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[Articles]

Digoxin Level and Clinical Manifestations as Determinants in the Diagnosis of Digoxin Toxicity

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Summary:

The aim of this study was to determine the relative importance of different risk factors in the diagnosis of digitalis toxicity. The authors recruited inpatients for whom serum digoxin level was requested and prospectively followed them for a week to ascertain if they showed digitalis toxicity. The predictive value of different factors for the assessment of digoxin toxicity was analyzed by multiple logistic regression. Forty-one toxic and 58 nontoxic patients were included. In the univariant analysis, intoxicated patients were older, most were women, and they had worse renal function and higher digoxin level; but there were no differences in serum electrolytes or other risk factors. In the multivariant analysis, digoxin level was the only independent factor related to digitalis toxicity. A different risk of toxicity for each clinical manifestation was found for a certain digoxin level. Patients with signs of automaticity in the electrocardiogram had a higher likelihood of being intoxicated than patients with gastrointestinal symptoms, atrioventricular block, or bradycardia. Therefore, in the population evaluated in this study, digoxin level is the key independent factor in digoxin intoxication, although the probability of being intoxicated is also a function of the type of clinical manifestations. A graphic approximation of this probability based on these two factors is presented.

Digoxin is a commonly prescribed drug, and the problem of digoxin toxicity is well recognized. Several studies performed in the 1970s showed that toxic effects developed in 6% to 29% of all patients taking digitalis (1–4). Although the incidence is smaller (2–5%) in more recent studies (5–8), digoxin is still a common cause of visits to emergency units and hospital admissions (3,9). In the emergency ward of our hospital, digitalis

toxicity constitutes 3% of mild adverse drug reactions, 5% of moderate ones, and 4% of severe ones (10), and it is the second most common cause of drug-related hospital admissions (11). Moreover, digitalis intoxication increases the length of hospitalization, and mortality was reported in 3–21% of patients who had clinical toxicity (4).

Several factors have been reported to modify the sensitivity of the myocardium to digoxin and to increase or decrease digitalis toxicity. Thus, hypokalemia, hypomagnesemia, hypercalcemia, hypoxia, ischemic heart disease, hypothyroidism, drug interactions, and advanced age all increase the likelihood of digitalis toxicity, while hyperthyroidism, childhood, and atrial fibrillation decrease it (4,12,13). All these factors interact (1,2,14–16), and it is probably the interrelation of all the factors present in a subject that determines the presence and extent of toxicity (17). However we do not know the relative contribution of each factor to the presence of toxicity.

The clinical diagnosis of digoxin intoxication is frequently difficult because the symptoms and electrocardiographic changes are nonspecific. There is controversy about the usefulness of serum digoxin levels in the diagnosis of digitalis intoxication because, as it is known, some overlap exists between “therapeutic” and “toxic” concentrations in relation to clinical symptoms of intoxication and vice versa. Despite this, serum digoxin level is an important predictor of digoxin toxicity and the most important predictor of mortality (6), and it is positively associated with mortality rate in patients treated with digoxin (18).

The aim of this prospective study was to determine the relative importance of every one of those factors reported as risk factors for digitalis toxicity (sex; age; digoxin level; concomitant drugs and diseases; serum sodium, potassium, magnesium, and calcium; and renal function), and to ascertain the role of serum digoxin level in the diagnosis of digitalis toxicity.

METHODS

We recruited inpatients taking digoxin from the requests for routine therapeutic digoxin monitoring received in the Clinical Pharmacology Service of “Hospital La Paz” during a period of 1-½ years. Patients were included in the study if they were age 14 years or older and if the venous blood sample had been obtained more than 6 hours after their last digoxin dose. They could be admitted in any service of this general hospital. We excluded patients with overdose intoxication and those having a pacemaker. We included all patients whose doctors suspected intoxication, and one or two patients randomly selected every day from the other serum digoxin requests. Patients were always selected for inclusion in the study before the digoxin concentration test was performed.

For a definitive classification of patients suffering from digoxin toxicity we established the criteria following those of other authors (15,19) (Table 1). Patients meeting any criteria of toxicity were classified as toxic provided this criteria disappeared after a week of digoxin withdrawal or dose reduction. Subjects meeting no

criteria, and those meeting any criteria that either disappeared without digoxin withdrawal or that did not disappear after digoxin withdrawal were classified as nontoxic. Patients meeting any criteria in whom digoxin was not withdrawn and the criteria persisted were excluded.

