CHAPTER IV

RESULTS AND DISCUSSION

1. Serum Digoxin Concentrations

The patients with congestive heart failure were evaluated for entry into the study. Twenty seven admitted patients who met the criteria were analyzed. The characteristics and clinical assessment of the patients who participated in this study are shown in Table 6 and Table 7. All of the patients had subjective and objective evidence of reduced exercise capacity, as demonstrated by exertional symptoms (New York Heart Association functional class II or III).

Three groups of patients were identified. Ten patients received digoxin therapy without angiotensin-converting enzyme inhibitor (the digoxin group). Nine patients received digoxin therapy with enalapril (the enalapril group). And eight patients received digoxin therapy with captopril (the captopril group). All received diuretics in the modified dose to achieve optimal fluid balance. The selection of a specific agent was determined by individual responses and the agent available at the time each patient was evaluated. Drug treatment was not randomized. In general, a series of drugs were tested in each patient until a satisfactory short-term hemodynamic effect was observed at a dose that produced no adverse reactions. Table8 demonstrates the variability seen in the dose of digoxin , captopril , and enalapril. The observed blood levels (serum digoxin concentrations) are shown in Table 9, 10, and 11. Mean values of each patient group are displayed as curves in Figure 7.

There are no rigid guidelines as to the range of serum concentrations that are most effecious but most patients will benefit, with little risk of toxic symptoms and signs developing, with digoxin concentrations from 0.8 ng/ml to 2.0 ng/ml. Above this range, toxic symptoms and signs become more frequent and levels above 3.0 ng/ml are quite likely to be toxic. When individual data was considered, serum digoxin levels of eight patients (29.6%) were in therapeutic range [0.8-2.0 ng/ml]. Five patients (18.5%) have measured concentrations lower than 0.8 ng/ml, one patient (3.7%) lower than0.5 ng/ml, one patient (3.7%) over 2.0 ng/ml, five patients (18.5%) over 2.5 ng/ml, three

patients (11.1%) over 3.0 ng/ml. Seventeen patients (62.96%) had serum concentrations in the range of 0.5 to 2.5 ng/ml, and a patient (3.7%) in the range of <0.5 to 2.5 ng/ml.

Table 6. Characteristics of patients.

No.	Sex	Age (yr.)	Bw (kg.)	Height (cm.)	IBW (kg.)	Scr. (mg/dl)
2	m	45	63	170	65.94	1.4
4	f	35	41.5	150	43.33	0.9
5	m	20	44	168	64.12	2.1
6	m	45	81	171	66.84	1.4
7	m	36	55	163	59.6	0.9
9	m	58	53	164	60.5	1.1
11	m	62	63	174	69.56	1.2
12	m	51	47	165	61.4	1.4
14	f	44	42.5	149	42.42	0.8
17	f	44	59	158	50.5	0.9
8	m	28	59	170	65.94	1.2
10	m	51	58	169	65.03	1
13	m	20	47	162	58.69	0.8
16	f	88	64	154	46.95	1.3
19	f	80	53	150	43.33	1.2
20	f	51	75.5	154	46.95	1.5
21	m	79	52.5	160	56.88	1
22	m	59	70	161	57.79	0.8
25	m	22	52	162	58.69	1
18	m	28	50	159	55.98	0.9
23	m	65	72.5	169.5	65.48	1.3
24	m	17	42.5	161	57.79	0.9
26	m	51	76	173	68.65	1.3
27	m	59	64.5	161	57.79	1.1
28	m	27	48	159	55.98	0.8
29	m	65	52	158	55.07	1
30	m	67	58.5	155	52.35	1.1

m = Male

f = Female

Bw = Body weight (kg)

IBW = Ideal body weight (kg)

Scr = Serum creatinine (mg/ml)

Table 7. Clinical assessment of patients.

No.	NYHA class	[1]	[2]	[3]	[4]	[5]	[6]	[7]	[8]	[9]
2	2	Y	Y	-	-	-	-	-	-	-
4	3	-	Y	Y	-	-	-	-	-	-
5	2	-	-	Y	-	-	-	-	-	-
6	2	-	-	-	-	Y	-	-	-	-
7	3	-	Y	Y	-	-	-	-	-	-
9	2	-	-	Y	-	-	-	-	-	-
11	2	-	-	-	-	-	-	-	-	-
12	3	-	Y	Y	-	-	-	-	-	-
14	3	Y	Y	-	-	-	-	-	-	-
17	3	Y	Y	Y	-	-	-	-	-	-
8	3	Y	-	Y	-	-	-	-	-	-
10	2	-	-	Y	-	-	-	-	-	-
13	3	Y	Y	Y	-	-	-	-	-	-
16	3	-	-	Y	Y	-	-	-	-	-
19	3	-	-	-	-	Y	-	-	-	-
20	2	-	-	-	-	-	-	-	-	-
21	2	-	-	Y	-	Y	-	-	-	-
22	3	-	-	Y	-	-	-	-	-	-
25	3	-	-	-	-	-	-	-	-	-
18	2	-	-	Y	-	-	-	-	-	-
23	2	Y	Y	Y	Y	-	-	-	Y	-
24	2	-	-	Y	-	-	-	-	-	-
26	2	-	-	-	-	-	-	-	-	-
27	3	-	Y	-	-	-	-	-	-	-
28	2	-	Y	-	-	-	-	-	-	-
29	2	-	-	-	-	Y	-	Y	-	-
30	2	Y	Y	-	-	Y	-	-	-	-

NYHA class = New York Heart Association Functional Class.

[1] = Abnormal sinus rhythm.

[2] = History of supraventricular arrhythmis or sustained ventricular arrhythmias.

[3] = Uncorrected primary valvular disease, active myocarditis, or an obstructive, hypertrophic, or restrictive cardiomyopathy.

[4] = Systolic blood pressure > 160 mmHg or < 90 mmHg or diastolic blood pressure > 95 mmHg.

[5] = Angina requiring continuous treatment.

[6] = Severe primary pulmonary, renal, or hepatic disease.

[7] = Myocardial infarction within the past 3 months.

[8] = Stroke within the past 12 months.

[9] = Thyroid disease.

Y   = Yes

Table 8 . Doses of digoxin, captopril, and enalapril.

No.	Digoxin dose	Enalapril dose	Captopril dose
2	0.25 mg/d	-	-
4	0.25 mg/d	-	-
5	0.25 mg/d	-	-
6	0.25 mg/d	-	-
7	0.25 mg/d	-	-
8	0.25 mg/d	5mg;BID.,p.c.[R]	-
9	0.25 mg/d	-	-
10	0.25 mg/d	2.5mg;OD.,p.c.[R]	-
11	0.25 mg/d	-	-
12	0.25 mg/d	-	-
13	0.25 mg/d	10mg;OD.,p.c.[R]	-
14	0.25 mg/d	-	-
16	0.25 mg/d	5mg;OD.,p.c.[E]	-
17	0.25 mg/d	-	-
18	0.25 mg/d	-	12.5mg;BID.,p.c.
19	0.25 mg/d	10mg;OD.,p.c.[E]	-
20	0.25 mg/d	5mg;BID.,p.c.[R]	-
21	0.25 mg/d	5mg;OD.,p.c.[E]	-
22	0.25 mg/d	5mg;OD.,p.c.[E]	-
23	0.25 mg/d	-	25mg;BID.,p.c.
24	0.25 mg/d	-	12.5mg;BID.,p.c.
25	0.125 mg/d	10mg;OD.,p.c.[E]	-
26	0.125 mg/d	-	12.5mg;BID.,p.c.
27	0.25 mg/d	-	12.5mg;BID.,p.c.
28	0.25 mg/d	-	25mg;BID.,p.c.
29	0.25 mg/d	-	12.5mg;BID.,p.c.
30	0.25 mg/d	-	25mg;BID.,p.c.

