INVESTIGATION INTO THE POSSIBLE MECHANISMS INVOLVED IN ALTERED DIGOXIN LEVELS IN DIABETIC PATIENTS

S. D. JOSHI, D. D. SANTANI, J. J. SHETH*,
H. C. MEHTA*, K. C. DAVE* AND R. K. GOYAL⁺

*Department of Pharmacology,
L. M. College of Pharmacy,
Ahmedabad - 380 009*

and

**K. M. School of Post-Graduate Medicine and Research,*
V. S. General Hospital,
Ahmedabad - 380 006

Abstract: The present study was undertaken to investigate the possible factors which may contribute to the altered digoxin levels in diabetic patients. The digoxin levels were found to be significantly higher in diabetics (1.74 ± 0.09 ng/ml) as compared to non-diabetics (0.76 ± 0.07 ng/ml). There was a positive correlation between digoxin levels and glycosylated haemoglobin levels. All diabetic patients had serum creatinine, urea and potassium levels within normal limits. However, serum TSH levels were found to be significantly higher in diabetics as compared to controls. Serum tri-iodo-1-thyronine (T_3) levels were found to be lower in diabetics as compared to non-diabetics. Our data suggests that diabetes-mellitus causes alteration of digoxin levels. One of the causes of this increase in digoxin levels may be a tendency towards mild hypothyroidism associated with diabetes mellitus.

Key words : digoxin   thyroid stimulating hormone
                 tri-iodo-1-thyronine   diabetes mellitus

INTRODUCTION

Various clinical (1), pathological (2) and experimental data (3) have strongly suggested that diabetes mellitus is associated with the development of heart failure. Besides the association between diabetes and heart disease, alterations in responses to various cardiotonic agents have also been reported by various workers (4). Clinically, it has been an experience that diabetic patients respond abnormally to digoxin (5). Many a time toxic manifestations and ineffectiveness of digoxin therapy in diabetics have been observed (6). Goyal and McNeill (7) reported that the responses to milrinone, a newer cardiotonic agent, were increased in atrial preparations obtained from diabetic rats. It was proposed that milrinone may be a preferred drug in the diabetic patients suffering from congestive cardiac failure (7). However, as of today digoxin is the drug of choice and one of the most frequently prescribed drugs for patients suffering from congestive cardiac failure (CCF).

Due to its narrow therapeutic index, the incidences of digoxin intoxication are also very high ranging from 20-30%. Olson et al (6) concluded that emergency medical services personnel should consider digoxin toxicity as a potential etiology of cardiac arrest. Digoxin is excreted through urine and there is a good

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⁺Corresponding Author

correlation between the status of kidney and digoxin levels (8). Further, long term diabetes has been shown to produce nephropathy (9). Thus, it is possible that increased levels of digoxin may be due to altered kidney function.

Diabetes is a multifactorial disorder causing alterations in carbohydrate, lipid and protein metabolism and endocrine function.

An intimate relationship between diabetes mellitus and altered thyroid function has also been recognised. Both hypothyrodism (10, 11) and hyperthyroidism (12, 13) are reported to be associated with diabetes in humans. However, in rats diabetes is known to cause a mild state of hypothyroidism (7, 14). Thyroid status is also known to alter the responsiveness to digoxin. Lower digoxin levels are found in hyperthyroid patients whereas higher digoxin levels are found in hypothyroid patients (15). It is reasonable to assume that higher digoxin levels in diabetic patients may as well be due to associated hypothyroidism.

In the light of these observations, the present study was undertaken to investigate serum digoxin levels in diabetic patients. Further, attempts were made to find out possible factors involved in altered levels of digoxin. In particular emphasis has been laid on the status of thyroid and kidney functions of the patients.

METHODS

Indoor patients admitted with the suspicion of cardiac disease in medical words of V.S. and Chinai Maternity Hospital, Ahmedabad (India) were selected for the present study. In the present study 30 patients, (17 male and 13 female) were included. The age of the patients was 48-68 years (56±9 years) and the weight range was 45-65 kg (56±5 kg). Out of these 30 patients included in our study 19 were diabetic and 11 were non-diabetic.

Patients were included in the study if they had CCF and left ventricular failure. The subjects were excluded if they had any vascular disease, mitral stenosis, severe retinopathy, renal or neurological diseases, or if they had been on digoxin therapy previously or had diabetes mellitus for a period of more than 3 years. After taking history of the patients, they were examined for the clinical data (blood pressure, jugular vein pressure, pulse rate etc.) and blood samples were taken for routine clinical biochemistry. The ECG of each patient was recorded to confirm the type of complications they had. Patients included in the study were informed about the study and their consent was taken.

