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ASSESSMENT OF HEPATOTOXIC EFFECTS OF QUETIAPINE AT REPEATED DOSES IN RATS

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ABSTRACT

Quetiapine is an atypical antipsychotic drug used for treatments of patients with schizophrenia. Although hepatotoxic effects related to quetiapine treatment were reported in a few studies, potential hepatotoxicity of this drug was not identified. Therefore, it was aimed to evaluate the possible hepatotoxic effects of quetiapine by oral administration of this drug at 10 and 20 mg/kg doses to rats for 30 days in our study. For this purpose, plasma aspartate aminotransferase, alanine aminotransferase, total bilirubin and direct bilirubin levels as markers of hepatotoxicity were determined and histopathological examination was performed in liver tissues. Additionally, we evaluated GSH levels in liver tissues. According to our results, serum aspartate aminotransferase and alanine aminotransferase levels were significantly increased in quetiapine-administered groups, whereas total and direct bilirubin levels were significantly increased in the high dose group. Histopathological investigation of liver tissue indicated that necrotic regions were present in 10 mg/kg quetiapine-administered group whereas prevalent necrotic regions accompanying sinusoidal dilatation were observed in 20 mg/kg quetiapine-administered group. Otherwise, there is not any significant difference among groups in terms of GSH levels. According to these results, we concluded that quetiapine treatment induced hepatotoxic effects in rats, dose-dependently.

Keywords: Quetiapine, Hepatotoxicity, Hepatic biomarkers, Oxidative stress

1. INTRODUCTION

Liver is an important target of xenobiotics including drugs due to its biochemical and physiological functions because of its high capacity of metabolizing enzymes and its anatomical location [1, 2]. On the other hand, it is known that hepatotoxicity is an important reason of drug withdrawal from the market [3-5]. Therefore, it is important to determine the hepatotoxic potential of drugs in the early stages of drug discovery / development processes [6]. Identification of idiosyncratic drug-induced liver damage is particularly difficult in the early stages [1, 7]. Therefore, investigating drug-induced hepatotoxic effects *in vivo* and *in vitro* is considered as an important field of research.

Quetiapine (QET) is an atypical antipsychotic drug that is frequently used for the treatment of negative and positive symptoms of schizophrenia. Additionally, it is also used to treat major depressive disorder and also the symptoms of mania or depression in people with bipolar disorder [8-11]. QET is one of the most prescribed drugs and there is also a remarkable increase in the use of QET among other antipsychotic drugs [9, 12]. Although, it is known that QET has rarely been associated with acute liver injury, cases of fulminant hepatic failure secondary to use of QET were described [13-16]. It was reported that a few QET-treated patients exhibited transient and asymptomatic increases in liver enzymes [17, 18]. Otherwise, fatal hepatotoxicity has been reported clinically related to the QET treatment [19].

In other studies, limited hepatotoxicity risks related to QET treatment were reported, however hepatotoxic effects of this drug were not adequately investigated. At this point, it is emphasized that it

is required to perform experimental and clinical studies regarding the effects of QET treatment. Therefore, unlike the other studies performed previously, in this study, we aimed to evaluate hepatotoxicity associated with QET administration at repeated pharmacological doses in rats. For this purpose, we evaluated the hepatotoxicity by determining the levels of hepatic biomakers such as plasma aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin levels and histological findings of liver tissue after QET administration in rats. In addition, levels of GSH, which has an important role in drug-induced hepatotoxicity, are determined in our study.

2. MATERIALS AND METHODS

2.1. Materials

QET was donated by IE Ulagay-Menarini Group, Istanbul, Turkey. The chemicals used for anesthesia were obtained from the following source: Ketamine (Ketalar®) (Pfizer, Turkey); Xylazine (Sigma, US). Plasma AST, ALT, total and direct bilirubin levels were determined by colorimetric kits from Biolabo S.A. (France). Glutathione (GSH) levels were measured using ELISA kit from Cayman Chemical Company (USA).

