A comparison between the effects of diltiazem and isosorbide dinitrate on digoxin pharmacodynamics and kinetics in the treatment of patients with chronic ischemic heart failure

Afaf A. Mahgoub, PhD, DTM, Azza H. El-Medany, PhD, MS, Ahmed S. Abdulatif, MD, MS.

ABSTRACT

Objective: To evaluate the effect of an arteriolar dilator (diltiazem hydrochloride) versus a venodilator (isosorbide dinitrate) on digoxin kinetics and to estimate the efficacy and tolerability of these vasodilators when combined with digoxin for 10 days therapy in patients with congestive heart failure secondary to ischemic heart disease.

Methods: A double blind randomized cross over study was carried out to investigate the effect of an arteriolar dilator (diltiazem hydrochloride 180 mg/day orally) versus a venodilator (isosorbide dinitrate 30 mg/day orally) on digoxin kinetics (0.25 mg/day orally), after 10 days therapy in patients with heart failure due to ischemic heart disease. Also, the effect of these drugs on blood pressure, heart rate, renal functions and serum electrolytes, and their efficacy and tolerability in combination with digoxin were studied. This study was carried out in the Department of Medicine, Main Alexandria University Hospital, Alexandria, Egypt, during the period May 1999 through to May 2000.

Results: Diltiazem caused a significant increase in digoxin maximum serum concentration without significant change in time to reach maximum concentration and the apparent volume of distribution. The total digoxin clearance was significantly reduced and the elimination half life was prolonged. Subsequently the area under time-concentration curve and the steady-state digoxin level were increased, but were still within therapeutic margin. On the other hand isosorbide dinitrate significantly increased digoxin maximum serum concentration but without change in the other digoxin pharmacokinetic parameters. Isosorbide dinitrate, but not diltiazem, caused significant reduction in supine and standing blood pressure, while both drugs did not significantly alter pulse rate, renal functions, serum sodium potassium and electrocardiographic pattern.

Conclusion: Patients who received diltiazem displayed a mean 51% increase in the area under the plasma concentration-time curve, 50% increase in mean steady state serum digoxin concentration, and 37% increase in peak serum digoxin concentration. While patients who received isosorbide dinitrate showed only a 15% increase in digoxin maximum serum concentration and no statistically significant change in mean steady state digoxin concentration or area under the plasma concentration-time curve. The elimination half life during the diltiazem phase was prolonged by 29% while there was no significant change with isosorbide dinitrate. Netiher diltiazem or isosorbide dinitrate significantly altered the time to reach maximum serum digoxin concentration. The addition of a vasodilator such as, diltiazem or isosorbid dinitrate to digoxin could significantly improve the symptoms and signs of heart failure compared to digoxin alone. They were well tolerated and without fear of electrolyte imbalance which potentiate digoxin toxicity.

Keywords: Arteriolar dilator, venodilator, ischemic heart failure, digoxin, pharmacodynamics, pharmacokenetics, diltiazem, isosorbide dinitrate.

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From the Department of Pharmacology, (Mahgoub, El-Medany), College of Medicine, King Saud University, Riyadh, Kingdom of Saudi Arabia and the Department of Medicine, (Abdulatif), Alexandria University, Alexandria, Egypt.

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Address correspondence and reprint request to: Dr. Afaf A. Mahgoub, Department of Pharmacology, College of Medicine, King Saud University, PO Box 22452, Riyadh 11495, Kingdom of Saudi Arabia. Tel./Fax. +966 (1) 4786768. E-mail: afaf_mahagoub@yahoo.com

