DIGOXIN TOXICITY IN THAI MEDICAL PATIENTS : CLINICAL MANIFESTATIONS AND AN APPROPRIATE DIAGNOSTIC SERUM LEVEL

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Abstract. This study considers the clinical manifestations and risk factors of digoxin toxicity and establishes an appropriate cut-off serum level for the diagnosis of toxicity. A retrospective study of 125 hospitalized patients whose serum digoxin was assayed in 1998 was conducted. Of the 125 subjects, 42 (33.6%) were classified as having definite digoxin toxicity, 9 (7.2%) were classified as having probable digoxin toxicity, and 74 (59.2%) were classified as non-toxicated. Of the patients with definite digoxin toxicity, 24 (57.1%) had cardiac manifestations, seven (16.7%) had non-cardiac manifestations, and 11 had manifestations of both types. The commonest manifestation was atrial fibrillation with block. Average daily doses of digoxin in the patients with definite digoxin toxicity and those without intoxication varied from 0.125 to 0.5 ng/ml. There was no significant statistical difference in digoxin dosage between those with and those without digoxin toxicity. Seven univariate factors of digoxin toxicity were examined: logistic regression analysis showed that, serum BUN and serum chloride were independent associated factors of digoxin toxicity: the finding suggests that renal impairment and volume contraction are strong determinants of digoxin toxicity. Mean (SD) serum digoxin levels among the patients with and without toxicity were 2.28 (1.3) and 1.05 (0.6) ng/ml respectively (p = 0.000). The best cut-off level determined by Receiver Operating Characteristic (ROC) analysis was 1.97 ng/ml. However, a low sensitivity and a high specificity make serum digoxin levels a diagnostic rather than a screening tool. The manifestations of digoxin toxicity among Thai inpatients are no different from those of other populations. The best cut-off level of serum digoxin for the diagnosis of toxicity is 2 ng/ml.

INTRODUCTION

Digoxin is commonly used in arrhythmia and cardiac pumping failure; however, it often cause adverse reactions (Tawakkol *et al*, 1967; Smith *et al*, 1984). The effects of digoxin toxicity are either cardiac and/or non-cardiac (Smith *et al*, 1984; Mahdyoon *et al*, 1990). There have been no reports of the effects of digoxin toxicity in Thailand.

In clinical practice, the serum digoxin level can be used to diagnose toxicity: a concentration of 2 ng/ml has been suggested as the cut-off level (Smith *et al*, 1984); this recommended cut-off value was adopted following various studies of Caucasian patients. However, this value has not been verified by a gold standard (criterion validity); moreover, we do not know whether the cut-off level is appropriate for the diagnosis of digoxin toxicity among Thai patients. This study was conducted to determine the effects of digoxin toxicity among Thai medical in-patients; an appropriate cut-off level for serum digoxin and the use of such a level in clinical practice were also studied.

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SUBJECTS AND METHODS

The sera of 125 subjects, who were admitted to the medical department of the King Chulalongkorn Memorial Hospital in 1998, were

obtained and sent for measuring level of digoxin by radioimmunoassay method; their medical records were systematically reviewed. The cardiac and non-cardiac manifestations of digoxin toxicity were recorded; patients whose manifestations resolved completely after the discontinuation of digoxin were categorized as *definite digoxin toxicity*; patients whose manifestations disappeared despite continued digoxin or persisted after the discontinuation of digoxin were categorized as *non-toxication*; the rest were classified as *probable digoxin toxicity*.

Only the subjects with definite digoxin toxicity and those non-intoxicated were further analysed in order to establish an appropriate cut-off level for, and the effects of, digoxin toxicity.

Data regarding the average daily dose of digoxin, indication for prescription, cardiac disease, co-morbidity, other medicines, total number of medicines, and laboratory data including hematocrit, serum sodium, serum potassium, serum chloride, serum bicarbonate, serum blood urea nitrogen (BUN), serum creatinine, serum albumin, serum globulin and liver enzymes were collected.

Receiver Operating Characteristic (ROC) analysis was used to identify the best cut-off value. Sensitivity, specificity, positive predictive value, negative predictive value, and likelihood ratio were computed. The unpaired *t*-test and the chi-square test were used for statistical analysis; univariate associated factors whose alpha errors were less than 5% were subjected to logistic regression analysis. Odds ratios and 95% confidence intervals were computed. The SPSS-PC program (version 8.0) was used.

RESULTS

The patients' mean age (SD) was 58.7 (19.1) years; 48.8% were male. Forty-two patients (33.6%) were classified as definite digoxin toxicity (42.9% of these were male), 9 (7.2%) had probable digoxin toxicity (66.7% of these were male), and 74 (59.2%) were non-intoxicated (50% of these were male).

