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Histopathological Evaluation of the Cardiotoxicity of Dihydroartemisinin-Piperaquine on Male Albino Rats

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Abstract

Problem Statement: Malaria's global impact necessitates effective treatments, like dihydroartemisinin-piperaquine (DHA/PQP), though safety concerns, notably drug-induced cardiotoxicity (DICT), persist. A knowledge gap exists regarding DHA/PQP's cardiac effects, warranting a comprehensive investigation. **Approach:** This study aimed to assess KROSH (DHA/PQP) impact on albino rat heart histology, examining structural changes and potential cardiotoxicity. 40 albino rats were grouped by KROSH dosage and duration, monitored for weight changes, and heart tissues were examined using hematoxylin and eosin (H & E) staining. Statistical analysis compared to control and treated groups. **Results:** KROSH administration led to varying rat weight effects, yet not statistically significant. Histological analysis revealed dose and duration-dependent cardiac tissue alterations, including distortion, adipose deposits, artery hypertrophy, fibrosis, and necrosis. These contrasts with prior research documenting DHA/PQP's non-toxic effects. **Conclusion/Recommendation:** This study highlights potential KROSH (DHA/PQP) cardiotoxicity concerns through histological changes, underscoring the need for further research into underlying mechanisms and human health implications. Given DHA/PQP's wide use, these findings should inform safety evaluations and administration practices.

Keywords

Dihydroartemisinin-Piperaquine, Histopathological Evaluation, Cardiac Muscles, Albino Rats

1. Introduction

Malaria continues to be a prominent infectious disease globally, posing a considerable challenge to public health especially resistance [1]. The WHO has recommended a dihydroartemisinin-piperaquine combination for malaria treatment, and although these drugs have shown effectiveness, safety concerns persist [1] [2] [3]. In order to counteract this resistance, the WHO the use of combination of two drugs targeting distinct biochemical sites within the Plasmodium falciparum malaria parasite. The mechanism is for a partner drug to kill the parasite when a resistance to the first-line drug arises [1]. Drug-induced cardiotoxicity (DICT) is a severe adverse drug reaction that disrupts the usual physiological functioning of the cardiovascular system and is becoming a primary concern for anti-malaria prophylaxis [4].

Piperaquine, a bisquinoline antimalarial structurally related to chloroquine, shares the potential of many quinoline and structurally related drugs to affect myocardial depolarization and repolarization [5]. Previous studies have linked chloroquine with drug-induced cardiotoxicity, manifesting as decreased blood pressure, irregular rhythmic activity of the heart, heart failure, marked enlargement of the heart, and electrocardiogram (ECG) changes, particularly in the T wave [6] [7] [8]. Halofantrine and quinidine, also structurally related antimalarials, have shown prolonged ECG intervals associated with sudden death [9].

KROSH (DHA/PQP), an antimalarial that has demonstrated high tolerance and efficacy against resistant malaria strains and is administered enterally is a commonly used agent [10]. However, the exact cardiovascular effects of this drug are not fully understood. Thus, this study was conducted to assess the histological effects of KROSH (DHA/PPQ) on the heart of an albino rat.

2. Materials and Method

2.1. Specimen Preparation

A cohort of forty albino rats, each weighing between 145 g and 152 g, were carefully weighed, housed, and nourished throughout the entire duration of the experimental period. Rats were divided into seven groups:

1) Control Group: Received receiving deionized distilled water.

2) Group IIa: Received oral administration of 10.5 mg/kg KROSH for a duration of 3 days.

3) Group IIb: Received oral administration of 10.5 mg/kg KROSH for a duration of 7 days.

4) Group IIIa: Received oral administration of 21 mg/kg KROSH for a duration of 3 days.

5) Group IIIb: Received oral administration of 21 mg/kg KROSH for a duration of 7 days.

6) Group IVa: Received oral administration of 31.5 mg/kg KROSH for a duration of 3 days.

7) Group IVb: Received oral administration of 31.5 mg/kg KROSH for a duration of 7 days.

The test and control rats were weighed 10 minutes before the administration of the first dose of KROSH and distilled water respectively and were weighed again 24 hours after the end of the administration of the last dose.

2.2. Heart Harvesting

Animals were humanely euthanized post 3-day and 7-day drug exposure. Hearts were dissected, fixed in 10% formal saline for 48 hours.

2.3. Histopathological Process

Tissues fixed in 10% formalin (2 hrs), distilled water rinsed (30 mins), dehydrated in alcohol series, cleared with xylene, impregnated with paraffin wax, embedded, sectioned (5 microns), stained with H & E, mounted with DPX.

2.4. Statistical Analysis

Numeric data presented as mean ± SEM. Mean differences between control and treated groups assessed with Instant Biostatistics ($p < 0.05$).

2.5. Histopathological Analysis

Photomicrographs compared treated and control rat heart tissues, aiding assessment of structural changes.

3. Result

Effect of DHA/PQP on Body Weight: The impact of dihydroartemisinin and piperaquine phosphate on albino rat body weight was examined across different dosage groups in (Table 1). Changes in body weight were observed for each group, ranging from initial to final measurements after treatment. The results indicate that KROSH administration had varying effects on rat body weight, with some groups experiencing increases and others showing fluctuations.

