The changing pattern of toxicity to digoxin

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Summary

Toxicity to digoxin was monitored in 437 consecutive recipients in a comprehensive drug surveillance programme. Adverse reactions developed in 19.5% and, in contrast to previous reports, were generally of a relatively benign nature. There were no drug-related deaths, but patients with adverse reactions spent longer in hospital. Low body weight, impaired renal function, old age and concurrent use of diuretics individually did not increase the risk of toxicity. This was attributed to improvements in the prescribing of digoxin. There was a highly significant excess of gastrointestinal reactions in women, which tended to occur early in the course of therapy. This susceptibility is not widely recognized. The use of loading doses may have caused many early reactions and it is suggested that this practice could be abandoned in all but the most urgent cases.

Introduction

In recent years there has been increased recognition of the importance of patient characteristics in determining the appropriate dose of digoxin, and aids to prescribing ranging from computer programmes (Jelliffe, Buell and Kalaba, 1972; Peck *et al.*, 1973; Mawer, 1976) to nomograms (Jelliffe and Brooker, 1974) and simple equations (Sumner, Russell and Whiting, 1976; Dobbs *et al.*, 1976; Ogilvie and Reudy, 1972) have been recommended. Some of these have been shown to reduce toxicity in the short term (Jelliffe *et al.*, 1972; Ogilvie and Reudy, 1972). Most physicians, although aware of the existence of these aids, continue to prescribe digoxin by intuition. The present authors have assessed the hazards of such intuitive prescribing by analysing the results of a period of monitoring all drug treatment conducted in medical wards of 2 Scottish hospitals between 1973-1975. This study was a satellite programme of the Boston Drug Surveillance Study.

Methods

The aims and methods of the Boston Collaborative Drug Surveillance Programme (BCDSP) have been

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described in detail elsewhere (Jick *et al.*, 1970). Trained nurse monitors based on medical wards in the Western Infirmary, Glasgow (WIG), and Stobhill General Hospital, Glasgow (SGH), used standardized self-coding data sheets to record information on consecutive admissions. The resulting record included demographic and diagnostic details as well as information on all drugs prescribed. For each drug recorded details included indications for starting and reasons for stopping therapy, dosage, frequency and occurrence of adverse effects. Adverse reactions were defined as any unwanted or unexpected effect attributed to the drug by the prescribing physician. A description of all such events was kept and reviewed by an independent clinical pharmacologist. Only those reactions deemed to be definitely or probably drug-related are analysed in detail.

For the purposes of the present study certain information in addition to that routinely collected was sought. In particular the proportion of digoxin recipients who had atrial fibrillation at the time of admission to the study was determined by review of hospital case records. This diagnosis was based on 2 or more electrocardiograms recorded on or shortly after admission.

Information about cardiac rhythm was available from 405 out of the 437 digoxin recipients and formed the basis of an analysis designed to evaluate toxicity amongst subgroups with particular combinations of presumed risk factors. The number of patients developing hypokalaemia was too small for it to be included in this analysis.

To explore the relationship between dose of digoxin and the occurrence of adverse reactions, each reactor was matched with one non-reactor, the matching criteria being hospital, sex, duration of admission (± 5 days), age (< 50 , $50-59$, $60-69$, ≥ 70 years) and blood urea concentration on admission (< 8 , $8-16$, ≥ 16 mmol/l). The total dose of digoxin received by the reactor from admission to the time of reporting the reaction was compared with the total dose received by the non-reactor in the same time interval. From this the mean daily dose of

digoxin received during this period was calculated and a note was also taken of the dose received on the day before the adverse reaction.

Between 1973 and 1975 a total of 2580 patients was monitored in the 2 hospitals (Lawson and Jick, 1978a). Their average age was 57 years and 8.1% died while in hospital.

Results

A total of 437 patients received digoxin during their stay in hospital, and of these, 190 (43.5%) had also received the drug before admission. The average age of the recipients was 67 years, 53% were female and 63 patients (14.4%) died during admission. The most common principal discharge diagnoses were: acute myocardial infarction (69 patients, 16%), congestive cardiac failure (56 patients, 13%), left ventricular failure (37 patients, 8.5%), chronic respiratory disease (37 patients, 8.5%) and acute respiratory infections (35 patients, 8%).

Of the 437 digoxin recipients, 85 (19.5%) developed an adverse reaction, the frequency being similar in each hospital: WIG 42/209 (20.1%) and SGH 43/228 patients (18.9%). The frequency of such reactions was unrelated to previous use of digoxin and body weight. Mortality was the same in those with adverse reactions (14.1%) as those without (14.5%), and no patient was judged to have died as a result of digoxin toxicity. Average hospital stay was 17.5 days for reactors and 13.1 days for non-reactors. In 49 of the 85 reactors (11.2% of digoxin recipients), nausea and/or vomiting was the sole manifestation of toxicity. Three of these were also drowsy or confused.

