An epidemiological study of digoxin prescribing in general practice

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SUMMARY. The epidemiology of prescribing long-term digoxin was studied in 241 patients from six group general practices. Each patient was assessed for the initial reason for prescribing digoxin and present clinical status, and the serum digoxin concentration was measured between six and 12 hours after the previous dose.

The results show that digoxin was most commonly prescribed for elderly patients; 90% of patients were aged 60 years or more. The reasons for prescribing digoxin were considered adequate in only 55% of the total group; 71% of the patients were judged to be clinically well and 75% of the 95 patients with atrial fibrillation had ventricular rates of less than 90 beats per minute. 'Therapeutic' serum digoxin concentrations (0.8–2.0 ng ml^{-1}) were observed in only 48% of patients; the level was sub-therapeutic in 46% and potentially toxic in 6%. No clear-cut relationship was found between clinical well-being and serum digoxin concentration. The type of supervision (whether hospital or general practice) did not affect appropriateness of prescribing, clinical well-being or likelihood of achieving a therapeutic serum digoxin level.

This study would suggest the need for critical review of digoxin therapy in all patients who are taking it long-term. In some patients its continuance would appear unnecessary; in others, efficacy may be improved either by dose adjustment or by ensuring compliance. On occasions, particularly in patients with sinus rhythm, measurement of serum digoxin concentrations may prove helpful in this evaluation.

Introduction

THE availability of a specific radioimmunoassay technique for measuring plasma digoxin concentrations in humans has renewed interest in cardiac glycosides almost 200 years after digitalis was first introduced into clinical practice. Speculation has focused on a number of issues, including the indications for using digoxin[1] and the reasons why so many patients on maintenance digoxin are found to have potentially toxic or sub-therapeutic plasma concentrations.[2] Many of these observations have been made on patient populations which were in direct contact with hospital. The present study investigates the epidemiology of digoxin prescribing in general practice — why the drug was given, the efficacy of its use and the role of general practice in the initiation and supervision of treatment.

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Method

The subjects were patients who had been taking digoxin therapy for at least six months and who were cared for by six group general practices. These practices were chosen because one principal in each is a part-time lecturer in the Department of General Practice, The Queen's University of Belfast. In each practice, the names of patients who were on long-term digoxin therapy were listed consecutively as they made contact with their doctor, either directly through a surgery appointment or a home visit or indirectly by requesting repeat medication.

Once a name was obtained, contact with the patient was established by telephone, where possible, or otherwise by letter. The intention was to offer an appointment with the doctor (M.C.) either at the local health centre or surgery or at home within 24 hours of the contact, in order to minimize anxiety and alterations in the usual pattern of taking medication. Patients were told that the purpose was to check their therapy.

Before interviewing each patient, details of age, prescribed drug therapy and date and place of commencement of digoxin, together with reason for starting it were obtained from his or her medical record. These details were confirmed with the patient. In addition, a clinical history was taken, a clinical examination performed and a 12-lead electrocardiogram recorded. A venous blood sample was then taken for estimation of serum digoxin, creatinine, urea and electrolyte concentrations. The time interval between the alleged last dose of digoxin and the blood sample was noted; all blood samples considered in this study were taken between six and 12 hours after the previous digoxin dose.

Criteria for assessment of cardiac failure and digoxin toxicity are shown in Table 1. Serum digoxin concentrations were measured by radioimmunoassay; the therapeutic range was taken as 0.8–2.0 ng ml^{-1}.[3] Serum creatinine, urea and electrolyte levels were measured by routine biochemical analyses.

The study was approved by the local University Ethical Committee.

Results

Study sample

The total number of patients listed as taking digoxin was 247; attempts to contact one were repeatedly unsuccessful, one declined to participate in the study and four other patients were excluded because their previous digoxin dose was within six hours of the appointment. Thus the study sample consisted of 241 patients, approximately 40 from each of the six general practices: 84 (35%) were male and 157 (65%) were female. Their ages ranged from 34 to 94 years (mean 71.0 ± standard error 0.6 years) with 216 (89.6%) aged 60 years or older. By contrast only 19.1% of the total patient population in these practices were older than 60 years. There was no significant difference between the age distributions of groups of patients from the different practices.

