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Toxicological Effect of Sub-therapeutic, Therapeutic and Overdose Regimens of Halofantrine Hydrochloride on Male Albino Rats

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ABSTRACT

Background: Halofantrine is a drug used for treatment of multi-drug resistant *Plasmodium falciparum* malaria but with cardiotoxicity effects. **Aim:** In this study, its toxicity effect in varying doses (sub-therapeutic dose, therapeutic and overdose) on the liver, kidney and heart were investigated using male Albino rats. **Method:** Ninety male Albino rats were randomly selected and divided into six groups (1-6) of fifteen rats each. Doses of 24.99, 50.01 and 13.95 mg kg^{-1} representing therapeutic, overdose and sub-therapeutic concentrations were administered to groups 1, 3 and 5, respectively while groups 2, 4 and 6 served as controls. For biochemical analysis and histopathological examination, blood and organs (liver, kidney and heart) of five rats from each group were excised after cardiac puncture on days 1, 3 and 7. **Result:** Overdosed rats (group 1) showed significant decrease in body weight ($p < 0.05$) on day 1 while for rats in groups 3 and 5, there were numerical increases in body weight but not significantly when compared with their controls. Significant changes in some enzyme markers (ALT, AST, γGT), creatinine and urea were observed for rats overdosed as well as those on therapeutic dose but with pronounced effects in overdose group. Histological examination of organs showed mild cellular infiltration of portal areas of the liver, congestion of glomerular capillaries in the kidney and congestion of myocardial capillaries in the heart in halofantrine-treated animals but not in their controls. **Conclusion:** Halofantrine hydrochloride exhibits cardiotoxic, hepatotoxic and renotoxic effects at therapeutic and overdose levels but not at sub-therapeutic doses in male Albino rats.

Key words: Halofantrine, toxicity, liver, plasmodium falciparum, biotransformation

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INTRODUCTION

The emergence of resistant strains of *P. falciparum* to so many antimalarial drugs such as chloroquine, sulphadoxine and mefloquine has prompted the evolution and search for alternative drugs for malaria chemoprophylaxis and chemotherapy. Halofantrine (Hf) is a phenanthrene-methanol antimalarial currently marketed as the hydrochloride, under the trade name Halfan®. Hf is highly lipophilic[1] and useful in the treatment of multidrug resistant strains of *P. falciparum*.[2] The principal metabolite of the drug, N-desbutylhalofantrine (DHf), is also active against sensitive and resistant strain of *P. falciparum*. Hf has been banned as an antimalarial drug due to its cardiotoxicity.[3] It is poorly soluble in aqueous medium[1,4] and absorption in human, when administered orally, is erratic with high inter individual variations which have been shown to be associated with food intake.[5,6] More so it is shown that fatty foods increase the absorption of Hf, thereby increasing its bioavailability which enhances the cardio-toxicity of the drug.

Hf has been associated with a significant number of adverse effects related to the cardiovascular system including elongation of QT interval, life threatening arrhythmias and sudden death. There is therefore need for more studies on the toxic effect of Hf. Liver function tests represent functions performed by the liver. They are carried out to assess the state of liver function. The liver function test enzymes are referred to as markers of disease and dysfunction. The enzyme markers determine the status of the integrity of the liver cell membranes and when found in the blood stream are indicative that some liver cells are damaged. The most commonly used markers of hepatocyte injury are:

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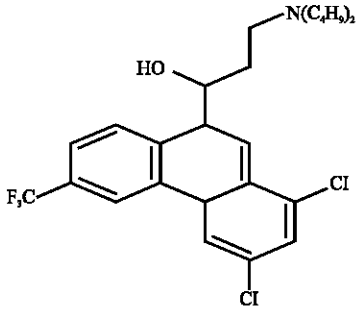

Fig. 1: Halofantrine molecule: 1,3-dichloro-α-[2-(dibutylamino) ethyl]-6-triflouromethyl-9-phenathrene methanol)

Alanine aminotransferase (ALT), Aspartate aminotransferase (AST) and Gamma-glutamyltransferase (γ-GT)[7].

