

On the Clinical Use of Digitalis
with reference to its prescription, maintenance therapy,
intoxication and the patient's knowledge.

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Kurt Boman
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Skellefteå 1983

Abstract

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Maintenance digitalis therapy has lately been questioned. In a retrospective study, digitalis was discontinued in 141 geriatric patients without contraindications to digitalis withdrawal. Digoxin treatment seemed to be unnecessary in 108 patients (81 per cent), followed up two months after digoxin withdrawal. A long-term study (mean: 20,5 months) was carried out in these 108 patients. Digitalis therapy was reinstated in 30 of 99 patients, equally distributed on the basis of clear, possible or uncertain indications. Significantly more patients ($p < 0,001$) with atrial fibrillation compared with sinus rhythm were restarted. A prospective, randomized, double-blind placebo-controlled study in 39 out of 66 geriatric patients confirmed the results of the retrospective study. During a two-month period 32 of 37 patients (86 per cent) managed without digitalis. Eighteen out of 66 patients (27 per cent) presented contraindications to digoxin withdrawal. Those who needed digitalis were restarted mainly during the first month (mean: 18 days) following digoxin withdrawal.

Digitalis intoxication has been studied earlier, mainly in hospitalized patients. A clinical examination and ECG of a random sample of outpatients treated with digoxin showed that about 5 per cent were certainly intoxicated and about 2 per cent suspected of being intoxicated.

Elderly patients are said to be more sensitive to digitalis. Eleven per cent of 66 geriatric patients were found, without doubt, to be digitalis intoxicated. The mean serum digoxin concentration was significantly higher in eight toxic patients compared with non-toxic patients, but 75 per cent of the toxic patients had serum digoxin concentrations within or below therapeutic range. Five of these intoxicated patients did not need maintenance digitalis therapy.

A questionnaire of 361 patients in Skellefteå and Uppsala revealed that about 45 per cent had taken digitalis for more than five years. Approximately 85 per cent took one tablet daily and stated compliance. About one fifth did not know why they were taking digoxin and about half of the patients were uncertain if they were improved by digitalis therapy. Although digitalis intoxication is such an important clinical problem, some 55 per cent did not know about digitalis's side-effects and some 50 per cent stated that no or insufficient information had been given. Only 15 per cent were satisfied with the information they had received. A significant negative correlation between digoxin dosages and the age of the patients was found.

Key words: Digitalis, prescribing habits, dosages, defined daily doses, geriatric patients, maintenance therapy, withdrawal, intoxication, serum digitalis concentration, patient's knowledge.

ERRATA

- Sid 19, 3:e st, r 2: skall vara 100 out of 1408.
- Sid 26, 1:a st, r 2: 100 inh skall vara 1000 inh.
- Sid 26, 3:e st, r 2 resp Arb I, sid 4, r 18: 66,5 resp 65,5
skall vara 62,1.
- Sid 30, rad 4: 2,6 skall vara 2,7.
- Sid 31, 3:e st, r 2 och 3: Saknas: ~~Y~~
- Sid 37, 1:a st, r 1: incidence skall vara prevalence.
- Sid 38, 2:a st, r 4: (1930) skall vara (1970).
- Sid 49, 4:e ref: Within skall vara with.
- Sid 59, 4:e ref: Tillägg efter medical uses: with practical
remarks on dropsy,
- Arb I: Sid 2, r 5: Tillägg (Table 1)
- Arb III: Sid 2, r 12 resp sid 7, r 5: ($p < 0,001$) skall vara
($p < 0,01$).
- Arb III: Sid 6, 2:a st, r 9: After two months i stället för
Thus
- Arb V: Sid 2, 1:a st, r 1: 1488 skall vara 1408, och r 3:
digoxin skall vara digoxin intoxication.
Sid 10, table II: Saknas sort mg, kg och /kg,ug.
- Arb VI, sid 14, table III: Saknas < efter ASAT, ALAT och >
efter p raden längst ned.
- Arb VII: Sid 3, längst ned: Tillägg ($p < 0,001$), sid 7, r 4:
One third skall vara five per cent, Fig 2A och 2B: På y-
axeln saknas . framför sifferorna.

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Skellefteå and the Institution of Internal Medicine, University of Umeå, Umeå, Sweden.

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Keywords: Digitalis, prescribing habits, dosages, defined daily doses, geriatric patients, maintenance therapy, withdrawal, intoxication, serum digitalis concentration, patient's knowledge.

To CARIN

OLOV and NILS

It is much easier to write
upon a disease
than upon a remedy.

The former is in the hands of Nature
and a faithful observer with
an eye of tolerable judgement
cannot fail to delineate a likeness.

The latter will ever be subject
to the whim,
the inaccuracies and
the blunder
of mankind.

William Withering, 1741-1799

CONTENTS

ABBREVIATIONS	6
ORIGINAL PAPERS	7
INTRODUCTION	8
A historical perspective of the prescribing of digitalis	8
Indications for digitalis treatment	9
Antiarrhythmic agent	9
Inotropic agent in sinus rhythm	10
The effect of digitalis in various heart diseases	11
Digitalis intoxication	13
Patients' knowledge	16
AIMS OF THE STUDY	17
MATERIAL AND METHODS	18
RESULTS	26
Prescribing habits	26
Withdrawal of digoxin therapy	26
ECG rhythm	27
Dosage	28
Digoxin and diuretics	28
Indication for resuming digitalis therapy	28
Digitalis intoxication	29
Clinical and laboratory data	29
Serum concentration of digoxin	29
Patients' knowledge	30
DISCUSSION	32
Prescribing habits	32
Withdrawal of digitalis	33
Digitalis intoxication	37
Patients' knowledge	40
CLINICAL IMPLICATIONS	41
Digitalis prescribing habits	41
Digitalis maintenance therapy	41
Digitalis intoxication	43
Patients' knowledge	44
GENERAL SUMMARY AND CONCLUSIONS	46
ACKNOWLEDGEMENT	48
References	49

ABBREVIATIONS

AF = atrial fibrillation
AFL = atrial flutter
AV = atrio-ventricular
ADL = patients daily activities
ALAT = alanin-amino-transferas
ASAT = aspartat-amino-transferas
COCM = congestive cardiomyopathy
DDD = defined daily doses
HOCM = hypertrophic cardiomyopathy
SR = sinus rhythm
SVT = supraventricular tachycardia
WPW = Wolff-Parkinson-White

ORIGINAL PAPERS

This thesis is based on the following papers which will be referred to by their Roman numerals:

- I. Boman, K., Ögren, J-E.: The treatment of out-patients by digitalis in Skellefteå health district. *Läkartidningen* 1981; 78:3899-3901
- II. Boman, K., Allgulander, S., Skoglund, M: Is maintenance digoxin necessary in geriatric patients? *Acta Med Scand* 1981; 210:493-495
- III. Boman, K: Withdrawal of digoxin in geriatric patients.
A retrospective long-term follow-up study. Submitted for publication.
- IV. Boman, K: Digoxin and the geriatric patient. A randomized trial of digoxin versus placebo. Submitted for publication.
- V. Boman, K, Möllerberg, H: The occurrence of digoxin intoxication.
Läkartidningen 1979; 76:4108-4110
- VI. Boman, K: Digitalis intoxication in geriatric patients. Submitted for publication.
- VII. Boman, K., Möllerberg, H., Ögren, J-E.: What do patients know about their digitalis? A comparison between two different areas in Sweden.
Submitted for publication.

INTRODUCTION

A historical perspective of the prescribing of digitalis

Withering (1785) identified *Digitalis purpurea* as the diuretic ingredient of the Shropshires woman's herbal brew. He studied 160 patients and found that digitalis could relieve dropsy in most of his cases. Although he knew that the drug influenced the pulse, the primary cardiac action was not then known. The indications for its use were ill-defined and with more widespread prescription, many patients developed toxic side-effects. After digitalis had been recognised as a dangerous drug of dubious efficacy, Mc Kenzie (1911) reintroduced the drug because of its nodal blocking properties, which slowed the ventricular response in atrial fibrillation. Later, comparisons were made of the action of digitalis in sinus rhythm as well as atrial fibrillation. Christian (1922), Luten (1924) and Marvin (1927) reported that digitalis was associated with improvement in half their patients. They considered that patients in sinus rhythm benefited as much as those with atrial fibrillation. Similar findings were made by Gavey and Parkinson (1939). However, patients in atrial fibrillation who showed the greatest reductions of heart rate responded best of all.

With the advent of hemodynamic studies in man (Lagerlöf & Werkö 1949, Werkö et al 1958), the place of digitalis as first choice in the treatment of heart failure became more firmly established. The glycosides were shown to have an inotropic action in animals and in man with both normal and abnormal hearts (Smith & Haber 1973). This action reinforced the teaching in several medical textbooks, which stated that digoxin is indicated in all form of heart failure irrespective of the cause and the rhythm (Goodman & Gilman 1975, Cullhed 1972). Although some doubts were expressed for such a practice (Editorial Lancet 1976) the number of prescriptions of digoxin continued to rise in the United Kingdom (Guz & Mc Haffie, 1979), and in the United States digitalis glycosides have become the fourth most commonly prescribed drug (Schich & Scheuer, 1974). In Sweden digitalis glycosides were the most commonly prescribed drugs in 1978 (Information. Drug Department of the National Social Welfare Board, 1978).

Looking at the prescribing habits for digitalis glycosides in 10 European countries, there were great differences, West-Germany being the highest with 64.29 defined daily doses (DDD,Halse 1977) per 1000 inhabitants/day . On the contrary in France the prescription of digitalis glycosides was only 8.81 DDD/1000 inhabitants/day (Friebel 1982). The wide differences between countries are interesting but the prescribing habits within a single country and a single health district could be just as informative.

