Pharmacological Effect of Digoxin on some cardiac electrical properties and clinical signs in the Rabbit Model

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Abstract

This study involved evaluation the effects of digoxin administration on the heart electricity and clinical signs that associated with therapeutic dose in the rabbits. The experiment were carried out on twenty rabbit were divided into two groups equally (10 rabbit in each group) which were dosed for two and four weeks daily as follows: The first group was treated with distilled water as control, the second group was treated with digoxin (10 µg/kg B.wt. orally).The electrocardiograph results of lead II were referred to the value of P amplitude was significantly increased, also the QRS amplitude was significantly increase. The T duration there was not decrease significantly, furthermore there was significant decreases in P-R duration, while S-T duration found that was significant differences, prominent of some cardiac, neurological and gastrointestinal signs. We concluded that digoxin have pharmacological activity on some cardiac electrical properties associated with appearance of unwanted clinical signs. .

Key words: Digoxin, Electrical properties, Rabbit

INTRODUCTION

Digoxin is a cardiac glycoside derived from leaves of the foxglove plant, Digitalis lanata, has been in use for over 200 years as a heart medication. The drug raises the intracellular Ca^{++} concentration resulting in an increase in the force of heart muscle contractions (positive inotropic effect) and a reduction in ventricular heart rate [1 and 2].

Digoxin is the primary cardiac glycoside in clinical use, is used for the treatment of congestive heart failure (CHF) because of its inotropic effects on the myocardium and for the treatment of atrial fibrillation because of its chronotropic effects on the electrophysiological system of the heart [3]. The positive inotropic effect of digoxin is caused by binding to sodium- and potassium activated adenosine triphosphatase, also known as Na^{+}, K^{+}-ATPase or the sodium pump [4]. Furthermore the use of digoxin for patients with normal sinus rhythm, left ventricular dysfunction, also fetal tachycardia, supra-ventricular tachycardia, and pulmonary hypertension [5].

Digoxin has been around for centuries, but its use has been limited by several factors, because of its narrow therapeutic window, digoxin requires close monitoring, also, two major drawbacks of digoxin are its adverse effects and multiple drug interactions, despite these limitations, digoxin still considered adjunctive therapy, rather than first-line therapy, for these indications [6 and 7].

Digoxin-induced inhibition of Na^{+}, K^{+}-ATPase leads to decreased transport of sodium out of myocardial cells and increased intracellular sodium concentrations that aid calcium entry and decrease calcium elimination via the sodium-calcium exchanger(6). The increased intracellular calcium is stored in the endoplasmic reticulum so that action potential–induced calcium release is augmented causing enhanced myocardial contractility [3 and 5].

This study aimed to explain the pharmacological effect of digoxin on heart by recording ECG in rabbit model.

MATERIALS AND METHODS

Digoxin pediatric/ Geriatric was oral solution, elixir (0.05 mg/ ml), 60 ml. Aspen, Germany with dose of (10 µg/kg B.Wt.)

Experiment animals:

Twenty rabbits were divided into two groups, equally (10 rabbits in each group) which were used as following:
1. The first group was treated with distilled water as control group.
2. The second group treated orally with digoxin (10 µg/kg B.Wt.) for two weeks and four weeks.

Electrophysiology:

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 [8]. The measurement was obtained after two weeks and after four weeks. Recorded of the ECGs were by direct written work electrocardiogram [9], 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 [10 and 11].
 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 (9). Limb leads poses purposes of "Einthoven's triangle" [12].

Rabbit's hair was shaved for electrodes placement. Leads of limb, electrodes were placed on each leg after placed the rabbits in dorsal position [13] on a table and then immobilized by ligation the four limb 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

After administration of digoxin drug to the rabbits have many symptoms of Nausea, anorexia, tachycardia then convert to bradycardia, drowness, weakness and lethargy.
The ECG results (figure: 1) of lead II were found that in P duration not significant at ($P<0.05$) in the digoxin with

