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Digoxin intoxication: the relationship of clinical presentation to serum digoxin concentration

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Research Article

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Patients with cardiac rhythm disturbances due to digoxin intoxication tended to be older and to have diminished renal function compared with the nontoxic group; body weight, serum potassium concentration, underlying cardiac rhythm, and nature of cardiac disease were not significantly different for the groups as a whole. Despite comparable mean daily digoxin dosages, digoxin intoxicated patients had a mean serum digoxin concentration of 3.7 ±1.0 (SD) ng/ml, while nontoxic patients had a mean level of 1.4 ±0.7 ng/ml ($P < 0.001$), 90% of patients without evidence of toxicity had serum digoxin concentrations of 2.0 ng/ml or less, while 87% of the toxic group had levels above 2.0; the range of overlap between the two groups extended from 1.6 to 3.0 ng/ml. Patients with atrioventricular block as their principal toxic manifestation had a significantly lower mean serum digoxin concentration than those in whom ectopic impulse formation was the chief rhythm disturbance.

Patients with equivocal evidence of […]

Digoxin Intoxication: the Relationship of Clinical Presentation to Serum Digoxin Concentration

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ABSTRACT A radioimmunoassay for serum digoxin concentration has been used to study the interrelationships of circulating levels of the drug and various factors in the clinical setting in 48 hospitalized patients with cardiac rhythm disturbances due to digoxin intoxication. 131 patients on maintenance doses of digoxin without toxicity and 48 patients with equivocal evidence of digoxin excess were also studied and compared with the toxic group.

Patients with cardiac rhythm disturbances due to digoxin intoxication tended to be older and to have diminished renal function compared with the nontoxic group; body weight, serum potassium concentration, underlying cardiac rhythm, and nature of cardiac disease were not significantly different for the groups as a whole. Despite comparable mean daily digoxin dosages, digoxin intoxicated patients had a mean serum digoxin concentration of 3.7 ±1.0 (SD) ng/ml, while nontoxic patients had a mean level of 1.4 ±0.7 ng/ml ($P < 0.001$). 90% of patients without evidence of toxicity had serum digoxin concentrations of 2.0 ng/ml or less, while 87% of the toxic group had levels above 2.0; the range of overlap between the two groups extended from 1.6 to 3.0 ng/ml. Patients with atrioventricular block as their principal toxic manifestation had a significantly lower mean serum digoxin concentration than those in whom ectopic impulse formation was the chief rhythm disturbance.

Patients with equivocal evidence of digoxin excess had received comparable daily maintenance doses of digoxin but had a mean serum concentration of 1.9 ±0.8 ng/ml, intermediate between those of the nontoxic ($P < 0.005$) and toxic ($P < 0.001$) groups. Renal function as judged by mean blood urea nitrogen concentration was also intermediate.

The data indicate that knowledge of the serum digoxin concentration, weighed in the clinical context, is useful in the management of patients receiving this drug.

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INTRODUCTION

Clinical use of digitalis glycosides is complicated by a reported incidence of cardiac toxicity varying from 7 (1) to 20% (2) in hospitalized patients receiving these drugs. Continuing interest in this problem and its management is emphasized by a recent monograph (3) and several reviews (4–8) which discuss the difficulties associated with use of these drugs.

Disturbances of cardiac impulse formation and conduction occurring as manifestations of digitalis intoxication have been extensively documented and catalogued (4, 5, 7, 8). Nevertheless, it has been difficult to obtain data relating the occurrence of rhythm disturbances to quantitative estimates of blood or myocardial digitalis concentration because of the lack of reliable methods for measurement of nanogram amounts of cardiac glycosides. Recent progress in the assay of serum or plasma concentrations of the widely used glycoside digoxin (9) has made possible initial explorations of the relationship between serum or plasma digoxin concentration and the occurrence of cardiac rhythm disturbances in limited numbers of patients (10–13), and a correlation has been demonstrated with acetyl strophanthidin tolerance in experimental animals (14). The present study extends the definition of the interrelationships among digoxin intoxication, pertinent factors in the clinical setting, and serum concentration of the drug as determined by a sensitive and specific radioimmunoassay (11) in a large series of hospitalized patients.

METHODS

Assay technique. Duplicate determinations of serum digoxin concentration were carried out by a previously reported radioimmunoassay method (11). Details of preparation and characterization of the antidigoxin antiserum

TABLE I

Criteria for Absence or Presence of Digoxin Intoxication

Absence of toxicity

Electrocardiographically documented stable sinus rhythm with PR interval 0.20 sec or less, atrial fibrillation with ventricular response between 70 and 100 beats/min, or atrial flutter with degree of atrioventricular block in the 2:1 to 4:1 range.

Presence of digoxin intoxication

One or more of the following disturbances of impulse formation or conduction:

A. Supraventricular tachycardia (atrial or atrioventricular junctional) with atrioventricular block.

B. Frequent or multifocal ventricular premature beats, ventricular bigeminy, or ventricular tachycardia.

C. Atrial fibrillation with high grade atrioventricular block (ventricular response less than 50/min) and ventricular premature beats.