Thus it was of interest to study the prescribing habits, the types of cardiac glycosides used and the dosages in a smaller health district of Sweden (Skellefteå).

Indications for digitalis treatment (table 1)

Table 1. Clinical application of digitalis

1. Indication

- A. Supraventricular arrhythmias
 - 1. Atrial fibrillation and flutter
 - 2. Paroxysmal atrial tachycardia
 - a) acute attack
 - b) chronic prophylaxis
- B. Myocardial failure secondary to chronic valvular, coronary, congenital, hypertensive or primary myocardial disease.

Non-indications and/or limited use

- A. Acute myocardial infarction
- B. Acute myocarditis
- C. Mitral stenosis with sinus rhythm
- D. Asymptomatic hypertensive or valvular heart disease
- E. Constrictive pericarditis
- F. Cor pulmonale
- G. Prophylactic in surgery

Antiarrhythmic agent

(Duca & Brest 1974)

Since Mc Kenzie (1911) reintroduced digitalis in the treatment of atrial fibrillation, there has been no doubt of the long-term efficacy of digitalis in the control of rapid (> 100 beats/min) atrial fibrillation (AF) and flutter (AFL), (Cullhed 1972). Some patients with a normal heart rate at rest but an important increase during physical exercise, also seem to benefit from treatment by digitalis (Redfors 1971). However, some patients, particularly the elderly, with a natural degree of atrio-ventricular block (AV), may have AF and AFL without a fast ventricular rate and may not need digitalis or any other specific treatment (Editorial Br J Clin Pharmac 1979, Cullhed 1972, Chamberlain et al 1979).

In paroxysmal supraventricular tachycardia (SVT), digitalis is given in order to stop the acute attack as well as for prophylaxis. The indication for prophylactic treatment lies in the frequency and severity of the attacks. However, newer drugs such as verapamil and beta-receptor-blocking agents are nowadays available as alternatives in both acute and long-term cases (Chamberlain et al 1979).

AF, AFL and SVT are sometimes manifestations of the Wolf-Parkinson-White syndrom (WPW). In patients with suspect or known WPW-syndrom digitalis should not be given.(Chamberlain et al.1979).

Inotropic agent in sinus rhythm (SR)

The positive inotropic effect of digitalis glycosides demonstrated experimentally and in acute studies is undoubtedly (Smith & Haber 1973, Crawford et al 1976). The subcellular and ionic mechanisms for this action are thought by most workers to result from a glycoside-induced inhibition of membrane-bound sodium and potassium dependent adenosine triphosphatase (ATP-ase), which results in a rise in the intracellular pool of free calcium. The mechanism of this rise is not well understood but the effect could be a facilitation of excitation-concentration coupling (Lee & Klaus, 1971).

In the treatment of heart failure (HF) several considerations have to be made before starting digitalis therapy, such as the aetiology of the heart disease, whether it is an acute or chronic HF, the role of diuretics, vasodilating drugs and other therapeutic proceedings.

In acute HF due to myocardial infarction, the clinical results of digitalis therapy have been disappointing (Werkö et al 1966, Balcon et al 1968, Sjögren 1970) or even harmful (Cohn et al 1969). Moreover, Cohn, Tristiani & Khatri (1969) found little effect in cardiogenic shock. The well-known acute constrictor effect of intravenous digoxin (De Mots et al 1975) may provoke hypersensitivity-stress on the heart or cause myocardial ischaemia by coronary vasoconstriction. Evidence of clinical benefit is thus very uncertain in acute myocardial infarction complicated by HF, and diuretics are recommended as the first line therapy. (Cullhed 1972, Opie 1980).

Doubts have been raised as to whether the inotropic action of digoxin persists in its long-term use (Davidson & Gibson 1973, Cohn et al 1975). However, Crawford, Karliner & O'Rourke (1976) demonstrated an improvement of

myocardial performance over a period of 10-14 days. Lately, long-term digitalis therapy has been shown to improve left ventricular function (Arnold et al 1980., Lee et al 1982).Moreover, Murray et al (1982) found that a hemodynamic benefit was manifest only during exertion. In summarising these recent data, Arn et al, Lee et al and Murray et al suggest that long-term digoxin therapy is clinically beneficial, especially in more severe chronic heart failure.

The effects of digitalis in various heart diseases

It is debatable whether digitalis benefits patients in SR with angina pectoris. In a series of patients not receiving beta-blockers, acute digitalisation relieved the left-ventricular failure which arose with the onset of angina (Sharma et al 1972), but long-term digitalisation might be less effective (Opie 1980). In a double blind study (Smith et al 1966) digitalis failed to influence exercise tolerance in angina pectoris. A theoretical fear has been raised concerning the use of digitalis in ischemic heart disease (IHD), in that cardiac sensitivity and the vasoconstrictive property of cardiac glycosides (Davidi Ku & Luchessi 1979, De Mots et al 1975) might lead to ischemic-induced alteration of reactions to digitalis. However, in patients with cardiomegaly and/or failure, a reduction of heart volume would be beneficial by decreasing oxygen consumption (Braunwald 1971). Moreover, in anginal patients with cardiomegaly, digitalisation may avert the precipitation of cardiac failure by beta-blockade (Oeff et al 1979).

In summary, studies of the value of digitalis in angina pectoris have shown conflicting results. However, a therapeutic trial might be justified in some patients with cardiomegaly and/or failure (Cullhed 1972).

Before starting treatment with digitalis in patients with valvular disease consideration should be given to surgical therapy (Jonsson 1978). In chronic mitral regurgitation with heart failure, digitalis is conventionally in the first line of treatment (Cullhed 1972, Opie 1980), but vasodilatators may provide a useful alternative (Opie 1980).The same treatment could be used for chronic aortic incompetence. By using digitalis in this valvular disease a slower heart rate would increase the regurgitation and thereby the load on the left ventricle (Cullhed 1972, Enghoff 1972), which might be a disadvantage. In mitral stenosis with sinus rhythm there is no indication for digitalis (Werkö 1958, Cullhed 1972) and in aortic stenosis in heart failure a trial with digitalis could be justified, even if the effect is likely to be limited (Cullhed 1972). After the surgical treatment of valvular disease the withdrawal of digitalis therapy should be considered. (Cullhed 1972).

Left ventricular failure may result from an inadequately treated hypertension, when the inotropic effect of digitalis could relieve the symptoms of congestive heart failure. However, in hypertensive heart disease the basic problem is an increased afterload, so the more logical approach is antihypertensive therapy with the emphasis on vasodilators (Opie 1980).

Constrictive pericarditis is characterized by a mechanical constriction of a more or less normal myocardium. The filling pressures of all chambers are increased and congestive signs and symptoms ensue. Digitalis is ineffective in this condition (Duca & Brest 1974). In symptoms of heart failure the only way to increase cardiac output is to increase the heart rate, which almost contraindicates the use of digitalis (Cullhed 1972). On the other hand digitalis may be of some value in rapid AF and constrictive pericarditis.

The use of digitalis in cor pulmonale has resulted in variable hemodynamic effects. In one study (Ferrer et al 1950) an increased cardiac output and a decreased enddiastolic pressure in the right ventricle were found after digoxin therapy, but this was not confirmed by Berglund et al (1963). In addition the hypoxemia associated with pulmonary diseases increases the sensitivity to digitalis glycosides (Harrison et al 1968). An increased risk of digitalis intoxication together with the fact that the basic problem in cor pulmonale is pulmonary rather than cardiac dysfunction, are reasons why digitalis should not be the therapy of first choice.

Digitalis is widely used in the treatment of symptoms in congestive cardiomyopathy (COCM). The value of digitalis in this condition is mostly empiric (Swedberg 1976) and is regarded by some authors as beneficial (Starstein 1977, Arnold et al 1982), by another as disappointing (Counitran 1982). In hypertrophic obstructive cardiomyopathy (HOCM) Brauwald and co-workers (1962) demonstrated that the administration of digitalis in HOCM increased the obstruction to the left ventricular outflow. Because of the increased gradient, digitalis preparations are generally contraindicated in HOCM, unless there is rapid AF.

Prophylactic preoperative digitalisation is still controversial if there are no symptoms of heart failure or rapid atrial fibrillation (Cullhed 1972). Wheat & Burford (1961) stated that digitalis used prophylactically reduces significantly the cardiac complications in patients over the age of 55, who have undergone thoracic surgical procedures. Burman (1972) also favoured prophylactic digitalisation in patients undergoing thoracotomy. Contrarywise, Juler and co-workers (1969) cited an increased incidence of postoperative

arrhythmias in digitalized versus non-digitalised patients. However, none of the aforementioned studies was carefully controlled or randomized. Since digitalis has a small therapeutic ratio and since there is no distinct end point for effective digitalization, it seems unwarranted to use this drug prophylactically (Duca et al 1974).

As can be seen there are various states in which digitalis therapy is controversial and of limited use. In addition newer therapeutic procedures and/or drugs are available nowadays, which may influence the need for chronic digitalis therapy.

Dall (1970) found that three quarters of elderly British patients receiving digoxin did not need it. Starr and Luchi (1969) reported no deterioration in six highly selected elderly (6 out of 110) women in sinus rhythm. The study was performed double-blind, placebo-controlled. In another placebo-controlled study by Fonrose et al (1974), 16 out of 31 patients in sinus rhythm, selected from 88 patients on digitalis, deteriorated. However, these studies could not directly be applied to Swedish conditions, but there was a communication at the Swedish National Congress of Medicine in 1975 on the withdrawal of digoxin in geriatric patients (Löfgren). Within eight months after digoxin withdrawal digitalis was restarted in four out of fourteen geriatric patients. Because of this, a new policy on digoxin treatment was introduced in 1974 on the geriatric wards of Skellefteå hospital. Digoxin therapy was withdrawn - in the absence of contraindications to withdrawal - when the initial indications was not obvious or the treatment of doubtful value. So one raised the questions: Does the patient really need digitalis? Do the proposed benefits outweigh the possible harmful effects? Especially in physically inactive geriatric patients, who are said to be more sensitive to digitalis, could the old dictum once on digitalis always on digitalis be upheld any longer? Thus it became important to try to answer the questions cited above. It was also important to identify those from whom digoxin may be withdrawn safely.

