International Journal of Pharmacology

ISSN 1811-7775

science alert

ansinet
Asian Network for Scientific Information

International Journal of Pharmacology 8 (3): 209-211, 2012
ISSN 1811-7775 / DOI: 10.3923/ijp.2012.209.211

The Acute Hepatotoxic Effect of Halofantrine on Healthy and Uninfected Adult Wistar Rats

[1]I.O. Osonuga, [2]O.A. Osonuga, [3]A. Osonuga, [1]A.A. Onadeko and [4]A.A. Osonuga
[1]Department of Physiology,
[2]Department of Pharmacology, Olabisi Onabanjo University, Remo Campus, Ikenne Remo, Nigeria
[3]School of Medical Sciences,
[4]Department of Nursing, University of Cape Coast, Ghana

Abstract: The aim of the research was to evaluate the likely effects of Halofantrine on liver enzymes in healthy and uninfected Wistar rats of both sexes. Thirty albino rats (randomly assigned into 3 groups of 10 rats each) with body weight of 150 - 230 g were used for the 2-phase study. In phase 1, the drug was administered orally at Therapeutic (T) dose of 2.15 mg per 100 g body weight to 10 rats (5 males and 5 females) daily at 6 h interval for 18 h. Phase II was a recovery study involving 10 rats (5 males and 5 females) exposed to dose regimen as in phase 1 and sacrificed after 18 h withdrawal of treatment. The control-group made of 10 rats was given sterile water and rat feed *ad-libitum*. Halofantrine caused significant increase ($p< 0.05$) in the liver enzymes (ALK, ALT and AST) of the animals. Discontinuation of the drug use caused significant decrease in the liver enzymes values in the recovery group. The results suggested that halofantrine could induce hepatotoxicity in the treated animals.

Key words: Halofantrine, liver enzymes, Wistar rats, antimalarial

INTRODUCTION

Halofantrine, a phenanthrene-methanol, is highly effective drug for *Plasmodium falciparum* malaria and remained effective in multi-drug resistant areas (Maduka *et al*., 2003). It has a simple dosage regimen and is relatively cheap (http://www.drugbank.ca/drugs/DB01218). It is a blood schizonticide, acting by forming toxic complexes with ferriprotoporphyrin IX that damage the membrane of the malaria parasite (Obi *et al*., 2004). It is prescribed as standby treatment among travelers to the tropics who develop febrile illnesses. It has been proposed as a radical cure to avoid the constraints of prolonged chemoprophylaxis (WHO, 2010).

The absorption of halofantrine is variable because it is lipophilic and hydrophobic, hence, its absorption is increased when taken with fatty foods. Halofantrine-induced prolongation of the QT interval of the heart, linked to arrhythmias and cardiotoxicity has been well documented in literature (WHO, 2010). This is the reason halofantrine should be taken on an empty stomach. Plasma levels peak at 16 h and the half-life of the drug is about 4 days (Wesche *et al*., 2000).

The effect of other antimalarials like chloroquine on biochemical liver functions and liver tissue has been studied. It increased alanine transaminase (ALT) and aspartate transaminase (AST) (Okonkwo *et al*., 1997).

This research was an effort to investigate the effects of short-term oral administration of halofantrine on some liver enzymes in healthy adult Wistar rats to determine if it has any hepatotoxic effect in addition to its established cardiotoxic effect.

MATERIALS AND METHODS

The halofantrine tablets used for the project were obtained from Boluke Pharmacy, Agege, Lagos. The halofantrine was manufactured by GlaxoSmithKline, France. The male and female Wistar rats used for the study were obtained from the animal house of the Physiology department of the University of Ibadan, Oyo State, Nigeria. Rat cubes were obtained from Sesco Feeds (Sesco feeds and Concentrates), Ikenne, Ogun State. Thirty rats were used in this study. The animals were allowed to acclimatize to the environment for a period of seven days before the study. Approval for the use of animals was obtained from the animal use committee of the Department of Physiology, Olabisi Onabanjo University, Nigeria.

Housing: The animals were maintained in wire mesh cages under photo-period controlled environment (12 h dark; 12 h light cycles; 24-25°C).

Corresponding Author: Osonuga Ayokunle, School of Medical Sciences, Universty of Cape Coast, Ghana

Materials: The materials used to carry out the research include: Dissecting set, 2 mL needles and syringes, cotton wool, methylated spirit, distilled water, diethyl ether, ethylenediaminetetraacetic acid (EDTA) bottles, AST, ALT and ALK kits from Randox Laboratories, Ltd., UK and spectrophotometer.

