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DIGOXIN COMPLIANCE IN PATIENTS FROM GENERAL PRACTICE

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1 Compliance with digoxin therapy has been assessed in a group of fifty patients receiving the drug in general practice but not attending hospital.

2 Compliance was estimated by comparing plasma digoxin concentrations before and after a 10 day period of measured digoxin consumption and by tablet counting.

3 Twelve patients had plasma concentrations which increased by more than 0.4 ng/ml during monitored intake and eight other patients took less than 80% of their tablets. These twenty patients were considered non-compliant.

4 A further three patients in whom plasma digoxin levels were zero when first seen but increased substantially during the run-in period were also adjudged non-compliant.

5 Non-compliance with prescribed digoxin dosage occurred, therefore, in 46% of the patients studied.

Introduction

In a recent study of sixty patients being admitted to hospital in emergency (Johnston, Kelly & McDevitt, 1978) in which plasma digoxin concentrations on admission were compared with levels obtained after seven days treatment with their pre-admission digoxin doses, it was found that almost one-half of the patients were taking their digoxin improperly—nearly one-third of the total group were considered to be taking too little digoxin and to be non-compliant.

One criticism of this study was that these patients could have been admitted to hospital *because* they were not complying with their therapy and that, therefore, the level of compliance in the general non-hospital patient community may be much greater.

To study this possibility, we have now investigated digoxin compliance in patients receiving digoxin in general practice and not requiring either hospital admission or regular hospital attendance.

Methods

Names and addresses of patients on maintenance digoxin therapy were obtained from a general practitioner's surgery by noting those patients who had recently renewed their prescription for digoxin. Patients were selected consecutively, although three were removed from the list on the advice of the general practitioner.

Patients were visited at home by one of us (GDJ) on three separate occasions, the first without prior warning. A general outline of the study was given to each patient without any undue emphasis on digoxin compliance and he/she was asked to take part: only two patients refused. On the first visit, a careful history was taken with particular respect to digoxin therapy—dose, frequency of dosage, timing of last dose, symptoms of digoxin toxicity and compliance. Other drugs were also noted and the total number of tablets taken daily. An ECG was performed in each patient and a blood sample taken for estimation of plasma digoxin, urea and serum creatinine concentrations. Patients were revisited seven days later and the tests repeated. On this second visit, each patient was given a bottle containing a specific number of digoxin tablets (as Lanoxin, Burroughs Wellcome), asked to take his usual digoxin dose from the bottle and to record the time of each dose daily for a further 10 days. At the end of this period, ECG and blood tests were repeated and the patient asked about symptoms which could have indicated digoxin toxicity. The forms were collected and the number of digoxin tablets remaining in each bottle counted. Patients were considered compliant on tablet counting if they took 80% or more of the measured consumption. In each case, blood samples were taken 6–8 h after the last stated digoxin dose.

Plasma digoxin concentrations were measured by radioimmunoassay using a modified Wellcome β Lanoxitest kit method (Ojala, Karjalainen & Reissell, 1972). On the basis of a recent study of variation of plasma digoxin and serum creatinine concentrations at 'steady state' in this laboratory (Johnston & McDevitt, 1978), changes in plasma digoxin concentrations of greater than 0.4 ng/ml (conversion

