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Effects of Renal Function on Plasma Digoxin Levels in Elderly Ambulant Patients in Domiciliary Practice

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Summary

An investigation into the relations between the daily dose of digoxin, drug regimen, serum digoxin concentration, and creatinine and digoxin clearance was carried out in a group of elderly ambulant patients in domiciliary practice. Moderate to severe impairment of renal function was found both in patients taking digoxin and in elderly control subjects. Plasma digoxin levels were not related to blood urea concentrations or creatinine clearance. Digoxin clearance was less than creatinine clearance. Now that plasma digoxin levels can be measured relatively easily their estimation should become part of clinical practice.

Introduction

Despite nearly 200 years of clinical experience since the publication of William Withering's *An Account of the Foxglove and Some of its Medical Uses*, difficulties are still encountered in prescribing cardiac glycosides. Toxic symptoms are often produced in one patient with doses therapeutically effective for another. With the advent of radioimmunoassay techniques (Smith *et al.*, 1969) for measuring serum digoxin concentrations it has been appreciated that this may be largely due to overlap between toxic and therapeutic blood levels (Chamberlain *et al.*, 1970; Smith and Haber, 1970), although individual variation in sensitivity to the glycosides is important, and other factors—including potassium (Sampson *et al.*, 1943), calcium (Moe and Farah, 1965), and magnesium (Seller *et al.*, 1970) concentrations, sodium balance (Harrison and Wakim, 1969), thyroid status (Doherty, 1968), the presence of severe heart disease, or chronic pulmonary disease (Beller *et al.*, 1971)—influence the liability to develop toxicity.

From 67 to 77% of the digoxin is present in the blood in the protein-free (Evered *et al.*, 1970) pharmacologically active (Lullman and Van Swieten, 1969) state, and its concentration

is to a great extent a function of its rate of renal clearance. The tendency for elderly patients to require smaller doses of digoxin to achieve adequate digitalization or therapeutic blood levels (Dall, 1965; Doherty, 1968; Ewy, *et al.*, 1969; Chamberlain *et al.*, 1970) and the poor correlation between serum levels and the daily dose in the presence of impaired renal function (Chamberlain *et al.*, 1970) have been noted, suggesting that renal function should be assessed before prescribing digoxin. In the studies reported (Smith *et al.*, 1969; Chamberlain *et al.*, 1970; Smith and Haber, 1970; Beller *et al.*, 1971) renal function was judged by measuring the blood urea concentration, a notoriously late and insensitive index of renal disease which has moreover been shown on occasion to be well within "normal limits" when the renal digoxin clearance was seriously reduced (Doherty *et al.*, 1967).

More valuable information is provided by measuring the creatinine clearance, and this has been used as a method of adjusting digitalis therapy before blood measurements became available (Jelliffe and Blankenhorn, 1967). Ideally, the serum digoxin concentration should be maintained at a more or less constant, effective level throughout the day, and more accurate knowledge of renal function will influence the dose and mode of administration. Paediatric doses, 0.065 mg, may be useful in some cases. This report describes the results of an investigation into the relations between the daily dose of digoxin, drug regimen, serum digoxin concentration, and creatinine clearance in a group of elderly ambulant patients in general practice.

Patients and Methods

Thirty-one randomly selected subjects who had clinically been well controlled by a constant dose of digoxin for at least one month were investigated. Blood samples were taken when these patients presented at the surgery, either spontaneously (usually to obtain a repeat digoxin prescription) or by request. Clinical details recorded in each case include: name, age, date of birth, sex; nature of the heart condition; other significant diseases present; drugs; digoxin therapy (with details of dosage, duration of therapy, frequency of administration, and exact time relations between venepuncture and taking the previous dose); and history of symptoms which could be due to digoxin therapy.

Second and sometimes third blood samples were collected from most patients at a prearranged time of day to gain further information about the plasma digoxin level at varying intervals after taking the drug. In 25 patients creatinine clearances were measured. Each patient was given precise verbal and written instructions how to collect a 24-hour sample of urine and was visited during that period for blood sampling. (Only one blood

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sample was taken from each patient although diurnal variations in serum and urinary creatinine are now known to occur (Pasternack and Kuhlback, 1971).

Creatinine clearances were also measured in 10 healthy subjects who were spouses of the experimental subjects. All were aged 64 to 86 and were not receiving digoxin therapy. They were considered to be typical examples of the older age group of the practice. None had known evidence of renal disease; one was receiving treatment for hypertension and one for epilepsy; the remainder were not receiving any regular medication. Renal function in this group provided the norm with which patients on digoxin could be compared, since it was our impression that the normally accepted levels of creatinine clearance would not stand fair comparison with those of our extremely aged group.

