J. Expt. & Clin. Anat. 3(1): 35-38 (2004).

Liver And Kidney Morphologies Following Vitamin E Supplementation During Caffeinated And Non-Caffeinated Paracetamol Administration In Rats

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ABSTRACT

Liver and Kidney morphology following vitamin E supplementation during caffeinated and non-caffeinated paracetamol was studied in rats for 2 weeks. The control group received distilled water orally. The treated groups designated A-D, received oral doses of 171.43mg/kg body weight of paracetamol, 171.43mg/kg body weight of panadol extra, 171.43mg/kg body weight of paracetamol and 4.286mg/kg body weight of vitamin E, 171.43mg/kg body weight of Panadol extra and 4.286mg/kg body weight vitamin E respectively. Histological examination of the rat liver revealed that while sections of the liver from the groups on paracetamol and panadol extra + vitamin E showed signs of hepatic necrosis, vacuolations and sinusoidal dilation; liver sections of the group on panadol extra, paracetamol + vitamin E showed markedly improved cytoarchitecture of the hepatocyte with distinct cell outline and nuclei. Histological examination of the rat kidney revealed that while sections of the kidney from the groups on paracetamol and panadol extra showed slight loss of glomerular architecture, slight cell shrinkage, and less distinct nuclei; kidney sections of the groups on paracetamol + vitamin E and panadol extra + vitamin E showed markedly improved cytoarchitecture of kidney cells. Our results suggest that supplementation with vitamin E may be effective in remitting the hepatotoxicity and nephrotoxicity induced by paracetamol; and that however, co-adminstration of vitamin E with caffeinated paracetamol may potentiate the hepatoxic effects of paracetamol.

Keywords: Paracetamol; Caffeinated paracetamol; Vitamin E; Kidney; Liver; Wistar rats.

Paracetamol is a widely used non-prescription analgesic and antipyretic agent. It is a suitable substitute for aspirin in patients with gastric intolerance and bleeding tendencies (Laurence *et al.*, 1997). The easy availability of the analgesics in shops and pharmacies without prescription has led to it being kept in many homes. It is therefore not surprising that it is often involved in episodes of accidental or deliberate self-poisoning (Bauer *et al.*, 1999).

Literature abounds with evidence of toxicity of paracetamol. The most serious adverse effect of overdose of paracetamol is hepatic necrosis (Thomas, 1993; Miles *et al.*, 1999; Bauer et al; Lawson *et al.*, 2000); and renal tabular necrosis (Blakely and McDonald, 1995; Jones and Vale 1993, McJunkin et al; Dark *et al;* 1986).

The hepatotoxic effects of paracetamol is exerted by the toxic metabolite N-acetyl p benzoquinine imine formed through the cytochrome P_{450} drug metabolizing system (Raucy *et al*, 1989; McClain *et al.*, 1999). Recently it has been demonstrated that activated kupffer cells and their secreted cytokines may contribute to liver injury (McClain *et al* 1999).

Co-administration of paracetamol and caffeine is becoming more popular; and caffeine has been shown to enhance the analgesic effect of paracetamol (Laurence *et al;* 1997) and to reduce histopathological changes in the liver consequent upon paracetamol intoxication (Rainska *et al.*, 1992)

Early studies have suggested that depletion of vitamin E increases the hepatotoxicity of paracetamol (Mitchell *et al*, 1977). Mansy *et al;* (1986) and Younes *et al.* (1988) have demonstrated that antioxidants and inhibitors of lipid peroxidases such as diethyldithiocarbamate and anisyldithiolthione reduce the hepatotoxicity of paracetamol intoxication. Halim *et al.*, (1997) has shown that antioxidant vitamins may protect the liver against carbon tetrachloride induced hepatotoxicity in rats. This study therefore was designed to determine the modulatory effect of vitamin

Fig. 1 Liver Section (Control)