2.1.1. Animals

Female Sprague-Dawley rats weighing 300-350 g were used. The animals were housed and used in accordance with ethical recommendations of Local Ethical Committee on Animal Experimentation of Anadolu University, Eskisehir, Turkey (**Protocol Number**: 2013-9). Three experimental groups were used in the present study:

Control group: animals received distilled water orally for 30 days (n=8).
QET-20 group: animals received 20 mg/kg dose of QET orally for 30 days (n=8).
QET-10 group: animals received 10 mg/kg dose of QET orally for 30 days (n=8).

All drugs were administered at a volume of 1 mL/100 g by dissolving in distilled water. The doses of QET were determined according to the previous studies [20-22].

At the end of 30 days, the animals were anesthetized by intraperitoneal injection of 60 mg/kg ketamine and 5 mg/kg xylazine [23]. Blood samples for the analysis of biomarkers (AST, ALT and bilirubin (total and direct)) were collected from the right ventricle of the animals via syringe.

The animals were euthanatized via withdrawal of large amounts of blood from the heart.

Liver tissues were removed and cleaned from blood in phosphate buffer solution (PBS) (8 g/L NaCl, 0.2 g/L KCl, 0.2 g/L KH_2PO_4, 1.14 g/L Na_2HPO_4, pH 7.4). The left lateral lobe of liver was used to determine the levels of GSH. The right superior lobe of liver was cleared of blood and other contaminants in PBS and fixed for histological examination.

2.2. Methods

2.1.1. Determination of plasma hepatic biomakers in rats

After 30 minutes of drawing the blood to allow clotting, blood samples from rats were centrifuged at 1,000 g for 15 minutes at 4°C, and plasma was separated. The enzyme analyses were performed using the commercially available kits according to manufacturer's instructions.

2.1.2. Histological analysis of liver tissue

The livers tissues were sliced into small pieces (5 mm^3) and then fixed a 10% buffered formalin solution for 48 hours. They were dehydrated in a graded series of alcohols. Then, samples were stained with haematoxylin and eosin and examined by light microscopy. All sections were observed under an Olympus BH-2 (Olympus Corp., Tokyo, Japan) microscope.

2.1.3. Determination of GSH levels in liver tissues

The principle of the GSH assay is that the sulfhydryl group of GSH reacts with DTNB (5,5'-dithio-bis-2-nitrobenzoic acid, Ellman's reagent) and produces a yellow colored 5-thio-2-nitrobenzoic acid (TNB). The mixed disulfide, GSTNB (between GSH and TNB) that is concomitantly produced, is reduced by glutathione reductase to recycle the GSH and produce more TNB. The rate of TNB production is directly proportional to this recycling reaction which in turn is directly proportional to the concentration of GSH in the sample. Measurement of the absorbance of TNB at 405 or 412 nm provides an accurate estimation of GSH in the sample. GSH is easily oxidized to the disulfide dimer GSSG. Because of the use of glutathione reductase in the assay kit, both GSH and GSSG are measured and the assay reflects total glutathione.

The left lateral lobe of liver was homogenized in a proportion of 1:20 (w/v) in cold buffer containing 50 mM MES and 1 mM EDTA, pH 6-7. The samples were centrifuged at 10,000g for 15min at 4 ^{0}C and the supernatant aliquots were used for the total GSH assay.

At the end the assay, average absorbance values for samples and standards at 405 and 412 nm were determined after 25 minutes. Absorbance values for standards and samples were subtracted from themselves to obtain corrected absorbance values. Absorbance values of each standard were plotted as a function of total GSH. Then, total GSH was calculated according to the formula below:

Total GSH or GSSG = [(Absorbance at 405-Absorbance at 414)- (y-intercept)/slope] x 2 x Sample dilution

2.1.4. Statistical analysis

Data are presented as mean ± standard error. Statistical analyses were performed using one-way variance analysis (ANOVA) with Tukey test as post hoc test on SPSS program version 15 with the significance level $P<0.05$.