Plasma sodium and potassium were determined by flame photometry on a Baird and Tatlock Analmatic, and chloride, bicarbonate, urea, and total protein by standard Technicon AutoAnalyzer techniques. Creatinine was determined by the Jaffe reaction after elimination of non-creatinine chromogens (Henry, 1964). Calcium was determined by EDTA titration and magnesium by atomic absorption spectrophotometry with a Hilger and Watts Atomspek. Plasma and urine digoxin were measured by a radioimmunoassay technique as described by Smith *et al.* (1969), using the Wellcome Lanoxitest digoxin radioimmunoassay kit. Tritium (³H)-labelled and unlabelled digoxin compete for digoxin-specific antibody, and an inverse relation is established between the amount of unlabelled digoxin bound to the antibody and radioactivity. Unbound digoxin is removed by precipitation with charcoal and the bound digoxin estimated by counting tritium in a suitable scintillation medium.

Results

Fourteen men and 17 women aged 58 to 91 years were investigated. The distribution of patients according to varying clinical indications for digitalization is shown in Table I (groups 1-4). Digoxin, diuretic, and potassium therapy was similar in all groups.

TABLE I—Patients Taking Digoxin: Age, Sex, and Clinical Indications for Therapy

Group 1. Right Ventricular Failure		Group 2. Left Ventricular Failure		Group 3. Right and Left Ventricular Failure		Group 4. Hypertension with Failure	
Age	Sex	Age	Sex	Age	Sex	Age	Sex
80	M.	75	M.	79	F.	70	F.
76	F.	73	M.	70	F.	87	F.
74	F.	74	F.	76	M.	82	F.
78	M.	78	M.	73	F.	88	M.
		66	M.	91	F.	58	F.*
		67	M.	85	F.	86	F.
		74	M.	70	M.	86	M.
		77	M.	81	F.	91	M.
				70	F.		
				80	F.		
				82	F.		

*Hypertension and fibrillation.

Blood Biochemistry.—All patients were normokalaemic and had normal levels of plasma sodium, chloride, and bicarbonate. Plasma calcium was just below the lower limit of normal in four patients in the hypertensive group and three of them also had mild hypomagnesaemia. One of these patients (with hypocalcaemia) was receiving diuretic therapy. Low plasma magnesium concentrations were found in three other patients (in group 3), all of whom were receiving diuretics; the remainder had normal concentrations of both magnesium and calcium. Haemoglobin levels were all within normal limits. Total protein was normal in all cases, and the blood urea concentration was below 45 mg/100 ml in all but five.

Renal Function.—The endogenous creatinine clearance showed moderate to grossly impaired renal function in most subjects taking digoxin despite “normal” blood urea concentrations (Table II). The total lack of correlation between the

TABLE II—Results of Renal Function Tests in Patients Taking Digoxin

Patient		Blood Urea (mg/100 ml)	Creatinine Clearance (ml/min)
Age	Sex		
80	M.	39	49
78	M.	79	8
75	M.	51	67
73	M.	43	123
74	F.	26	40
78	M.	38	67
66	M.	31	88
67	M.	24	44
74	M.	46	64
79	F.	47	33
76	M.	55	97
73	F.	19	32
91	F.	55	45
85	F.	28	44
80	F.	38	44
82	F.	42	21
58	F.	33	86
86	M.	33	21
91	M.	55	11
74	F.	—	52
77	M.	—	53
81	M.	—	51
70	F.	—	34
87	F.	—	9

blood urea and creatinine clearance is shown in Fig. 1. One patient with a blood urea of 79 mg/100 ml and a creatinine clearance of 8 ml/min was known to be in renal failure; the remainder had no obvious signs of renal dysfunction. Seven of

FIG. 1—Relation between the blood urea concentration and creatinine clearance.

the 10 control subjects also had clearances below 80 ml/min (Table III), the clearance usually quoted as the lower limit of normal, but on average showed less impairment of renal function than the test subjects. The differences between patients, controls, and a group of healthy younger adults (aged 20-45 years) are shown in Fig. 2.

Plasma Digoxin and Digoxin Clearance.—Plasma digoxin levels measured at comparable time intervals after taking a dose

TABLE III—Results of Renal Function Tests in Elderly Control Subjects

Patient		Blood Urea (mg/100 ml)	Creatinine Clearance (ml/min)
Age	Sex		
79	F.	58	27
79	F.	37	70
72	M.	50	90
65	M.	32	87
76	M.	38	75
72	F.	37	43
64	F.	22	46
74	F.	40	36
86	F.	53	31
73	F.	38	123

FIG. 2—Creatinine clearance histograms.

