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EFFECT OF QUNINE IN HEPATOTOXICITY AND KIDNEY FUNCTION IN MALE RAT

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Abstract

The present study was designed to evaluate its effects of Quinine on body weight and its hepato-nephrotoxicity. Twenty mice were randomly divided into four different groups of five animals in each group, (600 mg/Kg, 650 mg/Kg, 700 mg/Kg and control) groups. The treatments were administered for two weeks. Quinine produces a significant increase in the mean values of body weights and aspartate and alanine aminotransferase, alkaline phosphatase and a total bilirubin level of treated mice of 700mg/kg group compared with the animals in the control group, compared with a control group.

Key Ward: Quinine, liver, kidney, toxicity.

Introduction

During the last 20 year, more than 25% of drugs were derived from plant species while the other 25% were chemically altered natural product (Achan *et al.*, 2011). It was highlighted that only 5-15% of approximately 250.000 higher plants have been investigated for bioactive (Wen *et al.*, 2018). Plant-based natural constituents can be derived from any part of the plant like bark, leaves, flowers, root, fruits, seeds, etc. *i.e.* any part of the plant may contain active components (Dondorp *et al.*, 2010). On the other hand, the plant has been a source of medicine for thousands of years and phytochemicals play an essential role in medicine (Kaufman and Rúveda, 2005). The goal of screening the medicinal plant is to search for the best anticancer antiinflammation agent avertable to human malignancies (El-Tawil *et al.*, 2015).

Quinine is Natural alkaloid, has been isolated from the bark of the *Rauvolfia caffra*, that exhibits wide pharmaceutical activities like antipyretic, anti-inflammatory, anti-tumor and anti-malarial (Roitman, Wheeler and Carelli, 2005). Quinine has a low therapeutic index and adverse effects with its use are substantial (White, 2005). The side effects commonly seen at therapeutic concentrations are referred to as cinchonism, with mild forms including tinnitus, slight impairment of hearing, headache and nausea (Dunlap and Stephens, 2014). Impairment of hearing is usually concentration-dependent and reversible (Stork *et al.*, 2001). Aim of the study evaluates of quinine effect on toxicity in lab animals hoping to help in cancer treatment.

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Materials and Methods

Experimental design:

The present study was designed to evaluate its effects of Quinine on body weight and its hepatic and nephrotoxicity. Twenty mice were randomly divided into four different groups of five animals in each group; (600 mg/Kg, 650 mg/Kg, 700 mg/Kg, and control) groups. The treatments were administered for two weeks (Kadhim, Aldujaili and Homady, 2017).

Animal management:

Twenty of healthy adult males of albino mice aged (2-3) months, (25-30g) were used in this study. The animals were provided with food and water and were kept at 12h light: 12h dark cycles at room temperature at least 2 days before the experiment. This experiment was approved by the Central Committee for Bioethics in the collage of Sciences, Kufa, Iraq.

Preparation of the drug:

Preparation of the drug was dissolved in normal saline and ethanol. Three groups of mice were received various doses of the Quinine intraperitoneally as a once time (600 mg/Kg, 650 mg/Kg and 700 mg/Kg) respectively (Jawad, Homady and Aldujaili, 2017).

Detection Method:

Determination biochemical parameters:

Blood was collected in gel tube for biochemical estimations of (GOT, GPT, ALP, B. urea, Creatinine and total bilirubin) that were performed using mouse Elisa kits provided by (MyBiosource, Inc.- USA) Sandwich immunoassay technique.

Analytical Discussion:

Results are represented as mean ± standard error (SE) and performed using one-way ANOVA by GraphPad Prism® software (GraphPad Software, Inc., La Jolla, CA, USA) L.S.D was $P \leq 0.05$ in study groups and data were compared between groups using T-test (Cortesi and File, 2003).

Results

Quinine produces a significant increase in the mean values of body weights of mice treated at (700mg/kg), (650mg/kg) and (600mh/kg) respectively, compared with a control group.

Table 1-1: effect of quinine on the body weight of mice treated at different doses (600, 650 and 700 mg/kg).

Treated Dose	Pre- treated (g)	Post-treated (g)	L.S.D (0.05)
700 mg/kg	28.6	32.4	2.6±0.68
650 mg/kg	29.6	30.2	2.8±0.97
600 mg/kg	23.4	28.4	5±0.63
Control	22	28	5±0.5

Table 1-2: effect of quinine on the liver function test of mice treated at different doses (600, 650 and 700 mg/kg).