Heart failure is a common end point of various cardiac diseases whose natural history results in symptomatic or asymptomatic left ventricular dysfunction.[1] However, the criteria that have used to determine the cause of heart failure have been varied between different studies. Recent reports confirmed that coronary heart disease and hypertension (either singly or together) account for the great majority of cases of heart failure within the developed world. Whereas rheumatic heart disease and nutritional cardiac disease are more common causes in the developing world.[2] Thus, heart failure is more frequent in elderly populations in developed countries and in younger age groups in underdeveloped countries. The pathophysiological definition of heart failure refers to the inability of the heart to deliver blood and therefore oxygen at a rate commensurate with the requirements of the metabolizing tissues at rest or during light exercise. This leads to characteristic systemic pathophysiological symptoms and signs.[3] A number of basic and clinical investigations have highlighted the major importance of the renin-angiotensin-aldosterone system (RAAS) in the generation and progression of heart failure. An improved understanding of the factors that promote progressive cardiac dysfunction focused attention on the ability of various neurohormones to cause progressive remodeling or structural alteration of the heart in the form of dilatation and hypertrophy.[4] Current therapeutic approaches stress the role of angiotensin - converting enzyme (ACE) inhibitors, diuretics, vasodilators, calcium channel blockers and digoxin in the management of heart failure.[5-8] Therapeutic strategies to counteract neurohormonal activation have traditionally focused on inhibition of the renin-anigotensin system through the blockade of ACE, a key catalytic protein in the generation of angiotensin II and the break down of bradykinin. Definitive evidence for the use of ACE inhibitors to limit the morbidity and mortality of heart failure patients has been established through numerous clinical trials and investigations.[9,10] Digoxin a drug that is inexpensive and can be given once daily, represents the only orally effective drug with positive inotropic effects, approved for the management of heart failure. The efficacy of digoxin has been attributed to its relatively weak positive inotropic action that comes from inhibition of sodium-potassium adenosine triphosphatase (ATP ase), that results in an increase in cardiac myocyte intracellular calcium.[8] In addition, digitalis has important, neurohormonal modulating effects in patients with chronic heart failure, including a sympatho-inhibitory effect that can not be ascribed to its inotropic action.[11] Also, digoxin ameliorates autonomic dysfunction, which indicates increased parasympathetic and baroreceptor sensitivity during therapy.[12]

There are attractive features of combining diogxin with β–blocker therapy in the treatment of heart failure. The majority of heart failure patients have coronary artery disease and may be at risk for transient episodes of myocardial ischemia that could cause catecholamine release and sudden cardiac death. Combining digoxin with a β–blocker may preserve the beneficial effects of digoxin on the symptoms of heart failure while minimizing the potential detrimental effects of this therapy on catecholamine release in the setting of ischemia.[5,13] The European guidelines on treatment of heart failure approved that diuretics are indicated in virtually all forms of heart failure; the exception being milder forms in the absence of fluid retention. Potassium-sparing diuretic could be potentially safer.[8] Diltiazem is a calcium channel-blocking agent with electrophysiologic and antiarrhythmic properties similar to those of verapamil; it lengthens the functional and effective refractory period of the atrioventricular node, prolonging conduction time across the calcium-dependent structure.[14,15] The wide use of calcium channel-blocking agents in the treatment of a variety of cardiac diseases have resulted in elevated digoxin serum concentrations which may lead to significant digoxin adverse effects. Verapamil induces a marked increase in serum digoxin concentration, which is dose dependent.[16] The effect of verapamil on the serum digoxin level has largely been attributed to a decrease in renal clearance due to alteration of tubular secretion of digoxin.[16] On the other hand diltiazem was found to have no significant effect on renal digoxin clearance.[17] This data may, therefore, suggest an advantage of diltiazem over verapamil when a calcium channel blocker is indicated in patients who are already treated with digoxin. Furthermore, several dihydropyridine calcium antagonists have been proved to be beneficial in improving exercise tolerance and quality of life in ischemic heart failure patients.[18] However potential interactions with digoxin have been frequently reported but still are confusing and inconsistent.