E	=	Enaril [Biolab.]
R	=	Renitec [M.S.D.]
OD.	=	Once daily
BID.	=	Twice daily
Captopril	=	Capoten [Squibb]

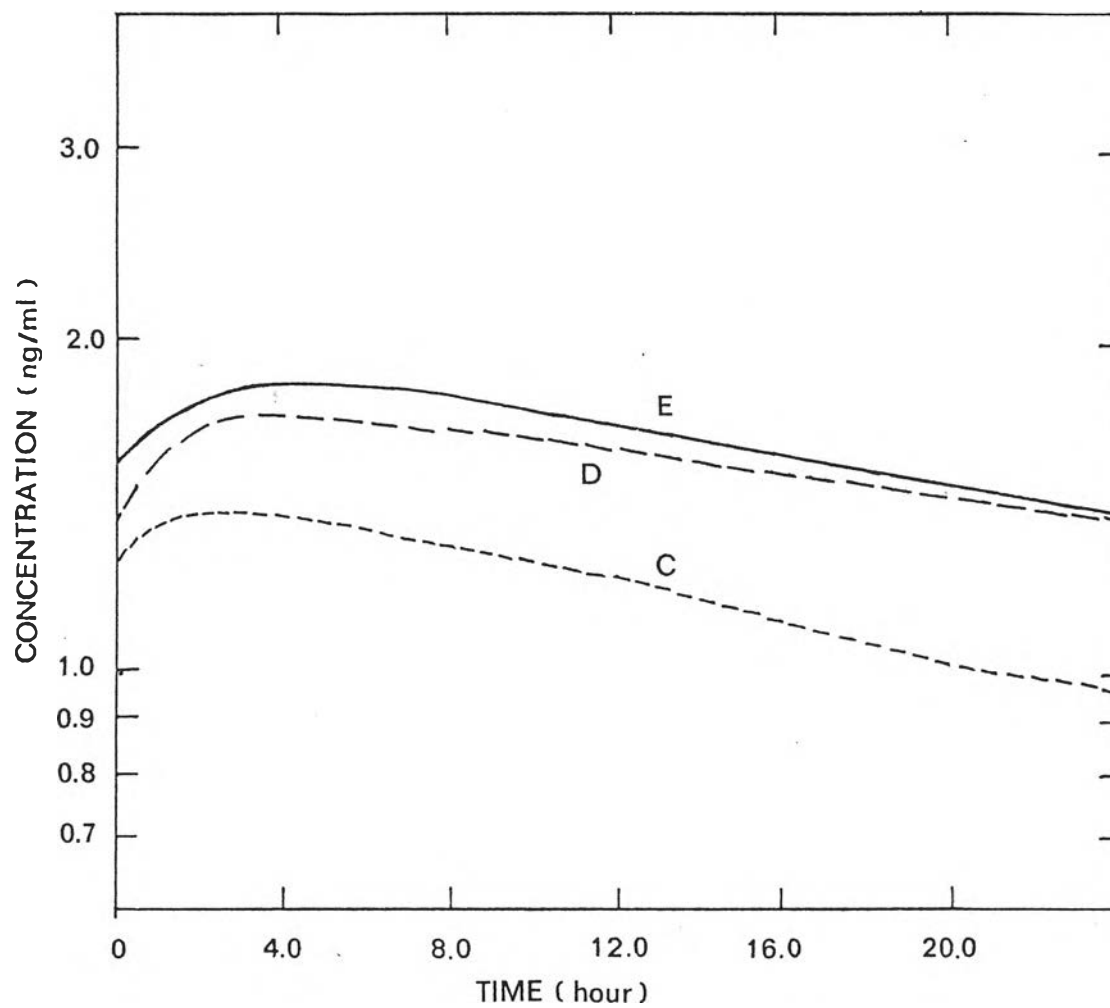**Table 9**   The observed serum digoxin concentrations of the digoxin group.

case2 digoxin	Time (hr)	C (ng/ml)
	0.00	1.36
	0.25	1.73
	0.75	2.56
	1.00	2.72
	1.50	2.39
	2.03	2.21
	4.25	1.52
	8.00	1.64
	11.83	1.53
	23.00	1.41

case4 digoxin	Time (hr)	C (ng/ml)
	0.00	1.45
	0.25	1.53
	0.55	2.07
	1.00	2.68
	2.08	5.78
	2.95	3.66
	4.08	2.57
	8.42	2.01
	12.00	2.09
	23.58	1.76

case5 digoxin	Time (hr)	C (ng/ml)
	0.00	0.41
	0.53	1.64
	1.02	2.13
	2.15	1.16
	3.05	0.98
	4.58	0.71
	8.00	0.71
	12.00	0.51
	23.00	0.52

case6 digoxin	Time (hr)	C (ng/ml)
	0.00	0.54
	0.53	1.28
	0.95	1.08
	2.02	1.03
	3.03	1.18
	4.00	1.05
	8.25	0.66
	12.25	0.63
	22.83	0.54

case7 digoxin	Time (hr)	C (ng/ml)
	0.00	0.65
	0.50	0.85
	1.00	1.40
	1.95	1.78
	2.90	1.52
	4.00	1.04
	7.72	0.93
	12.08	0.81
	23.33	0.87

case9 digoxin	Time (hr)	C (ng/ml)
	0.00	1.58
	0.50	2.22
	0.92	2.40
	1.58	2.64
	2.08	2.48
	2.97	2.42
	4.25	2.26
	7.50	1.82
	12.58	1.75
	23.08	1.52

case11 digoxin	Time (hr)	C (ng/ml)
	0.00	1.12
	0.50	1.31
	1.00	1.77
	2.08	1.99
	2.97	1.72
	3.95	1.72
	7.45	1.13
	11.58	1.12
	23.62	1.05

case12 digoxin	Time (hr)	C (ng/ml)
	0.00	0.70
	0.45	0.91
	0.92	1.06
	1.88	1.33
	2.92	2.42
	4.17	1.79
	7.83	1.16
	12.67	0.83
	23.17	0.73

case14 digoxin	Time (hr)	C (ng/ml)
	0.00	0.69
	0.58	2.08
	1.08	2.00
	2.00	1.55
	3.08	1.07
	4.00	0.91
	7.58	0.62
	12.17	0.63
	23.00	0.66

case17 digoxin	Time (hr)	C (ng/ml)
	0.00	1.01
	0.50	1.54
	1.25	1.84
	2.00	1.34
	3.03	1.18
	4.50	1.09
	7.55	0.79
	12.67	0.71
	23.00	0.89

Table 10 The observed serum digoxin concentrations of the enalapril group.

case8 digoxin enalapril	Time (hr)	C (ng/ml)
	0.00	0.62
	0.50	0.78
	1.00	1.07
	1.95	2.07
	2.85	1.91
	4.00	1.48
	7.72	0.89
	12.08	0.81
	23.17	0.95

case10 digoxin enalapril	Time (hr)	C (ng/ml)
	0.00	0.82
	0.50	1.02
	1.00	1.93
	1.95	2.03
	2.67	1.96
	3.67	1.34
	8.42	0.90
	12.17	0.93
	23.00	0.84

case13 digoxin enalapril	Time (hr)	C (ng/ml)
	0.00	1.17
	0.47	2.51
	1.00	2.75
	1.87	1.95
	3.00	1.60
	3.83	1.57
	7.75	1.39
	12.33	1.35
	22.75	1.33

case16 digoxin enalapril	Time (hr)	C (ng/ml)
	0.00	1.42
	0.50	1.97
	1.00	2.27
	2.00	2.26
	3.00	2.73
	3.67	2.63
	8.08	2.01
	12.67	1.81
	23.17	1.84

case19 digoxin enalapril	Time (hr)	C (ng/ml)
	0.00	2.20
	0.67	4.89
	1.08	5.08
	2.00	5.04
	2.95	4.30
	7.87	2.74
	12.92	2.38
	23.17	2.09
	72.00	1.75

case20 digoxin enalapril	Time (hr)	C (ng/ml)
	0.00	0.85
	0.50	1.11
	1.08	1.24
	2.00	2.18
	2.87	2.35
	4.20	1.81
	8.25	1.41
	15.33	1.24
	23.00	0.99

case21 digoxin enalapril	Time (hr)	C (ng/ml)
	0.00	0.76
	0.50	1.09
	1.03	1.69
	2.08	1.86
	2.75	1.83
	3.67	1.77
	7.67	1.29
	10.75	1.32
	23.17	1.11

case22 digoxin enalapril	Time (hr)	C (ng/ml)
	0.00	0.83
	0.48	0.99
	0.90	1.00
	2.00	1.25
	2.60	1.17
	3.53	1.12
	8.45	1.16
	12.45	1.14
	22.95	1.09

case25 digoxin enalapril	Time (hr)	C (ng/ml)
	0.00	0.88
	0.38	1.01
	0.98	1.23
	1.97	1.37
	3.08	1.52
	4.08	1.69
	8.17	1.29
	11.38	1.10
	24.00	0.95

