Histological Study of the Effects of Olanzapine on the Liver of Adult Male Albino Rat with and without Vitamin C

Original Article

Reda H. Elbakary

Histology Department, Faculty of Medicine, Tanta University, Tanta, Egypt

ABSTRACT

Introduction: Olanzapine is an atypical antipsychotic drug widely used in treatment of schizophrenia for prolonged time.
Aim of the work: The present study was carried out to evaluate the effect of olanzapine on the liver and the possible protective effect of vitamin C.
Material and Methods: Forty adult male albino rats were used in this work. They were divided into: Group I as a control, group II was given Olanzapine (2mg/kg B. wt. orally once daily) for one month, group III was given Olanzapine (at the same previous dose) plus vitamin C (15 mg /Kg. B. wt of orally once daily) for one month and group IV was given only vitamin C (for the same dose and period of the previous group). At the end of the experiment, liver specimens were processed for histological study by light and electron microscopes. Also blood samples were collected for estimation of liver enzymes.
Result: Significant increase in the level of liver enzymes was observed in Olanzapine treated group. While the microscopic examination of the liver sections of this group revealed several histological changes including, dilatation and congestion of central veins and blood sinusoids, inflammatory cellular infiltration in the portal areas and cytoplasmic vacuolation of hepatocytes that present mainly around the central veins. Mitochondrial degeneration, bile ducts dilatation and excessive deposition of lipid droplets were also observed. These changes were ameliorated by vitamin C administration.
Conclusion: Results of this experimental work revealed that administration of vitamin C greatly reduced the histological alterations induced by Olanzapine, suggesting that vitamin C has a protective effect on the liver.

Key Words: Olanzapine, liver, vitamin C, rat.

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Corresponding Author: Reda Hassan Elbakary, **Tel.:** 01125900338, **E-mail:** redahassan99@gmail.com

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INTRODUCTION

Olanzapine is a second-generation atypical antipsychotic drug. Using Olanzapine is preferred than older antipsychotic agents due to its less side effects on extra pyramidal tract[1, 2].It is widely prescribed for the treatment of schizophrenia[3]. It is effective against the positive and the negative symptoms of schizophrenia[4]. Olanzapine is a thienobenzodiazepine, structurally related to the older dibenzodiazepine[5]. It is a serotonin-dopamine receptor antagonist, that binds to a large number of neurotransmitter receptors, including the dopamine receptors, serotonin receptors, histamine H1 receptor, muscarinic receptors, α- and β-adrenergic receptors, γ-amino butyrate receptor, and the benzodiazepine binding sites[6].

The typical therapeutic dose of Olanzapine is 10 to 20 mg per day. Olanzapine is well absorbed following oral administration. It is metabolized extensively within the liver. Glucuronidation of Olanzapine is the major metabolic pathway[7]. By the help of liver enzymes other p450, mainly CYP2C8 help in its oxidative metabolism through catalysis of Olanzapine N-demethylation[8]. It is excreted in the urine and feces. The elimination half-life about 37 hours. Plasma levels of Olanzapine appear to increase slowly over a period of months[9].

Compared with traditional agents, Olanzapine shows only a few adverse events such as dry mouth, sedation, and increase in appetite that lead to greater increases in weight gain and body mass index. Atypical antipsychotic drugs commonly cause asymptomatic increase in the liver enzymes and serum bilirubin[10].The mechanisms of these adverse effects are not known. The liver and adipose tissue are the principal organs implicated in the development of antipsychotic-induced metabolic adverse effects[11].

Ascorbic acid (vitamin C) is an important water-soluble antioxidant. It is mostly known as a cofactor for proline hydroxylase. Ascorbic acid acts as an antioxidant

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by donating an electron to free radical species, such as tocopherol radical, thereby interrupting the radical chain reaction in biological membranes[12]. Many reports of serious hepatotoxicity induced by Olanzapine have been published[13]. From this point this work aims to evaluate the effect of Olanzapine on the histological structure of rat liver and the possible protection by vitamin c.

MATERIAL AND METHODS

This work was carried out on 40 adult male albino rats weighing 200–220 g each. Animals were housed in clean, properly ventilated cages under the same environmental conditions, and were fed on a standard laboratory diet. They were acclimatized to their environment at least two weeks before starting the experiment.

Rats were divided equally into four groups:

Group I:

Control group (CG) received orally one ml of distilled water which is the drug solvent of both Olanzapine and vitamin C.

Group II:

Olanzapine-treated group (OZ), were given 2mg/kg B.wt for one month which equal to human dose[14]. Olanzapine (ZyprexaTM) present in the form of 10 mg tablet obtained from (Eli Lilly Company, Indianapolis, Indiana, USA). The content of each tablet was dissolved in 25 ml distilled water to get a final concentration of 0.4 mg/ml.

Group III:

Olanzapine plus vitamin C (OZC) treated group received the same dose of Olanzipine as group II, plus (15 mg/Kg) of vitamin C orally for the same period.

Group IV:

Received only vitamin C at the same dose of group III. All doses were calculated according to Paget and Branes formula[15].

Rats' mortality:

There were four dead rats in Olanzapine treated group after receiving the drug for one week.