	Toxic (n 41)	Nontoxic (n 58)
1. Supraventricular tachycardia with atrioventricular block	2	0
2. Premature ventricular beats >5 beats/min, bigemini or multifocal	15	0
3. Ventricular tachycardia	2	0
4. Atrial fibrillation with a ventricular response <60 beats/min in the presence of premature ventricular beats	3	1
5. Second or third degree atrioventricular block	1	2
6-a. Premature ventricular beats <5 beats/min	2	1
6-b. First degree atrioventricular block	3	2
6-c. Sinus bradycardia <60 beats/min	0	1
6-d. Atrial fibrillation with a ventricular response <60 beats/min	8	3
6-e. Nausea, vomiting or anorexia†	24	5
6-f. Diarrhea or abdominal pain†	3	1
6-g. Visual aberrations†	3	1
6-h. Syncope or dizziness†	9	1
6-i. Weakness, insomnia or headache†	2	0
Number of patients with any criteria	41 (100%)	12 (20.7%)

* Patients were classified as toxic if this criteria disappeared a week after digoxin withdrawal.

† Without any other clear cause.

TABLE 1. *Criteria for the diagnosis of digoxin toxicity and number of patients meeting any criteria the first study day*[*]*Patients were classified as toxic if this criteria disappeared a week after digoxin withdrawal.†Without any other clear cause.

Digoxin level and serum ions (potassium, sodium, magnesium, and calcium) were estimated in the same serum sample. Serum digoxin was measured by

fluoroimmunoassay using the Abbott TDX system. If the sample was hemolyzed the patient was excluded for potassium, magnesium, and sodium, because hemolysis can alter serum ions. Also, the creatinine clearance for each patient was calculated through the Cockroft and Gault equation (20). Between 2 and 4 hours after the sample extraction, a full clinical assessment of each subject was performed by one of the investigators in a case-record form and an electrocardiogram was obtained. The physicians attending the patients were told about the digoxin level but not about this study. Patients were prospectively followed for at least 1 week by the same investigator.

Patients classified as toxic and nontoxic were compared univariantly using unpaired *t*-test and chi-square test. Results are reported as mean ± standard error of mean (M ± SEM) for numerical data and percentages for qualitative variables. A stepwise multiple logistic regression (BMDP Statistical Software) was carried out including all independent variables (sex; age; concomitant drugs or diseases; creatinine clearance; serum sodium, potassium, magnesium, and calcium; and digoxin level) to evaluate their predictive value for the assessment of digoxin toxicity. Although signs and symptoms are nonindependent factors, another analysis including them (grouped as automaticity, bradycardia or block, and gastrointestinal symptoms) was performed to evaluate the relative weight of each one to the digoxin toxicity status and their relationship with digoxin level. Odds ratio and 95% confidence intervals were calculated for the significant independent variables from the coefficients and standard errors of the logistic regression.

RESULTS

A total of 109 patients were included; 10 of them were excluded because they were discharged from the hospital in less than a week (5 patients) or because they continued taking digoxin in spite of meeting some of the criteria (5 patients). Nine patients were not considered for potassium, magnesium, and sodium because they had hemolyzed serum samples (5 patients), their serum samples were lost (3 patients) and we could not measure the ions, or they showed a severe acidosis that modified serum ions (1 patient).

Forty-one of the 99 evaluable patients (10 male, 31 female; mean age 76.6 years) were classified as toxic and 58 (28 male, 30 female; mean age 71.7 years) as nontoxic. Table 1 shows the electrocardiographic disturbances and symptoms presented by these patients according to the diagnosis of toxicity.

At least one symptom of toxicity was present in 53 patients, and 41 (77.4%) of them were finally toxic. Gastrointestinal symptoms were present in 29 patients, and 24 (82.8%) of those were ultimately toxic. In 25 patients there were electrocardiographic signs of automaticity (premature ventricular beats or tachycardia); 23 (92.0%) of them were finally toxic. Bradycardia or atrioventricular block were present in 24 patients, 15 (62.5%) of whom were classified as toxic.

The characteristics of the patients with digoxin intoxication were univariantly compared with those of the nontoxic subjects (Tables 2 and 3). Intoxicated patients were more frequently women, were older, had a smaller body mass, and had worse renal function. As expected, serum digoxin levels were significantly higher in toxic patients (3.08 ± 0.20 ng/mL) than in nontoxic ones (1.58 ± 0.10 ng/mL), but there was considerable overlap between the two groups. Digoxin level was below 2 ng/mL in 10 intoxicated patients and higher than 2 ng/mL in 16 asymptomatic subjects.

