CHAPTER II

REVIEW OF LITERATURE

Review of Digoxin

A large number of plant extracts containing cardiac glycosides have been used by natives in various parts of the world as arrow and ordeal poisons, Digitalis, or foxglove, was mentioned in 1250 in the writings of Welsh physicians. It was described botanically 300 years later by Fuchsius, who gave it the name Digitalis purpurea. In 1785, William Withering published his famous book, entitled "An Account of the Foxglove and Some of Its Medical Uses : With Practical Remarks on Dropsy and Other Diseases." Withering was aware that digitalis was effective only in certain forms of dropsy (edema) but apparently did not associate this with the cardiac actions of the drug. However, he recognized that the heart was affected. Apparently John Ferriar in 1799 was the first to ascribe to digitalis a primary action on the heart and to relegate the diuretic effect to a position of secondary importance.

Even during the nineteenth century digitalis was used indiscriminately for many disorders, often in toxic dose. During the early twentieth century, the drug gradually came to be looked upon as specific for the treatment of atrial fibrillation. Only subsequently was it established that digitalis is also valuable for the therapy of congestive heart failure.

Digoxin is the most frequently employed cardiac glycoside. Digoxin structure (in Figure 1) represents the combination of an aglycone, or genin, with three molecules of sugar. Pharmacological activity resides in the aglycone, but the particular sugars attached to the aglycone modify water and lipid solubility, potency, and the pharmacokinetic properties.

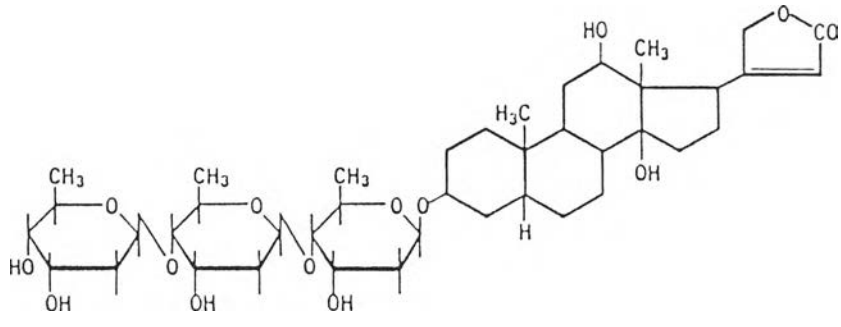


Figure 1. A diagram of molecular structure of digoxin.

A. Pharmacological properties

The Principal actions of digoxin are an increase in the force of myocardial contraction and a reduction in the conductivity of the heart, particularly in conduction through the atrioventricular (AV) node. Digoxin also has a direct action on vascular smooth muscle and indirect effects mediated primarily by the autonomic nervous system, and particularly by an increase in vagal activity. There are also reflex alterations in autonomic activity due to the effects on the circulation. Overall, these actions result in positive inotropic effects, negative chronotropic effects, and decreased AV nodal activity.

In cardiac failure, the increased force of myocardial contraction results in increased cardiac output, decreased end-systolic volume, decreased heart size, and decreased end-diastolic pressure and volume. The decrease in systemic pressure and the reduction in sympathetic tone increase the blood flow through the kidneys causing diuresis with a reduction in edema and blood volume, and the decrease in pulmonary venous pressure relieves dyspnea and orthopnea. In atrial arrhythmias, direct and indirect actions cause a decrease in the conduction velocity through the AV node and an increase in the effective refractory period thus reducing ventricular rate. In addition there is a decrease in the refractory period of the cardiac muscle and depression of the sinus node partly in response to the increase in vagal activity. (Reynolds, 1989)

The most widely accepted primary cellular mechanism of action is inhibition of a Na-K ATPase transmembrane pump. Although the precise cell fraction location of this enzyme is uncertain considerable, evidence exists to supports its involvement in digoxin action. Inhibition of this pump promotes intracellular accumulation of sodium ions, which subsequently displace calcium ions from binding proteins. Increased intracellular free calcium ions are associated with positive inotropic effect, increasing the force of myocardial contraction. Altered sodium-potassium transmembrane gradients significantly affect myocardial electrical activity and impulse conduction.(Rosenbloom and Craven, 1983)

B. Clinical pharmacokinetics

The absorption of digoxin is essentially a passive nonsaturable diffusion process, although a saturable carrier-mediated component also plays an important role. An oral dose of digoxin is absorbed, mainly in the proximal part of the small intestine. Gastric absorption is of minor importance. First pass hepatic metabolism does not seem to significantly influence absorption of digoxin. Absorption, which is independent of gastric acidity and the presence of bile, occurs twice as fast in the proximal as it does in the distal small intestine. (Mooradian, 1988) The extent to which digoxin is absorbed depends largely on the formulation used. The average bioavailability of digoxin is 67% from tablets of fast dissolution rate (> 70% in solution in 1 hour), 80% from elixir, and up to 100% from encapsulated elixir.(Aronson,1980)

Bioavailability was not altered when digoxin was administered either with or after a usual breakfast, however it may be reduced by as much as 17% when digoxin is given with a breakfast of high fiber content. (Keyes, 1980) Digoxin-inactivating bacteria in human gut flora may have a significant effect on the bioavailability of digoxin, thus explaining the rare cases of apparent resistance to this drug. (Mooradian, 1988) The first order rate constant for absorption is several times greater than the elimination rate constant and, therefore, variation in the rate of absorption has little clinical relevance.

