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Plasma and Urinary Digoxin in Thyroid Dysfunction

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Summary. The response to a single oral dose of 0.5 mg digoxin has been studied in eight patients, of whom four were hyperthyroid and four were hypothyroid, both before and after treatment for their thyroid dysfunction. The post-dose plasma digoxin levels were significantly lower in the hyperthyroid patients when they were thyrotoxic than when they became euthyroid. In only one hypothyroid patient was the post-dose plasma digoxin level significantly higher before treatment than it was after and in the others the digoxin values reached were either the same as, or lower than, before treatment. There was a significant correlation between the creatinine clearance and the urinary concentrations of digoxin and these both altered with change in thyroid status. Total urinary digoxin excretion did not change. Pharmacokinetic analysis suggested that digoxin was distributed in a way compatible with a two-compartment model and that the volume of the central compartment was high in thyrotoxic patients and low in hypothyroid patients. In both cases it reverted to a median value after treatment. It is recommended that plasma digoxin levels should be monitored in all patients with thyroid dysfunction who require therapeutic digoxin.

Key words: Digoxin, hypothyroid, hyperthyroid, thyroid dysfunction.

It has been known for many years that thyrotoxic patients are resistant to digoxin [1] and that hypothyroid patients are particularly sensitive to the drug [2]. Several studies have shown that the metabolism of zoxazolamine and hexobarbital [3], aminopyrine, aniline and p-nitrobenzoic acid [4] is affected by thyroid status. In man, thyroid status has also been shown to influence the plasma half-life of antipyrine and altering the thyroid status in individual patients changed the half-life [5, 6] and, in hyperthyroid patients, the clearance of antipyrine [5].

Doherty and Perkins [7] gave tritiated digoxin, orally and intravenously, and found that, in both cases, the resultant plasma digoxin levels were decreased in hyperthyroid patients and increased in hypothyroid patients when compared with a normal group. Similar results have been obtained with ^{3}H-ouabain and ^{3}H-digitoxin [8]. Croxson and Ibbertson [9], using a radioimmunoassay method, measured serum digoxin after a seven day course of the drug and found that the levels in thyrotoxic patients were significantly lower than those in hypothyroid patients. They also showed a negative correlation between corrected creatinine clearance and both serum digoxin concentration and serum half-life of digoxin. Gilfrich [10] gave intravenous digoxin to 8 thyrotoxic patients before and after treatment and found that plasma levels of digoxin seemed to decline more rapidly when they were thyrotoxic.

A recent review [11] has indicated that there is little information available about changes in digoxin levels attained, following a standard oral dose, in individual patients before and after treatment of hypo- and hyperthyroidism. The present study was designed to provide this information.

Material and Methods

Patients

Eight female patients were studied, four of whom had thyrotoxicosis (Table 1) and four who had hypothyroidism (Table 2). None of them had renal

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Table 1. Details of thyrotoxic patients; mean age 48 years (42–55)

	Before treatment	After treatment	Reference range
Mean Weight (kg)	62.9 (49.3–73.0)	61.5 (52.5–74.2)	–
Mean PBI (μg/100 ml)	14.4±0.4	4.85±0.6	3.0–8.0
Mean FTI	18.9±1.9	5.90±0.9	3.4–7.1
Mean I^{131} Uptake (4 hour)	64.8±4.9	21.10±2.2	15–25%

Table 2. Details of hypothyroid patients; mean age 60 years (43–77)

	Before treatment	After treatment	Reference range
Mean Weight (kg)	70.2 (39.0–88.0)	68.5 (39.1–85.2)	–
Mean PBI (μg/100 ml)	1.8±0.13	7.2±0.7	3.0–8.0
Mean FTI	1.8±0.14	7.7±1.4	3.4–7.1
Mean I^{131} Uptake (24 h)	7.3±1.7%	–	Greater than 20%

disease, abnormal plasma proteins or any form of heart disease requiring treatment with digoxin.

