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ORIGINAL ARTICLE

Imipramine Treatment Is Associated with Impaired Liver Function in Mice.

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ABSTRACT

Background: Besides its antidepressant effect, imipramine is also used as an effective therapy for the management of nocturnal enuresis in children. This study aimed to investigate the potential effects of imipramine administration on liver function and architecture

Methods: Wild type male BALB/c mice were treated orally with imipramine at low (5mg/kg) and high (10mg/kg) doses, once a day, for four weeks. The animals were allocated to three groups, each including ten mice: control group, low dose group (5mg/kg), high dose group (10mg/kg). The biochemical and histological effects of the treatment were evaluated via intergroup comparison, using one way ANOVA test

Results: the animals that had received low dose of imipramine showed significantly higher serum levels of aspartate transaminase (AST), alanine transaminase (ALT), and alkaline phosphatase (ALP) compared with the control group. The high dose group displayed significant higher levels of AST, ALT, and ALP compared with that in the control group. Additionally, the high dose animals showed significantly elevated levels of serum AST, ALT, and ALP compared with that in the low dose group. The microscopic assessment of the liver sections from the low dose group exhibited mild swelling of the centrilobular hepatocytes and vascular congestion. These changes were considerably more evident in the high dose group

Conclusions: The hepatotoxic effect of imipramine appears to be dose dependent as indicated by the considerable elevation in liver function tests along with histopathological changes in the high dose animals. These findings remain factual observations, the clinical relevance of which warrants further investigations

Keywords: Imipramine, Hepatotoxicity, AST, ALT, ALP.

INTRODUCTION

The accurate *preclinical* assessment of human drug toxicology remains a major challenge in drug design and development [1]. As stated by Lasser *et al*., more than five hundred new chemical entities were approved by the US food and drug administration (FDA) between 1975 and 2000. Of these, sixteen drugs were subsequently withdrawn from the market, with seven drugs approved and marketed since 1993 and subsequently withdrawn due to their potential associations with over 1000 deaths [2].

The liver is the largest organ in the human body. It performs multiple indispensable functions that can significantly impact the functionality and efficiency of all body systems. Owing to its crucial role in drug metabolism and detoxification, the liver is especially susceptible to medication-related toxicity attributable to the concentration of drugs and their metabolites in portal blood [3; 4]. Due to the rising number of identified hepatotoxic drugs in current use, drug-induced hepatotoxicity remains a clinical challenge not only for *health care* professionals, but also for pharmaceutical industry and regulatory authorities [5]. Drug-induced liver disease is estimated to be the fourth leading cause of liver dysfunction in Western countries. It is furthermore the most frequent reason for drug withdrawal after initial marketing approval [6]. Approximately 1,000 medications used in clinical practice have been associated with some form of liver injury [7].

The tricyclic antidepressant imipramine, a dibenzoazepine derivative, was approved by the FDA as antidepressant medication in the 1950s [8]. Imipramine is considered a second-line treatment prescribed primarily for serious depression with atypical features [9]. Besides its antidepressant effect, imipramine has strongly been suggested as an effective adjunctive therapy for the treatment of nocturnal enuresis in children older than six years of age [10]. Physicians are also given some flexibility to use imipramine off-label for the management of chronic neuropathic pain [11]. Even with the continuing development of newer and less toxic antidepressants, the prescription of tricyclic antidepressants, with imipramine as first member, is still common as they are inexpensive and still considered to be the most effective class of antidepressants [12].

As for other tricyclic medications, the risk of developing toxicity from imipramine is particularly greater at higher cumulative doses. An overdose of imipramine is associated with serious side effects, including cardiac dysrhythmia, critical hypotension, convulsions followed by coma and respiratory depression [13]. Imipramine is still available as tablets (10, 25 and 50 mg) and capsules (75, 100, 125, 150 mg) with over one million prescriptions being written annually [8; 9]. Unfortunately, there is still a lack of accurate statistics upon which to make reliable estimates of the number of imipramine prescriptions dispensed in Libya.

