Some Observations on Serum Concentrations of Digitoxin and Digoxin

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SUMMARY

Serum concentrations of digitoxin and digoxin were measured in 145 cases with various heart diseases receiving maintenance doses of digitalis. Digitalis toxicity was seen in only 2 cases (1.4%).

Day-to-day variation of serum concentration while taking the same daily dose was small in digitoxin therapy (13.8%), but a considerable variation was seen in digoxin therapy (24.4%).

Serum concentrations of both digitoxin and digoxin were measured in the patients receiving digitoxin, and there was a positive correlation between the two (r=0.66, p<0.001). This fact suggested that the effect of digitoxin was the sum of the effects of digitoxin and its metabolite, digoxin. In the patients taking digoxin, digitoxin was not detected in the serum.

Serum digitoxin level had a significantly positive correlation to serum albumin level, presumably because digitoxin was retained in serum in the bound form to albumin. Minimal effective level, 10 ng/ml, was however obtained with higher daily dose of digitoxin in patients with lower serum albumin.

Additional Indexing Words:
Digitoxin  Digoxin  Serum concentration  Serum albumin
Day-to-day variation

DIGITALIS is the most important drug for treatment of heart failure, but the difference between therapeutic and toxic doses is rather small, and digitalis intoxication comes into problem clinically not infrequently. Diagnosis of digitalis toxicity is not always easy, because some of the symptoms and signs are not specific for toxicity of the drug, for example, gastrointestinal disturbances may be a symptom of the toxicity or of the gastrointestinal con-
gestion due to heart failure. Arrhythmias such as ventricular extrasystoles may be due to digitalis intoxication or due to heart disease itself.

Recently, a method for measuring serum concentration of digitalis by radioimmunoassay became available for routine clinical use, and has been applied to diagnose intoxication and to study pharmacokinetics of the drug.

In this paper, serum digitoxin and digoxin concentrations in the patients receiving maintenance doses of the drugs were studied in relation to other laboratory findings.

**Materials and Methods**

The subjects studied were 145 cases with various heart diseases who received maintenance doses of digitalis preparations (75 males and 70 females). The age ranged from 16 to 93 (mean 57.3) years. Sixty-one cases had ischemic or hypertensive heart diseases and 84 cases had congenital or valvular heart diseases. Digitoxin was administered in 59 cases and digoxin in 86 cases orally once a day (Table I). Serum concentration of digitalis was measured using GammaCoat I²I digitoxin and digoxin radioimmunoassay kits (Clinical Assays Inc, Cambridge, Mass, USA).

Serum albumin, creatinine, urea nitrogen, electrolytes (sodium, potassium, calcium, magnesium), GOT, GPT, and LDH were measured simultaneously, and ECG and chest X-ray films were taken.

In order to examine the time course of the serum digitalis concentration, blood was obtained before and 1, 2, 4, 6, 8, 12, and 24 hours after the administration of daily dose of the drug in 7 cases treated with oral digitalis maintenance dose. Serum concentrations of the drugs were measured several times on different days for determination of the day-to-day variation of serum concentration in 20 cases, who were

<table>
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<tr>
<th>Table I. Clinical Data of Cases</th>
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<tr>
<td>Male</td>
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<tr>
<td>Female</td>
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<tr>
<td>Digitoxin</td>
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<td>0.05 mg (1/2 Tab.)</td>
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<td>0.075 (1/4 Tab.)</td>
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<td>0.1 (1 Tab.)</td>
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<td>0.15 (1 1/2 Tab.)</td>
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<tr>
<td>Digoxin</td>
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<tr>
<td>0.125 mg (1/2 Tab.)</td>
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<td>0.188 (1 Tab.)</td>
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<td>0.25 (1 Tab.)</td>
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<td>0.375 (1 1/2 Tab.)</td>
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<td>Total</td>
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taking the same maintenance dose.

Furthermore, in 11 cases who were not receiving digitalis, 39 cases with digitoxin and 62 cases with digoxin, serum concentrations of both digitoxin and digoxin were measured simultaneously.

**RESULTS**

Daily variation of serum digitoxin concentration in the patients received maintenance digitoxin therapy was not large. Small temporary elevation of the concentration by 50% was seen 1 to 2 hours after administration of the daily dose, the level decreased slowly thereafter, and there was no other fluctuation. On the other hand, digoxin concentration in patients taking digoxin increased above 200% between 1 to 4 hours after administration, but returned approximately to the level before administration 6 hours later. Therefore, equilibrium serum concentration was required to be measured at least 6 hours after administration of the drugs, as shown by Smith and Haber. Since the majority of the cases in this study were outpatients and blood samples could not be taken in the same time sequence after taking the drug in all patients, the blood samples obtained within 6 hours after taking the drug were excluded from this study.

Serum concentration was measured twice or 3 times on different days in 12 cases with digitoxin and 8 cases with digoxin. The same daily dose of digitalis was maintained and clinical findings were stable during the periods. On average the observed range of variation was 13.8% of the mean level in digitoxin and 24.4% in digoxin respectively (Fig. 1).

