Clinical Studies on Digoxin Intoxication I

Serum Concentration of Digoxin in the Elderly and the Effect of Diuretics

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SUMMARY

We measured the concentration of digoxin in sera of 136 patients by a radioimmunoassay during maintenance digoxin therapy. The serum digoxin concentration in patients with 0.25 mg of tablet was compared with that with 0.25 mg of powder produced by the same manufacturer to study the effect of digoxin form on serum digoxin concentration. Mean serum digoxin concentration in patients with 0.25 mg of tablet per day was 1.34 ng/ml, while in patients with 0.25 mg of powder per day was 2.11 ng/ml. Mean serum concentration was 1.23 ng/ml in both preparations, if toxic patients were omitted. Mean serum digoxin concentration in 8 patients with a definite digoxin intoxication was 3.16 ng/ml. Mean serum digoxin concentration in patients with 30 mg/100 ml or more of BUN was significantly higher than those with 20 mg/100 ml or less of BUN ($p < 0.001$), but there was no significant difference in serum digoxin concentration between patients with and without high creatinine level. There was a significant negative correlation between the creatinine clearance and serum digoxin concentration. Mean serum digoxin concentration was significantly higher in patients with both digoxin and furosemide than those with digoxin only ($p < 0.01$), and in patients with digoxin, furosemide, and spironolactone than in those with only digoxin ($p < 0.001$). Serum digoxin concentration was elevated with advance of cardiac failure. There was no significant difference between the elderly (60 years or more) and the adult (less than 60 years old) groups in mean serum digoxin concentration. There was no difference between the 2 groups in prevalence of digoxin intoxication.

Additional Indexing Words:

Furosemide Spironolactone Bioavailability Blood urea nitrogen (BUN) Creatinine clearance

THE digoxin intoxication is an important clinical problem because of the narrow margin between therapeutic and toxic dose of digitalis. Fol-

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lowing the introduction of serum concentration measurement,¹⁾ the intoxication rate has been reduced. But the increase of the opportunity to treat the elderly, and the administration of potent drugs such as furosemide and spironolactone with digoxin therapy have increased the unwanted cardiac effects of digitalis. The purpose of the present study was to examine the factors affecting the serum digoxin concentration and these factors were compared between the elderly and the adult patients.

MATERIALS AND METHODS

Patients studied:

One hundred thirty-six serum samples from 86 patients (male 47, female 39, mean age 66.2 years) receiving maintenance digoxin therapy were assayed. Blood samples were drawn about 8 to 24 hours after the last oral dose of digoxin. Forty-three had rheumatic valvular heart disease (male 27, female 16, mean age 60.4 years). The concentration of digoxin was studied in 49 elderly patients (male 28, female 21, mean age 70.7 years, all above 60 years old) and in 37 adult patients (male 19, female 18, mean age 40.7 years). The underlying heart disease was predominantly ischemic (25 patients) in the elderly and valvular in the adult (26 patients).

Furosemide and spironolactone were frequently used in combination with digoxin therapy. Eighty-four were treated with furosemide and 46 were treated with both furosemide and spironolactone in addition to the maintenance digoxin therapy. There was no case with a combination of spironolactone and digoxin. Patients were, therefore, divided into 3 groups; the first was a group with digoxin only (N=43), the second was a group with both furosemide and digoxin (N=28), and the third was a group with furosemide, spironolactone, and digoxin (N=56).

Preparation of bovine serum albumin-digoxin conjugate:

According to the method described by Butler,²⁾ 30 ml of 0.1 M sodium periodate was added to 218.8 mg digoxin suspended in 40 ml of absolute ethanol at room temperature. The reaction mixture was added to 250 mg bovine serum albumin (BSA) in 10 ml H₂O and was placed for 24 hours at room temperature. One ml of formic acid was added to lower the pH to 5.5. The mixture was kept at room temperature and 1.5 ml of 1 M NH₄OH was added to raise the pH to 8.5. The reaction mixture was dialyzed overnight against running tap water. The pH was then lowered to 4.8 by addition of 1.85 ml of HCL. After 4 hours at 4°C, the mixture was centrifuged at 1,000×g. The precipitate was dissolved in 0.15 M NaHCO₃, dialyzed against the running tap water for 5 days and lyophilized. Thus 80 mg of digoxin-BSA conjugates was obtained.