Vasodilators comprise a heterogeneous group of drugs with the only common property being dilatation of the vessels of the systemic vascular system. All vasodilators have the universal property of reducing cardiac afterload or the preload, or both and some, such as the nitrates, have dose-dependent activity; at low doses nitrates dilate the systemic venous capacitance system and in high doses also dilate the arterial resistant vessels. As a heterogeneous group, vasodilators improve the hemodynamic profiles of the patients with heart failure but their individual effects on the neuroendocrine and metabolic profiles are less well documented.[19,20] The vasodilator drug combination of isosorbide dinitrate (venodilator) and hydralazine

(arterodilator) was found to reduce mortality in patients with mild to modrate heart failure that were treated with digoxin and diuretics.[21] The aim of the present study was to compare the effects of 2 different vasodilators namely, diltiazem and isosorbide dinitrate, on digoxin pharmacokinetics and the efficacy and tolerability of such vasodilators when combined with digoxin, and diuretic in patients with chronic heart failure secondary to ischemic heart disease.

Methods. The present study included 8 patients admitted to the Department of Internal Medicine, Main Alexandria University Hospital, Alexandria, Egypt, during the period May 1999 through to May 2000, with chronic heart failure secondary to ischemic disease (moderate to severe), according to New York Heart Association Classification (NYHA). There were 4 males and 4 females, their ages ranged between 48 years - 61 years with a mean of 54.75 ± 3.1 years. The Hospital Ethics Committee obtained informed written consent from each patient after approval of the study protocol. All patients were put on digoxin (Lanoxin, hydrochlorothiazide and amiloride hydrochloride (Hcl) (moduretic) and dipyridamole (persantin) throughout the trial period. Exclusion criteria included patients with clinically significant renal, hepatic or thyroid dysfunction.

Drugs used. Digoxin (Lanoxin, 0.25mg/tablet, Wellcome) the dose was given as one tablet once daily. Hydrochlorothiazide 50mg and amiloride Hcl 5mg/tablet (Moduretic, Kahira Pharm and Chem Ind. Co. under licence of Merck), was given as one tablet once daily. Dipyridamole 75mg/tablet (Persantin, Chemical Industries Development), given twice daily. Diltiazem Hcl, 60mg/tablet (Tildiam, Rhone Poulene-Alexandria), administered as one tablet 3 times daily. Isosorbide dinitrate, 10mg/tablet (Isordil, Ayrest), administered as one tablet 3 times daily.

Study design. 1. Pretrial phase. All patients were subjected to the following: (a) Thorough history, especially for manifestations of volume overload, ischemic heart disease, hypertension, diabetes mellitus, kidney or liver disease and drug history. (b) Complete clinical examination especially for body weight, pulse rate, standing and supine blood pressure and signs of heart failure. (c) Investigations including complete blood picture, liver enzymes; serum aspartate aminotransferase and serum alanine aminotransferase, lactate dehyrogenase, blood urea, serum creatinine, creatinine clearance, fasting and postprandial blood sugar, serum soduim and potassium.[22] Also, a 12 lead, electocardiogram (ECG) was carried out.

2. Trial phase. Comprises 33 days as follows 1. Base line period consists of 10 days during which the patient received digoxin, moduretic and dipyridamole. 2. Randomized double blind crossover trial period during which either diltiazem or isosorbide dinitrate was added to the aforementioned drugs for an extra 10 days (phase one and phase 2). Three days washout period was allowed between each treatment to insure complete elimination of the drug under trial. Blood samples were taken in the different studied phases at zero, one, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8 and 12 hours. They were centrifuged at 3000 rpm for 10 minutes to obtain the serum and were stored at -20^{o}C until analyzed. Serum digoxin was measured by using enzymatic digoxin antibody immunoassay kit.[23] During each period, patients were subjected to the same procedures including clinical examination and investigations as in the pretrial phase.

Analysis of data. The plasma concentration time profile curve of digoxin baseline and after the addition of diltiazem or isosorbide dinitrate was determined for each patient. The observed time to peak (T_{max}) and the observed peak serum digoxin concentration (C_{max}) were determined for individual subjects and group means were obtained for each treatment period. The area under the plasma concentration-time curve (AUC) for the dosing interval was calculated by means of the trapezoidal rule. Terminal half-lives ($t_{1/2}$) were calculated from the log-linear part of the slope.