To date, there has been relatively *little empirical research* designed to investigate the potential influence of imipramine treatment on liver structure and function. For instance, Wadi [14] investigated the impact of daily administration of imipramine at 10 mg/kg for a duration of three weeks on mice. This study revealed significant increases in the liver enzymes (i.e., AST, ALT, and ALP) along with prominent changes in the hepatocellular morphology in the treated mice compared with the control animals. Furthermore, after eight weeks of imipramine treatment (10mg/kg), the treated mice exhibited elevated body and liver weights; increased serum triglyceride, ALT and AST, in addition to increased expressions of fatty acids [15]. Comparable results have been reported by Atta *et al.*, who examined the changes in liver architecture and functions after the treatment of albino rats for four weeks with amitriptyline, another therapeutic antidepressant with a similar tricyclic structure to imipramine. These authors also found a substantial elevation in serum levels of ALT, AST, ALP with moderate fibrosis and remarkable diffuse necrosis of hepatic tissue in treated rats [16].

The very few empirical studies available focused primarily on the possible side effects of imipramine at its minimal therapeutic doses (10mg/kg), which represents the lowermost concentration that results in the required Pharmacological response, whilst the potential impact associated with the regular consumption of imipramine at doses of lesser than the minimum effective concentration (e.g., 5mg/kg) has apparently been disregarded.

In this context, the aim of the present study was to ascertain whether imipramine administration have any effects on liver function. This was attained by comparing the influence of two different dose levels; the sub-effective or "low" dose (5mg/kg) and the minimal therapeutic or "high" dose (10mg/kg) of imipramine, which are proportional to the therapeutic doses used by humans, on liver biochemical and histological markers in wild type male BALB/c mice.

METHODS

The study was conducted on a total number of 30 healthy wild type male BALB/c mice, weighing 20-30g and aged 6-8 weeks. All the experimental animals fed with standard laboratory chow and water ad libitum. All animal experiments complied with the ARRIVE guidelines and were carried out in accordance with the U.K. Animals Act. Animal handling and treatment were performed in accordance with the Institutional Ethics Committee. To be predictive of human response, the doses of the drug applied were calculated based upon the human therapeutic dose according to Paget and Barnes conversion tables. The therapeutic imipramine doses were selected based on available literature [17; 18].

Study Design and Drug Administration

To be acclimated to diet and housing conditions, all the experimental animals were retained in the animal facility for one week. Thereafter, they were allocated at random into three groups, each including ten mice: First: control group, which had a free access to food and distilled water for four weeks. Second: low dose group, which were given low dose of imipramine 5mg/kg. Third: High dose group were given high dose of imipramine 10mg/kg. Each group of mice were housed in separate cage and were maintained under standard diet and housing conditions as well as other environmental surrounding. For the treated animals, the designed dosages of imipramine were administered orally, once a day, for four weeks using a disposable tip and automatic pipette. All precautions were taken to minimize the number and suffering of the animals used in the study. All mice survived until the end of the experiment and were at last euthanized at scheduled time by decapitation under either anesthesia.

Blood sample and tissue collection

A blood sample of about 2 mL was collected from facial vein from each individual mouse using biochemistry tubes. The blood specimens were centrifuged at room temperature, 3000rpm for 10min within 30min of collection. The obtained serum was stored to be used for subsequent biochemical analysis. The animal's livers were cautiously removed, rinsed, weighed and fixed with 10 % formalin solution at room temperature until further tissue processing and histopathological examination.

Biochemical assessment

Serum total bilirubin, alanine transaminase (ALT) aspartate transaminase (AST), and alkaline phosphatase (ALP) levels were measured using Selectra Prom Analyzer (ELITechGroup Vital, Dieren, The Netherlands), with commercially available kit (ELITech clinical system, Dieren, The Netherlands) in compliance with the manufacturer's guidelines. Biochemical tests were performed at Qasser Ahmed Hospital Laboratory.

Tissue processing and histological assessment

The animal's livers were cautiously collected and fixed with 10 % formalin solution for 24 hours at room temperature. Fixed tissues were dehydrated in a series of ascending concentrations of ethanol, followed by embedding in molten paraffin at a temperature of 55°C. Thereafter, the tissue paraffin blocks were cut equally into tissue slices at 5 µm thickness using a rotary microtome (pfm 3004, MicroHM315 thermoscientific, Germany). The paraffin section was transferred onto a slide and the tissue slides were handled to remove embedding medium and rehydrated and subsequently stained with hematoxylin and eosin (H&E) staining. Once dry, the slide was covered with a cover slip using Canada balsam. Microscopic examination and imaging of the stained liver tissue sections was carried out by means of Hayer digital microscope camera (Labomed Microscope, Los Angeles, America).

