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Abstract: This experiment was carried out to evaluate the role of vitamin E in decreasing the toxic effect of digoxin. Electrocardiographic recordings of New Zealand rabbits which were treated with digoxin-only or digoxin+vitamin E were used. Recordings were obtained before and 24 hours after treatments. It was found that digoxin-only treatment caused a sinusoidal tachicardia without changing the durations or amplitudes of any wave on the trace. However, digoxin+vitamin E treatment did not produce any increase in heart rate. It was concluded that vitamin E injection along with digoxin injection might lower the toxic effect of digoxin. More studies are needed to convince these findings.

Key Words: Digoxin, Vitamin E, Rabbits, Electrocardiogram.

Digoksin'in Toksik Etkisini Azaltmada Vitamin E'nin Rolü

Özet: Bu çalışma digoksin'in toksik etkisini azaltmada vitamin E'nin rolünü araştırmak amacıyla yapıldı. Bu amaçla, digoksin veya digoxin+vitamin E enjekte edilmiş tavşanlardan elde edilen elektrokardiyogramlar değerlendirildi. Kayıtlar ilaç uygulamasından hemen önce ve 24 saat sonra elde edildi. Digoksin'in yanlız uygulaması, elektrokardiyogram üzerindeki dalgaların boyunda ve süresinde herhangi bir değşiklik oluşturmazken, sinozoidal taşikardiye sebep olduğu gözlendi. Ancak digoksin ile birlikte vitamin E'nin enjeksiyonu kalp atım sayısında herhangi bir artış oluşturmadı. Digoksin ile birlikte vitamin E'nin enjeksiyonunun digoksinin toksik etkisini azaltabileceği sonucuna varıldı. Ancak bizim bulgularımızın desteklenmesi için daha fazla çalışmaya gereksinim vardır.

Anahtar Sözcükler: Digoksin, Vitamin E, Tavşan, Elektrokardiyogram

Introduction

Medical plants containing cardiac glycosides were known to the ancient Egyptians 3000 years ago (1). However, these agents were used erratically and with variable success until the 18th century, when William Withering, an English physician and botanist, published a monograph describing the clinical effects of an extract of the fox glove plant (*Digitalis purpurea*) a major source of the agents (1).

Digitalis, including digoxin, has multiple direct and indirect cardiovascular effects, with both therapeutic and toxic (arrhythmogenic) consequences (2). In addition, it has undesirable effects on the central nervous system and gut (2). A small direct renal (diuretic) effect has been demonstrated but is probably no clinical significance (2).

The effects of digitalis on the electrical properties of the heart in intact organisms are a mixture of direct and indirect (autonomic) actions. Direct action of digitalis is due to an inhibition of Na-K-ATPase that causes an increase in the intracellular Ca^{2+} concentration and a positive inotropic action (3,4,5). Indirect actions of cardiac glycosides on the heart involve the autonomic nervous system and occur throughout the therapeutic and toxic dose ranges (6). The most common cardiac manifestations of glycoside toxicity include atrioventricular junctional rhythm, premature ventricular depolarizations, bigeminal rhythm and second-degree atrioventricular blockade (7)

Oxygen consumption and metabolic activity are elevated due to increased muscle contractions causing electron leakage from mitochondrial transport system and an increase in toxic reactive oxygen metabolites in cells (8,9,10). Increased metabolic activity causes cell membrane depolarization, opening of calcium channels, activation of adenosine and lytic enzymes and oxidation of membrane phospholipids (11,12). Thus, not only mechanic-traumatic factors but also radical metabolites cause muscle cell damage (8).

Vitamin E is the first line of defense against peroxidation of polyunsaturated fatty acids contained in the cellular and subcellular membrane phospholipids (13). Vitamin E also acts as an antioxidant, breaking free-radical chain reactions as a result of its ability to transfer a phenolic hydrogen to a peroxyl free radical of a peroxidized polyunsaturated fatty acid (14,15).

Since the toxic concentrations of digoxin increase the intracellular Ca^{2+} concentration causing oxidation of membrane phospholipids and an increase in lytic enzymes, the antioxidant activity of vitamin E might lower the toxic effect of digoxin. Thus, this study was designed to evaluate if the toxic effect of digoxin could be lowered by the Vitamin E injection.

Materials and Methods

Preparation of animals for recording:

In this study, 10 male 1 year old New Zealand rabbits weighting about 2 kg were used. Alligator clip electrodes were attached to the skin at the triceps brachii muscle (coput longum and coput laterale) of the right and left limbs and biceps femoris muscle of the right and left hips. Electrode gel was rubbed into the skin in the area where the alligator clips were attached to act as a decreasing agent and thereby decrease the resistance of the skin (16). The rabbits were immobilized by wrapping a light cotton around them and then placed on a table. We waited about 10 min. for rabbits to get calm. The rabbits were not anesthetized at any time. All recordings were made on the same day.

