

Digoxin level in digitalis intoxication and after surgery involving cardiopulmonary bypass

Felix Arakaki, M.D.*

Division of Medicine

Manjula S. Kumar, Ph.D.†

Division of Research

Sharad D. Deodhar, M.D.,
Ph.D.

Department of Immunopathology

C. Charles Welch, M.D.

Department of Clinical Cardiology

* *Fellow, Division of Medicine.*

† *Fellow, Division of Research.*

Digitalis toxicity is a relatively common clinical problem and, in the past, the diagnosis of the condition was based primarily on clinical and electrocardiographic findings. Since none of these findings is diagnostic of digitalis toxicity, attempts have been made in recent years to introduce a more direct and objective approach involving the determinations of the serum levels of digitalis preparations by radioimmunoassay for evaluation of this problem. Since digoxin is probably the most widely used digitalis preparation at present, most studies have concentrated on the radioimmunoassay for digoxin, and preliminary reports have already indicated that there is a good correlation between serum digoxin levels and digoxin toxicity. The purpose of our study was to investigate a similar relationship in a group of patients in the Cleveland Clinic Hospital. Another important aspect of this study involved the determination of serum digoxin levels in patients undergoing cardiopulmonary bypass for cardiac surgery. These patients often have cardiac arrhythmias, but the relationship to serum digoxin level is not clear.

Materials and methods

Reagents for the radioimmunoassay were obtained.* This assay involves the competitive binding of labeled digoxigenin derivative (3-0 succinyl digoxigenin tyrosine—¹²⁵I) and serum digoxin to specific antibodies. The incubation period was 1 hour at room temperature. Free and bound labeled antigen were separated by dextran-coated charcoal and both were counted in β/γ liquid scintillation counter.† The mean recovery of added digoxin in the serum was 90%.

Patient groups

Serum specimens were obtained from hospitalized patients: Group 1 included 37 patients with no toxic reactions. Blood samples were drawn between 5 and 7 hours after the last dose of digoxin (0.25 mg) was given orally as a maintenance dose. It is known that digoxin reaches optimum serum levels in this period. Group 2 included 10 patients with toxic reactions to digoxin. Blood samples were drawn as soon as clinical and electrocardiographic evidence of digitalis toxicity occurred. Group 3 included 20 patients in whom serum digoxin levels were measured before and after cardiopulmonary bypass for cardiac surgery. In these patients, the digoxin maintenance doses ranged from 0.125 mg to 0.50 mg daily, given orally for more than 6 months. Digoxin was stopped 1 day before the surgery and three blood samples were drawn from each patient; the first at 2 hours before the bypass, the second at 2 hours after the bypass, and the third at 16 hours after completion of bypass.

* Schwarz-Mann, Orangeburg, New York.

† Picker Nuclear, White Plains, New York.

Results

The 37 patients who had no toxic reactions (Group 1) ranged in age from 30 to 86 years, mean age 59 years. There was no clinical or electrocardiographic evidence of digitalis toxicity, and the hepatic and renal functions in these patients were normal. Results of serum sodium, chloride, potassium, carbon dioxide, calcium, phosphorus, creatinine, and BUN tests were also normal. The mean serum digoxin level in these patients was 0.66 ng/ml $\pm$ 0.44 with the values ranging from 1.9 ng/ml to less than 0.4 ng/ml.

In the 10 patients with toxic reactions to digoxin (Group 2) the ages ranged from 29 to 73 years; mean age 58 years. In these patients there was clinical and electrocardiographic evidence of digitalis toxicity and the blood samples were drawn immediately after the diagnosis was made. The mean digoxin level in these patients was 3.26 ng/ml $\pm$ 1.87, with a range of 1.7 to 8.0 ng/ml. In all of these patients the symptoms abated, and the electrocardiographic abnormalities disappeared after digoxin therapy was discontinued. Comparison of toxic and nontoxic values is shown in the *Figure*.

Of the 20 patients who underwent cardiopulmonary bypass for cardiac surgery (Group 3), 8 had valve replacement; 7 had myocardial revascularization; 3 had a combination of valve replacement and myocardial revascularization; 1 had open mitral commissurotomy; and 1 had exploratory cardiomy. The pulmonary bypass procedure utilized the mini-prime GLF disposable bubble oxygenator with the patient under normal thermic condition. The priming volume was

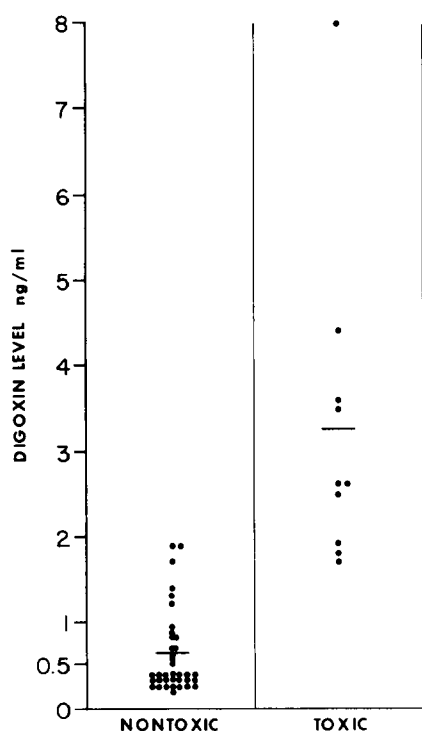


Figure. Serum digoxin concentrations in 47 patients. Mean values, denoted by horizontal lines, are 0.66 ng/ml $\pm$ 0.44 SD for patients with no toxic reaction, and 3.26 $\pm$ 1.87 for the patients with a toxic reaction ($P < .0001$).