Digitalis intoxication

Withering (1785) soon understood the toxic properties of the foxglove. He wrote: 'Foxglove, when given in very large and repeated doses, occasions sickness, vomiting, purging, confused vision, objects appearing green and yellow, increased secretion or urine, with frequent motions to part with it and sometimes inability to retain it; slow pulse, even as slow as 35 in a minute, cold sweats, convulsions, syncope, death'. Ever since then digitalis intoxication has been an important clinical problem (Bertler & Redfors 1971,

Böttiger 1972, Beller et al 1971, Smith 1975) and continues to be one of the most common adverse reactions observed in clinical medicine (Smith, T.W 1975).

The reported incidence of digitalis toxicity ranges from about 4 per cent to as high as 35 per cent in different series of hospitalized patients. The mortality rate has averaged 22 per cent in seven published studies, with a range from 7 to 50 per cent (Beller et al 1971).

Previous clinical studies have for the most part been on patients in hospital and retrospective. Criteria for the diagnosis of digitalis intoxication have been variable. Unfortunately as Withering pointed out as early as 1785, one of the major problems is that individual patients vary considerably both in the dosage of digitalis required to produce a good therapeutic response and in their sensitivity to the serious toxic effects of cardiac glycosides.

The introduction of the radioactive labelling of digitalis and radioimmunoassay opened a new field and thus has widened our knowledge of the pharmacokinetics of digitalis (Doherty et al, 1975). Radioimmunoassay has also made it possible to analyze serum and plasma digitoxin and digoxin levels in patients (Oliver et al, 1968). These serum measurements present a promising approach to the problems of digitalis toxicity. Several studies have shown significantly higher plasma digoxin levels in patients with signs of digitalis toxicity than in non-toxic patients (For a summary see Smith, 1975). However, there is an overlap between toxic and non toxic groups, and the value of serum digitalis concentration measurements has been questioned (Ingelfinger & Goldman 1976).

Many factors are known to alter sensitivity to digitalis (listed in table 2), but we still do not know all the factors which are responsible for the marked variability in this sensitivity and the dosages required.

A growing problem is the interactions of other drugs with digoxin (Editorial B. M J., 1982). The clinical significance of these interactions as reported from pharmacokinetic studies is listed in table 3.

Among other factors discussed when considering sensitivity to digitalis is the age of the patient. Ewy et al (1969) found that a constant dose of digoxin resulted in higher blood concentrations and longer blood half-life in

the elderly. They concluded that this was due to the smaller body size and a diminished urinary excretion of digoxin in these patients. The question is whether the elderly are more sensitive to digitalis beyond what could be explained from the factors mentioned above. This issue has not been satisfactorily examined. Further no more is known about the prevalence of digitalis intoxication in out-patient's than in geriatric patient's.

Table 2. Factors altering digitalis sensitivity

1. Systemic disorders

- Renal failure (reduced excretion)
- Low lean body mass (reduced binding to skeletal muscle)
- Chronic cardiac disease (impaired intracellular Ca^{2+} transport)
- Chronic pulmonary disease (hypoxia, acid-base changes)
- Myxoedema (prolonged half-life)
- Acute hypoxaemia (sensitises to digitalis arrhythmias)

2. Electrolyte disorders

- Hyperkalaemia or hyponatraemia (reduced digitalis binding to heart)
- Hypokalaemia (increased binding to heart)
- Hypomagnesaemia (sensitises to toxic effects)
- Hypercalcaemia (increases sensitivity to digitalis)
- Hypocalcaemia (decreases sensitivity)

3. Cardiac disorders

- Acute myocardial infarction (increased sensitivity?)
- Acute rheumatic carditis (danger of conduction block)
- Thyroid heart-disease (decreased sensitivity)
- Chronic ischaemic cardiomyopathy (decreased sensitivity)

4. Concomitant drug therapy

- Diuretics with K^+ loss (increased sensitivity)
- Quinidine (reduce digitalis dose by about half)
- B-blockade (combined effects on A-V conduction)
- Verapamil (combined effects on A-V conduction)
- Barbiturates, phenylbutazone, phenytoin (decreased blood levels; increased hepatic microsomal metabolism?)

(Opie 1980)

Table 3. Reported pharmacokinetic studies of possible interactions between digoxin and other drugs (March 1982)

<u>Interaction</u>	<u>Clinical significance</u>	<u>No interaction</u>
quinidine	yes	disopyramide
quinine	at high doses	procainamide
verapamil	probable	lidocaine
nifedipine	not assessed	mexiletine
amiodarone	not assessed	
propafenon	not assessed	
spironolactone	minor	
amiloride	minor	
triamterene	minor	
erythromycin	minor	
vasodilating drugs	minor	

(K Schenk-Gustavsson
Medical Dissertation 1982)

Patients' knowledge

Several clinical investigations have shown that out-patients have a limited knowledge of the drugs they are receiving and often fail to take them as prescribed. (Ander & Tibblin, 1974, Böttiger 1969, Hellström & Leijd 1976).

Digitalis, one of the drugs prescribed most frequently among the elderly, has a narrow therapeutic range. So it is especially important to ensure that they take them as prescribed. However, Johnston & Mc Dewitt (1978) found that almost half their patients did not take their prescribed doses of digitalis. The narrow therapeutic range of digitalis glucosides is associated with a high risk of intoxication, but what do the patients know about the side effects? Do they know why treatment was started, and, did they improve? Who gave them the information and was it satisfactory? If not, perhaps better information would improve the results of digitalis therapy.

AIMS OF THE STUDY

The principal aims of the present study were:

1. To study prescribing habits, the varieties of cardiac glucosides and the dosages used in the Skellefteå health district.
2. To investigate the need for maintenance digoxin therapy in geriatric patients and define those from whom chronic digitalis treatment could be withdrawn.
3. To study the occurrence of clinical digitalis intoxication in unselected out-patients and geriatric patients confined to hospital and to ascertain the value of measuring serum digitalis concentration in digitalis-intoxicated geriatric patients.
4. To study the patients' knowledge of their digoxin treatment.

MATERIAL AND METHODS

Study I

The report on the sales of cardiac glucosides in 1978, was received through the statistics of Apoteksbolaget (The National Corporation of Swedish Pharmacies). Information was available for each Pharmacy within the Skellefteå health district, including the prescriptions for the hospital out-patients. The supplying of glucosides for the in-patients from the hospital pharmacy was excluded. The delivery statistics to the Pharmacies state the number of defined daily doses (DDD), that are sold. For digoxin one DDD equals 0.25 mg. Information was obtained from the statistical central office about the population and its age distribution in the different parts of the Skellefteå health district (old urban and rural districts). The issue of digitalis is presented as DDD/1000 inh. and day, but will further be written as DDD/1000 inh. The different cardiac glucosides and the dosages of digoxin used were also obtained from these statistics.

Studies II and III

To study the need for maintenance digoxin therapy in geriatric patients two retrospective (II, III) studies and one prospective study (IV) were performed. In the retrospective studies the need for digitalis was assessed within 2 months (II) and after 2 months (III) following the withdrawal of digoxin. Originally there were 141 patients with various heart diseases, 70 females and 71 males, mean age 80 (range 67-95) of whom 134 were eligible for the study (II). In these 141 patients in SR or AF digoxin therapy had been withdrawn over a four-year period (since 1974) in the geriatric wards of Skellefteå hospital. Digoxin had been withdrawn if the indications for it were not clear, the medication was of doubtful value, and there were no contraindications to withdrawal. Contraindications comprised symptoms of cardiac failure at rest or during light physical activity, x-ray signs of pulmonary congestion, a proven need for digoxin therapy following earlier withdrawal, or atrial fibrillation with a ventricular rate higher than 95 beats/min. A patient who within 2 months presented signs of cardiac failure or an arrhythmia requiring digoxin was considered to be in need of digoxin. Patients who showed signs of cardiac failure but who were treated with diuretics, were also regarded as digitalis-dependent at the time of withdrawal. The need for digoxin was also examined in patients who had had their diuretic treatment maintained after digoxin withdrawal and in patients who had had both digitalis and diuretics withdrawn. In addition the need for digitalis was studied in relation to the digoxin dosage prior to the withdrawal.

In the long-term follow-up study (III) the patients were the same as in study II, except for those patients who had deteriorated within 2 months following digoxin withdrawal. There were 108 patients, of whom it was possible to study 99 (9 case records were missing). There were 49 females and 50 males, mean age 79 (range 61-91). The study was carried out in 1981, the longest observation following digoxin withdrawal was 6 years, the shortest 2 months.

Study IV (For the design of the study see figure 1).

In this prospective, randomized, double-blind study there were 23 female (mean age 80) and 18 males (mean age 77) (age range 55-90) eligible for the study (IV). These patients were selected from 66 geriatric patients in five nursing homes. 18 patients with contraindications to digoxin withdrawal, and 7 in whom digitalis intoxication was suspected were excluded.

Study V

To investigate the occurrence of clinical digitalis intoxication in outpatients 1408 patients treated with digoxin and selected at random were called for a clinical examination and ECG. There were 100 patients with various heart diseases, of whom 91 were clinically examined, 53 female (mean age 74) and 38 male (mean age 70), (age range 50-90).

