Evaluation of the Hepatoprotective And Nephroprotective Activities of Vitamin C and E in Paracetamol induced toxicity in Wistar Albino Rats

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ABSTRACT

Free radical-mediated cell damage can be prevented by well-known antioxidant vitamins such as Vitamins E and C, and it has been reported that Paracetamol can cause hepatotoxicity at high doses. This study evaluated the efficacy of the combination of Vitamin C and Vitamin E in the prevention of renal and hepatic cell damage caused by paracetamol toxicity. Twenty-eight male albino rats were grouped into seven of four rats per group. Vitamin C at prophylactic dosage; (200mg, 150mg, 100mg, 50mg, 25mg) and Vitamin E at prophylactic dosage; (500iu, 400iu, 300iu, 200iu, 100iu) were administered orally to the rats in groups 1 through 5, respectively with concomitant administration 1000mg/kg bw of paracetamol twice daily for seven days. Group 6 was administered 1000mg/kg of paracetamol only (untreated), and Group 7 served as the normal control. The results revealed a significantly (P < 0.05) increase in serum ALT, AST, ALP, Urea and Creatinine of the group administered 1000mg/kg of paracetamol only. The prophylactic doses of ascorbic acid and α-tocopherol significantly (P < 0.05) decrease serum ALT, AST, ALP, Urea and Creatinine level compared to the untreated rats. This study validates that co-administration of ascorbic acid and α-tocopherol at the proposed prophylactic dosages could be used in the prevention of renal and hepatic cell damage caused by paracetamol toxicity.

INTRODUCTION

Hepatotoxicity could be caused by the ingestion of chemical substance such as Drug. It is not in doubt that the liver is involved in drug and chemical metabolism and is primarily the major sites for biotransformation (Elias and Brambaifa, 2012). Chemical agents such as drugs are continually screened for Hepatoprotective efficacy, and Vitamins E and C have been reported to possess Hepatoprotective effects. The protective effect of the two vitamins could be due to the antioxidant activities. Paracetamol is capable of inducing hepatotoxicity at higher doses, and the toxicity is due to the formation of N-acetyl-p-benzo quinine imine (NAPQI), which causes glutathione (GSH) depletion and oxidative stress when a part of it is metabolized by cytochrome P-450 (Gulec et al., 2006). Free oxygen radical rises during hepatotoxicity and an increase in reactive oxygen species and free radicals above the endogenous antioxidants leads to liver function compromise. This, in turn, causes a great increase in serum liver function biomark-
ers (Mcmurtry et al., 2005; Mudge et al., 2005). The deleterious effects of toxic agents could be prevented with the aids of antioxidants (Domitrović et al., 2009). Certain type of drugs and some toxic chemical can also induce nephrotoxicity (Jaeschke and Bajt, 2006). Nephrotoxins are the agents displaying nephrotoxicity. There could be an increase in the degree of nephrotoxic effect in patients that has an existing case of renal impairment, and the chronic administration of certain drugs can also increase the manifestation of nephrotoxicity (Reid et al., 2005; Rousar et al., 2009).

Paracetamol-induced nephrotoxicity is less commonly seen than is hepatotoxicity. In some cases, after an overdose, acute renal failure can occur as a complication of hepatotoxicity (Loh and Ponampalam, 2006; Satirapoj et al., 2007). Being that administration of paracetamol is common among the populace of the developing country. A continuous search for an agent that could prevent its toxic health-related complication is imperative.

MATERIALS AND METHODS

Experimental Animals

The experimental Wistar albino rats used in this study are 28, and they have an average weight of 150-200g. The rats were procured from the animal house of the faculty of Veterinary Medicine, University of Nigeria Nsukka and housed in the animal unit of the Department Biochemistry, Michael Okpara University of Agriculture, Umudike. The animals were acclimatized to a standard environmental condition for two weeks, with a 12hours lights/dark cycle. All animals had free access to food and water. All procedures were carried out in accordance with the institutional animal care and use.

Experimental design

After acclimatization, the animals were randomly selected and separated into 7 groups of 4 animals per group. The administrations were as follows:

Group 1: Treated with 1000mg/kg b.w of paracetamol with concomitant administered of vitamin C (50mg) and vitamin E (200iu), 2 times daily with an interval of 12 hours for 7days.

Group 2: Treated with 1000mg/kg b.w of paracetamol with concomitant administered of vitamin C (25mg) and vitamin E (100iu), 2 times daily with an interval of 12 hours for 7days.