Statistical analysis. Data is presented as mean ± standard deviation (SD). Statistical analysis of results are carried out by the Student's t-test or by analysis of variance (ANOVA) test as appropriate (Graph pad software Inc, San Diego, California, United States of America) significance is accepted when $P< 0.05$.

Results. ***Pharmacodynamic study.*** The subjective symptoms and signs, dyspnea, orthopnea, paroxysmal nocturnal dyspnea, congested neck veins, fine basal crepitations and edema of the lower limbs were significantly improved by the concomitant treatment with diltiazem or isosorbide dinitrate. Hemoglobin, serum transaminases, lactate dehydrogenases, fasting and postprandial blood sugar were within the normal range. Electrocardiogram showed ischemic changes in 6 patients, an old infarct in 2, atrial fibrillation in 2 and ventricular premature beats in 3 patients. No significant changes were observed in the different trial phases than that of the baseline phase in the ECG. **Table 1** shows the pharmacodynamic parameters of digoxin. Diltiazem has no significant effects on the hemodynamic parameters studied. Isosorbide dinitrate significantly reduced systolic blood pressure in both supine and standing positions without affecting the heart rate. Both drugs significantly reduced ankle circumference and body weight. Only minor adverse effects occurred during the different phases of the study as, headache, dizziness, gastrointestinal disturbances, warm or cold extremities. Symptoms were improved with continuation of treatment or with minor decrease in the dose

Table 1 - Pharmacodynamic parameters of digoxin given orally (0.25 mg/day) to patients with ischemic heart failure under baseline, diltiazem hydrochloride (180 mg/day) and isosorbide dinitrate (30 mg/day) phases (Mean ± standard deviation).

Parameter	Baseline	Diltiazem Phase	Isosorbide Dinitrate Phase
Body weight (kg)	66.50 ± 20.60	62.25 ± 19.50*	62.44 ± 18.74*
Ankle circumference (cm)	25.65 ± 4.27	23.94 ± 4.40*	24.40 ± 3.80*
Radial pulse (Beat/min)	94.25 ± 11.09	86.13 ± 11.98	96.88 ± 12.85
Apical pulse (Beat/min)	99.88 ± 12.76	90.00 ± 11.74	101.50 ± 8.60
Pulse deficit (Beat/min)	5.63 ± 5.37	3.88 ± 3.56	4.64 ± 5.80
Systolic blood pressure (mmHg)			
Supine	127 ± 23.70	122.00 ± 13.28	112.63 ± 11.25*
Standing	120.25 ± 24.27	115.75 ± 14.05+	97.38 ± 21.01*+
Diastolic blood pressure (mmHg)			
Supine	86.75 ± 27.97	78.00 ± 6.68	70.00 ± 7.78
Standing	78.25 ± 28.40	69.38 ± 6.52	59.75 ± 3.62

Hcl - hydrochloride, * - significant difference between baseline and other phases (P<0.05)
+ - significant difference between diltiazem and isosorbide dinitrate (P<0.05)

Pharmacokinetic study. Mean ± standard deviation (SD) serum digoxin concentration-time profiles of ischemic heart failure patients at baseline, diltiazem and isosorbide dinitrate phases are presented in **Figure 1.** Derived group mean digoxin pharmacokinetic parameters are listed in **Table 2.** Patients who received diltiazem displayed a mean 51% increase in AUC from 18.24 ± 1.34 to 26.18 ± 3.62 ng.h/ml (P<0.05), and 50% increase in mean steady-state (S-S) serum digoxin concentration from 1.34 ± 0.14 to 2.01 ± 0.29 ng.h/ml (P<0.05), and 37% increase in peak serum digoxin concentration C_{max} from 2.04 ± 0.39 to 2.81 ± 0.49 ng.h/ml (P<0.05). By contrast patients during isosorbide dinitrate showed only a 15% increase in digoxin C_{max} from 2.04 ± 0.39 to 2.35 ± 0.34 ng.h/ml (P<0.05) and no