calculated with about 20 ml/kg body weight using Travenol 2.5% dextrose in electrolyte solution no. 11* and one unit of blood. During the operation the blood gases, hemoglobin, hematocrit, and electrolytes were monitored at intervals and corrected when necessary. The hemoglobin level was kept at about 9 g/100 ml with more blood or Ringer's solution added when indicated. Hemodilution ranged from 1,100 ml to 5,000 ml, with a mean of 2,365 ml. The pump oxygenator was in operation an average of 56 minutes, with a range of 26 to 86 minutes. The

* Travenol Laboratories, Inc., Deerfield, Illinois.

mean serum digoxin level 2 hours before the cardiopulmonary bypass was 0.66 ng/ml, with a range of 0.4 to 2.1. At 2 hours and 16 hours after the bypass, the mean levels were 0.7 and 0.73 ng/ml, respectively. In 11 of these patients, the digoxin levels remained unchanged, and in 4 patients the levels showed a slight decrease. However, five patients had increased digoxin levels at 2 hours and 16 hours after the bypass procedure. In four of these patients this increase was minimal, but in one patient with rheumatic heart disease who had undergone mitral valve replacement, the digoxin level before bypass was 2.1 ng/ml, and at 2 hours and 16 hours after the bypass it had reached toxic levels of 3.35 and 3.2 ng/ml respectively. Signs of toxic reactions also developed. All the patients received fluids intravenously or blood after the bypass, but no digoxin had been administered at the time of these studies.

Discussion

The serum levels of digoxin in the patients who had no toxic reactions (Group 1) as found in our study (0.66 $\pm$ 0.44 ng/ml, a range of 0.4 to 1.9), agree with the findings reported by others. Smith et al¹ reported a mean value of 1.1 $\pm$ 0.3 ng/ml in patients who had no toxic reactions and were receiving 0.25 mg digoxin daily orally. Oliver et al² found a mean value of 0.53 in patients who were judged clinically to be inadequately digitalized. In our study, 24 of the 37 patients in Group 1 were in this category and the mean level in this group was less than 0.4 ng/ml. Functional status of the kidney is an important consideration in arriving at the proper therapeutic serum level of digoxin. After a single

dose of digoxin, given orally, the serum level usually reaches an optimum between 5 to 7 hours^{3, 4} and, thereafter, the levels gradually decrease because of excretion by the kidneys. Patients with normal renal function excrete about 40% of the orally administered digoxin in the urine in 24 hours, and about 70% to 80% is excreted in 7 days.^{5, 6} In patients with renal failure, only 30% to 40% of the administered dose is excreted in 7 days; the biological half-life has been reported to be as high as 19 days.⁶ In the treatment of toxic reactions to digoxin it is therefore important first to evaluate the renal function. In our study of the 10 patients who had digoxin levels in the toxic range, 2 had impaired renal excretory function.

The mean level of serum digoxin found in our group of patients with toxic reactions (3.26 ± 1.87 ng/ml) agrees with that reported by others.^{1, 2, 7} It should be pointed out, however, that there is a certain overlap between the serum levels in the patients without toxic reactions and the group with toxic reactions. Therefore, the serum levels as determined by the radioimmunoassay should be evaluated in the light of clinical and electrocardiographic findings. However, levels higher than 2 ng/ml strongly suggest toxicity, and the likelihood of toxicity is less with levels below 2 ng/ml.

Results of studies of the digoxin levels in patients undergoing cardiopulmonary bypass showed some interesting data. In most patients, as expected, there was either a slight decrease in the digoxin level after cardiopulmonary bypass or no significant change. However, in 25% of the cases (5 of 20), there was an actual increase

in the digoxin level after cardiopulmonary bypass and in one of these latter cases, the level rose to a toxic range after the bypass procedure. The decrease in digoxin level has been attributed to hemodilution and loss of digoxin through renal excretion during the bypass procedure. The increase or "rebound" in the level of digoxin is more difficult to explain, although this phenomenon has been reported by others.^{8, 9} It has been suggested that this increase in digoxin level may result from release of digoxin from the tissue storage. Thus, the digoxin concentration in the myocardial tissue is 30 times higher than that in the serum,¹⁰ and decreases in the tissue storage up to 28% have been reported after bypass procedure.¹¹ The unchanged level of digoxin during and after bypass may be explained on the basis of an equilibrium between the amount lost and the amount released from the tissues to maintain a constant serum level. From our studies it seems possible that release of tissue-bound digoxin during cardiac surgery may result in abnormal elevations of the serum digoxin level and therefore, the level should be determined before restarting digoxin treatment in the immediate postoperative period. Since it has been found that arrhythmias may occur at lower levels of serum digoxin in the first 24 hours after bypass,⁹ myocardial sensitivity to digoxin may be increased in this situation.

Summary

The serum digoxin levels, as measured by radioimmunoassay, in 37 patients with no toxic reaction receiving 0.25 mg dose orally had a mean value of 0.66 ± 0.44 ng/ml with a range of

1.9 ng/ml to less than 0.4 ng/ml. Ten patients with toxic reactions to digoxin had a mean value of 3.26 ± 1.87 with a range of 1.7 to 8.0 ng/ml. Two of the patients in the latter group had renal failure, indicating the importance of renal function in the metabolism and excretion of digoxin. In 20 patients, serum digoxin levels were studied before and after cardiopulmonary bypass procedures and, in 5 of these, an increase after the bypass procedure was attributed to release from tissue-bound sources. The radioimmunoassay for serum digoxin is a useful laboratory tool in the management of patients receiving digoxin therapy.

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