



Original Paper

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Albendazole potentiates the neurotoxic effect of ivermectin in rat

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ABSTRACT

The study was carried out to investigate whether an interaction between albendazole and ivermectin could lead to enhanced central nervous system (CNS) toxicity. Ivermectin (0.4mg/kg body weight (b.w)) and/or albendazole (15mg/kg b.w) were daily and orally administered to albino rats for 14 days. Activities of acid phosphatase (ACP), alkaline phosphatase (ALP), catalase (CAT), Na⁺-K⁺ ATPase, Ca²⁺-Mg²⁺ ATPase and malondialdehyde (MDA) level which are considered essential to correct functioning of the brain were determined. The co-administration of the two drugs significantly caused reduction ($p < 0.05$) in the activities of brain ACP, ALP, Na⁺-K⁺ ATPase and Ca²⁺-Mg²⁺ ATPase with corresponding increase in the serum. Separate administration of ivermectin or albendazole did not show any significant changes ($p > 0.05$) in the activity of these enzymes. These suggest that in the presence of albendazole, ivermectin is able to reach the CNS and impair its function through neurochemical changes. Also, co-administration of ivermectin and albendazole led to a significant increase ($p < 0.05$) in brain CAT activity as well as serum and brain MDA concentrations. This may be an indication that the drugs have other mechanisms of action, such as increasing oxidative damage in the CNS. Overall, these findings suggest that both drugs exert additive effect when co-administered.

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INTRODUCTION

Brain is a vital organ of the body whose function controls the activities of the cellular system. It consists of three parts viz. forebrain, midbrain, and hindbrain. It is involved in sensory perception, motor control, memory association, thought and personality, regulating temperatures, water metabolism, blood sugar level, productive cycle, hunger, thirst, anger and pleasure (Cicerone et al, 2005), and several forms of reflex actions. Due to the complexity of its functions, the brain receives some 15% of the total cardiac output and accounts for about 20% of the total oxygen consumption of the body at rest

(Alavijeh et al, 2005). The high oxygen utilization by the brain during metabolism increases its susceptibility to oxygen free radicals which is the major mode of action of neurotoxicant. However, the brain regulates transport of materials in and out through the action of blood-brain barrier which is composed of specialized endothelial cells that prevent various substances from entering the brain except those that are either small or lipophilic (Rubin and Staddon, 1999) thereby reducing accumulation of toxic materials in the brain.

Ivermectin and albendazole are synthetic drugs used for the treatment of

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Lymphatic filariasis (Elephantiasis) and Onchocerciasis (river blindness) respectively. Both diseases are major public health problems in several tropical countries (Ottesen and Ramachandran, 1995). An estimated 120 million people in more than 80 endemic countries are infected with Lymphatic filariasis (Molyneux et al., 2003) and 50 million individuals remain at risk with 17.7 million infected with *Onchocerca volvulus* predominantly in 22 sub-Saharan African countries. The strategy that has been shown to be most effective is the treatment of affected populations with the drug ivermectin - a white or slightly yellow crystalline powder (Chabala et al., 1980). However, report of resistance to ivermectin in nematodes is becoming increasingly common (Richard, 1994; Sangster, 1996). In view of this and the co-endemic nature of the two diseases, clinical trials of ivermectin and albendazole combination commenced in some African countries like Ghana (Awadzi et al., 2003). The advantageous pharmacologic action of this combination therapy is that while ivermectin is only microfilaricidal (Goa et al., 1991) albendazole is toxic to all intra-uterine stages (Awadzi et al., 1995). Although, this regimen has been tried in many countries with reports of high efficacy in the treatment of onchocerciasis and lymphatic filariasis (Ismail et al., 1998; Awadzi et al., 2003), their effect on various metabolic processes, tissues and cellular systems of the mass human populations receiving these drugs is yet to be clarified. This study is thus aimed at elucidating the toxic effect of the combination therapy on the cellular integrity of the brain of wistar rats.