The plasma protein binding of digoxin occurs, principally to albumin, ranges from 20 to 30%. The drug molecules which are not bound to plasma proteins are freely distributed into the body fluids and the possibility of reducing digoxin protein binding by as much as 20% would lead to less than 2% increase in the free concentration in the tissues. (Iisalo, 1977)

After an intravenous bolus dose of digoxin, plasma concentration decay is biphasic. The first phase which lasts 4 to 8 hours, represents the time required for drug distribution to the tissues and the subsequent phase comprises the elimination of the drug from the body. Kinetic analysis of plasma concentration data obtained with frequent blood sampling suggested 3 drug compartments :1 large peripheral compartment, and 2 small compartments representing plasma water or extracellular fluid spaces and highly vascularized tissues. The slow drug distribution phase accounts for the delay between the inotropic effects of the drug and the plasma concentration profile. (Mooradian, 1988)

At steady state digoxin are extensively bound to tissues, particularly myocardium, kidney, skeletal muscles and red blood cells.The ratio of myocardial to plasma concentrations of digoxin is 50:1. Morphological changes in the myocardium due to an underlying cardiac disease may also alter the extent of digoxin tissue binding and thus cause variability in serum to myocardium concentration ratios. The apparent volume of distribution of digoxin is usually 5 to 7.3 L/kg (Koup, Greenblatt et al., 1975). The steady-state volume of distribution(Vss) of digoxin is large and extremely variable. Differences in renal function account for some of the intersubject variation. The Vss averages 510 liters in subjects with normal renal function, whereas in patients with renal impairment, the average is only 330 liters. (Reuning, Sams, and Notari,1973) Although Vss appears to covary with renal function, marked variation still exists in individuals with similar creatinine clearances. Koup, Jusko et al.(1975) observed a range of 386 liters to 1,026 liters in subjects with creatinine clearances of 101±13 ml/min/1.73 $m^2$and a range of 189 liters to 481 liters in patients with creatinine clearance less than 8 ml/min/1.73 m^2.

A variety of factors alter distribution volume by interfering with drug binding to tissues. For example, electrolyte abnormalities such as hyperkalemia or hyponatremia reduce digoxin binding to the myocardium. Some drugs, notably quinidine, can displace digoxin from tissue binding sites and reduce the apparent volume of distribution of digoxin. On the other hand, hyperthyroidism is associated with a modest increase in digoxin distribution space. The majority of digoxin's body store is bound to skeletal muscle since its mass may reach 40% of total body weight. Digoxin distributes poorly into adipose tissue and thus, lean body weight provides a better estimate of volume of distribution than does total body weight.

The metabolism of digoxin follows two pathways. (Figure 2) One pathway is the stepwise cleavage of the three sugars to form digoxigenin didigitoxiside, digoxigenin monodigitoxiside and digoxigenin. Following removal of the sugar portions, digoxigenin is converted to 3-ketodigoxigenin in the liver by NAD-dependent 3β-hydroxysteroid dehydrogenases. The 3-keto intermediate is further reduced to the 3-epimer of digoxigenin by 3α -hydroxysteroid dehydrogenases. Both digoxigenin and epidigoxigenin are conjugated into sulfate and glucoronide products. Various percentages of these metabolites are found in bile and stool as well as urine. The other pathway involves reduction of the lactone ring to form dihydrodigoxin with subsequent cleavage of the sugars to produce the monodigitoxiside and didigitoxiside of

dihydrodigoxigenin and dihydrodigoxigenin itself. Formation of these reduction metabolites varies considerably between individuals.(Keyes, 1980)

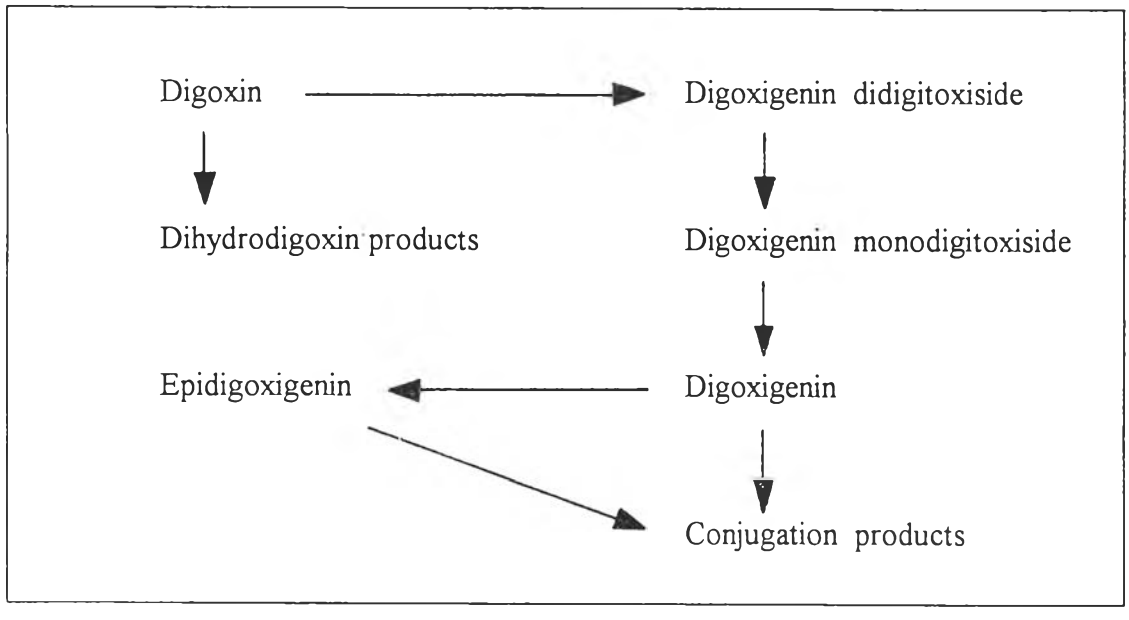


Figure 2. Digoxin Metabolic Pathways

The stepwise cleavage of the sugar moieties progressively decreases the cardioactivity of the digoxin-related compounds. Epimerization and conjugation renders the metabolites almost completely cardioinactive. All dihydrometabolites are substantially less cardioactive than digoxin. For any given body load of digoxin, the average percentage of the various metabolites excreted in the urine by patients with normal hepatic and renal function is 12 to 13% dihydrometabolites (cardioinactive),1 to 10% conversion products (cardioinactive), and 9 to 14% digoxigenin and its sugars (cardioactive). Similar patients excreted in the stool an average of 40% digoxigenin and its mono- and digitoxisides, 4 to 20% conversion products and an undetermined percentage of the dihydrometabolites.

Digoxin is excreted by predominantly renal route. Approximately 60 to 80% of bioavailable digoxin is excreted unchanged, by passive glomerular filtration and active tubular secretion, although there is also some reabsorption of digoxin from the tubular fluid. The remaining one-third (approximately) of the drug is eliminated by an extrarenal route.