D. Sinus rhythm with second or third degree atrioventricular block.

Disappearance of the rhythm disturbance when digoxin was withheld.*

* Two patients died while continuing to show classical manifestations of digitalis intoxication, and thus represented exceptions to this criterion.

employed (previously designated 46/97)[1] have also been published (15). Tritiated digoxin, added in vitro, competes with unlabeled digoxin in the patient's serum for binding sites of digoxin-specific antibodies raised in rabbits immunized with a digoxin-human serum albumin conjugate. Antibody-bound and free ligand are separated by selective adsorption of the free fraction to dextran-coated charcoal. Sensitivity (0.2 ng/ml), precision (standard deviation for replicate samples, 3-4%), rapidity (1 hr), and specificity of the method are well defined.

In order to expedite calculation of assay results, the previously reported semilogarithmic standard curve (11) plotting per cent of labeled digoxin bound by the antibody vs. log unlabeled digoxin present in the serum sample has been replaced by a plot better suited to computer usage. A Sigma 7 time sharing computer was used to correct raw counts per minute of tritium labeled, antibody-bound digoxin for background and quenching and to plot a standard curve relating reciprocal corrected bound counts to known concentrations of unlabeled digoxin in a series of duplicate standard sera. The computer program then compared data from unknown samples with the standard curve and printed out digoxin concentrations. An additional modification has been the use of a ^{137}Cs external standard for quenching correction of each sample in place of the more time consuming internal standard method previously reported. Agreement between the two methods was 5% or better in each of 90 consecutive samples.

Clinical studies. Adult patients hospitalized on the Medical or Surgical Services of the Massachusetts General Hospital were studied. All were receiving digoxin for the management of congestive heart failure, supraventricular tachyarrhythmias, or a combination of the two indications.

Surveillance over both private and ward services during a period of 6 months yielded a total of 131 patients on maintenance doses of digoxin for 5 or more days in whom there was no evidence of cardiac toxicity as defined in Table I, and in whom serum digoxin concentrations and detailed clinical information were available. None of these were included in a prior series of nontoxic subjects (11). Clinical data on all patients studied were collected within 24 hr of the time blood was drawn for serum digoxin assay and included age, sex, weight, clinical diagnoses, and standard 12-lead electrocardiogram. Blood chemistry determinations including blood urea nitrogen (BUN), sodium, potassium, chloride, and bicarbonate concentrations were carried out by AutoAnalyzer in the routine clinical laboratory. Other information pertinent to individual clinical problems were tabulated. Each patient was interviewed and questioned in detail concerning possible extracardiac manifestations of digitalis intoxication including anorexia, nausea, vomiting, scotomata, blurred vision, and chromatopsia. Diarrhea and neurologic evidence of toxicity other than visual symptoms were sought but not recognized in any of the patients included in this study. Information concerning dosage schedules of digoxin as well as other drugs concurrently received was obtained from nursing records. Blood samples from these patients were obtained between 8 and 12 hr after the last dose of digoxin.

Cardiac diagnoses were reviewed in detail for accuracy; electrocardiograms were independently interpreted by cardiologists who were not directly involved in the study. The diagnosis of chronic pulmonary disease was based on clinical criteria including history of chronic productive cough and physical and radiologic evidence of chronic obstructive pulmonary disease.

Over a period of 15 months (September 1968 through December 1969) complete clinical data were collected and serum digoxin concentrations were measured on 48 patients with evidence of digoxin intoxication by the criteria listed in Table I; 18 of these were included in a prior report (11). Methods of data collection were identical with those described for patients without evidence of toxicity. Serial visits and electrocardiograms were used to follow the progress of these patients. Blood for serum digoxin assay was

TABLE II

Criteria for Questionable Digoxin Excess

Presence of one or more of the following disturbances of impulse formation or conduction:

A. Occasional ventricular premature beats (less than 5/min).

B. First degree atrioventricular block in the absence of other drugs capable of impairing conduction and in the absence of a prior history of this finding when off digoxin.

C. Atrial fibrillation with occasional atrioventricular junctional escape beats.

D. Marked sinus bradycardia (less than 50 beats/min) without a prior history of this finding off digoxin.

E. Atrial fibrillation with a relatively slow ventricular response (50–65 beats/min).

[1] This antiserum was the generous gift of Dr. Vincent P. Butler, Jr.