Immunological procedure:

The BSA-digoxin conjugate obtained was resolved in 0.85% of NaCl (2 mg/ml) and equal volume of complete Freund's adjuvant mixture was added. Ten rabbits (2.9–4.2 Kg) were immunized by the injection of 0.1 ml of antigen preparation into toe pads once weekly for 3 weeks and then by intramuscular injection of 0.4 ml of antigen preparation once weekly for 13 weeks. Antisera were obtained from an ear lobe of 10 weeks immunized rabbits and was diluted with veronal buffer

(pH=7.4). Ninety-six to sixty-nine % of diluted antisera were bound to H³-digoxin and excess antibody was eliminated by the contact with dextran coated charcoal. It was evident from the data that efficiency of antibody production was variable in rabbits. A 1:20,000 dilution of antibody in veronal buffer was used for a radioimmunoassay of digoxin.

Digoxin radioimmunoassay

Assay of digoxin in human serum:

Plasma digoxin levels were measured by a radioimmunoassay according to the method described by Smith et al.¹⁾ To duplicate aliquots of 0.5 ml plasma containing an unknown amount of unlabelled digoxin, 1.2 ng of tritiated digoxin was added. A 2.5 ml solution of antibody was then added, which was a quantity to bind 40% of the tritiated digoxin in the absence of unlabelled drugs. The mixture was incubated at room temperature for 15 min. One ml of dextran coated charcoal was then added and centrifuged at 3,000 rpm. The supernatant was mixed with 8 ml of liquid scintillation medium (Bray's solution), heated in an oven at 60°C for 10 min and centrifuged at 3,000 rpm. The supernatant was placed to a counting vial and was counted in Beckman LS-335 liquid scintillation counter.

Preparation of standard curve:

The standard curve for plasma digoxin assay was made as follows: A stock digoxin solution in absolute ethanol was diluted in human digoxin-free plasma. One ml plasma samples each containing 0.1, 0.2, 0.5, 1.0, 2.0, 5.0, and 10 ng digoxin were prepared. A typical standard curve is shown in Fig. 1.

Radioimmunoassay (RIA) and Enzyme immunoassay (EMIT) compared for the determination of digoxin:

Enzyme immunoassay with an advantage that radioisotope is not necessary has been developed by Engvall in 1971.³⁾ A technique of homogeneous enzyme immunoassay was described for the quantitative determination of opiate in biological fluid by Rubenstein⁴⁾ and was applied to the assay of digoxin by Chang et al.⁵⁾ In comparison with RIA and homogeneous enzyme immunoassay of digoxin (EMIT), we found an excellent correlation in 65 patients' sera ($r=0.93$) as shown in Fig. 2. Six supplemental serum samples containing weighed amounts of pure digoxin to make up serum concentrations of 0.8, 1.5, 2.0, 2.5, 3.0, and 4.5 ng/ml were

Fig. 1. A typical standard curve for RIA of digoxin.

Fig. 2. Correlation of serum digoxin concentration between Homogeneous Enzyme Immunoassay (EMIT) and RIA in 65 patients.

Table I. Effect of Incubation Time on RIA of Digoxin with Use of Dextran Coated Charcoal

Incubation time (min.)	Digoxin concentration		
	0.50 ng/ml (B/T %)	1.00 ng/ml (B/T %)	5.00 ng/ml (B/T %)
0	1.70 (22.5)	1.85 (20.9)	7.6 (5.8)
5	0.85 (31.6)	1.50 (24.6)	7.6 (5.8)
10	0.74 (34.0)	1.30 (26.9)	6.4 (6.9)
15	0.64 (35.0)	1.20 (28.1)	5.0 (7.9)
20	0.64 (35.0)	1.20 (28.1)	5.0 (8.5)
30	0.46 (39.3)	1.15 (28.6)	4.2 (10.1)
60	0.53 (37.3)	1.05 (29.9)	3.8 (10.9)
Linear regression	a = -0.01 b = 1.05	a = -0.01 b = 1.53	a = -0.07 b = 7.06
Y = aX + b			
Correlation coefficient	r = 0.6164	r = 0.7348	r = 0.8775

