Use of digitalis in general practice

Liverpool Therapeutics Group

British Medical Journal, 1978, **2**, 673-675

Summary and conclusions

A study, which arose out of a general-practitioner teaching programme in clinical pharmacology, was designed to assess the use of digitalis in 391 patients in general practice. Clinical, biochemical, and pharmacological data were used to assess whether digitalis treatment should be discontinued (89 patients; 22·8%); the dose kept unchanged (47; 12%); or the dose increased (47; 12%) or decreased (24; 6·1%). Serum concentrations of cardiac glycoside were below a defined therapeutic range in 159 patients (40·7%), above this range in 37 (9·7%), and within the range in 195 (49·3%).

Studies of this kind may help to promote a more critical attitude to prescribing widely used drugs such as digitalis.

Introduction

Several aspects of accepted practice in digitalis treatment have been challenged by the ability to measure serum concentrations of cardiac glycosides. The old therapeutic adage of "once on digitalis always on digitalis" has been questioned, and the suspicion that many patients receiving long-term digitalis treatment do not take their drugs regularly has been clearly shown. Furthermore, the relation between serum concentrations of digitalis and clinical efficacy and toxicity are still debatable.[1]

A research programme, which arose from discussions in one of the therapeutic sessions described elsewhere,[2] was established in Liverpool to examine the use of digitalis in general practice. This programme aimed at determining how many patients receiving cardiac glycosides benefited from long-term treatment and how many were taking the appropriate dose. The study was carried out by general practitioners attending one of the therapeutics courses run by the department of pharmacology and therapeutics. Laboratory and technical facilities were provided by the department, who also co-ordinated the study. The project was funded by the Mersey Regional Health Authority.

Plan of studies

Twenty-two general practitioners took part in the project. Each practitioner reviewed all patients in his practice who were currently taking a cardiac glycoside and entered them into the study. Background clinical information for each patient included the reason for starting treatment with a cardiac glycoside, duration of treatment, type of preparation and dose prescribed, and frequency of doses.

University of Liverpool, Department of Clinical Pharmacology, Liverpool L69 3BX

STUDY CO-ORDINATED BY: Professor A Breckenridge, Dr M Orme, and Dr M J Serlin.

GENERAL PRACTITIONERS PARTICIPATING IN STUDY: Dr L Adamson; Dr L Antal; Dr S K Bose; Dr H Davidson; Dr A M Duguid; Dr K Early; Dr C M Edis; Dr J Heyes; Dr B J Hawe; Dr H Kean; Dr L Kinloch; Dr D Lambert; Dr D Leslie; Dr F Naylor; Dr L Ratoff; Dr H V Roberts; Dr R Singer; Dr C Taylor; Dr D Thomas; Dr M J Williamson; Dr G Yates; Dr M Yates.

Each patient was seen by his practitioner at least twice at four-weekly intervals. On the first occasion data on the state of the patient's cardiovascular system were collected: heart rate and rhythm, presence or absence of heart failure, and symptoms and signs of possible cardiac glycoside toxicity. A blood sample was taken for measurement of serum concentrations of cardiac glycoside, electrolytes, and urea. Blood samples were taken four to eight hours after the last dose of the glycoside. Measurement of the digitalis concentration was repeated four weeks later at the second visit. Whenever possible patients were told that the reason for repeated blood sampling was "related to their drug treatment," but were not told that it specifically concerned digitalis, so that drug compliance would not be affected. Collected blood was centrifuged at 2000 rpm for 10 minutes, and serum stored at $-20°C$ before assay.

When possible serum electrolyte and urea concentrations were measured on the day of collection; the serum potassium concentration was not measured in samples that had been kept uncentrifuged overnight because of the possible risk of haemolysis.

Methods

Serum digoxin or lanatoside C concentrations were measured by radioimmunoassay using the Lanoxitest β kit (Wellcome Reagents). Chemically, lanatoside C differs from digoxin only in having one glucose and one acetyl group more in the terminal digitoxose grouping of the sugar moiety of the molecule. Because the steroid nucleus is the same in these two glycosides and the digoxin antibody is specific for the steroid molecule[1] digoxin antiserum may also be used for determining serum concentrations of lanatoside C. The antiserum of Lanoxitest shows a cross-reactivity of 70%.[3]

Serum concentrations of potassium and urea were measured by autoanalyser. Clinical, biochemical, and pharmacological data were collated on a printed form and entered on punch cards for subsequent analysis by computer.

DECISIONS

Data from individual patients were reviewed jointly by the general practitioner and the clinical pharmacologists, and decisions on management were based on the clinical, biochemical, and pharmacological findings. Possible decisions were: (1) to continue digitalis in the previous dose; (2) to discontinue digitalis; (3) to adjust the dose. All aspects of information, especially the practitioner's knowledge of the patient, were used in making the decision.

