

## Effect of Chronic Oral Administration of Chloroquine on the Weight of the Heart in Wistar Rats

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**Abstract:** The effect of chronic oral administration of chloroquine, an antimalarial and antirheumatic drug on the weight of the heart in wistar rats was investigated. Ten wistar rats were randomly grouped into two, control and treated. The treated group rats were administered 20 mg/kg body wt, weekly of chloroquine for 4 weeks while the control group rats were given distilled water for 4 weeks. The rats were fed with grower's mash purchased from Edo feeds and Flour Mill Ltd, Ewu, Edo state, Nigeria and were given water *ad libitum*. On day 29th of the experiment, the rats were weighed and sacrificed. The heart were carefully dissected out, freed from adherent tissues and weighed to the nearest 0.001 g. The result showed that chronic oral administration of chloroquine resulted in significant increase in the weight of the heart ( $p < 0.05$ ). Thus, our result suggests that though chloroquine may be a widely used antimalarial and antirheumatic drug, its chronic administration may result in cardiotoxicity. It is therefore recommended that the drug be prescribed with caution in patients with cardiac abnormality, such as cardiomyopathy.

**Key words:** Antimalarial, cardiomyopathy, cardiotoxicity, chloroquine, heart

### INTRODUCTION

Over the last decade, several reports have raised the issue of cardiotoxicity associated with drugs currently used to treat *Plasmodium falciparum* malaria (Touze, 2002). Specifically, the cardiotoxicity of halofantrine has been reported (Ter Kuile *et al.*, 1993; Gundersen *et al.*, 1997; Nosten *et al.*, 1993; Sanguinetti and Jurkiewicz, 1990; Wesche *et al.*, 2000). It has also been reported that there are adverse cardiac effects after treatment with other aryl-amino-alcohol agents such as quinine and mefloquine (Martin *et al.*, 1997; Laothavorn *et al.*, 1992; Fonteyne *et al.*, 1996; Ofosuri *et al.*, 2008).

Chloroquine is a widely used antimalarial agent (Sharma and Mishra, 1999). It is also used to treat rheumatoid arthritis and systemic lupus erythematosus (Ducharme and Farinotti, 1996; Dubois, 1978). Available data show that chloroquine is concentrated in the liver and many other tissues following its administration (Adelusi and Salako, 1982). In toxic doses, it is known to cause appreciable cellular damage to liver, kidney and heart muscle (deGroot *et al.*, 1981; Ngaha, 1982). Cardiotoxicity following accidental or suicidal chloroquine overdose has been reported. Ironically, such effects have been associated with usual doses of chloroquine administered for short or long term therapy (Good and Shader, 1981).

The heart is a muscular organ present in all vertebrates, and responsible for pumping blood through

the blood vessels by repeated rhythmic contractions (Heath *et al.*, 1999). The heart of a vertebrate is composed of cardiac muscle (myocardium), an involuntary muscle tissue which is found only within this organ. The myocardium is the heart's muscular wall (Heath *et al.*, 1999). It contracts to pump blood out of the heart and then relaxes as the heart refills with returning blood. Its outer surface is called the epicardium. Its inner lining is the endocardium (Heath *et al.*, 1999).

The effects of chronic oral administration of chloroquine on the weight of the heart were not found in existing literatures. This study was considered important since rheumatoid arthritis and malaria are common ailments in the tropics and the need to avoid the risk of cardiomyopathy resulting from prolonged oral administration of chloroquine. Moreover, it has been suggested that chloroquine has the potential to induce hypertrophic cardiomyopathy (Baguet *et al.*, 1999; Guedira *et al.*, 1998; Teixeira *et al.*, 2002). Thus, the aim of this study is to investigate the effect of prolonged oral administration of chloroquine on the weight of the heart in wistar rats.

### MATERIALS AND METHODS

**Location and duration of study:** This study was conducted at the histology laboratory of the College of Medicine, Ambrose Alli University, Ekpoma, Edo State, Nigeria. The preliminary studies, animal acclimatization,

Table 1: Effect of chronic oral chloroquine administration on the body and heart weights of wistar rats

Group	Body weight (g)		Heart weight (g)	
	Initial	Final	%	Increase
Control	150.00	175.00±0.00	16.67	0.798±0.096
Treated	150.00	175.00±0.00	16.67	0.647±0.053*

Values are expressed as mean±SD

\*: Significantly different statistically from the control at  $p < 0.05$ , t-test

drug procurement, actual animal experiment and evaluation of results, lasted for a period of two months (February and March, 2010). However, the actual administration of the drug to the test animals lasted for one month.

**Animals:** Experiments were carried out on ten (10) Wistar rats (150 g) procured and maintained in the Animal Holdings of the College of Medicine, Ambrose Alli University, Ekpoma, Edo State, Nigeria. The animals were housed under a controlled room temperature of about 25-28°C, relative humidity of about 60-80% and photo-periodicity of 12 h day / 12 h night, and fed with rat pellets (Bendel Feeds and Flour Mills, Ewu, Nigeria) and water ad libitum. They were randomly assigned into two groups, the control (n = 5) and treated (n = 5) groups.