Statistical analysis

The biochemical effects of the imipramine treatment were evaluated via intergroup comparison using Factorial Analysis of Variance (ANOVA) (one-way or two-way), with Graph Pad Prism™ software (GraphPad™ Software, Version 6.0, San Diego, CA, USA). All data were reported as mean ± Standard Deviation (SD). Statistical significance was set at $p < 0.05$.

RESULTS

Biochemical findings

As shown in Figure 1, results obtained from the present study revealed that the total serum bilirubin (0.447±0.046 vs. 0.457±0.0441, $p>0.05$) in the group of animals receiving low dose of imipramine were not significantly different from that in the control group. Also, the animals that had received high dose of imipramine showed relatively, though not statistically significant, higher levels of total bilirubin (0.561±0.0699) compared to that in the control group ($p>0.05$). Similarly, no significant differences in the total serum bilirubin levels could be seen between the low dose and the high dose mice groups (0.447±0.046, vs. 0.561±0.0699, $p>0.05$).

Furthermore, the animals receiving low dose of imipramine showed significantly higher serum levels of AST (250±10.5 vs. 243.5±9.62, $p<0.05$), ALT (81.8±5.58 vs. 52±2.62, $p=0.008$), ALP (195.9±22.8 vs. 155.2±6.2, $p<0.05$), compared with the control group. Also, the high dose group displayed significant higher levels of AST (305.8±22.4, $p=0.025$), ALT (92.3±6.67, $p=0.001$), ALP (218.7±26.5, $p=0.045$) compared to that in the control group. Likewise, the animals that had received high dose of imipramine showed significantly elevated levels of serum AST (305.8±22.4 vs. 250±10.5, $p=0.043$), ALT (92.3±6.67 vs. 81.8±5.58, $p<0.05$), ALP (218.7±26.5 vs. 195.9±22.8, $p<0.05$) when compared with animals that had received low dose (Figures 2, 3, 4).

Histopathological findings

Three hematoxylin-eosin-stained slides per mouse from each group were analyzed at different magnifications using Labomed CXL microscope (LC-1 USB2). Variations in hepatic lobular architecture, fatty modifications, nuclear alterations and congestion of the sinusoids were evaluated. As visualized by light microscope (100x and 400x), the liver sections in the control group of animals (Figure 5) showed normal cellular and typical architecture of hepatic lobules. However, the hepatic tissues from the animals which had been given low dose of imipramine (Figure 6) exhibited mild swelling of the centrilobular hepatocytes and vascular congestion. At higher dosages, imipramine-induced hepatic lesions included prominent pathological changes characterized by manifest centrilobular hepatocyte swelling (Figure 7), portal inflammation and widespread infiltrations of inflammatory cells i.e., eosinophils (Figure 8) and lymphocytes as well as even more extensive vascular congestion (Figure 9).

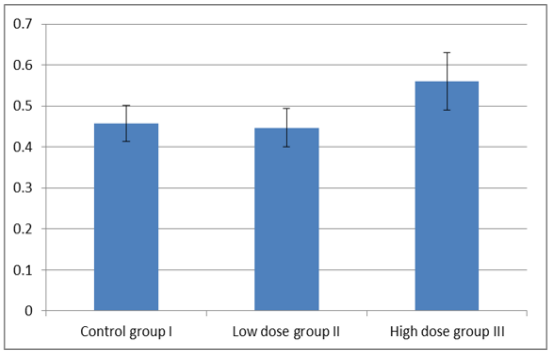

Figure 1. Serum total bilirubin concentrations (mg/dL) in the different experimental groups (Mean ± SD).

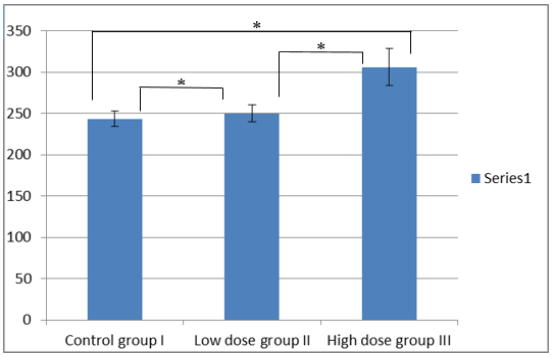

Figure 2. Serum AST concentrations (U/L) in the different experimental groups (Mean ± SD). * = ($p<0.05$).

