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Electrocardiographic Effect of Hydroxychloroquine on Rabbit's Heart

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Abstract

This study involved evaluation the effects of Hydroxychloroquine administration on the heart that associated with therapeutic dose in the rabbits. The experiment was carried out on twenty rabbit were divided into two groups equally (10 rabbits in each group) which were dosed for four weeks daily as follows: The first group was treated with distilled water as control, the second group was treated with Hydroxychloroquine (400 mg/kg B.wt.) orally. The electrocardiograph results of lead II were referred to the value of R-R was significantly decreased, but the QRS duration was significantly increase. The T duration there was increased significantly, but there were significant decreases in P-R duration, while Q-T duration found that was significant increase. We concluded that Hydroxychloroquine has adverse effect on the rabbit's heart.

Key words: Hydroxychloroquine, Heart, ECG.

Introduction

Hydroxychloroquine (HCQ) is a 4-aminoquinoline in the addition of a hydroxyl group. Hydroxychloroquine can be administered via parenteral or oral routes. Acute toxic effects were recorded more frequently when the drugs were given via the parenteral (especially the intravenous) route [1]. Drug absorption is practically complete even when administered via the oral route, but the concentration profile reaches lower peak levels postcentral than post parenteral administration [2]. The drugs accumulate into cells, due to ion trapping in more acidic environments, especially in lysosomes [3, 4], where the concentration can be many orders of magnitude higher than in the blood. The biological half-life is as long as 30-60 days [5, 6]. Hence there is possibility for progressive drug accumulation on repeated administration even of small doses, and the drug effects also develop following different time scales: from seconds or minutes, to hours or days, and to many months or years.

Hydroxychloroquine is a medication used to treat autoimmune conditions such as rheumatoid arthritis and systemic lupus erythematosus [7, 8 and 9]. Hydroxychloroquine and the related quinine derivatives

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chloroquine and amodiaquine have also been used for malaria treatment and prophylaxis, though this is becoming less common as rates of resistance to these drugs increase [10, 11 and 12].

Hydroxychloroquine toxicity is largely due to its effects on the heart. Sodium and potassium channel blockade result in QRS and QT prolongation, respectively, on the electrocardiogram (ECG). These prolonged intervals put patients at significant risk for dysrhythmias, included torsade de pointes and ventricular fibrillation. Other cardiac effects include delayed conduction as well as decreased contractility due to a negative inotropic effect [13]. These effects can lead to profound hypotension, dysrhythmias, and cardiovascular collapse [14]. HCQ cardiotoxicity may lead to progressive and potentially irreversible heart failure, heart transplant, and death [15].

The Electrocardiography passes on data with respect to the electrical capacity of the heart, by adjusting the state of its constituent waves to be specific the P, QRS and T waves which is exact estimation of clinically essential parameters measured for the transient conveyance of the ECG constituent waves [16**].**The measurement was obtained after two weeks and after four weeks. Recorded of the ECGs were by direct written work electrocardiogram [17**]**, all ECGs were institutionalized at 1mV = 10 mm, with a diagram velocity of 50 mm/sec., each box (small square) is 1 mm^2.Normally, more than two electrodes are utilized, and they can be joined into various sets bipolar limb (I, II and III) leads and unipolar (aVR, aVL and aVF) Leads. Each lead looks at the heart from a different angle [18–19].

Electrocardiography was evaluated by lead II which is limb lead. Leads of limb which are I, II and III. The signals that form by electrodes are situated one on the left leg and on the limbs one on each arm [17**]**.

Materials and method:

Experimental Animals

Total Twenty of local female rabbits were purchased from the animal house of the College of Veterinary Medicine, University of Baghdad with the range weight 1000-1900 gm and age 3-6 months. The animals were raised in the animal house of College of Veterinary Medicine, University of Baghdad for two weeks before starting the experiment for acclimatization under suitable condition of temperature 25±1 C° and dark/light cycle 12/12 hours. The animals were fed *ad labium* with standard pellet, green grass and water in an air-conditioned room.

Animals:

Twenty rabbits were divided into two groups equally (n=10) which were used as following:

1. The first group was administrated distilled water orally as control group for four weeks.

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2. The second group administrated orally Hydroxychloroquine (treated dose for four weeks).

Electrocardiography (ECG):

Limb leads poses purposes of "Einthoven's triangle" (Lippincott Williams & Wilkins, 2009). Rabbit's hair was shaved for electrodes placement. Leads of limb, electrodes were placed on each leg after placed the rabbits in dorsal position [20and 21**]** on a table and then immobilized by ligation the four limbs by bandage and they were left for 10-20 minutes to get calm. ECG were recorded. Modified wood table was used to record ECG waves.

