ISSN: 0975-833X

Available online at http://www.journalcra.com

International Journal of Current Research
Vol. 7, Issue, 08, pp.19071-19075, August, 2015

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

RESEARCH ARTICLE

DIGITOXICITY RELATED TO MAGNESIUM LEVELS

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ARTICLE INFO

Article History:
Received 21st May, 2015
Received in revised form
28th June, 2015
Accepted 09th July, 2015
Published online 21st August, 2015

Key words:

Magnesium,
Digoxin toxicity,
Digitoxicity,
Colour vision.

ABSTRACT

Aim: to find the relationship between Magnesium levels and patients who are digoxin therapy and correlated with those who developed digitoxicity.

Methods: Eighty-one hospital patients receiving digoxin were separated into groups with and without digitoxicity (digoxin toxicity) using clinical criteria. Serum digoxin, sodium, potassium, calcium, creatinine, magnesium and monocyte magnesium concentrations were compared. Subjects with digoxin toxicity had impaired colour vision ($P < 0.0001$, Farnsworth-Munsell 100 hue test) and increased digoxin levels (1.89 (1.56-2.21) vs 1.34 (1.20- 1.47) nmol l^{-1}, $P < 0.01$) (mean (95% confidence limits)), though there was considerable overlap between the two groups.

Results: Subjects with digoxin toxicity had lower levels of serum magnesium (0.80 (0.76-0.84) vs 0.88 (0.85-0.91) mmol l^{-1}, $P < 0.01$) and monocyte magnesium (6.40 (5.65-7.16) vs 8.76 (7.81-9.71) mg g^{-1} DNA, $P < 0.01$), but there were no significant differences in other biochemical parameters. A greater proportion of toxic subjects were receiving. concomitant diuretic therapy (20/21 vs 37/60, $P < 0.05$).

Conclusion: Magnesium deficiency was the most frequently identified significant electrolyte disturbance in relation to digoxin toxicity. (Young *et al*., 1991) In the presence of magnesium deficiency digoxin toxicity developed at relatively low serum digoxin concentrations.

***Citation*:** Dr. K. Saradamba and Dr. M. Lakshmi Rajeswari, 2015. "Digitoxicity related to magnesium levels", *International Journal of Current Research*, 7, (8), 19071-19075.

INTRODUCTION

Digoxin is a commonly prescribed drug and the problem of digoxin toxicity is well recognised. Serum digoxin concentrations are widely used to monitor treatment but are a relatively poor predictor of toxicity (Storstein *et al*., 1977). A number of factors will increase the risk of digoxin toxicity at a given digoxin concentration, including hypo-kalaemia, hypercalcaemia and hypomagnesaemia. Patients receiving digoxin are often given concomitant treatment. with diuretics (Storstein *et al*., 1977), increasing the risk of electrolyte disturbances. The risk of potassium depletion is widely appreciated; routine monitoring of potassium concentrations is common and patients are frequently given potassium supplements or potassium sparing drugs. However, magnesium depletion is less likely to be monitored or treated, and for this reason hypomagnesaemia may now be the most common electrolyte abnormality in patients receiving digoxin (Whang *et al*., 1985). The aim of this study was to determine the prevalence of electrolyte abnormalities in patients receiving digoxin, with particular reference to disturbances of magnesium metabolism, and to assess their contribution to the development of digoxin toxicity. Serum magnesium represents less than 1% of the total body magnesium pool and correlates poorly with intracellular magnesium levels (Elin and Hosseini, 1985) and the development of cardiac arrhythmias (Boyd *et al*., 1984) We have therefore measured monocyte magnesium concentrations as an additional indicator of magnesium status. Monocyte magnesium has been shown to be a better predictor of the development of magnesium responsive cardiac dysrhythmias (Cohen and Kitzes, 1983) and to correlate well with levels of magnesium in other body tissues in both animals (Martin *et al*., 1988) and human subjects (Sjogren *et al*., 1986).