Decision 1—The decision to continue digitalis in the previous dose was taken if: the patient was out of heart failure; the resting heart rate was less than 90/minute, irrespective of rhythm; there were no signs or symptoms of digitalis toxicity; and both measurements of serum cardiac glycoside concentration were within the considered therapeutic range (defined below), or the mean of the two readings fell within that range, provided that the two values did not differ by over 20%.

Decision 2—The decision to discontinue digitalis was taken if: both measurements of serum cardiac glycoside concentration were below the considered therapeutic range; the patient was out of heart failure; the patient's sinus rhythm was normal; the heart rate was 90/min or less; and the initial indication for digitalis treatment had clearly passed. If one measurement of serum cardiac glycoside concentration was below the considered therapeutic limit, or if the two measurements differed by over 20%, a third blood sample was taken for repeat estimation and a mean of the three values calculated. All patients whose digitalis was discontinued were reviewed by the general practitioner at least once three months later, and a further estimation of serum digitalis concentration was made to ensure that the patient had stopped the drugs.

Decision 3—To adjust the dose. The dose of digitalis was *increased* if the patient's clinical condition demanded it because of rapid atrial fibrillation or heart failure; one or both or the mean of three values of serum digitalis concentrations were below the considered therapeutic range; the general practitioner had previously emphasised to the

TABLE I—*Clinical data on 391 patients taking digitalis. Figures are numbers (%) of patients; values are means*

Sex		Age (years)		Cardiac glycoside		Daily dose (mg)		Duration of treatment (years)	Blood urea (mmol/l)	Serum potassium (mmol/l)	Other drugs	
M	F	M	F	Digoxin	Lanatoside C	Digoxin	Lanatoside C				Diuretics	Potassium supplements
126 (32·2)	265 (67·8)	68·3	69·4	330	61	0·27±0·15	0·43±0·19	4·76	6·3	5·5	286 (73·1)	167 (42·7)

Conversion: SI to traditional units—Blood urea: 1 mmol/l ≈ 6 mg/100 ml. Serum potassium: 1 mmol = 1 mEq.

patient the importance of complying with the agreed therapeutic range; and signs or symptoms of digitalis toxicity were absent. The dose of digitalis was *decreased* if signs and symptoms of digitalis toxicity were present; and measurements of serum digitalis concentration were above the considered therapeutic range. Whenever the dose of digitalis was adjusted the patient was reviewed later by the practitioner at an appropriate time after dose adjustment and a further sample of blood taken for digitalis estimation.

The *considered therapeutic ranges* for estimations of serum digoxin[4] and lanatoside C,[3] the glycoside in Cedilanid, were 0·8-2·0 μg/l and 0·4-1·0 μg/l respectively.

Results

Of the 391 patients entered into the study, 330 were taking digoxin (digoxin BP, Lanoxin, or Lanoxin PG), and 61 were taking lanatoside C (Cedilanid). Table I shows some clinical data on the patients. Two hundred and thirty-eight (60·9%) of them were in atrial fibrillation and 185 (47·3%) had been in heart failure. The commonest indication for starting treatment with digitalis was a combination of these two conditions. In 21 patients (5·4%) the initial indication was not clear; these were usually patients who had been receiving the drug for many years. The mean daily doses of digoxin and lanatoside C were 0·27± 0·15 mg and 0·43±0·19 mg respectively. The commonest regimen was digoxin 0·25 mg/day. Twenty-four patients died during the study. Six of them died from heart failure, and all had serum digoxin concentrations within the accepted therapeutic range. Out of 10 patients who died of a cerebrovascular accident, only one had atrial fibrillation. Three died after myocardial infarction. The remaining five died of carcinoma of various sites. Altering the dose of digitalis was not responsible for any patient's death. Table II shows numbers of patients whose plasma concentration of cardiac glycosides were above, within, and below the defined therapeutic range.

TABLE II—*Proportions of patients whose serum digitalis concentrations were above, within, or below defined therapeutic ranges,* according to daily digoxin dose*

	No (%) of patients	Mean daily digoxin dose (mg)
Serum digitalis concentrations:		
Above therapeutic range	37 (9·5%)	0·32
Within therapeutic range	195 (49·9%)	0·30
Below therapeutic range	159 (40·7%)	0·27

**Defined therapeutic ranges*: Serum digoxin—0·8–2·0 μg/l; serum lanatoside C—0·4–1·0 μg/l.

DECISIONS

In 231 of the 391 patients (59·1%) the dose of digitalis was continued unchanged. Seventeen (7·3%) of these 231 patients had digitalis concentrations below the accepted therapeutic range, but it was decided, usually on the general practitioner's advice, not to increase the dose. In 201 (87%) the serum digitalis concentration was within the therapeutic range and in 13 (5·6%) concentrations were above this range.