The patients were studied on two occasions – when initially diagnosed and when they were judged to be clinically and biochemically euthyroid (Tables 1 and 2). Three of the thyrotoxic patients were treated with I^{131} in a dose of 6 μci and the other received carbimazole which, by the time of the second study, was in a maintenance dose of 5 mg twice daily. All the hypothyroid patients were treated with thyroxine. Three of them required 0.2 mg thyroxine daily and the fourth 0.15 mg daily. The mean interval between the two studies was 8.25 months in the thyrotoxic group and 4.5 months in the hypothyroid group.

Plan of Study

The patients were fasting on the morning of the study days and ingested 0.5 mg of digoxin. Lanoxin (Wellcome) was used and all the tablets came from the same manufacturing batch (No. 150174). Blood samples were taken before the dose was given, at half-hourly intervals for 3 h and then at 4, 6, 8, 12 and 24 h. A total 24 h urine collection was made following the dose. The patients were not allowed breakfast but otherwise ate a normal diet during the study. The same plan was followed on the second study day, with lunch, tea and supper being eaten at the same times on the two occasions.

Pulse rates were measured, before blood was taken, for the first eight hours.

Laboratory Methods

The pre-dose blood specimen was used for the estimation of protein bound iodine (PBI), urea, plasma proteins and creatinine by the standard autoanalyser techniques, and also the T_3 resin uptake ratio which was determined by the method of Horn [12]. The digoxin concentration was measured using the Lanoxitest radioimmunoassay kit (Wellcome Reagents Ltd., Beckenham, England) and the urine digoxin concentrations by a modification of the method of Greenwood et al. [13] in which the extracted residue was redissolved in horse serum. This method has been shown to be as sensitive as that of Greenwood. It has a coefficient of variation of 5.2% at a urine digoxin concentration of 130 μmol/l and 3.7% at 260 μmol/l.

The statistical differences were calculated using a student's paired 't' test and correlation coefficients by the method of least square analysis. Initial kinetic analysis was performed using a computer programme Autoan [14]. This suggested that a two-compartment model was appropriate and further analysis, based on this assumption, was done with a nonlinear programme designed by Metzler [15].

Results

As expected, the mean pulse rate was higher in the thyrotoxic patients (121 ± 4.6 per min) than in the hypothyroid patients (66.4 ± 2.9 per min), and both groups achieved "normal" values after treatment, namely 78.5 ± 3.7 per min in the thyrotoxic group and 77.2 ± 4.1 per min in the hypothyroid group. There was no correlation between pulse rate and plasma digoxin level in any of the patients.

Figure 1 shows mean (± SEM) plasma digoxin concentrations for the four thyrotoxic patients before and after treatment. The mean peak plasma level was 5.6 ± 1.4 nmol/l (4.3 ± 1.1 ng/ml) when the patients were thyrotoxic, and this level was reached at half-an-hour after the dose. When the same patients were euthyroid, the mean peak plasma level was 8.0 ± 1.9 nmol/l (6.15 ± 1.47 ng/ml), but this level was not reached until one hour had elapsed. On both occasions the steady state was reached by six hours but the level for the euthyroid state was at least 0.65 nmol/l (0.5 ng/ml) higher. At

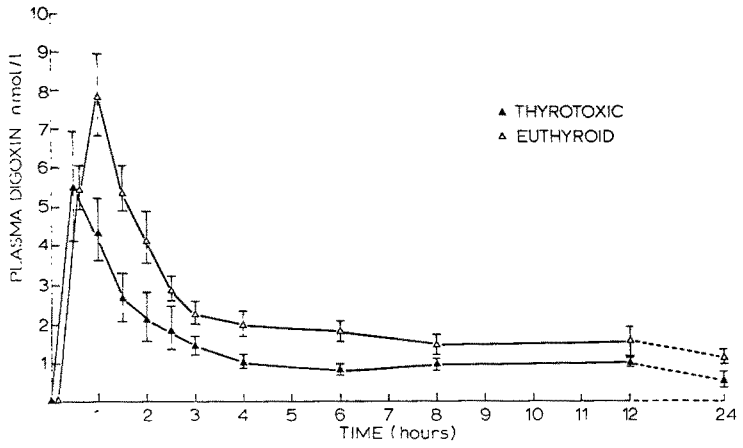

Fig. 1. Plasma Digoxin Levels – Thyrotoxic Patients (Mean ± SEM)