Reasons for prescribing digoxin

The reasons for which digoxin was prescribed in these 241 patients are summarized in Table 2. On the basis that indications for digoxin therapy are atrial tachyarrhythmias and congestive heart failure which has not been controlled by diuretic therapy, 132 patients (54.8%) were considered to have been prescribed digoxin for adequate reasons. The reasons for prescribing digoxin appeared to be inadequate in 109 patients (45.2%).

Table 1. Criteria used in the study for diagnosis of cardiac failure and digoxin toxicity.

Symptoms	Signs
Criteria for diagnosis of cardiac failure	
Orthopnoea	Central cyanosis
Paroxysmal nocturnal dyspnoea	Gallop rhythm
Dyspnoea after walking up one flight of stairs or after walking briskly 100 yards or less	Basal or widespread crepitations
	Increased jugular venous pressure
	Oedema
	Hepatomegaly

Patients were classified as having cardiac failure if a minimum of one symptom and one sign were present.

Criteria for diagnosis of digoxin toxicity	
Anorexia	Paroxysmal atrial tachycardia with or without atrioventricular block
Nausea	Atrial flutter with or without atrioventricular block
Vomiting	Atrial extrasystoles
Diarrhoea	Ventricular extrasystoles — coupled or multiple and multifocal
Yellowed or misty vision	Paroxysmal ventricular tachycardia

Patients were classified as having digoxin toxicity if: (1) in the presence of any ECG sign of digitalis effect (ST segment depression, sinus bradycardia, first or second degree atrioventricular block with sinus rhythm) any of the above symptoms was present, or (2) any of the above signs of toxicity was present.

Table 2. Reason for which digoxin was prescribed in 241 patients.

Prescribing indication	No. (%) of patients
Adequate indications	
Atrial tachyarrhythmias	112 (*46.5*)
Congestive heart failure with sinus rhythm after prior diuretic therapy	20 (*8.3*)
Total	132 (*54.8*)
Inadequate indications	
Congestive heart failure with sinus rhythm without prior diuretic therapy	20 (*8.3*)
Valve disease without atrial fibrillation or congestive heart failure	7 (*2.9*)
Post-myocardial infarction	30 (*12.4*)
Other reasons — including dizziness, tiredness, hypertension, dyspnoea, palpitations, alcoholic cardiomyopathy	19 (*7.9*)
Reason unclear	33 (*13.7*)
Total	109 (*45.2*)

This was analysed further in terms of where the decision to prescribe digoxin was made. Digoxin was commenced for adequate reasons in 87 of 148 patients (58.8%) by hospital doctors compared with 45 of 92 patients (48.9%) by general practitioners. This difference was not significant (chi-square test).

Efficacy of therapy

Of the 241 patients, 172 (71.4%) were considered to be clinically well. Cardiac failure was diagnosed in 63 patients (26.1%) and evidence of digoxin toxicity was observed in six patients.

Only 95 of the 112 patients who had been given digoxin for control of atrial tachyarrhythmias had atrial fibrillation when examined. However, the indication for prescribing digoxin was supraventricular tachycardia in nine patients: all of these and eight other patients who had had atrial fibrillation had reverted to sinus rhythm. Of the 95 patients with atrial fibrillation, 24 had ventricular heart rates (measured from the electrocardiogram) greater than 90 beats min^{-1} and would be considered to be inadequately controlled.

Serum digoxin levels

One hundred and sixteen patients (48.1%) had serum digoxin concentrations within the usual therapeutic range of 0.8–2.0 ng ml^{-1}; 15 patients (6.2%) had levels greater than 2.0 ng ml^{-1}, in the potentially toxic range; and 110 patients (45.6%) had sub-therapeutic levels, with 10 having no measurable digoxin in the blood (Figure 1). A significant relationship was observed between the daily digoxin dose prescribed and serum digoxin concentration ($\chi^2 = 54.79$, 2 df, $P<0.001$, combining digoxin doses of 0.25 mg and >0.25 mg). Thus only 13.6% of patients taking 0.0625 mg day^{-1} achieved therapeutic concentrations in contrast to 65.6% of patients who took 0.25 mg day^{-1} (Figure 2). The majority of patients (86.4%) taking 0.0625 mg day^{-1} had sub-therapeutic levels; conversely, 14 of the 15 patients with potentially toxic concentrations were taking 0.25 mg day^{-1} or more of digoxin.