Renal function can be impaired such that kidneys fail in their ability to carry out their normal metabolic and endocrine functions.[8] Impairment of renal function results in the retention of constituents in the plasma that are normally removed by the kidney. Nitrogenous waste products of protein catabolism (urea and creatinine) are particularly elevated within the plasma. The intra-vascular elevation of these nitrogenous waste products is termed Azotemia.[9] Renal impairment can be estimated using serum creatinine and serum urea.

This study was aimed at investigating the toxicity effect of Hf on the heart (cardiotoxicity), kidney (renotoxicity) and liver (hepatoxicity) by giving an overdose (50.01 mg kg^{-1}), therapeutic (24.99 mg kg^{-1}) and sub-therapeutic (13.95 mg kg^{-1}) doses of Hf HCl (Fig. 1) in 3 divided doses, respectively using 90 male Albino rats as experimental animals.

MATERIALS AND METHODS

Drugs: Halfan® tablet (250 mg; Batch No. 781) and Halfan® suspension (100 mg/5 mL; Batch No. 4015), both of Smith Kline Beecham France, were purchased commercially.

Reagents: Randox serum urea, serum creatinine, alanine aminotransferase, aspartate amino-transferase and gamma glutamyl transferase, (all from Randox Laboratories, United Kingdom), distilled water provided by Pharmaceutical Chemistry Laboratories, University of Ibadan.

Equipments: Sonicator (Langford Electronic Ltd., Birmingham B30), electronic mettler-weighing balance (H80, 110-240V, Western Germany), refrigerator, water bath, ultracentrifuge (Sugifriend Medicals, England), UV-spectrophotometer, thermometer, oral canula and plain tube.

METHOD

Ninety male Albino rats were obtained from the Veterinary Institute, University of Ibadan, Nigeria. The rats were housed and fed until they weighed between 150-240 g. They were acclimatized under standard housing conditions of an ambient temperature. The rats were randomly selected and divided into groups 1-6, with each group containing 15 rats. The grouping and dose of halofantrine hydrochloride were assigned as outlined in Table 1.

Collection of organs and blood from the albino rats: The rats were weighed and difference in body weight was recorded before the collection of serum and organs. Five rats in each group were sacrificed on day 1, 3 and 7, respectively after the last drug administration. The blood of the rat was collected using non-heparinized tubes through cardiac puncture. It was allowed to clot and centrifuged at 3,000 rpm for about 20 min. The serum obtained was transferred into another non-heparinized tube with the aid of a precision pipette and stored in the freezer at -20°C for the assay of serum enzyme activities (ALT, AST and γGT) and renal function estimations (creatinine and urea).

The rats were dissected and the liver, kidney and heart were carefully removed, weighed and kept in 10% formalin in carefully labeled containers, preserved for histopathological investigations.

Data analysis: The statistical significance of difference between groups was analyzed using the one-way analysis of variance (ANOVA) followed by Fisher Least Significance Difference (LSD) post hoc test. Statistical tests were performed using SPSS (version 11) package.

RESULTS

Percentage change in body weight: Following administration of the varying doses of halofantrine hydrochloride given in three divided doses to albino rats as shown in Table 2, percentage change in body weight was significantly decreased ($p<0.05$) after day 1 for the overdose group (50.01 mg kg^{-1}) while there weren't too obvious changes in body weight for the 24.99 and 13.95 mg kg^{-1} groups. Though a change in percentage body weight was observed in all three medication groups after days 3 and 7, they were not significantly different with respect to control as shown in Table 3 and 4.

Table 1: Treatment of various groups with Halofontorin HCl

Groups	Dose of Halofontrin HCl
1 Overdose group	Treated with halofantrine HCl suspension 50.01 mg kg^{-1} in three divided doses
2 Control	Treated with 3 mL kg^{-1} distilled water in three divided doses, serving as control to group 1
3 Therapeutic group	Treated with halofantrine HCl suspension 24.99 mg kg^{-1} in three divided doses
4 Control	Treated with 3 mL kg^{-1} distilled water in three divided doses, serving as control to group 3
5 Sub-therapeutic group	Treated with 13.95 mg kg^{-1} halofantrine HCl tablet dissolve in corn oil (as vehicle) in three divided doses
6 Control	Treated with 3 mL kg^{-1} corn oil in three divided doses, serving as control to group 5