Rate of elimination is proportional to the serum concentration. Total body clearance varies from individual to individual depending on both the degree of renal function and extent of metabolism. In eight subjects with normal renal and hepatic function, total clearance averaged 188 ± 44 ml/min/1.73m^2 with renal clearance comprising 75% of the total (Koup, Greenblatt et al., 1975) ; whereas, in four patients with severe renal impairment and apparently normal hepatic function, total clearance averaged only 49 ml/min/1.73m^2 with nonrenal clearance (primarily metabolism) comprising 75% of the total. (Koup, Jusko et al., 1975)

The biologic half-life ($t_{1/2}$) of digoxin in healthy individual with normal renal and hepatic function is about 1.6 days. Reduction in renal clearance results in prolongation of $t_{1/2}$; however, the relationship between $t_{1/2}$ and renal function is confounded by concurrent reduction in volume of distribution and variability in nonrenal clearance. (Keyes, 1980) Figure 3 represents the steady-state distribution of digoxin.

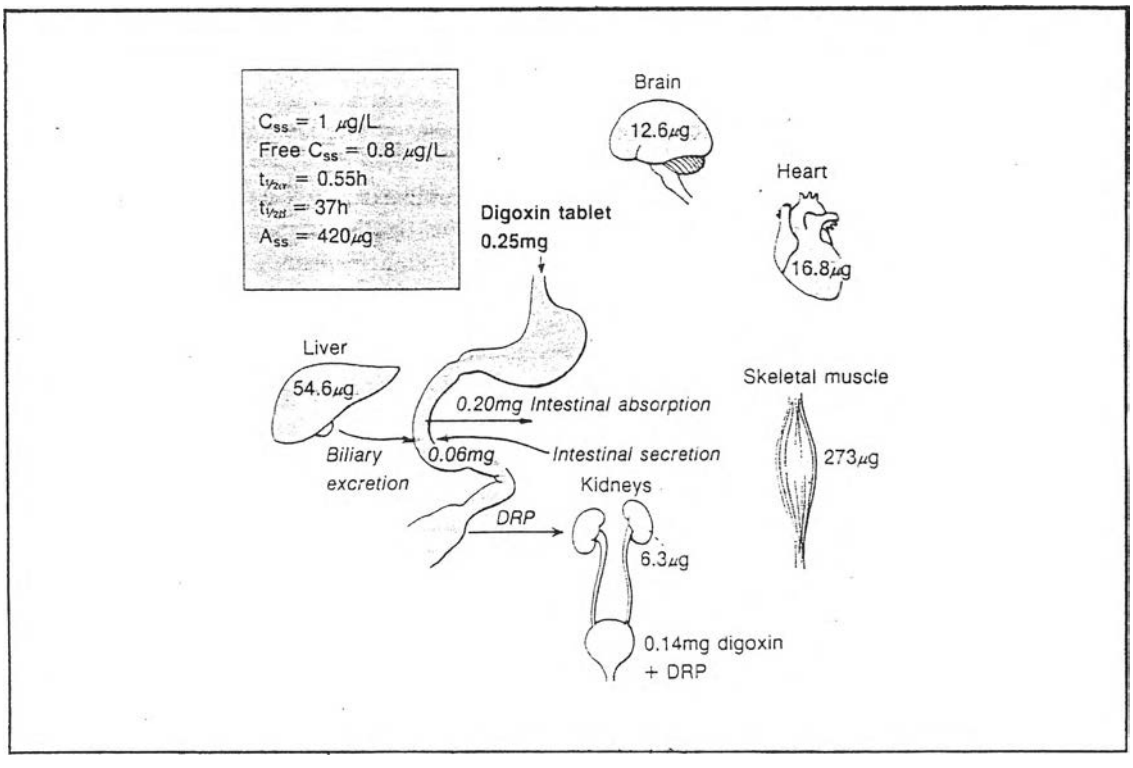


Figure 3. Schematic representation of the steady-state distribution and the fate of a 0.25 mg digoxin tablet in an adult with a bodyweight of 70 kg. Calculations are based on a volume of distributions of 6 L/kg and digoxin absorption of 80%. The amount of drug in the body at steady-state (Ass) and in different tissues is shown.

Abbreviations : DRP = digoxin reduction products ;
Css = steady-state serum concentration;
t 1/2, α = distribution half-life;
t 1/2, β = elimination half-life.

Table 1 summarizes the effects of different disease states on the pharmacokinetics of digoxin. Digoxin passes across the placenta in early pregnancy and at term after maintenance therapy can be found in neonatal serum concentrations similar to those found in maternal serum. In general digoxin clearance is increases with the pregnancy-related increase in creatinine clearance. The distribution volume of digoxin is slightly large in children than in adults. Steady-state serum concentrations are substantially higher, but do not lead to overt cardiac toxicity. The mechanism for this relative digoxin insensitivity in infants is not clear. In contrast, the incidence of digoxin toxicity in hospitalized geriatric patients has been reported to be as high as 20% (Williamson and Chopin, 1980), a reflection of age-related alterations in the pharmacokinetics of digoxin. In aged persons, for instance, great interindividual differences of the distribution volume probably influence dose requirements of digoxin as well as the decreased clearance with deterioration of renal function.

The interaction of cardiac glycosides with other drugs has been extensively discussed in numerous papers. Interactions can occur at any phase of absorption, distribution, metabolism and elimination. Table 2 summarizes the list of commonly used drugs that alter serum digoxin concentration by interfering with the usual pharmacokinetics.

Table 1. Effect of disease states on pharmacokinetics of digoxin.

Disease state	Altered pharmacokinetic variable	Clinical implication
Renal disease	Decreased elimination and Vd	Loading& maintenance dose should be reduced
Hepatic disease	No significant changes	-
Congestive heart failure	Decreased elimination, Increased Vd when patient is edematous	Frequent monitoring of serum concentrations
Thyroid disease	Increased renal elimination and Vd in hyperthyroidism	Increased dose is required in hyperthyrodism & reduced dose in hypothyroidism
Gastrointestinal disease	Decreased absorption in those with malabsorption syndromes	Increased dose may be required
Diabetes insipidus	No significant changes	-
Obesity	No significant changes	-

Table 2. Agents affecting the pharmacokinetics of digoxin.