Relationship between clinical efficacy and serum digoxin levels

The relationship between clinical efficacy and serum digoxin concentration is illustrated in Figure 3. Approximately three-quarters of the patients with either sub-therapeutic or therapeutic concentrations were judged to be clinically well; one-quarter of both groups were in cardiac failure. With the higher serum concentrations a smaller proportion of patients was thought to be satisfactorily treated, but the number of patients with possible digoxin toxicity was too small for statistical comparison. Of the six patients with clinical evidence of digoxin toxicity five had digoxin levels within the therapeutic range and one in the potentially toxic range. All six patients had normal serum potassium levels.

Twenty-four of the 95 patients with atrial fibrillation (25.2%) had ventricular rates greater than 90 beats min^{-1} and were thus inadequately controlled; of these only seven had sub-therapeutic serum digoxin concentrations and appeared to be under-treated (Table 3). In contrast, 24 patients (25.2%) with ventricular rates less than 90 beats min^{-1} had sub-therapeutic digoxin levels and may not have required digoxin therapy. Forty-two patients (40%) had therapeutic levels and a controlled ventricular rate.

Different types of supervision

Although 148 patients (62%) had started digoxin therapy in hospital, the majority (68%) were supervised in general practice alone and only 32% attended hospital departments. This

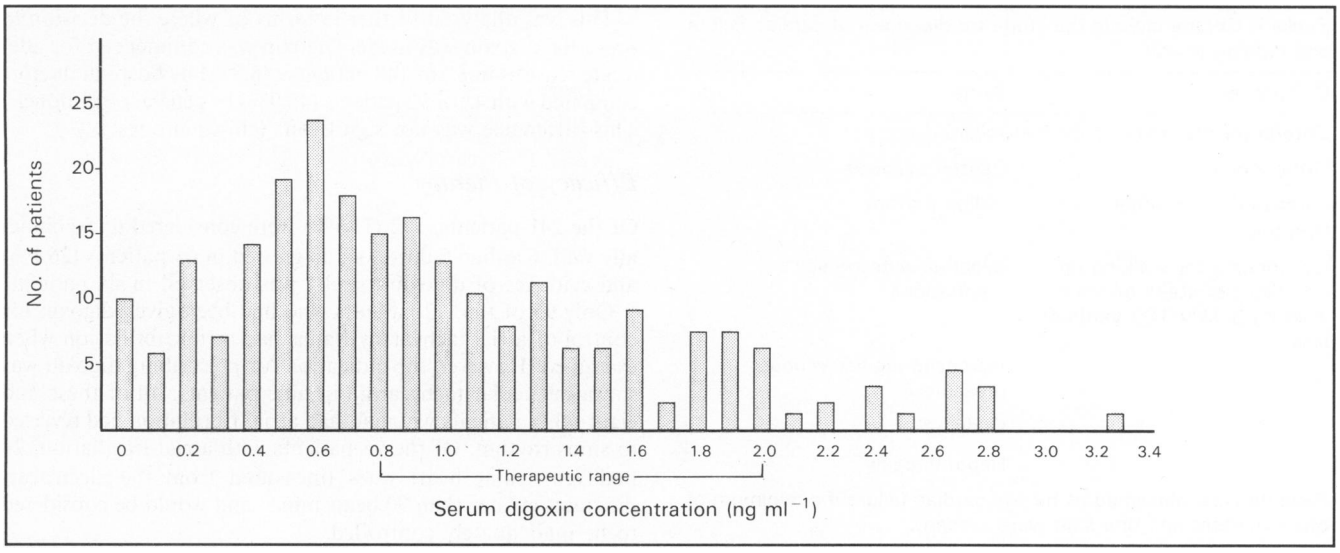

Figure 1. *Serum digoxin concentration of the 241 patients.*

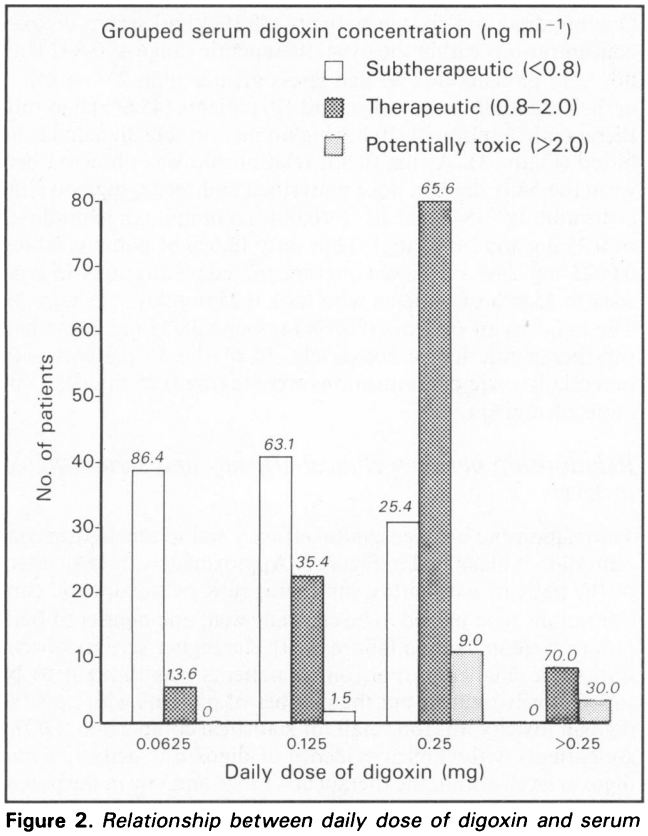

Figure 2. *Relationship between daily dose of digoxin and serum digoxin concentration (percentages shown over bars).*

Table 3. Relationship between heart rate and serum digoxin concentration in 95 patients with atrial fibrillation (percentages in parentheses).

	Serum digoxin concentration (ng ml^{-1})		
Heart rate (beats min^{-1})	Subtherapeutic (<0.8)	Therapeutic (0.8–2.0)	Potentially toxic (>2.0)
<70	2	4	0
70–90	22	38	4
>90	7	13	4
Total	31 (*33*)	55 (*58*)	8 (*8*)