MATERIALS AND METHODS

Materials

Experimental animals

A total of 20 male albino rats (*Rattus norvegicus*) of average weight $157.50 \text{ g} \pm 2.50 \text{ g}$ were obtained from the Animal Holding Unit of the Department of Biochemistry, University of Ilorin, Ilorin, Nigeria. The rats

were maintained on normal rat chow and water *ad libitum* and were housed in wooden cages. Animal husbandry and experimentation were consistent with the Guiding Principles in the Use of Animals in Toxicology (Derelanko, 2000).

Drugs and reagents

Ivermectin and albendazole were products of Merck and Co. England and Glaxo Smithkline Beecham, Netherlands respectively. All reagents used were of analytical grade and were prepared in all-glass distilled water. The reagents were stored in clean, air tight reagent bottles.

Methods

Animal grouping and drug administration

The rats were randomly divided into four groups of five rats each. Group I (control) received an appropriate volume of distilled water. Group II (Iver) received a human therapeutic dose of 0.4 mg/kg body weight (b.w.) ivermectin; Group III (Alb) received a human therapeutic dose of 15 mg/kg body weight albendazole while group IV (Iver + Alb) received a dose of 0.4 mg/kg body weight ivermectin co-administered with 15 mg/kg body weight albendazole. The administration was done orally on a daily basis for fourteen (14) days at 24 h interval (at 9.00a.m). This duration was based on the clinical trial conducted by Ismail et al. (1998) to evaluate the potency of the combination therapy. The animals were sacrificed 24 h after the fourteenth day administration.

Preparation of serum and brain homogenate

At the end of the experimental period, approximately 5 ml of venous blood was collected from each of the experimental animals according to the method of Narayanan et al. (1984) The serum was prepared by centrifuging the blood samples at 3000 rpm for 5 min (Ogbu and Okechukwu, 2001) and serum collected with a Pasteur Pipette. Immediately after the collection of blood, the brain was removed and transferred into a well labelled container of ice-cold 0.25 M sucrose solution (1:5 w/v) and

homogenized. The homogenates were kept frozen overnight to ensure maximum release of the enzymes before being used for the various biochemical assays (Adebayo et al., 2003).

Assay of enzyme activities and lipid peroxidation

Acid phosphatase activity was assayed using the method of Armstrong (1964). The method of Bessey et al. (1946) as modified by Wright et al. (1974) was employed for the assay of alkaline phosphatase activity. ATPase activities were assayed using the method of Ronner et al. (1977) and catalase by the method of Sinha (1971). Determination of malondialdehyde level was done by the method of Varshney and Kale (1990). Protein content of the homogenate and serum were determined using the Biuret method (Gornall et al., 1949).

Statistical analysis

All data are presented as mean \pm standard deviation. Statistical analyses were carried out using Duncan Multiple Range test (Montgomery, 1976). In all cases, probability level of 95% was taken as significant.

RESULTS

Figure 1 shows the effect of administration of ivermectin and /or albendazole for 14 days on rat brain-body weight ratios. Combined administration of both drugs significantly reduced ($p < 0.05$) brain-body weight ratios of rats. There was no significant change in this parameter in rats administered separately with ivermectin or albendazole when compared with controls.

Figure 2 shows the activity of ALP in brain of rats following the administration of ivermectin, albendazole and their combination for 14 days. The serum ALP activity was significantly increased ($P < 0.05$) in all treatment groups when compared with the controls. There existed no significant

difference ($P > 0.05$) in the brain ALP activity of rats administered separately with ivermectin or albendazole when compared with the control. However, about two folds reduction in activity was observed following co-administration of both drugs for 14 days when compared with control.

Figure 3 presents the effects of both separate and combined administration of ivermectin and albendazole for 14 days on the activity of acid phosphatase (ACP) of rat brain. The serum acid phosphatase activity increased significantly ($P < 0.05$) following combined administration of ivermectin and albendazole while there was no significant differences ($P > 0.05$) when each drug was separately administered to rats compared with control. There was no significant difference ($P > 0.05$) in the brain ACP activity of rats administered ivermectin and albendazole separately while in rats administered combined ivermectin and albendazole, there was a significant increase ($P < 0.05$) in activity when compared with control.