Characteristics	Toxic (n = 41)	Nontoxic (n = 58)	p (X^2)
Sex (Male/Female)	10/31	28/30	p = 0.0161
Congestive heart failure	30 (73.1%)	35 (60.3%)	p = 0.1856
Atrial fibrillation	34 (82.9%)	48 (82.8%)	p = 0.9826
Ischemic heart disease	12 (29.3%)	16 (27.6%)	p = 0.8548
Other diseases*	11 (26.8%)	15 (25.9%)	p = 0.9142
Drugs†	10 (24.4%)	15 (25.9%)	p = 0.8681
Diuretics	33 (80.5%)	44 (75.9%)	p = 0.5855
Gastrointestinal symptoms‡	24 (58.5%)	5 (8.6%)	p = 0.0001
Automaticity§	23 (56.1%)	2 (3.5%)	p = 0.0001
Bradycardia or block‖	15 (36.6%)	9 (15.5%)	p = 0.0160
Clinical suspicion	32 (78.1%)	14 (24.1%)	p = 0.0001

* Hypothyroidism, chronic obstructive pulmonary disease, myocardiopathy.

† Drugs that increase digoxin levels: amiodarone, quinidine, spironolactone, verapamil, diltiazem and other calcium antagonists.

‡ Items 6e or 6f of Table 1.

§ Items 1, 2, 3, 4 or 6a of Table 1.

‖ Items 4, 5, 6b, 6c or 6d of Table 1.

TABLE 2. *Qualitative variables in patients with or without digoxin toxicity**Hypothyroidism, chronic obstructive pulmonary disease, myocardiopathy.†Drugs that increase digoxin levels: amiodarone, quinidine, spironolactone, verapamil, diltiazem and other calcium antagonists.‡Items 6e or 6f of Table 1.§Items 1, 2, 3, 4 or 6a of Table 1.[//]Items 4, 5, 6b, 6c or 6d of Table 1.

Characteristics	Toxic (n = 41)	Nontoxic (n = 58)	p (*t* Student)
Age (years) M ± SEM	76.6 ± 1.5	71.7 ± 1.6	p = 0.0369
(Range)	(49–92)	(22–86)	
Weight (kg) M ± SEM	59.8 ± 1.7	66.3 ± 1.5	p = 0.0054
(Range)	(40–80)	(40–100)	
Dose/weight (μg/kg/week) M ± SEM	26 ± 2	25 ± 1	p = 0.6358
(Range)	(7–54)	(9–54)	
Initial heart frequency (beats/min) M ± SEM	75.3 ± 3.5	87.7 ± 3.1	p = 0.0098
CrCl (mL/min) M ± SEM	36.3 ± 3.2	51.7 ± 3.7	p = 0.0038
(Range)*	(7.2–126.4)	(6.3–136.5)	
Na^+ (mEq/L) M ± SEM	137.3 ± 0.9	139.0 ± 0.7	p = 0.1177
(Range)†	(128.9–157.6)	(127.0–150.6)	
K^+ (mEq/L) M ± SEM	4.54 ± 0.16	4.29 ± 0.10	p = 0.1678
(Range)†	(3.39–7.34)	(2.59–5.95)	
Mg^{++} (mEq/L) M ± SEM	2.08 ± 0.06	2.07 ± 0.04	p = 0.8260
(Range)†	(1.5–2.9)	(1.2–2.7)	
Ca^{++} (mg/dL) M ± SEM	8.86 ± 0.16	8.97 ± 0.12	p = 0.5917
(Range)	(7.2–11.2)	(6.8–11.0)	
Digoxin level (ng/mL) M ± SEM	3.08 ± 0.20	1.58 ± 0.10	p = 0.0001
(Range)	(1.21–6.90)	(0.44–3.37)	

M, mean; SEM, standard error of the mean.
* Creatinine clearance.
† n = 39 toxic and 51 nontoxic patients because of serum hemolysis (5), loss of serum samples (3), and extreme acidosis (1).

TABLE 3. *Quantitative variables in patients with or without digoxin toxicity*M, mean; SEM, standard error of the mean.*Creatinine clearance.†n = 39 toxic and 51 nontoxic patients because of serum hemolysis (5), loss of serum samples (3), and extreme acidosis (1).

