SKELETAL MUSCLE DIGOXIN BINDING IN PATIENTS WITH RENAL FAILURE

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For digoxin analyses blood and skeletal muscle samples were taken from seven digoxin-treated patients with chronic renal failure. The ratio between skeletal muscle and serum digoxin concentration in the patients with renal failure was not significantly different from the ratios in two control groups consisting of subjects with normal renal function. In the group of patients with renal failure there was no relationship between the glomerular filtration rate and muscle digoxin binding (specific plus unspecific). The present study does not indicate reduced skeletal muscle digoxin binding in patients with chronic renal failure.

Keywords digoxin skeletal muscle renal failure binding

Introduction

A decrease in the apparent volume of distribution of digoxin has been reported in uraemic patients (Reuning *et al.*, 1973; Szeffler & Jusko, 1973; Aronson & Grahame-Smith, 1976). This reduction of the volume of distribution has been considered to indicate either a decrease in the volume of extracellular fluid or decreased binding of digoxin to such quantitatively important tissues as skeletal muscle (Reuning *et al.*, 1973). The aim of the present investigation was to estimate the skeletal muscle digoxin binding in patients with chronic renal failure and to compare it with digoxin binding to skeletal muscle in subjects with normal renal function.

Methods

Patients and procedures

Seven undialyzed male patients (aged 57–74 years; mean age 64.1) with chronic renal failure took part in the study, which was approved by the Ethical Committee of the Karolinska Hospital.

All patients had been treated with digoxin in a dose range of 0.13–0.375 mg/day for at least 1 month previously. Six of the patients were also being treated with diuretics and two with a β -adrenoceptor blocker. None of the patients was being treated with quinidine, verapamil, nifedipine or spironolactone.

Serum creatinine concentrations ranged between 180 and 1032 $\mu\text{mol/l}$, with a decrease in the glomerular filtration rate in all patients (Table 1). Potassium and sodium concentrations in the serum were normal in all patients (Table 1).

No patient showed signs of digitalis intoxication according to the clinical criteria given by Beller *et al.* (1971).

The investigations were performed 24 h after the last dose of digoxin. The patients rested in the supine position for 1 h before blood and muscle specimens were taken for the analysis of serum and skeletal muscle digoxin. The muscle biopsies were taken from the quadriceps femoris muscle (vastus lateralis), using the percutaneous needle biopsy technique (Bergström, 1962).

Two groups of previously investigated subjects were used as controls. The first group consisted of eight male patients (aged 43–64 years; mean age 55.1) with atrial fibrillation and normal renal function (Table 1). These patients were on maintenance treatment with digoxin in doses of 0.25 mg/day. None of them was being treated with quinidine, verapamil, nifedipine or spironolactone and there were no electrolyte disturbances (Table 1). The second group consisted of seven healthy men (aged 24–38 years; mean age 29.7) who ingested digoxin, 0.375–0.50 mg/day, for 2–3 weeks before the investigation. They had normal renal function and exhibited no electrolyte disturbances (Table 1). Blood and skeletal muscle specimens were taken after 1 h of rest in the supine position, 24 h after the last dose of digoxin, as described above.

Methodology

The skeletal muscle samples were freeze-dried and carefully freed from connective tissue and fat. Appro-

Table 1 Serum creatinine, glomerular filtration rate and serum electrolytes in seven patients with chronic renal failure (individual values) and in two control groups (mean values $\pm$ s.d.).

Patient	Serum creatinine ($\mu\text{mol/l}$) (< 120)*	Creatinine clearance ($\text{ml min}^{-1} 1.73 \text{ m}^{-2}$)	Serum potassium (mmol/l) (3.4–5.2)*	Serum sodium (mmol/l) (135–147)*	Serum calcium (mmol/l) (2.2–2.6)*
1	990	8	4.5	141	2.4
2	510	9	4.1	141	2.3
3	730	7	4.2	141	2.2
4	180	26**	3.9	137	2.2
5	285	22	4.5	142	3.0
6	450	24	4.6	145	1.7
7	1030	8	4.5	140	2.1
Patients with atrial fibrillation $n = 8$	92 ± 7	79 ± 8 ***	4.2 ± 0.4	142 ± 3	2.5 ± 0.1
Healthy subjects $n = 7$	91 ± 7	104 ± 13 ***	4.3 ± 0.2	140 ± 4	2.4 ± 0.1

* : Reference range of the laboratory

** : Glomerular filtration rate measured as ^{51}Cr -EDTA clearance ($\text{ml min}^{-1} 1.73 \text{ m}^{-2}$)*** : Estimated by using the nomogram of Siersbaek-Nielsen *et al.* (1971)

priate amounts of the freeze-dried muscle tissue were weighed and homogenized in phosphate buffer, after which digoxin was extracted from the tissue with dichloromethane. After evaporation of the dichloromethane phase the residue was redissolved in human serum and the digoxin concentration was measured by radioimmunoassay (Smith *et al.*, 1969), using a commercial ^{125}I -RIA-Kit (New England Nuclear, Mass, USA). The method has been described in detail previously (Jogestrand, 1980; Jogestrand & Sundqvist, 1981). The serum digoxin concentrations were measured with the ^{125}I -RIA-Kit without extraction. The coefficient of variation for duplicate analyses was 11% for skeletal muscle concentration and 6% for serum concentration. The skeletal muscle and serum concentrations given are the mean values of duplicates. The digoxin concentration is expressed as nmol/kg dry weight in skeletal muscle and as nmol/l in serum.