Combined administration of ivermectin and albendazole for 14 days caused significant ($P < 0.05$) drop in brain $\text{Na}^+ - \text{K}^+$ and $\text{Ca}^{2+} - \text{Mg}^{2+}$ ATPase activities (Figures 4 and 5). However, no significant changes ($p > 0.05$) were observed following separate administration for the same period.

Separate administration of ivermectin and albendazole did not affect ($P > 0.05$) brain catalase activity (Figure 6). However their co-administration led to a significant increase ($P < 0.05$) in the enzyme activity of brain when compared with control.

Neither of the drugs caused any significant change ($P > 0.05$) in the concentration of MDA in the serum and brain when compared with controls following 14 days administration (Figure 7). However, co-administration of ivermectin with albendazole for 14 days caused a significant elevation ($P < 0.05$) in both serum and brain malondialdehyde levels.

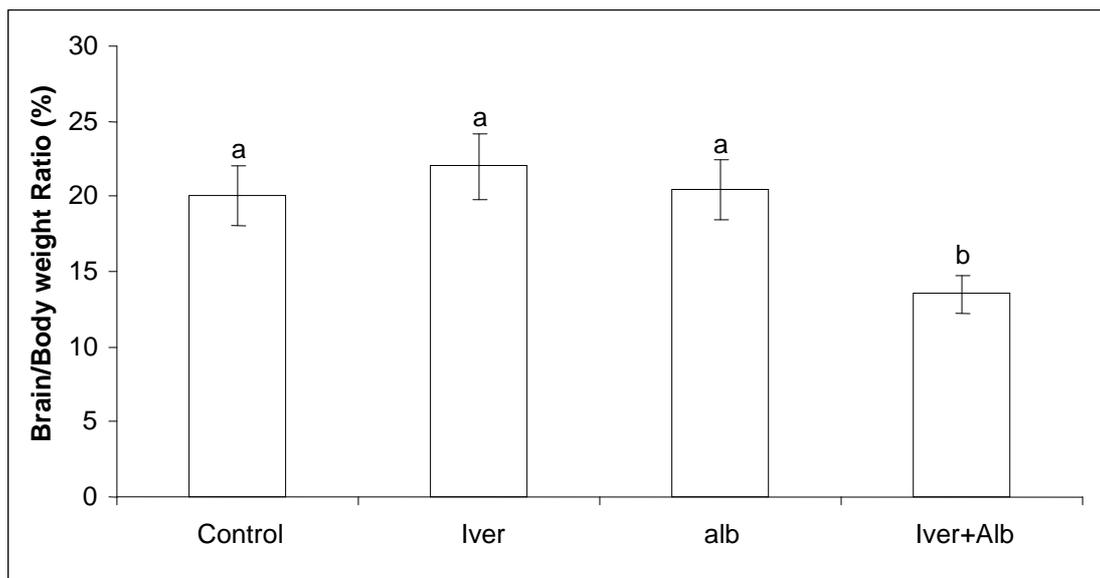


Figure 1: Brain-body weight ratio of rats following the daily administration of ivermectin and/or albendazole for fourteen days.

Values are means (n = 5) ± S.D (bars with different superscripts are significantly different at P<0.05).

Iver = Ivermectin; Alb = Albendazole.