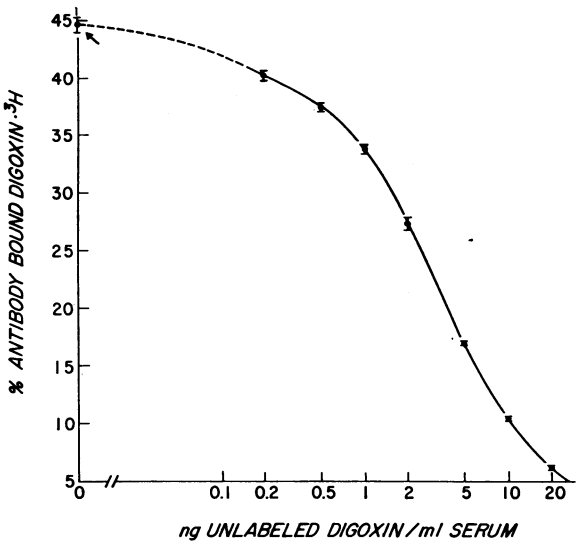

FIGURE 1 Semilogarithmic plot of standard curve. The percentage of a 3 ng tracer quantity of tritiated digoxin bound by digoxin-specific antibody is shown as a function of log concentration of unlabeled digoxin in a series of standard sera. The arrow on the vertical axis denotes binding of tritiated digoxin in the absence of unlabeled drug. Ranges of duplicate determinations are encompassed by horizontal lines.

drawn between 8 and 24 hr after the last dose, somewhat later on the average than was the case for the nontoxic group.

An additional group of 48 patients was defined by the criteria listed in Table II in an attempt to gain further insight into the difficult group of patients in whom, even in retrospect, digitalis intoxication can neither be ruled in nor out with certainty. Clinical data collection and serum sampling for digoxin assay were carried out as described for the toxic group.

Statistical analysis. Significance of differences between observed means or proportions of patients in a given category were carried out by the use of Student's *t* test or Chi square analysis, respectively (16), with the aid of a Sigma 7 time sharing computer.

RESULTS

Standard curve. Fig. 1 shows a standard curve plotted by the method previously reported, relating per cent of the tracer quantity of tritiated digoxin bound by the antibody to the log of concentration of unlabeled digoxin in samples of normal serum to which gravimetrically determined amounts of digoxin have been added. The same data are plotted in Fig. 2 as reciprocal cpm of antibody bound tritiated digoxin (corrected for background and quenching) vs. concentration of unlabeled digoxin in the standard serum samples. The rectilinear relationship obtained over the concentration range studied is a consequence of relative restriction of heterogeneity of antibody binding site affinities expressed at the high final dilution (1:40,000) of antiserum used in the assay system (15). This type of plot lends itself well to computer usage, and the equations and correlation coefficients of the lines obtained by least squares linear regression analysis are useful in day to day monitoring of the over-all precision of the method. 49 consecutive standard curves plotted in this way have shown a mean correlation coefficient of 0.995 (SD 0.011). It should be noted that although the values at low concentrations of unlabeled digoxin fall close together on the reciprocal plot, these actually represent large absolute differences in cpm bound and are quite precisely determined, as indicated by the ranges of duplicate values shown.

Clinical observations. Data relating to the 131 patients without evidence of digoxin intoxication and for the 48 patients meeting the stated criteria for toxicity are summarized in Table III. Mean age and mean BUN level of digoxin toxic patients were significantly greater than the corresponding means for nontoxic patients, while mean body weight and serum potassium concentration were not significantly different. Incidence of uremia, defined as BUN greater than 50 mg/100 ml was also greater in the toxic group. Visual and gastrointestinal symptoms attributable to digoxin intoxication were over 10 times more common in patients with evidence of cardiac toxicity. Comparable over-all incidences of the various types of cardiac disease and underlying cardiac rhythms were found for the two groups, and the difference in incidence of chronic pulmonary disease was without statistical significance.

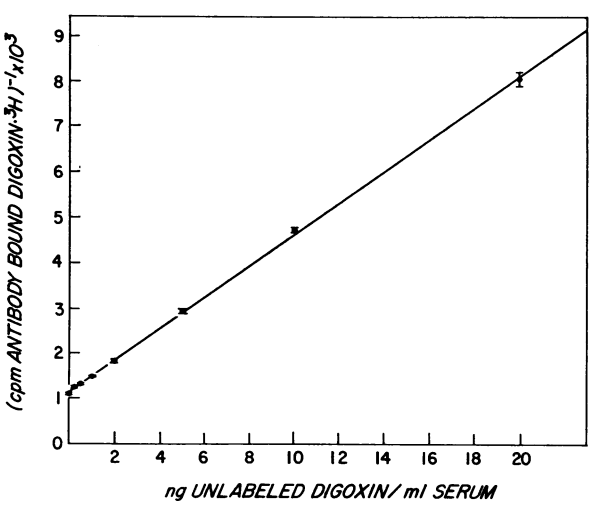

FIGURE 2 Reciprocal plot of standard curve. The same data shown in Fig. 1 are plotted here as reciprocal cpm antibody bound tritiated digoxin (corrected for background and quenching) vs. concentration of unlabeled digoxin in the standard sera. The equation of the line obtained by least squares linear regression analysis is $Y = 1.16 \times 10^{-3} + 3.49 \times 10^{-4}X$, and the correlation coefficient is 0.9994. Ranges are depicted as in Fig. 1.