Digitalisation and collection of blood samples: The patients were digitalised by giving a high dissolution tablet of 0.25 mg digoxin (Lanoxin[R]) thrice a day for first two days followed by one oral dose of digoxin (0.25 mg) for five days. After five days patients were advised to continue digoxin therapy daily with once a week interruption in the dose of digoxin to avoid cumulation. For our study, once admitted to the wards, each patient received the fixed dose of digoxin (0.25 mg) administered daily between 8.30 to 9.00 am. After 8 hrs of digoxin administration, the blood samples were drawn by venepuncture. The samples were analysed for serum digoxin by radio-immunoassay method as described by Smith et al (16) using 'coat-a-count' RIA kit obtained from Diagnostic Products Corporation (U.S.A.). They were also analysed by radioimmunoassay for serum T_3 and T_4 (using RIA kits obtained from B.A.R.C. Bombay, India) and TSH (using IRMA count TSH kit obtained from Diagnostic Products Corporation (U.S.A.). Some of the samples were also analysed for connecting peptide (C-peptide) using double antibody C-peptide kit obtained from Diagnostic Products Corporation (U.S.A.).

Plasma glucose level was analysed by enzymatic (colorimetric) method whereas, serum cholesterol, creatinine and urea were estimated by spectrophotometric methods. Serum potassium (K^+) levels were estimated by emission flamephotometry method.

The results were analysed statistically and the level of significance was determined using

unpaired Student's "t" test. The value of P less than 5% (P<0.05) was considered to be significant.

RESULTS

While studying the case history of each patient, it was found that hypertension was more prevalent in diabetic patients as compared to non-diabetics. There was a marked difference in the B.P. observed in diabetics (156.2 ± 6.25 mmHg/98.7 ± 2.67 mmHg) as compared to non-diabetics (119.6 ± 3.72 mmHg/82.8 ± 2.18 mmHg).

Plasma glucose, glycosylated haemoglobin and serum cholesterol levels (Table I) in diabetic patients with cardiac diseases were found to be significantly higher (P<0.05) as compared to those in non-diabetics. C-peptide levels were estimated amongst diabetic patients in order to recognise the type of diabetes. All diabetic patients had the value of C-peptide within the normal limits (0.8 to 4.9 ng/ml).

Serum digoxin levels : Serum digoxin levels in non-diabetic patients after 8 hours of drug administration were found to be 0.76 ± 0.07 ng/ml. Serum digoxin levels in diabetic patients (1.74 ± 0.09 ng/ml) were found to be significantly higher (P<0.05) as compared to non-diabetics (0.76 ± 0.07 ng/ml). None of the diabetic patients showed any symptom of digoxin toxicity, although one of the patient had digoxin level

2.5 ng/ml. Except for three, all diabetic patients had digoxin levels above 1.5 ng/ml. As far as non-diabetics are concerned, serum digoxin levels were below 1.0 ng/ml in nine out of eleven patients. Glycosylated haemoglobin (GHb) values were apparently higher in diabetic patients with higher digoxin levels. Scatter diagram suggested a positive correlation between glycosylated Hb and serum digoxin levels. The correlation between these two appears to be partial as revealed from correlation coefficient (r=0.31).

No significant difference was found in serum creatinine values amongst diabetics (1.36 ± 0.20 mg/dl) and non-diabetic patients (1.08 ± 0.05 mg/dl). The serum K^+ levels were found to lie within the normal range in the diabetics (3.55 ± 0.21 milliEq/lit) as well as in the non-diabetics (3.78 ± 0.22 milliEq/lit).

Thyroid status of the patients : Serum TSH, T_3 and T_4 were analysed to check the thyroid status of the patients (Table I). Among diabetics, eleven out of nineteen patients had serum TSH levels more than 2.0 µU/ml. Out of them again two patients had serum TSH levels greater than 4.0 µU/ml and showed symptoms of hypothyroidism. Only three diabetic patients had serum TSH levels below 1.5 µU/ml. In contrast to these, none of the non-diabetic patients had serum TSH levels above 2.5 µU/

TABLE I : Biochemical parameters measured in diabetic and non-diabetic subjects.