Study VI

To investigate the occurrence of clinical intoxication in geriatric patients and to ascertain the value of serum digitalis concentration measurements when diagnosing digitalis toxicity , all 66 patients on digitalis preparations in five nursing-homes were examined. There were 38 female (mean age 81) and 28 male (mean age 80), (age range 55-95).

Study VII

To study the patients' knowledge of their digitalis therapy we questioned a random sample of 200 patients (128 female and 72 male) from 1183 unselected patients on digoxin in Skellefteå. We compared the results of the answers of the Skellefteå patients with those of 200 patients in Uppsala (105 female, 95 male). These patients were a random sample of 620 unselected patients on digoxin therapy. The majority of patients in Skellefteå and Uppsala were between 65 and 85 years old (range 25-94).

FIGURE 1 DESIGN OF STUDY

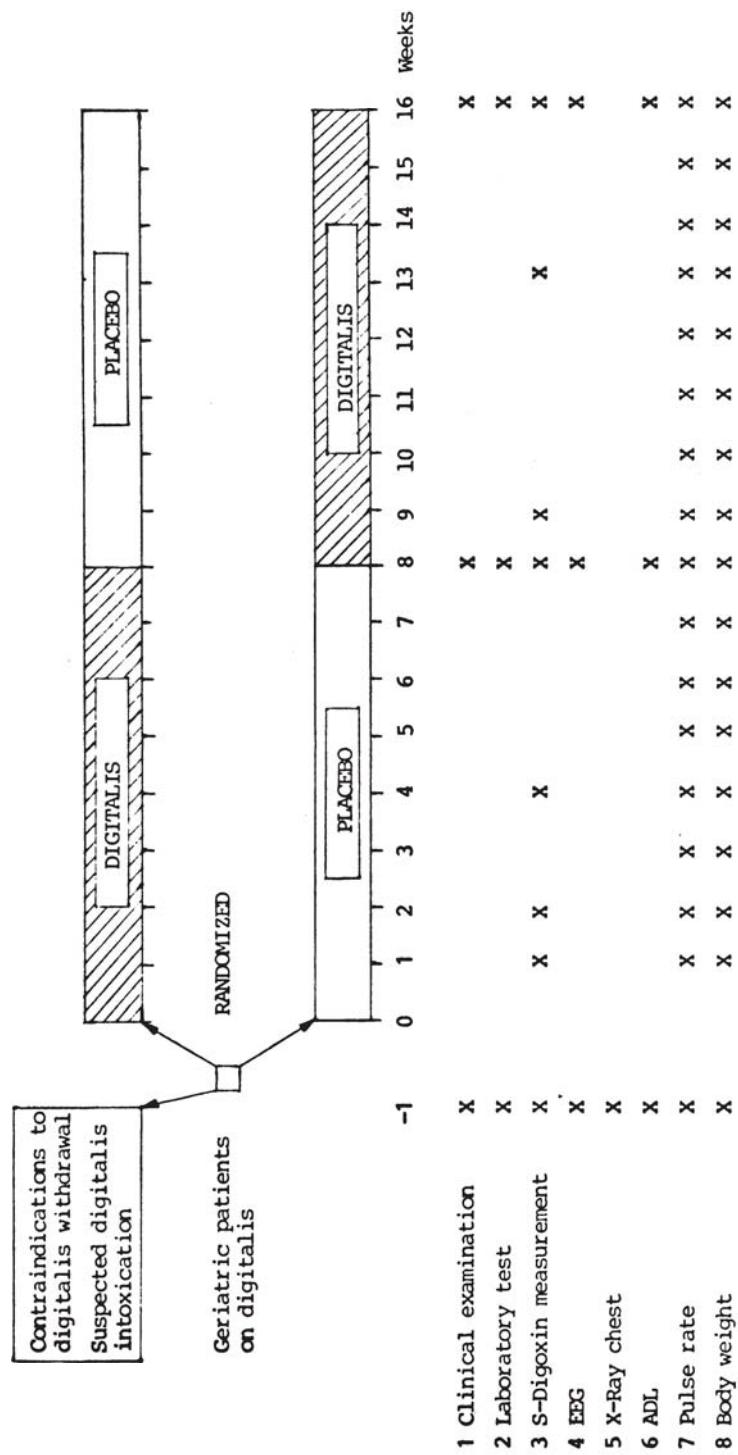


TABLE 4

CLINICAL SYMPTOMS AND SIGNS ASSESSED IN EACH PATIENT

Symptoms	Grade	Definition
a) Orthopnoea (no of pillows used)	1 2 3	≤ 3 Between grades 1 and 3 Enough to require that patients be propped up at 90°.
b) Nocturnal dyspnoea (no of episodes/week)	1 2 3	None Occasional Every night
c) Functional classification	0 1 2 3	Not able to classify: bedridden for reason other than heart failure. No symptoms during daily activities Symptoms during daily activities Symptoms during light physical activity or at rest
Signs	Grade	Definition
d) Gallop rhythm	1 2	Absent Present
e) Jugular venous pulse	1 2 3	≤ 2 cm above clavicle Between grade 1 and 3 To the angle of jaw
f) Oedema	1 2 3	Absent Between grade 1 and 3 Constantly present
g) Central cyanosis	1 2	Absent Present
h) Hepatomegaly and tenderness over the liver	1 2	Absent Present
i) Pulmonary oedema	1 2 3	Absent Between grade 1 and 3 Extensive râles over both lungs
j) Bronchospasm	1 2	Absent Present

The names of patients participating in this study were obtained from the list of prescriptions issued during the three months July-September 1978. A questionnaire of nine questions was sent to the participants. The nine questions dealt with digitalis treatment, duration, dosage, compliance, indications for treatment, improvement following treatment with digitalis, knowledge about the side effects of digitalis, who had given them the information and if it was considered sufficient. The participants were divided into two groups, A and B. The questions were equal in both groups but information they received differed. The A-group were instructed in writing: 'It is important not to take more of a drug than is needed. This is especially true for Lanacrist. If you take too much of the drug certain unpleasant side effects may arise'. The B-group were instructed also in writing: 'It is important not to take too little of a drug which is important for the treatment. This is especially true for Lanacrist. You shall take exactly the prescribed dosage and not be careless'. The patients in each group were reminded once to answer the questionnaires.

Clinical examination (IV, VI).

The clinical examination was performed according to a schedule (table 4). It also included determination of pulse rate, respiratory rate (measured over 30 seconds), body weight and blood pressure in patients with hypertension.

Retrospective criteria influencing the start or resumption of digitalis therapy (III, IV).

Clear indication: atrial fibrillation with a ventricular rate over 95 beats/min, X-ray signs of pulmonary congestion, pulmonary rales on auscultation.

Possible indication: notes in the records such as dyspnoea, pulmonary crepitations, atrial fibrillation of unknown ventricular rate, cardiac failure and heart enlargement.

Uncertain indication: nothing stated in the case records, and unclear conditions

Criteria for digitalis intoxication (V, VI).

A. No digitalis toxicity (Both of the criterium 1 and 2)

1. a) Absence of disturbances of rhythm or
b) Arrhythmia, remitted when digitalis was continued, or dosage increased or
c) Arrhythmia present irrespective of digitalis therapy.
2. No subjective symptoms of digitalis toxicity.

B. Possible digitalis toxicity (Either of the criterium 1 to 5)

1. Partial resolution of disturbance of rhythm when digitalis was reduced in dosage or discontinued.
2. Digitalis discontinued but the patient was discharged or left hospital before serial ECG tracings were obtained.
3. Concomitant electrocardiographic evidence of acute myocardial infarction or changes due to acute ischemia, although the disturbance of rhythm disappeared when digitalis was discontinued.
4. Partial resolution of subjective symptoms, when digitalis was reduced in dosage or discontinued.
5. Digitalis discontinued due to subjective symptoms but the patient had left hospital or could not be followed up.

C. Definite clinical digitalis toxicity (Any of the criterium 1 to 3)

1. Complete resolution of arrhythmia on discontinuing digitalis or reducing the dosage.
2. Any of the following in a patient who died before resolution of the disturbances of rhythm where no other aetiology for the arrhythmia was apparent:
 - a) Ventricular bigeminy, multifocal premature ventricular beats, episodes of ventricular tachycardia.

- b) Non-paroxysmal AV-junctional tachycardia or AV-junctional escape rhythm.
 - c) Paroxysmal atrial tachycardia with AV-block.
 - d) Mobitz type I 2:nd degree AV-block or AV-dissociation.
3. Complete resolution of subjective symptoms on cessation of digitalis therapy or reduction in dosage of the drug.

The following disturbances of rhythm were accepted as indicating possible digitalis intoxication:

- 1. Ectopic ventricular rhythm: Multifocal ventricular ectopic beats, unifocal ventricular ectopic beats (of more than five per minute), ventricular bi- or trigeminy, ventricular tachycardia.
- 2. Non-paroxysmal AV-junctional tachycardia (of more than 80 per minute), AV-junctional escape rhythm.
- 3. AV-dissociation with the ventricular rate exceeding the atrial rate.
- 4. Atrial fibrillation with ventricular rate less than 50 per minute if accompanied by aberrant QRS complexes.
- 5. Second or third degree AV-block.
- 6. Paroxysmal atrial tachycardia with AV-block.
- 7. Sinoatrial exit block or sinus arrest.

The following arrhythmias were rejected as manifestations of digitalis intoxications:

First-degree AV-block, paroxysmal atrial flutter or fibrillation, supraventricular premature beats, sinus tachycardia or bradycardia and a wandering atrial pacemaker.

Sodium, potassium and calcium concentration in serum was measured by flame photometry, magnesium by atomic absorption, ALAT, ASAT by Kinetic techniques, standard bicarbonate by blood gas analyzer IL 413, and creatinine by Multistat III Analyzer using a picrate method.