pattern of supervision was common to the six general practices. However, of the patients supervised in general practice alone, approximately half (attending three of the practices) were given personalized care by the same doctor and the other half were not. On the basis of clinical well-being and serum digoxin concentration, there appeared to be no influence on patient care of different types of supervision, whether hospital cardiac unit, hospital medical department, general practice, personal or non-personal care.

Discussion

The results of this study confirm the previous observations that digoxin is most commonly prescribed for elderly patients.[4-6] Two hundred and sixteen of the 241 patients taking digoxin were aged 60 years or over, even though this age band formed less than 20% of the patient population in the six general practices. Since there are known to be particular problems in using digoxin in the elderly because of their diminishing renal function and small lean body mass, this immediately emphasizes the need for maximum efficiency in prescribing for this group.

Against this background, the results of this study are alarming. It appeared that the reasons for prescribing digoxin were justifiable in little more than half of the patients. Opie[1] has argued that the reasons for prescribing digoxin 'are shrinking'. Those still considered legitimate include the control of ventricular heart rate in atrial tachyarrhythmias and congestive heart failure in sinus rhythm[7] although even the latter is now considered suspect by some. If it is agreed that digoxin should not normally be prescribed for patients with congestive heart failure in sinus rhythm before diuretics have been tried, then only 132 patients (54.8%) appeared to have adequate indications for maintenance digoxin therapy — 112 with atrial tachyarrhythmias and 20 with congestive heart failure. In the remaining 109 patients the reasons for prescribing digoxin were less clear. In particular, 30 patients had been given digoxin after a myocardial infarction and 19 for a variety of symptoms including dizziness, palpitations and even hypertension. Of equal concern were 33 patients (13.7%) for whom the reason why the drug was prescribed could not be decided; nine of these patients were subsequently found to have cardiac failure so it is possible that the original indication might have been legitimate. There was no evidence that accurate prescribing indications were more likely in hospital than in general practice.