Indications for the use of digoxin atrial fibrillation control (47.6% of intoxicated and 40.5% of non-intoxicated patients), pumping failure treatment (21.4% of intoxicated and 27% on non-intoxicated patients), both atrial fibrillation control and pumping failure treatment (28.6% of intoxicated and 29.7% of non-intoxicated patients), and no definite indication (2.4% of intoxicated and 2.7% of non-intoxicated patients).

Of the patients with definite digoxin toxicity, 24 (57.1%) had cardiac manifestations, 7 (16.7%) had non-cardiac manifestations, and 11 had both cardiac and non-cardiac manifestations. The most common manifestation was atrial fibrillation with block (Table 1).

The average daily doses of digoxin taken by the patients with definite digoxin toxicity and those non-intoxicated varied from 0.125 to 0.5 mg. Of the patients with definite digoxin toxicity, 14 (33.3%) received 0.125 mg/day, 27 (64.3%) received 0.25 mg/day, and 1 (2.4%) received 0.5 mg/day. Of the non-intoxicated patients, 28 (37.8) received 0.125 mg/day, 44 (59.5%) received 0.25 mg/day, 1 (1.4%) received 0.375 mg/day, and 1 (1.4%) received 0.5 mg/day. There was no significant statistical difference between the doses used by the patients with and without toxicity.

Seven univariate factors of digoxin toxicity were considered: a history of renal disease, use of nitrates, use of furosemide, serum blood urea nitrogen (BUN) above 20 mg/dl, serum chloride below 85 mg/dl, serum creatinine above 2 mg/dl, and hematocrit below 30% (Table 2). Logistic regression analysis showed that serum BUN (odds ratio = 2.9) and serum chloride (all subjects with serum chloride < 85 mEq/l were classified as definite digoxin toxicity) were independent associated factors of digoxin toxicity: of the patients with definite digoxin toxicity, 66.7% had one or both of these factors.

The mean (SD) of serum digoxin levels

Table 1
Clinical manifestations of digoxin toxicity among 42 patients with definite digoxin toxicity.

	Number	% group	% total
Cardiac manifestations	35	100.0	83.3
Sinus bradycardia	1	2.9	2.4
Sinus arrest	3	8.6	7.1
Sinus exit block	1	2.9	2.4
1st degree AV block	3	8.6	7.1
2nd degree AV block	1	2.9	2.4
3rd degree AV block	1	2.9	2.4
Atrial fibrilation with block	18	51.4	42.9
Non-paroxysmal junctional tachycardia	5	14.3	11.9
AV dissociation	1	2.9	2.4
Bi-directional ventricular tachycardia	1	2.9	2.4
Ventricular bigeminy	9	25.7	21.4
Ventricular tachycardia	1	2.9	2.4
Premature ventricular contraction	7	20.0	47.6
Non-cardiac manifestations	18	100.0	42.9
Nausea	7	38.9	16.7
Vomiting	9	50.0	21.4
Anorexia	5	27.8	11.9
Abdominal pain	4	22.2	9.5
Diarrhea	2	11.1	4.8
Fatigue	3	16.7	7.1
Dizziness	6	33.3	14.3
Visual disturbance	1	5.6	2.4
Headache	1	5.6	2.4

Table 2
Univariate factors of digoxin toxicity and their odds ratios (95% confidence intervals).

	Number (%) among definite group	Number (%) among non-intoxicated group	Odds ratios	95% confidence interval
Evidence of renal disease	9 (21.4)	5 (6.8)	3.8	1.2 - 12.1
Nitrate medication	17 (40.5)	15 (20.3)	2.7	1.2 - 6.2
Furosemide	33 (78.6)	43 (58.1)	2.6	1.1 - 6.3
Serum BUN > 20 mg/dl	25 (59.5)	26 (35.1)	2.7	1.2 - 5.9
Serum creatinine > 2 mg/dl	12 (28.6)	9 (12.2)	2.9	1.1 - 7.6
Serum chloride < 85 mEq/l	6 (14.3)	-	*	
Hematocrit < 30%	11 (26.2)	8 (10.8)	2.9	1.1 - 8.0

* Odds ratio not computed because no non-intoxicated subject had serum chloride less than 85 mEq/l.

among the patients with and without toxicity were 2.28 (1.3) and 1.05 (0.6) ng/ml respectively (p = 0.000) (Fig 1). The serum digoxin levels of those with definite toxicity varied from 0.21 ng/ml to ≥ 5 ng/ml; the levels of the non-intoxicated patients varied from ≤ 0.2 ng/ml to 2.76 ng/ml. The best cut-off level determined by ROC analysis was 1.97 ng/ml (Fig 2): the

