Monitoring the dose of digoxin

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SUMMARY. All patients being prescribed digoxin in a general practice were examined and the serum urea, creatinine, electrolytes, and digoxin concentrations were determined.

Sixty-six patients were identified (0·73 per cent of the practice population). After excluding six, whose tablet-taking was unreliable, it was found that two patients had serum digoxin levels above the usually accepted upper limit and a total of 23 patients (38 per cent of the digoxin takers) had some alteration made to their dose, including eight whose digoxin was stopped. We believe that serum digoxin estimations are useful in determining the optimum dose of digoxin in general practice.

Introduction

THE evidence of increasing problems in deciding the dose of digoxin has caused mounting concern in our practice in which control was previously based on clinical grounds alone. After the standardization of digoxin tablets on 1 October 1975 we decided to review all our patients taking this drug.

As all the digoxin takers being treated by us have to have their prescriptions repeated at intervals of about one month, we realized that a survey could be undertaken easily.

Aims

As trainer and trainee we agreed the following aims:

1. To establish the prevalence of digoxin use in the practice.

2. To find out whether patients on digoxin (with and without diuretics) need regular electrolyte estimations.

3. To establish the value of blood urea and serum creatinine measurements in determining renal function as a guide to digoxin dosage.

4. To find out whether patients, especially those with impaired renal function, need serum digoxin levels estimated periodically.

Method

We work in a group practice consisting of three partners and an assistant, in a suburban area. There are 9,030 patients. No locums were employed during this study. An agreed written protocol was established so that all five doctors in the practice carried out standardized examinations. Each doctor was given a copy of the same proforma so that data collection was also standardized. Each patient had a physical examination and the following were noted: name, diagnosis, sex, age, weight, digoxin dose, diuretic, potassium supplement, other drugs, serum potassium, sodium, chloride, bicarbonate, urea, creatinine, digoxin, urinary glucose, and albumin.

The time between the last dose of digoxin and the taking of blood was reported to the laboratory and was always between six and 24 hours. The study was deemed complete when no new patients presented for a period of two months. This ensured that no patients had been missed because a prescription had been given for a longer period than one month.

All patients whose digoxin dose was adjusted were seen again between two and four weeks later and re-examined, serum digoxin levels being repeated when thought necessary.

Each of the 60 patients left in the study, after excluding unreliable takers, was reviewed taking account of age, dose, pathology, renal function, heart rhythm, apex and radial heart rates, symptoms, and other drugs in the light of the individual serum digoxin concentrations. The normal limits of our laboratory were 1·3 to 2·6 nmol/l (1·0 to 2·0 ng/ml) for six to 24

Table 1. Numbers of patients in the practice and survey.

		Males	Females	Total
Number of patients in the practice		4,060	4,970	9,030
Number of patients in the survey	Included	29	31	60
	Excluded	1	5	6
	Total	30	36	66

Table 2. Prevalence of patients on digoxin as a percentage of the total number of patients in each age/sex group in the practice.

Age group/years	% Males	% Females	% Both sexes combined
0-5	*0*	*0*	*0*
6-10	*0*	*0.33*	*0.16*
11-15	*0*	*0*	*0*
16-20	*0*	*0*	*0*
21-25	*0*	*0*	*0*
26-30	*0*	*0*	*0*
31-35	*0*	*0*	*0*
36-40	*0.37*	*0*	*0.16*
41-45	*0*	*0*	*0*
46-50	*1.07*	*0*	*0.48*
51-55	*0.38*	*0.37*	*0.38*
56-60	*1.11*	*2.10*	*1.62*
61-65	*1.50*	*2.50*	*2.00*
66-70	*4.00*	*2.38*	*3.17*
71-75	*4.55*	*10.00*	*7.14*
76-80	*8.33*	*5.83*	*6.67*
81-85	*3.33*	*3.33*	*3.33*
86-90	*(100)*	*3.33*	*6.67*
All ages combined	*0.73*	*0.72*	*0.73*

hours after the last dose, and were not considered to be critical cut-off points. It was assumed there was effective digoxin action below 1·3 nmol/1 (1·0 ng/ml).