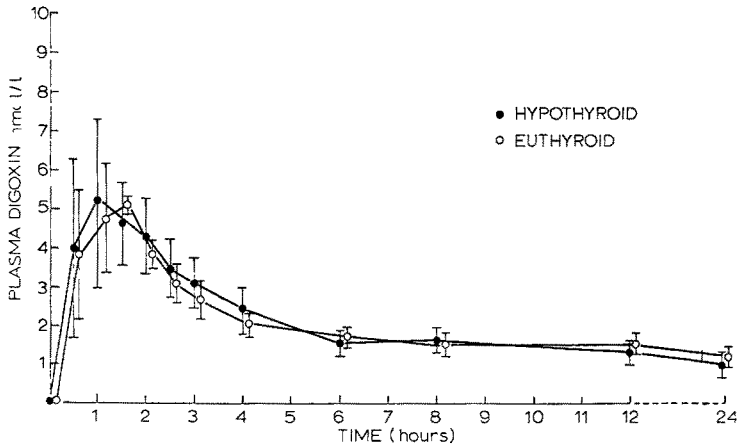

Fig. 2. Plasma Digoxin Levels – Hypothyroid Patients (Mean ± SEM)

all times in all patients after half-an-hour the difference between the two concentrations on the two occasions was significant ($0.05>p>0.01$). Using students 't' test, the results for the plasma concentrations were analysed for each individual patient and, in all cases, there was a significant difference (p never >0.025). The mean plasma distribution half-life, which is the time taken for the plasma level to fall from the peak value to half that concentration, was 45 min when the patients were thyrotoxic and 72 min when they were euthyroid ($p>0.01$).

Comparable results for the four hypothyroid patients are shown in Figure 2. The mean peak plasma digoxin level was 5.3 ± 2.2 nmol/l (4.05 ± 1.7 ng/ml) when the patients were hypothyroid, and this level was reached at one hour after the dose. When the same patients were euthyroid, the mean level was 5.2 ± 0.26 nmol/l (4.0 ± 0.2 ng/ml) and was reached at 1.5 h. At no time was there a significant difference between the two concentrations and, in both cases, the steady state was reached by 6 h.

An analysis of the results for the individual patients revealed that one patient (JP, Fig. 3) did show a significant difference before and after thyroxine ($0.01>p>0.005$). The peak plasma level was 11.7 nmol/l (9 ng/ml) when the patient was hypothyroid, falling to 7.8 nmol/l (6 ng/ml) when she was euthyroid. One patient showed a non-significant trend in the opposite direction, whereas the remaining two patients showed similar results in each study.

In the hyperthyroid group the mean creatinine clearance, corrected to body surface area of 1.73 m^2, was 99.8 ± 5.2 ml/min, falling to 78.1 ± 12.3 ml/min after treatment. In the hypothyroid group it was 51.5 ± 7.4 ml/min before treatment, rising to 66.3 ± 5.4 ml/min after thyroxine therapy. Table 3 shows mean 24 h urinary digoxin excretion in each group of patients. This excretion was higher in the thyrotoxic patients but showed no significant change after treatment in either group.