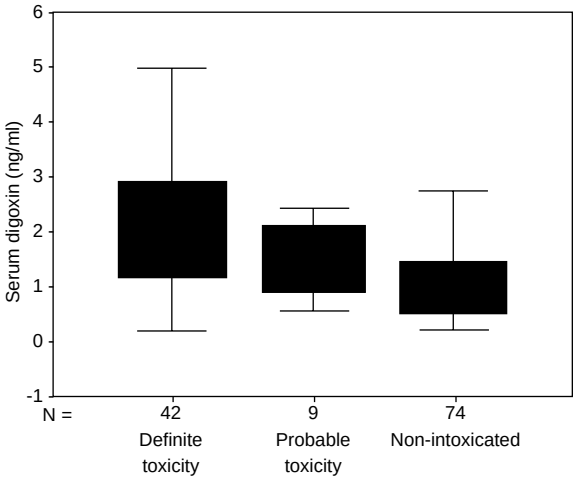

Fig 1–Serum digoxin level of patients with definite digoxin toxicity, probable digoxin toxicity, and non-intoxication.

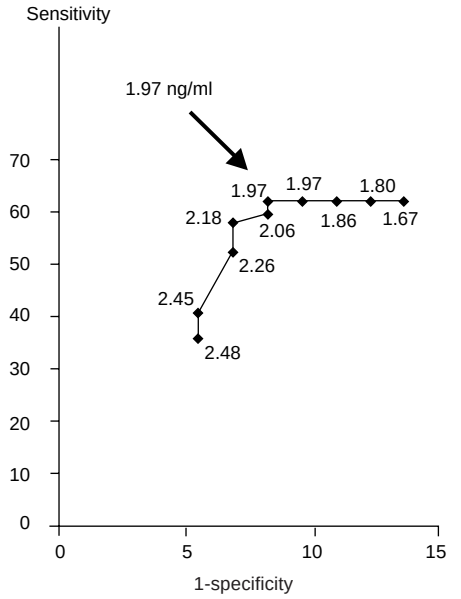

Fig 2–Receiver Operating Characteristic (ROC) analysis of serum digoxin level for diagnosis of digoxin toxicity.

sensitivity was 0.62 and the specificity was 0.92. Twenty-two subjects (10.3%) were therefore misclassified an the basis of this cut-off level. The positive and negative predictive values were 0.81 and 0.81 respectively; the likelihood ratio for a positive test was 3.45.

DISCUSSION

This is the first study of Thai patients that describes digoxin intoxication and evaluates the validity of using a serum digoxin level for the diagnosis of toxicity. Although there is general concern about the limitations of retrospective studies, problems reviewing records in this study were few. Only 9 patients (7.2%) were classified as probable digoxin intoxication. Because the doses of digoxin used by patients with toxicity did not differ from those used by patients without toxicity, the diagnosis of digoxin toxicity cannot be reliant upon dosage.

The manifestations of digoxin toxicity found in this study were not different from those mentioned in other reports (Smith *et al*, 1984; Mahdyoon *et al*, 1990). The cardiac manifestations were common (83.3%), particularly atrial fibrillation with block. However, 43% of the subjects had non-cardiac manifestations: gastrointestinal symptoms and dizziness were common. One in six of the subjects with digoxin toxicity had only non-cardiac manifestations.

Associated factors of digoxin toxicity imply an underlying pathogenesis, *eg* volume contraction, renal impairment, impaired myocyte function, and poor general health (Smith *et al*, 1984). The results of logistic regression analysis showed that high BUN and low serum chloride were independent factors of digoxin toxicity. This finding suggests that renal impairment and volume depletion are strong risk factors of digoxin toxicity among Thai patients. Patients who are treated with digoxin and who have these associated factors should be closely monitored for digoxin toxicity.

Our findings support the use of a serum digoxin level of ≥ 2 ng/ml as a cut-off level (Smith *et al*, 1984; Smith, 1975; Doering *et al*, 1977). However, there is an overlap of therapeutic and toxic serum digoxin levels (Beller *et al*, 1971; Smith *et al*, 1984); it needs

to be emphasized that nearly 20% of the patients with positive results did not have digoxin toxicity and nearly 20% of those with negative results did have digoxin toxicity. Since the sensitivity is rather low, the use of serum digoxin as a screening tool is warrant. Its high specificity and its likelihood ratio suggest that it would serve better in the diagnosis of digoxin intoxication. Nevertheless, the serum level alone may be of limited use in assisting clinicians to establish a diagnosis of toxicity (Ingelfinger and Goldman, 1976).

In conclusion, manifestations of digoxin toxicity among Thai inpatients are no different from those of other populations. The best cut-off level of serum digoxin for the diagnosis of toxicity is 2 ng/ml. The level of serum digoxin should be used as a diagnostic tool rather than as a screening tool. In order to avoid serious adverse reactions, levels of serum digoxin must be taken into account, along with all other relevant clinical data, before management decisions are made. Awareness of and regular surveillance for the clinical-manifestation of digoxin toxicity are central to good clinical practice.

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