Study group	Diabetics	Non-diabetics
Serum glucose (mg/dl)	179.03 ± 3.84*	117.54 ± 3.02
C-peptide (IU/ml)	0.80 – 4.0	–
Glycosylated Haemoglobin	7.20 ± 0.17*	3.35 ± 0.30
Serum Cholesterol (mg/dl)	288.42 ± 13.49*	194.50 ± 20.69
Serum Digoxin (ng/ml)	1.74 ± 0.09*	0.76 ± 0.07
Serum Creatinine (mg/dl)	1.36 ± 0.20	1.08 ± 0.05
Serum K^+ (mEqu/lt)	3.55 ± 0.21	3.78 ± 0.22
Serum T_3 (ng/ml)	0.78 ± 0.06*	1.00 ± 0.06
Serum TSH (µU/ml)	2.28 ± 0.23*	1.55 ± 0.18
Serum T_4 (µg/dl)	9.56 ± 0.81	9.10 ± 1.02

*Significantly different from non-diabetic patients (P<0.05).

ml. Only four out of eleven had serum TSH levels above 2.0 µU/ml. Mean serum TSH levels of diabetics (2.28±2.3 ng/ml) were significantly higher (P<0.05) as compared to those of non-diabetics (1.55±0.18 µU/ml).

Serum T_4 levels were not significantly (P>0.05) different in diabetic and non-diabetic patients. All the patients had serum T_4 levels in the range of 7 to 12 µg/dl. Serum T_3 levels were found to be significantly reduced in diabetics (0.78±0.06 ng/ml) as compared to non-diabetics (1.0±0.06 ng/ml). Most of the non-diabetic patients had serum T_3 levels above 0.95 ng/ml, whereas most of diabetic patients had serum T_3 levels below 0.8 ng/ml. Serum T_3 levels were found to be lower in diabetic patients with higher serum digoxin levels. Scatter diagram revealed a negative correlation between serum T_3 and digoxin values, as the correlation between these two appears to be partial (r = —0.12).

DISCUSSION

In the present investigation serum digoxin levels in diabetic patients were found to be significantly higher as compared to non-diabetics. The increase in digoxin level was proportionate to the increase in glycosylated Hb value. The correlation coefficient was on the positive side (r=0.31), though not significant, it indicates that diabetes mellitus may be one of the many factors causing an increase in serum digoxin levels.

The mechanisms involved in alteration of digoxin pharmacokinetics are many to speculate; however, in clinical practice hypokalaemia and renal failure are commonly ascribed to be the major factors. Hypokalaemia, which is usually associated with diuretic treatment, is known to potentiate digitalis induced ventricular arrhythmias (17). In the present study potassium levels were observed to be within the normal range in both diabetics and non-diabetics.

Since digoxin is excreted through urine, and there is good correlation between the renal function and digoxin levels (9). It could be stated that one of the causes for higher digoxin levels in diabetics could be the abnormal renal function.

The patients included in the present study were diagnosed as diabetics for not more than 3 years. Since renal disease is known to occur after a long duration of diabetes, it is unreasonable to suggest renal impairment as the possible mechanism responsible for the raised digoxin levels in these patients. Further serum creatinine or serum urea levels were not found to be altered in diabetics as compared to non-diabetics.

Apart from reduction in insulin levels, serum levels of other hormones are also altered in diabetes mellitus (15, 17). An intimate association of diabetes with thyroid dysfunction was indicated by Sugrue et al (11). Thyroid disease alters the patient's response to digoxin. Hyperthyroid patients are relatively resistant to digoxin and hypothyroid patients are extremely sensitive to it. Croxson and Ibertson (15) have reported that digoxin levels are significantly higher in patients with hypothyroidism and lower digoxin levels are achieved in hyperthyroid patients, with no difference in either digoxin excretion or serum half times. It was postulated that increased tissue distribution in hyperthyroid patients may contribute to the low serum digoxin levels. It has been suggested that patients with diabetes mellitus should be screened routinely for the evidence of thyroid dysfunction (18).

In our studies diabetic patients showed significantly higher TSH levels than non-diabetic group. However, except for two patients showing TSH levels above the normal range (4.0 ng/ml), none could be called hypothyroid. Thus, primary hypothyroidism could not be the sole factor for higher digoxin levels.

Tri-iodothyronine plays an important role in health and disease (19). because it is a metabolically more potent calorigenic agent than T_4. Serum T_3 levels are low in uncontrolled diabetic men (19). This effect appears to be due to a reduced production of T_3 from T_4 (20). Results of our study also support that there is impaired production of T_3 from T_4 in diabetics. While T_4 levels are unchanged in diabetics,

there was a significant reduction in T_3 levels in diabetics. In addition our data also indicate a partial positive correlation (r=+0.15) between TSH and digoxin levels and partial negative correlation (r=—0.12) between T_3 and digoxin levels. There was no correlation between T_4 and digoxin levels.

In conclusion, our data suggests that diabetes mellitus may be considered as an independent factor altering pharmacokinetics of digoxin. Although, it is too pre-mature to conclude hypothyroidism to be the sole factor causing elevated digoxin levels in diabetics, a tendency towards primary (mild) hypothyroidism associated with diabetes cannot be ruled out.

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