Histological technique and serological study:

At the end of experiment all rats were sacrificed and the left lobes of liver were dissected then divided into two parts one for routine histological preparation by H&E while the other for electron microscopic study. Also the blood samples were collected through cardiac puncture for analysis of liver enzymes (SGOT, and SGPT) in all groups.

For electron microscopic examination, parallel tissue specimens were fixed at 40C in 2.5% glutaraldehyde in 0.1mol/l phosphate buffered (pH 7.3) for 2 h, rinsed in 0.1 mol/l phosphate buffer and post fixed in phosphate buffered 1% osmium tetroxide for 1 h, then dehydrated in ascending grades of ethanol. After immersion in propylene oxide, the specimens were embedded in an epoxy resin mixture. Semithin sections (1 mm thick) were stained with 1% toluidine blue, and were examined by a light microscope for proper orientation. Ultrathin sections (80–90 nm) were stained with uranyl acetate and lead citrate to be examined by a JEOL electron microscope at80 kV in Faculty of Medicine, Tanta University[16].

The experiment was approved by the Local Ethics Committee of the Faculty of Medicine, Tanta University.

Statistical analysis

Student-t test was used for statistical evaluation of the data using Minitab Statistical Software, version16 for Windows. Data expressed as mean ± standard deviation, t = Student (t) test, P. value = probability of chance, $P > 0.05$ is not significant and $P < 0.001$ is highly significant.

RESULTS

Liver enzymes analysis of the control group as well as the vitamin C treated group revealed the normal range of liver enzymes. The Olanzapine treated (group two) showed statistically highly significant values of liver enzymes in comparison to that of the control group (p value < 0.001).Group III (Olanzapine plus vitamin C treated) revealed statistically highly non-significant value in comparison to group II, and these value was less than that of Olanzapine treated group Table 1.

Histopathological results:

A- Light microscopic results:

Group I and group IV: examination of liver sections obtained from control rats as well as from vitamin c treated rats revealed normal liver architecture with central veins and radiating hepatic cords. Thin walled blood sinusoids separating the hepatocyte cords were observed. The liver cells appeared polygonal with acidophilic cytoplasm and large rounded vesicular nuclei with prominent nucleoli. Portal tracts containing branches of hepatic artery, vein and bile duct were also detected (Figs. 1A&B).

Group II: revealed different degrees of liver affection. There were dilatation and congestion of the central vein and blood sinusoids (Fig. 2). Extensive cellular infiltration

was observed mainly in the portal tracts; however these infiltrations were replaced areas of damaged hepatocyte in other regions (Fig. 3). Areas of homogenous acidophilic substance were seen in between the liver cells (Fig. 4). As regard to the liver cells they revealed multiple vacuoles in the cytoplasm that became completely vacuolated in the zone around the central vein (Figs. 5&6). Hepatocytes in other areas appeared totally destroyed and were replaced by inflammatory cellular infiltrate (Fig. 7).

Group III: Olanzapine plus vitamin C treated group revealed some improvement which appeared as a decrease in the dilatation of the blood vessels, less cellular infiltration and no vacuoles in the hepatocytes (Fig. 8).

B- Electron microscopic results:

Ultrathin sections of control group and that of group IV revealed: polyhedral hepatocytes with rounded vesicular nuclei and prominent nucleoli. The cytoplasm was contain multiple cell organelles mainly mitochondria which appeared rounded or oval with homogenous matrix, RER were appeared as parallel cisternae studded with ribosomes and glycogen granules were seen (Fig. 9). Bile canaleculi in between the liver cells were seen and were surrounded by cell junctions from both sides (Fig. 10).

Group II: Oz treated group indicated that the most prominent lesion was deposits of multiple lipid droplets of variable size, shape and density (Fig. 11). Dilatations of RER were also detected (Fig. 12). The mitochondria were affected in some cells. It lost its homogenous appearance and appeared as swollen with destroyed cristae (Fig. 13). Dilatation of RER and areas of cytoplasmic rarefaction were observed. The nucleus was appeared with irregular outline and dilatation of perinuclear membrane (Fig. 14).

The inflammatory cells in the form of eosinophils and neutrophils were observed in dilated blood sinusoids and in between the liver cells. Also Kuppfer cells were increased in number with multiple vacuoles in its cytoplasm (Fig. 15 and 16). Dilatations of bile canaleculi with decrease in its microvilli were detected (Fig. 17).

Group III: OZC group showed an improvement to some degree. The most characteristic sign was a decrease in lipid droplets which became saturated dense droplets; however some RER remained dilated (Fig. 18).