Table 11   The observed serum digoxin concentrations of the captopril group.

case18 digoxin captopril	Time (hr)	C (ng/ml)
	0.00	0.61
	0.50	0.59
	1.03	1.20
	2.22	1.13
	3.18	0.81
	3.88	0.68
	8.08	0.57
	11.88	0.47
	22.97	0.63

case23 digoxin captopril	Time (hr)	C (ng/ml)
	0.00	0.77
	0.55	1.64
	1.00	1.80
	2.00	1.42
	2.60	1.58
	3.83	1.38
	8.53	0.82
	12.58	0.85
	23.08	0.77

case24 digoxin captopril	Time (hr)	C (ng/ml)
	0.00	0.88
	0.42	1.78
	1.02	1.89
	2.00	1.41
	3.12	1.21
	4.12	1.15
	8.17	0.99
	11.45	0.92
	24.00	0.79

case26 digoxin captopril	Time (hr)	C (ng/ml)
	0.00	0.65
	0.50	1.28
	1.00	1.15
	2.00	0.87
	2.97	0.67
	4.50	0.68
	8.00	0.57
	11.17	0.51
	22.92	0.60

case27 digoxin captopril	Time (hr)	C (ng/ml)
	0.00	1.02
	0.53	1.16
	0.95	1.87
	1.78	2.78
	2.83	2.08
	3.58	1.62
	7.70	1.29
	11.67	1.03
	23.17	0.88

case28 digoxin captopril	Time (hr)	C (ng/ml)
	0.00	0.60
	0.42	1.09
	0.85	1.91
	1.67	1.48
	2.72	1.08
	3.53	1.19
	7.75	0.72
	11.58	0.68
	23.05	0.68

case29 digoxin captopril	Time (hr)	C (ng/ml)
	0.00	0.78
	0.58	0.88
	2.00	1.75
	3.00	1.29
	6.25	0.93
	8.50	0.87
	24.00	0.83

case30 digoxin captopril	Time (hr)	C (ng/ml)
	0.00	1.53
	0.45	1.82
	1.00	2.32
	1.97	2.36
	2.75	3.35
	4.10	3.01
	6.93	2.37
	11.58	2.01
	23.05	1.87

Figure 7 Mean concentration values of each group of patients.
D = The digoxin group , E = The enalapril group , C = The captopril group

2. Calculation of the parameters and comparison among groups of patients.

The digoxin pharmacokinetic parameters were estimated. Table12 Shows the calculated values of pharmacokinetic constants of digoxin in Thai patients. These pharmacokinetic parameter estimations were made by using data only from the patient's chart. Creatinine clearance can be estimated from the patient's serum creatinine using Equation 5-6. Total digoxin clearance is the sum of its metabolic and renal clearance as illustrates by Equation 8. Volume of distribution was calculated from Equation 10, Elimination rate constant from Equation 11, and Terminal half life from Equation 12.

Table13 shows absosrption rate constant, distribution rate constant, elimination rate constant, volume of distribution, and elimination half-life of digoxin were calculated from the serum digoxin concentrations by various methods. Comparison of treatment groups with respect to these pharmacokinetic parameters was assessed using ANOVA. No significant difference between the means of these parameters at the 95% level of confidence was found among the three groups of patients.(Table 14-Table 22) Both captopril and enalapril did not show a significant difference on steady state digoxin pharmacokinetics.

The mean values ±SD of elimination rate constant calculated from serum digoxin concentrations by RSTRIP program and non compartmental program were 0.01±0.0244 and 0.011±0.0074 (/hr) respectively. The mean calculated elimination rate constant obtained from patient's data was 0.011±0.0011(/hr). The elimination half life of digoxin estimated by RSTRIP program and the patient's data were 137.53±100.91 and 63.54 6.35 (hr) respectively. While the reported elimination half life 36 hours.[minimum =18, maximum =72 hr ; approximated limites baesd upon normal renal function,ideal body weight =70 kg, no thyroidism, no congestive heart failure, no concurrent therapy factor such as none of the following drugs: quinidine, verapamil, etc.]

Table 12 Pharmacokinetic parametrs calculated from the patient's data.

No.	CrCl (ml/min.).	Cl dig (ml/min.)	Cl dig (L/d)	Vd (L)	Ke (/day)	Ke (/hr)	t1/2 (d)	t1/2 (hr)
2	59.38	74.23	106.89	423.48	0.25	0.0104	2.74	66.63
4	57.16	65.14	93.80	334.90	0.28	0.0117	2.48	59.23
5	34.92	345.95	66.17	275.45	0.24	0.0100	2.88	69.30
6	62.99	78.75	113.40	449.26	0.25	0.0105	2.74	66.00
7	88.27	97.59	140.53	482.64	0.29	0.0121	2.38	57.27
9	54.87	66.87	96.30	371.50	0.26	0.0108	2.67	64.17
11	56.88	71.98	103.65	415.73	0.25	0.0104	2.78	66.63
12	41.50	52.86	76.12	307.25	0.25	0.0103	2.80	67.28
14	60.10	68.09	98.05	347.51	0.28	0.0117	2.46	59.23
17	63.59	73.90	106.41	389.03	0.27	0.0114	2.53	60.79
8	76.48	88.30	127.15	461.29	0.28	0.0117	2.51	59.23
10	71.69	83.66	120.47	442.64	0.27	0.0113	2.55	61.60
13	97.92	103.64	149.24	482.15	0.31	0.0129	2.24	53.72
16	22.17	35.45	51.04	247.14	0.21	0.0086	3.35	80.53
19	31.28	42.45	61.13	261.62	0.23	0.0098	2.96	71.08
20	32.89	45.09	64.94	280.37	0.23	0.0097	2.99	71.81
21	44.48	57.36	82.59	337.39	0.24	0.0102	2.83	67.94
22	81.27	92.21	132.79	471.54	0.28	0.0117	2.46	59.06
25	85.22	93.86	135.16	461.78	0.29	0.0122	2.37	56.82
18	86.42	94.28	135.76	457.90	0.30	0.0124	2.34	56.11
23	52.47	68.83	99.12	411.48	0.24	0.0100	2.88	69.30
24	80.67	86.63	124.74	411.58	0.30	0.0126	2.29	54.88
26	65.28	81.41	117.22	463.24	0.25	0.0105	2.74	65.73
27	59.10	72.26	104.05	402.81	0.26	0.0108	2.68	64.39
28	94.17	100.59	144.85	474.33	0.30	0.0127	2.27	54.46
29	54.17	65.91	94.91	365.53	0.26	0.0108	2.67	64.05
30	48.25	60.70	84.98	348.50	0.24	0.0102	2.84	68.21

x D	57.97	99.54	100.13	379.68	0.26	0.0109	2.65	63.65
x D+E	60.38	71.34	102.72	382.88	0.26	0.0109	2.70	64.64
x D+C	67.57	78.83	113.20	416.92	0.27	0.0112	2.59	62.14
x All	61.61	84.00	104.87	391.78	0.26	0.0110	2.65	63.54

SD D	14.1241	87.3246	20.2611	64.9484	0.0169	0.0007	0.1703	4.1715
SD D+E	27.7604	26.0592	37.5261	99.6034	0.0331	0.0014	0.3584	8.7057
SD D+C	17.2888	14.2348	20.9519	45.8261	0.0263	0.0011	0.2503	6.0682
SD All	20.0798	55.3147	26.9292	73.1874	0.0252	0.0011	0.2613	6.3471

[x = Mean value , SD = Standard deviation , D = The digoxin group , E = The enalapril group , C = The captopril group , All = All of the patients . CrCl = Creatinine clearance , Cl dig = Digoxin clearance , Vd = Volume of distribution , Ke = Elimination rate constant , t 1/2 = half life.]