Mean values $\pm$ s.d. are indicated unless stated otherwise. Student's *t*-test for mean of two samples was used for testing statistical significance.

Results

The serum digoxin concentration in the patients with chronic renal failure was 1.73 ± 0.45 nmol/l (Table 2). The corresponding concentration in the patients with atrial fibrillation was 0.75 ± 0.11 nmol/l and in the healthy subjects 1.23 ± 0.31 nmol/l. The differences in serum digoxin concentration between the patients with renal failure and the control groups were statistically significant ($P < 0.001$ and $P < 0.05$, respectively).

The patients with renal failure also had a significantly higher skeletal muscle digoxin concentration (60.4 ± 16.1 nmol/kg dry weight; Table 2) than those

Table 2 Digoxin concentrations in serum and skeletal muscle and skeletal muscle/serum digoxin ratios in seven patients with chronic renal failure.

Patient	Digoxin concentration in serum (nmol/l)	Digoxin concentration in skeletal muscle ($\text{nmol/kg dry weight}$)	Skeletal muscle/serum digoxin ratio
1	1.4	54	38
2	2.2	83	38
3	1.3	66	51
4	1.1	36	33
5	2.0	76	38
6	2.0	49	24
7	2.1	59	28
Mean	1.73	60.4	35.7
s.d.	0.45	16.1	8.7

with atrial fibrillation (34.4 ± 9.3 nmol/kg dry weight; $P < 0.01$) and the healthy subjects (39.9 ± 12.9 nmol/kg dry weight; $P < 0.05$).

The ratio between skeletal muscle and serum digoxin concentration in the patients with renal failure (35.7 ± 8.7 ; Table 2) was not significantly different from the ratios in the two control groups (patients with atrial fibrillation: 46.2 ± 11.3 ; healthy subjects: 32.9 ± 9.1). In the group of patients with renal failure there was no relationship between glomerular filtration rate or serum creatinine and skeletal muscle digoxin binding (specific plus unspecific) expressed as the ratio between skeletal muscle and serum digoxin concentration.

Discussion

Decreased binding of digoxin to skeletal muscle has been suggested as the most probable explanation of the reduced apparent volume of distribution of this drug in patients with renal failure (Reuning *et al.*, 1973). The results of the present study do not support this assumption.

Other possible explanations of the decrease in the volume of distribution of digoxin in renal failure are: (1) reduction of the tissue mass (*e.g.* skeletal muscle, kidney and extracellular fluid), (2) reduced digoxin binding to other organs than skeletal muscle.

In patients with chronic renal failure and serum creatinine concentrations below $1000 \mu\text{mol/l}$ the total body water was not significantly different from that in patients with normal renal function (Ericsson & Carl-

mark, 1982). Furthermore, Aronson & Grahame-Smith (1976) reported marked changes in the volume of distribution of digoxin paralleling changes in renal function in a patient with acute renal failure without any change in the patient's body weight.

The heart is the only other organ in which digoxin binding during uraemia has been studied. In a post-mortem study Jusko & Weintraub (1974) found decreased myocardial digoxin binding in patients with renal failure. However, only a few hundredths of the total body content of digoxin are found in the heart (Steiness, 1978). Thus, a change in myocardial digoxin binding alone cannot significantly influence the apparent volume of distribution.

Finally, the selection of patients in our study may be different from that in the cited studies of the apparent volume of distribution of digoxin in patients with renal failure (Reuning *et al.*, 1973; Szefer & Jusko, 1973; Aronson & Grahame-Smith, 1976). Despite the fact that the glomerular filtration rates were of the same magnitude, the serum electrolyte balance was probably less disturbed in our patients. Thus, in our study the serum potassium range was $3.9\text{--}4.6$ mmol/l, whereas the potassium concentrations in the previous studies, when indicated, were usually higher. Since hyperkalaemia has been suggested as a possible cause of reduced tissue binding of digoxin in renal failure (Aronson & Grahame-Smith, 1976), this difference in serum electrolytes may be of importance.

In conclusion, the present study does not indicate reduced skeletal muscle digoxin binding in patients with chronic renal failure.

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