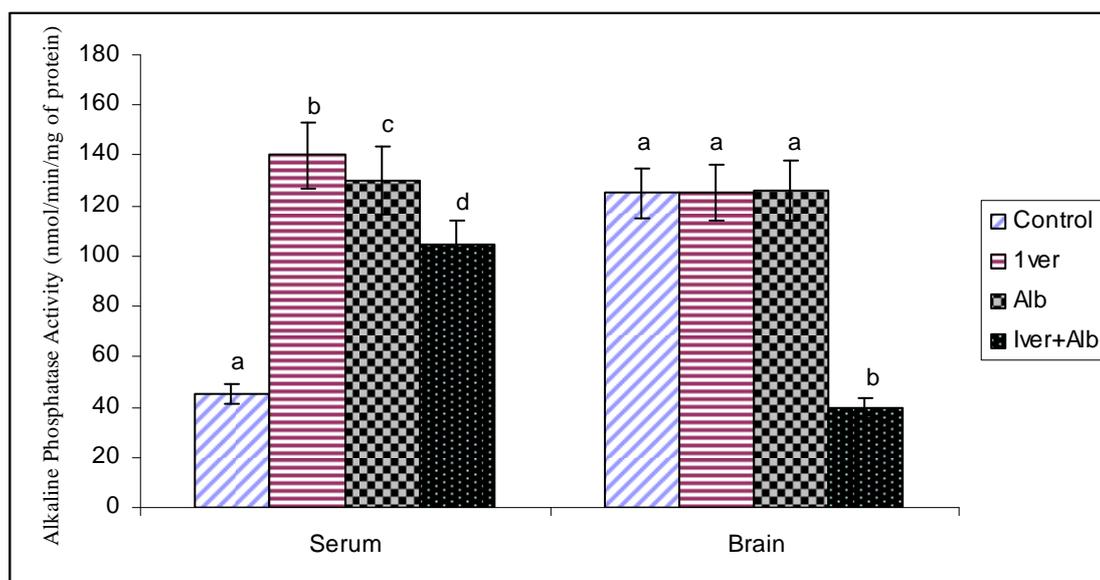


Figure 2: Specific activities of alkaline phosphatase in rat brain following the daily administration of ivermectin and/or albendazole for fourteen days.

Values are means (n=5) ± S.D (bars with different superscripts are significantly different at P<0.05).

Iver = Ivermectin; Alb = Albendazole.

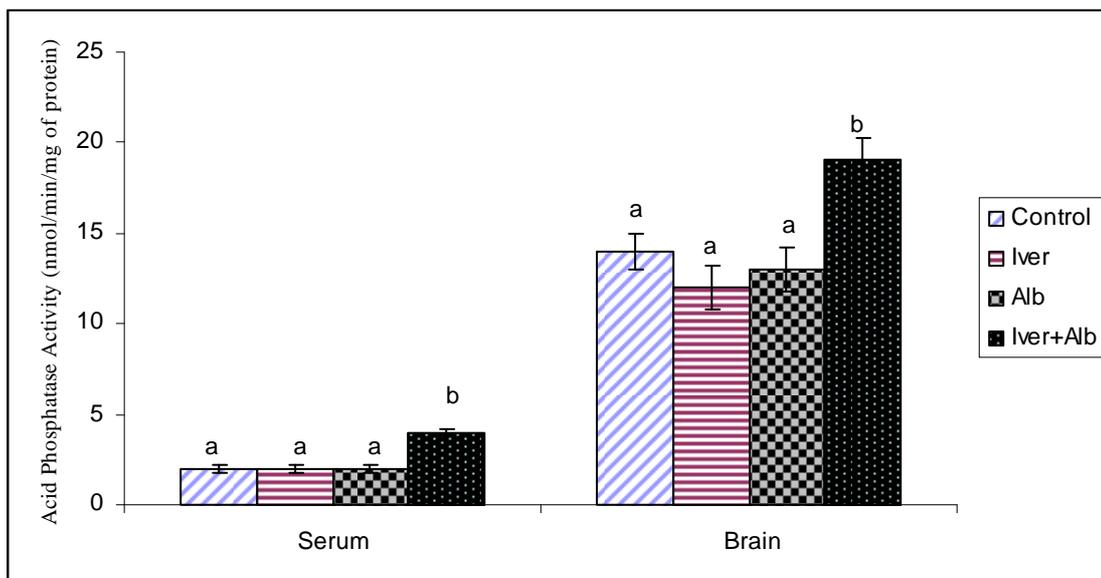


Figure 3: Specific activities of acid phosphatase in rat brain following the daily administration of ivermectin and/or albendazole for fourteen days.