The urine digoxin excretion for each individual

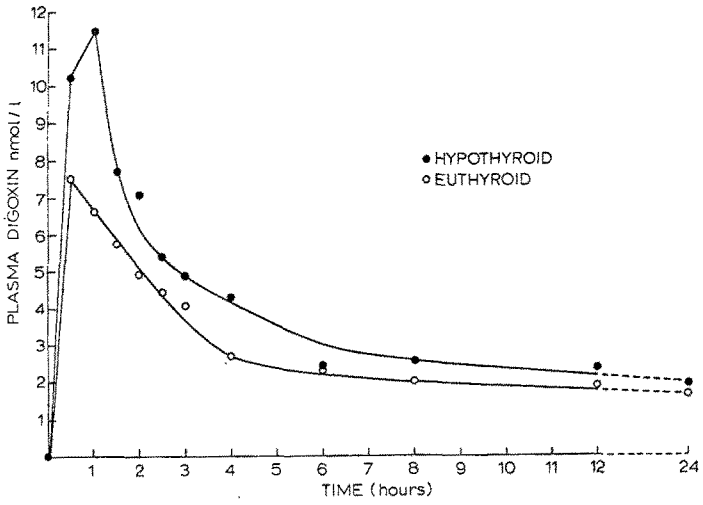

Fig. 3. Plasma Digoxin Levels – Patient JP

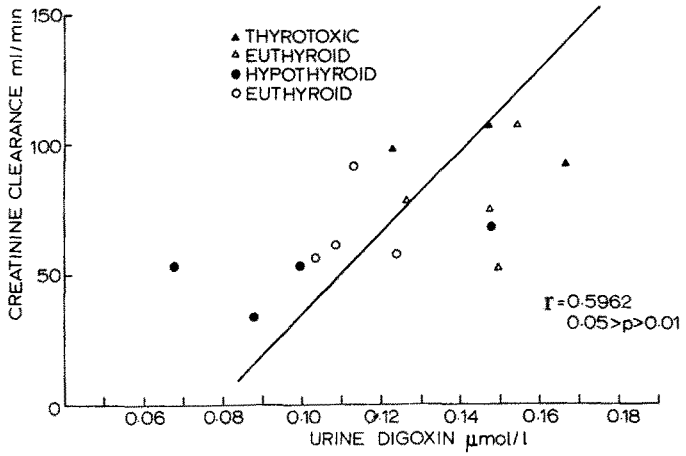

Fig. 4. 24 h Digoxin v. Corrected Creatinine Clearance

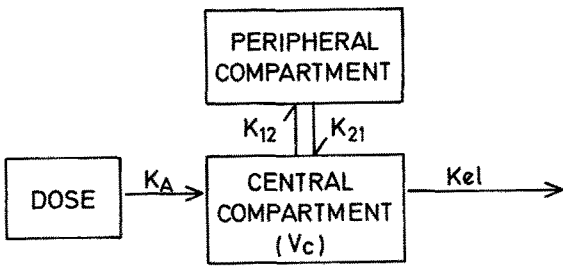

Fig. 5. Two Compartment Open Model with First Order Input

Table 3. Mean 24 h urinary digoxin

	Volume (l)	Digoxin (µg)	Digoxin (% Dose)
Thyrotoxic	1.53±0.27	123±7.1	24.6±1.42
Euthyroid	1.56±0.18	121±4.8	24.2±0.96
Hypothyroid	1.16±0.10	87±13.4	17.4±2.68
Euthyroid	1.30±0.16	96±2.1	19.2±0.42

study had a significant correlation with corrected creatinine clearance (Fig. 4) and, in general, the hypothyroid patients had a low clearance and low urinary concentration of digoxin whereas the opposite was true of the thyrotoxic patients. After treatment, both groups tended to more median values. Peak plasma levels of digoxin did not correlate with corrected creatinine clearance or with the level of protein bound iodine.

Computer analysis by Nonlin [15] supported that by Autoan [14] and indicated that for all four groups the data fitted a 2-compartment model (Fig. 5).

The values for the rate constants K_{12} and K_{21} and for the volume of distribution of the central compartment Vc(1) are shown in Table 4. Using these values an estimate of total volume of distribution was obtained using the formula K_{12}/K_{21} x Vc.