3. RESULTS

3.1. Effects of QET Administration on the Serum Hepatic Enzymes in Rats

When the groups were compared in terms of plasma AST levels, dose-related increases were observed in the QET-administered groups compared to the control group. AST levels were increased in QET-10 and QET-20 groups 39.57% and 43.89%, respectively when compared to control group. A statistically significant increase was found in the plasma ALT levels of 10 and 20 mg/kg QET-administered groups compared to the control group. Additionally, ALT levels were increased in QET-10 and QET-20 groups 31.77% and 29.13%, respectively when compared to control group. No significant differences were obtained among the QET-administered groups in terms of plasma AST and ALT levels. When the groups were compared in terms of plasma total bilirubin and direct bilirubin levels, statistically significant increases were found in 20 mg/kg QET-administered group compared to the control group. Additionally, total bilirubin and direct bilirubin levels were increased 50.00% and 17.40%, respectively in QET-20 group when compared to control group. Among the QET-administered groups, the plasma total bilirubin and direct bilirubin levels did not show any statistical differences (Table 1).

Table 1. Effects of QET administration on the serum hepatic biomarkers in rats

	C	QET10	QET-20
ALT (U/L)	40.58 ±1.39	53.47 ±4.23 (*)	52.40 ±3.31 (*)
AST (U/L)	83.60 ±2.49	116.68 ±10.83 (*)	120.29 ±13.10 (*)
BILD (mg/dL)	0.034 ±0.004	0.04 ±0.002	0.051 ±0.004 (*)
BILT (mg/dL)	0.063 ±0.001	0.071 ±0.001	0.074 ±0.004 (*)

ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, BILD: Direct bilirubin, BILT: Total bilirubin. C: Control group; QET-10: 10 mg/kg quetiapine administered rats for 30 days group; QET-10: 20 mg/kg quetiapine administered rats for 30 days group.
All data were expressed as mean ± standard error.
* Significant differences when compared with control group ($P < 0.05$).

3.2. Effects of QET Administration on the Liver Histology in Rats

In liver tissues of the control group, normal hepatic architecture and normal hepatocytes with prominent nucleus, central vein, and portal areas with no sign of inflammation or necrosis were observed (Figure 1). Necrotic cell foci in the parenchyma tissue were rarely observed in 10 mg/kg QET-administered group (Figure 2). In liver tissues of the QET-20 group, intense necrotic cell foci and sinusoidal dilation were seen in the parenchyma tissue (Figure 3).
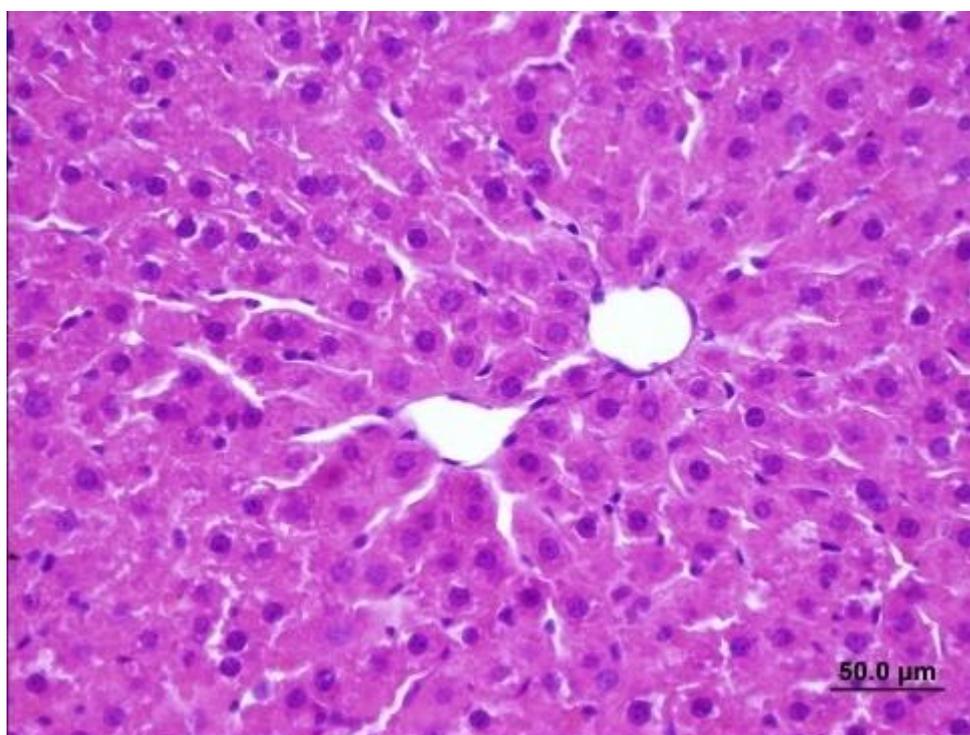