TABLE III

Clinical Data for Nontoxic and Toxic Patients

	Nontoxic patients	Toxic patients	P*
n	131	48	
Age, *yr*‡	59 ±17 (20–92)	66 ±12 (46–96)	<0.005
Weight, *lb.*‡	146 ±62 (90–610)	155 ±29 (110–250)	NS
BUN, *mg/100 ml*‡	29 ±31 (9–144)	48 ±43 (8–246)	<0.005
Serum K^+, *mEq/liter*‡	4.2 ±0.5 (2.9–7.1)	4.4 ±0.8 (3.0–7.3)	NS
Male sex (%)	60	75	NS
Cardiac diagnosis (%)			
Coronary artery disease	68	74	NS
Valvular heart disease§	27	22	NS
Hypertensive heart disease	2	2	
Cor pulmonale	3	2	
Underlying cardiac rhythm (%)			
Sinus rhythm	60	58	NS
Atrial fibrillation	30	35	NS
Atrial flutter	2	0	
Varying between sinus rhythm and atrial fibrillation	8	7	
Chronic pulmonary disease (%)	20	26	NS
Uremia (BUN > 50 mg/100 ml) (%)	5	31	<0.01
Extracardiac symptoms of toxicity (%)	3	38	<0.01

* *t* or Chi square test; NS denotes $P > 0.05$.

‡ Expressed as mean ±SD (range).

§ Classification includes rheumatic valvular disease and calcific aortic stenosis.

Duration of manifestations of digoxin intoxication following withdrawal of the drug ranged from less than 24 hr to 7 days, the latter interval occurring in a patient with severe renal impairment due to acute tubular necrosis. The average was 2 days. In addition to withdrawal of digoxin, management of the episode of intoxication included short term administration of suppressant drugs in a total of 65%. 15 of the 48 patients received diphenylhydantoin, 11 lidocaine, 10 procaine amide, 5 quinidine, and 2 propranolol for suppression of ectopic impulse formation. Intravenous or oral potassium supplements were used in all instances of hypokalemia associated with dysrhythmia categories A and B (Table I) and in about one-half of such patients with normal serum potassium levels. Two of the patients with high grade atrioventricular block as the toxic manifestation required temporary ventricular pacing via a pervenous catheter electrode.

TABLE IV

Digoxin Dosages and Serum Concentrations: Nontoxic and Toxic Patients

	Nontoxic	Toxic	P*
n	131	48	
Digoxin dosage, mg/day			
Mean ±SD	0.31 ±0.19	0.36 ±0.19	NS
Range	0.0625–1.0	0.125–1.0	
Serum digoxin concentration, ng/ml			
Mean ±SD	1.4 ±0.7	3.7 ±1.0	<0.001
Range	0.3–3.0	1.6–13.7	

* *t* test; NS denotes $P > 0.05$.

Two patients died while continuing to show the following manifestations of digoxin intoxication: one with simultaneous atrial and atrioventricular junctional tachycardias and complete atrioventricular dissociation (serum digoxin concentration 8.7 ng/ml), the other with atrial fibrillation and an accelerated atrioventricular junctional pacemaker with intermittent 2:1 exit block and ventricular premature beats (serum digoxin concentration 4.9 ng/ml).

Serum digoxin concentrations. As summarized in Table IV, a highly significant difference in mean serum digoxin concentration is observed between the nontoxic and toxic groups of patients taken as a whole. The mean daily dosage of the toxic group was not statistically different from that of the nontoxic group.

These groups were further subdivided according to dosage level as shown in Fig. 3. 87% of the patients without evidence of toxicity could be placed in dosage categories of 0.25, 0.50, or 0.75 and above mg/day, while 90% of the toxic patients could be similarly grouped. Significantly higher mean serum digoxin concentrations in toxic patients are evident in the 0.25 and 0.50 mg/day

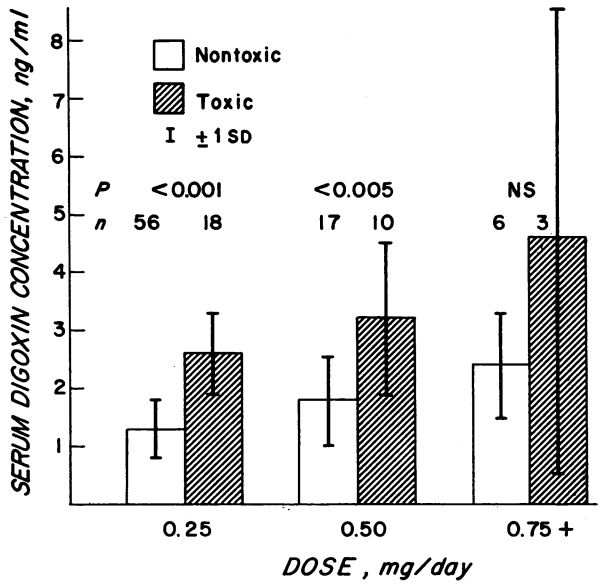

FIGURE 3 Serum digoxin concentrations in nontoxic and toxic patients. Results are subdivided according to daily maintenance digoxin dosages.