FIG. 3—Plasma digoxin levels at varying times after taking a single dose of digoxin in patients classified according to creatinine clearance.

were similar in the four groups of patients. The time interval caused pronounced differences in some cases and was not necessarily related to the state of kidney function. Fig. 3 illustrates the variation of plasma digoxin with time in patients with severely impaired renal function (creatinine clearance below 30 ml/min), moderately impaired function (30-60 ml/min), and normal function (over 60 ml/min). No relation was found between plasma digoxin and urea or between plasma digoxin and creatinine clearance (Fig. 4). Fig. 5 shows the relation between clearance of creatinine and digoxin.

FIG. 4—Above: Relation between plasma digoxin levels (six or more hours after the last dose of digoxin) and blood urea. Below: Relation between plasma digoxin levels (six or more hours after the last dose of digoxin) and creatinine clearance.

FIG. 5—Relation between creatinine clearance and digoxin clearance.

Discussion

Despite the relatively small number of patients investigated several interesting and potentially important points emerged from this study. The patients investigated were clinically judged

to be adequately digitalized and free from toxic symptoms. The biochemical findings were in agreement. Only four patients had plasma digoxin levels above 2 ng/ml—the concentration above which toxicity may be encountered (Chamberlain *et al.*, 1970)—at any time. None was hypokalaemic and few showed any other disturbance of electrolytes. The two patients with blood levels consistently above 2 ng/ml subsequently had their total doses of digoxin reduced as a precaution against precipitation of digoxin toxicity by, for example, intercurrent illness.

Peak plasma digoxin levels are reached 30-60 minutes after oral administration in the fasting state, or after about two hours if the digoxin is taken with food, and fall to a plateau by six to eight hours (White *et al.*, 1971). The variations in digoxin levels with time illustrated in Fig. 3 reflect this and show the necessity for accurate knowledge of the interval between taking a dose of digoxin and venepuncture when interpreting results of plasma digoxin assay.

The lack of correlation between plasma urea concentrations and plasma digoxin demonstrated by us (Fig. 4) has been noted previously (Smith and Haber, 1970). Digoxin is mainly excreted, unchanged, by the kidneys (Doherty, 1968), therefore the plasma level will be considerably influenced by the glomerular filtration rate. Our results confirmed that the blood urea concentration is a very poor indicator of this function (Fig. 1). Specific examples include two patients with a "normal" blood urea of 33 mg/100 ml who had creatinine clearances of 21 and 86 ml/min respectively and three patients each with an "increased" blood urea of 55 mg/100 ml associated with creatinine clearances of 11, 45, and 97 ml/min.

We were unable to confirm the suggestion by Jelliffe and Blankenhorn (1967)—that a linear relation exists between creatinine and digoxin clearances—which formed the basis of their proposal that digoxin dosage could be regulated by knowledge of the creatinine clearance. However, our results do suggest that, despite the poor correlation between creatinine and digoxin clearance (correlation coefficient 0.240, $P > 0.1$), digoxin clearance is consistently lower than creatinine, irrespective of whether the patient is receiving diuretics or potassium supplements. In all the subjects examined by us the digoxin clearance was less than that of normal subjects (average 93 ml/min), as reported by Doherty *et al.* (1967).

The difference between the creatinine and digoxin clearances probably reflects tubular secretion of creatinine and reabsorption of digoxin, processes apt to be influenced by additional drugs (diuretics and others). Consequently, adjusting the dose of digoxin in relation to the creatinine clearance does not in our experience seem to be a suitable alternative to monitoring plasma digoxin concentrations.

Nevertheless, measurement of the endogenous creatinine clearance was important as it showed that renal function was considerably worse in most of the patients receiving digoxin and the healthy elderly control subjects than had been sus-

pected. Similar results have also been reported by Mitchell (1966). In principle, reduced renal function is a well-recognized hazard of prescribing, especially in the elderly (Davison, 1971), and ideally it should be assessed by carrying out a creatinine clearance before prescribing a potentially dangerous drug such as digoxin. Blood electrolyte concentrations should be determined at the same time. We have shown that this is a practical proposition even in a scattered, rural, general practice. Blood digoxin levels should then be monitored during the period of digitalization, and at suitable intervals thereafter. Now that measurement of plasma digoxin has become a relatively simple and quick procedure the distressing and sometimes fatal results of digoxin toxicity need never occur.

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