Table 13 Pharmacokinetic parameters calculated from serum digoxin concentrations

No.	k 6hr	Vs	rs:k1	rs:k2	rs:k3	rs:t1/2 1	rs:t1/2 2	rs:t1/2 3
2	0.0095	439.60	0.0050	0.9402	1.4879	139.02	0.74	0.47
4	0.0106	412.50	0.0070	0.5246	0.5506	99.42	1.32	1.26
5	0.0166	493.75	0.0147	1.0182	1.5844	47.03	0.68	0.44
6	0.0145	800.00	0.0031	0.1226	*	221.54	5.66	0.00
7	0.0022	1823.26	0.0057	0.4846	0.7820	120.80	1.43	0.89
9	0.0120	344.83	0.0110	0.5475	0.8283	63.24	1.27	0.84
11	0.0048	16125	0.0020	0.4559	0.5641	339.57	1.52	1.23
12	0.0281	207.95	0.0131	0.2539	0.3828	52.84	2.73	1.81
14	*	*	0.0005	0.5990	2.5390	*	1.16	0.27
17	*	*	0.0002	0.6614	1.3655	*	1.05	0.51
8	*	*	0.0060	0.4035	0.5200	115.58	1.72	1.33
10	0.0059	1723.4	0.0041	0.5571	0.6582	168.67	1.24	1.05
13	0.0027	1806.9	0.0015	0.9625	2.2172	463.38	0.72	0.31
16	0.0046	6050.00	0.0025	0.3392	0.4946	278.45	2.04	1.40
19	0.0060	116.38	0.0041	0.3004	1.7302	167.50	2.31	0.40
20	0.0245	215.42	0.1275	0.1348	12.5170	5.44	5.14	0.06
21	0.0111	290.72	0.0054	0.3542	0.7149	128.54	1.96	0.97
22	0.0043	1460.46	0.0035	0.3125	0.9810	196.41	2.22	0.71
25	0.0172	292.75	0.0069	0.2902	0.3049	100.56	2.39	2.27
18	*	*	0.0049	0.5938	0.8656	140.57	1.17	0.80
23	0.0055	470.37	0.0093	0.2745	2.7316	74.88	2.53	0.25
24	0.0140	518.31	0.0159	1.0794	2.0599	43.53	0.64	0.34
26	0.0062	*	0.0001	0.7057	4.2535	*	0.98	0.16
27	0.0230	228.74	0.0137	0.3824	0.7809	50.51	1.81	0.89
28	0.0029	2735.14	0.0000	0.5482	1.5740	*	1.26	0.44
29	0.0052	2793.33	*	*	*	*	*	*
30	0.0132	206.71	0.0251	0.0264	0.7717	8.12	7.70	0.04

	k 6hr	Vs	rs:k1	rs:k2	rs:k3	rs:t1/2 1	rs:t1/2 2	rs:t1/2 3
x D	0.012	2580.86	0.01	0.56	1.12	135.43	1.75	0.77
x D+E	0.010	1494050	0.02	0.41	2.24	180.50	2.19	0.95
x D+C	0.010	1158.77	0.01	0.52	1.86	63.52	2.30	0.42
x ALL	0.011	1797.98	0.01	0.50	1.73	137.53	2.05	0.74

	k 6hr	Vs	rs:k1	rs:k2	rs:k3	rs:t1/2 1	rs:t1/2 2	rs:t1/2 3
SD D	0.0080	5496.26	0.0052	0.2727	0.6893	100.3272	1.4833	0.5435
SD D+E	0.0076	1976.01	0.0411	0.2362	3.9058	129.4845	1.2313	0.6782
SD D+C	0.0071	1249.98	0.0092	0.3358	1.2876	49.2539	2.4597	0.3188
SD ALL	0.0074	3482.60	0.0244	0.2764	2.4288	100.9123	1.6700	0.5680

[x = Mean value , SD = Standard deviation , D = The digoxin group , E = The enalapril group , C = The captopril group , All = All of the patients , k 6hr = Digoxin elimination rate constant{noncompartmental program}(/hr) , Vs = Digoxin steady state volume of distribution(L) , rs:k1 = Elimination rate constant{RSTRIP}(/hr) , rs:k2 = Distribution rate constant{RSTRIP}(/hr) , rs:k3 = Absorption rate constant{RSTRIP}(/hr) , rs:t1/2 1= Elimination half life(hr), rs:t1/2 2= Distribution half life(hr) , rs:t1/2 3=Absorption half life(hr).]

Table 14 Comparison of the digoxin elimination rate constants calculated from serum digoxin concentrations by using RSTRIP program among different treatment groups.

rs:k1d	rs:k1e	rs:k1c
0.0050	0.0060	0.0049
0.0070	0.0041	0.0093
0.0147	0.0015	0.0159
0.0031	0.0025	0.0001
0.0057	0.0041	0.0137
0.0110	0.1275	0.0000
0.0020	0.0054	0.0251
0.0131	0.0035	
0.0005	0.0069	

ANOVA: Single
Factor

SUMMARY

Groups	Count	Sum	Average	Variance
rs:k1d	10	0.0623353	0.006235	2.68331E-05
rs:k1e	9	0.1615642	0.0179515	0.001691059
rs:k1c	7	0.0690241	0.0098605	8.38061E-05

ANOVA

Source of Variation	SS	df	MS	F	P-value	F crit
Between Groups	0.000669356	2	0.0003346	0.539319	0.59034	3.42213
Within Groups	0.014272809	23	0.0006205			
Total	0.014942166	25				

rs:k1d = Digoxin elimination rate constant of the digoxin group estimated from serum digoxin concentrations by using RSTRIP program.(/hr)

rs:k1e = Digoxin elimination rate constant of the enalapril group estimated from serum digoxin concentrations by using RSTRIP program.(/hr)

rs:k1c = Digoxin elimination rate constant of the captopril group estimated from serum digoxin concentrations by using RSTRIP program.(/hr)

Table 15 Comparison of the digoxin distribution rate constants calculated from serum digoxin concentrations by using RSTRIP program among different treatment groups.

rs:k2d	rs:k2e	rs:k2c
0.9402	0.4035	0.5938
0.5246	0.5571	0.2745
1.0182	0.9625	1.0794
0.1226	0.3392	0.7057
0.4846	0.3004	0.3824
0.5475	0.1348	0.5482
0.4559	0.3542	0.0264
0.2539	0.3125	
0.5990	0.2902	
0.6614		

ANOVA: Single Factor

SUMMARY

Groups	Count	Sum	Average	Variance
rs:k2d	10	5.60789	0.560789	0.0743687
rs:k2e	9	3.65434	0.406037	0.0558118
rs:k2c	7	3.610335	0.515762	0.1127314

ANOVA

Source of Variation	SS	df	MS	F	P-value	F crit
Between Groups	0.1175276	2	0.0587638	0.7541381	0.481696	3.422130
Within Groups	1.7922018	23	0.0779218			
Total	1.9097295	25				

rs:k2d = Digoxin distribution rate constant of the digoxin group estimated from serum digoxin concentrations by using RSTRIP program.(/hr)

rs:k2e = Digoxin distribution rate constant of the enalapril group estimated from serum digoxin concentrations by using RSTRIP program.(/hr)

rs:k2c = Digoxin distribution rate constant of the captopril group estimated from serum digoxin concentrations by using RSTRIP program.(/hr)

Table 16 Comparison of the digoxin absorption rate constants calculated from serum digoxin concentrations by using RSTRIP program among different treatment groups.

rs:k3d	rs:k3e	rs:k3c
1.4879	0.5200	0.8656
0.5506	0.6582	2.7316
1.5844	2.2172	2.0599
*	0.4946	4.2535
0.7820	1.7302	0.7809
0.8283	12.5170	1.5740
0.5641	0.7149	0.7717
0.3828	0.9810	
2.5390	0.3049	
1.3655		

ANOVA: Single Factor

SUMMARY

Groups	Count	Sum	Average	Variance
rs:k3d	9	10.0845	1.1205	0.475124
rs:k3e	9	20.1380	2.237563	15.25492
rs:k3c	7	13.0371	1.862455	1.657991

ANOVA

Source of Variation	SS	df	MS	F	P-value	F crit
Between Groups	5.784804	2	2.892402	0.468617	0.631971	3.443361
Within Groups	135.7883	22	6.172198			
Total	141.57318	24				

rs:k3d = Digoxin absorption rate constant of the digoxin group estimated from serum digoxin concentrations by using RSTRIP program.(/hr)

rs:k3e = Digoxin absorption rate constant of the enalapril group estimated from serum digoxin concentrations by using RSTRIP program.(/hr)

rs:k3c = Digoxin absorption rate constant of the captopril group estimated from serum digoxin concentrations by using RSTRIP program.(/hr)

* = The data could not estimated.