TABLE V

Serum Digoxin Concentrations in Patients with Toxicity

Dysrhythmia category*	n	Serum digoxin concentration‡
		ng/ml
A. Supraventricular tachycardia with block	18	4.1 ±1.9 (2.0–8.7)
B. Ventricular dysrhythmias	21	3.7 ±2.7 (1.6–14.0)
C. Atrial fibrillation with ventricular response <50 and ventricular premature beats	5	2.2 ±0.5 (1.6–3.0)
D. Sinus rhythm with second or third degree atrioventricular block	4	3.2 ±1.2 (2.0–4.6)

$P < 0.025$

* Classifications corresponding to Table I.
‡ Mean ±SD (range).

dose categories, while the difference in means for the 0.75 mg/day and above category fails to achieve statistical significance. Also of interest is the stepwise progression to higher mean serum digoxin levels with each increment in dosage in patients both with and without evidence of intoxication.

The mean BUN level of nontoxic patients receiving 0.25 mg digoxin per day was 24 ±18 (SD) mg/100 ml and was significantly lower ($P < 0.01$) than the value of 56 ±56 for toxic patients at the same dose level. No significant mean BUN difference was observed in the 0.50 mg/day category (nontoxic patients 31 ±32, toxic 27 ±12). A rather marked difference (mean BUN for nontoxic patients 16 ±14, toxic patients 40 ±20) in the smaller 0.75 mg/day and above category escapes statistical significance.

Subdividing the patients with evidence of digoxin intoxication according to the categories listed in Table I, the serum digoxin concentration data shown in Table V were obtained. If one combines categories A and B as primarily disturbances of impulse formation and categories C and D as disturbances of conduction, a significantly higher mean serum digoxin concentration ($P < 0.025$) is observed in the A and B classification compared with the C and D. The small difference between categories A and B is not significant, nor is that between C and D.

In order to better define the degree of overlap of serum digoxin concentrations in nontoxic and toxic patients, a frequency histogram is shown in Fig. 4, plotting the proportion of patients in each category with serum digoxin levels in the ranges shown. Although the total area of overlap extends from serum concentrations of 1.6–3.0 ng/ml, 90% of the patients with no evidence of digoxin intoxication had levels of 2.0 or below, while 87% of the toxic group had concentrations above 2.0.

In order to further define the area of overlapping serum digoxin concentrations, clinical characteristics of

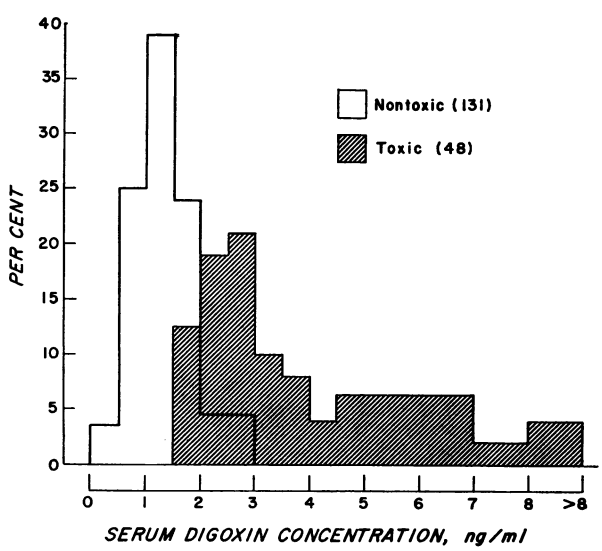

FIGURE 4 Frequency histogram: serum digoxin concentrations in all nontoxic and toxic patients studied. Proportions of each group with levels in a given range are shown. 90% of patients with no evidence of digoxin intoxication had levels of 2.0 ng/ml or below, while 87% of the toxic group had concentrations above 2.0.

TABLE VI

Comparison of Patients with Intermediate Serum Digoxin Concentrations

	Nontoxic; serum digoxin > 2.0 ng/ml	Toxic; serum digoxin ≤ 2.0 ng/ml
n	10	6
Age, *yr**	62 ±17 (24–77)	71 ±5 (65–81)
Serum K^+, *mEq/liter**	4.2 ±0.5 (3.5–4.9)	4.1 ±0.7 (3.0–5.2)
BUN, *mg/100 ml**	29 ±12 (13–54)	25 ±13 (10–43)
Digoxin dosage, *mg/day**	0.43 ±0.18 (0.25–0.75)	0.31 ±0.10 (0.25–0.50)
Cardiac diagnosis‡		
Coronary artery disease	4	6
Acute myocardial infarction	0	2 definite 1 probable
Valvular heart disease§	3	0
Cor pulmonale	1	0
No documented cardiac disease (carcinoma with pleural effusion)	2	0
Underlying cardiac rhythm		
Sinus rhythm	4	4
Atrial fibrillation	4	
Atrial flutter	1	
Varying between sinus rhythm and atrial fibrillation	1	2

* Expressed as mean ±SD (range).