Thirty-six patients were noted to develop cardiac arrhythmias which were attributed to digoxin. Bradycardia (ventricular rate <55/min) was observed in 26 individuals (16 cases of slow atrial fibrillation and 10 cases of sinus bradycardia). Frequent ventricular ectopic beats occurred in 4 cases, atrial tachycardia in 4 cases, nodal rhythm in one case and complete atrio-ventricular dissociation in one case.

Potassium status and concomitant diuretic use

Drug-induced hypokalaemia ($K < 3.4$ mmol/l) was found to be an uncommon development amongst this group of digoxin recipients. Although adverse reactions were more common in hypokalaemic patients, 4/14 patients (28.6%) than in normokalaemic patients, 81/423 (19.1%), these were sufficiently uncommon as to preclude drawing any valid conclusions. The mean admission serum potassium concentration in each group of patients was identical: non-reactors 4.2 ± 0.6 (s.d.) mmol/l; cardiotoxic group 4.2 ± 0.5 ; gastrointestinal toxicity 4.2 ± 0.6 .

Forty-six (19.7%) of the 233 patients who received diuretics developed digoxin toxicity. This is almost

identical to the adverse reaction frequency amongst non-recipients (39/204; 19.1%). The nature of the adverse effects was the same in each group.

Basic cardiac rhythm

The cardiac rhythm at the time of admission to the study was determined from the original case records in 405 patients. This included all the 85 individuals who developed adverse effects. The frequency and nature of the adverse reactions in relation to the cardiac rhythm (sinus rhythm or atrial fibrillation) is shown in Table 1.

TABLE 1. Nature and frequency of adverse reactions to digoxin in relation to cardiac rhythm

Rhythm	Adverse reactions		Total
	Cardiac	Gastrointestinal	
Sinus	18 (7.3%)	32 (13%)	248
Atrial fibrillation	18 (11.6%)	17 (11%)	157
All	36 (8.9%)	49 (12.1%)	405

Gastrointestinal complications were equally common in both groups. Patients with atrial fibrillation developed more cardiotoxicity, but this difference was not statistically significant (χ^2 (Yates) = 1.61, $P < 0.30$). However, bradycardia (ventricular rate <55/min) was identified significantly more frequently in patients with atrial fibrillation (16/157, 10.2%) than in those with sinus rhythm (10/248, 4.0%) (χ^2 (Yates) = 5.09, $P < 0.05$).

Effect of renal impairment

Information on admission blood urea concentration was available for 423 patients. There were no statistically significant differences in either the incidence of cardiotoxicity or gastrointestinal symptoms in relation to admission blood urea levels (Table 2). However, inclusion of the data relating to

TABLE 2. Incidence and nature of adverse reactions to digoxin in relation to blood urea concentrations on admission to hospital

Blood urea (mmol/l)	Adverse reactions		Total
	Cardiac	Gastrointestinal	
<8	*16 (6.7%)	27 (11.3%)	240
8-16	*15 (10.6%)	18 (12.7%)	142
16+	*5 (12.2%)	4 (9.8%)	41

* χ^2_1 for trend towards increasing cardiotoxicity with increasing blood urea concentrations = 2.45; ($P < 0.20$).

basic cardiac rhythm showed that there was a significant excess of cardiac arrhythmias amongst uraemic subjects who were in atrial fibrillation (Table 3). By contrast, the rates of gastrointestinal toxicity were constant in all subgroups.

Day of development of adverse reactions

Adverse reactions tended to occur early in the course of treatment and the trend was similar in patients with sinus rhythm and those with atrial fibrillation. Of a total of 85 adverse reactions over 50% (47 cases) had occurred by day 5 of treatment. Of these 47 reactions, 34 (72%) were gastrointestinal, whereas of the 38 reactions occurring on or after day 6 of treatment, only 15 were gastrointestinal (39%). (χ^2 (Yates) = 8.0, $P < 0.005$).

TABLE 3. Frequency and nature of adverse reactions to digoxin in relation to admission blood urea concentration and cardiac rhythm

Rhythm	Blood urea (mmol/l)			
	< 8		≥ 8	
	No.	(%)	No.	(%)
Gastrointestinal toxicity				
Sinus	18/142	(12.7)	16/108	(14.8)
Atrial fibrillation	12/89	(13.5)	8/66	(12.1)
Cardiotoxicity				
Sinus	6/142	(4.2)	8/108	(7.4)
Atrial fibrillation	6/89	(6.7)	*11/66	(16.7)

* Rate of toxicity compared with patients in sinus rhythm and blood urea < 8.0 mmol/l; χ^2 (Yates) = 7.71 ($P < 0.01$).