Y=digoxin concentration ; X=periods of incubation (min.).

assayed by the methods of RIA and EMIT respectively. The correlation coefficients were as follow: supplemental digoxin vs, RIA 0.99 and supplemental digoxin vs, EMIT 0.99. We concluded that 2 methods reflected accurate digoxin concentration in the serum. In the therapeutic digoxin level, coefficients of variation were 3.2% in RIA and 6.1% in EMIT respectively.

Problems of RIA for measurement of digoxin:

In the radioimmunoassay of digoxin by the dextran coated charcoal method for the adsorption of unbound digoxin, it was known that the accuracy of the measurement deteriorated with the adsorption time to absorbent.⁶⁾ We examined the changes due to various conditions with polyethylene glycol 600 and the dextran coated charcoal.

Effects of incubation and adsorption times on radioimmunoassay of digoxin:

Supplemental serum samples containing weighed amounts of pure digoxin to make up serum concentrations of 0.5, 1.0, and 5.0 ng/ml were assayed at various incubation times (0, 5, 10, 15, 20, 30, and 60 min). Apparent values for serum digoxin concentration measured by RIA decreased with incubation time but was stable between 15 and 20 min as shown in Table I.

In RIA of digoxin with dextran coated charcoal and polyethylene glycol to separate unbound digoxin, serum digoxin concentration was studied at various adsorption times. Apparent serum concentration increased with the time of adsorption at either low (0.65 ng/ml), optimum (1.0 ng/ml), or toxic concentrations (4.6 ng/ml) linearly. As shown in Table II, the most suitable adsorption time to measure the digoxin concentration with the dextran coated charcoal was between

Table II. Effect of Adsorption Time on RIA of Digoxin with Use of Dextran Coated Charcoal

Adsorption time (min.)	Digoxin concentration		
	0.65 ng/ml (B/T %)	1.00 ng/ml (B/T %)	4.60 ng/ml (B/T %)
0	0.14 (46.0)	0.66 (35.0)	2.6 (17.0)
5	0.55 (37.1)	1.50 (30.0)	2.8 (14.2)
10	0.90 (31.9)	1.38 (26.0)	4.0 (10.6)
20	1.70 (22.2)	1.90 (20.0)	7.0 (6.5)
30	2.2 (17.6)	2.9 (14.0)	7.8 (6.0)
40	2.0 (19.4)	3.6 (13.0)	7.2 (6.4)
60	2.7 (14.6)	4.8 (9.0)	20.0 (2.4)
Linear regression	a=0.04 b=0.48	a=0.07 b=0.67	a=0.26 b=1.27
Y=aX+b			
Correlation coefficient	r=0.9434 p<0.001	r=0.9950 p<0.001	r=0.9165 p<0.005

Y=digoxin concentration ; X=periods of adsorption (min.).

Table III. Effect of Adsorption Time on RIA of Digoxin with Use of Polyethylene Glycol

Adsorption time (min.)	Digoxin concentration		
	0.50 ng/ml (B/T %)	1.00 ng/ml (B/T %)	5.00 ng/ml (B/T %)
0	0.90 (27.5)	0.92 (27.3)	6.40 (6.2)
5	0.61 (33.7)	0.94 (27.0)	5.0 (8.3)
10	0.78 (30.6)	1.25 (23.0)	5.3 (7.8)
20	0.76 (30.9)	1.15 (23.9)	5.0 (8.3)
30	0.82 (29.5)	1.25 (22.9)	5.0 (8.3)
60	0.76 (31.1)	1.10 (24.3)	6.4 (6.2)
Mean±SD	0.77±0.09	1.10±0.13	5.52±0.63

Table IV. Clinical Serum Digoxin Determination by Homogeneous Enzyme Immunoassay (EMIT) and RIA