Alteration	Agents
Decreased absorption	Activated charcoal, antacids, cholestyramine,colestipol, cytotoxicagents [cyclophosphamide, doxorubicin (adriamycin)], dietary fibre, kaolin-pectin, metoclopramide, neomycin, sulphasalazine
Increased absorption	Antibiotics (by inhibiting gut flora), anticholinergics (propantheline)
Enhanced renal excretion	Hydralazine, levodopa, nitroprusside
Inhibition of renal tubular secretion	Quinidine, spironolactone, triamterene, trimethoprim, verapamil
Inhibition of extrarenal clearance	Diltiazem, quinidine, verapamil
Decreased volume of distribution	Quinidine
Increased serum digoxin concentrations (mechanism unknown)	Amiodarone, aspirin, diltiazem, flecainide, ibuprofen, indomethacin,nifedipine, nicardipine, nisoldipine, nitrendipine.

C. Dose of digoxin

Various nomograms have been designed for calculation of the dose, taking into account lean body mass and renal function, but none appears to be more effective than the experienced physician's intuitive estimation of the correct digoxin dosage. A loading dose may be required for urgent indications because a certain amount of digoxin is required to saturate the skeletal muscle receptors through out the body and for tissue penetration until equilibrium is reached. The usual IV loading dose of digoxin is 0.75 to 1 mg. which gives transient peak digoxin levels as high as 95 ng/ml without toxic effects. An oral loading dose of 1 mg produces peak blood levels of over 1 ng/ml on about 1 to 5 hours and a maximum inotropic effect at 4 to 6 hours.

Digitalization is now commonly started with multple doses over a longer period (0.5 mg 2 x daily for 2 days or 0.5 mg 3 x daily for 1 day followed by 0.25 mg daily) to allow for variable gastrointestinal absorption, variable cardiac responses, and possible drug interactions. When no loading dose is given, steady-state plasma and tissue concentrations are achieved in 5 to 7 days. Rapid digitalization can be achieved with a combination of IV digoxin (0.5 mg IV, followed by oral digoxin 0.25 mg, one or two doses) to a total of 0.75-1.0 mg. The usual maintenance dose of digoxin remains 0.25 mg daily, even with a wide range of renal and hepatic function. The optimal dose required varies from 0.1 to 0.75 mg daily, and renal function is the most important determinant.

D. Adverse drug reactions

The typical patient with adverse drug reactions is usually elderly with advanced heart disease and atrial fibrillation, often associated with pulmonary disease and abnormal renal function. Digitalis toxicity should, however, be considered in any patient receiving digitalis who presents with a new GI, ocular, or CNS complaint, or in whom a new arrhythmia or AV conduction disturbance develops. Symptoms do not necessarily precede serious cardiac arrhythmias.

While there is considerable variation between patient, plasma digoxin concentrations of approximately 0.8 to 2 mcg/L (ng/ml) are considered to be within the therapeutic range.

Table 3. Adverse drug Reactions of Digoxin.

Gastrointestinal effects :
Anorexia
Nausea
Diarrhea
Abdominal pain/Cramps
Central Nervous System effects :
Fatigue
Weakness
Visual Symptoms
Dizziness
Headache
Insomnia/Sleep Disturbance
Psychic Disorders
Cardiac effects :
Premature ventricular contractions
AV junctional rhythms
Atrioventricular block
Supraventricular tachycardia
Ventricular tachycardia
Atrial fibrillation

Review of ACE Inhibitors in the Treatment of Heart Failure.

Heart failure is a complex pathophysiological condition resulting from impaired cardiac function that may be due either to a defect in myocardial contractility or to an excessive hemodynamic burden. Clinical features develop as a consequence of reduce cardiac output, increased filling pressures, disturbances in the balance of electrolytes and water, activation of neurohormonal systems, metabolic abnormalities within many tissues and organs, and side effects of medications. Of the neurohormonal systems, the renin-angiotensin system (RAS) plays an important pathophysiological role.

Until recently, treatment for heart failure focused on augmentation of myocardial contractility and correction of fluid and electrolyte imbalance. (Fig.4) Digoxin, however, is the only orally effective inotrope that is so far widely available. Diuretics reduce congestive symptoms and remain a mainstay of therapy, but they do not correct the functional cardiac abnormality. Indeed, by lowering ventricular filling pressure, they can reduce cardiac output; they increase activity of the RAS and the sympathetic system; and they reduce plasma and tissue potassium and magnesium levels and perhaps thereby predispose to ventricular arrhythmias. (Crozier, Ikram, and Nicholls, 1993)

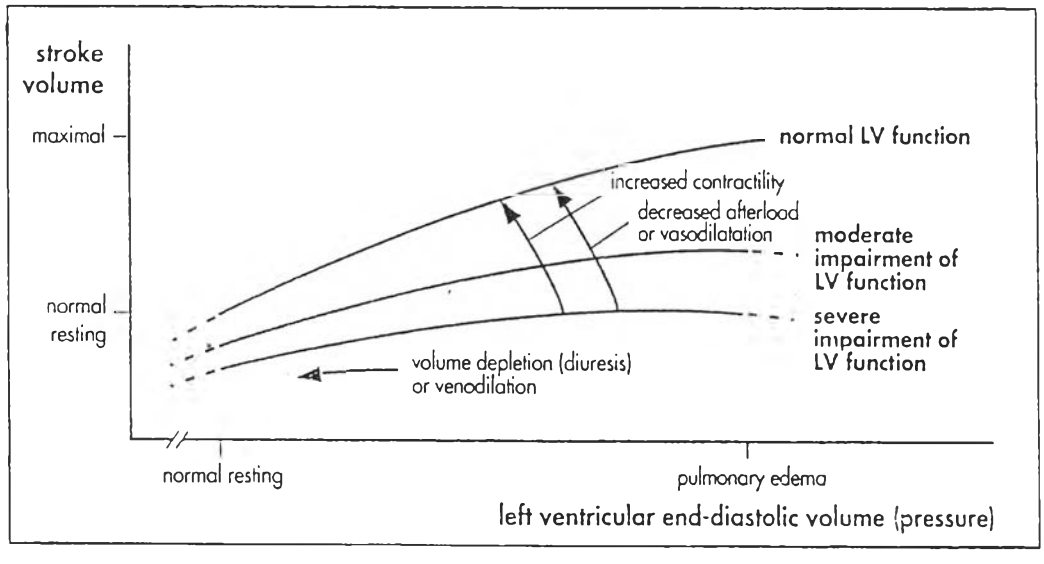


Figure4. Relationships between left ventricular (LV) end-diastolic volume [and pressure] and stroke volume, and the effects of different treatment modalities.

