CLINICAL RESEARCH

Correlation between manifestations of digoxin toxicity and serum digoxin, calcium, potassium, and magnesium concentrations and arterial pH

MOSHE SONNENBLICK, ABRAHAM S ABRAHAM, ZION MESHULAM, U EYLATH

Abstract

In 18 patients with gastrointestinal manifestations of digoxin toxicity the mean serum digoxin concentration ($\pm$ SEM) was $3.16 \mu\text{g/l}$ (± 0.25), the calcium to potassium ratio 0.31 (± 0.01), and the mean arterial pH 7.406 (± 0.017). In contrast 19 patients with digoxin induced automaticity had a mean serum digoxin concentration of $1.24 \mu\text{g/l}$ (± 0.15 ; $p < 0.001$), a calcium to potassium ratio of 0.38 (± 0.01 ; $p < 0.01$), and an arterial pH of 7.498 (± 0.008 ; $p < 0.001$). Eight out of 13 patients with digoxin induced cardiotoxicity had serum concentrations of the drug within the therapeutic range (0.8 - $2.0 \mu\text{g/l}$). The calcium to potassium ratio, however, was lower than in the patients with automaticity (0.31 ± 0.02 ; $p < 0.01$) and the arterial pH was 7.370 (± 0.033 ; $p < 0.05$). Serum magnesium concentrations were similar in all groups.

In this study patients with digoxin induced gastrointestinal symptoms had high serum concentrations of the drug, whereas those with drug induced automaticity had therapeutic concentrations. This second group, however, was identified by their higher calcium to potassium ratios and higher pH values.

Introduction

Measurement of the plasma digoxin concentration is widely used as an aid to diagnosing digoxin toxicity. There have been numerous studies in which plasma digoxin concentrations have been measured in patients defined clinically and electrocardiographically as either being or not being in a state of digoxin toxicity. In many of these, however, there was a substantial overlap of concentrations between toxic and non-toxic groups,^{1 2} while in others there was no relation between the presence or absence of clinical or electrocardiographic signs of digoxin toxicity and serum digoxin concentrations.^{3 4}

In general, manifestations of digoxin toxicity may be divided into two main types, cardiac and gastrointestinal. Patients with cardiac manifestations may be further subdivided into those with digoxin induced automaticity and those with various other manifestations of cardiotoxicity, such as bradycardia, atrio-ventricular block, and supraventricular tachycardia with block. Interestingly in none of the studies on the correlation between digoxin concentrations and toxicity was an attempt made to separate the patients into subgroups according to their symptoms. That digoxin toxicity may be expressed in different ways in different patients, however, with cardiac or gastrointestinal symptoms the sole or predominating manifestation in different subjects, has not been explained. In addition, some patients may have manifestations of digoxin toxicity although their digoxin concentrations are in the therapeutic range, while in others high concentrations of digoxin are found even though they have no clinical or electrocardiographic evidence of toxicity.

Theoretically digoxin toxicity may be enhanced by an increased serum calcium⁵ or reduced serum potassium concentration,⁶ yet many patients have neither gross hypokalaemia nor frank hypercalcaemia.^{7 8} The combination of a relative hypokalaemia and relative hypercalcaemia, however, might be more closely related to digoxin induced automaticity.⁹

The following study was carried out (a) to see if there was a relation between serum digoxin concentrations and the type of symptoms in patients with digoxin induced cardiac or gastrointestinal abnormalities, (b) to confirm our previous finding of a relation between digoxin induced automaticity and the ratio

Department of Medicine, Shaare Zedek Medical Center, PO Box 293, Jerusalem 91002, Israel

MOSHE SONNENBLICK, MD, lecturer in medicine
ABRAHAM S ABRAHAM, MD, FRCP, associate professor of medicine
ZION MESHULAM, MD, registrar
U EYLATH, PHD, head, department of biochemistry

Correspondence to: Dr Moshe Sonnenblick.

of serum calcium to potassium,⁹ and (c) to study the relation between the manifestations of digoxin toxicity and serum magnesium concentrations and arterial pH.

Patients and methods

A total of 96 patients admitted to the department of medicine during 1980 with symptoms or signs compatible with digoxin toxicity were considered for the study. None was receiving any antiarrhythmic drug apart from digoxin. Each was examined by one of us, had a 12 lead electrocardiogram and one minute rhythm strip recorded, and was provisionally diagnosed as having or not having digoxin toxicity. Forty four of the patients were subsequently excluded—namely, those whose serum digoxin concentrations were undetectable ($<0.2 \mu\text{g/l}$) or whose gastrointestinal symptoms or electrocardiographic manifestations did not disappear after the digoxin had been discontinued for at least three days. The remaining 52 patients in whom the symptoms or signs of digoxin toxicity did disappear when the digoxin was discontinued were included. We also studied 69 other patients who were receiving digoxin but who had neither symptoms nor signs of digoxin toxicity.