MATERIALS AND METHODS

Patients were recruited following their admission to acute medical or Cardiology wards of the King George Hospital, Visakhapatnam. Patients were included in the study if they had been taking a stable dose of digoxin for greater than 10 days. All subjects gave verbal informed consent and the study was approved by the Medical Ethics Committee of the King George Hospital, Visakhapatnam.

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A full clinical assessment of each subject was performed and an electrocardiogram obtained. The clinical assessment was performed by an independent observer without any knowledge of the laboratory results. Subjects were classified as clinically toxic or non-toxic using established criteria (Aronson *et al*., 1978) (Table 1). In subjects in whom digoxin was withdrawn the electrocardiogram was repeated after 1 week. Colour vision was assessed using the Farnsworth-Munsell 100 hue test and colour vision scores corrected for age (Aronson *et al*., 1978).

Table 1. Criteria for the diagnosis of digoxin toxicity (taken from Aronson *et al*., 1978)

Criteria	Number of subjects
1. SVT with AV block	3
2. PVB - >5/min, bigeminal or multifocal	11
3. Ventricular tachycardia	2
4. AF with a ventricular response of <60/min In the presence of PVP	3
5. Second or third degree AV Block	0
6. Any of the following dysarhythmias/symptoms if resolution has occurred one week following the withdrawl of digoxin:	2
- PVB < 5/min, first degree AV block	
- sinus bradycardia <60/min.	
- AF with ventricular response <60/min.	
- anorexia, nausea or vomiting.	

Subjects unable to co-operate were excluded from colour vision testing as were those with diabetes mellitus, which is known to impair colour perception. Male patients with red-green colour blindness were also excluded from the analysis. A venous blood sample was taken 6 h after the last dose of digoxin for the estimation. of serum digoxin, sodium, potassium, creatinine,calcium and albumin, serum magnesium and monocyte magnesium. Biochemical measurements including serum magnesium were performed on an American Monitor Parallel Analyser. Serum digoxin was estimated by immunoassay using the Abbott TDX system. Monocyte magnesium measurements were performed as previously described (Elin Hosseini *et al*., 1985). The cells were lysed by ultrasonicfication and stored at -70° C before analysis. The magnesium content of the cell preparation was measured by atomic absorption spectroscopy. Cell DNA content was measured[11] and the monocyte magnesium expressed as mg g^{-1} of DNA. The intraassay coefficient of variation averaged 4.7% between 4.5 and 13.0 mg g-1 DNA. Toxic and non-toxic subjects were compared using unpaired t-tests and the chi-square test. Results are given as mean with 95% confidence limits unless otherwise stated. Correlations were sought using the linear correlation coefficient, except for those involving colour vision scores when the Spearman rank correlation coefficient was used. Discriminant analysis was performed using regression coefficients. Statistical analyses were performed using the Solo statistical package (BMDP Statistical Software, Cork Technol-ogy Park, Cork, Ireland) on a Nimbus microcomputer.

RESULTS

A total of 81 subjects were recruited. Digoxin was the preparation used in all patients, in a dose of 62.5ug day^{-1} in 22 patients, 125 p.g day^{-1}in 30 and 250 ug day^{-1} in 29. Twenty-one of the 81 subjects (8 female, 13 male; mean age 65.0 years, range 27-83), were classified clinically as suffering from digoxin toxicity (Table 1) and 60 (22 female, 38 male; mean age 68.4 years, range 42-85) as non-toxic. Colour vision as assessed using the Farnsworth-Munsell test was impaired in the toxic subjects (age corrected colour vision score 272 (241-303) vs 180 (152-209), $P < 0.0001$). As expected,serum digoxin levels were significantly higher in toxic subjects (1.89 (1.56-2.21) vs 1.34 (1.20-1.47) nmol l-1, $P < 0.01$), but there was considerable overlap between the two groups (Figure 1). There was a weak positive correlation between colour vision scores and digoxin levels ($r = 0.31$, $P < 0.05$) but colour vision did not correlate significantly with any of the other biochemical parameters measured.