‡ Numbers denote numbers of patients in given category.

§ Includes rheumatic valcular disease and calcific aortic stenosis.

the 10 nontoxic patients with levels above 2.0 ng/ml and of the six toxic patients with levels of 2.0 and below are compared in Table VI. Although the numbers are too small for useful statistical correlation, the ages of toxic patients with relatively low serum digoxin levels tended to be more advanced, while their blood urea nitrogen and serum potassium concentrations were similar. Rhythm disturbances in the toxic subgroup were ventricular bigeminy in three (progressing to ventricular tachycardia in one), multifocal ventricular premature beats in two, and atrial fibrillation with a ventricular response between 30 and 40 and occasional ventricular premature beats in the sixth patient. Of particular interest is the fact that all toxic patients with levels of 2.0 or below had coronary artery disease. In the three patients with definite or probable acute myocardial infarction the rhythm disturbances encountered might have occurred without cardiac glycosides having been administered. However, since they met the formal criteria (dysrhythmias disappearing concurrently with withholding of digoxin), they have been included in this category. Also of possible significance was the observation that 4 of the 10 nontoxic patients with serum digoxin levels above 2.0 ng/ml were receiving antiarrhythmic drugs including quinidine in one, propranalol in another, and both quinidine and propranalol in the remaining two.

Intermediate group: patients with possible digoxin excess. Clinical data and serum digoxin concentrations for the 48 patients meeting the criteria listed in Table II are summarized in Table VII. As a group they were comparable in age with toxic patients and older than the nontoxic group. Body weight was less, consistent with the lower proportion of male patients. Mean blood urea nitrogen concentration fell in an intermediate position, higher than that of nontoxic patients but lower than the toxic group, with the differences significant ($P < 0.05$) in both instances. Also significant at the 0.05 level was a somewhat lower over-all incidence of coronary artery disease. The proportion of uremic patients fell between those in the nontoxic and toxic groups but was significantly different only from the nontoxic group. Also intermediate was the incidence of extracardiac manifestations of toxicity; the difference was significant in comparison with frankly toxic patients. Mean serum potassium concentration, underlying cardiac rhythm, and incidence of chronic pulmonary disease were comparable with those of patients in the other two categories.

Although mean daily digoxin dosage did not differ significantly from values for either nontoxic or toxic patients, mean serum digoxin concentration fell in an intermediate position which was higher than that of nontoxic patients ($P < 0.005$) but substantially lower ($P < 0.001$) in comparison with the toxic group. Not unexpectedly, the range of values encountered in this intermediate group was quite broad, extending from 0.8 to 4.4 ng/ml. Serum digoxin concentration data corresponding to each dysrhythmia category listed in Table II are summarized in Table VIII. The mean concen-

TABLE VII

Clinical Data for Patients with Questionable Digoxin Excess

			Comparison with nontoxic group (*P**)	Comparison with toxic group (*P**)
No.	48			
Age, *yr*‡	67	±12 (42–83)	<0.001	NS
Weight, *lb.*‡	130	±26 (84–184)	<0.01	<0.001
BUN, *mg/100 ml*‡	36	±22 (10–108)	<0.05	<0.05
Serum K^+, *mEq/liter*‡	4.3	±0.9 (2.6–7.1)	NS	NS
Digoxin dosage, *mg/day*‡	0.30	±0.18 (0.125–1.0)	NS	NS
Serum digoxin concentration, ng/ml‡	1.9	±0.8 (0.8–4.4)	<0.005	<0.001
Male sex (%)	46		NS	NS
Cardiac diagnosis (%)				
Coronary artery disease	50		<0.05	<0.05
Valvular heart disease§	33		NS	NS
Hypertensive heart disease	2			
Cor pulmonale	4			
Cardiomyopathy	4			
Other	6			
Underlying cardiac rhythm (%)				
Sinus rhythm	59		NS	NS
Atrial fibrillation	30		NS	NS
Atrial flutter	2			
Varying between sinus rhythm and atrial fibrillation	7			
Ventricular pacing	2			
Chronic pulmonary disease (%)	19		NS	NS
Uremia (BUN > 50 mg/100 ml) (%)	21		<0.01	NS
Extracardiac symptoms of toxicity (%)	10		NS	<0.01

* *t* or Chi square test; NS denotes $P > 0.05$.

‡ Expressed as mean ±SD (range).

§ Classification includes rheumatic valvular disease and calcific aortic stenosis.