Effects of age and sex

The frequency of adverse reaction in relation to age is shown in Table 4. The incidence of cardiotoxicity remained fairly constant throughout all

TABLE 4. Effect of age on incidence and nature of adverse reactions to digoxin

Age (years)	Adverse reactions		Total
	Cardiac	Gastrointestinal	
< 59	7 (6.8%)	*8 (7.8%)	103
60-69	14 (9.0%)	*18 (11.5%)	156
70-79	10 (8.2%)	*14 (11.5%)	122
> 80	5 (8.9%)	*9 (16.1%)	56
All	46 (8.2%)	49 (11.2%)	437

χ^2_1 for trend towards increasing gastrointestinal toxicity with age = 2.03; ($P < 0.20$).

age groups and occurred with the same frequency in men (9.5%) and women (7.1%). Gastrointestinal reactions increased somewhat with age although this trend did not reach statistical significance. However, there was a highly significant excess of gastrointestinal reactions in women, which was present in all age groups (Table 5). The higher rate of toxicity in females and their over-representation in the older age groups accounted for all of the excess reactions in elderly patients noted in Table 4. For females the incidence of gastrointestinal reactions increased with age (Table 5), but this trend failed to reach statistical significance (χ^2 for trend = 2.03, $^{\circ}F = 1$, $P < 0.20$).

Digoxin dosage

Figure 1 shows the wide variation in average daily doses of digoxin received by 80 patients with adverse reactions and their controls. The mean

FIG. 1. Mean daily doses of digoxin employed in 80 patients with adverse reactions and 80 controls matched for age, sex, renal function and length of hospital stay.

(± 1 s.d.) value was 0.54 ± 0.28 mg/day for reactors, being higher (0.61 ± 0.29 mg) in those who developed side effects before day 5 of therapy. Equivalent values for controls were 0.33 ± 0.18 mg and 0.37 ± 0.21 mg/day. Doses were the same in patients with sinus rhythm as in those with atrial fibrillation. A matched pairs analysis revealed that reactors received significantly more digoxin per day than did non-reactors ($P < 0.001$; Wilcoxon's signed rank test); reactors receiving a higher average daily dose of digoxin than controls in 55 cases, the same dose in 9 cases, and a lower dose in 16 cases. Comparable figures in respect of the dose received on the day before the noted toxicity were 47 cases, 16 cases and 17 cases respectively ($P < 0.001$).

Of the 47 early reactors (day 5 or before), 18 received mean daily doses of 0.75 mg or more; 13 of these developed nausea or vomiting of whom 11 were women.

Discussion

The overall digoxin adverse reaction frequency of 19.5% seen in this group of Scottish in-patients is similar to previously reported figures (Ogilvie and Reudy, 1972; Rodensky and Wasserman, 1961; Hurwitz and Wade, 1969; Shapiro *et al.*, 1969; Beller *et al.*, 1971). It is lower than the 35% recorded by Jelliffe *et al.* (1972) but they were dealing with a complex and selected group of patients referred for

TABLE 5. Rates of gastrointestinal toxicity attributed to digoxin in relation to age and sex

Age (years)	Male			Female		
	No. with reactions	(%)	Total	No. with reactions	(%)	Total
< 59	3	(5.7)	53	5	(10)	50
60-69	6	(7.4)	81	12	(16)	75
70-79	3	(5.2)	58	11	(17.2)	64
≥ 80	1	(7.7)	13	8	(18.6)	43
All	*13	(6.3)	205	*36	(15.5)	232

* Gastrointestinal toxicity in all women compared with all men: χ^2 (Yates) = 8.31 ($P < 0.005$).

computer assistance with dosage. The frequencies of digoxin toxicity of 9.9% and 4.1% reported by Duhme, Greenblatt and Koch Weser (1974) from 2 Boston hospitals using methods identical to those in the present programme, may be due in part to the fact that these workers concentrated on patients who had received digoxin for more than 5 days. This is reflected in the preponderance of cardiac arrhythmias which have been shown here to be a relatively late manifestation of toxicity. Exclusion of early reactors (day 5 and before) from the present analyses produces an overall adverse reaction rate of 8.7%. Sixty-one per cent. of these late reactors experienced cardiac arrhythmias as the predominant manifestation of toxicity.

In this study the nature of the adverse effect was ascertained clinically. There was no systematic review of the ECGs or continuous cardiac monitoring. The observed frequency of rhythm disturbances is almost certainly an under-estimate, particularly if viewed in the light of studies which have demonstrated 'serious' arrhythmias in 12% of normal individuals (Clarke *et al.*, 1976) and 76% of patients following myocardial infarction, irrespective of therapy (Roland *et al.*, 1979). These authors employed continuous electrocardiographic monitoring and their studies provide information inherently different from that obtained from a comprehensive drug surveillance programme, where there is a tendency selectively to report arrhythmias which are most apparent clinically, such as slowing of the pulse. The strengths of this essentially epidemiological approach are uniform ascertainment of clinically important toxicity, large numbers of subjects and provision of controls where necessary from a large group of drug recipients who had no manifestation of toxicity.