Results

1. Prevalence

Sixty-six patients on digoxin were found (Tables 1 and 2).

2. Electrolytes

Forty-six patients (70 per cent of those on digoxin) were on diuretics. Of these, four (8·7 per cent of those on diuretics) had a low serum potassium (Table 3).

All four of these patients were receiving frusemide, two being on a big dose of frusemide and one on an obviously small dose of potassium. In view of the fact that a total of 22 of the diuretic takers were on frusemide, the incidence of hypokalaemia in frusemide takers is suggestively high (18 per cent).

3. Diabetes

Glycosuria was found in five patients. Four of these were known diabetics. A glucose tolerance test was performed on the fifth patient, leading to a new diagnosis of diabetes.

4. Renal function estimation

Thirteen patients were regarded as having impaired renal function. The criteria used were raised serum creatinine and blood urea concentrations. One of these (patient 22 in Table 4) was regarded as being severely impaired. Three of these patients had their dose of digoxin increased on clinical grounds, two patients had their dose of digoxin stopped on clinical grounds, and in eight patients the dose of digoxin was left unchanged.

In four of these patients there was a raised urea but normal creatinine, and in one there was a raised creatinine but normal urea. There was poor correlation between the two levels in the remaining patients. The overall product moment correlation coefficient was calculated r = 0·49.

One patient had proteinuria. This was the only

Table 3. Hypokalaemic patients.

Patient number	Sex	Age	Serum Na^+ nmol/l	Serum K^+ nmol/l	Daily frusemide dose (mg)	Potassium supplement
13	F	81	136	3.0	40	'Slow K' 1 tds
22	M	78	135	3.4	80	'Slow K' 1 tds
34	F	76	140	2.7	40	'Slow K' 1 od
53	M	73	140	3.3	80	'Slow K' 1 tds

Normal values of local laboratory: Serum K (potassium$^+$). 3.6-4.7 nmol/l.
Serum Na (sodium$^+$). 134-143 nmol/l.

Table 4. Characteristics of 13 patients with impaired renal function.

Patient number	Serum urea mmol/l	Serum creatinine μ mol/l	Proteinuria	Pulse rate		Digoxin dose mg/day	Previous knowledge of renal function	Clinical decision about dose of digoxin	Value of renal function test in decision-taking
				Radial /min	Apex /min				
2	22.2	130	0	100	108	0.0625	None	Increase dose	No value
6	19.8	170	0	70	72	0.1875	None	No change	No value
8	8.8	113	0	88	90	0.25	None	No change	No value
22	18.7	300.6	Present (''')	120	124	0.25	None	No change	Clinical parameters unsatisfactory, high normal serum digoxin (2.3 nmol/l) in presence of impaired renal function precludes increased digoxin dose
						0.125	None	No change	No value
28	8.8	79.5	0	76	76	0.25	None	No change	No value
32	13.5	132.6	0	78	78	0.125	None	Digoxin stopped —on beta blocker	No value
33	7.7	123.76	0	60	64				
37	10.17	88.4	0	68	68	0.125	None	Digoxin stopped —serum digoxin 0.52 nmol/l	No value
45	8.7	132.6	0	64	64	0.50	None	No change	No value
53	8.83	168	0	60	100	0.25	None	Digoxin increase	No value
57	9.67	97.2	0	76	76	0.125	None	Small digoxin increase	No value
58	9.83	141.4	0	70	76	0.375	None	No change	No value
64	9.83	167.96	0	80	80	0.0625	None	No change	No value

Normal values of local laboratory: Serum urea: 2.5-6.5 mmol/l.
Serum creatinine: 60-120 μmol/l.

patient whose renal function test results influenced the final clinical decision.

5. Serum digoxin estimations

Digoxin doses were related to serum digoxin concentrations for each relevant age decade. Six patients were excluded as they had either admitted not taking the tablets regularly or were confused. The range of results was great.

The doses being given differed remarkably little between the age decades (Table 5). (Standard deviation = 0·02 mg daily.)

A total of 23 (38 per cent) of the patients on digoxin had their dose altered, including eight whose digoxin was stopped.