The central volume of distribution was higher in the thyrotoxic group than in the hypothyroid group

Table 4. Rate constants and volumes of distribution

	Vc (l)	K_{12}	K_{21}	Estimated Vd (l)
Thyrotoxic	77.3±4.9	0.38	0.021	1399±88.7
Euthyroid	40.2±5.4	0.60	0.042	575±77.1
Hypothyroid	28.8±0.6	0.96	0.056	492±10.2
Euthyroid	38.2±4.0	0.78	0.058	512±53.8

Vc = Volume of distribution of central compartment
Vd = Total volume of distribution

and after treatment it was approximately the same in both groups. The estimated total volume of distribution was very high in the thyrotoxic group but of a similar, lower, order in the other three groups. The ratio of K_{12}/K_{21} ranged from 13.4 (treated hypothyroid) to 18.1 (thyrotoxic).

Discussion

It is generally accepted that hyperthyroid patients are resistant to digoxin and hypothyroid patients sensitive to the drug [1, 2], but there is no complete explanation of these variations [11]. There is evidence that the pharmacology of heart muscle changes with altered thyroid function [2, 16, 17] although this does not vary consistently with the circulating level of thyroid hormones [18]. There is also evidence of altered digoxin pharmacokinetics in thyroid disorders and this has recently been reviewed [11]. Some workers, however, dispute that there is any significant alteration in digoxin requirements [19] or in digoxin excretion [20] with altered thyroid status.

Our results in thyrotoxic patients support the view that, in that group, there is a definite alteration in digoxin kinetics. Plasma levels were significantly lower in thyrotoxic patients and rose when they became euthyroid. This confirms, for individual patients, the group findings of Doherty and Perkins [7] and the work of Gilfrich [10] using intravenous digoxin. The plasma levels in our hypothyroid patients are more difficult to interpret. One patient showed results compatible with previous findings [7, 8] but the others did not. Doherty and Perkins [7], in an appendix to their study, presented results for one patient given intravenous H^3-digoxin when hypothyroid and again when euthyroid. There were only slight differences in plasma concentration and excretion of digoxin. Eickenbusch et al. [8] gave H^3-ouabain to one hypothyroid patient before and after treatment and although they demonstrated a fall in plasma levels the results after treatment did not reach control values. It may therefore be that additional factors are influencing the results in hypothyroid patients.

The reasons for these alterations in plasma levels of digoxin are not completely clear [11]. Croxson and Ibbertson [9] found a close correlation between plasma digoxin levels and corrected creatinine clearance in patients with hyper- and hypothyroidism. Falk et al. [19] did not find a direct correlation between the degree of thyroid dysfunction and digoxin renal clearance although they confirmed other findings [21, 22] that glomerular filtration rate correlated with digoxin renal clearance. Digoxin clearance is also known to be directly related to creatinine clearance [21].

Our findings show the apparent paradox that urinary volume and total urinary digoxin were not affected by thyroid status but that urinary digoxin concentration correlated with corrected creatinine clearance which was, in turn, altered by thyroid status. The latter correlation is consistent with the results of Croxson and Ibbertson [9] who found a mean corrected creatinine clearance of 111.6 ± 34.1 ml/min in their thyrotoxic group and 64.4 ± 14.7 ml/min in their hypothyroid group. They also found that serum digoxin levels and half-lives were related to creatinine clearance although results were more consistent in the thyrotoxic patients than in the hypothyroid group. Doherty and Perkins [7] showed little difference in urinary excretion of digoxin after oral administration, whereas Gilfrich [10], giving intravenous digoxin, found excretion to be lower in thyrotoxics than in the same patients when euthyroid. Eichenbusch et al. [8], using intravenous H^3-ouabain, found that 48 hour urinary excretion was 52% of the dose in euthyroid, 64% in hyperthyroid and 37% in hypothyroid patients.