Table 1: The mean level of liver enzymes (SGPT &SOPT) in different studied groups

	SGPT control group	SGPT Olanzapine treated (group II)	SGPT Olanzapine treated+ vitamin C group III	SGOT control group	SGOT Olanzapine treated (group II)	SGOT Olanzapine treated+ vitamin C(group III)
Mean ± SD	10.4±1.429	54.8±10.239	19.7±4.6	10.0±1.76	55.2±12.4	19.6±3.33
't' value		13.58	9.872		11.38	8.74
P value		< 0.001	< 0.001		< 0.001	< 0.001

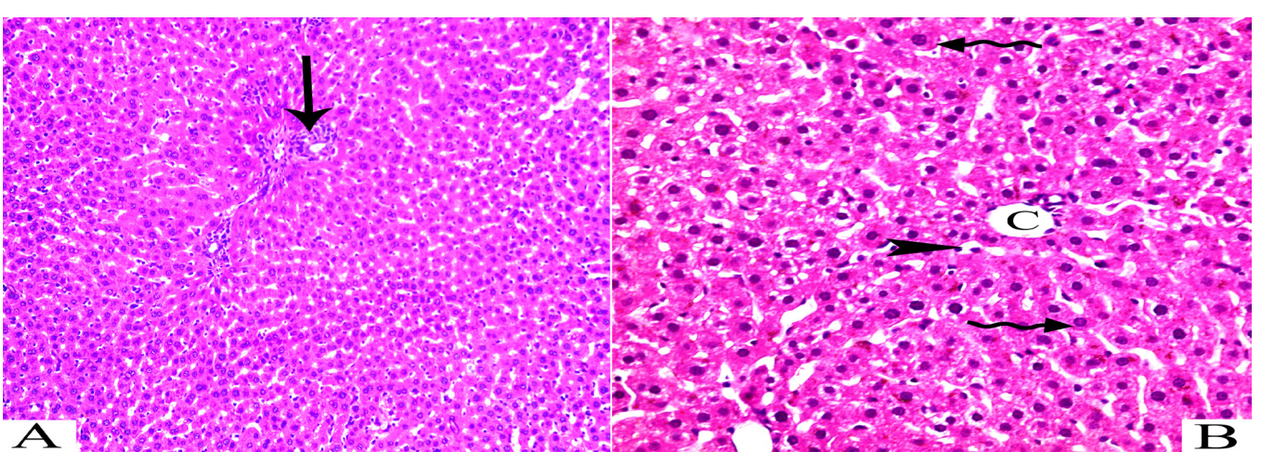

Fig.1A: Showing normal hepatic lobular architecture with portal tract (→)B. Showing central vein(C) at the center of classic hepatic lobule and cords of hepatocytes with large rounded vesicular nuclei(zigzag arrows) radiating from it and separated by the blood sinusoids(◄).
(Control group, H. & E., A X 200. B X 400)

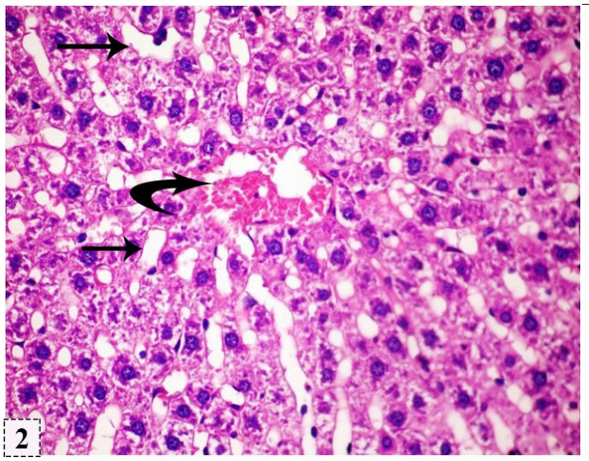

Fig. 2: Showing dilation of blood sinusoids (arrows) and a dilated congested central vein (curved arrow) (Group II H&E x 400)

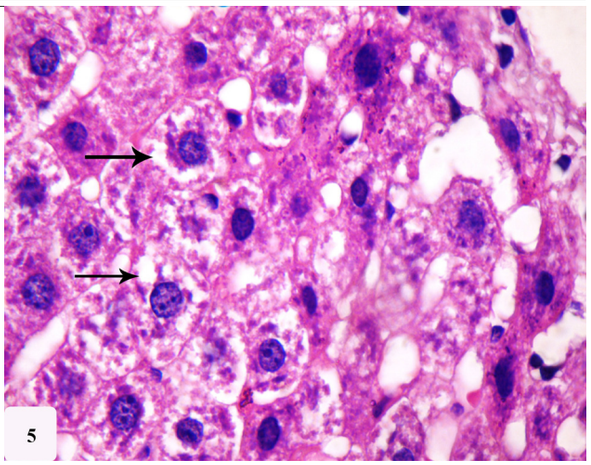

Fig. 5: Showing vacuolization of the hepatocytes cytoplasm (arrows). (Group II H&E x1000)

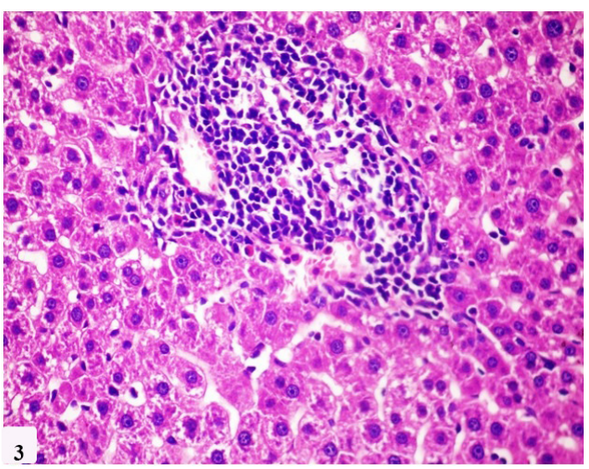

Fig. 3: Showing cellular infiltrate in the portal tract. (Group II H&E x 400)