Duplicate determinations of serum digoxin were performed by radioimmunoassay methods (Gammacount Clinical Assay) 24 hours after the last oral dose. The results of the digoxin analyses were calculated by a logit method and standardized with four digoxin solutions of known concentrations. The precision was 4.3 per cent of 2.32 nmol/l ($n=10$).

Twelve-lead ECG:s (I, II, III, aVR, aVL, aVF and six chest leads) were recorded using a direct-writing ECG apparatus with conventional amplification (1 mV = 10 mm) and a paper speed of 50 mm/second. A long strip (equivalent to about 60 seconds) was obtained.

The radiological heart volume was determined with the patient in the upright position according to Jonsell and Kjellberg et al and expressed in ml/m² BSA. Upper normal limit: men 500 ml/m² BSA, women 450 ml/m² BSA.

Patients daily activities (ADL) (IV,VI).

ADL scores were assessed in each patient at two monthly interval.

Ability to move score: 0 = without aid, 2 = with aid, 3 = sitting in a wheel chair, 4 = sitting on an ordinary chair, 5 = bed-ridden

Personal hygiene score: 1 = without aid, 3 = washing only the face, 6 = washed by the nurse

Dressing score: 0 = without aid, 4 = some aid, 6 = dressed by the nurse

Ability to eat score: 0 = without aid, 3 = some aid, 6 = fed by the nurse.

The studies (IV, VI) were approved by the Ethical Committees of the University of Umeå and Skellefteå, and by the Drug Department of the Social Welfare Board (VII).

Statistical methods

Results are given as the mean +/- S.D., unless marked otherwise. The differences between means were tested using student's t-test for unpaired variables. The test was modified if the variances were significantly different ($p < 0.05$; F-test). The chi-square test with Yates correction was employed for comparisons of proportions in two independent samples. Product moment correlation coefficients (r) were calculated for selected variables and tested using student's t-test.

RESULTS

Prescribing habits

The prescribing of cardiac glucosides in the areas studied varied greatly and ranged from 20.4 to 62.4 DDD/100 inh (see table 5). The range was even wider than that observed in the counties of Sweden (c p 28.8-60.4 DDD/1000 inh). The range of prescribing differences between the primary care areas decreased when the population was corrected for age. When compared with the prescribing of other cardiac vascular drugs, it was apparent that areas with a high rate of prescription of cardiac glucosides also had a high prescription-rate of other cardiovascular drugs.

Digoxin was the drug most frequently prescribed in all areas, varying between 90-98 per cent of all cardiac glucosides used, compared with an average of 86.5 per cent for the whole of Sweden (1978), (Dahlström et al 1978).

The issue (1978) of digoxin in doses of 0.25 mg and 0.13 mg (expressed in DDD) varied between 66.5-84.8 per cent and 15.2-37.9 per cent in the different primary care areas.

Withdrawal of Digoxin Therapy

After exclusion of patients, who presented contraindications to the withdrawal of digoxin, it was possible to discontinue maintenance digoxin therapy in 108 (81%) of 134 patients during a two-month period. Almost the same result, 32 (86%) out of 37 patients, was achieved in the prospective, randomized, double-blind study (IV), where comparison was made between digoxin and placebo. In the retrospective long-term follow-up study of the 108 patients described above, digoxin therapy was restarted in 30 (30%) out of 99 patients observed. The mean digoxin-free observation-time was 20.5 ± 16.1 months, range (2-80.7) months, beginning at the time of withdrawing the drug.

Deterioration occurred mainly during the first month. The time interval between withdrawal and restarting digitalis treatment averaged 17 days (range 3-46) in the retrospective study (II), and 18 days (range 8-41) in the prospective study (IV).

TABLE 5

Primary care area	Percentage of the population \geq 65 years	2 A
Burträsk	22,9%	62,4
Lövånger	21,4%	47,9
Jörn	20,7%	46,4
Byske	19,6%	38,0
Norsjö	18,2%	47,2
Bureå	18,0%	45,8
Skellefteå stad	13,8%	32,7
Boliden	12,1%	27,7
Skelleftehamn	11,6%	20,4
The county of Västerbotten	14,8%	37,9
Sweden	15,7%	34,7

The population and number of patients \geq 65 years in the primary care areas and the selling (1978) of drugs against heart failure (2A) expressed in DDD/1000 inhabitants and day/primary care area.

ECG rhythm

During the first two months there were 14 out of 101 patients (14 per cent) in SR and 12 out of 33 (36 per cent) in AF who were restarted on digoxin (II). Deterioration was significantly more common ($p < 0.01$) in patients in AF. However, there was rapid AF only in six of these twelve patients. In the prospective study (IV) rapid AF developed in three out of eight patients in AF and a rapid paroxysmal AF occurred in one patient with SR. Another patient in

SR developed symptoms of HF and was restarted on digoxin. In the long-term follow-up study (III) 14 out of 25 (56 per cent) in AF were restarted on digoxin compared to 13 out of 70 (19 per cent) in SR ($p < 0.01$). In the retrospective studies (II, III) one patient with SVT and two with paroxysmal AF were restarted on digoxin.

Dosage

Two months after digoxin withdrawal digoxin (II) had been significantly more often ($p < 0.05$) started in patients on a prewithdrawal dosage of 0.25 mg than 0.13 mg (30 per cent versus 14 per cent). No significant difference could be found in either the longterm follow-up study (III) or the prospective study (IV).

Digoxin and diuretics

In the first study (II) digoxin and diuretics were withdrawn from 20 patients, of whom only two patients in SR developed HF. In the long-term follow-up study (III) 14 patients (70 per cent) managed without digoxin and diuretics. In 25 patients who had digoxin withdrawn, but in whom diuretics were maintained, 10 patients (40 per cent) deteriorated during the first two months, and during the long-term follow-up another 8 patients were restarted on digoxin.

Indications for resuming digitalis therapy

A clear indication was found in the retrospective studies (II, III) in 21 patients (38 per cent) out of 56 patients restarted on digitalis. Two patients were in SR, the others in AF. A possible indication was found in 24 patients (43 per cent). Fourteen patients had SR, seven AF, one paroxysmal AF, and one had SVT. The indication was uncertain in eleven patients (19 per cent). Nine were in SR, one was in AF, and one had paroxysmal AF.

In the prospective study (IV) there were clear original indications in three patients, a possible indication in 18 patients and an uncertain indication in 20 patients.

Digoxin therapy had often to be restarted in the presence of infectious diseases or pulmonary embolism. In the prospective study (IV) there were infections in three out of five patients, who had to be restarted on digoxin. In the long-term follow-up study (III) infections had been present in 17 per cent and pulmonary embolism in 13 per cent of those patients in whom digitalis was restarted.

Digitalis intoxication

In 91 unselected out-patients 5 per cent were certainly clinically intoxicated and 2 per cent were suspected of being intoxicated. In 66 long-stay geriatric patients in hospital 11 per cent were definitely clinically intoxicated. The difference between the out-patients and the geriatric patients is not statistically significant.

Clinical data (VI)

The toxic geriatric patients had a higher mean age and a higher prevalence of AF and diuretic therapy than the non-toxic, but those differences were not statistically significant. All toxic patients had any of the symptoms anorexia, nausea or vomiting and five had electrocardiographic findings acceptable for consideration of digitalis toxicity.

Two patients out of eight improved in ADL besides symptomatic improvement. Notably there was no need for maintenance digoxin therapy in five out of eight digitalis intoxicated patients.

There was a significantly higher mean digoxin dosage ($p<0.05$) and digoxin per Kilogram body weight ($p<0.01$) in the toxic women than the non-toxic.

Laboratory data (VI)

Mean serum creatinine was higher in toxic men and women than in non-toxic, but the difference was not statistically significant. Four out of eight patients had elevated serum creatinine values (82, 130, 160, 167 $\mu\text{mol/l}$) and two patients had hypokalemia (3.3 and 3.4 mmol/l). Hypokalemia was present in 6 out of 50 non-toxic patients (12 per cent).

Serum concentration of digoxin

In the geriatric patients the mean serum drug concentration was significantly higher in toxic than in non-toxic patients ($p < 0.001$).

However, six clinically toxic patients had serum digoxin concentrations within (four patients) or below (two patients) the therapeutic range (digoxin: 1.3-2.6 nmol/l; digitoxin: 13-33 nmol/l). Two toxic patients lay slightly above the therapeutic range (s-digoxin 2.6 nmol/l resp s-digitoxin 36 nmol/l) (Fig 2).

Patients' Knowledge

Answers to the questionnaires were obtained from 196 patients (98 per cent) in Skellefteå, and from 163 patients in Uppsala (82 per cent). This difference is statistically significant ($p < 0.05$). In Skellefteå there was a significantly higher ($p < 0.05$) patient compliance in the B-group as compared to the A-group. A similar tendency was found in the answers from Uppsala. This could have depended on the influence of the additional instruction given to the B-groups 'that they should take the medication exactly as prescribed and not be careless'.