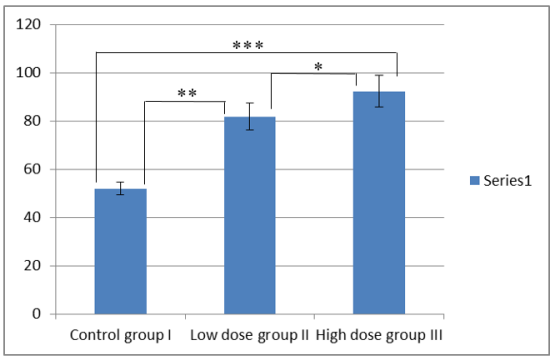

Figure 3. Serum ALT concentrations (U/L) in the different experimental groups (Mean ± SD). * = ($p<0.05$), **= ($p<0.01$), *** = ($p\leq0.001$).

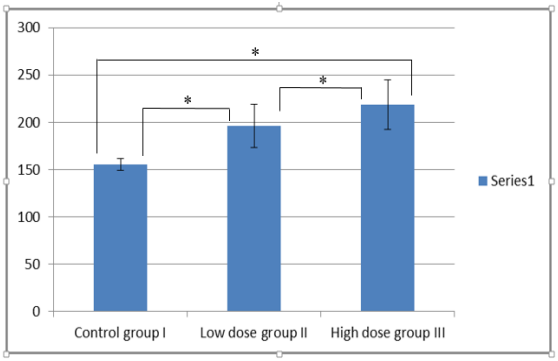

Figure 4. Serum ALP concentrations (U/L) in the different experimental groups (Mean ± SD). * = ($p<0.05$).

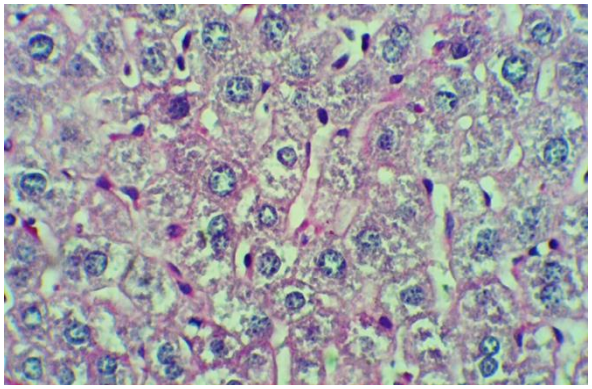

Figure 5. Liver section in the control mice showing normal hepatocytes and sinusoids (H&E, 400X).

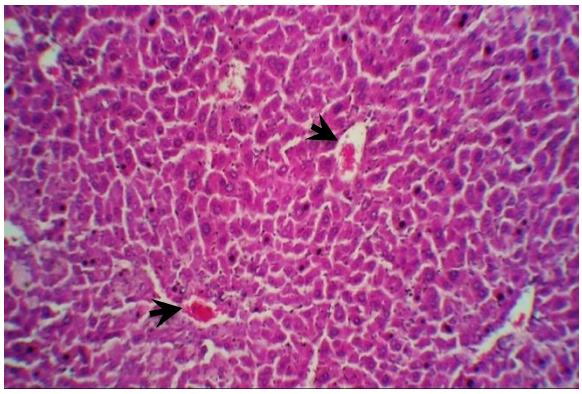

Figure 6. Liver section in mice treated with low dose of Imipramine, showing venous congestion (H&E, 100X).

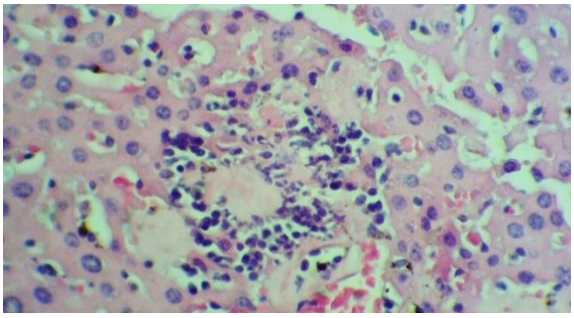

Figure 8. Liver section in mice treated with high dose of Imipramine, showing eosinophilic infiltration (H&E, 400X).