Figure 1. Histological images of liver tissues of the control group
Normal aspects of liver tissue with hepatocyte cells and sinusoidal structures (bar:50.0µm, HE).
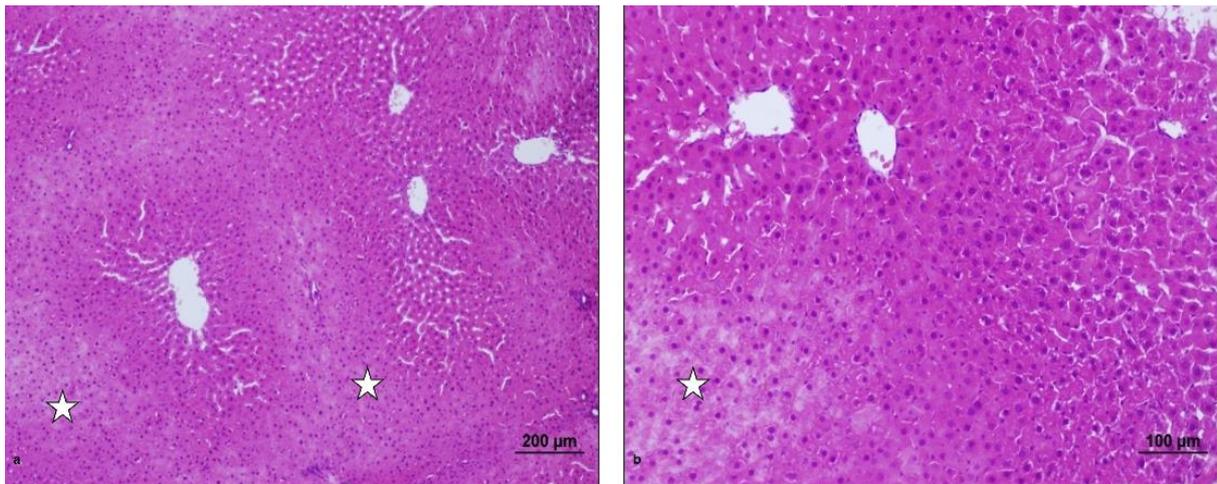
Figure 2. Histological images of liver tissues of the QET-10 group
Intense necrotic areas (*) in 10 mg/kg quetiapine administered rats (a, b) (bar:200µm, bar:100µm, HE).
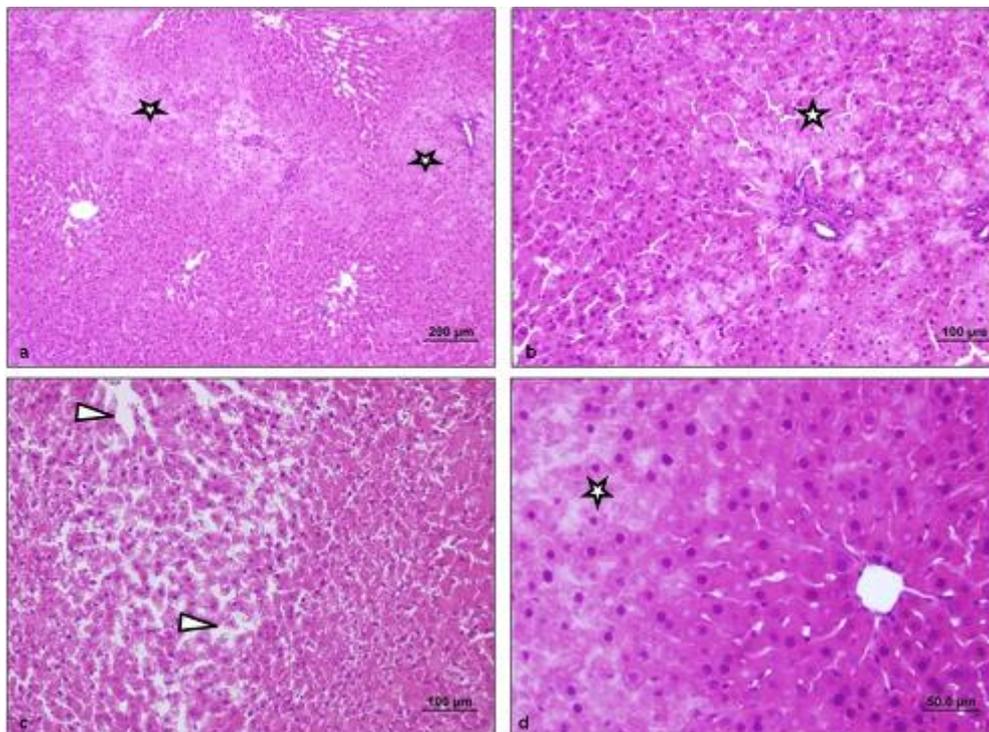