Although patients with toxicity experienced greater morbidity as shown by their longer hospital stay, side effects generally were of a relatively benign nature. This is reflected in the absence of any deaths directly attributed to digoxin, and a mortality rate which was equal in those patients with side effects

and those without. This is in contrast to earlier work which highlighted the deaths associated with digitalis toxicity (Ogilvie and Reudy, 1972; Rodensky and Wasserman, 1961). The apparent contradiction of a similar incidence of adverse reactions but lower mortality rate suggests a greater awareness of the dangers and earlier recognition of the signs of toxicity by the physicians involved in this study. Thus better education perhaps combined with improved drug bioavailability and a trend to confine use almost exclusively to digoxin, at the cost of other glycosides, appears to have resulted in a substantial improvement in the safety of digitalis therapy.

The absence of a clear-cut relationship between side effects and factors such as previous use of digoxin, low body weight and renal impairment (as judged by elevated blood urea concentration), when each of these was considered individually is surprising, as previous work has shown those to be predictors of toxicity (Ogilvie and Reudy, 1972; Hurwitz and Wade, 1969; Shapiro *et al.*, 1969; Beller *et al.*, 1971). However, at the time this study was in progress the importance of paying heed to these characteristics when adjusting dosage was widely appreciated and thus it is likely that during intuitive prescribing appropriate correction was made for some of these parameters.

However, the data show that subgroups of patients who exhibited combinations of risk factors had a higher risk of toxicity and there was a striking excess of cardiac arrhythmias in patients with elevated urea concentrations who also had atrial fibrillation. It is in these high risk groups that a strong case can be made for use of the prescribing aids mentioned in the introduction.

Over 50% of the patients were in sinus rhythm at the commencement of digoxin therapy. Despite fears about the appropriateness and difficulties of prescribing digoxin in sinus rhythm (Editorial, 1970) they received the same dose as and experienced similar toxicity to patients in atrial fibrillation. There has been much controversy in recent years regarding the efficacy of digoxin in the presence of sinus

rhythm (Leading Article, 1979). Although a careful study has recently shown that long-term digoxin therapy is unnecessary in most cases of sinus rhythm (Johnston and McDevitt, 1979), evidence remains for a transient inotropic effect (Editorial, 1970).

No increase in toxicity was observed amongst recipients of diuretics. This has been reported previously (Ogilvie and Reudy, 1972) and could have been due in part to the very low incidence of hypokalaemia in the present patients. Although there is experimental evidence for a true myocardial sensitivity in the presence of a low serum potassium concentration (Marcus, 1972) it is likely that the dangers of concurrent use of digoxin and diuretics in patients in hospital have been exaggerated.

The most striking finding in this study was the high incidence of gastrointestinal reactions amongst women. These occurred early in the course of therapy and accounted entirely for the excess toxicity in the elderly. The finding is unlikely to be due to chance, in view of the strength of the link and its presence in all age groups. The BCDSP has previously reported a high incidence of nausea amongst women during therapy with other drugs (Lawson and Jick, 1978b) so that local effects may be important. In the case of digoxin this could be dose-related. The alternative explanation is a central action. It has been claimed that the extra cardiac effects of digoxin correlate with high concentrations in the blood (Iisalo, 1977) and that women, because of their relatively low volume of distribution, may be at greater risk of experiencing these early in the course of therapy if single loading doses are used. Examination of the role of dosage in determining toxicity is difficult as the amount of digoxin administered to one patient may vary considerably during a course of therapy, and inter-individual susceptibility to a given dose is great. These facts are illustrated by the wide range of doses employed in the reactors and their matched controls. There was great overlap between the groups and a pairs analysis was considered the most suitable strategy. This demonstrated a consistent excess in the adverse reaction group, confirming that high daily dosage is the most important determinant of toxicity.

Doses >0.7 mg/day were almost invariably associated with side effects, and such values usually reflected large loading doses given over a short period. While this practice may be designed to achieve early therapeutic concentrations in the heart, more gradual digitalization in all but the most urgent cases and allowance for the particular susceptibility of women are simple measures which could effect a worthwhile reduction in overall digoxin toxicity. This suggestion is borne out by the prospective study of Ogilvie and Reudy (1972) who showed that a decline in digitalis adverse reactions could be brought about by a

reduction in the size of and frequency with which loading doses are used in patients in hospital.

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