No.	Name	EMIT (ng/ml)	RIA (ng/ml)	
			Dextran coated charcoal	Polyethylene glycol
1	S. T.	2.0	1.5	1.7
2	K. D.	1.1	0.8	1.2
3	K. O.	0.8	0.9	0.5
4	T. T.	1.5	1.4	1.6
5	H. M.	1.7	1.6	1.9
6	J. K.	1.0	0.8	1.2
7	Y. W.	1.0	0.9	0.8
8	H. W.	1.5	1.2	1.1
9	T. H.	1.2	1.6	1.5
10	K. N.	1.4	1.2	0.9
11	S. T.	2.4	2.4	2.3
12	M. K.	1.6	1.7	1.0
13	T. M.	0	0.4	0
14	I. K.	0.9	0.9	0.9
15	K. Y.	1.7	2.1	1.3
16	R. O.	0.2	0.5	0

EMIT versus RIA (D.C.C.): $Y=0.81X+0.23$ $r=0.8946$ (X: EMIT)

EMIT versus RIA (P.E.G.): $Y=0.94X-0.05$ $r=0.9055$ (X: EMIT)

RIA (D.C.C.) versus RIA (P.E.G.): $Y=0.91X-0.01$ $r=0.8367$ (X: RIA (D.C.C.))

5 min and 10 min. However, the measured value was stable during 60 min of adsorption at low, optimum, and toxic concentrations by RIA with polyethylene glycol as shown in Table III. We have measured digoxin concentration in each of 16 sera by 3 procedures; homogenous enzyme immunoassay, RIA with the dextran coated charcoal, and RIA with polyethylene glycol as shown in Table IV. The correlation between EMIT and RIA with polyethylene glycol was excellent ($r=0.906$). The correlation coefficients were 0.895 between EMIT and RIA with the dextran coated charcoal, 0.837 between RIA with the dextran coated charcoal and polyethylene glycol. From these results we kept in mind the following precaution in performing digoxin RIA with the dextran coated charcoal; more than 15 min of incubation and 10 min of adsorption to the dextran coated charcoal were kept strictly and the number of samples to be assayed at one time was limited to 10. The findings obtained in this study are expressed as the mean for the group $\pm$ standard error of the mean and were analyzed by Student's "t" test.

RESULTS

Effects of drugs on serum digoxin concentration during maintenance digoxin therapy:

Patients receiving 0.125 mg of digoxin daily had mean serum level of 0.97 ± 0.59 ng/ml, those with 0.16 to 0.19 mg of digoxin daily had the level

of 0.93 ± 0.56 ng/ml, with 0.2 mg of digoxin the level was 0.85 ± 0.50 ng/ml, with 0.25 mg of digoxin the level was 1.52 ± 1.02 ng/ml and with 0.30 mg or more it was 1.33 ± 0.75 ng/ml. Mean serum digoxin levels were higher in patients taking 0.25 mg or more digoxin than those taking 0.20 mg or less (Fig. 3).

Occurrence of digoxin intoxication :

The prevalence of digoxin intoxication may be different in hospitals with the degree of concern to digitalis intoxication. In this prospective study, 8 patients showed definite toxic signs. All of their toxic signs disappeared after interruption or reduction of their digoxin doses. Of these 8 toxic patients, three had marked anorexia, nausea and vomiting (mean digoxin concentra-

Fig. 3. Maintenance daily digoxin dose and serum digoxin concentration.

Fig. 4. Influences of digoxin (0.25 mg) tablet and powder in the same manufacturer on serum digoxin concentration. All cases with 0.25 mg tablet (N=34) and with 0.25 mg powder (N=15) are in the left side and in the right side (toxic cases were excluded).

tion 2.87 ng/ml), 2 had P.A.T. with block (4.30 ng/ml), 3 had multiple ventricular ectopic beats (2.86 ng/ml). Mean serum digoxin concentration in 8 toxic patients was 3.16 ± 1.36 ng/ml. Six of 8 toxic patients were prescribed 0.25 mg digoxin as a daily dose.