ECGs were recorded by a direct writing electrocardiograph (Cardiofax 6851; Nihon Kohden, Tokyo). All ECGs were standardized at 2 mV = 10 mm, with a chart speed of 50 mm/sec. Leads I, II, III, aVR, aVL and aVF were recorded before and 24 hours after digoxin or digoxin+vit-E was given. The durations and amplitudes of waves on the trace were measured in lead II and electrical axis also measured in leads I and III.

Drug used:

Intravenous injections of 1 mg/kg digoxin (Sandoz Ürünleri A.Ş., Levent, İSTANBUL) and 70 mg/kg vitamin E (Roche Müstehzarları Sanayi A.Ş., Levent, İSTANBUL) were used.

Statistical analysis:

Three treatments (control, 1 mg/kg digoxin-only treated and 70 mg/kg vitamin E+1 mg/kg digoxin treated) were used. Each treatment contained same number (n=5) of rabbits with same sex and weight. The data were expressed as mean ± standard deviation (SD) and analyzed using analysis of variance (ANOVA). Least significant difference (17) was used to test for differences among means for which ANOVA indicated a significant ($P \leq 0.05$) F ratio.

Results

Figure 1, 2 and 3 provide all leads of the ECGs of the normal, digoxin-only and digoxin+vitamin E treated rabbits, respectively. These readings are representative of the majority of rabbits. The durations and amplitudes of all waves in lead II are shown in the Table 1.

In control group, the P wave was negative in lead aVR and positive in other leads. The mean duration of the P wave was 0.020 sec (0.016-0.025 sec) and its average amplitude was 0.20 mV (0.18-0.23 mV). Q wave was

Variables	Control	1 mg/kg digoxin	1 mg/kg digoxin+70 mg/kg vitamin E
P (sec)	0.020 ± 0.005	0.020 ± 0.005	0.018 ± 0.004
P (mV)	0.20 ± 0.04	0.17 ± 0.03	0.18 ± 0.04
QRS (sec)	0.020 ± 0.003	0.017 ± 0.003	0.020 ± 0.003
QRS (mV)	0.50 ± 0.10	0.45 ± 0.08	0.5 5 ± 0.11
T (sec)	0.080 ± 0.022	0.080 ± 0.020	0.12 ± 0.029
T (mV)	0.50 ± 0.07	0.60 ± 0.09	0.60 ± 0.10
P-Q (sec)	0.060 ± 0.018	0.050 ± 0.015	0.055 ± 0.017
Q-T (sec)	0.14 ± 0.04	0.14 ± 0.04	0.14 ± 0.04
Heart rate	210.9 ± 31.6	300 ± 35.7*	240 ± 30.3
Mean electrical axis	$+63^{o}$ (-20^{o} to $+130^{o}$)	$+63^{o}$ (-20^{o} to $+130^{o}$)	$+63^{o}$ (-20^{o} to $+130^{o}$)

Table 1. Amplitudes and durations of waves and heart rates of 1 mg/kg digoxin treated and 1 mg/kg digoxin+70 mg/kg vitamin E treated rabbits (means ± standard deviations are shown, n=5). *denotes a significant difference between control and the treatment group.