Attempts have been made to relieve the burden of the failing heart by the use of vasodilator drugs. Whereas this approach is often successful under emergency conditions and in the short term, most drugs suffer from the development of "tachyphylaxis" due, in part, to further activation of the RAS and sympathetic system, and to fluid retention.

The renin-angiotensin-aldosterone (RAA) system plays a major role in the maintenance of blood volume, blood pressure, and electrolyte homeostasis. Renin is a proteolytic enzyme released from renal juxtaglomerular cells at the vascular pole of the kidney in response to : (1) a fall in systemic blood pressure from any cause (e.g., reduction in blood volume, drop in systemic resistance,decrease in cardiac out put), (2) a reduction in sodium load to the kidneys, and (3) sympathetic nervous stimulation secondary to a fall in blood pressure (BP), painful stimuli, or stressful emotional states. Renin, in turn, catalyzes the conversion of angiotensinogen to angiotensin I, a relatively inactive decapeptide prohormone.

Angiotensin-converting enzyme (ACE) is a rather nonspecific metalloenzyme that is widely distributed throughout the body, including the lungs, kidneys, brain, and blood vessels. Angiotensin I is converted via ACE to angiotensin II, an octapeptide with potent vasoconstrictive properties. In addition, angiotensin II stimulates the adrenal cortex to synthesize and secrete aldosterone, a hormone that acts on the cortical collecting tubules of the kidney to promote reabsorption of sodium and water and increase excretion of potassium. The presence of angiotensin II ,and its degradation product angiotensin III, normally inhibits further renin release via a negative feedback loop, effectively interrupting the RAA cascade. Angiotensin II formation therefore results in vasoconstriction and expansion of blood volume, which usually produces an increase in systemic BP.

In addition to the conversion of angiotensin I to angiotensin II, ACE is capable of degrading bradykinin (a vasodilator) to inactive peptides. ACE, which is identical to kininase II, therefore promotes both the formation of the vasoconstrictor angiotensin II and enhances the degradation of the vasodilator bradykinin, although other endogenous enzymes are also capable of catalyzing bradykinin. It has been found that bradykinin activates phospholipase, resulting in the formation of vasodilatory prostaglandins. Further, bradykinin causes the release of another vasodilator, histamine. It is clear that inhibition of the ACE may have widespread effects on the vascular system due to the many actions of angiotensin II, kinins, and associated prostaglandins. (Raia et al.,1990) Figure 5 represents the role of the renin-angiotensin-aldosterone system and the kinin-prostaglandin systems in the maintenance of the congestive heart failure state. The pharmacodynamic changes associates with the administration of ACE inhibitors are summarized in Table 4.

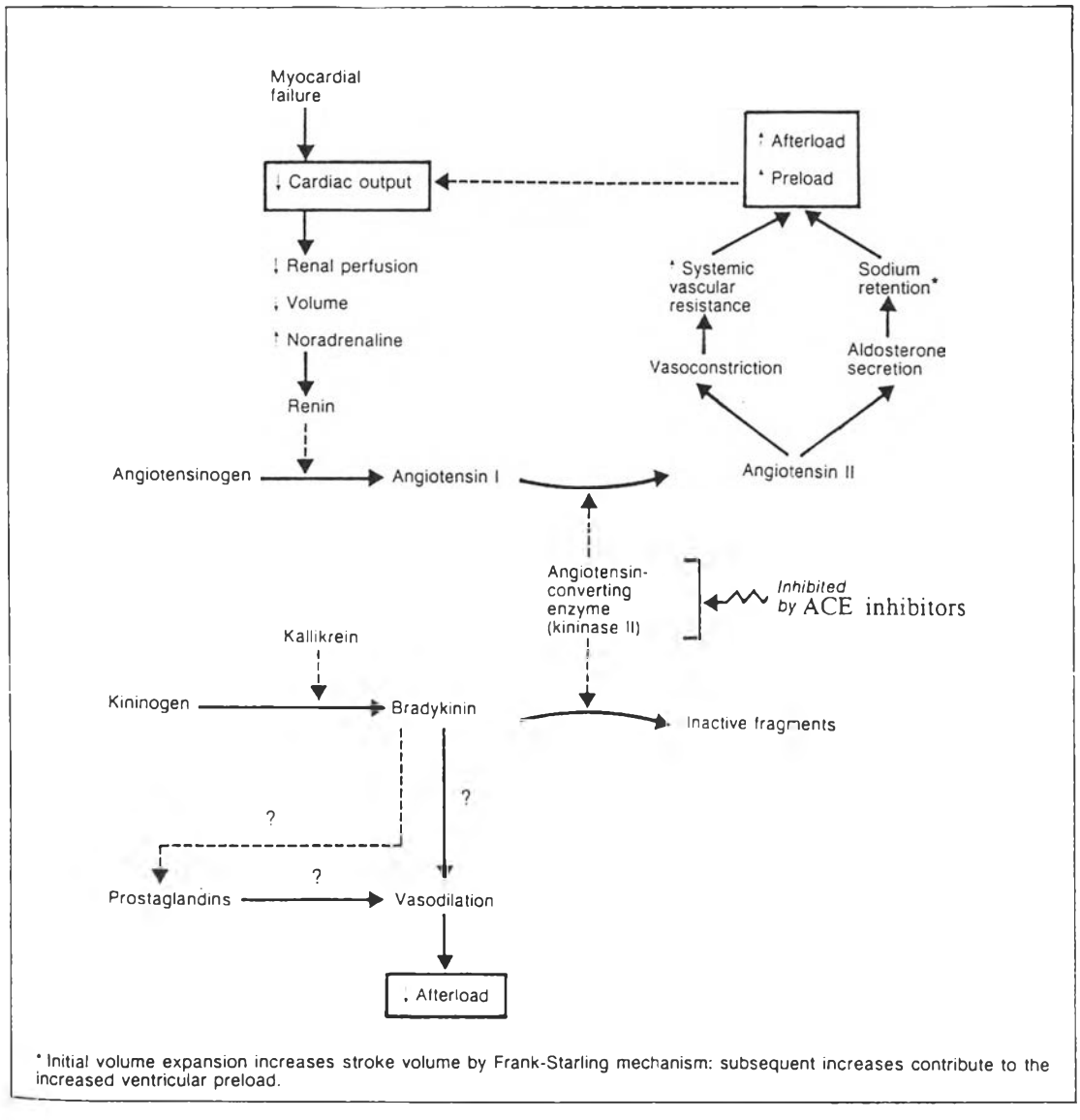


Figure 5 : Simplified representation of the role of the renin-angiotensin-aldosterone system and kinin-prostaglandin systems in the maintenance of the congestive heart failure state.