Effect of DHA/PQP on the Heart of albino Rats: Microscopic examination of heart tissue from different treatment groups was performed using H & E staining. The images at 400× magnification revealed various observations. Group I showed a normal photomicrograph of heart tissues showing myocytes (M) and connective tissues (CT) (Figure 1).

Group IIa displayed mild cardiac muscle distortion (MD), Group IIb showed mild MD and vascular congestion (VC) (Figure 2 & Figure 3).

Group IIIa exhibited adipose tissue deposits (AT), detachment of endothelial layer (DE), and mild MD (Figure 4). Group IIIb demonstrated mild enlargement of cardiac artery (CA), endothelium disruption (DE), and mild MD (Figure 5).

Group IVa presented hypertrophic artery (HA), adipose tissues (AT), and mild MD, while Group IVb showed fibrosis (F), necrosis (N), and mild MD (Figure 6 & Figure 7). These findings indicate different structural alterations in heart tissue due to KROSH treatment across the groups.

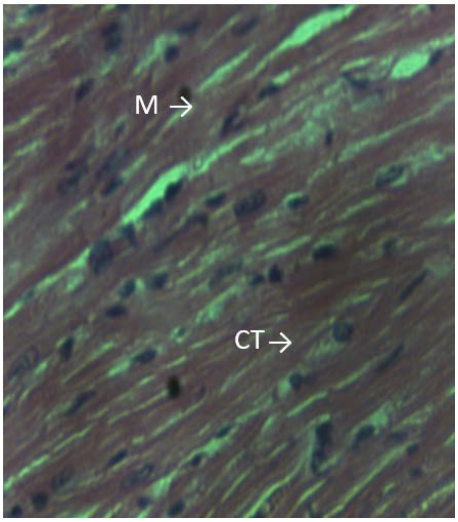

Figure 1. Shows the photomicrograph of heart tissue of Group 1 (control) rats. H and E stain ×400, showing myocytes (M) and connective tissue (CT).

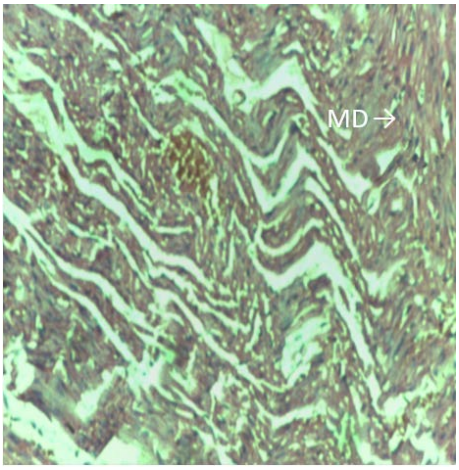

Figure 2. Shows the photomicrograph of heart tissue of Group IIa treated rats. H and E stain ×400, showing mild distortion of the cardiac muscle (MD).

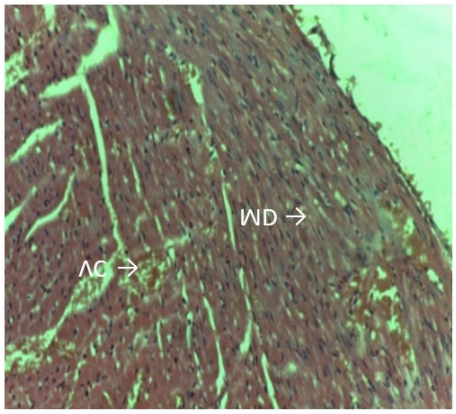

Figure 3. Shows the photomicrograph of heart tissue of Group IIb treated rats. H and E stain ×400, showing mild distortion of the cardiac muscle (MD) and vascular congestion (VC).

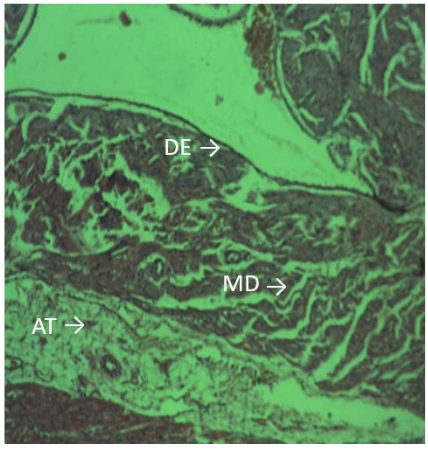

Figure 4. Shows the photomicrograph of heart tissue of Group IIIa treated rats. H and E stain ×400, showing adipose tissue deposits (AT), detachment of endothelial layer (DE) and mild distortion of the cardiac muscle (MD).