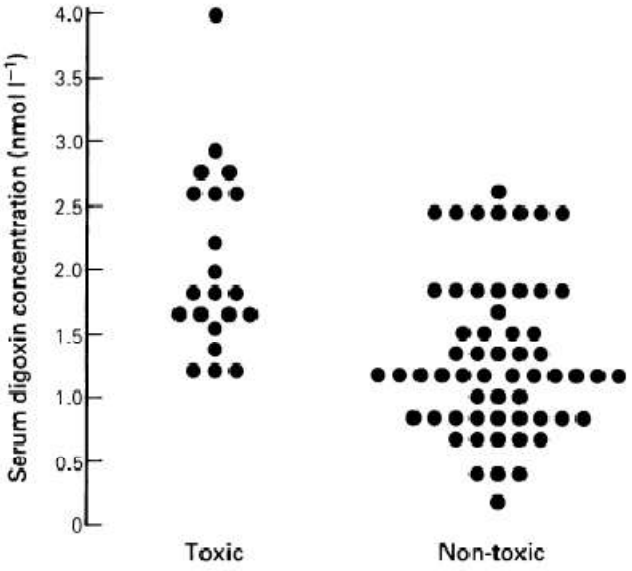

Figure 1. Serum digoxin concentrations in patients with toxicity and without toxicity of digoxin

The incidence of electrolyte abnormalities is shown in Table 2. Overall 24% of toxic subjects and 35% of non-toxic had one or more electrolyte abnormalities (P = NS). Of the electrolyte abnormalities which may accentuate digoxin toxicity, hypomagnesaemia was the most common.

Table 2. Incidence of electrolyte abnormalities in patients with and without digitoxicity

	Toxic (n=21)	No Toxicicity (n=60)
Hypernataremia (>145 mmol L^{-1})	0	0
Hyponatremia (<135 mmol L^{-1})	2	8
Hyperkalemia (>5.5 mmol L^{-1})	1	2
Hypokalemia (<3.5 mmol L^{-1})	0	2
Hypermagnesemia (>1.03 mmol L^{-1})	0	5
Hypomagnesemia(0.75 mmol L^{-1})	4	4
Hypercalcemia (2.50 mmol L^{-1})	1	4
Hypocalcemia (2.07 mmol L^{-1})	2	1

There were no significant differences in serum sodium, potassium, calcium or creatinine levels between toxic and non-

toxic subjects (Table 3). Both serum and monocyte magnesium levels were lower in the toxic group (Table 3). However, there was no significant correlation between serum and monocyte magnesium levels (r = -0.0039). In comparison with our normal range for monocyte magnesium (5.80-11.80 mg g-1DNA), 3 of 21 subjects with clinically diagnosed digoxin toxicity had a low monocyte magnesium level despite a normal serum magnesium, indicating the presence of a significant intracellular magnesium deficit which would otherwise have been overlooked. Discriminant analysis using colour vision score, serum magnesium, monocyte magnesium, serum potassium, creatinine, calcium and digoxin showed that age corrected colour vision score was the strongest individual predictor of the presence of digoxin toxicity, accounting for 21.7% of the multifractional regression. Monocyte magnesium accounted for 16.3% of the regression and serum magnesium 7.7%. Of the variables tested only colour vision score, monocyte magnesium, serum magnesium and creatinine were of value as independent predictors of digoxin toxicity. Using these variables in a multiple regression equation correctly classified 85% of subjects as toxic or non-toxic.