6. Patients with high levels

Two patients were found with raised serum digoxin levels. One patient had her dose reduced. No action was taken for the other (Table 6).

Table 5. Average digoxin dose by age decade.

Ages of patients	Daily mean average digoxin dose (mg)
41-50	0.292
51-60	0.294
61-70	0.296
71-80	0.271
Patients also taking beta-blockers	0.244

7. Patients with therapeutic levels

A total of 28 patients was found with serum digoxin levels within planned therapeutic range (Table 7). Twenty-two were considered clinically satisfactory. Two patients had their dose increased and in one the apical heart rate slowed. One patient was lost to follow-up because of admission to hospital for a non-cardiac reason. The remaining four patients were thought not to be controlled adequately, despite the digoxin level, but the doses were not altered for other clinical reasons.

8. Patients with sub-therapeutic digoxin levels

A total of 30 patients was found with serum digoxin levels below the therapeutic range (Table 8). Twenty of these had their dose altered without detriment. These patients had been on digoxin for many years and normal clinical findings had hitherto been interpreted as satisfactory control.

In 12 patients the decision was made to increase the dose of digoxin. Ten were improved (as judged by reduced apical/radial rates and/or deficit). Of the other two, one was admitted to hospital for prolonged bronchospasm. For reasons unstated his digoxin was stopped and he required a subsequent admission for acute congestive heart failure.

Fear of toxicity had inhibited these increases previously. In three patients it would be fair to criticize the former doses.

Discussion

Clinical judgement alone cannot be regarded as satisfactory in choosing the dose of digoxin. This has been noted before (Manninen *et al.*, 1972; Whiting *et*

Table 6. Patients at or above upper limit of digoxin concentration.

Case number	Serum digoxin nmol/l	Digoxin dose mg/day	Age	Heart rate		Serum urea mmol/l	Serum creatinine μmol/l	Comment	Action taken
				Radial	Apex				
8	2.60	0.25	62	88	90	8.83	176.8	Rheumatic HF	None
13	2.86	0.50	81	80	80	3.33	79.56	Ischaemic HF	Dose reduced

Table 7. Patients with normal concentration of serum digoxin.

Case number	Serum digoxin nmol/l	Digoxin dose mg/day	Age	Heart rate		Serum urea mmol/l	Serum creatinine μmol/l	Comment	Action taken
				Radial	Apex				
2	1.30	0.0625	79	100	108	22.17	132.6	To see again with a view to increasing dose	None
18	2.21	0.25	64	84	92	6.17	88.4	Severe rheumatic HF for surgical assessment	None
22	2.34	0.25	78	120	124	18.67	300.56	Severe failure (ischaemic)	None
49	1.43	0.25	65	98	100	6.00	79.56	Rheumatic HF	Dose increase
63	1.96	0.75	78	104	120	5.50	106.08	Incompletely controlled fibrillation	None
66	2.34	0.25	90	120	120	5.00	70.72	Incompletely controlled ischaemic failure	None

The following patients were regarded as satisfactory: 6, 7, 9, 17, 23, 28, 29, 31, 32, 34, 36, 38, 39, 40, 41, 45, 46, 54, 56, 59, 62.

Table 8. Patients with serum digoxin below 1.3 nmol/l.