Parameter Dose	ALKP (ng/mL)	GPT (ng/mL)	GOT (ng/mL)	TSB (ug/mL)
600 mg/kg	46.00±2.05	2.03±37.00	1.52±27.67	0.042±0.633
650 mg/kg	40.67±2.14	2.53±35.00	1.10±22.00	0.042±0.531
700 mg/kg	45.33±2.43	2.41±42.67	1.57±26.67	0.180±0.734
Control	45.67±1.84	1.90±28.00	1.48±21.67	0.021±0.567

Table 1-2: effect of quinine on the liver function test of mice treated at different doses (600, 650 and 700 mg/kg).

ParameterDose	S-Creatine(mg/dl)	B-Urea(mg/dl)
600 mg/kg	0.037±1.000a	0.73±49.00a
650 mg/kg	0.056±0.633a	1.56±42.57b
700 mg/kg	0.110±0.700a	2.56±45.67ab
Control	0.021±0.567b	0.63±30.00c

Toxicology examination of this study shows a significant increase ($P<0.05$) in aspartate and alanine aminotransferase, alkaline phosphatase and a total bilirubin level of treated mice of 700mg/kg group compared with the animals in the control group.

This study suggests there is considerable toxicity liver cell and this compound may behave changes considerable with high doses on liver functions, but its safety in low dose and may require proper evaluation as well as monitoring of liver function during such therapeutic interventions.

This study shows a significant increase ($P<0.05$) in S-Creatine and B-Urea level of treated mice of 700mg/kg group compared with the animals in the control group.

Discussion

To establish important treatment parameters before clinical trials, new compounds are tested extensively in animal models, in screening compounds against cancer, mouse models have shown high predictive reliability in studying the efficacy and activity (Jäger, Tye and Kowarik, 2007). Although toxicity is a major issue in the treatment of cancer, in this paper, we evaluated serum levels of liver enzymes in a mouse model after two concentrations exposure of this compound (Srinivas, Hopperstad and Spray, 2001). The liver is prone to Xenobiotics induced injury because of its central role in xenobiotic metabolism and its portal location within the circulatory system (Srinivas, Hopperstad and Spray, 2001). Many drugs and chemicals can result in adverse forms of liver injury and this may result in distortion of liver histology (Jones, Panda and Hall, 2015). In the assessment of liver condition after sub-chronic of Quinine (600 and 700mg/kg b.w) the determination of liver marker enzymes such as AST, ALT, ALP and bilirubin were used(Fitch, 2004). The increase in serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), ALP and total bilirubin level in the group of 700mg/kg may indicate liver tissue damage probably by altered cell membrane leading to the leakage of the enzyme from the tissues to the serum (Achan *et al.*, 2009). Alanine and aspartate aminotransferase are considered to be sensitive indicators of hepatocellular damage and within time can provide a quantitative evaluation of the degree of damage to the liver (Kempin *et al.*, 2017). A high level of AST indicates liver damage as well as cardiac infarction and muscle injury (Pukrittayakamee *et al.*, 2004). ALT catalyzes the conversion of alanine to pyruvate and glutamate and is released in a similar manner (Bassareo, De Luca and Di Chiara, 2002). Therefore, ALT is more specific to the liver and thus, a better parameter for detecting liver injury (Khozoie, Pleass and Avery, 2009). So elevated levels of these serum liver enzymes might indicate liver necrosis especially in mice administered Quinine (700mg/kg b.w) which significantly ($P<0.05$) increased more than the concentration of other enzymes assayed in the mice of

the other groups(Kyu and Fernández, 2009). Serum ALP and bilirubin level, on the other hand, are related to the function of the hepatic cell (Hopf *et al.*, 2010). The decrease in serum ALP level may be due to decrease in synthesis in the absence of biliary pressure while an increase in bilirubin level observed in this study may be as a result of hepatic dysfunction or injury (PrayGod, de Frey and Eisenhut, 2008). The exact mechanism by which Qunine cause adverse hepatic effect have not been elucidated, Piola *et al.*, 2010 reported that drug-induced liver injury occurs via at least six, mechanisms involving various intracellular organelles, with consequent disruption of intracellular Calcium homeostasis, decline ATP levels and finally hepatocyte swelling and rupture (Lalloo *et al.*, 2007; Suzuki *et al.*, 2009; Kovacs, Rijken and Stergachis, 2015).

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