Figure 3. Histological images of liver tissues of the QET-20 group
Intense necrotic areas (*), sinusoidal dilation (►) and abnormal nuclear structure in 20 mg/kg quetiapine administered rats (a-d) (bar:200µm, bar:100µm, bar:50.0µm, HE).

3.3. Effects of QET Administration on GSH Levels in Liver Tissues

The GSH level of liver tissues did not show any significant difference in the among groups (Figure 4).
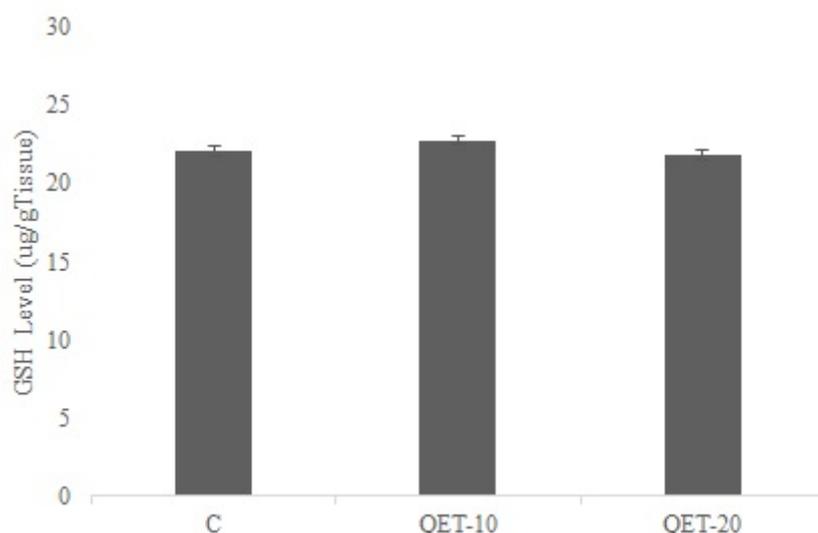

Figure 4. Effects of QET administration on GSH level in liver tissue.
GSH: glutathione; C: Control group; QET-10: 10 mg/kg quetiapine administered rats
for 30 days group; QET-20: 20 mg/kg quetiapine administered rats for 30 days group.
All data were expressed as mean ± standard error.

4. DISCUSSION

The hepatic adverse effects of QET were evaluated at repeated pharmacological doses in our study, which we performed independently of other risk factors related to hepatotoxicity. Pathological findings attracted attention in the QET-20 group. In our study, it was determined that plasma AST, ALT, total and direct bilirubin levels were increased after QET administration in rats, dose-dependently. Necrotic cells and sinusoidal dilation were observed in the histological sections of the liver tissue in the QET-20 group, while necrotic cells were rarely observed in the liver tissue of 10 mg/kg QET-administered rats. However, when the GSH levels in the liver tissue after QET administration was evaluated, no significant differences were observed.