TABLE VIII

Serum Digoxin Concentrations in Patients with Questionable Toxicity

Dysrhythmia category*	No.	Serum digoxin concentration	Comparison with nontoxic group	Comparison with toxic group
		ng/ml§	*P*‡	*P*‡
A. Occasional ventricular permature beats	29	1.9 ±0.6 (0.8–3.6)	<0.001	<0.001
B. First degree atrioventricular block	12	2.0 ±1.1 (0.8–4.4)	<0.001	<0.05
C. Atrial fibrillation with atrioventricular junctional escape beats	8	1.7 ±0.7 (0.9–3.0)	<0.001	NS
D. Sinus bradycardia	6	2.0 ±0.8 (1.0–3.2)	<0.001	<0.05
E. Atrial fibrillation with ventricular response 50–65 beats/min	2	(1.0–2.2)	—	—

* Classifications corresponding to Table II.

‡ *t* test; NS denotes $P > 0.05$.

§ Mean ±SD (range).

trations noted within each dysrhythmia category are quite similar and differ significantly from both nontoxic and toxic groups in most instances.

DISCUSSION

Successful application of the radioimmunoassay approach to measurement of serum digitoxin concentration by Oliver, Parker, Brasfield, and Parker (17) and the development of reliable methods for obtaining digoxin-specific antibodies by Butler and Chen (18) have led to a clinically applicable radioimmunoassay for serum digoxin concentration (11). The ability to accurately quantify serum or plasma concentrations of unlabeled digoxin as low as 0.2 ng/ml now enables one to extend observations initially made on volunteers with subtoxic doses of tritium-labeled digoxin (19) to the entire spectrum of patients under treatment with the drug. Three studies of relatively small numbers of patients, two by the red blood cell rubidium-86 uptake inhibition method (12, 13) and one by radioimmunoassay (11), have noted higher serum or plasma digoxin concentrations in patients with evidence of digoxin toxicity compared with nontoxic subjects.. Detailed clinical characterization of patients included in these reports is not available. The relative merits of the two assay systems and the differences in digoxin concentrations reported have recently been discussed (9) and will not be considered further here.

In the design of the present study, particular attention has been directed to two major areas: the description of a number of pertinent clinical characteristics of the patients under study, evaluated at the time of serum digoxin assay rather than retrospectively, and the analysis of serum digoxin concentrations in a sufficiently large series of patients that some impression of the predictive and diagnostic value of the assay can be formed. As a corrollary to the latter objective, data have been included in an attempt to characterize the clinically difficult group of patients in whom equivocal signs of digoxin excess exist, and to explore the intermediate range of serum digoxin concentrations where cardiac manifestations of toxicity may or may not exist depending on the multiple factors which affect individual sensitivity to the drug (20).

Although the criteria used to define toxicity, which lie at the crux of a study of this sort, include data available only after one has had the opportunity to observe the response to withdrawal of the drug, we have been impressed by the rarity with which dysrhythmias A and B in Table I fail to resolve following withdrawal of the drug. Only two patients, both in category B, failed to respond within 1 wk of discontinuance of digoxin and continued to have runs of ventricular bigeminy when dysrhythmia suppressants were temporarily discontinued. In categories C and D lack of response to withdrawal of digoxin was noted in one patient in each of the two groups, with consequent exclusion from the series. It must be recognized, however, that the selection of patients was not truly random, and the exclusion of nonhospitalized subjects forces the analysis of a considerably older, sicker, and more complicated population compared with the full spectrum of patients under treatment with the drug.

Comparing data obtained from patients classified as clearly toxic or nontoxic, significant differences were found in age, renal function, and noncardiac symptoms of toxicity in addition to the highly significant difference in mean serum digoxin concentration. The age difference observed, although not large, confirms the clinical impression (21) that older patients are more likely to become intoxicated on a given dose of the drug, a finding at least in part explained by the tendency to progressive diminution in renal function with age (22). Since digoxin is predominantly excreted unchanged by the kidney (19), it is not surprising that a significantly higher mean BUN as well as incidence of uremia was observed in the toxic group, both taken as a whole, and in the large subgroup receiving a maintenance dose of 0.25 mg/day. The lack of difference between mean blood urea nitrogen values of nontoxic and toxic patients at the 0.50 mg/day dose level despite a marked difference in serum digoxin concentration (see Fig. 3) illustrates the fact that the correlation between blood urea nitrogen and serum digoxin concentration at a given dose level is not as predictable as one might wish. Several factors probably contribute to this discrepancy, including the inadequacy of blood urea nitrogen concentration as a measure of glomerular filtration rate (23), variation in absorption of orally administered digoxin (24), and variation in nonrenal excretion.

The 38% incidence of extracardiac manifestations of digoxin toxicity among patients with digoxin induced rhythm disturbances, although more than 10-fold higher than the incidence in patients without cardiac toxicity, is still somewhat lower than that reported in most series of patients with digitalis intoxication (4). This may be related in part to the limitation of this study to patients receiving a crystalline glycoside which is thought by a number of authors (3, 4) to lower the incidence of extracardiac toxicity relative to rhythm disturbances below that encountered with digitalis leaf. Probably more important are our criteria for digoxin intoxication, which exclude patients exhibiting gastrointestional, visual, or neurologic symptoms but lacking cardiac dysrhythmias.