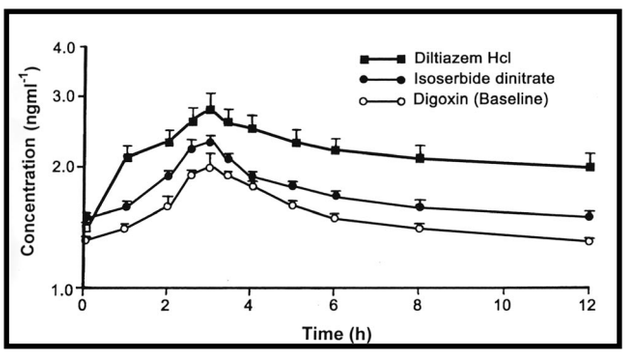

Figure 1 - Plasma concentration/time profile for digoxin (ng/ml/h) in ischemic heart failure patients at base-line, diltiazem and isosorbide dinitrate phases (Mean ± standard deviation). Hcl - hydrochloride.

Table 2 - Pharmacokinetic parameters of digoxin in ischemic heart failure patients at base line, diltiazem and isosorbid dinitrate phases (Mean ± standard deviation).

Parameter	Baseline	Diltiazem Phase	Isosorbide Dinitrate Phase
Maximum serum concentration (ng/ml)	2.04 ± 0.39	2.81 ± 0.49*+	2.35 ± 0.34*+
Maximum concentration (h)	2.94 ± 0.18	2.88 ± 0.23	2.88 ± 0.23
Area undertime concentration curve $_{0-12}$ (ng/h/ml)	18.24 ± 1.34	26.18 ± 3.62*+	20.44 ± 2.23+
$T_{1/2}$ (h)	18.05 ± 6.92	23.30 ± 7.80*+	20.22 ± 4.89*+
Average steady state			
Steady state digoxin level (ng/ml)	1.34 ± 0.14	2.01 ± 0.29*+	1.50 ± 0.15+
Total digoxin clearance (L/h)	2.59 ± 0.72	1.87 ± 0.66*+	2.44 ± 0.87+
Volume of distribution at a steady state (L/kg)	9.95 ± 3.24	9.22 ± 3.51	10.16 ± 4.31

* - significant difference between baseline and other phases (P<0.05), + - significant difference between diltiazem and isosorbide dinitrate (P<0.05)

statistically significant change in mean steady state digoxin concentration S-S or AUC. The elimination half-life ($t_{1/2}$) during diltiazem phase was prolonged by 29% ($P<0.05$) from 18.05 ± 6.92 to 23.30 ± 7.80 while there was no significant change with isosorbide dinitrate. Total body clearance (Cl/F) was significantly reduced ($P<0.05$) by diltiazem. Neither diltiazem or isosorbide dinitrate significantly altered time to reach maximum serum digoxin concentration (T_{max}).