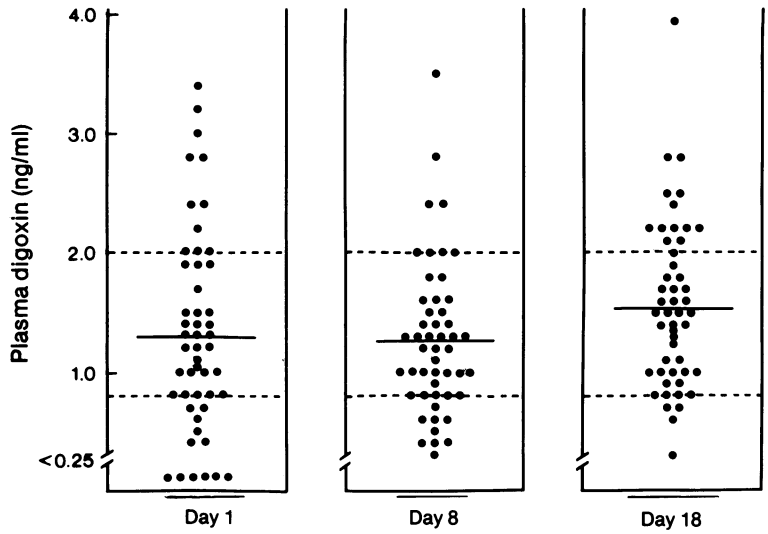

Figure 1 Plasma digoxin concentrations in fifty patients on days 1, 8 and 18. Horizontal bars indicate mean concentrations. Dotted lines indicate therapeutic range.

factor 1.0 ng/ml = 1.3 nmol/l) and changes in serum creatinine of greater than 32.3 μmol/l were considered to be real, and to represent poor digoxin compliance (if creatinine was unaltered) and altered renal function respectively.

Results are shown as the mean ± s.d. Statistical analysis were carried out using Student's paired and unpaired *t*-tests and the χ^2 test.

Results

Fifty patients were studied of whom 19 were male and 31 female. Their characteristics are shown in Table 1.

On the first visit, four patients complained of nausea but, as none had any other clinical or ECG findings consistent with a diagnosis of digoxin toxicity, they were included in the study. At this time two of these patients had plasma digoxin concentrations less than 0.8 ng/ml, one a concentration between 0.8 and 2.0 ng/ml, and one a concentration greater than 2.0 ng/ml. Neither these nor any other patient developed evidence of clinical toxicity during the course of the study and previous digoxin maintenance therapy was continued throughout in every patient. At the end of the study, however, the general practitioners were informed about patients with plasma digoxin concentrations greater than 2.0 ng/ml and advised about possible dosage adjustments.

Only one patient showed clinical improvement during the study. In this case, substantial slowing of a heart in atrial fibrillation and improvement in exercise tolerance was associated with a rise in plasma digoxin level from subtherapeutic to the normal range.

The plasma digoxin concentration in the 50 patients on days 1, 8 and 18 are shown in Figure 1. The mean plasma digoxin level on day 1 was 1.31 ± 0.87 ng/ml. Using 0.8–2.0 ng/ml as the 'usual therapeutic range' (Whiting, Sumner & Goldberg, 1973), 60% of patients had digoxin concentrations in the therapeutic range, 24% were subtherapeutic and 16% were potentially toxic. By day 8, the mean concentration was 1.28 ± 0.64 ng/ml and the number of patients in the

Table 1 General characteristics of fifty patients in general practice studied (Mean ± s.d.).

Number of subjects	*Plasma digoxin (ng/ml)*	*Mean daily digoxin dose (mg)*	*Age (years)*	*Blood urea (mg/100 ml)*	*Serum creatinine (μmol/l)*	*History of taking digoxin as prescribed (%)*
Total 50 M:19 F:31	1.31 ±0.87	0.22 ±0.12	72.8 ±11.5	43.1 ±12.3	97.0 ±26.5	90%

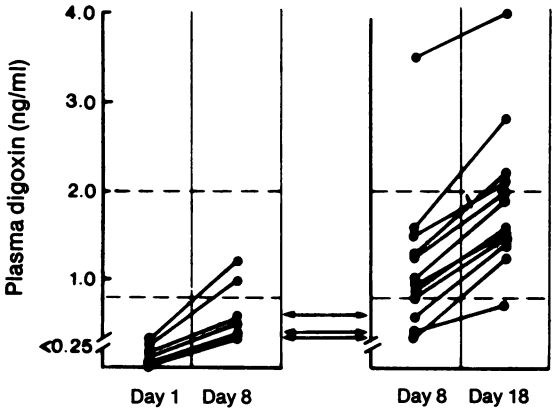

Figure 2 Plasma digoxin concentrations which increased more than 0.4 ng/ml in patients from day 1 to day 8 and from day 8 to day 18. Results in individual patients are joined by solid lines. Patients whose levels rose in both periods are shown by arrows.