control in zero time, two and four weeks, also within same group at different time no significant increase at (P<0.05) in both groups (table 1). The results shown in table (2) for P amplitude were found to be no significant change at (P<0.05) for digoxin and control in zero time, and significantly increased at (P<0.05) for digoxin and control after two weeks, also there was no significant increase at (P<0.05) with digoxin as compared with control after four weeks. Furthermore there was no significant increased at (P<0.05) within control group at different time, digoxin group have significant increase at (P<0.05) after two weeks only as compared to control. Table (3) shows that QRS duration there was not significant increase at (P<0.05) at four weeks between digoxin and control groups, also there was non-significant differences at (P<0.05) at different time in both groups. Table (4) for QRS amplitude results shown there were not significantly differences at (P<0.05) in digoxin and control groups at different time. Also there was not significant differences at (P<0.05) between zero time and two weeks. In digoxin group there was significant increase differences at (P<0.05) between zero time and two weeks, also there was no significantly differences at (P<0.05) between four and two weeks. The results shown in table (5) for T duration there was significant decrease at (P<0.05) between digoxin and control groups at four weeks. Also there was no significant differences at (P<0.05) within control group at different time, also there was no significant decrease at (P<0.05) between zero time and four and two weeks within digoxin group. Table (6) for P-R duration shows there was not significant differences at (P<0.05) between digoxin and control groups in all different time. There was significant decrease at (P<0.05) between four and two weeks in control group, furthermore there was significant decrease at (P<0.05) between zero time and four weeks, also there was significant decrease at (P<0.05) between four and two weeks in digoxin group. Table (7) for S-T duration not significant differences at (P<0.05) in the digoxin with control in zero time and four weeks, while there was sig decrease between control and digoxin in two weeks also within same group at different time no significant differences at (P<0.05) in control groups, but there was significant decrease between control, four week time and two weeks in digoxin group.

Table 1: P Duration values (ms).

Group/time	control	Digoxin
At zero time	40.0±0.0	40.0±0.0
After 2weeks	40.0±0.0	40.0±0.0
After 4 weeks	40.0±0.0	40.0±0.0

Table 2: P Amplitude (mv or mm) values.

Group/time	control	Digoxin
At zero time	1.37±0.11 Aa	1.50±0.08 Ab
After 2weeks	1.50±0.15 Ba	1.88±0.09 Aa
After 4 weeks	1.62±0.09 Aa	1.75±0.11 Aab

LSD= 0.3
The different capital letters refer to a significant differences between different groups at (P<0.05).
The different small letters refer to a significant differences between different times at (P<0.05).

Table 3 : QRS Duration (ms).

Group/time	control	Digoxin
At zero time	20±0.0	26.70±4.12
After 2weeks	20±0.0	25.0±3.86
After 4 weeks	20±0.0	30.0±4.46

LSD=11.09

Table 4 : QRS Amplitude (mv or mm)

Group/time	control	Digoxin
At zero time	7.90±0.75 a	**6.10±0.27 b**
After 2weeks	9.50±1.01 a	9.0±0.34 a
After 4 weeks	6.0±0.54 b	6.50±0.67 b

LSD=1.79
The different small letters refer to a significant differences between different time at (P<0.05).

Table 5 : T Duration values (ms).

Group/time	control	Digoxin
At zero time	82.0±2.0 A	84.0±4.76 A
After 2weeks	**85.0±3.86 A**	75.0±13.21 A
After 4 weeks	86.0±3.99 A	70.0±4.46 B

LSD=15.22
The different capital letters refer to a significant differences between different groups at (P<0.05).

Table 6: P-R Duration (ms).

Group/time	control	Digoxin
At zero time	67.50±3.09 ab	70.0±3.33 a
After 2weeks	75.0±3.86 a	70.0±4.46 a
After 4 weeks	60.0±0.0 b	60.0±0.0 b

LSD=9.27
The different small letters refer to a significant differences between different times at (P<0.05).

Table 7 : S-T Duration (ms).

Group/time	control	Digoxin
At zero time	40.0±0.0 Aa	40.0±0.0 Aa
After 2weeks	40.0±0.0 Aa	35.0±3.86 Bb
After 4 weeks	40.0±0.0 Aa	40.0±0.0 Aa