Table 2: Summary effect of sub-therapeutic, therapeutic and overdose of halofantrine hydrochloride on male Albino rats Day 1 after drug administration in comparison with controls

Treatment	Change in b.wt. (%)	Liver weight (g)	Kidney weight (g)	Heart weight (g)	AST (μ L^{-1})	ALT (μ L^{-1})	γGT (nm min^{-1})	CTN (μ moL^{-1})	Urea (mmol L^{-1})
Corn oil (control)	1.25±1.25	6.10±0.25	1.52±0.25	0.8±0.08	57.8±6.5	75.0±12.5	5.8±2.3	183.9±3.6	4.4±1.5
Halofantrine tablet									
13.95 mg kg^{-1}	1.25±1.25	5.6±0.62	1.46±0.08	0.86±0.06	58.5±8.5	73.6±18.1	7.7±3.3	154.0±22.8	5.2±1.8
p-value	0.307	0.301	0.566	0.811	0.950	0.729	0.665	0.262	0.739
Significance	Not significant	Not significant	Not significant	Not significant	Not significant	Not significant	Not significant	Not significant	Not significant
Distilled H_2O (control)	4.99±0.59	7.1±0.72	1.46±0.15	0.62±0.04	32.7±0.04	67.0±11.1	6.5±0.6	140.8±9.7	12.1±0.5
Halofantrine susp.									
24.99 mg kg^{-1}	6.26±0.05	1.24±0.04	0.82±0.10	69.2±6.5*	84.0±44.7	13.1±2.6	186.5±3.4*	4.7±2.2*	
p-value	0.554	0.520	0.602	0.082	0.005	0.729	0.071	0.007	0.026
Significance	Not significant	Not significant	Not significant	Not significant	Significant	Not significant	Not significant	Significant	Significant
Distilled H_2O (control)	0.00± 0.00	7.10±0.72	1.46±0.15	0.82± 0.05	32.70±0.60	67.00±11.14	6.49±0.59	140.84±21.7	12.09±0.49
Halofantrine susp.									
50.01 mg kg^{-1}	-9.44±0.99	5.82±0.33	1.38±0.04	0.76± 0.06	70.20±3.68	279.00±60.18	18.24±6.96	190.00±3.81	3.95±0.77
p-value	0.000	0.089	0.619	0.570	0.000	0.000	0.031	0.000	0.019
Significance	Significant	Not significant	Not significant	Not significant	Significant	Significant	Significant	Significant	Significant

Values are Mean±SEM for n = 5 , *p< 0.5-Significantly different from control

Table 3: Summary effect of sub-therapeutic, therapeutic and overdose of halofantrine hydrochloride on male Albino rats Day 3 after drug administration in comparison with controls.

Treatment	Change in b.wt. (%)	Liver weight (g)	Kidney weight (g)	Heart weight (g)	AST (μ L^{-1})	ALT (μ L^{-1})	γGT (nm min^{-1})	CTN (μ moL^{-1})	Urea (mmol L^{-1})
Corn oil (control)	10.9±1.06	5.54± 0.98	1.12±0.19	0.8±0.08	41.8±2.3	75.4±14.7	73.4±27.6	94.8±12.1	5.0±1.8
Halofantrine tablet									
13.95 mg kg^{-1}	5.0± 0.48	9.1±0.48	5.2±0.07	0.86±0.06	32.9±2.10	94.0±11.0*	87.7±29.9	101.1±10.3	7.9±2.9
p-value	0.444	0.431	0.889	0.082	0.095	0.022	0.344	0.705	0.412
Significance	Not significant	Not significant	Not significant	Not significant	Not significant	Significant	Not significant	Not significant	Not significant
Distilled H_2O (control)	4.9±0.36	5.36±2.5	1.32±0.17	0.42±0.02	33.1±1.3	88.0±2.5	74.6±1.9	124.9±10.1	11.5±0.3
Halofantrine susp.									
24.99 mg kg^{-1}	10.19±1.06	4.68±0.3	1.6±0.62	0.6±0.07	60.5±3.7*	61.0±10.9	87.1±16.5	116.3±10.1	25.1±3.5*
p-value	0.526	0.622	0.814	0.098	0.001	0.067	0.504	0.563	0.029
Significance	Not significant	Not significant	Not significant	Not significant	Significant	Not Significant	Not significant	Not significant	Significant
Distilled H_2O (control)	4.89±0.54	5.36±0.22	1.32±0.17	0.86±0.12	33.10±1.27	88.00±2.55	74.57±1.85	11.54±0.31	124.94±10.12
Halofantrine susp.									
50.01 mg kg^{-1}	4.39±0.54	5.26±0.14	1.10±0.03	0.60±0.05	63.90±5.66	50.00±9.22	85.69±18.90	166.88±24.78	25.50±1.70
p-value	0.561	0.896	0.268	0.036	0.000	0.158	0.674	0.096	0.001
Significance	Not significant	Not significant	Not significant	Significant	Significant	Not significant	Not significant	Not significant	Significant