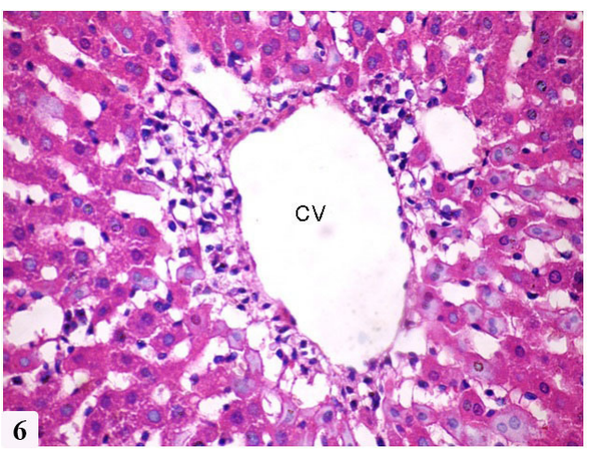

Fig. 6: Showing massive dilatation of central vein (cv) and extensive vacuolated hepatocytes around it. (Group II H&E x400)

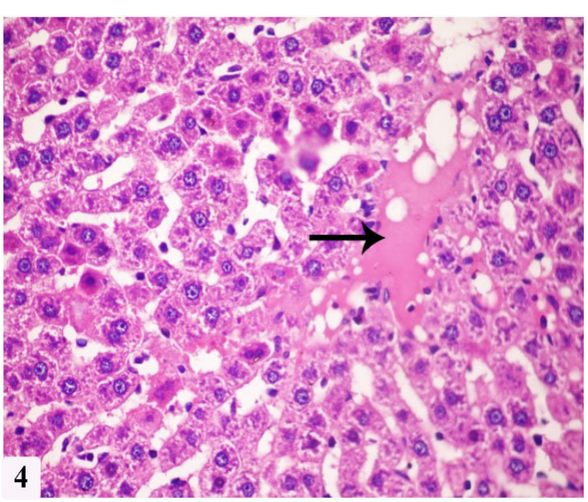

Fig. 4: Showing an area of homogenous acidophilic substance in between the liver cells (arrow). (Group II H&E x400)

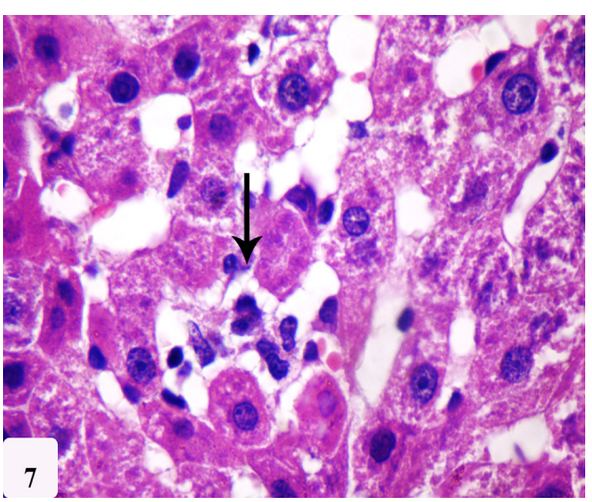

Fig. 7: Showing replacement of some hepatocytes (arrow) by inflammatory cellular infiltrate. (Group II H&E x 1000)

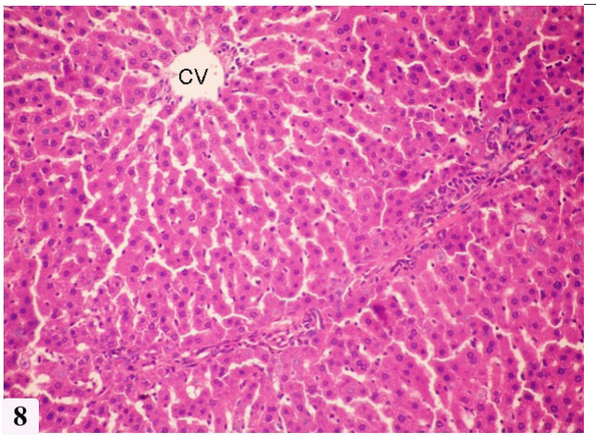

Fig. 8: Showing decrease in cellular infiltrate in portal tract and less dilated central vein (CV). (Group III H&E x200)

