

Quantifying non-compliance in patients receiving digoxin — a pharmacokinetic approach

I. C. WISEMAN, R. MILLER

Summary

Non-compliance has a major influence on the successful outcome of a therapeutic regimen. It also unnecessarily increases the costs of health care. In a study involving 137 outpatients receiving digoxin 55 patients (40%) were found to be non-compliant. Patients who experienced communication problems and who lacked a meaningful relationship with their doctor showed a marked deterioration in compliance.

An applied pharmacokinetic approach was used to predict the serum digoxin concentration for each patient. The creatinine clearance was determined and the degree of severity of heart failure was assessed. Total body clearance was then calculated. The predicted concentration was also calculated and compared with the measured digoxin concentration enabling an objective assessment of compliance. Twenty-four of the non-compliant patients who had subtherapeutic levels of digoxin (< 0,8 ng/ml) had signs of cardiac failure. Eighteen of these patients were receiving additional medication (1,7 ± 0,5 items) for the treatment of cardiac failure.

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It has been shown that the level of non-compliance is often underestimated and that non-compliant individuals are difficult to identify.¹ Patient non-compliance has a major influence on the successful outcome of a therapeutic regimen and the underutilisation of the prescribed drug may result in a recurrence or worsening of the illness, unnecessarily increasing the costs of health care. Patients appear reluctant to discuss their lack of compliance honestly. Doctors must be aware of the likelihood of non-compliance even when their patients deny such a possibility.² Patients suffering from chronic illnesses are prone to non-compliance, especially if the effects of missing a dose or two is not immediately apparent.

Patients attending two cardiac outpatient clinics were studied to establish the incidence of non-compliance in those receiving digoxin. An applied pharmacokinetic approach, together with interviews, were used to determine compliance.

Patients and methods

One hundred and thirty-seven outpatients attending two cardiac clinics were involved in the study. All patients had been receiving the same brand of digoxin for at least 10 days to ensure that 'steady state' levels had been reached. Each patient was clinically assessed and the degree of cardiac failure was scored by a physician (Table I). Ninety-eight of the patients

studied were seen by a specialist cardiologist, and 39 patients were seen by two medical officers on different occasions. An interpreter was used in the second group, where language difficulties were encountered. A careful history was taken, including a detailed digoxin dosage history (frequency of dosage, time of previous dose, concurrent medication, and any symptoms of toxicity). Patient compliance was initially ascertained by asking how often patients missed taking digoxin. Those patients who indicated that they never missed a dose were classified as compliant with all other patients being regarded as non-compliant even if they had taken the most recently prescribed dose. In addition to using the patient interview for the detection of non-compliance, a serum digoxin determination was performed on each patient in the study. This enabled acknowledged non-compliance to be confirmed as well as identifying low serum digoxin levels in patients who claimed they were compliant. Serum digoxin concentrations were measured by radio-immunoassay using Gammacoat iodine-125-labelled digoxin.

The expected (predicted) average digoxin plasma concentration ($C_{p_{ss}}$) was determined using an estimate of the total body clearance (Cl_B) of digoxin for the patient.

In order to calculate Cl_B , the serum creatinine clearance for each patient was determined. Creatinine clearance was estimated using the formula of Cockcroft and Gault³ from knowledge of the patient's sex, age, ideal body weight (IBW) (kg)* and serum creatinine (mg/dl).

$$Cl_{Cr} \text{ ml/min} = \frac{(140 - \text{age}) \text{ IBW}}{S.Cr \times 72}$$

(For women multiply by 0,85)

Total body clearance is a combination of renal clearance (Cl_R) and non-renal clearance (Cl_M). Koup *et al.*⁵ described the relationship between these two clearances as:

$$Cl_B = 1,303 Cl_{CR} + Cl_M$$

The Cl_M was assumed to be 40 ml/min for subjects with only mild heart failure where the degree of heart failure was scored at less than 5 (see Fig. 1). In subjects with moderate to severe heart failure, where the degree of heart failure was scored at ≥ 5 , Cl_M was assumed to be 20.