LSD=4.49
The different capital letters refer to a significant differences between different groups at (P<0.05).
The different small letters refer to a significant differences between different times at (P<0.05).
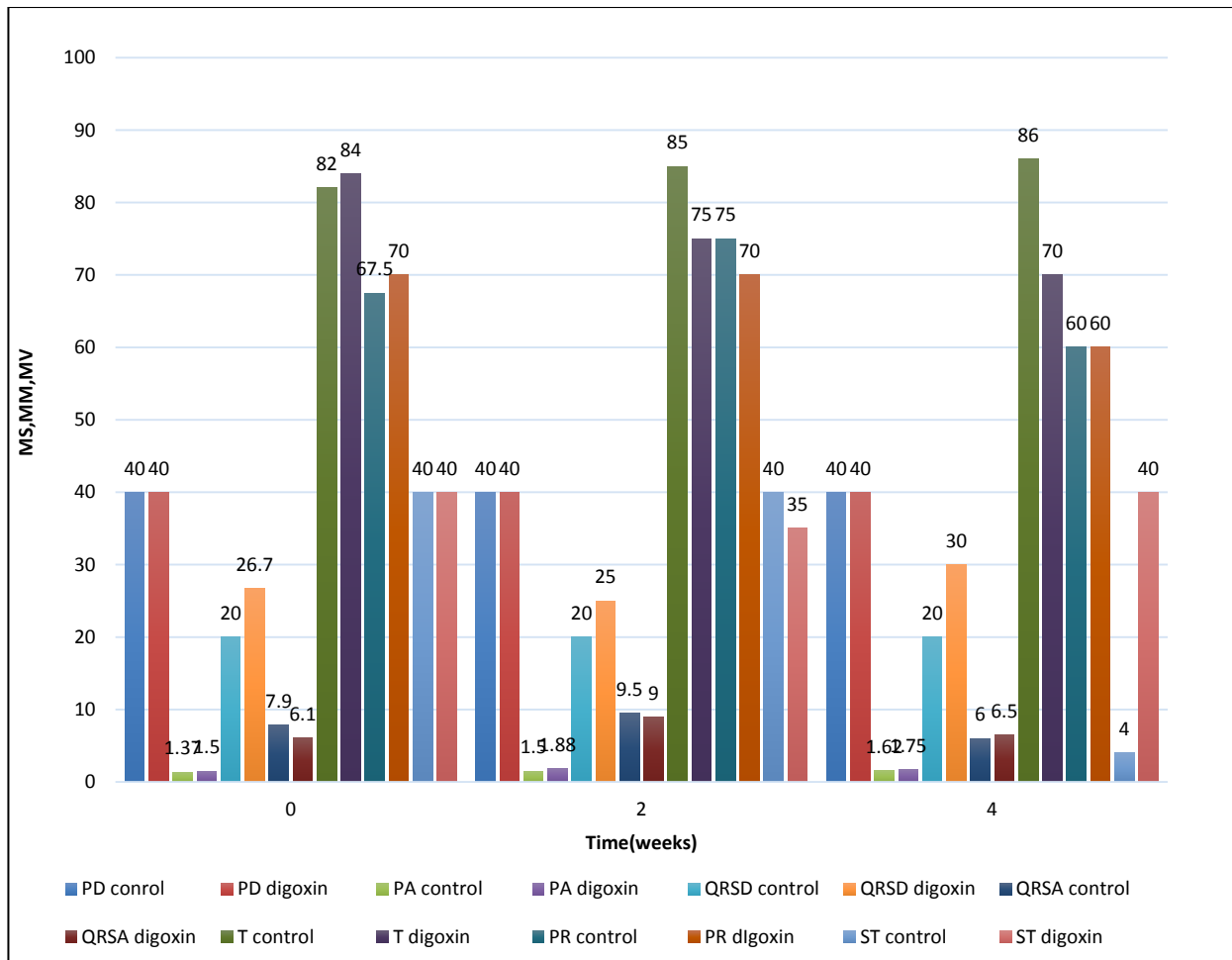
Figure (1): Relationship between time and the of digoxin on P Duration value (ms) , P Amplitude (mv or mm) value, QRS Duration (ms), QRS Amplitude (mv or mm), T Duration values (ms), P-R Duration (ms) and S-T Duration (ms).

DISCUSSION

[14] Found that the anorexia related to the plasma concentration of digoxin. Digoxin also affect dizziness (vertigo). Several other symptoms of digoxin significant arterial vasoconstriction, in agreement with this present study, also this in agreement with [15] who found that commonly clinical features include lethargy, and gastrointestinal symptoms (anorexia, nausea,), and cardiac arrhythmias.

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 [16]. 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 [17].

The values of P duration was calculated statistically and found not significant, while the value of P amplitude was significantly increased after two weeks which indicate increase of atrial contraction and this agreement with (18) in digoxin group. The QRS duration was not significantly increased this indicate there was abnormality of conduction (19), also in QRS amplitude there was significant increase at two weeks which indicate increase of ventricular contraction and this agreement with [18].

[20] Had reported that there is a direct correlation between the level of myocardial impairment and the effectiveness of digoxin therapy on cardiac function. At T duration there was not significant decrease, this may be represent abnormalities of ventricular repolarization, or T-wave changes may be secondary to abnormalities of depolarization, ie, pre-excitation or abnormalities of QRS voltage or duration. On the other hand, ST-segment and T wave abnormalities may be unrelated to any QRS abnormality, in which case they are called primary repolarization abnormalities. These are caused by ischemia, pericarditis, myocarditis, drugs (digoxin, antiarrhythmic) [21]. For P-R duration there was significant decreases and this differ with the effect of digoxin. Furthermore S-T duration found that was significant differences which indicate it's not normal and effected with digoxin treatment as primary repolarization abnormalities [21].

CONCLUSION:

Digoxin have pharmacological activity on some cardiac electrical properties associated with appearance of unwanted clinical signs.

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