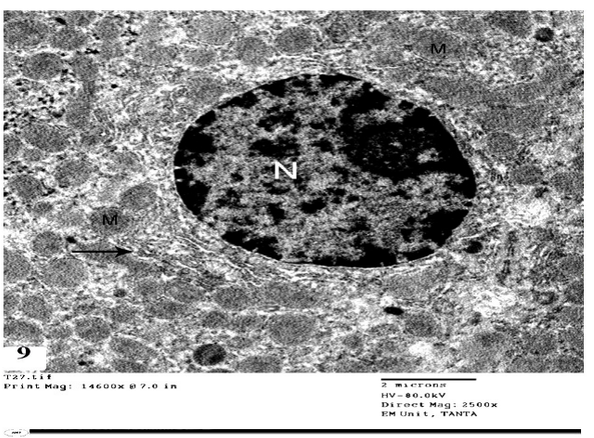

Fig. 9: Electron micrograph showing hepatocyte contains prominent RER (arrow) multiple mitochondria with homogenous consistency and variable shape (M) and the nucleus (N) with extended chromatin and prominent nucleolus

(Control group Mic. Mag. X 2500)

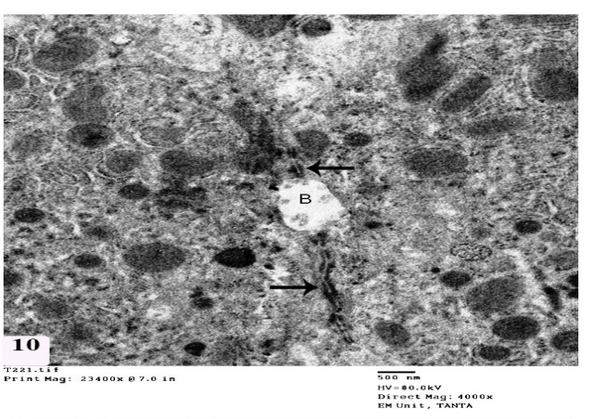

Fig. 10: Electron micrograph showing parts of two hepatocyte with bile canaliculus (B) in between and it is surrounded from both sides by cell junction (arrows).

(Control group, Mic. Mag, X4000).

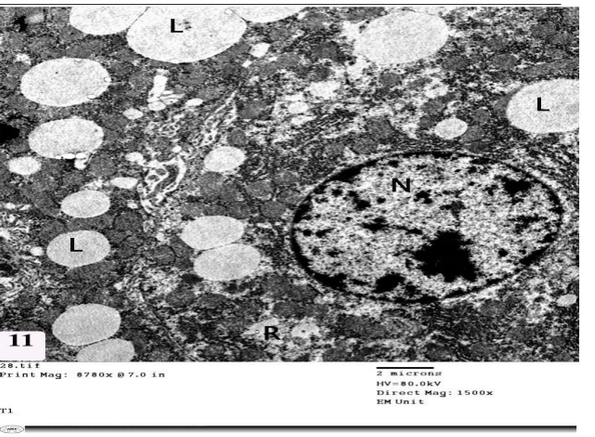

Fig. 11: Electron micrograph showing parts two hepatocytes with multiple lipid droplets of variable size and shape (L), area of rarified cytoplasm (R) and normal nucleus (N).

(Group II, Mic. Mag., X 1500)

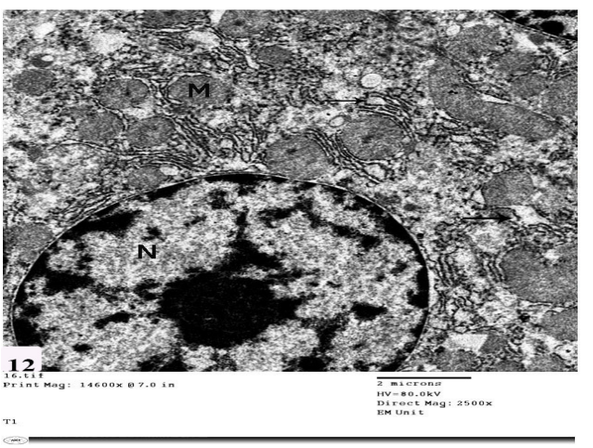

Fig. 12: Electron micrograph showing dilated RER (arrow), mitochondria (M) and nucleus (N) with extended chromatin and nucleolus. (Group II, Mic. Mag. X2500)

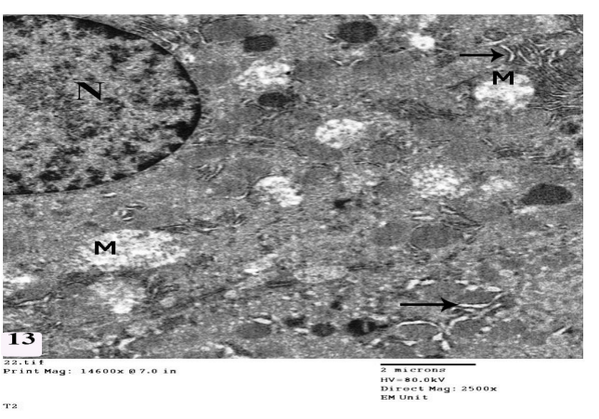

Fig. 13: Electron micrograph showing multiple swollen destroyed mitochondria (M). Notice presence of a part of the nucleus (N) and dilated RER (arrow) (Group II, Mic. Mag.X2500).