Table 17 Comparison of the digoxin elimination rate constants calculated from serum digoxin concentrations by using noncompartmental modeling program among different treatment groups.[1]

k4hrd	k4hre	k4hrc
0.0060	0.0152	0.0014
0.0170	0.0198	0.0242
0.0188	0.0073	0.0176
0.0296	0.0153	0.0033
0.0080	*	0.0296
0.0181	0.0295	0.0218
0.0184	0.0196	*
0.0410	0.0020	0.0211
0.0111	0.0249	
0.0058		

ANOVA: Single Factor

SUMMARY

Groups	Count	Sum	Average	Variance
k4hrd	10	0.1738369	0.01738	0.000122
k4hre	8	0.13374	0.01671	7.973E-05
k4hrc	7	0.119032	0.017004	0.000113

ANOVA

Source of Variation	SS	df	MS	F	P-value	F crit
Between Groups	2.00723E-06	2	1.003E-06	0.009425	0.990622	3.443361
Within Groups	0.002342453	22	0.000106			
Total	0.00234446	24				

k4hrd   = Digoxin elimination rate constant of the digoxin group estimated from serum concentrations by using noncompartmental modeling program.; the first data used to calculate is the concentration at about 4 hours after the last dose.(/hr)

k4hre   = Digoxin elimination rate constant of the enalapril group estimated from serum concentrations by using noncompartmental modeling program.; the first data used to calculate is the concentration at about 4 hours after the last dose.(/hr)

k4hrc   = Digoxin elimination rate constant of the captopril group estimated from serum concentrations by using noncompartmental modeling program.; the first data used to calculate is the concentration at about 4 hours after the last dose.(/hr)

*   = The data could not estimated.

Table 18 Comparison of the digoxin elimination rate constants calculated from serum digoxin concentrations by using noncompartmental modeling program among different treatment groups.[2]

k 6hrd	k 6hre	k 6hrc
0.0095	*	*
0.0106	0.0059	0.0055
0.0166	0.0027	0.0140
0.0145	0.0046	0.0062
0.0022	0.0060	0.0230
0.0120	0.0245	0.0029
0.0048	0.0111	0.0052
0.0281	0.0043	0.0132
*	0.0172	
*		

ANOVA: Single Factor

SUMMARY

Groups	Count	Sum	Average	Variance
k 6hrd	8	0.09823	0.012279	6.34418E-05
k 6hre	8	0.07628	0.009536	5.85012E-05
k 6hrc	7	0.06982	0.009975	5.04181E-05

ANOVA

Source of Variation	SS	df	MS	F	P-value	F crit
Between Groups	3.435E-05	2	1.7175E-05	0.2971176	0.746179	3.492829
Within Groups	0.0011561	20	5.78055E-05			
Total	0.0011904	22				

k6hrd = Digoxin elimination rate constant of the digoxin group estimated from serum concentrations by using noncompartmental modeling program.; the first data used to calculate is the concentration after at least 6 hours since the last dose.(/hr)

k6hre = Digoxin elimination rate constant of the enalapril group estimated from serum concentrations by using noncompartmental modeling program.; the first data used to calculate is the concentration after at least 6 hours since the last dose.(/hr)

k6hrc = Digoxin elimination rate constant of the captopril group estimated from serum concentrations by using noncompartmental modeling program.; the first data used to calculate is the concentration after at least 6 hours since the last dose.(/hr)

* = The data could not estimated.

Table 19 Comparison of the digoxin half-life calculated from serum digoxin concentrations by using RSTRIP program among the different treatment groups.

rs:t1/2 1d	rs:t1/2 1e	rs:t1/2 1c
139.02	115.58	140.57
99.421	168.67	74.878
47.028	463.38	43.526
221.54	278.45	11899
120.8	167.5	50.512
63.235	5.4355	1.49E+17
339.57	128.54	8.1183
52.839	196.41	
1454.4	100.56	
3967.2		

ANOVA: Single Factor

SUMMARY

Groups	Count	Sum	Average	Variance
rs:t1/2 1d	10	6505.053	650.5053	1537730.8
rs:t1/2 1e	9	1624.5255	180.502833	16766.225
rs:t1/2 1c	7	1.49E+17	2.128E+16	3.171 E+33

ANOVA

Source of Variation	SS	df	MS	F	P-value	F crit
Between Groups	2.31769E+33	2	1.158E+33	1.400641	0.266682	3.422130
Within Groups	1.90294E+34	23	8.273 E+32			
Total	2.13471E+34	25				

rs:t1/21d = Digoxin elimination half-life of the digoxin group estimated from serum digoxin concentrations by using RSTRIP program.(hr)

rs:t1/21e = Digoxin elimination half-life of the enalapril group estimated from serum digoxin concentrations by using RSTRIP program.(hr)

rs:t1/21c = Digoxin elimination half-life of the captopril group estimated from serum digoxin concentrations by using RSTRIP program.(hr)

* = The data could not estimated.

Table 20 Comparison of the digoxin half-life calculated from serum digoxin concentrations by using noncompartmental modeling program among the different treatment groups.[1]

t1/2n4hrd	t1/2n4hre	t1/2n4hrc
120.73	44.42	486.28
41.47	35.18	28.4
38.08	94.78	39.83
23.1	44.14	210.89
86.77	*	23.49
38.08	23.26	31.36
37.06	35	*
16.04	345.46	31.95
63.58	26.86	
118.87		

ANOVA: Single Factor

SUMMARY

Groups	Count	Sum	Average	Variance
t1/2n4hrd	10	583.78	58.37	1442.4021
t1/2n4hre	8	649.1	81.137	11900.872
t1/2n4hrc	7	852.2	121.74285	30357.098

ANOVA

Source of Variation	SS	df	MS	F	P-value	F crit
Between Groups	16593.178	2	8296.5893	0.655549	0.52900	3.443361
Within Groups	278430.31	22	12655.923			
Total	295023.49	24				

t1/2n4hrd = Digoxin elimination half-life of the captopril group estimated by using noncompartmental modeling program. The first data used to calculate is the concentration at about 4 hours after the last dose.(hr)

t1/2n4hre = Digoxin elimination half-life of the enalapril group estimated by using noncompartmental modeling program .The first data used to calculate is the concentration at about 4 hours after the last dose.(hr)

t1/2n4hrc = Digoxin elimination half-life of the captopril group estimated by using noncompartmental modeling program. The first data used to calculate is the concentration at about 4 hours after the last dose.(hr)

* = The data could not estimated.

Table 21 Comparison of the digoxin half-life calculated from serum digoxin concentrations by using noncompartmental modeling program among the different treatment groups.[2]

t1/2n6hrd	t1/2n6hre	t1/2n6hrc
73.33	*	*
67.94	120.06	129.75
43.31	258.33	50.58
49.86	151.53	*
321.32	116.13	31.22
58.73	28.875	241.04
146.66	63.58	133.96
25.38	161.6	52.86
*	40.53	

ANOVA: Single Factor

SUMMARY

Groups	Count	Sum	Average	Variance
t1/2n6hrd	8	786.53	98.3162	9410.754
t1/2n6hre	8	940.63	117.57937	5661.4939
t1/2n6hrc	6	639.41	106.56833	6213.3944

ANOVA

Source of Variation	SS	df	MS	F	P-value	F crit
Between Groups	1492.5757	2	746.28788	0.1038235	0.901892	3.521890
Within Groups	136572.71	19	7188.0375			
Total	138065.28	21				

t1/2n6hrd = Digoxin elimination half-life of the digoxin group estimated by using noncompartmental modeling program .The first data used to calculate is the concentration after at least 6 hours since the last dose.(hr)

t1/2n6hre = Digoxin elimination half-life of the enalapril group estimated by using noncompartmental modeling program. The first data used to calculate is the concentration after at least 6 hours since the last dose.(hr)

t1/2n6hrc = Digoxin elimination half-life of the captopril group estimated by using noncompartmental modeling program. The first data used to calculate is the concentration after at least 6 hours since the last dose.(hr)

* = The data could not estimated.