There were no significant differences between the two groups in serum electrolytes (Table 3), the frequency of ischemic heart disease, heart failure, atrial fibrillation, treatment with diuretic or antiarrhythmic drugs (Table 2), or incidence of electrolyte abnormalities. Only 4 toxic and 5 nontoxic patients had hypokalemia (<3.5 mEq/L), 4 toxic and 4 nontoxic patients had hypomagnesemia (<1.6 mEq/L), and 6 toxic and 3 nontoxic patients had hypercalcemia (>10.6 mg/dL).

The doctor who requested the digoxin level determination suspected digoxin toxicity in 78.1% of toxic patients and in 24.1% of nontoxic patients (Table 2). Thus 23 patients (23%) were incorrectly diagnosed. It is probable that this percentage would be smaller in a study specifically designed to examine this aspect.

Toxicity developed in 10 patients with serum digoxin levels lower than 2 ng/mL. Three of them had hypokalemia and another 3 had hypomagnesemia. These 10 patients had lower serum potassium concentrations than the other toxic patients with digoxin levels higher than 2 ng/mL (3.84 ± 0.12 vs. 4.79 ± 0.19 mEq/L, p = 0.006). Serum magnesium levels were also somewhat lower in toxic subjects with low digoxin concentrations, though this difference did not reach statistical significance (1.95 ± 0.15 vs. 2.13 ± 0.07 mEq/L, p = 0.205).

Logistic regression analysis including independent variables showed that only serum digoxin level was significantly associated with digoxin intoxication. None of the other independent variables improved the statistical prediction. As in the univariant analysis, serum potassium, magnesium, and calcium; ischemic heart disease; and other variables that have been considered in the literature as risks factors for digoxin toxicity did not improve the statistical prediction. Age, sex, weight, dose, and creatinine clearance, which showed statistical differences between toxic and nontoxic patients in univariant analysis, lost their significant association in multivariant analysis, probably because they correlate with digoxin level.

Multivariant analysis including toxicity criteria (grouped as shown in Table 2) confirmed the statistical significance of the association between serum digoxin concentration and diagnosis of toxicity. They also showed that signs of automaticity are more strongly associated to toxicity, while gastrointestinal symptoms and bradycardia or atrioventricular block present a weaker association (Table 4).

Variable	β	p	Odds ratio	95% confidence interval
Digoxin level	1.505	<0.01	4.51†	1.62–12.5
Gastrointestinal symptoms	2.117	0.011	8.31	1.59–43.5
Bradycardia or block	1.532	0.089	4.63	0.784–27.3
Automaticity	3.810	<0.001	45.2	7.14–285.0
Constant	−5.552	<0.001		

* By logistic regression analysis.
† For every 1 ng/mL increase.

TABLE 4. *Relative values of the best predictors for digoxin toxicity and their odds ratios*[*]*By logistic regression analysis.†For every 1 ng/mL increase.

Based on the logistic regression, it is possible to draw a figure showing the probability of intoxication at a digoxin concentration for patients having a specific manifestation of toxicity (Fig. 1). We can see that, for the same serum digoxin level (e.g., 2 ng/mL), a patient with electrocardiographic signs of automaticity has a higher likelihood of being intoxicated (about 80%) than a patient with gastrointestinal symptoms or bradycardia (lower than 40%). The association of bradycardia and gastrointestinal symptoms increase the risk to the level found with isolated automaticity signs, and the association of this with any other sign or symptom increases the risk of toxicity to more than 90% at a 2 ng/mL level.