There are, therefore, considerable discrepancies in the literature. It has been suggested [20] that in hypothyroid patients the unchanged digoxin excretion rate with high plasma concentrations is due to a decrease in true renal plasma clearance of digoxin expressed as ml/min. Bradley et al. [23], in an extensive review of renal function in thyroid disorders, conclude that there is definite evidence of increased renal plasma flow in thyrotoxicosis and reduced renal plasma flow in hypothyroidism. This would affect glomerular filtration and creatinine clearance and account for our results and those of Croxson and Ibbertson [9], since there is a direct relationship between urinary digoxin excretion and both creatinine clearance [21] and GFR [22]. However, we found no significant change in urine volume and would therefore expect little change in total urinary digoxin. In addition there is some evidence that renal handling of digoxin may be partly due to tubular

reabsorbtion [24] and tubular secretion [25] and it is possible that both these functions are affected by thyroid hormones.

An additional reason for some of the discrepant results may be that, as in rats [26], there is increased hepatic metabolism and biliary excretion of digoxin in the hyperthyroid patient compared with the normal. There is certainly evidence that liver enzyme induction is of importance when considering the effects of thyroid hormones on the metabolism of other drugs such as barbiturates [4], antipyrine [5, 6] and methinazole [5].

In their original study, Doherty and Perkins [7] suggested that their results could be explained by differences in volumes of distribution of digoxin. We have found that thyrotoxic patients have a high central compartment volume of distribution (77.3 l), that hypothyroid patients have a low central volume of distribution (28.8 l) and that, when they became euthyroid, both groups had a volume of distribution of about 40 litres. Kinetic calculations from plasma levels after oral dosing are subject to some problems but our results agree well with those of Sumner et al. [22] who gave intravenous digoxin and estimated the central compartment in normals to be between 23.66 and 44.15 litres. While our estimates of total volume of distribution are probably subject to greater error, they are in the same range as those calculated by other workers in normals [27] (420–1026 l). It would appear that these changes in central volume of distribution may well be of great importance in determining plasma levels in thyroid disorders and further studies are expected to provide more detailed information.

Thyroid hormones affect so many basic metabolic processes that it is likely that additional factors are also operating. For example, digoxin is mainly absorbed from the stomach [28] and changes in gastric emptying times or rates of absorption might affect peak plasma levels. It has been suggested that the steatorrhea and malabsorption seen in thyrotoxicosis [29] influence the plasma levels of digoxin attained [30] although one study has found no evidence of this [19]. It is of interest that, in our patients, peak plasma levels occurred later in hypothyroid than in hyperthyroid patients.

In serum, digoxin is only 25% protein bound [31]. It is unlikely that, in our patients, protein binding can have had a significant effect since all of them had plasma protein values within the reference range. However, it is possible that the degree of saturation of binding sites may alter as is the case with thyroxine binding globulin and this might influence binding of digoxin. The fact that, in all our patients, the rate constant to the peripheral compartment (K_{12}) was considerably greater than that back to the central compartment (K_{21}) is consistent with the high binding affinity of digoxin to tissue proteins [32].

It has also been suggested that the "resistance" to digoxin in thyrotoxicosis might be due to similar actions of thyroxine and digoxin on Na^+- and K^+-dependent adenosine triphosphatase [33]. It may well be that a range of different functions are operating in these patients and further studies are necessary to determine how much effect each has.

However, we have clearly shown that treating individual patients suffering from thyrotoxicosis will alter peak plasma levels of digoxin. Therefore no thyrotoxic patient should be judged digoxin-resistant until adequate therapeutic plasma levels of digoxin have been reached. This is particularly important in view of the finding of Chamberlain et al. [34] that plasma digoxin levels greater than 2.6 nmol/l (2 ng/ml) are frequently necessary to control atrial fibrillation. It is especially important since a high proportion of thyrotoxic patients with heart disease are receiving digoxin therapy [35].

Results are less clear in the hypothyroid patients but caution should be exercised when digoxin is used in them since even transiently elevated plasma levels of the order seen in one of our patients may be dangerous. It follows that, when hypothyroid patients are being given digoxin, frequent monitoring of plasma levels is necessary to avoid digoxin overdosage.

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