Table 22   Comparison of digoxin volume of distribution estimated from serum digoxin concentrations among the different treatment groups.

Vs d(L)	Vs e(L)	Vs c(L)
439.6	1723.4	470.37
412.5	1806.9	518.31
493.75	6050	228.74
800	116.38	2735.14
1823.26	215.42	2793.33
344.83	290.72	206.71
16125	1460.46	
207.95	292.75	

ANOVA: Single
Factor
SUMMARY

Groups	Count	Sum	Average	Variance
Vs d(L)	8	20646.89	2580.861	30208927
Vs e(L)	8	11956.03	1494.504	3904611
Vs c(L)	6	6952.6	1158.767	1562437

ANOVA

Source of Variation	SS	df	MS	F	P-value	F crit
Between Groups	8091569	2	4045785	0.31171	0.735867	3.52189
Within Groups	2.47E+08	19	12979313			
Total	2.5E+08	21				

Vs d   =   Digoxin volume of distribution of the digoxin group estimated from serum digoxin concentrations at about 8 and 24 hours after the last dose.(L)

Vs e   =   Digoxin volume of distribution of the enalapril group estimated from serum digoxin concentrations at about 8 and 24 hours after the last dose.(L)

Vs c   =   Digoxin volume of distribution of the captopril group estimated from serum digoxin concentrations at about 8 and 24 hours after the last dose.(L)

*   =   The data could not estimated.

3. **Comparison among different methods of elimination rate constant and volume of distribution estimation.**

Table 23 shows the digoxin elimination rate constants estimated from various methods. The rs:k1 is digoxin elimination rate constant calculated from serum digoxin concentrations by using RSTRIP program ; k6hr and k4hr calculated from serum digoxin concentrations obtained after at least 6 hours and after about 4 hours respectively (by using noncompartmental modeling program) ; and Ke cal calculated frombasic data from the patient's chart included age, sex, weight, height, and serum creatinine. An analysis of variance was performed. No significant difference was seen at the 95% level of confidence.

The steady-state volume of distribution of digoxin estimated from various methods are shown in Table 24. Vs was the steady-state volume of distribution of digoxin estimated from serum digoxin concentrations obtained at about 8 and 12 hours after the last dose ; Vd cal calculated from the available data from the patient's chart included age, sex, weight, height and serum creatinine ; and Vx pop calculated from the population's mean value (7.3 L/kg). Significant differences were found among the means of the four different methods at the 95% level of confidence. It was further analyzed by the Least Significant Dufference test as modified for unequal groups to determine which of the groups were difference. The results are presented in Table 25. The mean digoxin volume of distribution estimated from serum digoxin concentrations was significantly different from the other methods.

Table 23 Comparison of the digoxin elimination rate constants estimated from various methods.

k 6hr	k4hr	Ke cal	rs:k1
0.0095	0.0060	0.0104	0.0050
0.0106	0.0170	0.0117	0.0070
0.0166	0.0188	0.0100	0.0147
0.0145	0.0296	0.0105	0.0031
0.0022	0.0080	0.0121	0.0057
0.0120	0.0181	0.0108	0.0110
0.0048	0.0184	0.0104	0.0020
0.0281	0.0410	0.0103	0.0131
*	0.0111	0.0117	0.0005
*	0.0058	0.0114	0.0002
*	0.0152	0.0117	0.0060
0.0059	0.0198	0.0113	0.0041
0.0027	0.0073	0.0129	0.0015
0.0046	0.0153	0.0086	0.0025
0.0060	*	0.0098	0.0041
0.0245	0.0295	0.0097	0.1275
0.0111	0.0196	0.0102	0.0054
0.0043	0.0020	0.0117	0.0035
0.0172	0.0249	0.0122	0.0069
*	0.0014	0.0124	0.0049
0.0055	0.0242	0.0100	0.0093
0.0140	0.0176	0.0126	0.0159
0.0062	0.0033	0.0105	0.0001
0.0230	0.0296	0.0108	0.0137
0.0029	0.0218	0.0127	0.0000
0.0052	*	0.0108	*
0.0132	0.0211	0.0102	0.0251

ANOVA: Single Factor

SUMMARY

Groups	Count	Sum	Average	Variance
k 6hr	23	0.2444	0.01062	5.4E-05
k4hr	25	0.4266	0.01706	9.8E-05
Ke cal	27	0.2972	0.01101	1.2E-06
rs:k1	26	0.2929	0.01127	0.0006

ANOVA

Source of Variation	SS	df	MS	F	P-value	F crit
Between Groups	0.0007	3	0.00023	1.22553	0.30465	2.6984
Within Groups	0.01851	97	0.00019			
Total	0.01921	100				

Table 24 Comparison of the digoxin volume of distribution estimated from various methods.

Vs(L)	V x pop(L)	Vd(L)
439.60	459.90	423.48
412.50	302.95	334.90
493.75	321.20	275.45
800	487.93	449.26
1823.26	401.50	482.64
344.83	386.90	371.50
16125	459.90	415.73
207.95	343.10	307.25
*	309.67	347.51
*	368.65	389.03
*	430.70	461.29
1723.40	423.40	442.64
1806.90	343.10	482.15
6050	342.74	247.14
116.38	316.31	261.62
215.42	342.81	280.37
290.72	383.25	337.39
1460.46	421.87	471.54
292.75	379.60	461.78
*	365.00	457.90
470.37	478.00	411.48
518.31	310.25	411.58
*	501.15	463.24
228.74	421.87	402.81
2735.14	350.40	474.33
2793.33	379.60	365.53
206.71	382.16	348.50

ANOVA:

SUMMARY

Groups	Count	Sum	Average	Variance
Vs(L)	22	39555.52	1797.98	12128501.02
Vx pop(L)	27	10413.888	385.70	3319.00
Vd(L)	27	10578.04	391.78	5356.40

ANOVA

Source of Variation	SS	df	MS	F	P-value	F crit
Between Groups	31044094.54	2	15522047.27	4.444889798	0.0150799	3.1221034
Within Groups	254924081.4	73	3492110.71		6	65
Total	285968176.8	75				

Table 25   Least Significant Difference test for digoxin volume of distribution estimation methods.

Variable	Vs (L)	Vd cal (L)	Vx pop (L)
Mean±SD	1797.98±3482.6	391.78±73.187	385.7±57.611
		x—————————x	

(Any two means not underscored by the same line were significantly different at the 5% level.)

Abbreviation for Table 23-Table 25.

k6hr   =   Digoxin elimination rate constant calculated from serum digoxin concentrations by using noncompartmental modeling program.[The first data used to calculate is the concentration after 6 hours since the last dose.] (/hr)

k4hr   =   Digoxin elimination rate constant calculated from serum digoxin concentrations by using noncompartmental modeling program.[The first data used to calculate is the concentration at about 4 hours after the last dose.] (/hr)

Ke cal   = Digoxin elimination rate constant calculated from the patient's data.(/hr)

rs:k1   = Digoxin elimination rate constant calculated from serum digoxin concentrations by using RSTRIP program.(/hr)

Vs   = Digoxin volume of distribution estimated from the two serum digoxin concentrations at about 8 and 24 hours after the digoxin dose. (L)

Vx pop   =   Digoxin volume of distribution estimated from the mean population value [7.3 L/kg]. (L)

Vd   = Digoxin volume of distribution estimated from the data available from the patient's chart.(L)

*   = The data could not estimated.