Fig. 2 showed the interrelationship between digitoxin and digoxin concentrations. In cases taking digoxin, there was no noticeable rise in serum

![Fig. 1. Day-to-day variation of serum concentrations of digitoxin and digoxin under stable maintenance doses.](image-url)
digitoxin concentration. On the contrary, in cases taking digitoxin, there was a significant positive correlation between the serum concentrations of these 2 substances ($r=0.66$, $p<0.001$).

Serum concentration was shown in Fig. 3 in relation to age and daily dose of the drugs. As for patients who received higher doses of the drugs (digitoxin 0.1 mg, digoxin 0.25 mg) daily, serum concentrations were significantly higher in older patients.

Fig. 4 showed the relationship between serum albumin and digitoxin concentrations and there was a positive correlation between them. If serum albumin concentration was below 4.7 Gm/100 ml, administration of 0.05 mg digitoxin daily was inadequate for some patients, but if albumin concentration was more than 4 Gm/100 ml, 0.075 mg or more digitoxin daily was adequate in almost all patients to obtain serum digitoxin concentration of over 10 ng/ml, which was thought to be the lowest therapeutic level of digitoxin in Japanese.3

Digitalis intoxication was seen in only 2 cases in this series of study (1.4%).

There was no relation between serum digitalis concentration and type of heart disease, serum electrolytes as well as cardiothoracic ratio on X-ray film.

Abnormal SGOT and SGPT levels were seen in only 8 patients and elevated serum creatinine levels in only 3 cases. It was, therefore, unable to
Fig. 3. Age, dose and serum digitalis concentration. Broken lines indicate 5 ng/ml for digitoxin and 0.3 ng/ml for digoxin indicating the minimal sensitive levels for our methods. X denotes the case with digitalis intoxication.

Fig. 4. Serum albumin and digitoxin concentrations in cases with maintenance doses of 0.05 mg (a), 0.075 mg (b), and 0.1 mg (c). Dotted lines indicate 10 ng/ml of digitoxin concentration.

examine the effects of hepatic and renal dysfunctions on the serum digitalis concentration.

**DISCUSSION**

The incidence of digitalis toxicity in conventional digitalis therapy has once been reported 20 to 30%. However since Williams et al showed that
relation between the dose and the action of digitalis on myocardial contractile force was essentially linear, it is now well known that maximally tolerated dose does not need to be administered to achieve therapeutic effect. In addition skillful designs for digitalis administration based on pharmacokinetics were reported. Recently, prevalence of toxicity was expected to decrease, and Storstein et al reported that the incidence was 5.9% in 649 patients. Although majority of our cases were outpatients and some of the minor signs of toxicity could be overlooked, only 2 cases (1.4%) of digitalis intoxication were seen in this series.

Toxicity is, however, still a serious complication of digitalis therapy and its diagnosis is very important. In 1969, the radioimmunoassay for serum digoxin concentration was reported by Smith et al, and since then many studies on digitalis concentration and toxicity were reported. It is generally agreed that serum concentration of digitalis is higher in toxic cases than in non-toxic cases, but there is a significant overlap. Therefore, digitalis intoxication cannot be diagnosed by serum concentration alone. Many factors which affect digitalis tolerance are known. At present, serum concentration of digitalis is of limited value in clinical use for diagnosis of toxicity.

Day-to-day variation was rather small in the case of digitoxin (13.8%) but digoxin showed unnegligible variation (24.4%) in this study. One of the reasons may be due to variation of bioavailability of digoxin.

Major excretory pathway of digoxin is kidney and unmetabolized digoxin is excreted, but digitoxin is metabolized in the liver and changes to many metabolites including digoxin. Some metabolites possess cardioactive properties, and others not. Serum digitoxin and digoxin concentrations measured in the patients receiving digitoxin had a significant positive correlation (r = 0.66, p < 0.001). It should be noted that in the patients with high serum digitoxin concentration, serum digoxin level was also high. Hence, effects of given digitoxin may be sum of the effects of digitoxin and its metabolite, digoxin. It is uncertain whether the radioimmunoassay technique for digitoxin measures digitoxin only or digitoxin and its metabolites. However, Weissler et al showed that the turnover rate of digitoxin was similar when studied by serum concentration and by systolic time intervals. Therefore it can be considered that the measurement of digitoxin concentration is valuable in clinical application.

Because 90 to 95% of digitoxin in blood is bound to albumin, serum albumin and digitoxin had a positive correlation. For the purpose of obtaining serum digitoxin concentration of higher than 10 ng/ml, serum albumin level of higher than 4.7 Gm/100 ml was necessary in cases with daily dose of 0.05 mg digitoxin. In patients with serum ablumin of higher than 4 Gm/
100 ml, 0.075 mg digitoxin daily is adequate to obtain serum concentration of over 10 ng/ml.

REFERENCES