Values are means (n=5) ± S.D (bars with different superscripts are significantly different at P<0.05).

Iver = Ivermectin; Alb = Albendazole.

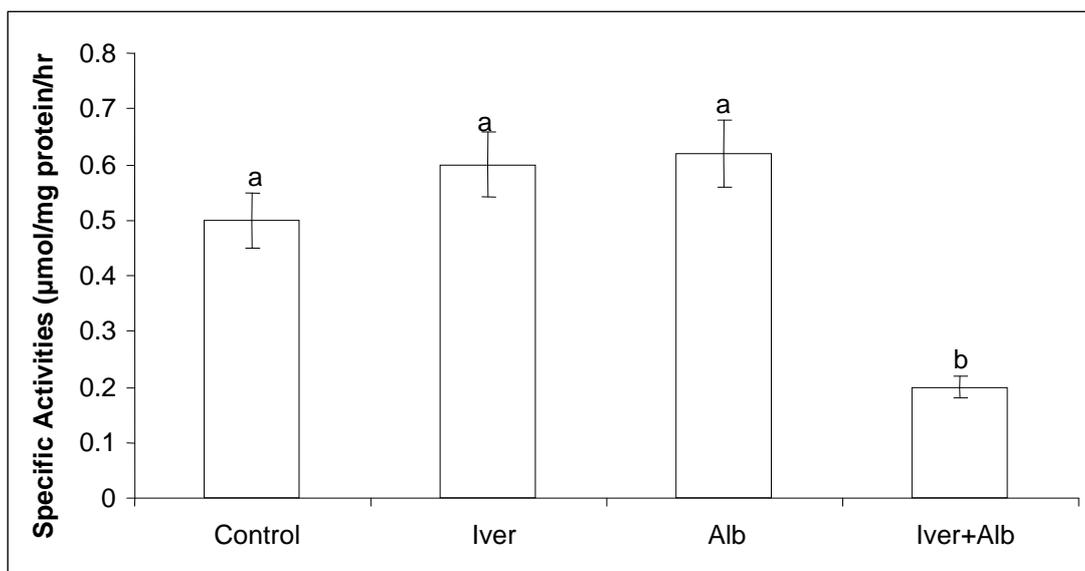


Figure 4: Specific activities of rat brain Na⁺-K⁺ ATPase following the daily administration of ivermectin and/or albendazole for fourteen days.

Values are means (n=5) ± S.D (bars with different superscripts are significantly different at P<0.05).

Iver = Ivermectin; Alb = Albendazole.