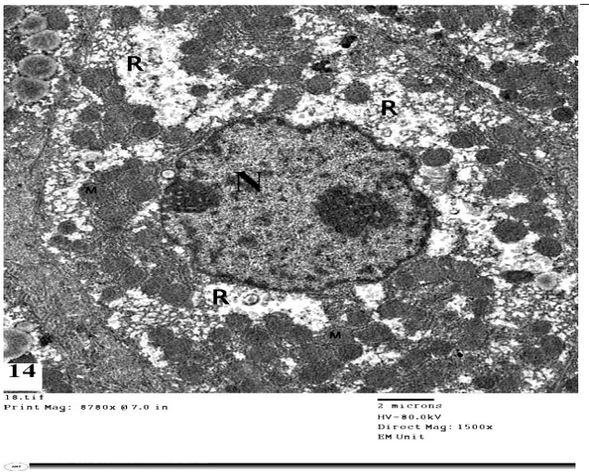

Fig. 14: Electron micrograph showing hepatocyte with irregular out lined nucleus (N) areas of cytoplasmic rarefaction (R), and mitochondria (M). (Group II, Mic. Mag. X1500)

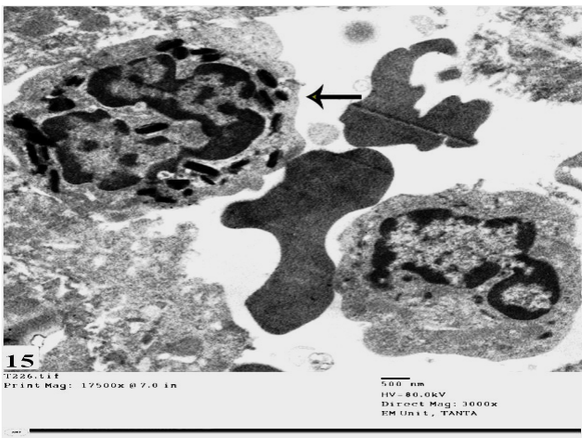

Fig. 15: Electron micrograph showing inflammatory cells in blood sinusoid mainly eosinophile (arrow).
(Group II, Mic. Mag. X3000)

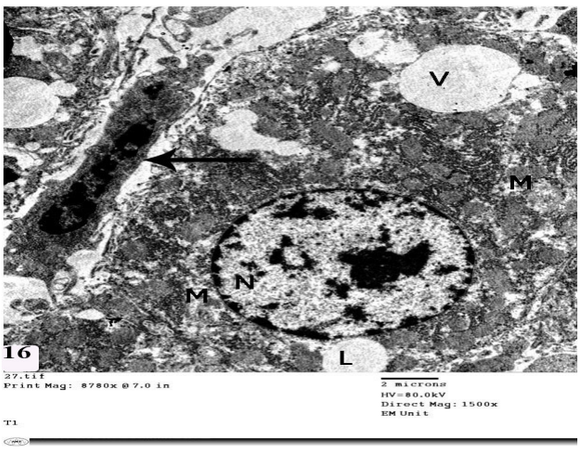

Fig. 16: Electron micrograph showing Kupffer cell (arrow), hepatocytes with some destroyed mitochondria (M), vacuoles (v) and lipid droplet (L). (Group II, Mic. Mag. X1500)

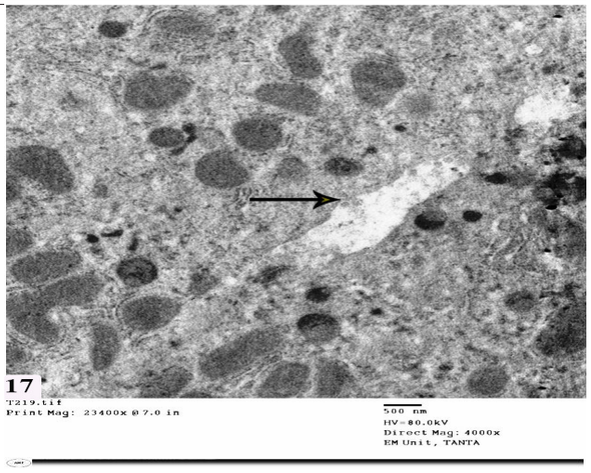

Fig. 17: Electron micrograph showing dilated bile canaliculus (arrow). (Group II, Mic.Mag.X4000)

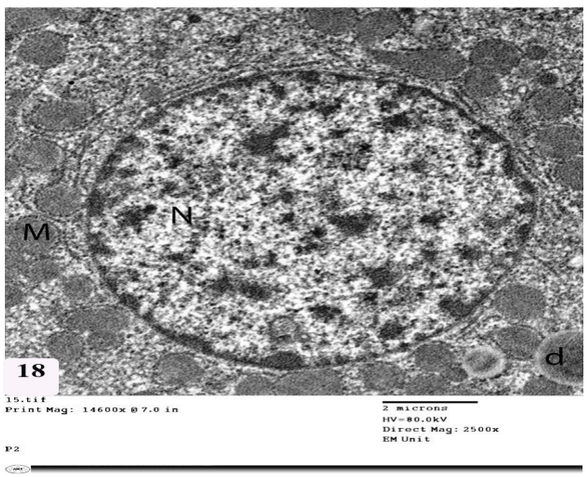

Fig. 18: Electron micrograph showing hepatocyte with central rounded nucleus and extended chromatin (N), normal mitochondria (M) and electron dens lipid droplet (d).
(Group, III Mic. Mag..X 2500)

DISCUSSION

Idiosyncratic drug-induced liver injury has been the top reason for withdrawing drugs from the market. From these drugs atypical antipsychotic medications which have largely replaced the older antipsychotic groups. Olanzipine is one of this group, where its use was associated with clinical evidence of hepatotoxicity[17 and 18].

