DOES THE FREQUENCY OF DAILY DOSAGE INFLUENCE COMPLIANCE WITH DIGOXIN THERAPY?

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- 1 The influence of daily dosage frequency on drug compliance has been studied in 80 outpatients for whom maintenance digoxin 0.25 mg daily had been prescribed.
- 2 Each patient took one tablet (0.25 mg) daily, two tablets (0.125 mg) daily and four tablets (0.0625 mg) daily in randomised order for 2 month periods.
- 3 Compliance was assessed by tablet counting and by serial measurement of the plasma digoxin concentration.
- 4 Of the 67 patients (100%) who could have completed the study, 19 (28.4%) were withdrawn for a variety of reasons; in the majority these were consistent with gross non-compliance.
- 5 The remaining 48 patients (71.6%) took significantly more tablets when prescribed once daily ($98.5 \pm 1.0\%$ of the total) or twice daily ($96.4 \pm 1.6\%$) than when given four times daily ($92.2 \pm 1.9\%$). However, there were no significant differences between the plasma digoxin levels obtained at the three dosage frequencies.
- 6 We conclude that the small improvement in compliance with once or twice daily dosage was clinically unimportant. Dosage frequency did not appear to have a major influence on the grossly non-compliant patients.

Introduction

Recently the pharmaceutical industry has put much effort into the development and promotion of long-acting drug preparation which need to be taken only once daily. The rationale behind this is that patients will take their medications more reliably if prescribed once a day than several times daily and, overall, that compliance will be increased. However, the scientific evidence for this assumption is surprisingly scarce and conflicting (Gatley, 1968; Porter, 1969; Parkin, Henney, Quirk & Crooks, 1976). We have shown previously that only 40–50% of patients taking prescribed maintenance digoxin therapy are compliant (Johnston & McDevitt, 1978a; McDevitt & Johnston, 1978). The present study was undertaken to determine the effect of varying the frequency of daily digoxin dosage on compliance.

Methods

Patients taking maintenance digoxin therapy were assessed at either a cardiac or a general medical outpatient clinic. Those receiving digoxin 0.25 mg daily were asked to enter a study comparing different

dosage frequencies of digoxin but they were not informed about the measurement of drug compliance. Each patient was assigned to receive his/her digoxin dosage in three different forms, each for a 2 month period—one tablet daily (0.25 mg each), two tablets daily (0.125 mg each) and four tablets daily (0.0625 mg each). The sequence in which each patient received these dosage regimes was determined randomly using a latin square design. Following the initial assessment, each patient was reviewed at 4-weekly intervals for a period of 6 months. At each visit, a blood sample was taken exactly 12 h after the last digoxin dose for measurement of plasma digoxin concentration and serum creatinine: a bottle was supplied containing a known, but variable, number of digoxin tablets and the bottle from the previous 4 week period with any remaining tablets was collected. Tablet counts were expressed as a mean compliance index calculated as actual number of tablets taken/number of tablets prescribed. Plasma digoxin levels were measured by radioimmunoassay using a modified Wellcome Lanoxitest β kit method (Ojala, Karjalainen & Reissell, 1972). Compliance was measured by pill counting and by estimation of plasma digoxin

concentrations. At each dose frequency, two sets of results were obtained for compliance index and plasma digoxin concentration at four week intervals: these results were meaned for each individual patient. Results are expressed as the mean $\pm$ s.e. mean. Statistical analyses were done by analysis of variance and Student's paired *t*-test.

Results

Eighty-five patients taking maintenance digoxin 0.25 mg daily were asked to enter the study but five refused. Of the 80 patients remaining, 42 were male and 38 female. Their mean age was 62.7 ± 1.1 years. Details of their subsequent course are shown in Table 1. Thirteen patients were withdrawn during the study because of either admission to hospital (9) or death (4). Of the 67 patients who could have completed the study, 19 had to be excluded (18 during the first 2 months) for a variety of reasons: four asked to be withdrawn because of difficulty keeping their monthly appointments, four failed to re-attend despite being sent repeated appointments, and 11 were excluded because they reverted to their previous dosage regimen or used digoxin from another source. The dose frequency at the time of their withdrawal in these 11 patients who misinterpreted or ignored their instructions was once daily in two, twice daily in three and four times daily in six.