The absence of a significant difference in mean serum potassium concentration of nontoxic and toxic patients does not gainsay the importance of this factor as a de-

terminant of sensitivity to cardiac glycosides but rather seems to reflect the fact that all patients in the study were under close surveillance, with potassium supplementation in all who were hypokalemic at the time of admission or who were receiving potassium wasting diuretics.

The distribution of the types of rhythm disturbances reported here is in general agreement with the large series of patients with digitalis toxicity compiled by Chung (3), Fisch and Stone (6), and Fisch and Knoebel (8). The difference in mean serum digoxin concentration noted between the 39 toxic patients with ectopic impulse formation and the nine whose primary manifestation of toxicity was depression of conduction (Table V) is probably related to the nature of the patient population reported here rather than a general characteristic of digoxin action. A substantial proportion of patients with conduction disturbances probably had some degree of latent organic disease of the atrioventricular conducting system to which was added the vagal and direct effects of digoxin. If digitalis glycosides in fact tended to produce conduction disturbances at lower concentrations than those resulting in ectopic impulse formation, many of the patients in categories A and B would presumably have developed clinically apparent atrioventricular block before serum and myocardial digoxin concentrations reached levels causing active dysrhythmias. Furthermore, it has been our experience as well as that of others (25) that patients with normal hearts, who ingest very large amounts of digitalis by accident or with suicidal intent tend to develop atrioventricular conduction disturbances more commonly than acceleration of subsidiary pacemakers.

As we have noted, mean serum digoxin concentration is strongly correlated with presence of cardiac toxicity when one looks at patients fulfilling rigid criteria for the presence or absence of digoxin intoxication. The degree of overlap in digoxin levels for the two groups, as shown in Fig. 4, is relatively small and would be smaller still if one excluded the three patients with definite or probable acute myocardial infarction from the toxic group (Table VI) and the four patients receiving dysrhythmia suppressant drugs from the nontoxic group. The high incidence of coronary artery disease among patients with digoxin intoxication at relatively low serum levels is of interest and is consistent with the hypothesis that ischemic myocardium may respond with toxic manifestations at concentrations which are better tolerated by the well-perfused heart. A disproportionately high incidence of coronary artery disease has also been noted in patients with digitoxin intoxication and intermediate serum concentrations of the drug (26).

From the standpoint of clinical management, most decisions to give or withhold cardiac glycosides in patients meeting the criteria in Table I will be straightforward, and knowledge of serum digoxin concentration will be chiefly of investigative interest. Exceptions occur when an accurate history of dosage cannot be obtained, the extent of absorption of orally administered doses is uncertain (27), or in hemodynamically unstable patients with fluctuating renal function as after acute myocardial infarction or cardiac surgery. When confronted by the sorts of rhythm disturbances listed in Table II, however, difficult decisions tend to be the rule, particularly in patients badly in need of the inotropic support of digitalis glycosides. As indicated in Table VII, these patients tend, like those classified as definitely toxic, to be advanced in age and clinically complicated with a relatively high incidence of impaired renal function. A wide range of serum digoxin concentrations was found, and it is clear that no arbitrary level can be chosen below or above which digoxin should or should not be continued.

In cases of organic disease of the conducting system, even low digoxin levels may precipitate significant atrioventricular block. On the other hand, relatively high doses and serum digoxin concentrations may be necessary to control ventricular rate in some patients with supraventricular tachyarrhythmias despite equivocal manifestations of digitalis excess such as occasional ventricular or atrioventricular junctional premature beats. Bearing in mind these caveats, however, it may be stated that levels below 1.5 ng/ml are unlikely to be associated with significant digoxin intoxication, while levels above 3.0 ng/ml by our method carry a high probability of digoxin induced rhythm disturbance in patients with cardiac disease. In view of the multiple factors governing individual response to cardiac glycosides (20), the serum digoxin concentration should be viewed as just one of many important factors to be weighed in a complex clinical setting.

Finally, some mention should be made of the relationship between serum digoxin concentration and effective concentration of the drug in myocardium. The studies of Doherty and his coworkers (Perkins, and Perkins and Flanigan) with tritiated digoxin have suggested a relatively constant ratio between serum and myocardial digoxin concentration, both in dogs studied experimentally (28) and in human subjects coming to postmortem examination (29). Nevertheless, alterations in sodium (30) and potassium (31–33) metabolism and thyroid function (34) appear to alter this ratio. Relatively little is known about homogeneity of myocardial digoxin distribution, particularly in the heart with areas of focal ischemia or infarction. Furthermore, until the elusive digitalis receptor is better characterized one is unable to define even the relationship between total myocardial and effective receptor site concentrations. In any case, on the basis of the results presented above, it seems

justified to conclude that whatever the serum to myocardial digoxin concentration ratio may be, a clinically meaningful relationship exists between serum digoxin concentration and disturbances of rhythm in a broad spectrum of hospitalized patients with cardiac disease.

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