Values are Mean±SEM for n = 5, *p< 0.5-Significantly different from control

Weight of organs (heart, liver and kidney): While generally were no significant changes in the weight of the organs of the treated rats as compared to the untreated ones (controls), a significant change in heart weight was observed in the overdose group on day 3 (Table 2).

Serum tests: Day 1 of the study reveals significant differences ($p<0.05$) in the levels of both liver and kidney function parameters examined in the group of rats administered an overdose of halofantrine hydrochloride. In rats given the therapeutic dose, there was similar significant increase in AST and creatinine levels with significant decrease in urea. No significant changes were observed at the sub-therapeutic dose (Table 2).

On day 3 post the drug administration, AST and urea concentrations in both the overdose and therapeutic groups were still significantly different from the values obtained in their controls whereas, differences in ALT, γGT and creatinine were no longer significant. Noticeably on day 3 is the significant difference in ALT level in rats administered sub-therapeutic dose of halofantrine hydrochloride (Table 3).

Day 7 of the experiment reveals AST and ALT levels being significantly different from controls at both therapeutic and overdose regimens of halofantrine hydrochloride while changes in levels of the other parameters are not too significant (Table 4).

Table 4: Summary effect of sub-therapeutic, therapeutic and overdose of halofantrine hydrochloride on male Albino rats Day 7 after drug administration in comparison with controls

Treatment	Change in b.wt. (%)	Liver weight (g)	Kidney weight (g)	Heart weight (g)	AST (μL^{-1})	ALT (μL^{-1})	γGT (nm/min)	CTN (μ molL^{-1})	Urea (mmol L^{-1})
Corn oil (control)	10.9±1.06	4.96±0.23	1.06±0.05	0.52±0.04	32.7±2.5	36.0±1.1	20.0±11.4	106±10.2	11.3±0.5
Halofantrine tablet 13.95 mg kg^{-1}	7.24±0.51	4.8±0.22	0.96±0.06	0.66±0.06	23.9±3.6	37.6±7.5	31.3±11.6	139.3±16.2	11.0±0.6
p-value	0.604	0.812	0.082	0.099	0.102	0.842	0.545	0.174	0.704
Significance	Not significant	Not significant	Not significant	Not significant	Not significant	Not significant	Not significant	Not significant	Not significant
Distilled H_2O (control)	9.56±1.28	6.16±0.2	1.16±0.1	0.46±0.02	36.3±1.0	9.0±0.3	8.8±1.7	100.6±22.6	11.3±0.5
Halofantrine susp. 24.99 mg kg^{-1}	9.58±1.28	4.34±0.18	1.02±0.02	0.58±0.03	24.1±2.3*	32.3±1.3*	14.2±4.0	90.7±2.6	11.3±1.7
P-value	0.307	0.285	0.450	0.312	0.007	0.000	0.273	0.384	0.978
Significance	Not significant	Not significant	Not significant	Not significant	Significant	Significant	Not significant	Not significant	Not significant
Distilled H_2O (control)	9.58±1.28	6.16±0.20	1.16±0.10	0.74±0.09	36.20±1.07	9.00±0.35	8.80±1.66	11.35±0.24	100.67±10.12
Hf 50.01 mg kg^{-1} suspension	6.22±2.55	5.58±0.75	1.08±0.07	0.72±0.12	29.00±3.53	33.10±5.23	4.70±0.67	107.36±15.16	12.38±0.89
p-value	0.307	0.395	0.476	0.864	0.023	0.004	0.678	0.671	0.244
Significance	Not significant	Not significant	Not significant	Not signififant	Significant	Significant	Not Significant	Not significant	Not significant