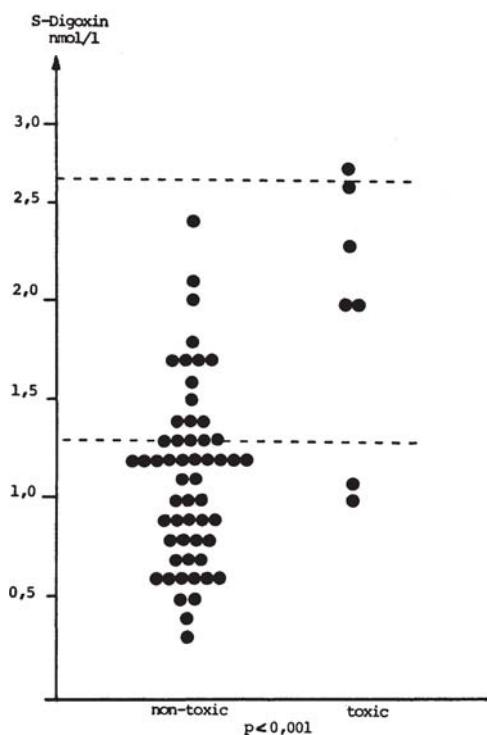


FIGURE 2. Serum digoxin concentrations in seven geriatric patients with digoxin toxicity (mean: 1.96 ± 0.68 nmol/l) and 55 without toxicity (mean: 1.11 ± 0.45 nmol/l). Therapeutic range: 1.3 - 2.6 nmol/l

The answers from Skellefteå and Uppsala could be summarized in the following manner:

- about 85 per cent stated that they took their medicine as prescribed
- about 85 per cent took digoxin once a day
- about 60 per cent indicated that they knew correctly why digoxin treatment was given
- about 20 per cent were uncertain as to why they took digoxin
- about 45 per cent stated that they felt better thanks to the digoxin therapy
- about 55 per cent did not know about the side effects of digitalis
- about 50 per cent mentioned that they had received no information about digitalis
- about 15 per cent were satisfied with the information they had been given
- about 50 per cent were unsatisfied with the information they had been given
- about 30 per cent had received some information from their doctors.

In Skellefteå and in Uppsala a significant negativ correlation ($p < 0.001$) was found between the age of the patients and dosage. (Skellefteå = 0.291; Uppsala = 0.243).

DISCUSSION

Prescribing habits

A potential error arises when the consumption of a drug is measured by means of DDD/1000 inh if patients do not fetch their digoxin from the local pharmacy. This source of error is probably smaller in the more remote pharmacies. Through a study of 200 prescriptions of digoxin handled in the central pharmacy it was found that 88 per cent of the prescriptions were from persons living in the central area. Only one of the prescriptions out of these 200 was from a person living in a very remote area. When sales statistics are used to measure drug consumption, this will be overrated by 14 per cent for the central area, and underrated in the areas lying immediately around it.

There are many factors which influence the ways in which a particular drug is prescribed in a particular health district. For digitalis the following factors are important; age of the population, sex, morbidity, and the indications the doctors use for digoxin therapy. One of the most important factors is the age distribution of the inhabitants of the district, for digoxin is prescribed mainly for elderly people. The proportion of people aged 65 or more varied from 11.6-22.9 per cent in the different primary care areas. Morbidity varies, although it is hard to say exactly how this affects the drug consumption. Morbidity will probably be less important when comparing drug consumption in primary care areas than between counties or countries.

Even when the age of the population was taken into account there were important differences between the areas within the health district. Perhaps the most important factor influencing over - or under consumption of drugs is the individual doctor's own policy when prescribing drugs. For digoxin this is true not only for the individual doctor in an area, but also for his predecessors, as digitalis therapy has seldom been withdrawn.

District areas with high prescribing of digitalis also had high prescribing of other cardiovascular drugs. This might depend on the number of vacancies in the different areas and their duration. If doctors are staying in a district for only a short period, it is difficult for them to withdraw cardiovascular drug- therapy as they cannot ensure clinical control after withdrawal . As shown in paper II-IV many geriatric patients are treated unnecessarily with digitalis. The initial indication for starting digitalis therapy was uncertain in about half of the patients (paper IV), judged

retrospectively. Not only the indication for starting drug treatment but also a clear account of the effectiveness of the treatment must be made when deciding to withdraw or maintain therapy with a specific drug. This is only possible when the doctor is staying a reasonable time. In the Skellefteå health district there have been many vacancies in the primary care areas. In 1978 only seven out of 25 doctors were permanently in post.

Withdrawal of digitalis

Several investigators have attempted to discontinue digitalis therapy, with widely differing results (Rogen 1943, Starr & Luchi 1969, Fonrose et al 1974, Dobbs et al 1977, Johnston & Mc Dewitt 1979, Liverpool Therapeutics Group 1978). The patient's deterioration rate has varied between 0 to 100 per cent. The results of all these studies suggest that there are some patient in sinus rhythm and even AF, who may not need digitalis in the long term. The longest study lasted until six months after the withdrawal of digoxin. The reasons why the results from other studies differ can be explained by differences in the methods of selecting patients, the inclusion of patients with sinus rhythm and/or atrial fibrillation. Many studies had one or more shortcomings, such as no determination of serum digoxin levels or no comparison of glycosides with a placebo or a relatively short follow up. Little light has been shed on which patients are likely to benefit from digoxin therapy, and which patients will not.

There is also some evidence that the clinical and pharmacological effects of digitalis demonstrated during short-term therapy, may not persist if the therapy is continued longer. First, in a study of patients with Starr-Edwards prosthetic aortic valves, a positive inotropic effect of digoxin was found at four to six hours after digoxin administration but was not found after ten days of continuous treatment (Davidson & Gibson 1973). Secondly, various pharmacological effects related to the inhibition of sodium and potassium -ATP-ase in patients' erythrocytes, which could be demonstrated after a few days of digoxin treatment, could not be demonstrated after two months digoxin therapy (Ford & Aronsson et al 1979).

On the other hand, Arnold et al (1980) reported haemodynamic deterioration following digoxin withdrawal both at rest and with exercise. They found an improvement in haemodynamics after six to seven weeks following the reinstitution of digoxin. Although the nine patients in this study were carefully examined haemodynamically, the conclusions were limited by the atypical characteristics of the smallness of the groups of patients - relatively young subjects with very high resting pulmonary capillary wedge

pressures, in whom idiopathic cardiomyopathy was the most common cardiac diagnosis. In another study by Murray (1982) the haemodynamic benefit, after six weeks, was manifest only during exercise. However, in the study by Fleg et al (1982), maximal exercise capacity was unchanged for three months following digoxin withdrawal.

The present studies (II-IV) also suggested, that many geriatric patients had been treated unnecessarily with digitalis, even in the long-term follow-up. It was obvious that one of the major reasons for concluding that digitalis could be withdrawn was that digitalis had been started initially on indications that were indefinite. Furthermore, in the long-term follow-up study about one third had been restarted on unclear indications. Other reasons might have been an acute heart failure, in which case an indication for long-term therapy never arose. This was apparent not only in those patients where digitalis alone, but also when concomitant diuretics, were successfully withdrawn.

The problem of patients in AF has still not been tackled. It is obvious from the present studies (II-IV) that AF was the main reason for restarting digoxin treatment. There is no disagreement that digitalis is effective in controlling rapid atrial fibrillation. However, it was possible to withdraw digitalis from some patients with AF without deterioration. This could mean that digitalis was started in AF with a normal ventricular rate, or AV-conduction had become impaired with increasing age. Dobbs et co-workers (1977) reported that digoxin withdrawal from 13 patients in AF with impaired AV-conduction had resulted in an increase of the ventricular rate to over 100 beats/min in only one case. On the other hand Rogen (1943) reported that 18 patients in AF (100 per cent) deteriorated, of whom 14 presented marked tachycardia when digitalis was discontinued. On withdrawing digitalis in patients with AF it is important to know whether there has been a rapid atrial fibrillation from the beginning. In the prospective study (IV) those three patients who deteriorated had originally had rapid AF.

The patients in the retrospective study (II) who deteriorated had received a significantly higher dosage of digoxin. There was a similar tendency in the prospective study (IV), but the differences did not reach statistical significance. In the prospective study there was also a statistically insignificant higher mean serum digoxin concentration (1.56 versus 1.10 nmol/l) in those who deteriorated. The Liverpool Therapeutics Group (1978) reported that digitalis was discontinued in 89 patients (22.8 per cent) all of whom had concentrations below the accepted range. None of these 89 showed any clinical deterioration when digitalis was withdrawn, either as a recrudescence of heart failure or an abnormal cardiac rhythm. These patients were in SR or AF, but the proportions were not stated. Johnson & Mc Dewitt (1979) also

found that discontinuation of digoxin did not lead to clinical deterioration in 33 of their 34 patients with sinus rhythm, whose prewithdrawal steady state digoxin concentration was less than 0.8 mg/ml. If the patient has no symptoms of heart failure, receives a low dosage of digoxin or has a low serum digoxin concentration, the continuance of digoxin therapy should be reviewed before the dosage is increased.

Diuretics are often used in combination with long-term digoxin therapy. On withdrawing digitalis it is important to know if the concomitant diuretic therapy alone is sufficient to control the heart failure. There is evidence from other studies (Rader et al 1964, Mc Haffie et al 1973) that digitalis may not produce additional beneficial effects during short-term treatment over and above the effects produced by maximal diuretic treatment.

In the retrospective studies (II, III) it was somewhat remarkable that patients, who had had diuretics maintained but digoxin withdrawn, deteriorated more often than those from whom both digoxin and diuretics had been withdrawn. It might be that patients in whom both drugs could be discontinued had been started on unclear criteria, had been wrongly diagnosed or had an acute heart failure and the need for chronic therapy never existed. On the other hand patients who deteriorated despite diuretic treatment may have had a more severe heart disease or may have been receiving inadequate diuretic treatment. However, the severity of the heart failure could not be assessed in the retrospective studies.

In the prospective study (IV) 34 per cent of the patients were on diuretic treatment and this was constant throughout the study, which perhaps contributed to the success of the digoxin withdrawal. In the study of Hull & Mc Kintosh in 1977, none of 17 patients deteriorated following withdrawal of digoxin, but the dosages of diuretics and antihypertensives had been increased in 10 cases.

