Digoxin toxicity: clinical and laboratory assessment

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Summary

A prospective study to correlate clinical digoxin toxicity with serum digoxin levels was carried out in 67 patients of whom 24 were clinically toxic and 43 were asymptomatic. The patients were clinically diagnosed to be toxic based on typical cardiac arrthymias (n = 11) or non-cardiac symptoms (n = 13). Blood samples were collected at least six hours after the last digoxin dose and the sera assayed for digoxin using a radioimmunoassay method. The mean serum digoxin level in the toxic group (x_1 = 2.09 +/– 1.28 ng/ml) was significantly higher than in the non-toxic group (x_2 = 1.20 +/– 0.75 ng/ml), $p < 0.01$. All the non-toxic patients had serum digoxin levels below 3 ng/ml. However, there was a considerable overlap of serum digoxin levels between the two groups of patients. Serum level cannot be the sole criterion in diagnosing digoxin toxicity. Nevertheless, raised serum digoxin levels especially above 3 ng/ml, in the presence of suggestive clinical features is strongly suggestive of toxicity.

Key words: Digoxin toxicity, Clinical diagnosis, Serum digoxin levels.

Introduction

Digoxin is one of the important drugs used in cardiovascular therapeutics. The diagnosis of digoxin toxicity is difficult and relies partially on the measurement of serum digoxin levels introduced into clinical practice nearly two decades ago. The present study was to determine the correlation between serum levels and clinical digoxin toxicity in local patients at the University Hospital, Kuala Lumpur.

Subjects and methods

The study was carried out on 67 digitalised patients seen at the Medical Unit of the University Hospital. The age, sex, race and weight of the patients, the cardiovascular diagnosis, the indication for digoxin therapy and the daily digoxin dosage were noted for each patient. The clinical diagnosis of digoxin tocity was based either on electrocardiographic features or non-cardiac symptoms. Blood was collected (at least six hours after the preceding dose of digoxin) and assayed for serum digoxin levels using a radioimmunoassay method [Wellcome double antibody coated cellulose system (Dac-cel), Dartford, Kent, England]. Serum electrolytes and creatinine were analysed using the Technicon Autoanalyser (Technicon Inc., Terrytown, New York, USA). Statistical analysis of the results was carried out using the Student's t-test and Chi-square methods.

Results

The major clinical cardiovascular diagnoses in the 67 patients studied were rheumatic valvular heart disease (46.3%), ischemic heart disease (17.9%), congenital heart disease (9.05%) and idiopathic cardiomyopathy (7.5%). Congestive cardiac failure was the indication for digoxin therapy in over 90% of the patients, with the majority being in sinus rhythm (Table 1a). Twenty-four patients were diagnosed to be digitoxic clinically, having either typical cardiac arrthymias or suggestive non-cardiac symptoms (Table 1b). The most frequent ECG feature of toxicity was ventricular bigeminy (9 out of the 11 cases). Different grades of atrio-ventricular block were noted in the other two patients. Nausea, vomiting or diarrhoea was noted in all patients with non-cardiac symptoms. The patients in clinical digoxin toxicity were comparable to the non-toxic in terms of age, body weight and sex ratio (Table 2).

There was a significant difference in the mean serum digoxin levels between the toxic and non-toxic group of patients. This difference reached an even higher degree of significance if only those on a daily digoxin dosage of 0.25 mg were considered (Table 3). Four toxic patients had serum levels greater than 3 ng/ml but all the non-toxic patients had levels below 3 ng/ml. However, there was a wide overlap of serum digoxin levels below 3 ng/ml. The range for toxic patients was 0.44 ng/ml to 5.30 ng/ml, while the range for non-toxic patients was 0.20 ng/ml to 2.98 ng/ml.