Effects of different digoxin preparations on serum digoxin concentration:

Mean serum digoxin concentration with 0.25 mg digoxin tablet was 1.34 ± 0.72 ng/ml and that with 0.25 mg digoxin powder was 2.11 ± 1.60 ng/ml. If we omitted toxic patients, mean serum concentrations with tablet and powder were identical (both 1.23 ng/ml) (Fig. 4).

Effects of BUN and serum creatinine on digoxin concentration:

The relationships between serum digoxin concentration, blood urea nitrogen and serum creatinine were determined. Mean serum digoxin concentration in patients with normal serum creatinine (1.1 mg/100 ml or less) was 1.03 ± 0.61 ng/ml and that with high serum creatinine (1.2 mg/100 ml or more) was 1.11 ± 0.68 ng/ml, but in our study no case with renal failure was included. As to the relation between mean serum digoxin concentration and BUN, it was 0.91 ± 0.55 ng/ml in patients with normal BUN (20 mg/100 ml or less), 1.11 ± 0.69 ng/ml in those with borderline BUN (21–30 mg/100 ml) and 2.06 ± 1.57 ng/ml in those with high BUN (more than 30 mg/100 ml). As the blood urea nitrogen increased, serum digoxin concentration were elevated. There was a significant difference between the groups with normal and high BUN in serum digoxin concentration ($p < 0.001$) (Figs. 5, 6).

Fig. 5. Serum creatinine and digoxin concentration.

Fig. 6. Blood urea nitrogen with normal (20 mg/100 ml or less), border-line (20-30 mg/100 ml) and high (30 mg/100 ml or more) and their serum digoxin concentrations.

Fig. 7. Correlation between creatinine clearance and serum digoxin concentration in 8 patients prescribed 0.25 mg digoxin.

Correlation between creatinine clearance and serum digoxin concentration :

There was a negative correlation between creatinine clearance and serum digoxin concentration as shown in Fig. 7 by the measurement of 8 patients receiving 0.25 mg daily dose.

Functional classification of heart disease and serum digoxin concentration :

Mean serum digoxin concentration in patients with heart disease in the functional class I-II (NYHA) who received 0.21 ± 0.57 mg of digoxin daily

was 0.79 ± 0.49 ng/ml. While that in class III who received 0.21 ± 0.58 mg was 1.14 ± 0.60 ng/ml, and that in class IV who received 0.22 ± 0.06 mg was 2.41 ± 1.50 ng/ml. There was a significant difference between NYHA I-II and NYHA III in mean digoxin concentration ($p < 0.005$) and it was found to be significantly higher in NYHA IV than in NYHA III ($p < 0.001$) as shown in Fig. 8. Similar result was obtained in patients who received 0.25 mg digoxin.

Effects of combined digoxin and diuretics on serum digoxin concentration:

Mean serum digoxin concentration was 0.73 ± 0.06 ng/ml in patients with 0.20 ± 0.47 mg/day of digoxin only, 1.11 ± 0.13 ng/ml in a group with

Fig. 8. Functional classification of heart failure (NYHA) and serum digoxin concentration.

Fig. 9. Effects of furosemide, spironolactone on serum digoxin concentration.

furosemide, digoxin (daily digoxin dose 0.22 ± 0.06 mg), and was 1.29 ± 0.10 ng/ml in a group with furosemide, spironolactone, and digoxin (daily digoxin dose 0.21 ± 0.07 mg). There was a significant difference between the group with digoxin only and that with both furosemide and digoxin ($p < 0.01$). Mean serum digoxin concentration in the group with furosemide, spironolactone and digoxin was significantly higher when compared with the group with digoxin only ($p < 0.001$) (Fig. 9).