Blood for estimating digoxin concentrations was withdrawn at least six hours after the last dose. Serum protein, calcium, potassium, and magnesium concentrations were also measured. Arterial pH was measured only when there was a medical indication. Serum ionised calcium concentrations were obtained using the formula $\text{Ca}^{++}(\text{mmol/l}) = \text{Ca}_{\text{total}} - (0.01833 \times \text{serum albumin (g/l)} + 0.00639 \text{ serum globulin (g/l)})^{10}$ and the calcium to potassium ratio calculated using the value for ionised calcium. Serum digoxin concentrations were measured by

Serum digoxin concentrations in initial series of 52 patients with digoxin toxicity as manifested by gastrointestinal symptoms, automaticity, and cardiotoxicity. Solid horizontal line represents upper therapeutic limit of serum digoxin. Dotted lines represent means and total of four standard errors of mean. (Two patients appear in more than one group.)

Correlation of manifestations of digoxin toxicity with serum digoxin concentrations, calcium to potassium ratios, and arterial pH. Values are means $\pm$ SEM

Symptoms and signs	No of patients	Digoxin dose (mg/day)	Serum digoxin ($\mu\text{g/l}$)	Ca:K ratio	Arterial pH
Gastrointestinal	18	$0.23 \pm 0.02^{**}$	$3.16 \pm 0.25^{***}$	$0.31 \pm 0.01^{**}$	$7.406 \pm 0.017^{***}$
Automaticity	19	0.13 ± 0.01	1.24 ± 0.15	0.38 ± 0.01	7.498 ± 0.008
Cardiotoxicity	13	$0.25 \pm 0.02^{**}$	$2.36 \pm 0.37^{***}$	$0.32 \pm 0.01^{**}$	$7.39 \pm 0.032^*$
None†	50	$0.24 \pm 0.02^{**}$	$2.97 \pm 0.07^{**}$	$0.34 \pm 0.05^*$	—
		0.15 ± 0.05	1.17 ± 0.35	$0.35 \pm 0.06^*$	—

Difference from mean of automaticity group significant at level of *5%, **1%, *** $<1\%$.

†This group studied in addition to main study group and comprised 69 patients taking digoxin who had no symptoms or signs of toxicity.

radioimmunoassay.¹¹ Therapeutic values in our laboratory range from $0.8\text{--}2.0 \mu\text{g/l}$.

Patients were divided into the following three groups according to their symptoms or signs.

Group 1 were patients with gastrointestinal symptoms such as nausea, vomiting, or diarrhoea.

Group 2 were patients with one of the following electrocardiographic changes of digoxin induced automaticity: (a) five or more ventricular premature beats a minute, (b) multifocal ventricular premature beats, even if fewer than five a minute, (c) bigeminy, (d) ventricular tachycardia.

Group 3 were patients with electrocardiographic evidence of cardiotoxicity but who did not have digoxin induced automaticity. They included patients with atrial fibrillation and a ventricular rate of less than 50/min, atrial flutter or tachycardia with changing block, a P-R interval of more than 0.28 s, and second degree atrioventricular block.

Since the purpose of the study was to ascertain the possible relation between the symptoms and signs of digoxin toxicity on the one hand and the calcium to potassium ratio, serum magnesium concentration, or arterial pH on the other, two patients who had both gastrointestinal and cardiovascular manifestations were excluded from the analysis.

Student's *t* test was used for statistical analysis.

Results

The 52 patients initially included in the series had 54 symptoms or electrocardiographic signs of digoxin toxicity. The figure shows their serum digoxin concentrations. There was a clear cut and significant difference in values between patients with gastrointestinal symptoms

and those with automaticity. Only two of the 20 patients with gastrointestinal symptoms had therapeutic concentrations of the drug in their sera, and the mean ($\pm$ SEM) for the group was $3.15 \pm 0.23 \mu\text{g/l}$. On the other hand, of the 21 patients with signs of automaticity, 18 had serum digoxin concentrations in the therapeutic range, and the mean for that group was $1.42 \pm 0.19 \mu\text{g/l}$ ($p < 0.001$). Eight out of 13 patients with cardiotoxicity had serum digoxin values in the therapeutic range.

The table shows the correlation between the three types of manifestations of digoxin toxicity and the calcium to potassium ratio and arterial pH. Patients with gastrointestinal symptoms had toxic concentrations of serum digoxin. The calcium to potassium ratio and arterial pH, however, were normal in these patients. Conversely, patients with drug induced automaticity had digoxin concentrations in the therapeutic range, but their mean calcium to potassium ratio and mean arterial pH were significantly different from those in the patients with gastrointestinal symptoms ($p < 0.01$ and $p < 0.001$, respectively). Patients with cardiotoxicity but who did not have automaticity had a mean serum digoxin concentration of $2.36 \mu\text{g/l}$ (± 0.37). Eight of these patients, however, had serum digoxin concentrations in the therapeutic range (mean $1.45 \pm 0.16 \mu\text{g/l}$); their mean calcium to potassium ratio was 0.31 ± 0.02 and their mean arterial pH 7.370 ± 0.033 . There was a significant difference in calcium to potassium ratio ($p < 0.01$) and arterial pH ($p < 0.05$) between these eight patients and the group with drug induced automaticity.