A difficulty in interpreting the results from other studies lies in the natural history of the heart disease being treated in terms both of its natural resolution and of its exacerbation. It is clearly important to distinguish between what may be excellent reasons for initial therapy and the indications for long-term therapy. If the cause of the cardiac failure is treatable, only temporary treatment may be required until the primary cause has been corrected. Withdrawal of digoxin from such patients, who never required long-term treatment, will of course not lead to clinical deterioration.

Throughout the present studies it was found that the primary indications were indefinite in about 50 per cent, (IV) judged retrospectively. Moreover, when digoxin therapy was resumed in the long-term follow-up study (III), the indications were uncertain in about one third of the cases. Even if there are difficulties in retrospect in judging exactly the indications for treatment, poor initial selection of cases is probably one of the major reasons why digitalis could be safely withdrawn from so many patients. Other reasons could be, wrong initial diagnosis, treatment of heart conditions known not to respond to digoxin therapy, treatment of hearts without failure observed to be enlarged by X-ray. A common reason for instituting digitalis therapy was heart failure and/or an arrhythmia provoked by infection, myocardial infarction or pulmonary embolism (III, IV). It can be debated whether these patients need long-term digoxin treatment, whether the benefits of long-term digoxin treatment really out-weigh the risks, or whether digoxin should be used only temporarily.

Another finding was the use of digitalis therapy pre- and peroperatively, which was then maintained (II, III). No indications for long-term treatment were found, and even the preoperative indications were debatable.

A factor which is important in explaining the results of digitalis withdrawal, was the low physical activity of the geriatric patients. Near half the patients in the prospective study (IV) were in bed or in a wheelchair, with low demands on their circulation. This might also explain how 19 patients with a diagnosis of hypertension, had mean systolic and diastolic pressures of only 155 and 76 mmHg respectively.

Digitalis intoxication

The incidence of digitalis intoxication was relatively low in the out-patients. However, because of the great number of patients on digitalis treatment (2.8 per cent of the population in Skellefteå), the proportion of intoxicated patients is high. If one is allowed to extrapolate the number of intoxicated patients in the health district, about 120-200 patients are definitely or possibly intoxicated.

Comparisons of the incidence of toxicity are difficult to make due to differences in the criteria used when diagnosing digitalis intoxication, as well as in the designs of the various studies. In many previous investigations the classification of digitalis toxicity has been based largely on ECG findings (Beller et al 1971, T W Smith & E Haber 1970). Unfortunately, there is no cardiac arrhythmia specific to digitalis toxicity. A problem in diagnosing digitalis toxicity by means of short conventional routine ECGs, are transitory arrhythmias such as ventricular ectopic beats, which are only possibly related to digitalis toxicity. On the other hand such arrhythmia can be judged erroneously, when digitalis is withdrawn, as a manifestation of digitalis toxicity. Our recordings lasted about 60 seconds and this could well be too short. On the other hand this length of recording is commonly used in practice when diagnosing digitalis toxicity.

Cardiac arrhythmias might not be sufficient justification for diagnosing digitalis toxicity. There were patients who showed subjective symptoms without cardiac arrhythmias (V, IV). Subjective symptoms indicating digitalis toxicity should therefore also be taken into account, and of course appraised in the light of the whole clinical picture. The criteria we have used in our studies for the diagnosis of definite or suspected digitalis intoxication are inevitably somewhat arbitrary and open to discussion. As digitalis itself might induce any arrhythmia, and this arrhythmia might also depend on the specific heart condition, there will always be a risk of under- or overestimating digitalis toxicity, dependent on the criteria used.

In the evaluation of plasma digoxin levels as an aid in the diagnosis of digitalis intoxication, the criteria used for diagnosing toxicity are evidently of decisive importance. Many studies have shown that mean serum digoxin and digitoxin levels are significantly higher in patients with electrocardiographic evidence of toxicity than in patients without such evidence. (For a summary see T W Smith 1975). However, there are studies (Fogelman et al 1971, Howard et al 1973) showing no such difference. Although many studies have shown a higher mean serum digitalis level in toxic as

opposed to non-toxic patients, there is a considerable overlap between the two groups. This could partly be explained by the numerous factors which affect digitalis sensitivity.

One of the factors that must be taken into account is the age of the patient. In some studies (Beller et al 1971, Shapiro et al 1969) no adverse digitalis reactions were related to the age of the patient, but Evered & Chapman (1971) and Smith & Haber (1930) found that subjects with toxicity were older, as well as having a diminished renal function. It is known that with increasing age there is a diminution in renal function (Evy et al 1969), but it is not known whether there is an increased sensitivity of the senile myocardium to normal concentrations of digitalis. It is important to look at the age of the patients studied in previous papers which deal with the problem of the patients' age and sensitivity to digitalis. The mean age of the patients in earlier studies has been between 60-70 years, (Beller et al 1971, Shapiro et al 1969), but in the present study the mean age was about 80 years.

In the present study, (IV) the mean serum digoxin level was significantly higher in toxic than in non-toxic patients, but six out of eight who were considered to be intoxicated patients had serum digoxin levels within or below the therapeutic range. It appears that no arbitrary level can be chosen which differentiates clearly between toxic and non-toxic serum cardiac glucoside concentrations.

The overlap seems to be even greater when the elderly are compared with younger patients. A similar finding was reported by Roe and Abbot (1974). As most of the serum digoxin levels were within or below therapeutic range a diminished renal function or low body-weight cannot explain the presence of digitalis toxicity in these patients. The present study (VI) indicates that sensitivity to digitalis increases with age, which is in accordance with the clinical impression that the older patients are more likely to become intoxicated after a given dose of the drug. As can be seen in the studies (VII) the dosage of digoxin is also gradually decreased in step with the age of the patient. Further evidence that sensitivity to cardiac glycosides is age-dependent was reported by Isalo et al (1973) in their studies of serum

digoxin levels in adults and children. They found that several children with serum levels of 3.0 to 4.4 ng/ml had no signs of toxicity when compared with all the adults with serum levels of over 3.0 ng/ml. However, as there are many factors which influence sensitivity to digitalis (table 2), this particular study provided that no definite proof of sensitivity to digitalis increases with age.

According to several publications the incidence of digitalis intoxication appears to have increased in the past few decades (von Cappeler et al 1959, Crouch et al 1956, Dubnow et Burchell 1965, Jörgensen et al 1970). An important cause of the development of digitalis intoxication seems to be the widespread use of modern agents in intensive diuretic treatment. (Dreifuss et al 1963, Dubnow et al 1965, Jörgensen et al 1977), which results in considerable loss of potassium. However, neither hypokalemia nor hypomagnesimia was present in our studies, but intracellular deficiency of these ions can not be excluded. Long-term diuretic therapy is known to cause such intracellular electrolyte disturbances (Wester & Dyckner 1978). Moreover digitalis by itself causes a reduction of intracellular potassium (Eriksson 1982). Further investigations are required into the role of these intracellular disturbances following diuretic treatment in relation to digitalis sensitivity.

Another interesting finding by Kearin et al (1980) was the variation in the digoxin-binding sites of erythrocytes in adults when compared with infants. They found a decreased number of digoxin-receptors in the elderly, which might explain increased sensitivity to the drug. However, the clinical significance of this finding has yet to be assessed.

Half of the patients in our study (VI) who showed digitalis toxicity were in AF. A high proportion of AF in toxic patients when compared with non-toxic (68 per cent versus 25) was also found by Beller et al (1971). A possible explanation might be an increased atrial digoxin binding in AF, as recently shown by Jogestrand (1980).

The serum digitalis level seem to be of limited value in the screening for digoxin toxicity in the elderly, since multiple factors influence the individual response to cardiac glycosides. It is important for the physician to remember that drug concentrations, even when measured accurately, represent only one source of information, and serum concentrations must be interpreted in the over-all clinical context.

Patients' knowledge

A very high percentage of the patients answered the questionnaires, especially in Skellefteå (98 per cent). The reason for the lower proportion who replied in Uppsala is unknown but may be because the investigation was carried out from Skellefteå. The patients in Skellefteå knew about the investigators, could more easily come into contact with them etc. Even if the answers from the patients in Uppsala were very similar to those in Skellefteå, the results have to be judged with some caution. A bias in the answers were observed, at least in Skellefteå, due to the additional information that was given in the questionnaires. Some information on the validity of the questionnaires was obtained as the dosages of digoxin agreed with the dosages in another study (V). Another similarity was that 15 per cent of patients thought that arrhythmia was the indication for their digoxin treatment, compared with the fact that AF was found by ECGs in 20 per cent of the population (V).

It is interesting that about half the patients found it difficult to be sure that they had been improved by digoxin therapy. Even if it cannot be concluded that the treatment was unnecessary, the results suggest that maintenance digoxin therapy was of questionable value in many patients, which agrees with the results of the present studies (II-IV).

The patients' knowledge of possible adverse effects of digoxin is important, as an increased knowledge of the side-effects of the drug might decrease the incidence of digitalis intoxication. More than half the patients both in Skellefteå and Uppsala knew nothing about digoxin side-effects, while only a few (less than 12 per cent) indicated that they knew the side-effects. In addition some patients gave wrong answers to the question on adverse reactions. They may have been given insufficient information. About half the patients reported that no information at all about digoxin had been given, or that the information was inadequate. Only one patient in six said the information was sufficient. It was impossible to find out what information was really given, or if they had forgotten it - or never understood it. Several other investigators have also disclosed that patients know very little about their drug therapy (Böttiger 1968, Hellström 1976).

In our study patients got their information mainly from their doctors. One of the commonest reason for the information being insufficient was probably changes of doctor. Other reasons might be lack of time of those who should give the information, wrong presentation of it, or difficulties caused by unintelligible medical terms. Patients taking digoxin are generally elderly, (mean age about 70 years (VII)) and may also have problems in hearing, or remembering. In any case there seems to be a great need for improvement in communicating information on their illness and its treatment.

