

## COMPARATIVE EFFECTS OF LOSARTAN AND ENALAPRIL ON SERUM DIGOXIN LEVELS IN PATIENTS WITH CONGESTIVE HEART FAILURE

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The aim of this study was to investigate the effect of AT<sub>1</sub>-receptor antagonist, losartan usage in place of angiotensin converting enzyme (ACE) inhibitor, enalapril, in patients with congestive heart failure (CHF) on serum digoxin concentrations. The study was performed in 17 patients (14 men, 3 women) with CHF of New York Heart Association (NYHA) functional class II. Their ages ranged from 42-73 (61.9±2.4) years and they all were being treated with enalapril and digoxin at the time of the study. Serum digoxin levels were measured after 15 days of enalapril treatment just before taking digoxin dose in the morning and 2<sup>nd</sup> and 6<sup>th</sup> hours after digoxin medication. Then, losartan was added to treatment instead of enalapril and after 15 days, serum digoxin levels were measured again in the same patients. Trough serum digoxin levels were 1.19±0.09 ng/mL after 15 days of enalapril treatment and 1.30±0.13 ng/mL after 15 days of losartan treatment, the digoxin levels at two and six hours after the morning dosage were 1.79±0.18 and 1.43±0.13 ng/mL after enalapril treatment, and 1.88±0.16 and 1.37±0.12 ng/mL after losartan treatment. Losartan treatment did not change the serum digoxin concentrations compared to enalapril treatment. Losartan usage in place of enalapril in patients with CHF receiving enalapril together with digoxin did not affect serum digoxin concentrations.

**Key words:** Digoxin, enalapril, losartan, pharmacokinetics.

### INTRODUCTION

Digoxin is known to be one of the most frequently administered drugs for cardiac diseases, and since most patients require it continuously for many years, there are frequent opportunities for interaction with other agents. This is potentially important, in view of the narrow range between effective and toxic digoxin dosage (1). The generally accepted therapeutic plasma concentration range is 0.5 to 2.0 ng/mL, but there are considerable interindividual variations. Hypertensive patients who also have congestive heart failure (CHF) may be treated by concomitant administration of digoxin and angiotensin-converting enzyme (ACE) inhibitors. Angiotensin-converting enzyme inhibitors are now recognized as an important therapeutic step to control blood pressure in

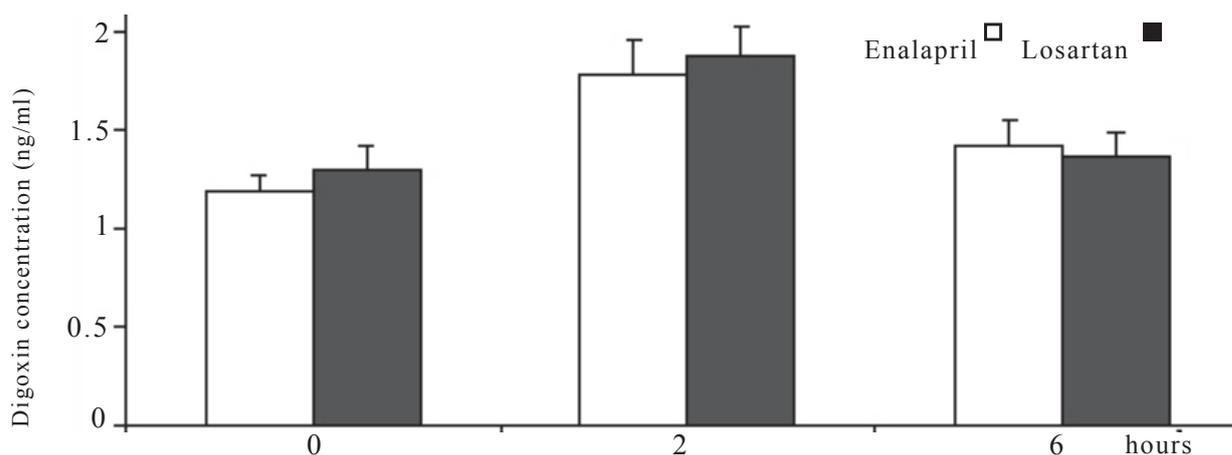
hypertensive patients and to reduce morbidity and mortality in patients with CHF (2). It has been reported that the administration of captopril increases plasma digoxin level in 28 men with CHF of NYHA class II (3).