Serum digoxin concentration in the elderly:

Mean serum digoxin concentration in the elderly group receiving a mean digoxin dose of 0.21 ± 0.04 mg/day was 1.06 ± 0.88 ng/ml, whereas that in the adult prescribed mean digoxin dose of 0.22 ± 0.08 mg/day was 1.12 ± 0.76 ng/ml. Four cases each of definite digoxin intoxication were found in both the elderly and the adult group. One case in the elderly and 2 cases in the adult group showed nausea, appetite loss and vomiting. One in the elderly and another in the adult group exhibited P.A.T. with block, and 2 patients in the elderly and 1 in the adult group had multiple ventricular ectopic beats. Mean serum digoxin concentration in the elderly with digoxin intoxication was 3.76 ± 1.66 ng/ml, whereas that in the adult was 2.56 ± 0.46 ng/ml. As to daily digoxin dose in digoxin intoxication, 3 patients in the elderly receiving 0.25 mg of digoxin per day, fell into digoxin intoxication. Mean digoxin concentration in infants below 1 year of age, receiving 0.05 mg of digoxin per day, was 2.2 ± 1.1 ng/ml and no sign of digoxin toxicity was found as shown in Fig. 10. No significant difference between the elderly and the adult group was found concerning blood urea nitrogen, serum creatinine, and digoxin level. In relation to NYHA classification and serum digoxin, there was no

Fig. 10. Maintenance digoxin dose and serum digoxin concentration in 8 toxic patients (4 cases in the adult and 4 cases in the elderly). Right side indicate the serum digoxin concentration in infant below 1 year old who showed no toxic sign.

Fig. 11. Functional classification of heart failure (NYHA) and serum digoxin concentrations in the adult and in the elderly.

significant difference between the elderly and adult as shown in Fig. 11. Mean serum digoxin concentration in patients with NYHA class I-II in the elderly receiving 0.19 ± 0.04 mg of digoxin per day was 0.76 ± 0.42 ng/ml, although that in the adult receiving 0.22 ± 0.08 mg per day was 0.81 ± 0.58 ng/ml. Mean serum digoxin concentration in the elderly of NYHA III prescribed 0.20 ± 0.04 mg of digoxin per day was 1.05 ± 0.55 ng/ml. On the other hand, in the adult receiving 0.22 ± 0.08 mg per day, mean serum digoxin level was 1.32 ± 0.59 ng/ml. In NYHA IV group, the elderly were prescribed 0.21 ± 0.07 mg of digoxin per day, and the adult were prescribed 0.23 ± 0.04 mg per day, and their mean digoxin levels were 2.37 ± 1.8 ng/ml and 2.46 ± 0.45 ng/ml respectively. There was no significant difference of mean digoxin concentration between the elderly and the adult under any combination of drugs. Mean serum digoxin concentration in the elderly receiving 0.19 ± 0.44 mg of digoxin per day only was 0.56 ± 0.32 ng/ml, that in adult receiving 0.22 ± 0.06 mg was 0.56 ± 0.32 ng/ml. Mean digoxin concentration in the elderly with furosemide and 0.21 ± 0.04 mg of digoxin per day was 1.07 ± 0.76 ng/ml and that in the adult with furosemide and 0.23 ± 0.04 mg digoxin per day was 1.21 ± 0.55 ng/ml. That in the elderly with furosemide, spironolactone and 0.20 ± 0.05 mg of digoxin daily was 1.16 ± 0.58 ng/ml and that in the adult with the combined drugs including 0.20 ± 0.04 mg of digoxin was 1.38 ± 0.80 ng/ml.

DISCUSSION

Incidence of digitalis intoxication has been progressively decreased owing

to the advance in basic pharmacology of cardiac glycosides and to the development of technics to measure serum or plasma cardiac glycoside concentration. Digitalis intoxication, however, still remains an important problem in clinical medicine, especially in use of potent diuretic agents in combination, in therapy of elderly patients with cardiac glycosides and in management of intractable cardiac heart failure. The incidence of digitalis intoxication ranges from 5 to 29% in series of hospitalized patients.⁷⁾⁻¹⁰⁾ In our prospective study, the incidence of digoxin intoxication in patients taking digoxin was 5.9% in agreement with the study of Hillestad et al.¹⁰⁾ All of the toxic patients had a serum digoxin concentration of 2.0 ng/ml or more. It was noteworthy that 6 of 8 toxic patients had been prescribed 0.25 mg of digoxin per day, a dose which is commonly considered to be moderate. Bioavailability is a term to express the amount of drug which enters the body and then available to exert its pharmacological effect. Manninen and Korhonen¹¹⁾ found a wide range of individual tablet content in European brands of digoxin. We compared the influence of digoxin tablet and powder on serum concentration. Digoxin tablet and digoxin powder produced by the same manufacturer were available for use in patients in our hospital. Mean serum digoxin concentration was 1.23 ng/ml both in patients with 0.25 mg tablet and in patients with 0.25 mg of powder. Serum protein binding ability of drugs influences their distribution, metabolism and excretion. In recent years, an attention has been drawn, moreover, to the influence of renal function on the pharmacokinetics of digoxin.^{12),13)} It is thought that the greater the protein binding of a cardiac glycoside, the slower is its excretion. In *in vitro* studies, about 25% of plasma digoxin was protein bound.^{14),15)} Enterohepatic circulation of digoxin was calculated to be about 5% and digoxin was not metabolized in the liver but excreted from the kidney into urine.¹⁶⁾