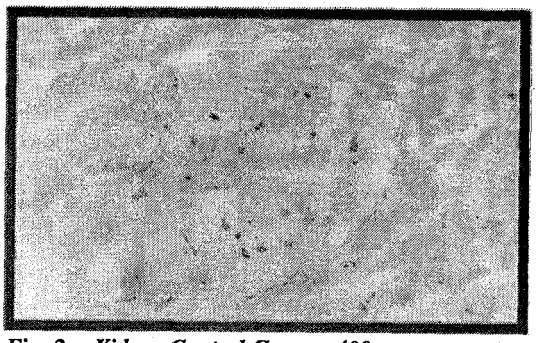

Fig. 2 Kidney Control Group x400

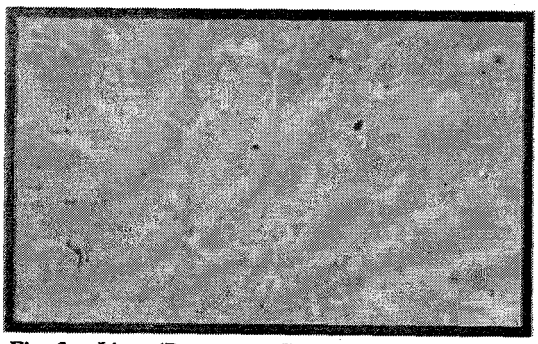

Fig. 3 Liver (Paracetamol)

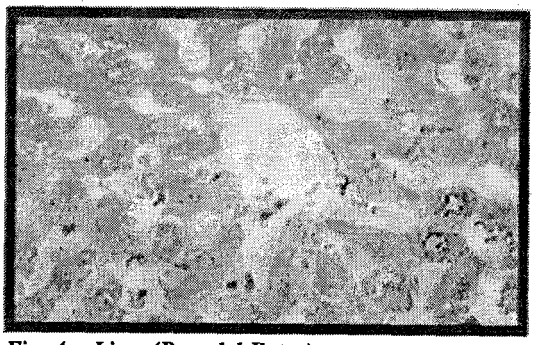

Fig. 4 Liver (Panadol Extra)

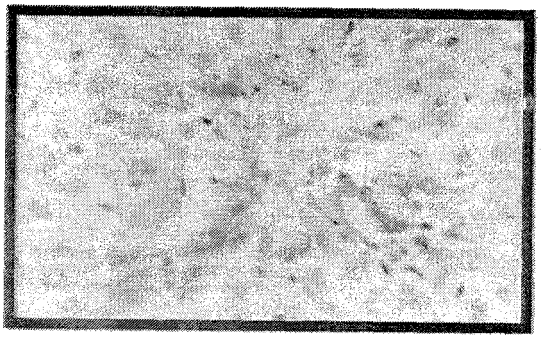

Fig. 5 Liver (Paracetamol + Vitamin E)

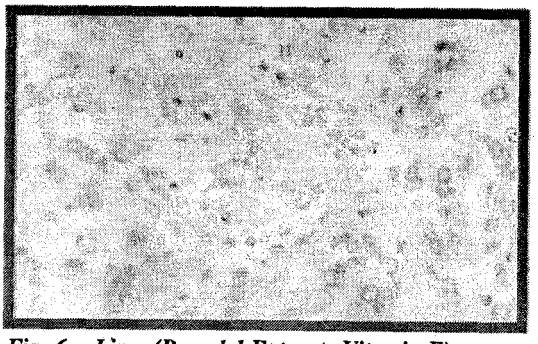

Fig. 6 Liver (Panadol Extra + Vitamin E)