There was no significant difference in the daily digoxin dosage between the toxic and non-toxic patients ($x^2 = 0.303$; $p > 0.5$). Neither was there a significant difference in the mean serum

Table 1a
Indications for digoxin therapy

	Number of patients (%)	
Cardiac failure	37	(55.2)
Sinus rhythm	37	(55.2)
Atrial fibrillation	24	(35.8)
Atrial fibrillation	6	(9.0)
Total	67	(100.0)

Table 1b
Criteria of toxicity

	Number of patients (%)	
Cardiac arrhythmias	11	(45.8)
Non-cardiac symptoms		
Gastrointestinal	13	(54.2)
Xanthopsia	2	(8.3)

Table 2
Characteristics of patients studied

	Clinically toxic		Clinically non-toxic	
Number	24		43	
Sex ratio: Male : Female	1.2 : 1		1 : 1	
	Mean	S.D.	Mean	S.D.
Age (years)	39.5	22.0	41.1	19.0
Weight (kg)	49.4	10.3	45.3	7.4

Table 3
Serum digoxin levels (ng/ml) in patients on digoxin therapy

	Clinically toxic		Clinically non-toxic	
	Mean	S.D.	Mean	S.D.
All patients	2.09	1.28	1.24	0.75%
	n = 24		n = 43	
0.25 mg dosage	2.42	1.32	1.46	0.85**
	n = 14		n = 28	
0.125 mg dosage	1.25	0.69	0.89	0.48***
	n = 10		n = 15	

Note: n = number of patients
* $p < 0.01$
** $p < 0.005$
*** $p > 0.05$, not significant

potassium levels of the toxic and non-toxic patients (x_1 = 4.39 +/– 0.58 mmol , x_2 = 4.19 +/– 0.76 mmol/l; $p > 0.1$). Similarly, the mean serum magnesium levels of the two groups were comparable (x_1 = 1.73 +/– 0.19 mmol/l, x_2 = 1.71 +/– 0.22 mmol/l; $p > 0.5$).

However, there were significantly more patients in atrial fibrillation in the toxic group ($x^2 = 6.59$; $p < 0.02$).

Further analysis revealed that frusemide therapy has no effect on the serum digoxin level whether at daily dose of 0.125 mg or 0.25 mg (Fig. 1). There was also no significant correlation between serum creatinine and serum digoxin level. ($r = 0.129$; $p < 0.1$).

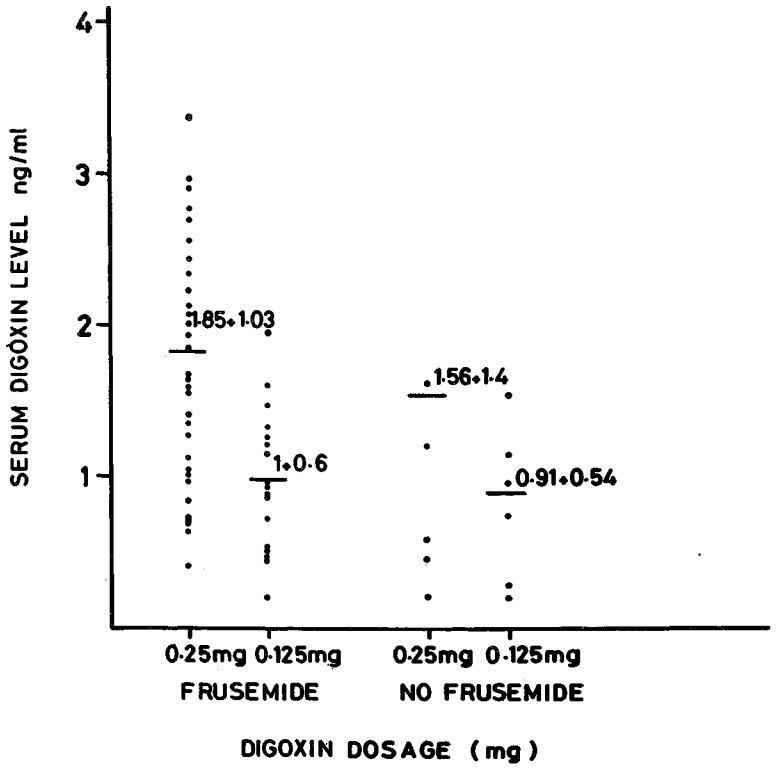

FIG. 1: RELATIONSHIP OF SERUM DIGOXIN LEVEL AND FRUSEMIDE THERAPY.