Table 3. Biochemical parameters with and without digoxin toxicity Results given as mean with 95% confidence limits (*p<0.01)

	With toxicicity	Without Toxicity
Sodium (mmol L^{-1})	137(136-138)	138(136-140)
Potassium(mmol L^{-1})	4.2(3.9-4.4)	4.5(4.3-4.6)
Calcium(mmol L^{-1})	2.22(2.15-2.29)	2.24(2.20-2.28)
Creatinine(µmol L^{-1})	110(93-126)	116(101-131)
Magnesium(mmol L^{-1})	0.80(0.76-0.84)*	0.88 (0.85-0.91)
Monocyte Magnesium (mg g^{-1} DNA)	6.40(5.56-7.16)*	8.76 (7.91-9.71)

Table 3. Biochemical parameters in patients receiving or not diuretic therapy. Results given as mean with 95% confidence limits (*p<0.05)

	diuretic (n=57)	no diuretic (n=24)
Sodium (mmol L^{-1})	138(137-139)	138(134-141)
Potassium(mmol L^{-1})	4.3(4.2-4.5)	4.5(4.3-4.7)
Calcium(mmol L^{-1})	2.25(2.22-2.28)	2.20(2.16-2.24)
Creatinine(µmol L^{-1})	124(108-141)*	92(77-108)
Magnesium(mmol L^{-1})	0.87(0.84-0.90)	0.84 (0.79-0.89)
Monocyte Magnesium (mg g^{-1} DNA)	7.55(6.82-8.28)*	9.52 (7.77-11.27)

The majority of subjects were receiving concomitant long term diuretic therapy, usually for congestive heart failure. However, a significantly greater proportion of subjects with toxicity were receiving such treatment (20/21 vs 37/60, P < 0.05). Electrolyte levels in subjects receiving diuretic therapy or no diuretic therapy are shown in Table 4. The groups did not differ significantly in either age or sex distribution. The only significant difference in electrolyte status was in monocyte magnesium concentrations, which were lower in subjects on diuretics. Of the 57 subjects receiving diuretics, 15 were taking potassium sparing drugs. There were no differences between subjects taking potassium sparing diuretics (n = 15) and other diuretics (n = 42) when electrolyte status was compared. There was clearly widespread awareness of the dangers of potassium depletion when a combination of digoxin and diuretics are used as 81% of subjects on diuretic therapy were taking potassium supplements or potassium sparing drugs (diuretics or angiotensin converting enzyme inhibitors).

There was no significant difference between toxic and non-toxic groups. To assess further the effects of magnesium status on the development of digoxin toxicity, toxic subjects were divided into two approximately equal groups – those with a serum digoxin of > 2.0 nmol l^{-1} (n = 9) and those with a serum digoxin of < 2.0 nmol 1^{-1} (n = 12). Patients developing toxicity in the presence of lower serum digoxin concentrations had lower serum magnesium concentrations (0.74 (0.67-0.81) vs 0.84 (0.78-0.89) mmol l^{-1}, P < 0.05). Monocyte magnesium levels were also somewhat lower in toxic subjects with low digoxin concentrations though this difference did not reach statistical significance (5.93 (4.12-7.74) vs 6.83 (5.61-8.04) mg g^{-1} DNA). This may be because numbers were small for this type of analysis. There were no differences in other biochemical parameters.

DISCUSSION

We have found that magnesium depletion was the most common significant electrolyte abnormality in subjects being treated with digoxin and have shown a relationship between intracellular magnesium depletion and the development of digoxin toxicity. Of the parameters assessed, age-corrected colour vision score proved to be the best individual predictor of the presence of digoxin toxicity, but formal colour vision testing has a number of disadvantages. There is a requirement for some expertise on the part of the examiner and a considerable degree of patient co-operation; the method is therefore unsuitable for use in ill or confused patients. Moreover, a significant proportion of male subjects will prove to be colour blind and the Farnsworth-Munsell colour testing kit is relatively expensive to buy.

Previous studies have shown features of digoxin toxicity in 15-25% of patients taking digoxin (Storstein *et al*., 1977) and our study supports these findings. Electrolyte abnormalities are present in up to 56% of subjects taking digoxin (Whang *et al*., 1985). Hypokalaemia has been a relatively common finding, but recent studies suggest that a high level of awareness of this has led to widespread treatment of patients receiving digoxin with potassium supplements or potassium sparing drugs. Hypomagnesaemia may now be more common than hypokalaemia in adults (Whang *et al*., 1985), children (Singh *et al*., 1975) and the elderly (Young *et al*., 1991) who are being treated with digoxin. Magnesium depletion might increase the risk of digoxin toxicity in several ways. At a cellular level digoxin inhibits the membrane bound sodium-potassium ATPase, causing an increase in intracellular sodium. This leads to increased activity of the membrane-bound sodiumcalcium exchanger and the resultant increase in intracellular calcium is believed to mediate many of the actions of digoxin (Ghani and Smith, 1974). Magnesium is an essential co-factor for the sodium-potassium ATPase and magnesium deficiency may potentiate its inhibition by digoxin. Alternately, magnesium may have direct effects on membrane calcium and potassium