Case number	Serum digoxin nmol/l	Digoxin dose mg/day	Age	Heart rate		Serum urea mmol/l	Serum creatinine μmol/l	Comment	Action taken
				Radial	Apex				
1	1.17	0.50	56	80	86	4.3	70.72	Fibrillation required observation	None
3	1.17	0.25	74	84	98	7.0	106.08	Fibrillating	Dose increase
4	0.78	0.125	72	78	88	6.67	114.92	Fibrillating	Dose increase
5	1.17	0.25	76	86	120	7.17	70.72	Increasing fibrillation	Dose increase
10	0.39	0.125	73	92	92	7.50	70.72	Inadequately controlled ischaemic HF	Dose increase
12	0.52	0.25	67	90	98	7.67	79.5	Inadequately controlled ischaemic HF	Dose increase
14	1.04	0.25	71	78	78	4.0	79.56	Ischaemic HF	None
16	1.17	0.25	76	100	100	3.5	61.88	Ischaemic HF. Beta-blocked; low level of comprehension and attendance	None
19	1.04	0.25	51	62	62	5.33	88.4	Ischaemic HF	None
21	1.04	0.50	68	84	96	6.17	88.4	Fibrillating high dose	None
24	1.04	0.185	57	74	84	5.50	70.72	Ischaemic HF fibrillating	Dose increase
25	0.65	0.25	58	90	100	5.33	79.56	Fibrillating rheumatic HF	Dose increase
26	0.52	0.125	72	60	60	5.17	53.04	Ischaemic HF; no obvious failure beta-blocker	Digoxin stopped
27	0.91	0.25	38	88	100	3.5	88.4	Ischaemic HF fibrillating	Dose increase
30	0.65	0.125	72	68	68	5.33	70.72	Ischaemic; no obvious failure	Digoxin stopped
33	0.52	0.125	70	60	64	7.67	123.76	Ischaemic; beta-blocker	Digoxin stopped
35	0.78	0.25	58	66	68	4.67	61.88	Diabetic ischaemia; procainamide	Digoxin stopped
37	0.52	0.125	74	68	68	10.17	88.40	Ischaemia; no obvious failure	Digoxin stopped
42	0.91	0.25	67	80	80	6.83	79.56	Ischaemic HF	None
44	0.65	0.125	69	74	74	6.83	127.30	Ischaemic; no obvious failure	Digoxin stopped
47	0.39	0.0625	64	96	96	7.00	106.08	Ischaemic HF	Dose increase
48	0.91	0.25	73	68	74	5.83	97.24	Confused; obstructive airways disease polypharmacy	Digoxin stopped
50	1.17	0.50	48	70	70	6.67	106.08	Ischaemic HF	None
51	1.04	0.25	66	70	70	6.50	114.92	Ischaemic HF	None
52	0.26	0.25	66	72	74	9.17	106.08	Ischaemic; doubtful taker admitted to hospital for prostatectomy	Digoxin stopped
53	0.76	0.25	73	60	100	8.83	167.96	Ischaemic HF fibrillating	Digoxin increase
57	0.91	0.125	68	76	76	9.67	97.24	Ischaemic HF	Dose increase
61	0.91	0.125	46	80	84	7.14	88.4	Rheumatic HD fibrillating; emboli	Dose increase
64	0.91	0.0625	81	80	80	9.83	167.96	Fibrillating	None
65	1.04	0.25	79	80	88	7.33	106.08	Hypertension	None

al., 1972). Patients, their indications and requirements, do alter insidiously.

Total assessment, which is more subjective and variable, must be the final arbiter. In theory, judgement of satisfactory clinical status should correlate with satisfactory serum digoxin levels. This should be true irrespective of bioavailability, a check on which was not available in this study. Periodically (for example, annually) the patient should be more systematically reassessed, including serum digoxin assays. We have been told digoxin assays cost £0.85p each to the NHS.

Standard potassium supplements are adequate except in the case of frusemide. Extra precautions are required when the dose is increased above 40 mg twice daily. Generally, routine serum electrolytes are not necessary if the doctor is satisfied that the patient is taking his potassium supplements. Periodic electrolyte estimations are indicated in frusemide takers and more caution should be exercised in selecting appropriate diuretics.

Neither serum urea nor creatinine is adequate to assess renal function. For digoxin we believe that creatinine clearance is the single most valid test (Halkin *et al.*, 1975).

It is claimed that the use of a nomogram (Kampmann *et al.*, 1974) can give a rough guide to creatinine clearance where only the serum creatinine, weight, and age of the patient are known. This conversion has not been used as there is doubt as to the acceptability of this, except in relationship to changes in the individual patient (Kerr and Davidson, 1975).

The absence of proteinuria is not evidence of normal renal function. A decision about the dose of digoxin was influenced by renal function tests in only one patient, and even then proteinuria was present. We do not believe routine blood urea and serum creatinine estimations are necessary.

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