EXPERIMENTAL DESIGN

Thirty rats (15 males and 15 females) were assigned into three groups by simple random sampling.

Group 1: Control group: This contained five male rats and five female rats that received distilled water and feed *ad libitum*.

Group 2: Test group: This group contained 10 rats (5 males and 5 females). Each rat in the group was treated with 2.15 mg 100 g^{-1} body weight of halofantrine every 6 h for 18 h.

Group 3: Recovery group: This group contained 10 rats (5 males and 5 females). The animals were given 2.15 mg 100 g^{-1} b.wt. of halofantrine each every 6 h for 18 h and allowed to recover from the treatment for another 18 h. This group served to determine if the effect of the drug was reversible upon withdrawal.

Autopsy: The animals were anaesthetized with diethyl ether. As soon as the animals were in surgical state of anesthesia, they were cut open from the abdomen and blood was collected via cardiac puncture with a syringe and needle into EDTA bottles for biochemical and hematological studies.

Analytical procedure: The rats were weighed prior to treatment and at the end of each phase to obtain differential weight gains (if any). The animals were anaesthetized with di-ethyl ether after which they were sacrificed by exsanguinations.

Enzyme analysis: Serum pyruvate aminotransferase, serum alanine aminotransferase and serum alkaline phosphatase values were determined using Randox kit (Randox Laboratories, Ltd., UK) with absorbance read on a spectrometer at wavelength range of 530-560 nm.

Statistical analysis: All calculations were done using the SPSS-V15 statistical software package for analysis of the data. The data were presented as Means±SD and statistical analysis carried out using the Student's t-test and ANOVA. Differences were considered to be of statistical significance at an error probability of less than 0.05 ($p<0.05$).

RESULTS AND DISCUSSION

On alkaline phosphatase: Administration of halofantrine at 2.15 mg 100 g^{-1} body weight to the rats daily for 18 h at 6 h interval significantly increased ($p<0.05$) the values of alkaline phosphatase in both male and female rats relative to the controls. The values tend to decrease upon withdrawal of the medication in the recovery group (Table 1).

On alanine aminotransferase: Significant increase in alanine aminotransferase ($p<0.05$) values in both male and female rats relative to the controls was observed. The values decreased after allowing the rats to recover from effects of the drug (Table 2).

On aspartate aminotransferase: Significantly increased pyruvate aminotransferase ($p<0.05$) values of in both male and female rats in the test group, relative to the controls. The values decreased after allowing the rats to recover from effects of the drug (Table 3).

This investigation demonstrated that administration of halofantrine to rats significantly ($p<0.05$) increased the liver enzymes (Table 1-3) thence a potential hepatotoxic effect of halofantrine.

The ability of halofantrine to produce liver damage *in vivo* often results from the interaction of a series of complex cellular processes involved in the uptake,

Table 1: Effect of halofantrine on alkaline phosphatase

Groups	ALP (U L^{-1})
Control group male	77.8±1.37
Control group female	49.2±7.50
Test group male	125.8±29.84*
Test group female	106.0±33.14*
Recovery group male	108.2±12.28*
Recovery group female	78.4±12.58*

*$p<0.05$ (p is significant at $p<0.05$)

Table 2: Effect of halofantrine on ALT

Groups	ALT (U L^{-1})
Control group male	74.3±10.25
Control group female	54.3±6.40
Test group male	110.6±25.12*
Test group female	95.3±10.48*
Recovery group male	100.4±20.22*
Recovery group female	90.6±9.46*

*$p<0.05$ (p is significant at $p<0.05$)

Table 3: Effect of halofantrine on AST

Groups	AST (U L^{-1})
Control group male	77.0±26.83
Control group female	57.0±08.56
Test group male	110.0±52.46*
Test group female	91.6±51.19*
Recovery group male	105.0±19.89*
Recovery group female	86.8±12.96*

*$p<0.05$ (p is significant at $p<0.05$)

biotransformation and elimination of potentially toxic compounds (Obi *et al*., 2004). Some other authors suggest that halofantrine's interaction with biological membranes (which is also implicated in its antimalarial action) could be responsible for its liver-toxicity (Nwanjo *et al*., 2007). Other antimalarials such as chloroquine (Iyawe and Onigbinde, 2009), fansidar and quinine (Gadir *et al*., 2006) and artemether (Obianime and Aprioku, 2011) are also reported to induce hepatic damage.