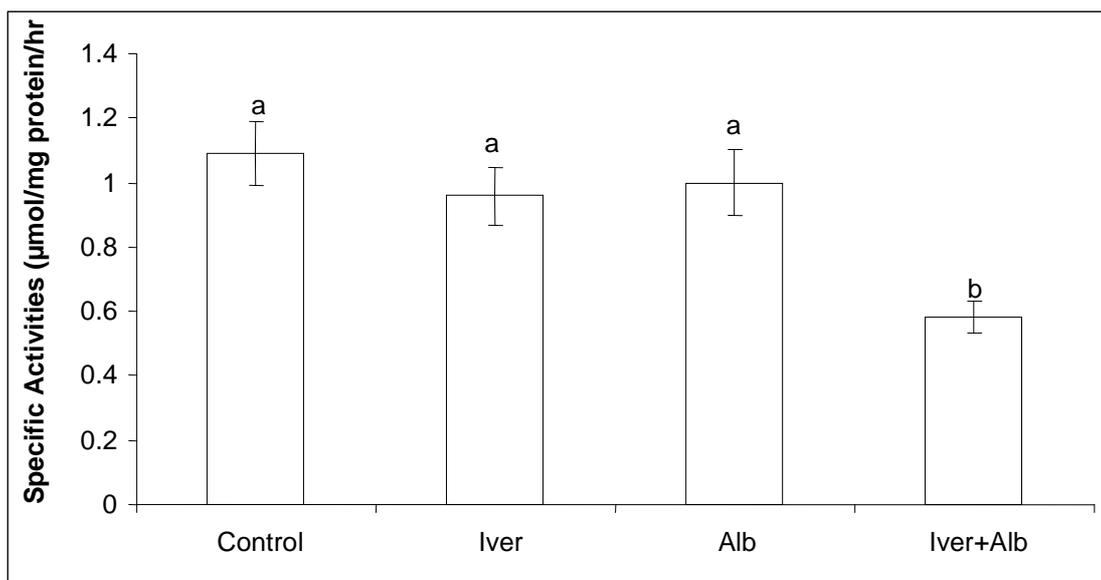


Figure 5: Specific activities of rat brain Ca²⁺-Mg²⁺ ATPase following the daily administration of ivermectin and/or albendazole for fourteen days.

Values are means (n=5) ± S.D (bars with different superscripts are significantly different at P<0.05).

Iver = Ivermectin; Alb = Albendazole.

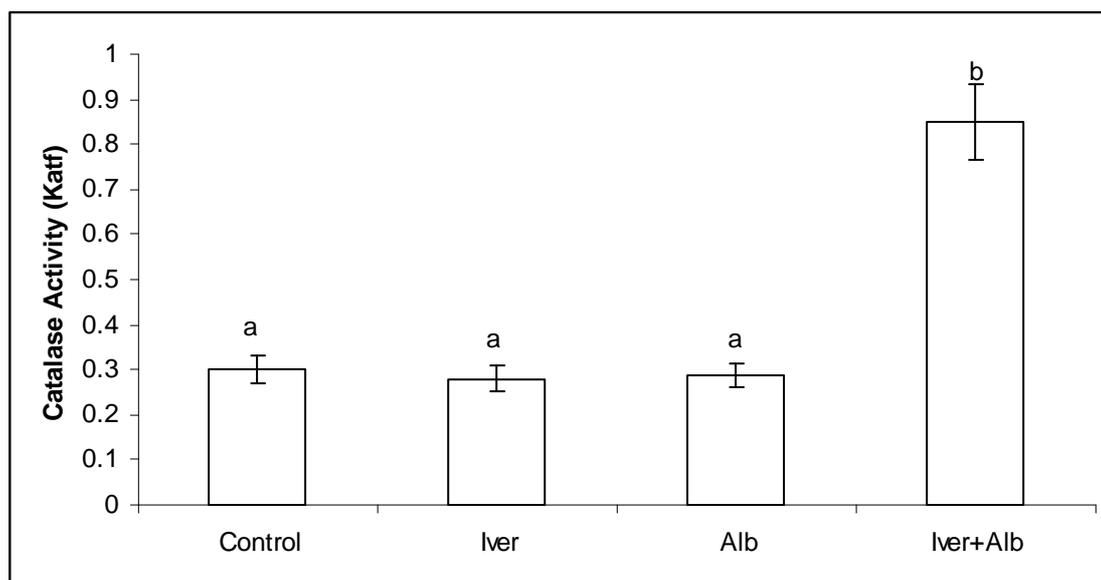


Figure 6: Effects of ivermectin and/or albendazole on rat brain catalase activities following fourteen days of drug administration.

Values are means (n=5) ± S.D (bars with different superscripts are significantly different at P<0.05).

Iver= Ivermectin; Alb= Albendazole.