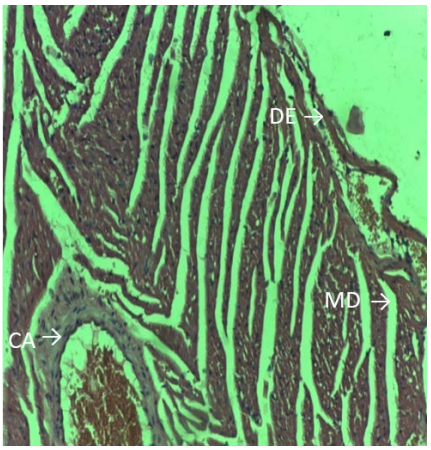

Figure 5. Shows photomicrograph of heart tissue of Group IIIb treated rats. H and E stain ×400, showing mild enlargement of the cardiac artery (CA), disruption of the endothelium (DE) and mild distortion of the cardiac muscle.

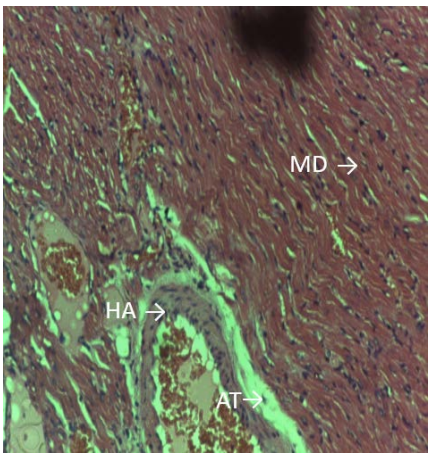

Figure 6. Shows the photomicrograph of heart tissue of Group IVa treated rats. H and E stain ×400, showing hypertrophic artery (HA), adipose tissues (AT) and mild distortion of the cardiac muscle (MD).

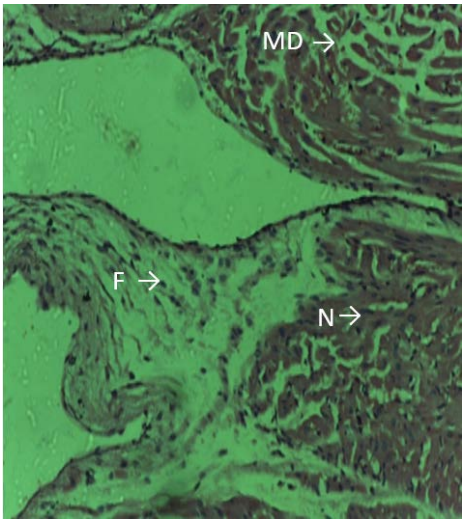

Figure 7. Shows the photomicrograph of heart tissue of Group IVb treated rats. H and E stain ×400, showing fibrosis (F), necrosis (N) and mild distortion of the cardiac muscle (MD).

Table 1. Effect of Dihydroartemisin and Piperaquine phosphate on the weight of albino rats.

Groups	Initial weight (g)	Final weight (g)
Group I	146 ± 5.477	152.8 ± 2.588
Group IIa	144 ± 4.183	150.2 ± 3.564
Group IIb	142 ± 4.472	151.4 ± 2.191
Group IIIa	149 ± 2.236	154 ± 2.345
Group IIIb	146.4 ± 5.899	151.6 ± 4.219
Group IVa	143 ± 4.472	151.4 ± 2.191
Group IVb	142 ± 4.472	150.6 ± 3.782

4. Discussion

After the text edit has been completed, the paper is ready for the template. Duplicate In this study, the effects of KROSH (DHA/PQP) on the histology of the heart in albino rats were investigated. It was observed that although the net weight of the rats changed upon administration of KROSH (DHA/PQP), this difference was not statistically significant ($p < 0.05$). However, this was in contrast to a study which recorded an increase in the weight of rats used [11].

Histological examination of the heart tissue section from rats administered with KROSH (DHA/PQP) in the present study revealed mild distortion of the cardiac muscle, adipose tissue deposits, hypertrophic artery, fibrosis and necrosis. These pathological features are however observed to be dose dependent as well as duration dependent. However, the present finding is contrary to those of Utoh-Ndeosa *et al.* and Izunya *et al.* who documented that administration of Dihydroartemisinin-pieraquine phosphate and its derivates produced no toxic

effect on the vital organs including the hearts of albino rats [11]. This difference in outcomes could be as a result of the dosage and duration as Utoh-Ndeosa *et al.* delivered a maximum of 2 mg/kg to the test organisms for 10 days with a 7-day break halfway [11]. Since the cardiotoxicty is dose-dependent, the minimum dosage used in this present study was 31.5 mg/kg which could have influenced the changes noticed in the heart of the rats.

5. Conclusion

The results of this study indicate that the administration of KROSH (DHA/PQP) may lead to dose and duration-dependent histological alterations in the heart tissue of albino rats. These findings suggest a potential impact of KROSH on cardiac health and raise concerns about its safety profile. However, seeing that DHA/PQP is a frequently used antimalarial drug in the tropical region, further research and investigation are warranted to better understand the mechanisms underlying these observed effects and to assess the implications for human health. It is important to consider these findings in the context of the broader literature on KROSH and its potential cardiotoxicity.

6. Limitations of the Study

This study was limited by paucity of published papers on the dihydroartemisinin-piperaquin on the cardiac muscles of either humans or animals. This resulted to a limited amount of information for comparison and for references to this current study.

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Conflicts of Interest

The authors declare no conflict of interest regarding the publication of this paper.

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