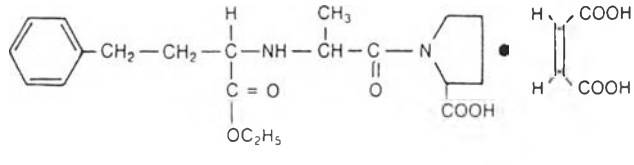
Table 4. Hemodynamic, hormonal, structural, renal and metabolic effects of ACEIs.

Hemodynamic	
	↓ blood pressure
	↓ total peripheral resistance
	↑ in cerebral, renal, coronary blood flow
	≈↑cardiac output
	≈ heart rate
	↓ arterial compliance
Renal	
	↑ renal blood flow
	≈glomerular filtration rate
	diuresis and natriuresis
Regression of vascular and cardiac hypertrophy	
Hormonal changes	
	↓ Angiotensin II
	↑ Angiotensin I
	↑ renin
	↓ renin substance
	↓ aldosterone
	≈blood kinins
	↑ urinary kinins
	? prostaglandins
Metabolic effects	
	↓ exchangeable sodium
	↑ plasma potassuim
	↓ plasma uric acid
	↑ insulin sensitivity

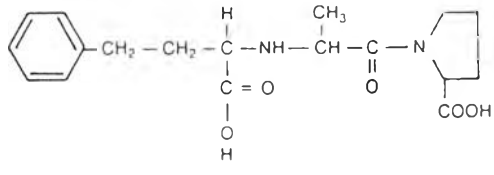
↑, increased ; ↓, decreased ; ≈ no change ; ? , uncertain

The development of the ACEIs, began with the discovery of a bradykinin potentiating factor in the venom of the South American pit viper Bothrops jararaca. This factor was determined to be a mixture of peptides that inhibit kininase II, an enzyme also known as angiotensin-converting enzyme. One component of the snake venom is teprotide which, although useful as an ACE inhibitor, has a short half-life and is effective only when administered parenterally. Based on findings with teprotides, chemists synthesized captopril, the first orally active ACE inhibitor in 1979.

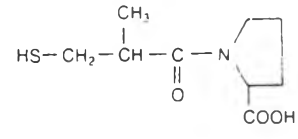
Captopril is dipeptide thiol (sulfur-containing) compound, its absorption from the gastrointestinal tract is not high and is reduced if taken with food. The sulfhydryl component has been implicated in various adverse effects experienced with this drug, including skin rash and loss of taste sense. Researchers attempted to formulate non-sulfur containing ACE inhibitors and, as a result, developed enalapril. Enalapril is an orally active prodrug that is hepatically metabolized via ester hydrolysis to the active inhibitory form, enalaprilat. Enalaprilat, which is much less effective when administered orally, is available as a parenteral preparation.(Figure 6)



Enalapril maleate



Enalaprilat



Captopril

Figure 6 : The graphic formulas of captopril (A), enalapril (B), and enalaprilat (C)

The next important consideration in the development of ACEIs was the introduction of prodrugs. Most of the newer compounds, with exception of lisinopril and ceranopril, are prodrugs. This was usually been achieved by adding an ester group which make compounds more lipophilic, improves their absorption from the gastrointestinal tract, prolong the duration of action, and increases their bioavailability. A summary of selected pharmacokinetic and pharmacodynamic characteristics of oral ACEIs is included in Table5.

Numerous placebo-controlled trials have documented the favorable effects of ACE inhibitor therapy on hemodynamic variables, clinical status, and symptoms. Hemodynamic effects observed with long term therapy include significant increases in cardiac index, stroke work index, and stroke volume index as well as significant reductions in left ventricular filling pressure (preload), systemic vascular resistance (afterload), mean arterial pressure, and heart rate. The beneficial effects on cardiac function are seen both at rest and during exercise. Significant improvements in clinical status, functional class, exercise tolerance, and left ventricular size with ACE inhibition are also well documented. When compared with placebo, patients treated with ACEIs have fewer treatment failures, fewer hospitalizations, fewer increases in diuretic dosage, and fewer ventricular premature beats on ambulatory electrocardiographic monitoring. (Johnson and Lalonde, 1992)

The beneficial effect of ACEI therapy on mortality has also been documented. (Furberg and Yusuf, 1985 ; Lee and Packer, 1986) The first clear evidence of improved survival with ACEIs was provided by the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) which examined the effects of enalapril in severe heart failure. After an average follow-up period of six months, the mortality was 44% in the placebo group and 26% in the enalapril group. The effect was confined to a reduction in deaths due to progressive heart failure (44 VS 22), whereas there were a similar number of sudden deaths in both groups (14 VS 14). (Consensus Trial, 1987) Benefit continued in terms of decreased mortality following completion of the trial, and with addition of an ACEI in the placebo group. (Swedberg et al., 1990) Although no formal survival study has been reported with ACEIs other than enalapril, the tendency towards beneficial effects with captopril (Captopril Multicenter Research Group, 1993 ; Furberg and Yusuf, 1985 ; Newman et al., 1988) suggests that ACEIs as a group decrease mortality in moderate and severe grades of heart failure.

Table 5. Pharmacokinetic and pharmacodynamic characteristics of oral ACEIs.