Hepatotoxicity in this work was manifested in the form of abnormal parameters of liver enzymes and changes in cellular structure. At the level of liver enzymes, there were statistically significant rise in

comparison to the control group. The differences in the rise of liver enzymes between the treated group and protective group were not statistically significant. Many results of other works documented that atypical antipsychotics commonly caused isolated asymptomatic increase in the aminotransferase levels[19].Also it was reported that transient liver biochemistry abnormalities were associated with Olanzapine. These abnormalities were in the form of hyperbilirubinaemia, leukocytosis, elevated liver enzymes, and hyponatraemia[10]. It was proved that atypical antipsychotics such as Clozapine and Olanzapine induce metabolic syndromes and elevation of liver enzymes[20].

On the other side some authors observed that Olanzapine rarely induce a clinical or biological hepatic toxicity. However it was reported in some cases that liver enzyme levels increased tenfold of normal ranges. The pathogenesis of Olanzapine-associated hepatotoxicity is not well known and it may be a transient phenomenon[21].

In this work examination of Olanzapine treated group revealed dilatation and congestion of the central vein and blood sinusoids. Extensive cellular infiltrations mainly were seen in the portal tract. Liver cells showed multiple vacuoles in the cytoplasm that became complete vacuolation in the zone around the central vein. The hepatocytes in other areas appeared totally destroyed and replaced by inflammatory cellular infiltrate. Electron microscope revealed mitochondrial destruction, dilatation of rER and multiple infiltrations of lipid droplets.

These results were in agreement with the results that obtained in many previous works which examined the effect of Olanzapine on the liver and documented that either low or high doses of Olanzapine damaged the rat liver at a cellular level. Also reports of Olanzapine-induced hepatic damage have been published both from animal experiments as well as clinical studies[13]. Degenerative changes as well as vascular congestion due to Olanzapine were detected[22].

Various hypotheses have been put to explain the edema and vasodilatation due to Olanzapine. The edema can be attributed to vasodilatation and decrease in vascular resistance, which is secondary to blockage of α1 receptors and 5HT2 blockage by Olanzapine. This led to vasodilatation through increasing cyclic adenosine monophosphate. Also dopaminergic blockage due to Olanzapine can alter the renal regulation of fluid and electrolytes[23]. Cellular infiltration was explained due to release of reactive oxygen species, cytokines, and chemokines from Kupffer cells. These factors induce neutrophil extravasations and activation[24].

On the same side it was reported that Olanzapine induced severe generalized pruritic skin eruption, fever, eosinophilia, and toxic hepatitis for some patients. Clinical features and the results of skin and liver biopsies indicated that the patients developed hypersensitivity syndrome[25].

Most of the drugs are metabolized in the liver via the cytochrome P450 pathway, so patients with past history of drug-induced hepatitis with any medication may be severely affected by antipsychotic drug. Also icteric hepatitis has been documented and zone three necrosis was demonstrated on liver biopsy in one case[26]. The most prominent manifestation in this work was severe infiltration of liver cells by lipid droplets of variable size and shape. It was observed that atypical antipsychotic drug activate lipid biosynthesis in cultured liver cells. Also it was reported that Clozapine and Olanzapine, have significant metabolic side effects in man. They strongly increased de novo lipid and cholesterol synthesis in rat hepatocytes[27 and 28].

In other work using the immortalized human hepatocyte cell model to study the effect of atypical antipsychotic drug on the sterol regulatory element binding protein (SREBP) transcription factor pathways which control lipogenesis and cholesterogenesis .They found that, Olanzapine increased expression of SREBP, which control the expression of numerous genes involved in fatty acid and cholesterol biosynthesis resulting in an accumulation of intracellular lipids[29 and 30]. Other hypothesis stated that lipid-related effects have been attributed to drug-mediated blockade or antagonism of histamine H1 and serotonin 5-HT2 receptors as well as activation of hypothalamic adenosine mono phosphate activated protein kinase. This explanation pointed to a hypothalamic site of action for the metabolic deregulation of atypical antipsychotics[31- 33].

Mitochondrial changes which observed in this work were explained by inhibition of electron transfer activity at respiratory complex. This observation was documented during studying the integrated bioenergetics functions of isolated rat liver mitochondria[34]. As regard to endoplasmic reticulum changes which detected in this work. It was found that certain atypical antipsychotic drugs induce endoplasmic reticulum stress via changes in Ca++ homeostasis in hepatocytes. This effect was considered as a part of their undesirable hepatic metabolic side effects[35].

Degenerative changes and cytotoxicity of Olanzapine in liver cells were initiated by overproduction of reactive oxygen species. That led to mitochondrial collapse and lysosomal membrane leakiness. Also decreased lipid peroxidation and glutathione depletion occurred. The end result of these changes was cell lysis[36].