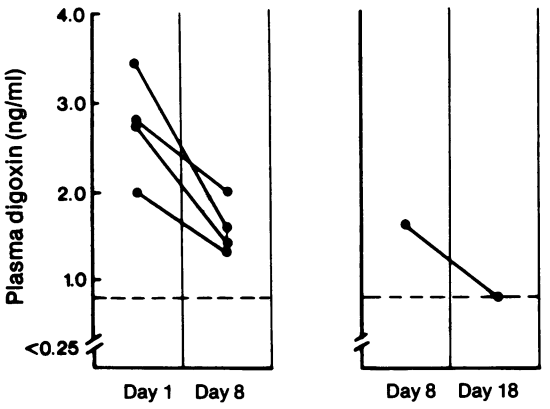

Figure 3 Plasma digoxin concentrations which decreased more than 0.4 ng/ml in patients from day 1 to day 8 and from day 8 to day 18. Results in individual patients are joined by solid lines

three concentration ranges were 74% (normal), 18% (subtherapeutic) and 8% (toxic). On day 18, the mean digoxin concentration was 1.54 ± 0.72 ng/ml.

The plasma digoxin concentration did not alter significantly between days 1 and 8, but a significant increase was observed between days 8 and 18 ($P < 0.01$). Fewer patients had levels less than 0.8 ng/ml and more patients levels greater than 2.0 ng/ml on day 18 than on days 1 or 8, but the changes were not significant.

Thirty patients (60%) had plasma digoxin concentrations which remained unchanged throughout the study. Changes in digoxin levels between days 1 and 8 and days 8 and 18 are shown in Figures 2 and 3. Six patients had zero levels on day 1 but measurable levels on day 8: in three of these a further increase occurred between days 8 and 18. A further nine patients had digoxin concentrations which increased only between days 8 and 18. Decreases in plasma digoxin concentration were seen in four patients between days 1 and 8, and in one patient between days 8 and 18 (Figure 3). No changes in renal function occurred in any patient during the study.

By tablet counting, ten patients took less than 80% of their prescribed dose and were adjudged non-compliant. In these, plasma digoxin concentrations increased in two patients from day 8 to day 18 and they were already labelled non-compliant by this method. Seven patients had digoxin levels which remained the same and must have been taking less than the prescribed dose regularly from day 1 to day 18. In the tenth patient, the plasma digoxin concentration decreased from day 8 to day 18.

Thus twelve patients were considered non-compliant because of increasing plasma digoxin concentrations on monitored digoxin therapy and eight others because they took insufficient digoxin tablets. In addition, it was felt that the three patients who were

Table 2 Characteristics of compliant and non-compliant patients with respect to age, number of digoxin and other tablets, duration of therapy and history of compliance (mean ± s.d.).

Number of patients	*Age (years)*	*Number of digoxin tablets*	*Number of other tablets*	*Duration of therapy (years)*	*% with history of compliance*
Compliant patients					
27	73.1	1.3	4.3	3.5	96%
M:12 F:15	±13.5	±0.5	±3.3	±4.2	
Non-compliant patients					
23	73.2	1.5	5.3	5.3	83%
M: 7 F:16	±8.9	±0.7	±3.5	±3.6	

taking no digoxin when first visited (as evidence by immeasurable plasma concentrations) but whose plasma digoxin levels appeared between days 1 and 8, were also non-compliant. Presumably there were alerted by the study to become compliant! This gives a total of 23 patients (46%) who were not taking their prescribed digoxin dose during the study and must be considered non-compliant.

When the 23 non-compliant patients were compared with the 27 compliant patients, no significant differences were found between the two groups with respect to age, number digoxin or other tablets prescribed, duration of therapy or history of compliance (Table 2). Over half of the women studied were considered to be non-compliant, compared with 7 out of 19 men.

Discussion

The results of this present study indicate that fewer patients receiving digoxin at home have plasma digoxin concentrations outside a 'usual therapeutic range' of 0.8–2.0 ng/ml (Whiting *et al.*, 1973) than in previous studies of patients being admitted to hospital in emergency (Carruthers, Kelly & McDevitt, 1974; Johnston *et al.*, 1978). However, 40% still represents a substantial number of patients either receiving inadequate digoxin therapy or at potential risk from digoxin toxicity.