Recently, there have been many studies about AT<sub>1</sub> receptor blocker losartan usage, instead of ACE inhibitors due to their adverse effects such as angioedema, dry cough etc. However, the effect of losartan on serum digoxin level in patients with CHF has not been studied up to now. The purpose of this study was to investigate whether usage of AT<sub>1</sub> receptor blocker (losartan) instead of ACE inhibitors (enalapril) effects the serum digoxin level in patients with CHF.

### MATERIAL AND METHODS

Seventeen patients (14 men, 3 women) aged 61.9±2.37 years (ranges 42 to 73), with CHF of New York Heart Association Class II, on chronic treatment (>3 months) with digoxin and enalapril were admitted to the study. The study protocol was approved by local ethical committee of Inonu University.

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**Figure 1. Serum digoxin levels (mean ± SEM) (ng/ml) in patients with CHF at 0., 2. and 6. hours treated with enalapril or losartan throughout the therapy regimen.**

All patients gave their written informed consent to participate in the study. Body weights of the patients ranged from 65 to 80 kg. None of the subject had a history of hepatitis within the past 3 years.

No subject had abnormal findings regarding AST, ALT, albumin, total protein, and complete blood count. Each patient received oral doses of digoxin 0.25 mg (Digoxin, Novartis) and enalapril 10 mg (Enapril, Ilsan) once daily at 8 a.m. for 15 consecutive days. Then, the same patients started to receive oral doses of losartan 50mg (Cozaar, Merck Sharp&Dohme) once daily at 8 a.m. instead of enalapril for 15 consecutive days.

The measurements of serum digoxin levels were done prior to medications, two hours and six hours after the medications because of the fact that oral administration of digoxin may reach the blood peak level after two hours from the beginning. On the other hand, the plato level of plasma digoxin can be reached at the time after 6 hours from the beginning. The elimination half life of digoxin has been suggested to be 1.5 to 2 days (4). Blood samples for digoxin assay were immediately centrifuged, serum fraction separated and then digoxin levels were determined by automated analyser by using commercial kits (Dade Behring Viva, Lieberbach, Germany).

Data were analyzed by paired Student's t test for parametric data with the SPSS 10.0 program;  $p < 0.05$  was used as level of significance. All findings are expressed as mean value ± standard error of mean (SEM).

## RESULTS

Digoxin-enalapril and digoxin-losartan co-administrations were well tolerated, and no safety problems were encountered during

either digoxin-enalapril or digoxin-losartan periods. The serum levels of digoxin for all periods prior to medication (0.), and 2<sup>nd</sup> and 6<sup>th</sup> hours after the medications are shown in Figure 1.

The serum digoxin levels were  $1.19 \pm 0.09$  ng/mL and  $1.30 \pm 0.13$  ng/mL at 0. time in enalapril and losartan periods, respectively. The digoxin levels after 2<sup>nd</sup> and 6<sup>th</sup> hours were  $1.79 \pm 0.18$  ng/mL and  $1.43 \pm 0.13$  ng/mL in enalapril period as co-administrated drug, and  $1.88 \pm 0.16$  ng/mL and  $1.37 \pm 0.12$  ng/mL in losartan period as co-administrated drug, respectively. Digoxin levels in enalapril and losartan periods were not significantly different from each other at 0., 2<sup>nd</sup> and 6<sup>th</sup> hours ( $P > 0.05$ ).

## DISCUSSION

In this prospective study, digoxin and enalapril were used for 15 consecutive days and then losartan was used in place of enalapril for another consecutive 15 days. It was showed that plasma digoxin level was not affected at the end of the treatment procedure. Due to the lack of baseline data for digoxin alone in this study, any possible addictive effect of enalapril or losartan on digoxin level with respect to only digoxin administration can not be verified. However, in a previous study by Douste-Blazy et al. (5) no interactive effect of once-daily doses of 20 mg of enalapril given for 30 days was seen in seven patients with CHF, despite a small and non-significant rise in serum creatinin levels.