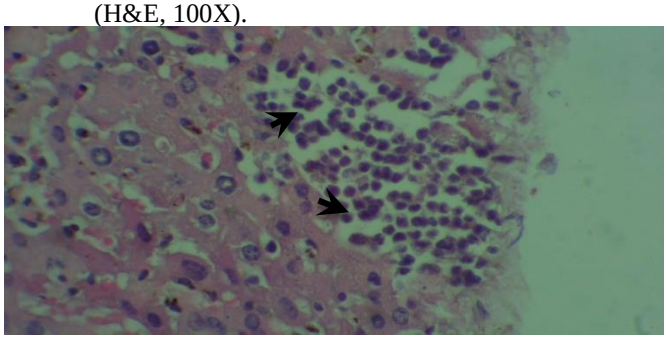

Figure 9. Liver section in mice treated with high dose of Imipramine, showing perivenular Lymphocytic infiltration (H&E, 400X).

DISCUSSION

This study aimed to assess the potential effects that imipramine may have on liver function parameters through the treatment of wild type male BALB/c mice with low (5mg/kg) and high (10mg/kg) dosages of the drug. The treatment was administered orally, once a day, for four weeks using a disposable tip and automatic pipette.

The current study has successfully established a mouse model of imipramine-induced liver injury at drug doses which are proportional to the therapeutic dosages and regimens used by humans. Adverse drug reactions have been considered as an established cause of liver injury. Several hundreds of drugs have been implicated in hepatotoxicity. The manifestations of drug-induced hepatotoxicity are extremely variable and can range from asymptomatic abnormalities in liver biochemical findings to complete hepatic failure [19]. Hepatotoxicity is commonly characterized by rises in liver function enzyme levels. The hepatotoxic effect of imipramine observed in the current study appears to be dose-dependent as evidenced by the prominent increase in liver function markers and histopathological changes in the high-dose animals (10mg/kg) compared with animals that had received low dose (5mg/kg).

These findings are consistent with those attained from the study by Wadi [14], who examined the effects of daily administration of imipramine at 10 mg/kg for a period of three weeks in mice. This study reported significant elevations in the liver enzymes (i.e., AST, ALT, and ALP) as well as prominent changes in the hepatocellular morphology (i.e., hepatocyte enlargement, degeneration and necrosis) in the treated mice compared with the control animals. *In* a recent experimental study, Chang *et al*. examined C57BL6/J mice subjected to a high-fat diet to evaluate the effect of imipramine on obesity, liver and kidney markers. In this study, Chang *et al*. observed that after eight weeks of imipramine administration (10mg/kg), the treated mice displayed higher body, and liver weights; higher serum triglyceride, ALT AST, creatinine and blood urea nitrogen as well as higher expression levels of fatty acids [15].

Imipramine-induced liver dysfunction was further supported by a case report of a patient who had been treated with imipramine for several years and displayed hepatic venous congestion along with considerable increases in serum levels of AST and ALT greater than ten times the upper limit [20]. Similar biochemical and histological abnormalities were revealed in another case report describing a middle-aged woman who had received a daily dose of imipramine for 7 days and developed severe cholestatic jaundice with features akin to primary biliary cirrhosis [21].

The liver is a primary site for drug metabolism as it plays a crucial role in the removal of metabolic waist products and detoxification of toxic substances as well as synthesis of valuable products [10]. Therefore, the liver is a common target organ of drug-induced toxic effects. *Clinically available biochemical markers of liver function* provide an expedient sensitive indicator of the extent of liver damage. A common classification of drug-induced liver injury comprises three main categories namely hepatocellular, cholestatic, or mixed injury. Hepatocellular injury is characterized by increased levels of serum ALT, along with slightly elevated or unchanged ALP levels. ALT is normally present at high concentrations in the hepatocyte cytoplasm, thereby *damage to the hepatocyte's membrane* increases the leakage of this enzyme into blood circulation [22]. AST is known to be less sensitive marker of liver injury as its serum levels may also be elevated in other conditions such as rhabdomyolysis and myocardial infarction [23]. However, simultaneous changes in serum levels of these enzymes, as observed in the present study, provide additional support about the existence of hepatocellular damage [24; 25]. In addition to these alterations in the hepatic function, imipramine was also shown to induce considerable pathological changes in the liver architecture of the treated mice, characterized by marked centrilobular hepatocyte swelling, portal inflammation as well as extensive infiltrations of inflammatory cells. However, these findings were substantially more perceptible among mice in the high-dose group. Accordingly, the hepatotoxic effect of imipramine appears to be dose-dependent as evidenced by the prominent increase in liver function markers and histopathological changes in the high-dose animals (10mg/kg) compared with animals that had received low dose (5mg/kg). These observations were further supported by the relative, though not significant elevation in the bilirubin levels in the high-dose group. The rationale is that increased serum bilirubin levels in the absence of bile duct obstruction indicates that large proportion of the liver tissue must have damages [7; 22].