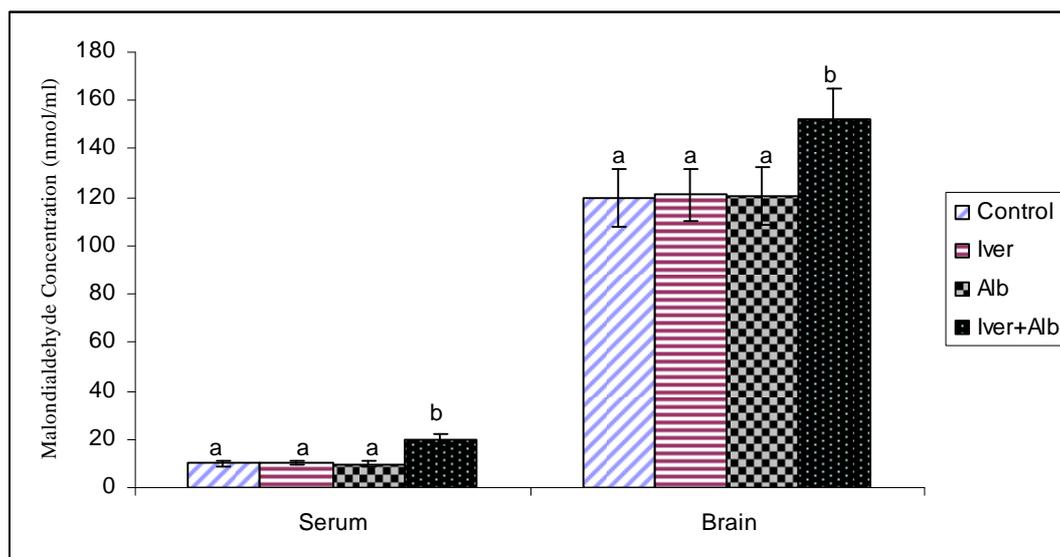


Figure 7: Effects of ivermectin and/or albendazole on malondialdehyde (MDA) concentration¹ in rat brain following fourteen days of drug administration.

Values are means (n=5) ± S.D (bars with different superscripts are significantly different at P<0.05). Key: Iver= Ivermectin; Alb= Albendazole

DISCUSSION

Organ/body weight ratios are normally investigated to determine change in size of the organ relative to the body (Bailey et al., 2004). High Organ to body weight ratio has been associated to inflammation while otherwise is necrosis. Xenobiotics (including drugs) have been reported to induce inflammatory responses (Omiecinski, 2011) disrupting respiration and affecting energy production. This may result in dependence of the brain cells on anaerobic respiration to generate energy. The eventual accumulation of the product of this process- lactic acid in brain cells may lead to cell damage as a result of lactic acidosis with consequent inflammation. Efflux mechanism at the blood-brain barrier is a limiting factor in the penetration of drugs. Drugs including ivermectin and albendazole are actively transported out of brain, thus limiting the concentration of these compounds in the brain (Taylor and Yan, 2002). The significant decrease in the brain/body weight ratio of rats administered combined ivermectin and

albendazole, suggests appreciable accumulation of ivermectin in the brain thus causing cell death. Ivermectin is known to be neurotoxic because of its action on GABA receptors (Leo et al., 1996). Both ivermectin and albendazole have been reported as cosubstrates of cytochrome P₄₅₀ (CY3A4) (Edwards, 2003). However it has also been proposed that albendazole may be substrate to *p*-glycoprotein (Redondo et al., 1999). Therefore, since *p*-glycoprotein may have higher affinity for albendazole, it may in the presence of ivermectin mediate the efflux of albendazole allowing ivermectin to accumulate appreciably in the brain.

The significant increase in serum ALP activity of all the treatment groups following 14 days administration (P<0.05) when compared with the control is suggestive of a possible damage to tissue cell plasma membrane by the administration of the drugs either singly or in combination, thus leading to leakage of membrane components into the extracellular fluid (Akanji et al., 1993). This is further supported by significant reduction in brain

ALP activity following the co-administration of ivermectin with albendazole for 14 days. This effect may be attributed to the role of *p*-glycoprotein of blood brain barrier (BBB) and the fact that albendazole has been proposed to be a substrate to *p*-glycoprotein (Redondo et al., 1999). It may be possible that *p*-glycoprotein has higher affinity for albendazole and in the presence of ivermectin mediated the efflux of albendazole thereby allowing ivermectin to accumulate appreciably in the brain to exert its neurotoxic effects on the brain cells, one of which is membrane derangement and hence the observed loss of ALP activity.