The relationship between Cl_B , the steady-state serum concentration ($C_{p_{ss}}$) and maintenance dose is shown in the following equation, which was used to calculate the predicted average plasma concentration of digoxin at steady state for each patient.

$$C_{p_{ss}} \text{ ng/ml} = \frac{D \times F \times 10^6}{Cl_B \text{ ml/min}} \times \tau$$

where D = maintenance dose (mg); F = fraction of dose absorbed (0,7)⁶; τ = dosing interval in minutes; and $C_{p_{ss}}$ = average plasma concentration at steady state.

The predicted average plasma digoxin concentration was then compared with the measured serum digoxin concentration.

*The ideal body weight was calculated for each patient using tables to correlate height, mass, frame size, and level of obesity.⁴

Department of Pharmacology, Port Elizabeth School of Pharmacy, University of Port Elizabeth/PE Technikon, Port Elizabeth, CP

I. C. WISEMAN, D.SC.

Department of Pharmacology, University of Durban-Westville, Durban

R. MILLER, D.SC.

TABLE I. TABLE USED TO SCORE THE DEGREE OF CARDIAC FAILURE

	Cardiac failure				Score	
	0	+1	+2	+3	CCF/Cor Pul.	LVF
Dyspnoea	None	Mod. exertion	Mild exertion	At rest		
Heart rate	< 100	100-115	116-130	> 130		
Added heart sounds	Absent	Absent	Absent	Present		
Lung crepitations/ bronchospasm	None	Minimal	Moderate	Severe		
JVP (cm ↑ clavicle at 45°)	0	0-2	> 2 < angle of jaw	To angle of jaw		
Oedema	None	Minimal	Moderate	Severe		
Hepatomegaly	None	< 2 fb	< 2 fb	> 2 fb + tenderness		
Total						

Non-compliance was assumed when the predicted serum digoxin concentration was found to be more than 50% greater than the measured serum digoxin concentration. Since digoxin has a long half-life ($t_{1/2}$), fluctuations between peak and trough values are small once distribution to the central compartment is complete, i.e. 6 - 12 hours after dosing. Taking exponential decay into account and using an elimination rate constant of 0,02/h, the plasma digoxin concentration will decrease by approximately 10% in a healthy patient after a further 6 hours have elapsed. Therefore if the plasma digoxin concentration was measured 12 hours after dosing, 90% of the plasma concentration at 6 hours after dosing would still be present. The plasma concentrations of patients studied were measured in this β phase between 6 hours and 12 hours after dosing. If congestive heart failure and renal impairment are present the loss of digoxin during this 6-hour period will be less than 10%.

Results

Of the 98 patients seen by the specialist cardiologist, 22 (22,4%) were found to be non-compliant; 16 of these patients admitted non-compliance when questioned. The 6 patients who denied being non-compliant had a mean predicted serum digoxin concentration of $1,18 \pm 0,49$ ng/ml, which was less than 61,6% of the mean measured concentration ($0,73 \pm 0,4$ ng/ml). The serum digoxin concentration in 13 of the 22 non-compliant patients was found to be sub-therapeutic (< 0,8 ng/ml); 6 patients showed signs of cardiac failure. The avoidance of digoxin toxicity was a possible reason for non-compliance in 2 patients, since the predicted serum digoxin concentration was calculated to be more than 2,0 ng/ml.

In the group of 39 patients seen by two registrars on different occasions, and in whom communication was a problem, 33 patients (84,6%) were found to be non-compliant; 32 patients had serum digoxin concentrations of < 0,8 ng/ml. Twenty-three patients admitted non-compliance when questioned. The 10 patients who denied being non-compliant had a mean predicted serum digoxin concentration of $0,93 \pm 0,2$ ng/ml, which was less than 151,4% of the mean measured concentration of $0,37 \pm 0,2$ ng/ml. Eighteen of the non-compliant patients with serum digoxin concentrations that were sub-therapeutic showed signs of cardiac failure and were receiving additional medication ($1,7 \pm 0,6$ items) for this condition.