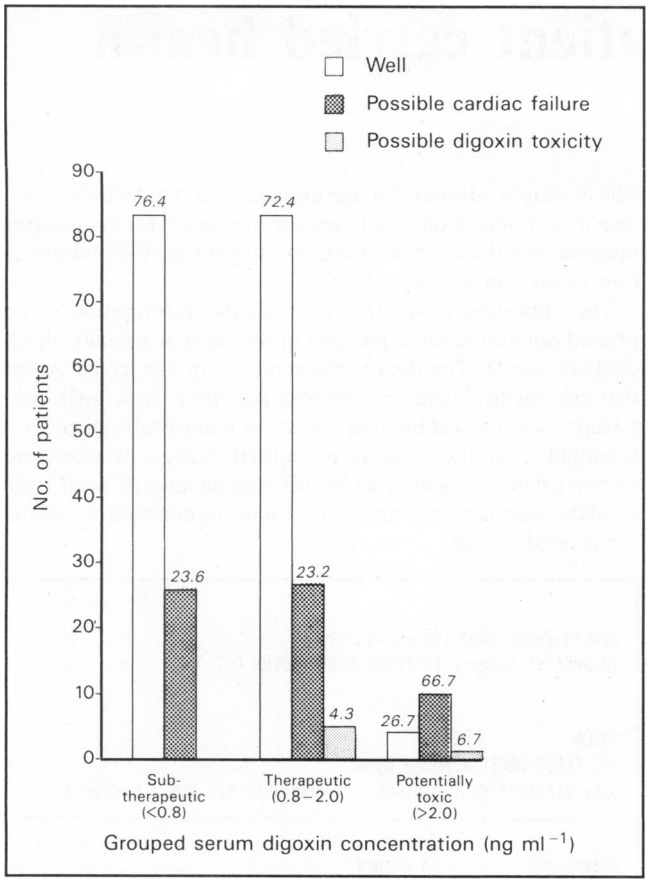

Figure 3. *Relationship between serum digoxin concentration and clinical condition (percentages shown over bars).*

In addition, the adequacy of digoxin therapy was assessed in terms of the clinical status of the patients. This can only be done adequately in the light of the patients' serum digoxin concentrations. Twenty-four patients with atrial fibrillation who had controlled ventricular heart rates (less than 90 beats min^{-1}) also had sub-therapeutic serum digoxin concentrations (below 0.8 ng ml^{-1}). Several studies have shown that patients with serum digoxin concentrations below this level can have their digoxin withdrawn without clinical detriment in most instances.[8,9] Thus it is possible that the ventricular rate of these patients might be controlled even if they did not take digoxin: only a supervised withdrawal of therapy could establish this. Similarly, seven patients with sub-therapeutic concentrations had uncontrolled atrial fibrillation and a dose increase would seem appropriate. As far as assessment of cardiac failure was concerned, in the sub-therapeutic group 76% of the patients were considered well, and in the absence of atrial tachyarrhythmias probably did not require maintenance digoxin, and 24% showed signs of heart failure and may have benefited from a trial of a higher digoxin dose. The group for whom digoxin withdrawal is most indicated are those who have a combination of inadequate reasons for initial prescribing and sub-therapeutic or potentially toxic digoxin levels.

The overall observation that less than 50% of patients prescribed maintenance digoxin therapy have serum concentrations within the therapeutic range has been demonstrated previously,[2,9,10] even in general practice.[11] There appear to be several contributory factors, including wrong dose selection[12] and poor patient compliance.[11,13] The present study did not assess compliance but it is interesting to note that almost all patients given digoxin 0.0625 mg daily, the so-called paediatric/geriatric tablet, had serum levels less than 0.8 ng ml^{-1}. Clearly this dose is likely to be inadequate unless the patient has very severely compromised renal function.

These results again emphasize the importance of measuring serum digoxin concentrations in patients taking maintenance therapy, particularly in patients with sinus rhythm where there is no clinical indicator of dose adequacy or compliance. However, as already discussed, even in patients with atrial fibrillation, knowledge of the serum digoxin level may suggest the need for further dose adjustment or even drug withdrawal. Given that digoxin is a drug with a narrow therapeutic ratio and serious toxicity, particularly in the elderly, it is disturbing to find that its use was associated with sub-therapeutic serum concentrations in 110 patients (45.6%). If it is ineffective at these levels, as most of the evidence suggests, it should either be given at an increased dose level, where the prescribing indications are justifiable and clinical control is lacking, or alternatively the possibility of withdrawal should be seriously entertained.

Finally, the present study did not suggest that the problems identified with digoxin prescribing were associated with any particular type of supervision. Thus inadequate reasons for initial prescribing, low serum digoxin concentrations and lack of clinical well-being seemed equally liable to occur when the drug was started in hospital or in general practice and whether regular supervision was by hospital or by general practice.

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Acknowledgements

The authors wish to acknowledge the technical assistance of Mrs S. Copeland for the digoxin radioimmunoassays and to thank Dr J.D. Merrett for his help in statistical analyses.

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