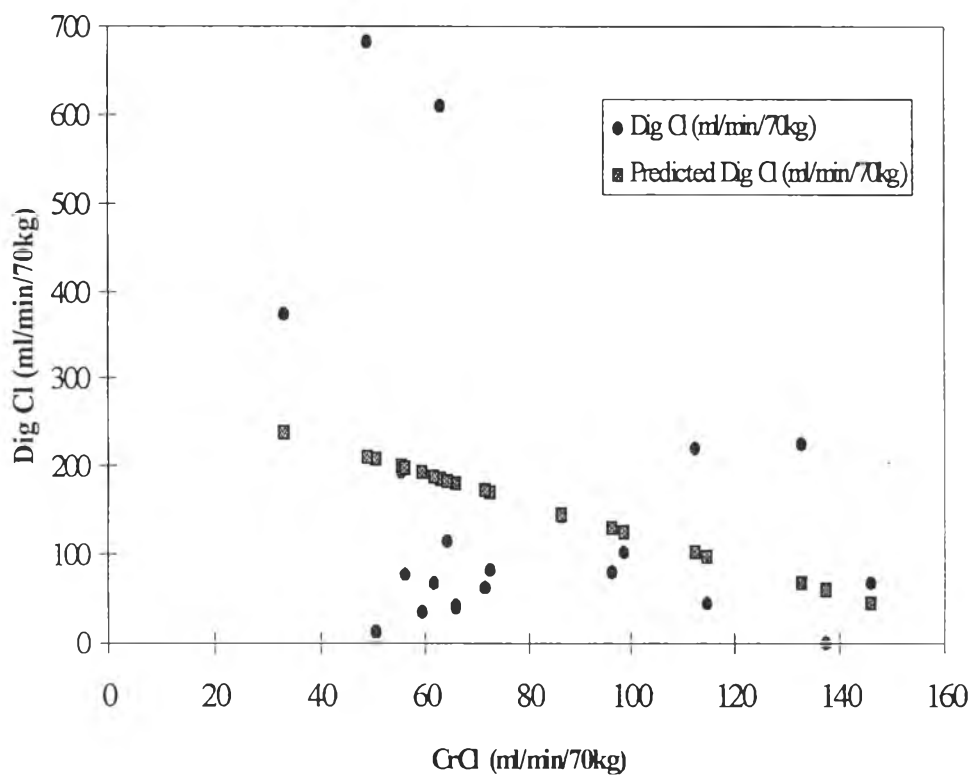## 4. Create an equation for estimating digoxin clearance from creatinine clearance.

Digoxin is excreated by a predominantly renal route. Approximately 60 to 80% of bioavailable digoxin is excreated unchange, by passive glomerular filtration and active tubular secretion. Renal function is usually assessed from the creatinine clearance. Many studies showed that the renal clearance of digoxin and creatinine clearance are in close correlation.(Iisalo, 1977) A relationship between total body clearance of digoxin and creatinine clearance illustrated by Equation :

$$Cl = 1.104 \ CrCl^* + 28.9$$

[When $CrCl^*$ is creatinine clearance ($ml/min/1.73m^2$)]

The relationship between digoxin and creatinine renal clearance in Thai patients were evaluated to considered the reliability of pharmacokinetic methodology for estimating digoxin dosages that are intended to produce a desired range of serum concentrations of the drug.

The digoxin clearances calculated from elimination rate constant obtained from serum digoxin concentrations by using RSTRIP program and digoxin volume of distribution obtained from available serum digoxin concentrations after at about 8 and 12 hours after the digoxin dose, were plotted against the creatinine clearance. The linear equation obtained was identified as the equation generated for Thai patients. The correlation between creatinine clearance and digoxin clearance are presented in Figure8. The correlation coefficient was poor.(Table 26) Further collection of the data in a larger group of patients was required, before any conclusion could be made.

Figure 8 The correlation between creatinine clearance and digoxin clearance.

Table 26   The correlation coefficient of creatinine clearance and digoxin clearance.

CrCl (ml/min./70kg)	Dig Cl.(ml/min./70kg)
65.98	40.59
96.41	80.85
55.55	192.96
65.97	43.69
112.34	221.92
72.47	83.20
63.20	609.55
61.81	67.71
86.52	142.46
145.84	67.09
33.05	374.19
50.53	12.97
49.03	682.61
59.31	34.84
98.44	104.05
114.72	45.27
56.09	77.58
132.87	226.58
71.59	63.37
137.33	0.00
64.52	115.77

	CrCl (ml/min./70kg)	dig Cl.(ml/min./70kg)
CrCl (ml/min./70kg)	1.0000	
dig Cl.(ml/min./70kg)	-0.294987236	1.0000

Dig Cl = 294.67 - 1.7128 CrCl

[CrCl = Creatinine clearance, Dig Cl = Digoxin clearance]

5. Comparison between the measured and the predicted digoxin serum concentrations.

The disposition of digoxin which is influenced by various factors, has a substantial interpatient variation. Trough concentrations determined before the next digoxin dose are shown in Table 27 as the measured values. The means trough digoxin serum concentrations were 1.044 ± 0.437 ng/ml(mean$\pm$ S.D.). Also contained in Table 27-30 are the predicted values calculated from different serum concentration data by using equations in APPENDIX A. C[RSTRIP] is the trough concentration obtained from RSTRIP program.; C[CAL] calculated by using only the data from patient's chart.; C[PRED,a], C[PRED,b], C[PRED,c], C[PRED,d], C[PRED,e], and C[PRED,f] predicted from one pair of concentration-time data at different sampling times.; C[PRED,g], C[PRED,h], C[PRED,i], C[PRED,j] predicted by using two pairs of concentration-time data.; C[PRED,k], C[PRED,l] predicted by using three pairs of concentration-time data.; C[PRED,m], C[PRED,n] predicted by using four pairs of concentration-time data.

Comparison of the data groups was performed to determine the effect of the number of sample and the sampling time on the prediction of digoxin levels. The results are presented in Table 31. The trough concentrations predicted from two serum digoxin concentrations at about 8 and 12 hours after the last dose and from serum digoxin concentrations at about 8 hours after the last dose was not significantly different from the measured value at the 95% level of confidence. The predicted concentrations estimated from two serum concentrations at about 8 and 12 hours after the last dose of digoxin was least different from the measured values.

Table 27   Measured and predicted trough serum digoxin concentrations[1].

No	C[MEAS] (ng/ml)	C[RSTRIP](ng/ml)	C[CAL] (ng/ml)
2	1.41	1.42	1.47
4	1.76	1.65	1.63
5	0.52	0.49	2.37
6	0.54	0.51	1.39
7	0.87	0.77	1.09
9	1.50	1.53	1.60
11	1.05	1.02	1.49
12	0.73	0.59	2.02
14	0.66	0.62	1.58
17	0.89	0.81	1.47
8	0.95	0.75	1.19
10	0.84	0.85	1.29
13	1.33	1.34	1.01
16	1.84	1.75	3.05
19	2.09	1.47	2.56
20	0.99	0.66	2.44
21	1.11	1.11	1.93
22	1.09	1.09	1.16
25	0.95	0.91	1.13
18	0.63	0.51	1.12
23	0.77	0.72	1.58
24	0.79	0.78	1.20
26	0.60	0.57	1.35
27	0.88	0.84	1.48
28	0.68	0.68	1.07
29	0.83	0.66	1.61
30	1.87	1.53	1.87
Mean	1.04	0.95	1.60
SD	0.44	0.39	0.51

C[MEAS]   = Serum digoxin concentrations (ng/ml)

C[RSTRIP]   = Concentrations obtained from RSTRIP program (ng/ml)

C[CAL]   = Concentrations predicted by using foreign equations (ng/ml)

Table 28   Measured and predicted trough serum digoxin concentrations[2].

No	C[MEAS] (ng/ml)	C[PRED,a] (ng/ml)	C[PRED,b] (ng/ml)	C[PRED,c] (ng/ml)	C[PRED,d] (ng/ml)	C[PRED,e] (ng/ml)	C[PRED,f] (ng/ml)
2	1.41	1.34	1.35	1.46	1.47	1.35	1.36
4	1.76	2.33	2.30	1.77	1.74.	1.85	1.82
5	0.52	0.46	0.49	0.46	0.49	0.27	0.30
6	0.54	0.88	0.90	0.50	0.51	0.47	0.48
7	0.87	0.88	0.85	0.77	0.74	0.65	0.62
9	1.50	2.05	2.06	1.61	1.62	1.54	1.55
11	1.05	1.52	1.54	0.94	0.96	0.93	0.95
12	0.73	1.54	1.56	0.91	0.94	0.59	0.61
14	0.66	0.70	0.67	0.42	0.39	0.43	0.40
17	0.89	0.90	0.89	0.60	0.59	0.52	0.51
8	0.95	1.31	1.30	0.72	0.71	0.65	0.63
10	0.84	1.17	1.16	0.73	0.72	0.76	0.75
13	1.33	1.41	1.35	1.23	1.17	1.19	1.13
16	1.84	2.31	2.40	1.70	1.78	1.50	1.58
19	2.09	4.00	4.05	2.44	2.49	2.08	2.13
20	0.99	1.54	1.59	1.14	1.19	0.97	1.02
21	1.11	1.54	1.57	1.06	1.09	1.09	1.12
22	1.09	0.96	0.94	1.00	0.98	0.98	0.96
25	0.95	1.60	1.58	1.20	1.18	1.01	0.99
18	0.63	0.52	0.48	0.41	0.38	0.32	0.28
23	0.77	1.19	1.22	0.64	0.66	0.67	0.69
24	0.79	0.95	0.89	0.79	0.73	0.72	0.67
26	0.60	0.60	0.60	0.49	0.49	0.43	0.43
27	0.88	1.43	1.43	0.90	0.91	0.84	0.85
28	0.68	1.03	0.97	0.56	0.51	0.52	0.47
29	0.83	1.07	1.07	0.71	0.72	0.65	0.66
30	1.87	2.78	2.80	2.15	2.16	1.79	1.81
Mean	1.04	1.41	1.41	1.01	1.01	0.92	0.92
SD	0.44	0.77	0.78	0.54	0.55	0.49	0.50

Table 29   Measured and predicted trough serum digoxin concentrations[3].