Digitalis was discontinued in 89 patients (22·8%), all of whom had concentrations below the accepted range. In 87 of them the serum digitalis concentration had fallen to zero when measurements were repeated two months later, but two had digoxin concentrations of 0·8 and 1·5 μg/l respectively owing to patient misunderstanding. None of these 89 patients showed any clinical deterioration when digitalis was withdrawn, either in recrudescence of heart failure or reversal to an abnormal cardiac rhythm.

The dose of digitalis was increased in 47 patients (12%), all of whom had subtherapeutic serum digoxin concentrations and either atrial fibrillation or heart failure. This included five patients whose treatment was changed from lanatoside C to digoxin. When serum digoxin was measured two months later 36 of the 47 patients had serum concentrations within the range 0·8-2·0 μg/l, while the remaining 11 had serum concentrations below 0·8 μg/l. Individual practitioners have been trying to improve patient compliance in this group.

The dose of digitalis was decreased in 24 out of 37 patients (64·9%; or 6·1% of total number of patients) who had concentrations above the accepted therapeutic range. No patient who had a raised serum digitalis concentration had cardiac arrhythmias, but 12 had persistent nausea and vomiting. In these patients and in those with a concentration 30% above the accepted upper limit the dose was reduced. In each case a repeat measurement of the serum digoxin concentration two months later showed a fall to within the therapeutic range, and seven of the 12 with symptoms improved considerably. Of the 37 patients with raised digitalis concentrations, 12 (32·4%) had raised blood urea concentrations.

Discussion

In carrying out a drug-related research project in the context of a general-practitioner teaching programme in therapeutics we aimed at critically appraising the use of a widely prescribed drug such as digitalis. We also aimed at gaining specific information on the use of digitalis in general practice, and finding the proportion of patients who were taking the drug unnecessarily and the proportion who were taking the appropriate dose. General practitioners who participated in this scheme thought that their assessment of individual patients had led to a more discriminating use of cardiac glycosides. One of the findings that caused most comment was the high degree of non-compliance in patients in whom this had never been suspected. Greater familiarity with the possibilities and limitations of available services for measuring serum drug concentrations was an added benefit.

Long-term digitalis treatment has aroused much interest lately, largely because of the ability to measure serum concentrations of cardiac glycosides. We ignored the important debate on the validity of "accepted" therapeutic digoxin concentrations.[5 6] Dobbs *et al*[7] showed that of 46 patients prescribed digoxin for heart failure, 16 deteriorated when changed to placebo. Eight recovered completely when the drug was reintroduced, the remainder requiring additional diuretics. These workers also showed that the initial inotropic action of digitalis is sustained during maintenance treatment. In another series[8] 24 patients in a general practice who were receiving long-term digoxin treatment were reviewed in a similar manner to that used by us. Seventeen out of 18 patients in sinus rhythm had digoxin discontinued without ill effect, and many of them had been receiving digoxin for several years. In a third study[9] digoxin could be safely discontinued in 75% of randomly selected geriatric patients who were in sinus rhythm. In our study digitalis was safely stopped in 89 patients (22·8%). Using the criteria laid down we could not say how many of the patients with therapeutic concentrations of digitalis could have had the drug withdrawn.

A principal finding was the high proportion of patients (40·7%) with serum digoxin concentrations consistently below the recognised therapeutic range despite apparently adequate dosing. The mean dose of digoxin in this group (0·27 mg/day) did not differ significantly from doses taken by those whose serum

digoxin concentrations were within the therapeutic range (0·30 mg/day) or above it (0·32 mg/day). The mean blood urea concentration in this first group (6·5 mmol/l (39·2 mg/100 ml)) was not significantly different from that of the second group (5·9 mmol/l (35·5 mg/100 ml)) or third group (7·6 mmol/l (45·8 mg/100 ml)). Hence an important contributory factor to subtherapeutic digitalis concentrations may be poor compliance. In 11 (2·8%) of our patients no digitalis was detected in the serum on either occasion, despite their apparent continued use of the drug. Non-compliance as a cause of low serum digitalis concentrations has been shown before,[10–12] and the absence of patient deterioration on stopping digitalis in 89 of our patients supports this finding.

Potent "loop" diuretics such as frusemide have provided alternatives to the use of digitalis in heart failure, and its continued use irrespective of the underlying disease must be questioned. Irregular patient compliance, however, did not seem a great problem, since serum digitalis concentrations varied by over 20% on both occasions in only 53% of patients. This is a highly arbitrary definition of variable compliance, and the influence of the practitioner's interest in the patient's drug regimen is unknown. Two patients continued to take digitalis in spite of agreeing with their practitioner to stop; both had received digitalis for at least five years. Psychological dependence in long-term drug treatment is an intriguing aspect of prescribing. Surprisingly few patients (37; 9·5%) had raised serum digoxin concentrations, and the incidence of side effects was lower than might be expected.[13]

Our main aim was not economic, and any savings on stopping digitalis were probably balanced by increasing the dose in other patients and paying for the study itself. We hope that we have created a more critical attitude to prescribing one group of drugs, which may have wide therapeutic implications.