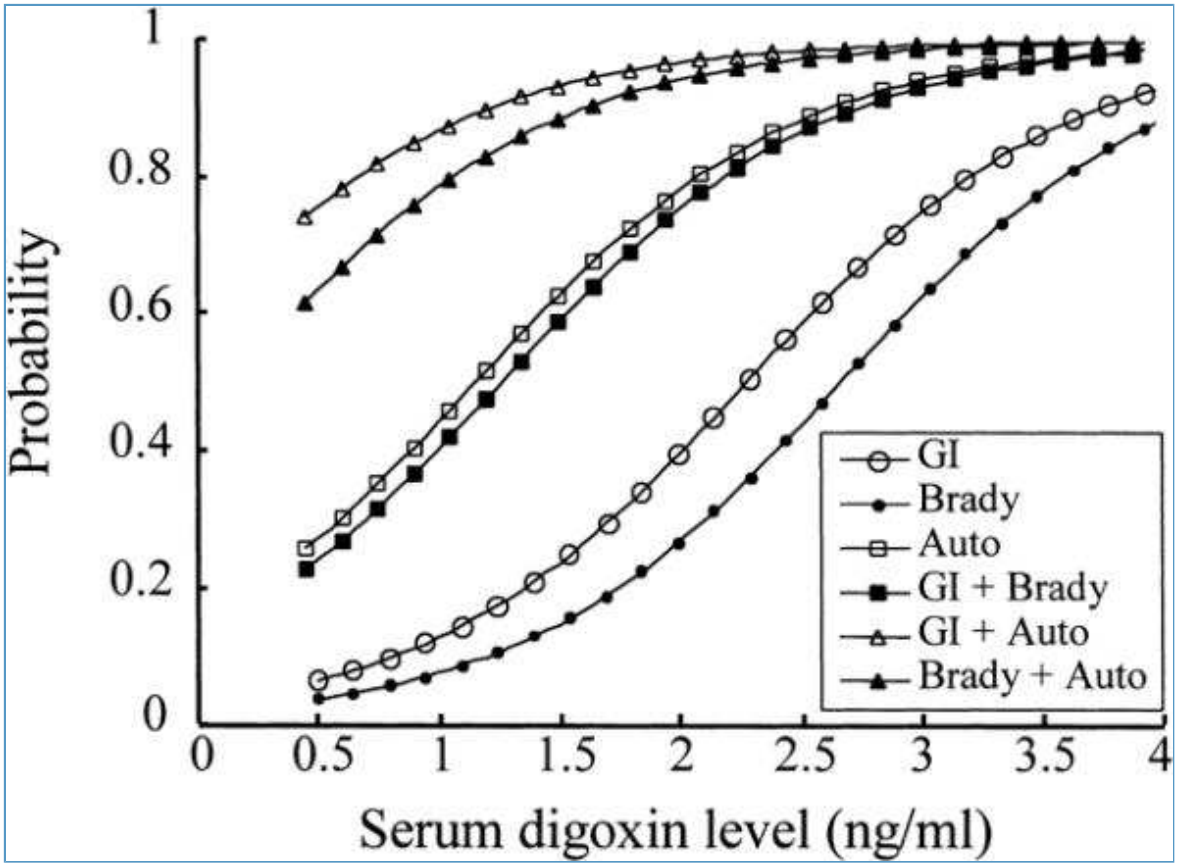

FIG. 1. Probability of being intoxicated depending on serum digoxin level and clinical manifestations: gastrointestinal symptoms (GI), bradycardia or atrioventricular block (Brady) or electrocardiographic signs of automaticity (Auto), as in Table 2.

DISCUSSION

Inpatients included in this study were selected from those whose attending physician asked for a serum digoxin determination. Therefore they are not a representative sample of all patients treated with digoxin. However we think that the sample included represents those patients that are more difficult to manage and in whom digoxin determination would be more useful. In any case this point should be taken into account in the interpretation of these results.

Most of the variables included in this study are generally considered as risk factors for digoxin toxicity. Our study shows digoxin level as the only important risk factor. In fact, in most of the published studies (1–3,6,8,14–16,19,21), serum digoxin is the only factor that is significantly higher in toxic than in nontoxic patients; the exceptions are two studies that included patients with digoxin levels higher than 3 ng/mL (22,23) and another study of seriously ill patients with more than one digoxin determination (24). In another study in which all the intoxicated patients had very low digoxin levels (19), serum digoxin was not an independent predictor of digitalis intoxication. Nevertheless, we have tried a logistic regression analysis with patients having digoxin levels lower than 2 ng/mL and serum digoxin level remained the only independent predictor of intoxication.

Digoxin concentrations show some overlap between toxic and nontoxic patients. This overlap has been classically attributed in part to various extra-cardiac factors which could influence the distribution of digoxin in the body (e.g., sex, age, and renal failure) or the response of the heart to the drug (e.g., electrolyte abnormalities) (15). The results in our study show that these factors are probably less important than usually considered. Inasmuch, a detailed review of the literature data shows that each factor has been found related to toxicity in very few studies (and frequently in only one), as set out below.