No	C[MEAS] (ng/ml)	C[PRED,g] (ng/ml)	C[PRED,h] (ng/ml)	C[PRED,i] (ng/ml)	C[PRED,j] (ng/ml)
2	1.41	*	0.77	*	0.71
4	1.76	0.18	*	0.20	*
5	0.52	*	0.11	*	0.09
6	0.54	0.03	1.23	0.03	1.13
7	0.87	0.35	0.33	0.42	0.39
9	1.50	0.13	2.33	0.12	2.24
11	1.05	0.03	7.95	0.02	7.18
12	0.73	0.04	0.14	0.03	0.13
14	0.66	0.05	*	0.05	*
17	0.89	0.04	0.71	0.05	0.75
8	0.95	0.02	0.57	0.02	0.61
10	0.84	0.07	*	0.07	*
13	1.33	0.34	2.21	0.48	3.11
16	1.84	0.22	0.99	0.16	0.71
19	2.09	0.09	0.72	0.07	0.59
20	0.99	0.20	1.16	0.16	0.95
21	1.11	0.10	*	0.09	*
22	1.09	*	3.39	*	3.79
25	0.95	0.05	0.08	0.06	0.10
18	0.63	0.23	0.17	0.29	0.21
23	0.77	0.04	*	0.03	*
24	0.79	0.30	0.60	0.39	0.79
26	0.60	0.08	0.15	0.08	0.14
27	0.88	0.05	1.08	0.05	1.03
28	0.68	0.03	0.87	0.03	1.18
29	0.83	0.05	0.46	0.05	0.44
30	1.87	0.08	0.39	0.08	0.35
Mean	1.04	0.12	1.20	0.13	1.21
SD	0.44	0.10	1.72	0.13	1.64

Table 30   Measured and predicted trough serum digoxin concentrations[4].

No	C[MEAS] (ng/ml)	C[PRED,k] (ng/ml)	C[PRED,l] (ng/ml)	C[PRED,m] (ng/ml)	C[PRED,n] (ng/ml)
2	1.41	0.42	0.38	0.42	0.38
4	1.76	0.52	0.58	0.53	0.58
5	0.52	0.65	0.55	0.65	0.56
6	0.54	0.40	0.36	0.40	0.37
7	0.87	0.36	0.44	0.36	0.44
9	1.50	0.48	0.46	0.48	0.46
11	1.05	0.42	0.38	0.42	0.38
12	0.73	0.58	0.52	0.59	0.53
14	0.66	0.50	0.56	0.51	0.57
17	0.89	0.45	0.47	0.45	0.48
8	0.95	0.38	0.40	0.38	0.41
10	0.84	0.40	0.42	0.40	0.42
13	1.33	0.36	0.51	0.37	0.51
16	1.84	0.71	0.51	0.72	0.52
19	2.09	0.67	0.56	0.67	0.55
20	0.99	0.64	0.52	0.64	0.53
21	1.11	0.52	0.46	0.53	0.46
22	1.09	0.37	0.42	0.37	0.42
25	0.95	0.19	0.23	0.19	0.23
18	0.63	0.38	0.47	0.38	0.48
23	0.77	0.43	0.37	0.43	0.37
24	0.79	0.43	0.56	0.43	0.56
26	0.60	0.19	0.18	0.19	0.18
27	0.88	0.44	0.42	0.45	0.43
28	0.68	0.37	0.50	0.38	0.51
29	0.83	0.48	0.46	0.48	0.46
30	1.87	0.51	0.46	0.51	0.47
Mean	1.04	0.45	0.45	0.46	0.45
SD	0.44	0.13	0.10	0.13	0.10

Table 31 Comparison between measured and predicted values estimated from different number and sampling times of serum digoxin samples.

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C[MEAS]	C[RSTRIP]	p=0.001665648
C[MEAS]	C[CAL]	p=1.09036E-06
C[MEAS]	C[PRED,a]	p=0.000134174
C[MEAS]	C[PRED,b]	p=0.000203935
C[MEAS]	C[PRED,c]	p=0.299289713
C[MEAS]	C[PRED,d]	p=0.355552008
C[MEAS]	C[PRED,e]	p=9.28912E-06
C[MEAS]	C[PRED,f]	p=1.8269E-05
C[MEAS]	C[PRED,g]	p=6.98851E-10
C[MEAS]	C[PRED,h]	p=0.683821213
C[MEAS]	C[PRED,i]	p=1.62792E-09
C[MEAS]	C[PRED,j]	p=0.650094662
C[MEAS]	C[PRED,k]	p=3.86511E-08
C[MEAS]	C[PRED,l]	p=9.07712E-08
C[MEAS]	C[PRED,m]	p=4.50191E-08
C[MEAS]	C[PRED,n]	p=1.05658E-07

Abbreviation for Table 28 - Table 31

C[PRED,a]   = Predicted concentrations estimated from the serum digoxin concentrations at about 4 hours after the dose, and Vd calculation.

C[PRED,b]   = Predicted concentrations estimated from the serum digoxin concentrations at about 4 hours after the dose, and Vd mean population.

C[PRED,c]   = Predicted concentrations estimated from the serum digoxin concentrations at about 8 hours after the dose, and Vd calculation.

C[PRED,d]   = Predicted concentrations estimated from the serum digoxin concentrations at about 8 hours after the dose, and Vd mean population.

C[PRED,e]   = Predicted concentrations estimated from the serum digoxin concentrations at about 12 hours after the dose, and Vd calculation.

C[PRED,f]   = Predicted concentrations estimated from the serum digoxin concentrations at about 12 hours after the dose, and Vd mean population.

C[PRED,g]   = Predicted concentrations estimated from the serum digoxin concentrations at about 4 and 8 hours after the dose, and Vd calculation.

C[PRED,h]   = Predicted concentrations estimated from the serum digoxin concentrations at about 8 and 12 hours after the dose, and Vd calculation.

C[PRED,i]   = Predicted concentrations estimated from the serum digoxin concentrations at about 4 and 8 hours after the dose, and Vd mean population.

C[PRED,j]   = Predicted concentrations estimated from the serum digoxin concentrations at about 8 and 12 hours after the dose, and Vd mean population.

C[PRED,k]   = Predicted concentrations estimated from k6hr and Vd calculation.

C[PRED,l]   = Predicted concentrations estimated from k6hr and Vd mean.

C[PRED,m]   = Predicted concentrations estimated from k4hr and Vd calculation.

C[PRED,n]   = Predicted concentrations estimated from k4hr and Vd mean.

Vd mean   = Digoxin volume of distribution estimated from the mean population volume of distribution.[7.3 L/kg] (L)

Vd calculation   = Digoxin volume of distribution calculated from the patient's data. (L)

k6hr   = Digoxin elimination rate constant calculated from serum digoxin concentrations by using noncompartmental modeling program.[The first data used to calculate is the concentration after 6 hours since the last dose.] (/hr)

k4hr   = Digoxin elimination rate constant calculated from serum digoxin concentrations by using noncompartmental modeling program.[The first data used to calculate is the concentration at about 4 hours after the last dose.] (/hr)