Ligand	Prodrug	Bioavailability (%)	Time to maximum concentration (hr)	Route of elimination	Daily dosage (mg)
Sulfhydryl					
-captopril	no	70	0.5-1.0	R	25-100
-alacepril	yes		1.0	G/R	25-100
-fentiapril	no			R	7.5-30
-zofenopril	yes	80		R/L	5-10
Carboxyl					
-enalapril	yes	50	1.0	R	5-40
-lisinopril	no	25	5.0	R	10-80
-ramipril	yes	60	2.5	R	2.5-10
-perindopril	yes	70	2.0	R	4-8
-cilazapril	yes	55	1.0	R/G	25-10
-quinapril	yes	75	1.5	R/L	5-20
-bunazapril	yes	80		R/L	5-20
-spirapril	yes	80	2.0	L	12.5-50
-delapril	yes			K	30-60
Phosphinyl					
-fosinopril	yes	25	3.0	L/G/R	5-40
-ceronapril	no	40	10.0	R	

G=Gastrointestinal ; K=Kidney ; L=Liver ; R=Renal

The CONSENSUS study was made in patients with the most severe grades (NYHA functional class 4) of cardiac failure. The Studies of Left Ventricular Dysfunction (SOLVD) were designed to assess the effect on mortality of enalapril in patients with reduced left ventricular ejection fraction and also revealed significant reductions in mortality in enalapril treated patients. In the latter study, patients with overt heart failure, mostly in NYHA functional class 2 and 3, were entered in the treatment trial where they were randomized double-blind to receive placebo (n=1284) or enalapril (n=1285) at dose of 2.5-20 mg/day for an average period of 41.4 months. There were fewer deaths in those receiving enalapril (452) than in the placebo group (510), which represents a 16% reduction in risk of death. (SOLVD Investigators,1991) This study and the CONSENSUS trial indicate that enalapril prolongs survival in mild, moderate and severe symptomatic cardiac failure.

Finally, the multicentre Veterans Administration Cooperative Vasodilator-Heart Failure Trial (V-HeFT II), a comparative trial of enalapril versus hydralazine-isosorbide dinitrate showed that enalapril therapy resulted in significantly lower than the hydralazine-nitrate combination. In this study of 804 men, mostly in NYHA functional class 2 and 3, the mortality at two years was lower in the enalapril group (18%) than in the combined vasodilator group (25%) although the overall mortality difference was not statistically significant ($P<0.08$). Of note were the fewer sudden deaths in patients receiving enalapril (57 compared with 92 in those on the combination of vasodilators) and the between group difference was statistically significant and most evident in patients with less severe grades of heart failure. (Cohn et al.,1991)

It soon became clear that ACEIs had sustained beneficial effects, and their subsequent widespread use has revolutionized the treatment of cardiac failure. Several ACEIs are currently available with many other underinvestigation. Captopril and enalaprl have Food and Drug Administration approval for use in congestive heart failure because of long term trials demonstrating their efficacy in reducing morbidity and mortality.

Information on the pharmacokinetics of captopril in patients with heart failure is limited, but because of the low hepatic extraction ratio of the drug its disposition is not expected to be significantly altered from that observed in healthy volunteers, except in those congestive heart failure patients with reduced renal function. (Romankiewicz et al., 1983)

Approximately 70 to 75% of an oral dose of captopril is absorbed by healthy fasting volunteers. Peak blood concentration are achieved 0.5 to 1.5 hours after administration. Ingestion of captopril in the non-fasting state reduces absorption by 35%. After a single dose of 25 mg in heart failure patients, maximum blood concentrations were achieved at 1.4 hours (121.5 ng/ml), which corresponded with peak haemodynamic and hormonal effects ; haemodynamic parameters returned toward baseline by 4 hours.(unpublished data on file, Squibb) Thirty percents of captopril is protein bound in human blood. The volume of distribution determined at steady state after a single 10 mg intravenous bolus dose of captopril in healthy volunteers is 0.7 L/kg.

In man, captopril is partially metabolized (approximately 50%) to inactive mixed disulfides with endogenous thiol compounds. Both metabolites and unchanged captopril appear in the urine. The primary mechanism of captopril renal elimination is tubular secretion. The average total body clearance was 0.8 L/kg/hr and the average renal clearance was 0.4 L/kg/hr. The elimination half-life of captopril is about 1.9 hours in healthy volunteers. In patients with heart failure given a single 25 mg oral dose of captopril, the mean half-life of unchanged drug in blood was 1.06 hours.

The individual elimination rate constants of captopril closely correlate with endogenous creatinine clearance, as demonstrated in a study of 15 patients with varying degrees of renal dysfunction receiving a single 100 mg dose. Marked increases in the elimination half-life of both captopril and metabolites occurred with creatinine clearance of less than 20 mL/min, necessitating careful dosage adjustment according to the degree of renal function. The presence of heart failure does not appear to affect the rate of clearance, although the dose should be reduced in the presence of severe renal impairment. Dosage should be extremely low initially because of the possibility of first-dose hypotension. Serum creatinine and potassium should be frequently monitored during long term therapy. The short half-life of captopril permits a rapid recovery of angiotensin II which may preserve renal function. Although this may facilitate dose titration, the short duration of action necessitates a frequent dosage schedule.

Following the oral administration of enalapril in healthy subjects, absorption is rapid, After absorption enalapril is de-esterified in the liver to form enalaprilat. Peak serum concentrations of unchanged enalapril are reached in about 1 hour and it disappears from circulation after about 4 hours. However, peak serum concentrations of the active metabolite, enalaprilat, are reached about 3 to 4 hours after enalapril

administration and detectable levels are still found after 72 to 96 hours. Using intravenous enalaprilat as a reference standard, the bioavailability of oral enalapril as enalaprilat is 36 to 44%. Absorption is unaffected by food. Enalaprilat is less than 50% bound to human plasma protein. Enalapril undergoes hydrolysis to enalaprilat after absorption. The principal site of hydrolysis appears to be the liver. The conversion of enalapril to enalaprilat was calculated to be about 60% efficient in healthy subjects. No further metabolism of enalapril or enalaprilat occurs in man, and excretion of the unchanged drugs occurs in urine and feces.