Group 3: Treated with 1000mg/kg b.w of paracetamol with concomitant administered of vitamin C (100mg) and vitamin E (300iu), 2 times daily with an interval of 12 hours for 7days.

Group 4: Treated with 1000mg/kg b.w of paracetamol with concomitant administered of vitamin C (50mg) and vitamin E (200iu), 2 times daily with an interval of 12 hours for 7days.

Group 5: Treated with 1000mg/kg b.w of paracetamol with concomitant administered of vitamin C (25mg) and vitamin E (100iu), 2 times daily with an interval of 12 hours for 7days.

Group 6 (Control 1): Control group treat with paracetamol 2 times daily with an interval of 12hours for 7 days.

Group 7 (control 2): Normal control group administered with placebo.

Biochemical analysis

Determination of serum alkaline phosphatase (ALP) activity

The determination of alkaline phosphatase in whole blood according to the method of (Reitman and Frankel, 1957) was done using Randox limited commercial kits.

Determination of Serum AST activity

The determination of aspartate aminotransferase was carried out according to the method of (Reitman
Figure 3: Effect of Vitamin E and C co-treatment on AST activity in paracetamol (PC) induced hepatic toxicity in rats.

Figure 4: Effect of Vitamin E and C co-treatment on ALP activity on paracetamol (PC) induced hepatic toxicity in rats.

Figure 5: Effect of ascorbic acid and α-tocopherol on serum urea level of paracetamol-induced nephrotoxicity

Figure 6: Effect of ascorbic acid and α-tocopherol on serum creatinine level of paracetamol-induced nephrotoxicity

Urea level was measured by commercially available standard Blood Urea Kit (Merck, Japan) using Semi-autoanalyzer (Merck, Japan) as described by Burtis and Edward (2010).

Determination ofblood creatinine:
The creatinine level was measured by a standard protocol for the photometric determination of creatinine-based on the Jaffe kinetic method without de-proteinization (Sabbagh et al., 2008).

Statistical analysis
Statistical analysis was performed with analysis of variance (ANOVA). The results are expressed as mean ±SEM, and the LSD test was used to test for significant difference between means with p<0.05 considered significant.

RESULTS AND DISCUSSION
The exposure of a high dose of paracetamol have been revealed by researchers and reported as an agent that could cause severe organ tissue toxicities. The exposure to paracetamol is capable of exerting deleterious effects on the hepatic and renal tissues. Paracetamol (PC) is well known to be primarily metabolized by sulphation and glucuronidation (unreactive metabolites) with the production of N-acetyl-p-benzo quinine imine and then activated by cytochrome P450 system to induce hepatic injury (Mitchell et al., 1988; Dahlin et al., 2006).

Vitamin E and Vitamin C proved to be a vital antioxidant in this study which was evident in the significant reduction of elevated hepatic enzymes induced by Paracetamol as shown in Figures 1, 2, 3, 4, and 6, and this may be as a result of the fact that Ascorbic acid can donate a hydrogen atom and form a relatively stable ascorbyl free radical and it has strong potency against the hydrogen peroxide, the hydroxyl radical, superoxide radical ion and singlet oxygen (Weber et al., 2008).
Vitamin E and C are known as free radical scavengers and a major contributor to non-enzymatic protection against lipid peroxidation. Many authors reported that vitamin C and E have the ability to prevent different paracetamol associated side effects (Antunes et al., 2010; Halliwell and Gutteridge, 2016). This is in agreement with the findings from this study. It was observed that the untreated group (group 6) had a significant (p≤0.05) increase in both hepatic and renal function biomarkers, and treated groups significantly (p<0.05) reduced the elevated biomarkers in a dose-dependent manner. Vitamin E been dietary supplementation suppresses oxidative stress and glomerulosclerosis in rat remnant kidney (Hahn et al., 2010). Vitamin E pre-treatment has also been reported to be beneficial in preventing formaldehyde induced tissue damage in rats Gurel et al. (2002); Gulec et al. (2006). Vitamin C and E was validated in this study as having the ability of protecting cells against oxidative damage caused by ROS, as reported by (Izzi et al., 2012).

CONCLUSION

This study validated the claims that Paracetamol could cause marked hepatic and renal cell damage, and co-administration of vitamin C and E prevented elevation of renal and hepatic function biomarkers.

Conflict of Interest

The authors declare that they have no conflict of interest for this study.

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