The hyper-sensibility mechanism is likely to be considered[19]. It may arise from the interaction of drug's reactive metabolite with a mild inflammation that renders the liver more sensitive to injury and increase its toxicity. This was observed in Clonzapine which increased the lipopolysaccharide-induced granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor. These inflammatory mediators increased liver toxicity[37].

Many investigations have shown that mitochondrial dysfunction is a major mechanism of drug-induced liver injury. The cause of this toxicity may be the drug itself or a reactive metabolite generated through cytochromes P450. Mitochondrial alterations are able to induce mild to fulminate hepatic cytolysis and lipid accumulation. If these changes are sever it lead to liver failure. Mechanism underlying this process is due to inhibition of mitochondrial fatty acid oxidation. Also it may be due to increased hepatic lipid synthesis and a decreased secretion of very low density lipoprotein. Other drugs act through primary alterations of white adipose tissue homeostasis that resulted in lipid accumulation, inflammation and fibrosis[38 and 39].

Result obtained from group three which received vitamin C as a protective showed great improvement at the level of cellular structure and function, however the liver enzyme did not return to its normal value. Vitamin C has been used as a protective for liver against many toxic compound like nickel sulfate that caused loss of normal architecture, fatty changes, extensive vacuolization in hepatocytes, eccentric nuclei, and Kupffer cell hypertrophy. It was found that simultaneous administration of L-ascorbic acid led to improvement in both the lipid profile and liver impairments. This indicated the beneficial effect of vitamin. C in preventing nickel-induced lipid alterations and hepatocellular damage[40].

This good effect of vitamin C were observed in protection of the liver against reperfusion liver injury by attenuating hydroxyl radical and nitric oxide release[41]. Also vitamin C was found to be more effective in restoring the endogenous antioxidant system and resulted in decreasing the liver enzyme levels towards their control[42]. At the level of cellular structure vitamin C showed improvement in mitochondrial structure and function. These improvements were mainly via anti-oxidative role of ascorbic acid[43, 44].

CONCLUSION

It can be concluded that Olanzapin has toxic effects on liver as indicated by biochemical and histological changes which observed in this experimental work. Vitamin C exerts protective effects against liver damage induced by Olanzapin.

CONFLICT OF INTEREST

Since antipsychotic drugs are widely used for prolonged time, may be years. The author suggests obtaining baseline liver enzyme tests before starting the therapy and monitoring it regularly specifically in patients with risk factors for liver damage during therapy. Also concomitant use of vitamin C helps in reducing the side effect of these drugs.

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الملخص العربى

دراسة هستولوجية عن تأثير الأولانزابين على كبد ذكر الجرذ الأبيض البالغ مع أوبدون فيتامين ج

رضا حسن البقرى

قسم علم الأنسجة ـ كلية الطب ـ جامعة طنطا ـ طنطا ـ مصر

المقدمة: الأولانزابين من مضادات الذهان الغير نمطية و يستخدم على نطاق واسع في علاج الفصام لفترات طويلة.

الهدف: أجريت هذه الدراسة لتقيم تأثير الأولانزابين على الكبد والتأثير والوقائي المحتمل لفيتامين ج.

مواد وطرق البحث: استخدم فى هذا العمل 40 من ذكور الجرذان البيضاء البالغة وقد قسمت إلى: المجموعة الاولى ضابطة ، المجموعة الثانية اعطيت 2مجم / كجم.من وزنها من الأولانزابين عن طريق الفم مرة واحدة يوميا لمدة شهر. أعطيت المجموعة الثالثة نفس الجرعة السابقة من الأولانزابين بالإضافة إلى 15مجم / كجم من وزنها فيتامين ج عن طريق الفم لنفس المدة. المجموعة الرابعة اعطيت فقط فيتامين ج بنفس جرعة ومدة المجموعه السابقة. فى نهاية التجربة تم الحصول على عينات الكبد و جهزت لدراستها هستولوجيا بواسطة الميكروسكوب الضوئي والميكروسكوب الإلكتروني. وكذلك تم تجميع عينات الدم لقياس مستوى انزيمات الكبد.

النتائج: أظهرت نتائج المجموعة المعالجة بالأولانزابين زيادة مؤثرة فى انزيمات الكبد. بينما أظهر الفحص الميكرسكوبى لعينات الكبد بهذه المجموعة العديد من التغيرات الهستولوجية شملت, تمدد واحتقان بالأوردة المركزية والجيوب الدموية وكذلك تجمعات من الخلايا الالتهابية في المناطق البابية. وفجوات بسيتوبلازم الخلايا الكبدية خاصة حول الاوردة المركزية. شوهد كذلك تكسر الميتوكوندريا، تمدد القنوات الصفراوية وترسب مفرط للدهون. اعطاء فيتامين ج قلل من هذه التاثيرات.

الإستنتاج: أوضحت نتائج هذه التجربة ان تناول فيتامين ج قلل الى حد كبير من التأثيرات النسيجية المستحدثة بالاولانزابين, مما يوحى بأن فيتامين ج له تأثير وقائى على الكبد.