The present study demonstrated that the toxic effect of short term administration of halofantrine on the liver is reversible (as noticed in the recovery group, Table 1-3).The reversal may result from plasma clearance of the drug and subsequent excretion (Obi *et al*., 2004). Also, drug induced hepatotoxicity has been linked to increased potential for regeneration and recovery of the liver (Ansari and Jamil, 2011). The percentage change in levels of the studied liver enzymes was significantly higher in the female animals than in the males. This correlates with a study that implicated hormonal profile in female susceptibility to hepatic toxicity (Uboh *et al*., 2007).

Serum AST, ALT, ALP and bilirubin are the most sensitive markers employed in the diagnosis of hepatic damage because they are cytoplasmic enzymes released into circulation after cellular damage (Patrick-Iwuanyanwu *et al*., 2011). The increased activities of AST, ALT and ALP we observed indicated halofantrine-induced hepatocellular damage (Obi *et al*., 2004). Liver enzymes are usually raised in acute hepatoxicity but tend to decrease with prolonged intoxication due to damage to the liver cells (Obianime and Aprioku, 2011). Other studies used higher doses because of higher elimination rates observed in animals (Adaramoye *et al*., 2008). In this study, we observed similar toxicity even with human-based therapeutic doses.

CONCLUSION

We conclude that halofantrine causes reversible elevation in the serum levels of hepatic enzymes, implying altered liver function. Therefore caution must be observed when administering it to patients with impaired liver function so as not to worsen their health status.

REFERENCES

Adaramoye, O.A., D.O. Osaimoje, A.M. Akinsanya, C.M. Nneji, M.A. Fafunso and O.G. Ademowo, 2008. Changes in antioxidant status and biochemical indices after acute administration of artemether, artemether-lumefantrine and halofantrine in rats. Basic. Clin. Pharmacol. Toxicol., 102: 412-418.

Ansari, J.A. and M. Jamil, 2011. Pathways of hepatic regeneration and pharmacological approaches for hepatoprotection: A brief approach. J. Pharmacol. Toxicol., 6: 24-29.

Gadir, W.S.A., M. Edeen, D.A. Alazaim, A.O. Bakhiet and I.M.T. Fadlalla, 2006. Effects of quinine and fansidar and their combination on bovans-type chicks. J. Pharmacol. Toxicol., 1: 383-388.

Iyawe, H.O.T. and A.O. Onigbinde, 2009. Impact of *Plasmodium berghei* and chloroquine on haematological and antioxidants indices in mice. Asian J. Biochem., 4: 30-35.

Maduka, H.C.C., A. Salihu and V.A. Onwuliri, 2003. Biochemical evaluation of combination drug interaction between phenobarbitone and halofantrine in weaning rats. J. Biol. Sci., 3: 711-717.

Nwanjo, H., G. Oze and M. Okafor, 2007. Biochemical evaluation of hepatic dysfunction as a result of Halofantrine toxicity in Wistar rats. The Internet J. Third World Med., Vol. 4.

Obi, E., O.E. Orisakwe, L.A. Asomugha, O.O. Udemezue and V.N. Orish, 2004. The hepatotoxic effect of halofantrine in guinea pigs. Indian J. Pharm., 36: 303-305.

Obianime, A.W. and J.S. Aprioku, 2011. Mechanism of action of artemisinins on biochemical, hematological and reproductive parameters in male guinea pigs. Int. J. Pharmacol., 7: 84-95.

Okonkwo, C.A., P.U. Agomo, A.G. Mafe and S.K. Akindele, 1997. A study of the hepatoxicity of chloroquine in mice. Nig. Qt. J. Hosp. Med., 7: 183-187.

Patrick-Iwuanyanwu, K.C., C.C. Onyemaenu, M.O. Wegwu and E.O. Ayalogu, 2011. Hepatotoxic and nephrotoxic effects of kerosene and petrol-contaminated diets in wistar albino rats. Res. J. Environ. Toxicol., 5: 49-57.

Uboh, F.E., M.I. Akpanabiatu, I.S. Ekaidem, P.E. Ebong and I.B. Umoh, 2007. Effect of inhalation exposure to gasoline fumes on sex hormones profile in wistar albino rats. Acta Endocrinol. (Buc), 3: 23-30.

WHO, 2010. Guidlines for the Treatment of Malaria. 2nd Edn., World Health Organisation, Geneva, Switzerland.

Wesche, D.L., B.G. Schuster, W.X. Wang and R.L. Woosley, 2000. Mechanism of cardiotoxicity of halofantrine. Clin. Pharmacol. Ther., 67: 521-529.