We thank Mrs J Felgate, SRN, and Miss S Newby for carrying out technical and statistical work; Dr H E Barber for statistical help, and Burroughs Wellcome for the gift of Digoxin assay kits. We also acknowledge the help of Dr W Taylor and his colleagues in the Department of Chemical Pathology, Liverpool Royal Infirmary. The Mersey Regional Health Authority gave valuable financial help.

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(*Accepted 9 June 1978*)

MATERIA NON MEDICA

A theatrical experience

Recently I attended what could be the last of the country road shows: a public auction of antiques, fine furniture, and bric-à-brac.

The setting was an old large rambling house, badly in need of the repairs it was receiving from the new owner, who was assiduously hammering throughout the day of viewing.

My quest was for a good Victorian mahogany dining table. Several dealers and housewives were edging through the packed rooms. The table I was stalking stood fine and solid, the right size, and in need of a good home. My play began by nonchalantly observing the piece, peering underneath, giving a tap or two, and exclaiming for all to hear "definitely a 1930 reproduction." This set everyone on edge. The dealers looked at me oddly, but it rattled a few housewives and I felt it would eliminate some competition. That night I rehearsed my part for the following day, agreed on a maximum bid, and slept fitfully.

The next day a blue marquee had been erected in the garden and seats were arranged in front of the auctioneer's stand. We got away to a prompt start, and the character of the occasion seemed peculiarly Australian. A day with cloudless blue sky, the clear nasal tones of the auctioneer, the blue-rinsed hair of the local matrons, the casual dress and ease as we rubbed shoulders, all being manipulated to buy. The hypnotic qualities of a good auctioneer enable him to hold his audience. The technique of alternately applauding the buyers' perspicacity with admonitions that "prices are far too low" exemplified the best in Pavlovian conditioning.

My time came and it wasn't a very auspicious start. The table was too heavy to be shown, and my wife, who hadn't seen the piece, wondered whether the foundations of our house would be strong enough. I began to get cold feet. Nevertheless, within sixty seconds I had bought the table for much less than I had expected. Maybe it really was a 1930 reproduction.

When the table was delivered it was so big the removers couldn't get it in the house. That evening, using what surgical skill still remains, the table was coaxed into its resting place and all are agreed that "It's just what we wanted," and "looks beautiful."

I wonder if they are just being kind.—HARRY OWEN WOOLLER (New South Wales).

Catamarans and croupiers

If you want somewhere very different why not try Bandjuwangi? Normally the weary traveller driving across Java to Bali spends one night at the Hotel Salmonella in this delightful fishing village. With luck you arrive late in the evening, eat the sandwiches you have brought with you, and leave early next morning on the ferry to Bali.

Twenty-five years ago we arrived late on Saturday afternoon. "The ferry always sails on Sundays," our travel agent had vowed in the face of our open disbelief. "The ferry never sails on Sundays," said the locals. The locals were right.

The Hotel Salmonella, which was to be our home for the next 36 hours, gives you a room conveniently situated next to the bathroom and lavatory. Both the latter functions are combined by having a sloping floor with central drainage hole, and a large petrol drum full of water with dipper. The drainage hole is usually partially obstructed.

Our fellow guests were the croupiers from the gaming tables at the fair across the road. The fair itself was delightful—all the sights and sounds of Hampstead Heath on a bank holiday, including the candy floss. The only dampers on our pleasure were a beauty specialist and the croupiers. The barker for the beauty preparation had a magnificent, penetrating voice and the name of his priceless face oil—"Minjak Wangi"—could be heard over a very wide area every 15 seconds for 18 hours a day. When the fair finished at midnight, and his voice was stilled, the croupiers left the gaming tables for our hotel, and we all reverberated to their piercing Chinese cross-talk (across the length of the hotel) until 4 am.

Apart from the fair and the hotel, Bandjuwangi has other attractions: a narrow channel leads from the sea to a small harbour busy with fishing boats. These boats have a long, narrow shell of a hull, with outriggers on both sides and a huge lateen sail. In port with the sail furled, they resemble some giant grasshopper, but at sea they have a breathtaking, fragile grace.

Despite our initial dismay at the delay and the hotel, we would not have missed the experience. There was the kindness of the local villagers to our very blond 2-year-old son; the fascinating life of the small harbour, and the comforting thought that early on Monday we were leaving for Bali.—BORIS GOLBERG (consultant radiologist, Edgware).