Following oral administration of enalapril 10 mg in healthy subjects, 33% of the dose is recovered in feces (6% as enalapril and 27% as enalaprilat) and 61% is recovered in urine (18% as enalapril and 43% as enalaprilat). Faecal recovery represents unabsorbed drug or biliary excretion. The degree of biliary excretion in man is unknown. Renal excretion appears to be the main route. In healthy subjects renal clearance of enalaprilat has been calculated as 8.1 to 9.5 L/hour, which is of a similar order to glomerular filtration. The renal clearance of enalapril is higher at 18 L/hr, implying some degree of active tubular excretion. During elimination, enalaprilat shows polyphasic kinetics with a prolonged terminal phase. In healthy subjects the terminal half-life of enalaprilat is about 30 to 35 hours after a single oral dose of 10 mg enalapril (Todd and Heel, 1986)

Review of Interaction of Digoxin and ACE inhibitors.

Some studies have found that serum digoxin levels rise by about 20-25% if captopril is used concurrently, but another found no significant changes. Enalapril, lisinopril and ramipril appear not to interact. A study in 20 patients with severe chronic congestive heart failure (NYHA functional class 3 and 4) showed that while taking captopril (mean total daily dose 93.75 mg ; 6 weeks) their serum digoxin levels were significantly higher (from 1.38 to 1.74 nmol/L) when patients were on captopril compared with placebo. (Cleland, Dargie, Hodsman, Robertson et al., 1984) A latter study showed that captopril increased serum digoxin levels by about 21%. The mechanism of the interaction is not fully understood. Both glomerular filtration and tubular secretion of digoxin are reduced (possibly related to aldosterone inhibition), but other mechanisms may have some part to play. (Cleland et al., 1986)

However, in a study of 10 patients with mild congestive heart failure (NYHA functional class 1 and 2), received combination therapy with once a day digoxin and 12.5 mg captopril thrice a day for 7 days, no significant change was recognized. (Miyakawa et al.,1987) And another controlled study in 31 digitalized patients gave no evidence of a significant interaction when 25 mg captopril three times daily (for 6 months period) was given to. (Magelli et al., 1989)

Douste -Blazy et al. (1986) studied the influence of enalapril on plasma and urine digoxin concentration, in order to determine if a similar interaction occurs with other ACEI. Seven patients with congestive heart failure (functional class 3) treated with 0.25 mg daily digoxin were studied before and after a treatment with enalapril(20 mg orally for 30 days). The results show no clinical or pharmacokinetic interaction between digoxin and enalapril.

A double-blind placebo-controlled study in 14 patients on digoxin showed that the concurrent use of 5 mg lisinopril daily over a four-week period had no significant effect on serum digoxin levels. (Vandenburg et al., 1988) This confirms the findings of a previous single dose study in 12 healthy volunteers received three separate oral treatments : digoxin 0.25 mg ; lisinopril 20 mg ; and digoxin 0.25 mg + lisinopril 20 mg. (Morris et al., 1985)

A study in 12 normal subjects given 0.5 mg digoxin daily showed that the concurrent use of 5 mg ramipril daily for 14 days had no effect on the serum levels of the digoxin. (Doering et al., 1987) Potential for spirapril to affect steady-state digoxin kinetics was studied. A double-blind crossover comparison of 48 mg/d spirapril with matching placebo was studied in 15 healthy volunteers. (each subject received 0.25 mg digoxin orally every 12 hours for the entire 5-week period) The results did not show a significant effect or even a suggestive trend for any interaction with steady-state digoxin pharmacokinetics. (Johnson et al., 1991)

Review of Fluorescence Polarization Immunoassay.

A number of test are available for measuring digoxin concentrations in biological fluids. These include radioimmunoassay (RIA), flurescence polarization immunoassay, enzyme-linked immunoassay, high performance liquid chromatography, Na^+-K^+-ATPase inhibition assays, gas-liquid chromatography, and thin layer chromatography. Methods based on competitive protein binding, such as the various types of immunoassay, have been extensively used. Automatic immunoassays that either use fluorescence or are enzyme linked are now available ; examples include : flurescence energy transfer immunoassay (FETI) [Syva Advance System] ; flourescence polarization immunoassay (FPIA) [Abbott TDx®] ; and enzyme linked immunoassay (EMIT) [Syva Co., Dade Stratus, and Dupont aca]

Discrepancies among different RIA kits are particularly likely in patients with liver disease or renal failure who have digoxin-like immunoreactive substances in their serum. The fluorescence polarization immunoassay is less likely than other methods to detect digoxin-like immunoreactive substances. (Mooradian, 1988) The fundamental principles of fluorescence polarization was first developed in 1926 by Perrin. Three decades later the technique was applied to biological systems by Weber, and its application to the antigen-antibody reaction was first described in 1961 by Dandliker and Feigen.

The Abbott TDx® system is based on FPIA technique. This method combines competitive protein binding with fluorescence polarization to give a direct measurement without the need for a separation procedure. The specificity of an immunoassay is thereby combined with the speed and convenience of a homogeneous method, providing a precise and reliable procedure for determining the concentrations of biologically interesting substances in serum and plasma. (Jolley et al., 1981)

All competitive binding immunoassays for measuring therapeutic drugs are based on competitive between the drug in the patient sample and a labeled drug, called tracer. Sample drug and tracer compete for a limited number of binding sites on antibodies specific to the drug being measured. The concentration of unlabeled drug from a patient sample will determine how much labeled drug can bind to the specific antibody. In the TDx® system, the label on the tracer drug is the fluorescent dye-fluorescein. Fluorescence polarization measures the change in the angle of polarized

fluorescent light emitted by the fluorescein dye with a sophisticated optical detection system. The changes of the polarization angle reflect tracer binding to antibody. The precise relationship between polarization and concentration of the unlabeled drug is established by measuring the polarization values of calibrators with known concentrations of the drug. A calibration curve stored in system memory is used to automatically determine the concentrations of unknown patient samples.

Oeltgen et al. (1984) evaluated and compared the Abbott TDx® FPIA system with well-established enzyme multiplied immunoassay technique (EMIT) and radioimmunoassay (RIA) methods utilizing five high-volume drug assays including theophylline, gentamicin, phenytoin, phenobarbital and digoxin. These drug assays were evaluated for precision, calibration stability, specificity, and accuracy. Comparison of these methods indicated on extremely good analytical correlation ($r>0.97$) for all five comparisons. The TDx® system offers significant advantages in calibration and reagent stability, and greater sensitivity in the low drug concentration ranges while maintaining accuracy and precision comparable with those of established EMIT and RIA procedures.