Discussion

The wide variation of cardiovascular diagnoses in this study is a reflection of the various cardiac problems encountered at the University Hopital. Cardiac failure by far was the most frequent indication for digoxin therapy. A large proportion of these patients were in sinus rhythm, reflecting the view that digoxin does improve cardiac contractility and clinical status even in patients in sinus rhythm.[2] Atrial fibrillation, with or without cardiac failure, is a definite indication for digoxin therapy.[3]

This study was not designed to address the question of incidence of cardiac arrythmias or non-cardiac symptomss in dogixin toxicity. The clinical diagnosis of digoxin toxicity was based on the presence of at least one of these features. However other workers have reported the incidence of extracardiac symptoms in digoxin toxicity as varying from 80% to 95%, with a similar occurrence of various cardiac arrhythmias.[4,5] The two could occur together or independently.[6] The problem in clinical diagnosis lies in distinguishing these non-cardiac symptoms and cardiac arrhythmias due to digoxin toxicity from those caused by the underlying cardiac disorder itself.[7,8] This suggests a role for monitoring serum digoxin levels in diagnosing digoxin toxicity.

Our results showed a statistically significant difference in mean serum digoxin levels between the toxic and non-toxic patients, in agreement with the comprehensive review by Smith, et al.[7] A level above 3 ng/ml is said to lend strong support to the diagnosis of toxicity.[9] Unfortunately,

there is a large overlap in the range of serum levels of the two groups of patients which means that a single serum level cannot be diagnostic of digoxin toxicity. Several reasons account for the occurrence of toxicity at therapeutic serum digoxin levels, and the absence of toxicity at "toxic" serum digoxin levels. The state of the myocardium influences its response to digoxin. A more diseased myocardium is more sensitive to the toxic effects of digoxin. Moreover, electrolyte and acid-base abnormalities such as hypokalemia, hypomagnesemia, hypercalcemia and acidosis also increases sensitivity to digoxin. Similarly, other conditions such as renal failure, myxoedema and hypoxia may result in clinical toxicity at "therapeutic" serum digoxin levels.[9,10,11] Conversely, endogenous digoxin-like immunoreactive substance, found in such states as heart failure, renal failure, liver diseases, neonates and the last trimester of pregnancy are also measured by the assay system[12,13] thus elevating the serum digoxin level and resulting in biochemical digoxin toxicity in a clinically normal patient. Radioimmunoassay also detects dihydrodigoxin, a metabolate of digoxin, which has only 10% of its cardioactivity. This will similarly cause a "toxic" level to be recorded in clinically non-toxic patients.[14] The clinical application of a specific digoxin immunoassay (using monoclonal antibody) may help in a clearer discrimination of toxic and non-toxic patients in the future.

The diagnosis of digoxin toxicity should thus be made on a combination of clinical features and serum levels. Aaronson[15] has advised that digoxin toxicity be suspected when the clinical context is associated with any one of the following:

1) serum digoxin level above 3 ng/ml,
2) hypokalemia,
3) any two of the following:
   a) plasma potassium level above 5 mmol/l
   b) plasma creatinine level above 150 mmol/l
   c) age above 60 years
   d) daily maintenance dose of digoxin at steady state above 6 ug/kg.

We found no difference in the age or serum potassium levels between the toxic and non-toxic patients, in agreement with the results of a pioneering study of digoxin toxicity by Beller, et al.[16] The larger proportion of patients in atrial fibrillation in the toxic group, (similarly noted by Beller), may be a reflection of more advanced heart disease in these patients.

Frusemide therapy had no effect on serum digoxin levels. This is reassuring since patients are often on both these drugs. It is the hypokalemia, and perhaps hypomagnesemia, induced by frusemide that may precipitate digoxin toxicity. This has led to the concept of a "digoxin-diuretic" cardiomyopathy.[17] This study shows that serum digoxin level cannot be the sole criterion in diagnosing digoxin toxicity and should be interpreted in the light of above mentioned non-digoxin factors.

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