The clinical manifestations of drug-induced liver injury are highly variable, mostly asymptomatic. For this reason, it is difficult to detect liver injury in the early stages [24-26]. Clinically, liver damage is detected by biomarkers that indicate the changes of normal liver function, such as plasma bilirubin levels, and biomarkers that indicate the changes of tissue and cell integrations, such as plasma ALT and AST. Plasma elevations of ALT and AST indicate hepatocellular damage [24, 27-29]. Although plasma AST level is used as a biomarker of hepatic damage, it is known that its specificity to liver damage is limited when compared with plasma ALT level [24, 30]. Therefore, ALT is considered to be the most important biomarker of liver damage [31]. Otherwise, elevation in plasma total bilirubin reflects loss of liver metabolism such as reduced hepatocyte uptake, impaired bilirubin conjugation, or reduced bilirubin secretion [32]. Therefore, plasma bilirubin level is a liver function biomarker that measures the clearance capacity of the liver to clear bilirubin from the blood [33]. ALT and bilirubin levels, which were defined as Hy's Law, indicate more severe injury than plasma enzyme elevations alone (ALT = 3 × upper limit of normal and total bilirubin = 2 × upper limit of normal) [24, 30, 34]. Similar to Hy's Law, FDA recommends a combination of plasma ALT, AST and total bilirubin concentration to identify potential liver injury [35]. QET administration to rats, especially the high dose QET, has significantly

increased plasma AST, ALT, direct and total bilirubin levels compared to the control group in our study. However, these increases did not reach the levels as Hy's Law and the FDA suggested when compared to the control group. At this point, it has to be emphasized that liver histopathological examination serves as the most important marker for identifying liver injury whether or not accompanied by significant serum biochemical changes. So, the presence of significant pathologic findings such as the pattern of cellular damage, the presence of cellular infiltrates, and the presence of necrotic and/or apoptotic cells should be addressed [35]. In QET treated groups, liver tissues were shown to be degenerated dose-dependently.

Generally, liver damage is induced by reactive metabolites that generate through biotransformation of drugs. These reactive metabolites interact with cellular macromolecules such as proteins, lipids, and nucleic acids, leading to protein dysfunction, lipid peroxidation, DNA damage, consequently induce oxidative stress in cells [36, 37]. Liver's being the main organ for drug metabolism serves it as a primary target of reactive metabolites of drugs. Reactive metabolites are often produced through oxidation and reduction by cytochrome P450 [38-40]. QET is metabolized mainly by hepatic metabolism via CYP450 3A4 and CYP450 2D6 enzymes. Although studies have shown that QET has less reactive metabolite formation with peroxidases, major metabolite of QET, 7-hydroxy QET, can react with the peroxidases, so free radical formation can occur. Toxic effects can be induced with the electrophilic quinone-imine metabolite [41]. However, the protective effects of QET have been demonstrated *in vitro* and *in vivo* experimental models in which oxidative stress plays a role in pathologies (42-49). GSH is a critical cellular antioxidant, which is important in combating cellular oxidative stress [24, 50]. Hepatotoxicants that are biotransformed to reactive metabolites by liver enzymes generally deplete GSH stores in the liver [24, 51-53]. Frequently, any condition related to oxidative stress results in decreased GSH levels or the GSH/GSSG ratio [52, 54, 55]. In our study, no change was observed in the GSH levels of QET-treated groups compared to the control group. However, we emphasized that liver malondialdehyde levels, the end product of lipid peroxidation, were not determined in our study. As it is known that oxidative stress is induced with the imbalance between production of reactive metabolites and antioxidant status [56, 57]. On the other hand, autoimmunity, idiosyncratic reactions (immune idiosyncrasy and metabolic idiosyncrasy), disruption of calcium homeostasis and cell membrane injury, stimulation of apoptosis and mitochondrial injury are the underlying mechanisms of drug induced liver injury [2, 36, 37, 58]. Although, oxidative stress is considered to play a critical role in the pathophysiology of liver injury, QET-induced liver toxicity did not generate oxidative stress (decrease in glutathione) in our study. In addition, the high amount of GSH reserves in the liver may be a cause of unchanged GSH levels in QET-administered groups.

5. CONCLUSION

According to our results which were obtained independently of other risk factors, QET-induced hepatotoxicity in rats, dose dependently. During QET treatment, patients should be aware of hepatotoxicity and biomarkers of hepatotoxicity may be suggested to be monitored. Particularly, in patients with hepatic impairment and elderly, QET should be cautiously used and minimum effective dose of QET should be recommended.

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