The underlying mechanism by which imipramine induces hepatic damage remains ambiguous and require more clarification. However, it is interesting to speculate on how this may occur. Owing to their *high* energy requirements, the hepatocytes contain a relatively large number of mitochondria, which are in a large measure the major site of intracellular Reactive Oxygen Species (ROS) production through the activation of the

electron transport mechanism [26; 27]. There is compelling *experimental evidence to suggest* the potential role of oxidative stress in mediating antidepressant-induced organ dysfunction [28]. For instance, Duda *et al*. found that recurrent imipramine administration resulted in a significant increase in ROS and malondialdehyde (MDA, a by-product of lipid peroxidation, commonly used as a marker of oxidative damage) levels in the homogenized liver tissue [8]. Lipid peroxidation is a cascade of successive reactions, during which membrane fatty acids are increasingly lost, resulting consequently in reduced membrane fluidity, increased non-specific permeability to ions, and inhibition of membrane bound receptors and enzymes [29; 30]. Similar findings were reported by Abdel-Salam et al., [18], who revealed a marked increase, of about 25 % in nitric oxide in a group of mice treated with higher dose of imipramine (20 mg/kg) compared to their control counterparts. *While the generation of nitric oxide* within physiological limits is essential endogenous regulator of liver *hemodynamic, excessively elevated levels can initiate lipid peroxidation and subsequent cytotoxicity [31]. Interestingly,* studies have shown a link between psychological disorders and increased nitric oxide levels and ensuing oxidative damage *to key enzymes involved in carbohydrate metabolism* [32].

Deducing from the above findings, it can be suggested that imipramine itself or its intermediate metabolites may interact with hepatocellular biomolecules to yield highly reactive agents that are presumably capable of evoking oxidation destructions and extensive damage to multiple biomolecules, including proteins and lipids and subsequently loss of hepatocyte membrane integrity, resulting eventually in histopathological alterations in the liver tissues and spilling of its enzymes into the systemic circulation. However, the precise mechanism by which imipramine therapy mediate liver dysfunction remains uncertain and required additional experimental investigations. Nevertheless, for safety purposes, patients who are recurrently treated with imipramine, or other therapeutic compounds with similar tricyclic structure, should cautiously be advised to have periodic assessments of ALT, AST and ALP serum levels. Regular monitoring of liver function during imipramine treatment is also advisable for patients with underlying liver diseases such as cirrhosis, hemochromatosis and chronic hepatitis, as the development of a severe form of liver injury could have even more devastating and potentially life-threatening consequences.

Although the present study has successfully attained its aim and contributed to the growing body of research regarding the potential hepatotoxic effects of chronic imipramine therapy, the generalizability of these findings is subject to certain limitations. For instance, the study focused on healthy mice, aged between 8-10 weeks. However, imipramine is also used for treatment of enuresis in children, thus, the inclusion of younger or even older animals' *groups* would provide a broader view on the potential age-related drug toxicity. *Future studies should also include female* animals to *clarify* mechanisms underlying *sex differences.* Furthermore, due to financial restrictions, the present study focused on the measurement of gold standard biomarkers that are commonly used as part of the routine assessment of liver function. However, in order to establish a causal relationship between imipramine therapy and liver functionality investigated in the current study, it would be interesting for future studies to investigate variations in the oxidative stress markers i.e., ROS, MDA, catalase, superoxide dismutase, glutathione as well as total antioxidant capacity in serum and liver homogenate.

CONCLUSION

The present study has successfully established a mouse model of imipramine-induced liver injury at drug doses (i.e., 5mg/kg, 10mg/kg) which are corresponding to the therapeutic dosages and regimens used by humans. The hepatotoxic effect of imipramine appears to be dose dependent. However, these finding remain factual observations and their clinical relevance is worthy of further investigations. Meanwhile, considerably more work will need to be done to allow better understanding of the underlying mechanism responsible for imipramine-induced hepatotoxicity. While further controlled trials are required, this study highlights the necessity to raise awareness among clinicians, allied healthcare workers, and the general public regarding the potential adverse health effects and long-term consequences associated with tricyclic antidepressants use.

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