Of the 69 patients studied who did not have symptoms or signs of digoxin toxicity, 50 had blood concentrations of the drug within the therapeutic range and 19 had toxic concentrations. In both groups, however, the calcium to potassium ratio was significantly lower than in patients with digoxin induced automaticity.

Mean serum magnesium concentrations were normal in all groups.

Discussion

Several studies have shown a large overlap of serum digoxin concentrations in groups of patients with and without digoxin toxicity.^{1,2} Nevertheless, the relation of digoxin values to the type of symptom or sign in patients with toxicity has not been studied. We find that most patients with digoxin toxicity who present with gastrointestinal symptoms have toxic concentrations of serum digoxin, whereas most patients with automaticity or cardiotoxicity have therapeutic concentrations. Why should patients with therapeutic blood concentrations of digoxin develop automaticity? Potassium protects sodium and potassium adenosine triphosphatase activity against digoxin toxicity, and the probability of toxicity increases with decreasing values of serum potassium. Thus almost any patient receiving digoxin may show signs of cardiotoxicity if the serum potassium concentration is below 3.0 mmol(mEq)/l.⁶ Only five of our patients had a value below 3.5 mmol/l, and in none was it less than 3.0 mmol/l.

Calcium has the opposite effect of increasing the inhibition of sodium and potassium adenosine triphosphatase activity by digoxin, so that hypercalcaemia will increase the likelihood of automaticity. Hypercalcaemia is relatively rare, however, and in experiments serum calcium concentrations must be raised to values not encountered in man before any increase in sensitivity of the heart to digoxin can be detected.¹²

Since most patients with symptoms of digoxin toxicity have neither severe hypokalaemia nor gross hypercalcaemia, we considered whether a combination of mild hypokalaemia together with mild hypercalcaemia might be responsible for the digoxin induced automaticity. Our study showed a clear relation between automaticity and the calcium to potassium ratio, with a significant increase in ratio in patients with automaticity. This relation became even more pronounced when the three patients with toxic concentrations of serum digoxin (which alone might have been responsible for their symptoms) were removed from the group. The mean calcium to potassium ratio for the other 16 patients was then 0.388 and even more significantly different from the ratio in patients with gastrointestinal symptoms ($p < 0.005$). Digoxin produces an increased influx of calcium, varying with the concentration of calcium surrounding the myocardial cell.¹³ Automaticity, manifested by ventricular extrasystoles, is at least partly due to the oscillatory release of this calcium from overloaded intracellular stores.⁵

Eight out of 13 patients had signs of cardiotoxicity without signs of automaticity. Since these manifestations are probably not due to inhibition of the sodium and potassium adenosine triphosphatase system it was not surprising that their calcium to potassium ratio was normal. The mechanisms in the production of cardiotoxicity are not apparent.

Acidosis is a factor in increased sensitivity of the myocardium to digoxin. Our patients with digoxin induced automaticity had appreciable alkalosis, whereas patients with other manifestations of cardiotoxicity or with gastrointestinal symptoms had a normal mean arterial pH. The mechanism by which automaticity is increased in the presence of alkalosis is not clear, though alkalosis may reflect intracellular potassium depletion and increased cellular calcium. Since many patients receiving digoxin may also be taking diuretics alkalosis may be an important factor leading to automaticity, even when the serum digoxin concentration is within the therapeutic range.

Hypomagnesaemia potentiates digitalis toxicity. In all our patients, however, the serum magnesium concentration was normal, ranging from 0.8 to 0.9 mmol/l (1.9 to 2.1 mg/100 ml) in the different groups. Hence hypomagnesaemia is apparently not a common cause for an increased myocardial sensitivity to digoxin.

The clear relation between gastrointestinal symptoms and toxic concentrations of serum digoxin is due to the central effect

of digoxin on the chemoreceptor trigger zone located in the area postrema of the medulla.¹⁴ Thus high concentrations of serum digoxin must be reached before a toxic effect on the medullary centres become evident. Three of our patients, however, had gastrointestinal symptoms in the presence of therapeutic concentrations of serum digoxin, and other patients with toxic concentrations of the drug had no symptoms or signs of digoxin toxicity. The area postrema is not under the influence of the blood-brain barrier¹⁵ and therefore changes in the ratio of cerebrospinal fluid to blood digoxin values are probably not responsible for the gastrointestinal symptoms. Nevertheless, these manifestations may be due to changes in the sensitivity of the medullary centres to digoxin.

Our study partly explains some of the known discrepancies and lack of correlation between serum digoxin values on the one hand and signs and symptoms of digoxin toxicity on the other. We have shown that there is indeed a good correlation between high serum digoxin concentrations and the occurrence of gastrointestinal symptoms. On the other hand, although patients with digoxin induced automaticity may have therapeutic concentrations of digoxin in their blood, their abnormal calcium to potassium ratio and arterial pH are more important factors leading to the increased myocardial sensitivity to even therapeutic serum concentrations of the drug. Undoubtedly other factors, such as the functional state of the myocardium, intercurrent disease, the arterial oxygen pressure, and the effects of other drugs, are also important. Nevertheless, it is essential to realise that a serum digoxin concentration which is in the therapeutic range does not rule out a diagnosis of cardiotoxicity, particularly when the effect is one of increased automaticity.

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