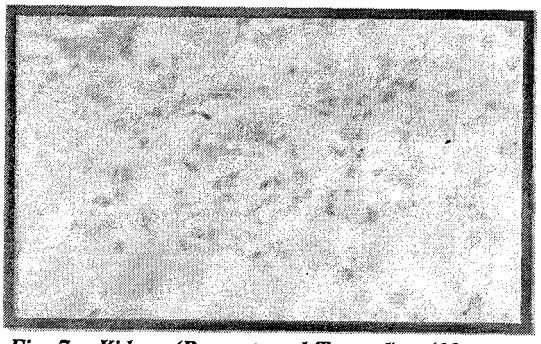

Fig. 7 Kidney (Paracetamol Treated) x400

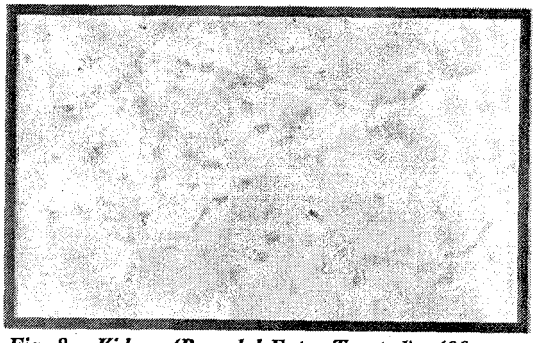

Fig. 8 Kidney (Panadol Extra Treated) x400

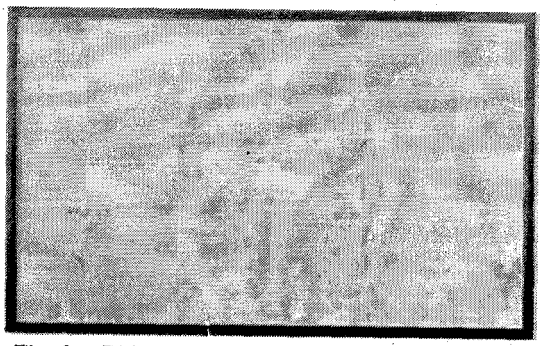

Fig. 9 Kidney (Paracetamol + Vitamin E)

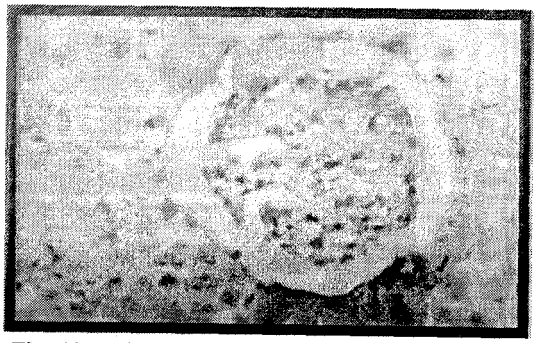

Fig. 10 Kidney (Panadol Extra + Vitamin E)

E supplementation during paracetamol administration.

MATERIALS AND METHOD

Twenty-five albino Wistar rats weighing between 200-300g, obtained from the animal house of the Department of Anatomy, University of Calabar, were used for the experiment. The animals were acclimatized for two weeks, kept in plastic cages in a ratio of five rats to one cage and were allowed commercial rat chow and tap water *ad libitum* . The rats were randomly divided into five groups of five rats and treated as follows:

Group A: Paracetamol
Group B: Panadol extra
Group C: Paracetamol + Vitamin E
Group D: Panadol extra + Vitamin E
Control : Distilled water

The drugs were purchased from Karmel pharmacy in Calabar. Paracetamol tablets (Emzor pharmaceutical industries, Lagos) was dispersed in distilled water and administered by daily dose of 171.43mg/kg body weight. Panadol extra tablets (Smithkline Beecham Pharmaceutical company, Lagos) was dispersed in distilled water and administered orally on daily dose of 171.43 mg/kg body weight. Vitamin E (Ephynal, Roche France) was dispersed in distilled water and administered on a daily oral dose of 4.286mg/kg body weight.

The treatment lasted for two weeks after which the animals were sacrificed by chloroform inhalation method. Following sacrifice, the liver and kidneys were dissected out and fixed in 10% buffered formalin. The tissues were processed and stained with Haematoxylin and Eosin. They were mounted with DPX and then viewed under the light microscope

RESULTS

No evidence of hepatic injury was observed in the liver (Fig.1) and kidney (Fig.2) cells from control rats. Sections of liver from groups on paracetamol (Fig.3) and panadol extra + vitamin E (Fig. 6) showed signs of hepatic necrosis, sinusoidal dilation, vacuolations, cell shrinkage and less distinct nuclei. Liver section of the group on panadol extra (Fig.4) and paracetamol + vitamin E (Fig.5) showed a markedly improved cytoarchtecture of the hepatocytes with distinct cell outline and distinct nuclei.

Section of kidney from groups on paracetamol (Fig.7) and panadol extra (Fig.8) showed slight loss of glomerular architecture, slight cell shrinkage, inflammation of tubules and glomerulus and less distinct nuclei. Kidney sections of the groups on paracetamol + vitamin E (Fig.9) and panadol extra +vitamin E (Fig.10) showed markedly improved cytoarchitecture of kidney cells.

DISCUSSION

This study reveals that caffeination protects the liver against hepatocellular degeneration. This is consistent with the report of Rainska *et al.*, (1992) that caffeine reduces the hepatoxicity of paracetamol in mice. Also, the study demonstrates that supplementation with vitamin E protects the liver against hepatocellular degeneration. This is in agreement with the report of Halim *et al.*, (1997) that antioxidant vitamins could protect the liver against carbon tetrachloride induced hepatotoxicity in mice. Other antioxidants have been reported to reduce paracetamol hepatotoxicity (Mitchell, 1977; Mansuy *et al;* 1986; Thomas, 1993)

However, co-administration of panadol extra and vitamin E resulted in hepatocellular degeneration; therefore, vitamin E was not effective in reducing the hepatotoxicity of caffeinated paracetamol. The mechanism for this is not clear.