**Drug administration:** The chloroquine phosphate tablets used for this experiment were manufactured by Emzor Pharmaceutical Industries, Lagos, Nigeria and were purchased from Irrua Specialist Teaching Hospital, Irrua, Edo State, Nigeria. Rats in the treatment group received 20 mg/kg body weight of chloroquine phosphate dissolved in distilled water weekly for 4 weeks. Rats in the control group received equal volume of distilled water using orogastric tube.

**Organ collection:** At the end of the experiment, on the 29th day, the rats were weighed again and then sacrificed using humane killing with chloroform. The hearts were excised, cleared of adherent tissue, weighed immediately on a mettler analytical balance (PE 1600, Mettler Instrument AG; Switzerland). The shape and colour of the heart were observed with the naked eyes.

**Statistical analysis:** The data for body and heart weights were expressed as the mean±SD. The treated group was compared to control using the Student's t test. Differences with values of  $p < 0.05$  were considered statistically significant (Mahajan, 1997).

## RESULTS

**Gross morphology:** No gross differences were observed between the two groups (control and experimental) of animals on day 29th day at the completion of experimental procedure. There were no unexpected deaths

recorded. There were also no obvious differences in the shape and colour of the heart in the two groups of animals.

**Effect of chronic oral chloroquine administration on body weight:** The data obtained from the mean body weights of the control and chloroquine treated rats are given in Table 1. A comparison of the mean body weight of the rats before and after treatment showed that both the treated and control rats manifested the same increase in body weight. The percentage increase in mean body weight of rats was 16.67%.

**Effect of chronic oral chloroquine administration on heart weight:** The data obtained from the mean heart weights of the control and chloroquine treated rats are given in Table 1. Using t-test analysis technique there was a significant difference in the mean heart weight between the two rat groups ( $p < 0.05$ ).

## DISCUSSION

Our investigation on gross/morphological changes indicated that there were no difference between the control and treated rats. The observed normal body weight gain in the control and test groups implied that chronic oral administration of chloroquine had no negative effect on somatic growth.

However, there was a significant increase in mean heart weight of treated group as compared with those of the control rats. In fact, an increase or decrease in relative or absolute weight of an organ after administering a chemical or drug, has been shown to indicate the toxic effect of that chemical (Simons *et al.*, 1995; Maina *et al.*, 2008). Thus, the observed increase in heart weight in the chloroquine treated group indicates that the drug may have toxic effect on the heart at that dose and duration.

As an antimalarial, chloroquine acts by inhibiting hemozoin biocrystallization, which gives rise to toxic free heme accumulation that is responsible for the death of the parasites (Barennes *et al.* 2006). It has indeed been shown that heme is a potentially damaging species, which can directly attack and may impair intracellular targets including the lipid bilayer, the cytoskeleton, intermediary metabolic enzymes, and DNA (Wagener *et al.*, 2003). Also, there are available reports indicating that high

levels of free heme cause severe toxic effects to kidney, liver, central nervous system and cardiac tissue and that free heme catalyzes the oxidation, covalent cross-linking and aggregate formation of protein and its degradation to small peptides (Kumar and Bandyopadhyay, 2005). Free heme is highly lipophilic and will rapidly intercalate into the lipid membranes of adjacent cells (Beri and Chandra, 1993), where it catalyzes the formation of cytotoxic lipid peroxide via lipid peroxidation and damages DNA through oxidative stress (Kumar and Bandyopadhyay, 2005). Acworth *et al.* (1997) revealed that increased lipid peroxidation can negatively affect the membrane function by decreasing membrane fluidity and changing the activity of membrane bound enzymes and receptors.

In fact, reactive oxygen species have been implicated in the pathophysiology of a large number of diseases (Barp *et al.*, 2002). Evidence from experimental as well as clinical studies suggests the role of oxidative stress in the pathogenesis of heart dysfunction (Singal *et al.*, 1998; Manolio, 1991; Piano, 2002; Reinke *et al.*, 1987). Furthermore, elevated ROS are implicated in the development of cardiac hypertrophy, reperfusion injury, remodelling and heart failure (Sorescu and Griendling, 2002). Accumulation of ROS such as superoxide, hydrogen peroxide, and hydroxyl radicals along with a compromised antioxidant capacity contribute to excess damage to cellular carbohydrates, proteins, lipids and nucleic acids (Amici *et al.*, 1989; Paradis *et al.*, 1997). This increase in ROS triggers cardiomyocyte expression of the proto-oncogene c-fos, one of the first indicators of hypertrophy (Cheng *et al.*, 1999). ROS also activate members of the Mitogen-Activated Protein Kinase (MAPK) family, protein kinase C, phosphatidyl inositol 3-kinase, and calcineurin, ultimately leading to increased cardiomyocyte protein synthesis, hypertrophic gene expression and increased cardiomyocyte volume (Sawyer *et al.*, 2002; Xiao *et al.*, 2002; Sabri *et al.*, 2003; Ghosh *et al.*, 2003). Based on these reports therefore, it is conceivable that the chloroquine used in this study may have acted through the generation of excess free heme or reactive oxygen species to induce the heart weight gain observed in the treated group.

### CONCLUSION

Our study suggests that chronic oral administration of chloroquine has no effect on somatic growth but causes a significant increase in heart weight. The present investigation also shows that though chloroquine may be a widely used antimalarial and antirheumatic drug, its chronic administration may result in cardiac damage. It is therefore suggested that the drug be prescribed with

caution in patients diagnosed with cardiac abnormality, such as hypertrophic cardiomyopathy.

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