean enzyme level increased from 95 to 106 U/L, and in the risperidone treatment group, the level of GOT was elevated from 131 to 120 U/L. The serum GPT values of the control group remained constant at approximately 25 U/L. In the aripiprazole-treatment group, the value of GPT increased from 22.5 to 30 U/L, and in the risperidone-treatment group, the value increased from 24 to 25 U/L. After three months, the ALP in the control group remained steady at 300 U/L, but the aripiprazole-treatment group rose from 343 to 402 U/L and the risperidone-treatment group increased from 380 to 325 U/L. (Figure 2).

A wide range of medications is toxic to the liver, leading to drug-induced liver injuries (DILI). However, most of the processes that lead to idiosyncratic DILI are unclear.[14] The liver microsomal enzyme is the site of metabolism for practically all psychotropic medications, which supports the results of this study. Risperidone is widely used for psychosis-induced schizophrenia and affective disorders. However, it is frequently related to weight gain, diabetes mellitus, pancreatitis, non-HDL cholesterol increase, and other side effects. It is metabolized in the liver by the enzyme cytochrome P450 2D6 (CYP2D6) and converted to the compound 9-hydroxyrisperidone by hydroxylation.[15] Various studies have been conducted to evaluate its adverse effects.[16-19] Although evidence suggests that these adverse effects can be addressed with diet control and regulated calorie intake, histological testing revealed no symptoms of hepatotoxicity or nephrotoxicity.[20] Similarly, the results of the histological analysis indicate no evidence of inflammation or cell necrosis. In comparison to other atypical antipsychotics such as risperidone and olanzapine, aripiprazole has the best side-effect/efficacy ratio.[21] Evidence suggests that aripiprazole causes the fewest extrapyramidal symptoms (EPS), cardiovascular adverse effects, serum prolactin increase, and weight gain.[22]

Hepatic performance after treatment with atypical antipsychotics was evaluated in a trial that significantly reduced GOT, GPT, ALP, and bilirubin, with no difference between males and females and no values outside the normal range.[19]

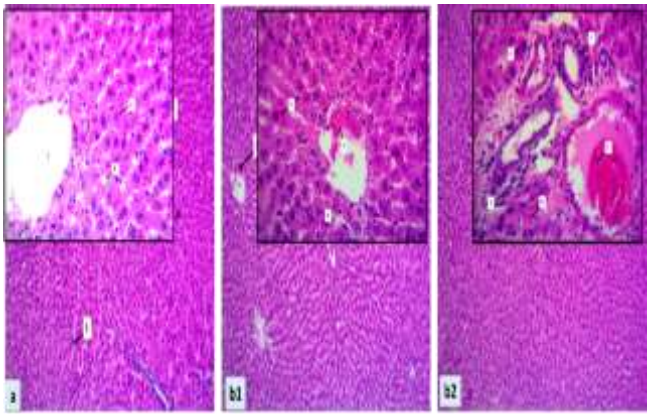

Figure 1: Histology of the liver tissues. a: Control; b: After 3 months of blocking serotonin receptors with either aripiprazole (b1) or risperidone (b2). H and E stain, 100X and 400X.

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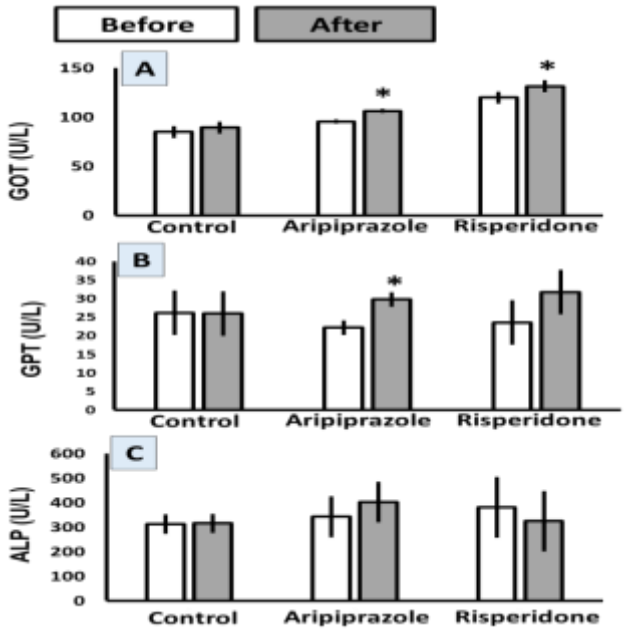

Figure 2: Elevation of liver enzymes [(a) GOT (b) GPT (c) ALP] after blocking serotonin receptor. GOT: Glutamic oxaloacetic transaminase; GPT: Glutamic pyruvic transaminase; ALP: Alkaline phosphate. Data were expressed as mean ± SD; $p<0.05$ as compared to baseline before stimulation of serotonin receptor or control group.

However, the slight increase in liver enzyme levels observed in this study could indicate an adaptive organ response. Several preclinical animal studies have been conducted on second-generation antipsychotic drugs, especially olanzapine, aripiprazole, quetiapine, and risperidone, to clarify their hepatotoxic effects. The steatogenic-type injury was connected with the administration of aripiprazole and olanzapine in the albino rat model. However, the injury was observed to be much greater with olanzapine than with aripiprazole.[24] In preclinical animal models, olanzapine has been shown to cause steatogenic liver injury, proinflammatory cell infiltration, or a combination of both defects.[25-31]
Similarly, risperidone-induced steatosis has been shown in preclinical animal models.[32-37] Furthermore, necrosis has been found in animal models after the administration of quetiapine.[38] The results of the present study revealed histological changes represented by distended veins, enlarged sinusoids, vacuoles, cell necrosis, bile ductule damage, and inflammatory cell infiltration. Nonetheless, liver enzymes were only modestly affected, and the defect was more prominent with aripiprazole than with risperidone.

Conclusion

The findings of this study revealed that the histological examination shows no obvious evidence of hepatotoxicity or hepatic tissue necrosis. However, minor histological observations were made, which included cellular distention, vacuoles, mild necrosis, and pro-inflammatory cell involvement. After three months of treatment with aripiprazole and risperidone, mild elevations in the liver enzymes GOT, GPT, and ALP were found within safe limits. The limitations of this study include small sample size, a relatively short time of exposure compared to use in chronic patients, and the use of a single dose rather than a range of doses of high, moderate, and low. It is therefore recommended that patients using antipsychotic drugs have regular laboratory evaluations for liver function tests to avoid inevitable liver injury in high-risk individuals using alternative, less liver-toxic antipsychotics.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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