Values are Mean±SEM for n = 5, *p< 0.5-Significantly different from control

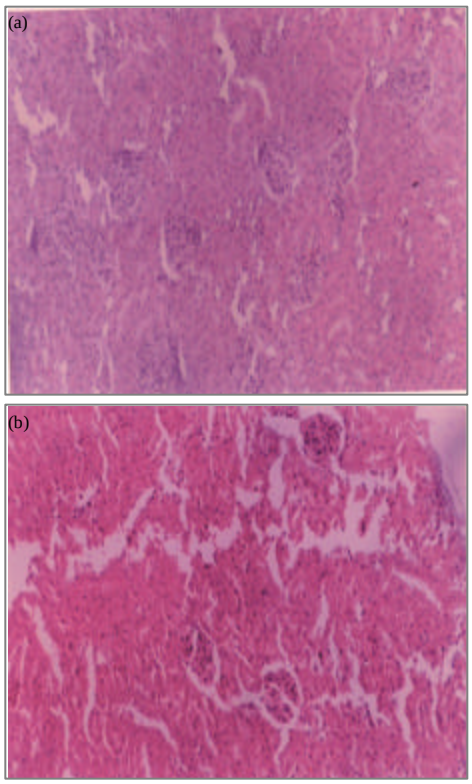

Fig. 2: Photomicrograph of HE-stained section of Albino rat kidney Day 3 after administering 50.01 mg kg^{-1} halofantrine hydrochloride, (a) Normal renal structure (kidney) and (b) Congestion of glomerular capillaries

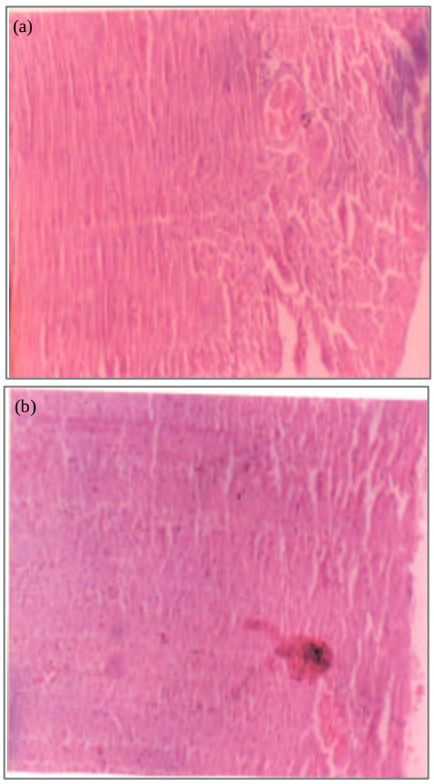

Fig. 3: Photomicrograph of HE-stained section of Albino rat heart on Day 3 after administering 50.01 mg kg^{-1} halofantrine hydrochloride, (a) Normal hepatic structure (Heart) and (b) Congestion of myocardial capillaries

Histopathology of the organs: Figure 2 shows the effect of 50.01 mg kg^{-1} of halofantrine suspension given in three divided doses, 3 days after administration to the rats. There was congestion of glomerular capillaries in the kidney of treated rats (B) when compared with the control (A) which exhibited normal renal structure. Figure 3 shows the effect of 50.01 mg kg^{-1} of halofantrine suspension given in three divided doses 3 days after being

administered to rats. There was congestion of myocardial capillaries in the heart of rats given the drug (D) as when compared with the control (C) which exhibited normal cardiac structure.