In this study, caffeination did not seem to protect the kidney against the toxic potential of paracetamol intoxication. However supplementation with vitamin E protects the kidney against renal tubular necrosis.

Vitamin E must have alleviated the toxic effect by breaking free radical chain reaction via its antioxidant capacity. So its role in the preventing of oxidation changes to body cells and tissues is evident (Frei, 1994). Gaby *et al.*, (1992) has reported that micronutrient supplementation could help protect the body against physiological stress; hence its ability to protect the tissues against damage (Frei, 1994).

In conclusion, histological examination of liver and kidney tissues has revealed that supplementation with vitamin E is effective in reducing histological changes in the liver and kidney accompanying paracetamol intoxication.

REFERENCES

Bauer, M., Babel, B., Giesen, H., Patzelt, D. (1999) Fulminant Liver failure in a young child following repeated acetaminophen overdosing. J. Forensic Science, 44(6) :1299-1303

Blakely, P., McDonald, B. R. (1995). Acute renal failure due to acetaminophen injection; a case report and review of the literature, J Am Soc Nephrol 6(1); 48-53

Clark, P. M.,Clark, J. D., Wheatley, T. (1986) Urine discoloration after acetaminophen overdose, Clin Chem 32(9): 1777-1778

Frei, B. (1994). Reactive oxygen species and antioxidant vitamins: Mechanisms of action. The American Journal of Medicine:97(suppl3a):5-13

Gaby, S. K., Bendich, A., Singh, V. N., Machlin, L. J. (1992) Vitamin intake and health: A scientific review. Marcel Dekker Inc. New York.

Halim, A. B., El-Ahmady, O., Hassab-Allah, S., Abdel-Galil, F., Hafez, Y., Darwish, A. (1997). Biochemical effects of antioxidants on lipids and liver function in experimentally induced liver damage.Am Clin Biochem 34:656-663

Jones, A. F., Vale, J. A. (1993).Paracetamol poisoning and the kidneys. J Clin Pharm Ther 18(1):5-8.

Laurence, D. R., Bennett, P. N., Brown, M. J. (1997) Clinical Pharmacology. Chuchhill Livingstone, New York. 249-688

Lawson, J. A., Farhood, A., Hopper, R. D., Bajt, M. L., Jaeschke, H. (2000). The hepatic inflammatory response after acetaminophen overdose: Role of neutrophils. Toxicol Sci 54 (2): 509-516.

Mansuy, D., Sassi, A.,Dansette, P. M., Plat, M., (1986) A new potent inhibitor of lipid peroxidation invitro and invivo: The hepatoproctective drug Ansisyldithioltbione. Biochem Biophys Res Commun 135:1015-1021.

McClain, C. J., Price, S., Barve, S., Devalarja, R., Shedslofsy, S. (1999). Acetaminophen hepatoxicity. Curr Gasteroenterol Rep 1(1) 42-49.

McJunkin, B., Barwick, K. W., Little, W. C., Winfield, J. B., (1976) Fatal massive hepatic necrosis following acetaminophen overdose. JAMA 236(16): 1874-1875.

Miles, F. K., Kamath, R,. Dorney, S. F., Gaskin, K. Z., O"Longhlin, E. V., (1999) Accidental paracetamol overdosing and fulminant hepatic failure in children. Med. J Aust. 171 (9):472-475

Mitchell, J. R. (1977). Host susceptibility and acetaminophen liver injury. Am Intern Med 87: 377-378

Murray, J. M., Harvey, A. R., Champe, H., (1997) Pharmacology 2nd ed. Lippeincot illustrated reviews. New York 412-413

Rainska, T., Juzwiak, S., Dutkiewez, T.,Krasowska,.B.,Olenderek, B., Rozsewicka, L.,Wojcicki, J., Samechowiec, L., Juzyszon, Z., (1992) Caffeine reduces the hepatotoxicity of paracetamol in mice. J Int Med Res 4:331-342.

Raucy, J. L., Lasker, J. M., Lieber, C. S., Black, M., (1989) Acetaminophen activation by human liver cytochromes P_{450} 2EI and P_{450}A2. Act Biochem Biophys 271:270-283.

Thomas, S. H., (1993) Paracetamol (acetaminophen) poisoning. Pharmacol Ther. 60:91-120.

Received on 4-02-04 and accepted on 7-05-04