transport which influence digoxin toxicity (Specter *et al*., 1975). The relationship between hypomagnesaemia and the development of digoxin toxicity has been addressed in a small number of reports. No difference was found in mean serum magnesium levels between 42 toxic and 25 non-toxic subjects [20], although serum potassium was significantly lower in the toxic group. A further study also reported no change in mean serum magnesium levels (Beller *et al*., 1974), although an increased prevalence of hypomagnesaemia in dioxin toxic subjects was found. In contrast, a slight reduction in serum magnesium was demonstrated in 113 subjects with suspected or definite toxicity when compared with 536 non-toxic patients (Storstein *et al*., 1977). The value of magnesium infusion in the treatment of refractory digoxin induced arrhythmias, in both hypomagnesaemic and normomagnesaemic patients is widely recognised. Five patients with digoxin associated cardiac arrhythmias in whom serum magnesium was normal but lymphocyte magnesium reduced responded to intravenous magnesium (Cohen and Kitzes, 1983). Two subjects with refractory ventricular fibrillation and tachycardia in the presence of digoxin therapy and hypomagnesaemia responded well to magnesium infusion (Iseri *et al*., 1975). However, prior to our study there has been no systematic survey of the relationship between the development of digoxin toxicity and cellular magnesium levels in a large group of patients. Monocyte magnesium levels do not correlate with serum magnesium but are related to muscle magnesium status (Iseri *et al*., 1975). Monocyte magnesium therefore provides information about body magnesium status not available from a simple measure of serum magnesium (Elin and Hosseini, 1985). In particular, patients may have a significant cellular magnesium depletion while maintaining a normal serum magnesium level and we identified three subjects who fell into this category. There is, however, considerable intra and inter individual variation in monocyte magnesium levels. This factor and the number of stages in the assay (cell separation and washing, magnesium determination, DNA determination) suggest that random measurements may be of limited use in individual subjects (Gallacher *et al*., 1987). Little information is available about the validity of the measurement in settings where there are increased numbers and turnover of white cells and the assay is labour intensive and not readily available. For these reasons we believe it may best be reserved for situations where magnesium depletion is strongly suspected but serum magnesium normal or near normal. In this study monocyte magnesium levels were lower in subjects receiving diuretic treatment. However, the study was not designed to assess the relationship between diuretic therapy and magnesium status and we do not believe that any direct causal relationship should be inferred from this association.

An alternative approach to the assessment of magnesium status is the use of the magnesium loading test (Jones *et al*., 1969). Using such a test a positive correlation has been shown between the degree of magnesium deficiency and the prevalence of ventricular premature beats (Lewis *et al*., 1991). However, the magnesium loading test is of limited use in patients taking diuretics or with renal impairment and it is in such patients that serial measurements of cellular magnesium status using a monocyte magnesium assay might be of particular value. We have shown that disturbances in magnesium status are the most frequently found significant electrolyte abnormality in patients receiving digoxin. We therefore believe that routine monitoring of electrolytes in these patients should include the measurement of serum magnesium, as this test is the most readily available biochemical indicator of magnesium status. However, as cellular magnesium depletion may be present despite a normal serum magnesium concentration, consideration should also be given to assessing cellular magnesium status in patients who develop digoxin toxicity in the absence of any obvious precipitating factor. (Young *et al*., 1991) The potential role of magnesium sparing diuretics and oral magnesium supplementation in reducing the incidence of digoxin toxicity remains to be tested.

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