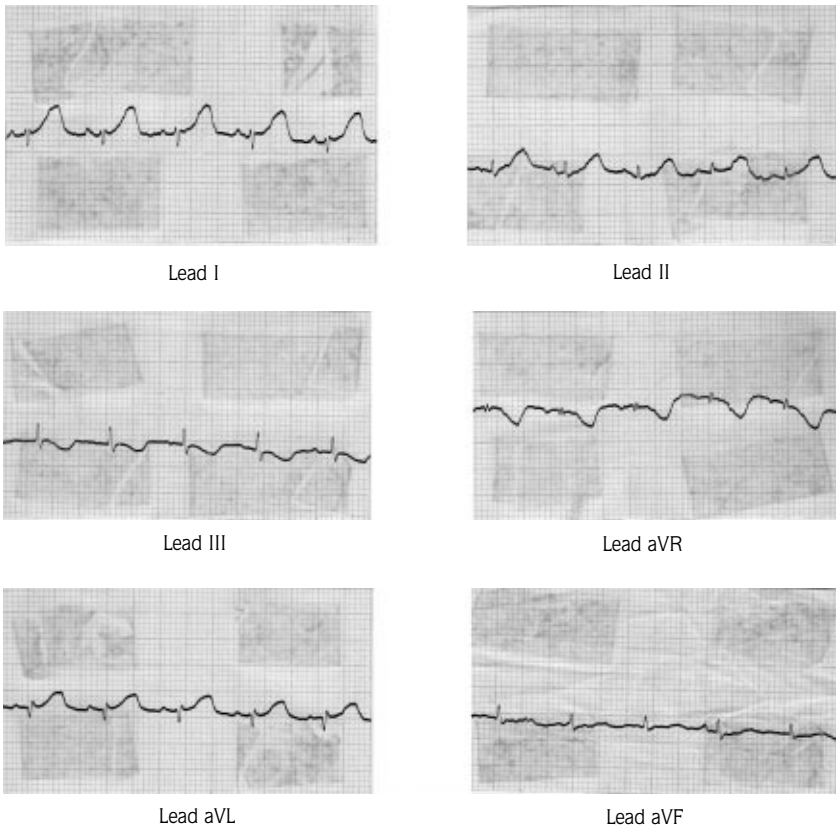

Figure 1. The leads of ECGs of the control rabbits (standardization, 2 mV=10 mm; chart speed, 50 mm/sec).

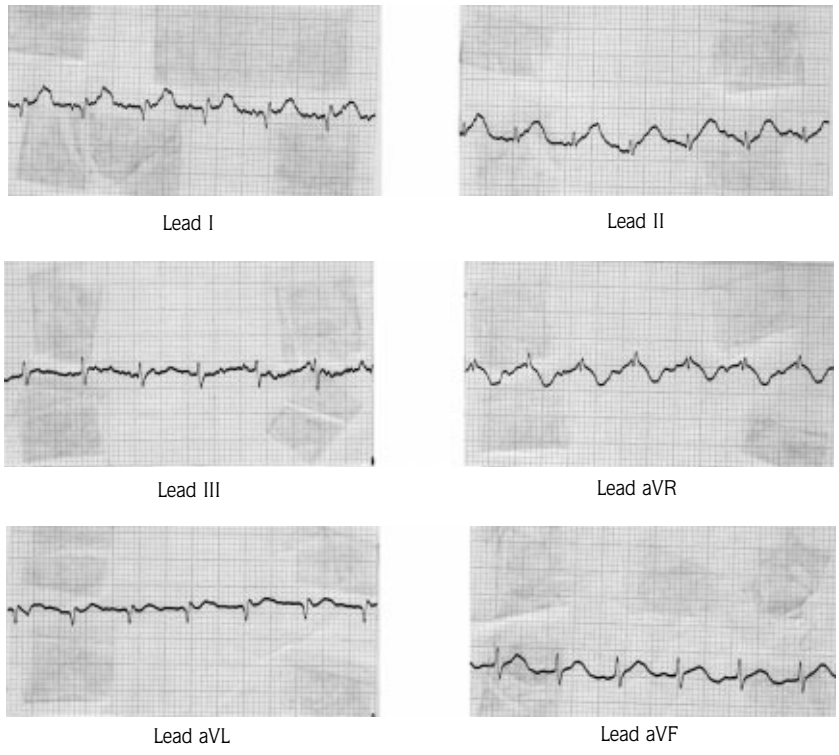

Figure 2. The leads of ECGs of the 1 mg/kg digoxin treated group (standardization, 2 mV=10 mm; chart speed, 50 mm/sec).