Hypokalemia has long been recognized as an important risk factor for the development of digitalis intoxication (15,25,26). However, old and recent studies did not show differences in potassium levels between toxic or nontoxic patients (1-3,7,8,14,15,19,21), nor between patients receiving or not receiving diuretics (19,21). In the present and in many other clinical studies serum potassium was not found to be a predictor of digoxin toxicity (6,7,19,23). Currently the incidence of hypokalemia is smaller than in older studies (15) because the risk of potassium depletion is widely appreciated and patients are frequently given potassium supplements or potassium-sparing drugs. Conversely, digoxin intoxication can produce hyperkalemia, and in some studies potassium is higher in toxic than in nontoxic patients (3). In fact, in our study there is a significant positive correlation between serum potassium and digoxin level (r = 0.36, p = 0.006), and this could explain why toxic patients with digoxin levels below 2 ng/mL have lower potassium levels than toxic patients with higher digoxin levels.

Magnesium is less likely to be monitored or administered, and hypomagnesemia should be more common than hypokalemia. Hypomagnesemia has been associated with digoxin toxicity in one study (19), but this is not the case in our study. Neither did any other authors find any relation between magnesium concentrations and digoxin toxicity (8,16,21).

As in our study, several authors have associated impaired renal function with digoxin toxicity (1,2,6,7,14), but the creatinine clearance is not a predictor of digoxin intoxication because its effect could be fully explained by the increased digoxin level (6). Nevertheless, Piergies et al (23) found that impaired renal function increases the risk of toxicity for patients with high digoxin levels.

Several authors have shown a correlation between advanced age and adverse drug reactions to digoxin (2,4,7,14), which can be a result of the physiologic changes seen in the elderly, such as decrease muscle mass and decrease renal function (1,14). This correlation could not be confirmed in the present and other studies (5).

Some authors have found that a higher proportion of toxic patients are women (5,8,23,27), but the numbers are statistically insignificant. In our study, intoxication was most frequent in women, probably because they were older than men (77.0 ± 1.1 vs. 68.4 ± 2.2 years, p = 0.0002), with lower muscle mass (weight and height significantly smaller), and with higher serum digoxin levels: 2.4 ± 0.16 ng/mL vs. 1.88 ± 1.73 ng/mL, p = 0.0412).

Therefore, in agreement with most of the published evidence, our study shows that digoxin level is the key independent factor in digoxin intoxication. All other factors appear to play a minor role in the whole population, although they may be important in a small group of patients. So serum digoxin determination should be one of the most important diagnostic tests in a patient with suspected digoxin toxicity.

A previous observation of Sonnenblick et al (16) shows that patients with gastrointestinal symptoms of digoxin toxicity had higher serum digoxin levels than those with digoxin-induced automaticity, suggesting different thresholds for the different manifestations of digoxin toxicity. Our study confirms that different clinical manifestations carry different risks of intoxication.

The usefulness of serum digoxin determination has been debated in the literature because of the lack of a clear therapeutic window and the overlap between "therapeutic" and "toxic" concentrations, as in fact happens with every drug. Diagnosis of toxicity is one of the most frequent reasons for digoxin monitoring, but the mentioned overlap makes difficult to do a diagnosis in many cases. In fact, to look for a certainty about diagnosis of digitalis toxicity is unrealistic at the present state of knowledge, and it would be more helpful to analyze which probabilities can improve our performance in this decision-making process. In our opinion the results obtained in this study give an estimation of these probabilities and could aid in this process on the basis of clinical signs and digoxin level.

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IMAGE GALLERY

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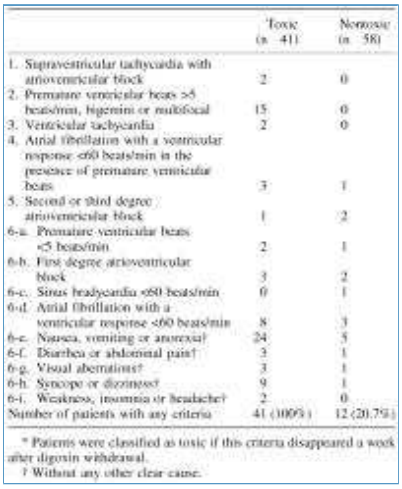
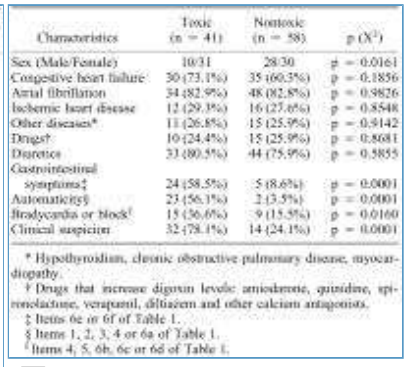