Acid phosphatase is an enzyme of the lysosomal membrane (Zhang et al., 2009). Acid phosphatase was chosen for assay on the basis of its specificity for lysosomal membrane. Its activity before and after exposure to insult with chemical compounds (in this case ivermectin and/or albendazole) gives a picture of the sequence of cell damage if any. Alteration in acid phosphatase activity will thus explain the suspected effects of these drugs on lysosomes (Zhang et al., 2009). The increase in ACP activity observed following combined administration of the drug could be a consequence of *de novo* synthesis induction by accumulation of ivermectin in the brain. Another possible explanation is the release of the enzyme from the brain lysosomal membrane, an indication of tissue damage.

$\text{Na}^+\text{-K}^+$ ATPase is a membrane bound enzyme involved in maintaining potential difference across the plasma membrane and also mediates transport of several other molecules into the cells. The brain $\text{Na}^+\text{-K}^+$ ATPase activity was significantly reduced in the combination group. This may be ascribed to the modulatory effect of albendazole in potentiating the neurotoxic effect of ivermectin by competitively preventing its efflux by *p*-glycoprotein while albendazole gets pumped out of the brain. The reduced activity observed could be attributed to the binding of the drug to various subunits

essential for the activity of the enzyme possibly via cysteine residues, as reported in the interaction of ivermectin with cytochrome P_{450} CY3A (Beers and Berkow, 1999; Rossi, 2000) which may reduce the enzyme activity. Ca^{2+} plays a very important role as second messenger, effecting brain signals. Its gradient is maintained by several of its transporter across the cellular membrane. The significant reduction in activity of $\text{Ca}^{2+}\text{-Mg}^{2+}$ ATPase following ivermectin, and albendazole administration may be attributed to membrane derangement or inhibition of the enzyme by the drugs. Ahern et al. (1999) reported that ivermectin increased Ca^{2+} release from sarcoplasmic reticulum vesicles and from endoplasmic reticulum by inhibiting Ca^{2+} uptake by $\text{Ca}^{2+}\text{-Mg}^{2+}$ ATPase.

Exposure to xenobiotics results into many complex processes which can be evaluated by antioxidant enzyme activity as well as by lipid peroxidation measures (Romeo et al., 2000). Increase in catalase activity could be attributed to compromise of the tissue xenobiotic protective biotransformation mechanism which may have resulted from accumulation of ivermectin in the brain mediated by albendazole thus leading to the production of reactive oxygen species and concomitant increased catalase activity to cope with these.

Lipid peroxidation is assessed by maximal rate of malondialdehyde formation (Chield et al., 1999). The integrity of cells could be assessed by evaluating the malondialdehyde level. Usually, the level is elevated under conditions such as oxidative stress where reactive oxygen group could react with unsaturated fat and increase malondialdehyde formation. In the brain, malondialdehyde levels can be used to measure various diseased conditions. Weigand et al. (1999) investigated cerebral formation of malondialdehyde as an index of lipid peroxidation in relation to different sources of reactive oxygen species in patients undergoing carotid endarterectomy. It has been proposed

to be one of the major mechanisms of secondary damage in traumatic brain injury. The brain is particularly prone to oxidative injury because the membrane lipids are essentially rich in polyunsaturated fatty acid (Halliwell and Gutteridge, 1989). Increased serum MDA levels have been found in patients with cancer (Huang et al., 1999). The increase in MDA level observed in this study suggests that the antifilarials are capable of inducing oxidative stress which is in agreement with the report of Yarsan et al.(2002) that albendazole caused increased formation of MDA in the blood of healthy mice.

Conclusion

The current study suggested that albendazole may mediate neurotoxic effect of ivermectin during combined administration for the treatment of filarial diseases. This study however, gives way to further study for the determination of kinetic parameters as a measure of affinity of *p*- glycoprotein for ivermectin and albendazole.

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