Discussion. Drug combinations is a difficult therapeutic policy that needs careful handling and thorough research in order to avoid possible harmful interactions and to get the best from its useful interaction. In the present study, orally administered diltiazem or isosorbide dinitrate in combination with oral digoxin for 10 days therapy, in ischemic heart failure patients, did not change the 2 compartment open pharmacokinetic profile of digoxin, however, the C_{max} was significantly increased without significant change in T_{max}. Cardiac failure is expected to alter the extent of digoxin absorption most probably secondary to hypoperfusion and gastrointestinal edema with subsequent reduction in epithelial mucosal permeability.[24] Therefore, the improvement in cardiac failure status after adding diltiazem or isosorbide dinitrate to digoxin might have lead to increase in the extent of digoxin absorption and an increase in its C_{max}. However, the increase in C_{max} should not be considered of clinical significance since this kinetic parameter lies in the first compartment of the digoxin log-time concentration curve and it is the 2nd rather than the first compartment from which digoxin exerts its pharmacological actions. Neither diltiazem nor isosorbide dinitrate could significantly affect digoxin distribution. However, diltiazem but not isosorbide dinitrate significantly reduced the total digoxin body clearance and since volume of distribution (vd) was not altered the elimination half-life ($t_{1/2}$) was prolonged. Subsequently both AUC and (S-S) levels were increased but the increase in the latter was within the therapeutic margin. The increase in digoxin plasma concentration after the administration of the calcium channel antagonist could be due to their influence on the enteral absorption of digoxin.[25] The role of calcium channel blockers in the treatment of heart failure is unclear. The potential benefits of these agents are derived not only from their vasodilator properties, but also from anti-ischemic effect, beneficial effects on endothelial function and the development of atherosclerosis and favorable effects on calcium cycling at a molecular level.[26] Against these potential benefits are the negative inotropic effects and for neuroedocrine activation. Diltiazem exerts beneficial effects in the pharmacological management of supraventricular tachyarrhythmia also its therapy affords adequate control of heart rate and appears superior to digoxin.[27] When compared to verapamil, diltiazem avoids some harmful side effects, since it exerts only a weak negative inotropic action[28,29] and its administration appears safe when left ventricular function is reduced. When Halawa and Mazurek[30] studied the effect of single dose diltiazem or nifedipine on pharmacokinetic parameters of digoxin, they found no significant changes in digoxin $t_{1/2}$, Vd or renal clearance. On the other hand, other investigators reported an increase in (S-S) plasma digoxin concentration and AUC while Vd was not relevantly altered.[31-33] The possible mechanisms by which diltiazem can reduce digoxin elimination have been suggested through the reduction in digoxin extrarenal clearance. Also decreased tubular secretion, glomerular filtration rate or changes or both in its Vd.[34] In the present study, as serum creatinine and digoxin Vd did not change, they may therefore be excluded. Exclusion or confirmation of the other mechanisms are beyond the scope of our findings.

This work has shown that diltiazem caused no significant change in radial or apical pulse, systolic and diastolic blood pressure, in both standing and supine positions while isosorbide dinitrate reduced the systolic blood pressure in the supine and standing positions without affecting heart rate. Meanwhile both drugs caused a significant improvement in the subjective symptoms and signs of heart failure as compared with digoxin alone.

Vasodilator drugs have been widely used to supplement traditional therapy with digitalis and diuretic agents, in the treatment of chronic heart failure.[7,19,20] The combination of the vasodilators hydralazine and isosorbide dinitrate was reported to reduce mortality in patients with mild to moderate heart failure when added to digoxin and diuretic therapy.[35] Also it reduced the severity of functional mitral regurgitation in dilated cardiomyopathy by lowering ventricular afterload and improving forward flow.[36] Furthermore in heart failure patients stabilized on conventional doses of ACE inhibitor (Lisinopril), the addition of isosorbide dinitrate improved ventricular systolic function and increased ventricular ejection fraction with a decrease in left ventricular size without any change in systemic blood pressure.[35]

In previous reports, high-dose diltiazem therapy (240mg/day) resulted in only negligible improvement in efficacy preceding a large increase of side effects and withdrawal from therapy.[37] This evidence suggests that the 180mg daily dose used in this study can be considered safe in ischemic heart failure patients but confirmation needs extension of the work to include a larger number of patients, as there were no changes in serum sodium and potassium or ECG pattern after the administration of either diltiazem or

isosorbide dinitrate. Therefore the addition of these vasodilators to digoxin suggests beneficial effects on the hemodynamics of patients who participated in this study also, the addition of a potassium sparing diuretic has prevented the electrolyte imbalance which predisposes to digoxin toxicity.[38]

In conclusion, diltiazem is a safe and well tolerated drug that can improve heart failure when added to digoxin therapy. However, diltiazem reduces digoxin clearance and increases its (S-S) level, although still within therapeutic margin, yet one should experience caution and close monitoring of digoxin levels when diltiazem is added to digoxin. Digoxin-isosorbide dinitrate is a good combination in ischemic heart failure. Digoxin kinetics are not affected by isosorbide dinitrate, although the latter should be carefully titrated in order to avoid excessive reduction in systolic blood pressure. Comparing the efficacy of the 2 vasodilators in ischemic heart failure one could say that diltiazem is a better addition to digoxin in that setting as it may afford a protective action against the arrhythemogenic side effect of digoxin.

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