Forty-eight patients (71.6%), 26 males and 22 females, completed the study. Their mean age was 62.5 ± 1.2 years. The results for the compliance index are shown in Table 2. The patients took $98.5 \pm 1.0\%$ of their tablets when treatment was given once daily, $96.4 \pm 1.6\%$ of tablets administered twice daily and $92.2 \pm 1.9\%$ of tablets prescribed four times a day. The compliance index was significantly poorer on four times daily dosage than at once or twice daily dosage ($P < 0.01$); however the difference between compliance indices for once and twice daily dosage did not reach statistical significance. Mean plasma digoxin concentrations at each of the dosage frequencies are shown in Table 3. There appeared to be a trend for decreasing plasma levels with increasing dosage frequency, with digoxin concentrations ranging from 1.32 ± 0.06 nmol/l (1.03 ± 0.05 ng/ml) on one tablet daily to 1.23 ± 0.08 nmol/l (0.96 ± 0.06 ng/ml) on four tablets daily, but the differences observed were not significant.

We have previously shown that variations in steady-state plasma digoxin concentrations of greater than 0.5 nmol/l (0.4 ng/ml) represent real changes in drug concentration provided they are not accompanied by changes in serum creatinine concentration of more than $32.2 \mu\text{mol/l}$ (0.4 mg/100 ml) Johnston & McDevitt, 1978b). Changes in plasma digoxin concentrations of greater than 0.5 nmol/l (0.4

Table 1 Summary of patients in compliance study (Figures in brackets are percentages)

Originally entered	80	
Withdrawn because of hospital admission or death	13	
Available to complete the study	67	(100)
Completed the study	48	(71.6)
Withdrawn		
Difficulty keeping appointments	4	
Failed to reattend	4	19 (28.4)
Altered own treatment	11	

Table 2 Mean compliance index ($\pm$ s.e. mean) in 48 patients taking digoxin 0.25 mg daily as 1, 2 or 4 doses for 2 months each.

	Dosage frequency (tablets/day)		
	1	2	4
Compliance index (%)*	98.5	96.4	92.2
	± 1.0	± 1.6	± 1.9
	[NS ——— $P < 0.01$]		
	[——— $P < 0.01$ ———]		

$$* \text{ Compliance index} = \frac{\text{Number of tablets taken}}{\text{Number of tablets prescribed}} \times 100$$

ng/ml) in patients taking maintenance digoxin have been taken as evidence of non-compliance (Johnston & McDevitt, 1978a, b). The results from individual patients in this study have been analysed in this way for the different dosage frequencies (Table 4). There is no obvious trend from these figures to link compliance with daily digoxin dosage frequency. Thus, although 11 patients had higher digoxin concentrations when taking their tablets once daily compared with the other dose frequencies, eight patients had higher levels when taking four tablets each day than when on one or two tablets each day.

Discussion

In the patients who completed this study, the results indicate that they took significantly more tablets when prescribed once or twice daily than when the dosage frequency was four times a day. However, these statistically significant differences need to be seen in perspective. In the first place, they were not accompanied by any significant differences between the steady-state plasma digoxin concentrations achieved with each dosage regimen. It could thus be argued that, for digoxin therapy, the differences in

Table 3 Mean plasma digoxin concentration ($\pm$ s.e. mean) in 48 patients taking digoxin 0.25 mg daily as 1, 2 or 4 doses for 2 months each.

	Dosage frequency (tablets/day)		
	1	2	4
Plasma digoxin concentration (nmol/l)	1.32 $\pm$ 0.06	1.28 $\pm$ 0.06	1.23 $\pm$ 0.08

Differences between groups shown are not significant.

Conversion: SI to traditional units—Plasma digoxin:
1.00 nmol/l $\approx$ 0.78 ng/ml.