	Toxic (n = 41)	Nontoxic (n = 58)
1. Supraventricular tachycardia with atrioventricular block	2	0
2. Premature ventricular beats >5 beats/min, bigemini or multifocal	15	0
3. Ventricular tachycardia	2	0
4. Atrial fibrillation with a ventricular response <60 beats/min in the presence of premature ventricular beats	3	1
5. Second or third degree atrioventricular block	1	2
6-a. Premature ventricular beats <5 beats/min	2	1
6-b. First degree atrioventricular block	3	2
6-c. Sinus bradycardia <60 beats/min	0	1
6-d. Atrial fibrillation with a ventricular response <60 beats/min	8	3
6-e. Nausea, vomiting or anorexia†	24	5
6-f. Diarrhea or abdominal pain†	3	1
6-g. Visual aberrations†	3	1
6-h. Syncope or dizziness†	9	1
6-i. Weakness, insomnia or headache†	2	0
Number of patients with any criteria	41 (100%)	12 (20.7%)

* Patients were classified as toxic if this criteria disappeared a week after digoxin withdrawal.
† Without any other clear cause.

Table 1



Characteristics	Toxic (n = 41)	Nontoxic (n = 58)	p (X^2)
Sex (Male/Female)	10/31	28/30	p = 0.0161
Congestive heart failure	30 (73.1%)	35 (60.3%)	p = 0.1856
Atrial fibrillation	34 (82.9%)	48 (82.8%)	p = 0.9826
Ischemic heart disease	12 (29.3%)	16 (27.6%)	p = 0.8548
Other diseases*	11 (26.8%)	15 (25.9%)	p = 0.9142
Drugs†	10 (24.4%)	15 (25.9%)	p = 0.8681
Diuretics	33 (80.5%)	44 (75.9%)	p = 0.5855
Gastrointestinal symptoms‡	24 (58.5%)	5 (8.6%)	p = 0.0001
Automaticity§	23 (56.1%)	2 (3.5%)	p = 0.0001
Bradycardia or block‖	15 (36.6%)	9 (15.5%)	p = 0.0160
Clinical suspicion	32 (78.1%)	14 (24.1%)	p = 0.0001

* Hypothyroidism, chronic obstructive pulmonary disease, myocardiopathy.
† Drugs that increase digoxin levels: amiodarone, quinidine, spironolactone, verapamil, diltiazem and other calcium antagonists.
‡ Items 6e or 6f of Table 1.
§ Items 1, 2, 3, 4 or 6a of Table 1.
‖ Items 4, 5, 6b, 6c or 6d of Table 1.

Table 2

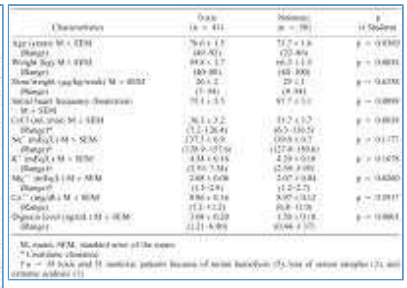
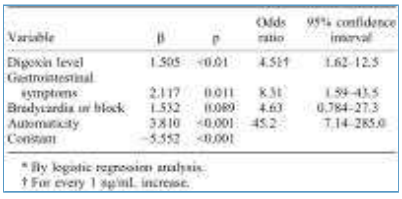


Table 3



Variable	β	p	Odds ratio	95% confidence interval
Digoxin level	1.505	<0.01	4.501	1.62–12.5
Gastrointestinal symptoms	2.117	0.011	8.31	1.59–43.5
Bradycardia or block	1.532	0.089	4.63	0.784–27.3
Automaticity	3.810	<0.001	45.2	7.14–285.0
Constant	−5.552	<0.001		

* By logistic regression analysis.
† For every 1 ng/mL increase.

Table 4

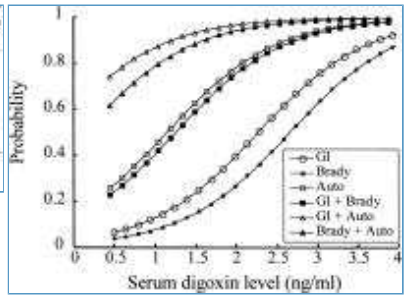


Fig. 1

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