Our results would also indicate that nearly one-half of the patients studied were taking their prescribed dose of digoxin improperly. The figure of 46% obtained in this study compares very closely with 44% from the previous in-patient study (Johnston *et al.*, 1978; Johnston & McDevitt, 1978). The methods used were not identical: in the latter study we were able to rely exclusively on plasma digoxin concentration changes as therapy was being administered by nursing staff, whereas here we have used a combination of plasma concentration measurement and tablet counting. In the in-patient assessment, estimates were made of patients probably taking too much digoxin prior to admission as well as those taking too little; in this study, only one patient had falling digoxin levels between day 8 and day 18 and she was considered non-compliant by tablet counting. Patients whose levels fell between days 1 and 8, who may have become more careful about their therapy once the study commenced and may fall into this category, cannot be properly assessed because of inadequate information about therapy in this period.

Overally then, almost half of a group of patients taking digoxin in general practice were taking less than their prescribed digoxin dose. It seems unlikely, therefore, that the figure obtained in the initial study (Johnston *et al.*, 1978) was influenced by patients being admitted to hospital because of non-compliance. Indeed, it might be argued that the true estimate of non-compliance is even worse than that obtained in this study because the patients studied were those who were renewing their prescriptions for digoxin. Presumably there is a further group of non-compliant patients who have given up their therapy completely and never attend the doctor's surgery for any reason.

Variation in the biological availability of different digoxin preparations has recently been highlighted, (Lindenbaum, Mellow, Blackstone & Butler, 1971; Shaw, Howard & Hamer, 1972). During the second part of the study, 'Lanoxin' tablets were given to all patients and the possibility that changes in plasma digoxin concentration were due to changes in digoxin brand, was considered. Forty-four out of the 50 patients had previously been taking 'Lanoxin' tablets. Of the remaining six patients, two took 100% of their tablets between day 8 and day 18 and showed no change in plasma digoxin concentrations; the other four were classified as non-compliant by tablet couting and in these, one showed an increase and three no change in plasma concentration. The results were, therefore, not influenced by changing the digoxin brand.

Drug interaction, as a possible cause of alteration in plasma digoxin concentration was also considered. Anticholinergic drugs, metoclopramide and spironolactone have all been reported to change digoxin levels (Manninen, Apajalahti, Meilen & Karesoja, 1973; Steiness, 1974). However, none of the 50 patients received any of these drugs during the course of the study.

The pattern of alterations in plasma digoxin concentrations was interesting. Six patients with initially zero levels had measurable plasma digoxin by day 8. Presumably these patients had not been taking their tablets at all before day 1 but had been influenced to start taking their tablets after the first visit. Of the remaining 17 patients considered non-compliant by changes in plasma level and tablet counting between day 8 and day 18, seven had also been influenced to take their tablets as directed, two took more than they had been taking but less than prescribed, and eight were unaffected by the regime.

Not all the patients whose levels increased had levels initially in the subtherapeutic range. Three patients had levels in the normal range on day 8 which rose to the toxic range on day 18 and one other patient had a substantial rise within the toxic range over the same period. Therefore, these patients may have been protecting themselves from potential digoxin toxicity by non-compliance. This may be an underestimate as ten patients took less than the prescribed dose through-out the whole study, eight with normal values on day 8, one in the toxic range and one in the subtherapeutic range.

These results confirm that there is a fundamental difference between the treatment which doctors prescribe and that which patients take. This problem

can be shown to exist not only in patients who have bcome ill enough to be admitted to hospital but also in those attending their general practitioner. Because there is a difference between patients who admit non-compliance and those who can be shown to be non-compliant, it would appear to be an area that patients are reluctant to discuss honestly and that doctors must be aware of even when patients deny such a possibility. We need to know more about why they are non-compliant and how we can prevent it. This present study did not identify factors that might be relevant with the possible exception of sex—females appear to be non-compliant more frequently than males. New potent and more efficient therapies will not help patients unless we can persuade them to do what we say and what we think they do. More information is urgently required.

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