Table 4 Number of patients showing changes in plasma digoxin concentration of greater than 0.5 nmol/l with changes in dosage frequency.

		Lower digoxin concentration		
	Dosage frequency (tablets/day)	1	2	4
	1		5	6
Higher digoxin concentration	2	2		4
	4	2	6	

tablet consumption at the three rates did not affect the clinical management of these patients. The results of looking for changes in plasma digoxin concentrations greater than 0.5 nmol/l (0.4 ng/ml) between the various dosage frequencies on an individual patient basis (Table 4) would tend to confirm this impression: overall, 11 patients and higher concentrations on once daily, six on twice daily and eight on four times daily treatment. In the remaining patients, dosage frequency alterations produced little or no change in plasma digoxin levels. Secondly, if we consider the tablets omitted from each regimen, using the mean compliance indices (Table 2), in a 2 month period, a patient on once daily digoxin would miss one tablet or one day's treatment, whereas a patient or four tablets daily would omit 17 tablets or approximately 4 days' treatment. Even if this non-compliance were consecutive, it would probably have little effect on the patient's condition: however it is more likely that a single tablet would be omitted sporadically. These differences between the two regimens appear small, particularly with a drug which has a slow rate of elimination.

Apart from the 13 patients who had to be excluded from the study because of admission to hospital or

death, a further 19 patients were withdrawn for a variety of reasons (Table 1). The majority (11 patients) altered their own treatment either by accident or design and four others failed to attend. This subgroup represents nearly 30% of the 67 patients: the 11 patients who altered their treatment must be considered definitely non-compliant and patients who are unreliable in their attendance must be suspect as far as compliance is concerned. At the time of withdrawal, six of the 19 patients were taking one tablet daily, 5 two tablets daily and 8 four tablets daily so it does not appear that dosage frequency was of major importance. The fact that 18 patients withdrew during the first dose period would support this. The failure of these patients to complete the study for whatever reasons would appear to have had a much more profound influence on overall compliance than the minor differences in tablet taking discovered in those who continued to take their treatment. The problems posed by these patients will not be solved simply by attention to daily dosage frequency.

This study illustrates the difficulties of investigating possible factors influencing compliance. By the very nature of the problem, the people for whom the results are most relevant are those who either refuse to participate or fail to complete. There may be other reasons why prescribing drugs once daily is desirable, but these results would suggest that the benefits of less frequent dosage administration will only be modest in terms of increase compliance.

The relevance of these results with digoxin to therapy with other drugs in different disease situations may be questioned. Digoxin has a long elimination half-life and takes at least one week to be excreted after discontinuation. However, with other drugs where slow-release preparations have been developed for once daily therapy, there is little correlation between plasma concentration and effect—for example, the antihypertensive effect of β -adrenoceptor antagonists persists for more than 24 h after they are withdrawn (Wilson, Morgan & Morgan, 1976). The minor benefits of increased compliance with once or twice daily treatment shown in this study would be of clinical importance only when a drug had a short half-life and there was a relationship between plasma drug concentration and effect, for example the use of procainamide in cardiac arrhythmias (Koch-Weser & Klein, 1971). In these circumstances the necessity for frequent drug administration, rather than compliance, would be the compelling reason for sustained-release therapy.

It has recently been suggested that non-compliance may not be harmful to many patients (British Medical Journal, 1979), since a substantial number of patients may not require the drug which is prescribed regularly (Johnston & McDevitt, 1979). Conversely, improved compliance may not always be beneficial—we have shown previously that in some non-compliant patients,

given their prescribed daily digoxin dosage in hospital, plasma digoxin concentrations rose into the potentially toxic range (Johnston, Kelly & McDevitt, 1978). Reduced frequency of daily dosage administration may not affect compliance greatly. Should we look for alternative methods of improving compliance or is it more important to identify areas where non-com-

pliance is clinically unimportant and, therefore, prescribing is unnecessary? This is currently a matter of debate (British Medical Journal, 1979).

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