CLINICAL IMPLICATIONS

Digitalis prescribing habits

The great differences in the consumption of digitalis could be explained by many factors. It was obvious that many other than the morbity influenced the prescription of digitalis. One value of studying prescribing habits is that one can take the figures relating to consumption as a starting-point for a discussion on courses of treatment and the experience gained by using different drugs. Regarding digitalis medication the following questions can be discussed:

- Actual indications for digitalis medication
- Factors increasing sensitivity to digitalis and the risk of producing digitalis toxicity
- What are the reasons for the differences in prescribing?
- Are there any advantages or disadvantages as between different cardiac glycosides?
- What dosages should be used?
- From whom can maintenance digitalis therapy be withdrawn or not?

Digitalis maintenance therapy

There are several factors that must be taken into consideration when attempting to withdraw digitalis medication. It is important to know the aetiology of the heart failure, the original reason for long-term therapy, if it was acute or chronic heart failure. Did the patient have sinus rhythm or atrial fibrillation from the beginning? Are there contraindications to the withdrawal of digoxin or has there been any attempt to withdraw digitalis earlier?

If geriatric patients are in sinus rhythm and have no symptoms or signs of cardiac failure, withdrawal of digitalis therapy should be considered in the following situations:

- The original indication for long-term treatment is not clear

- There was acute heart failure, not succeeded by chronic failure
- The original reason for digitalis medication has changed, such as after correction of valvular disease.
- After surgical procedures, if digitalis was used in a pre- or peroperative period
- The serum digitalis concentration is lower than is generally recognized as therapeutic
- There has been no improvement in the patient's condition following adequate digitalis dosage
- If the heart failure can be better controlled otherwise.

Maintenance digitalis therapy should not be withdrawn in the absence of digitalis toxicity in patients with sinus rhythm in the following conditions:

- If there is a chronic heart failure, where symptoms or signs have been found to be relieved by digitalis therapy on a follow-up examination
- If patients have symptoms and signs of heart failure at rest or during light physical activity, or X-ray signs of pulmonary congestion
- If there is a chronic failure, and an attempt to withdraw digitalis has been made, which resulted in deterioration within a few months.

In AF and AFL withdrawal is more difficult and a very careful control is then required. However, in some geriatric patients with no symptoms of heart failure, withdrawal of digitalis therapy could be considered in the following situations:

- AF or AFL with a normal or low ventricular rate, where rapid AF never existed at rest or only during light physical activity
- The underlying causes of the AF, or AFL have been cured, such as valvular heart diseases, thyrotoxicosis, AF or AFL in connection with acute myocardial infarction, and conversion to sinus rhythm has occurred
- If AF and AFL can be better treated otherwise.

Digitalis should not be withdrawn in the absence of digitalis toxicity in patients with AF and AFL under the following circumstances:

- If there was a rapid AF or AFL, initially, at rest, or during light physical activity
- If an attempt has been made to withdraw digoxin resulting in rapid AF within a few months.

Before digoxin withdrawal the patients must be made to understand that they might get worse, and be informed about symptoms that might necessitate resumption of digitalis medication. After discontinuance of digitalis medication, those who deteriorate will do so mainly during the first two months, especially within the first three weeks following withdrawal. In some cases it is advisable to begin with a reduction of dosage for a period of two months before digitalis medication is completely withdrawn.

Digitalis intoxication

Due to the narrow therapeutic range and widespread use of digitalis many patients are intoxicated by the drug. It is important to be aware of the symptoms and ECG-findings that might suggest intoxication. If there is a clear indication for maintenance therapy a temporary withdrawal is the best way to confirm or exclude toxicity. Otherwise discontinuation of digitalis therapy should be considered according to the criteria listed above. It must be remembered that many factors influence sensitivity to digitalis, that serum digitalis concentrations represent only one source of information, and that these determinations must be evaluated in the overall clinical context.

The value of serum digitalis estimations in the screening for digitalis toxicity in the elderly is limited, but can be used in the following way:

The serum digitalis concentration lies above the therapeutic range:

- If the patients present no symptoms, or ECG-findings suggest digitalis toxicity, the dosage should be reduced, unless there is an obvious need for an elevated serum digitalis level to control heart failure or arrhythmia. Careful observation for symptoms of digitalis toxicity is then advocated.

Serum digitalis concentration lies within the therapeutic range:

- A serum digitalis level within the therapeutic range does not exclude digitalis toxicity
- The diagnosis of digitalis toxicity should rely upon the whole clinical picture. Clinical findings suggesting digitalis toxicity should be confirmed or excluded by a trial withdrawal of the drug.

The serum digitalis concentration lies below the therapeutic range:

- A low serum digitalis level does not exclude digitalis intoxication. The diagnosis of digitalis intoxication must be based on clinical criteria. However, the lower the serum digitalis level is, the more unlikely that the patient is to be intoxicated by digitalis.

In addition, it is of great value to know the serum digoxin concentration when other drugs such as quinidine, verapamil, spironolactone or others that interact with digitalis are prescribed simultaneously with digitalis.

Serum digoxin levels are also valuable in preventing digitalis toxicity in patients with renal failure.

Other steps to be considered in order to prevent digitalis toxicity are as follows:

- Avoidance of unnecessary digitalis treatment as listed above
- Consideration as to whether both drugs in a combined digitalis-diuretic treatment are really needed to control heart failure.

Patients' knowledge

A condition for good patient-education is good doctor and patient continuity. Guided by the results of the present study, the following steps will assist in improving the patients' knowledge of their medication.

When digoxin treatment is started:

- State the name of the cardiac glucoside being used and why treatment has to be started
- Tell the patient what symptoms will probably be relieved by the treatment
- State the dosage, the length of treatment and the importance of taking the doses exactly as prescribed.
- Make the patient aware of those adverse effects which necessitate a new consultation with the doctor
- Give all this information to the patient in writing as well as verbally.
- Write on the prescription the symptom(s), which it is intended to relieve or cure.
- Record the indication for the treatment.

At the next visit:

- Ask for details of any improvement in heart symptoms and for any adverse effects
- Consider at each visit if the dosage should be changed or digitalis should be withdrawn
- Ask the patient if he/she understood the given information previously and supplement it if necessary.
- Emphasize the importance of taking the medicine in the doses and at the intervals exactly as prescribed.

It is not known whether these steps will improve patients' overall knowledge, but they should be tried in order to improve digitalis medication and make it safer.

GENERAL SUMMARY AND CONCLUSIONS

1. There were wide variations in the range of cardiac glucosides prescribed in different areas within the Skellefteå health district. Digoxin was the cardiac glucoside used most often with important variations in dosages between primary care areas. Many factors other than the morbidity in the areas concerned were likely to be responsible for these differences. A study and analysis of these factors may be one way in improving digitalis medication.
2. Digoxin therapy was withdrawn in geriatric patients if the indications for it were not clear, the medication was of doubtful value and there were no contraindications to withdrawal. Contraindications comprised symptoms of cardiac failure at rest or during light physical activity, X-ray signs of pulmonary congestion, a proven need for digoxin therapy following earlier withdrawal, or atrial fibrillation with a ventricular rate higher than 95 beats/min patient). A patient who within two months presented signs of cardiac failure or an arrhythmia requiring digoxin, was considered to be in need of digoxin. Digoxin was withdrawn from a total of 141 patients of whom 134 were examined after two months. During this two months-period 108 (81 per cent) did not require digoxin treatment, which indicates that many geriatric patients are treated unnecessarily with digoxin.
3. A retrospective long-term follow-up study was performed on these 108 patients who did not require digoxin treatment within two months after its withdrawal. During a mean observation-time of 20.5 months about one third were restarted on digoxin, distributed equally on clear, possible or uncertain indications. This also indicates that many geriatric patients are treated unnecessarily with digitalis, and that digitalis medication is resumed on indications that were uncertain as often as they were clear.
4. Using a randomized, double-blind, cross-over protocol, comparison was made of the effects of oral digoxin and placebo in 39 geriatric patients in sinus rhythm or atrial fibrillation. Five patients out of 37 (14 per cent) deteriorated during the placebo phase. This prospective study confirmed the results of the retrospective study namely that digitalis could be safely withdrawn from many geriatric patients who don't show contraindications to digoxin withdrawal.
5. A clinical examination and ECG made of a random sample of unselected out-patients treated with digoxin showed that about 5 per cent were certainly intoxicated and 2 per cent were suspected of being intoxicated. The clinical diagnosis of digoxin intoxication is discussed.

6. A prospective clinical study of geriatric patients revealed digitalis intoxication in 11 per cent. The mean serum drug concentration was significantly higher in toxic rather than non-toxic patients, but six out of eight patients had serum digitalis concentrations within or below the therapeutic range, and only two slightly above it. No need for maintenance digoxin therapy was found in five out of eight intoxicated patients. The value of serum digitalis concentrations is limited when in the screening for digitalis toxicity, but the serum glycoside level is of some value if it is considered within the overall clinical context.

7. In reply to a questionnaire on digitalis medication performed in Skellefteå and Uppsala, near half the patients stated that they had taken digitalis for more than five years, 85 per cent that they took the tablet once a day and regularly. About 60 per cent indicated that they were aware of the indications for digoxin treatment, but about 20 per cent did not know why had been prescribed for them the drug. About half the patients said that they felt better after digitalis treatment had been started. More than half the patients did not know about digitalis side effects, and just as many said that they had not been given any information about digitalis or regarded the information given as insufficient. One third had been informed by their doctors and only 15 per cent said that the information given was sufficient. There was a significant negative correlation between patient's age and digoxin dosage. Methods for improving the information given to, and its interpretation by patients, are proposed.

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