Thus, the renal function had an important influence on serum digoxin concentration and there was a close relationship between creatinine and digoxin clearances.¹⁷⁾⁻¹⁹⁾ In our study, there was a negative correlation between creatinine clearance and serum digoxin concentration. Furthermore, there was a significant difference in serum digoxin concentration between patients with normal BUN (20 mg or less) and with high BUN (30 mg or more).

There was, however, no significant difference of serum digoxin concentration between patients with normal and high creatinine levels. There are many reports concerning BUN, serum creatinine and serum digoxin concentration with some disagreements of results. Serum digoxin concentration correlated with only BUN,²⁰⁾ with both BUN and serum creatinine,⁷⁾ or logarithm of BUN.²¹⁾ Caution is necessary, however, in judging our result since the highest creatinine level was 3.5 mg/100 ml and there was no uremic

patient. Furosemide and spironolactone have been often prescribed for patients who require digoxin therapy. Since the introduction of these drugs, the treatment of cardiac failure became more easy, but the danger of digitalis intoxication increased due to an abrupt change of hemodynamics. Acute effects of furosemide showed an increase of glomerular filtration rate (GFR)²²⁾ and renal blood flow, especially in the cortex and the urinary excretion of digoxin increased with urine output.²³⁾

However, there are contradictions that an increase in urine flow is not accompanied by a parallel increase in digoxin output.^{24)–26)} There is no report on the chronic effect of these drugs on serum digoxin concentrations. In the maintenance digoxin therapy, mean serum digoxin concentration was significantly higher in patients with furosemide than in patients without furosemide ($p < 0.01$). Mean serum digoxin concentration in patients with furosemide and spironolactone was even higher than in those without diuretics ($p < 0.001$). These data suggest that furosemide and spironolactone cause digoxin retention in chronic therapy and may support the hypothesis by Steiness²⁴⁾ that spironolactone inhibits the tubular secretion of digoxin in the distal segment of renal tubule. The result that mean serum digoxin concentration elevates with advance of cardiac failure is thought to be due to the reduction of creatinine clearance and digoxin clearance with advance of cardiac failure. This observation may be related to the interesting finding of Dobbs et al,²⁷⁾ that creatinine clearance in advanced cardiac failure is lower than predicted. Dose setting of digoxin in advanced cardiac failure requires careful observation to avoid digoxin intoxication. It is generally held that the elderly are more intolerant to cardiac glycosides than the adult and lesser dose of the drug has been prescribed in the elderly than in the adult. In an attempt to elucidate these problems, we compared serum digoxin in the elderly with that in the adult. Contrary to the prediction, no difference was noted between the 2 groups either in serum digoxin level, in prevalence of factors affecting digoxin turnover, or in prevalence of digoxin intoxication. It is certain that the average creatinine clearance decreases with age,^{28), 29)} but the severity of cardiac failure might have much more influence on serum digoxin concentration than age-related decrease in renal function. However, there might be unresolved problems in the digoxin therapy in the elderly. In our study, a 92-year-old patient developed digoxin intoxication with her serum digoxin concentration elevated to 6.6 ng/ml, while receiving 0.25 mg of digoxin. There seems no doubt that an individualized digoxin therapy is desirable.

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