In the first group, 29% of the female patients were non-compliant compared with 18,3% of the male patients. In the second group 90% of the female patients were non-compliant compared with 66,7% of the male patients. The greater number

of non-compliant female patients has been observed in other studies.²

Discussion

This study showed that there was often a difference between the treatment prescribed and the amount of medication patients actually took. The physician's relationship with the patient and how clearly he explains the treatment regimen have a significant effect on compliance.⁷ It has also been shown that the effectiveness of physician-patient communication is inversely proportional to the error rate in the taking of drugs.⁸ Poor compliance has been reported more frequently in patients who are less well educated, are poorer or have language difficulties.⁹

These factors were evident when comparing the two groups of patients studied. The first group of 98 patients had a good relationship with one specialist cardiologist; only 22,4% of them were non-compliant. However, the second group of 39 patients, with 84,9% non-compliant, were seen by two different medical officers and communication was often a problem.

In both studies female patients were found to be non-compliant more frequently than males.

Non-compliance is a problem of serious dimensions in South Africa and poor communication — as experienced in the second group — as well as lack of a proper doctor-patient relationship are seen as major causative factors.

Recommendations

1. The risk of drug defaulting may be reduced by making every effort to ensure that all patients understand instructions and are supervised regularly.

2. It is important that when a patient shows a poor response to digoxin an attempt should be made to ascertain if the medication prescribed has been taken correctly before another drug is added to the treatment programme.

3. In patients who insist they are compliant but who have a sub-therapeutic serum digoxin concentration, it is recommended that the support of a pharmacokinetic service be used to provide an estimate of the probability of non-compliance by comparing the predicted and measured serum digoxin concentrations. This approach should always be considered before the dose of digoxin is increased to ensure that the dosage is not increased unnecessarily resulting in digoxin toxicity if the non-compliant patient becomes compliant.

With the considerable advances that have been made in the development of potent and effective drugs, it is unfortunate that in many situations drugs are not being optimally utilised. Non-compliance is a major cause of ineffective therapy and it adds considerably to the medicine bill in South Africa.

Patients cannot be coerced, frightened, threatened or cajoled into compliance. They can, however, be educated, advised and encouraged. It is essential that the compliant patient sees himself as an active member of the medication team, not the passive victim of disease.¹⁰

REFERENCES

1. Gillum FG, Barsky AJ. Diagnosis and management of patient noncompliance. *JAMA* 1974; **228**: 1563-1567.
2. Johnston GD, McDevitt DG. Digoxin compliance in patients from general practice. *Br J Clin Pharmacol* 1978; **6**: 339-343.
3. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976; **16**: 31-41.
4. Diem K, Lentner C. *Documenta Scientifica Tables*. 7th ed. Basle: J. R. Geigy, 1974: 712.
5. Koup JR, Jusko WJ, Elwood CM, Kohli RK. Digoxin pharmacokinetics: role of renal failure in dosage regimen design. *Clin Pharmacol Ther* 1975; **18**: 9-21.
6. Benet LZ, Sheiner LB. Design and optimization of dosage regimens: pharmacokinetic data. In: Goodman Gilman A, Goodman LS, Rall TW, Murad F, eds. *Goodman and Gilman's The Pharmacological Basis of Therapeutics*. 7th ed. New York: Macmillan, 1985: 1684.
7. Mazullo J, Cohn K, Lasagna L, Griner P. Variations in interpretation of prescription instructions. *JAMA* 1974; **227**: 929-931.
8. Swinyard EA. Principles of prescription order writing and patient compliance instruction. In: Goodman Gilman A, Goodman LS, Rall TW, Murad F, eds. *Goodman and Gilman's The Pharmacological Basis of Therapeutics*. 7th ed. New York: Macmillan, 1985: 1661.
9. Blackwell B. Patient compliance. *N Engl J Med* 1973; **289**: 249-252.
10. O'Dea P. Glaucoma therapy: the pharmacists' role in compliance. *Am Pharm* 1988; **NS28**: 38-42.