DISCUSSION

The ability of a drug to produce liver damage *in vivo* often results from the interaction of the uptake, biotransformation and elimination of potentially toxic compounds.[10] Many xenobiotics (drugs and environmental chemicals) are capable of causing some degree of liver injury and liver diseases have become one of the major causes of morbidity and mortality all over the globe.[11] The result on Table 2 shows a significant decrease ($p<0.05$) in the percentage change in body weight of rats (-9.44±0.99) when compared with control (0.00±0.00) one day after administration of 50.01 mg kg^{-1} Hf HCl as suspension. This is in agreement with the work of Simmons *et al.*[12] which states that an increase or decrease in either absolute or relative weight of an organ after drug administration is an indication of toxicity. The percentage changes in weight of the Albino rats used in this experiment following the administration of an overdose (50.01 mg kg^{-1}) of halofantrine on day 1 was found to be significant whereas it was no longer so on days 3 and 7. This is evident of an impact of the high drug concentration and the confirmation of this is reflected in the subsequent decrease in percentage weight change, days after the drug has been given, indicating a wearing-off effect of the drug on the heart. Also, the percentage change in weight of the rats with the 13.95 mg kg^{-1} halofantrine tablet and 24.99 mg kg^{-1} suspension administration when compared with their individual controls of corn oil and distilled water were not significant ($p>0.05$), implying that these concentrations are not as toxic as compared to the overdose.

Amount of alanine aminotransferase (ALT), aspartate aminotransferase (AST) and gamma-glutamyltransferase (γGT) increased with respect to control on day 1 after administration of 50.01 mg kg^{-1} Hf Hcl as suspension with a similar effect in the therapeutic dose (24.99 mg kg^{-1}) except for increase in ALT and γGT levels which were not so significant (Table 2). This is in agreement with the work of Bassey *et al.*[13] which reported a peak level of enzyme activities as the drug reached peak plasma concentration (6-12 h) after administration of 250 mg kg^{-1} of Hf HCl as tablet in a single oral dose to humans. The serum enzymes AST and ALT, after 3 days of 50.01 and 24.99 mg kg^{-1} HF HCl as suspension were significantly increased. Recent findings reported increased AST activities with respect to control in patients treated with Chloroquine.[14] Increased AST level may result to hepatotoxicity as transaminases are known to indicate cellular integrity of the liver.[15] Interestingly there's also an increase in ALT level on day 3 after 13.95 mg kg^{-1} halofantrine hydrochloride is given. Seven days after administration of 50.01 mg kg^{-1} Hf HCl as suspension, the level of ALT was increased significantly ($p<0.05$) to 33.10±5.23 with respect to control (9.00±0.35). Also AST level decreased significantly ($p>0.05$). The same is similar for animals given 24.99 mg kg^{-1} of the drug. The observed decrease in enzyme activities after seven days of drug administration possibly indicates recovery.[11] Bassey *et al.*[13] reported a similar decline in enzyme activity, as the drug concentration wanes off the system.

Creatinine (CTN) concentrations increased significantly ($p<0.05$) when both therapeutic and overdose regimens were given to the rats while urea concentrations decreased significantly ($p<0.05$). The kidneys eliminate water-soluble complexes of a drug and porphyrins produced in the mitochondria and lysosomes of hepatocytes. Creatinine test is used to diagnose impaired kidney function and to determine renal (kidney) damage. Since the rate of production is constant, elevation of serum creatinine (CTN) is an indication of under-excretion, suggesting kidney impairment. Decreased levels of urea indicate acute hepatic insufficiency.[15] and can also occur in severe liver disease.[16] Histopathological studies confirmed existence of kidney dysfunction with congestion of glomerular capillaries in the kidney (Fig. 2) viewed after staining as well as congestion of myocardial capillaries in the heart (Fig. 3) of rats on 50.01 mg kg^{-1} Hf HCl whereas the controls exhibited normal histopathological structures.

CONCLUSION

These findings aside of corroborating the cardiotoxicity effect of halofantrine hydrochloride in normal therapeutic doses also show that both at therapeutic dose and in overdose, hepatic and renal dysfunctions also occur. It is therefore further authenticating the cautious use or even ban of the drug.

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