Digoxin has been co-administrated with ACE inhibitors and AT<sub>1</sub> receptor antagonists because the renin-angiotensin system plays a central role in hypertension and congestive heart failure. It commonly produces side effects because the margin between the

therapeutic and toxic doses are narrow; plasma concentrations of digoxin in exceeding 2 ng/mL are considered to be an indication that the patient is at special risk although there is considerable interindividual variation. There have been many fatalities, particularly due to cardiac toxicity (4). There may be interactions between digoxin and drugs which alter its absorption, interfere with its excretion, or have additive effects on the myocardium.

Many reports have demonstrated that adverse effects may arise when certain drugs for hypertension and congestive heart failure are co-administrated with digoxin. When quinidine (6), verapamil, propafenon (7), amiodaron (8), nitrendipine (9), alprazolam (10) flecainid (11), ibuprofen (12) elevations in plasma digoxin levels and subsequent digoxin toxicity can be seen. On the other hand, diltiazem (13), urodipil (14), mexiletine, procainamid and rarely disopyramide do not effect plasma digoxin levels (11,15).

Until further data are available, the much larger body of data showing the benefits of ACE inhibitors in heart failure supports their routine use as first line agents. Conversely, although the present data do not allow the conclusion that AT<sub>1</sub> receptor blockers are equivalent to ACE inhibitors, it appears reasonable to use AT<sub>1</sub> receptor blockers as an alternative in patients intolerant to ACE inhibitors. Large trials are in progress that may provide more definitive data regarding the relative role of ACE inhibitors and AT<sub>1</sub> receptor blockers in the treatment of heart failure (16).

There are very few reported studies of other ACE inhibitors. Cleant et al.(17) showed a 20% increase in the mean serum digoxin level of a group of patients suffering from CHF after the addition of captopril to the treatment regimen. Nevertheless, a single oral dose of 20 mg of Lisinopril had no significant effect on the pharmacokinetics of a single 0.25 mg dose of digoxin in 12 healthy young men, even though a non-significant tendency for increased renal clearance of digoxin was noted (18). Daily dose of 5 mg ramipril for 14 days caused no change in mean serum digoxin level in 12 healthy volunteers (19).

In a study by Harder et al. (20), it was shown that plasma digoxin level had not been effected by co-administration of daily 10mg imidapril. Finally, 12 mg, 24 mg and 48 mg doses of spirasil were found to have no effect on the steady-state digoxin kinetics in 15 healthy volunteers (21).

Adverse effects of ACE inhibitors, especially dry cough, arise possibly from the

accumulation of bradykinin.

AT<sub>1</sub> receptor antagonists do not cause the dry cough. Therefore, AT<sub>1</sub> receptor blockers may be a good alternative for the patients which have some adverse effects of ACE inhibitors. Although, losartan and other AT<sub>1</sub> receptor blockers can be beneficial for patients with hypertension and congestive heart failure, current evidence of digoxin and losartan interaction is still scarce.

Olmesartan has been shown to have no clinically important pharmacokinetic interaction with digoxin (22). Also, De Smed et al. (23) reported that multiple 50 mg daily oral dose of losartan do not alter the pharmacokinetics of immunoreactive digoxin, following either intravenous or oral digoxin. Whereas, digoxin and losartan are absorbed from intestinal tract by the same transport system which is an ATP-dependent efflux membrane transporter involved in pharmacokinetics of many drugs in human (24). The excretion of these drugs is commonly achieved by the kidneys, furthermore, the co-administration of digoxin with losartan is well tolerated by healthy volunteers. But the effect of losartan on serum digoxin levels in patients with CHF has not been known hitherto.

In conclusion, for CHF patients losartan usage in place of enalapril together with digoxin in their therapy regimen did not affect serum digoxin levels.

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