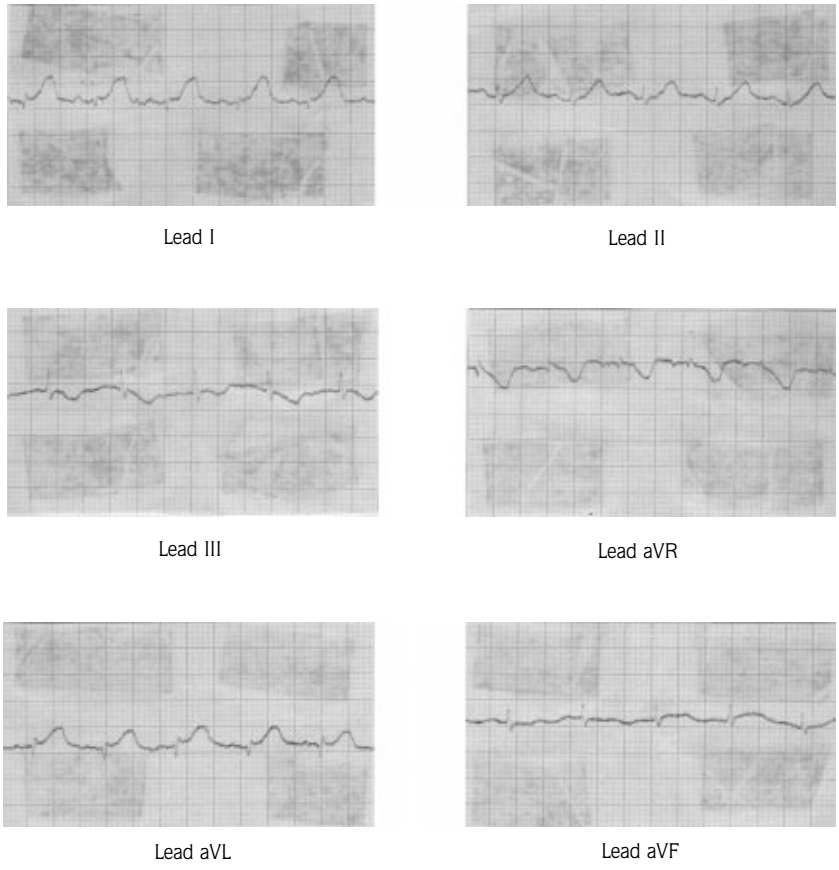

Figure 3. The leads of ECGs of the 1 mg/kg digoxin+70 mg/kg vitamin E treated group (standardization, 2 mV=10 mm; chart speed, 50 mm/sec).

only seen in leads I and aVL. The mean duration of QRS complex was 0.020 sec (0.017-0.022 sec) and its mean amplitude was 0.50 mV (0.40-0.63 mV). T wave, like P wave, was negative in lead aVR and positive in other leads. The mean duration of the T wave was 0.080 sec (0.05-1.12 sec) and its average amplitude was 0.50 mV (0.38-0.56 mV). The average value of the mean electrical axis of the rabbit heart was $+63^{o}$ (-20^{o} to $+130^{o}$). The heart rate of rabbits was 210.9 beats/min. (188-232 beats/min.).

One mg/kg digoxin treatment did not change the durations or amplitudes of any wave on the trace. However, it increased ($P<0.05$) the heart rate (from 210.9 to 300 beats/min.) by decreasing the time interval between two impulse production in sinoatrial node (sinusoidal tachicardia). One mg/kg digoxin+70 mg/kg vitamin E treatment also did not change the durations or amplitudes of any wave on the trace. In contrast to the digoxin only treatment, 1 mg/kg digoxin+70 mg/kg vitamin E treatment did not change the heart rate significantly.

Discussion

This study was carried out to evaluate if the toxic effect of digoxin could be lowered by the vitamin E injection. It was found that 1 mg/kg digoxin treatment did not change the durations or amplitudes of any wave on the trace. However, it increased the heart rate by decreasing the time interval between two impulse production in sinoatrial node (sinusoidal tachicardia). In contrast to the digoxin only treatment, 1 mg/kg digoxin+70 mg/kg vitamin E treatment did not change the heart rate significantly.

Many of the effects of digoxin on the electrical and mechanical activity of the heart result from glycoside-induced modification of both automatic neural activity and the sensitivity of the heart to the vagal and sympathetic neurotransmitters (18,19,20). It has been suggested that (21) digoxin induces an early, brief prolongation of the action potential, followed by a protracted period of shortening of the action potential (especially the plateau phase). This decrease in action potential duration could be the result of increased

potassium conductance that is caused by increased intracellular calcium. Shortening of the action potential by direct drug action might contribute to the shortening of atrial and ventricular refractoriness (21). This could be the reason why digoxin produced an increase in heart rate.

It has been also suggested that (22,23) at toxic levels, sympathetic outflow is increased by digitalis. This effect is not essential for typical cardenolide toxicity but sensitizes the myocardium and exaggerates all the toxic effects of the drug. An increase in sympathetic outflow will increase the impulse production in the sinoatrial node causing an increase in heart rate. This might be another reason for digoxin-induced tachicardia.

In this study, it was found that digoxin-induced tachicardia was lowered by vitamin E injection. This indicated that vitamin E might lower the severity of digoxin's toxic effect. Digoxin-induced tachicardia increased the oxygen consumption and metabolic activity of ventricular muscle. It has been suggested that increased metabolic activity causes cell membrane depolarization, opening of calcium channels, activation of adenosine and lytic enzymes and oxidation of membrane phospholipids (11,12). In this experiment we do not know whether digoxin increased the lytic enzymes or not but we certainly know that vitamin E decreased the digoxin-induced tachicardia by probably decreasing the potassium conductance that is caused by increased intracellular calcium.

In this study, the second-degree atrioventricular blockade could not be demonstrated with digoxin treatment. This was probably due to the short time of experiment. Only single dose of digoxin was used. This was not enough to produce a second-degree atrioventricular blockade. Administration of digoxin for longer time could produce a second-degree atrioventricular blockade.

It was concluded that injection of vitamin E along with digoxin could lower the toxic effect of digoxin. This experiment opens a door for further studies concerning this subject. More studies are needed to prove our hypothesis.

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