Results

A significant change was observed in the treatment group Hydroxychloroquine compared to the control group, The R-R duration, there is significant decrease at (P≤0.05) in 2 weeks as compared with control also significant decrease between 4 weeks as compared to control, also there is significant decrease at (P≤0.05) between 4 weeks as compared to 2 weeks (Table 1):

Table (1): The R-R duration values (ms) in rabbits

Groups / **Parameters**		M ±Sd	
		Week2	**Week4**
R-R	**H**	174.8± 31.4 b	114.8±40.1 c
	C	224.5± 21.48 a	229.2±20.02 a
	LSD	26.2575	

M ±Sd = Mean ± Stander deviation

H = Hydroxychloroquine

C= control

R-R= heart rate

QRS Duration, there is significant increase at (P≤0.05) in 2 weeks as compared with control, also significant increase between 4 weeks as compared to control but there are no significant differences between 4 weeks and 2 weeks (Table 2).

Table 2: QRS Duration (ms).

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Groups / Parameters		M ±Sd	
		\Week2	Week4
QRS Dur	H	40.00 ± 0.00 a	40.00 ± 0.00 a
	C	20.00 ± 0.00 b	20.00 ± 0.00 b
	LSD	0.0008	

M ±Sd = Mean ± Stander deviation

H = Hydroxychloroquine

C= control

T Duration, there is significant increase at (P≤0.05) in 2 weeks as compared with control also significant increase between 4 weeks as compared to control, but there are no significant differences between 4 weeks and 2 weeks (Table 3).

Table 3: T Duration values (ms).

Groups / Parameters		M ±Sd	
		\Week2	Week4
T Duration	H	104.00 ± 16.73 a	104.00 ± 21.91 a
	C	84.00 ± 8.94 b	86.00 ± 8.94 b
	LSD	14.3759	

M ±Sd = Mean ± Stander deviation

H = Hydroxychloroquine

C= control

The Q-T Duration, there is non-significant increase at (P≤0.05) in 2 weeks as compared with control, while there is significant increase between 4 weeks as compared to control, as well as there is significant increase at (P≤0.05) between 4 weeks as compared to 2 weeks (Table 4).

Table 4: The Q-T Duration (ms) in rabbits

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Groups / Parameters		M ±Sd	
		\Week2	Week4
QT duration	H	160.00 ± 14.14 b	166.00 ± 26.8 a
	C	150.00 ± 10.00 b	145.00 ± 8.66 b
	LSD	17.2332	

M ±Sd = Mean ± Stander deviation

H = Hydroxychloroquine

C= control

P-R Duration, there is significant decrease at ($P \leq 0.05$) in 2 weeks as compared with control but significant increase between 4 weeks as compared to control also There is significant increase between 4 weeks as compared to 2 weeks (Table 5)

Table 5: P-R Duration (ms).

Groups / Parameters		M ±Sd	
		\Week2	Week4
P-R Duration	H	44.00 ± 8.94 c	72.00 ± 10.95 ab
	C	75.00 ± 8.66 a	66.00 ± 8.94 b
	LSD	10.6105	

M ±Sd = Mean ± Stander deviation
H = Hydroxychloroquine
C= control

Discussion

Hydroxychloroquine provokes sodium and calcium channel blockades, which lead to membrane-stabilizing effects, negative inotropic effects, and peripheral vasodilatation. Membrane stabilization results in conduction disturbances with atrioventricular block, and QRS interval widening [22].

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The effect leads to the classic PR prolongation, QRS complex widening, and QT prolongation associated with toxicity [23]. Also similar to class IA antiarrhythmics is the dose-dependent ability of aminoquinolines to bind and inhibit the action of potassium channels. As potassium is responsible for myocyte repolarization, potassium channel blockade delays repolarization. Clinically, this produces additional QT prolongation predisposes to *torsades de pointes* (TdP). Delay of repolarization is greatest at slower heart rates [24].

Inflammation, with the associated release of mediators, cytokines and chemokines by inflammatory cells, plays an important role in the remodelling process, and an experimental model of inflammation-induced remodelling resulting in dilated cardiomyopathy is obtained in mice overexpressing tumor necrosis factor (TNF) [25].

Cardiac cells (cardiocytes) are animated by the development of sodium, potassium and calcium inside and outside cell through means of Na+ -K+ -ATPase pump, digoxin may attach to the ATP pump, which leads to an inhibition of ATPase and consequently to an inhibition of sodium transport, however, calcium continues to move into the cell, associated with inhibition of Na+ -K+ -ATPase [26]. Mechanical and electrical functions of the heart are influenced by proper electrolyte balance, important components of this balance are sodium, calcium, potassium, and magnesium, Electrical activity that originates in the heart can be detected on the body's surface through an electrocardiogram [27].

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