The effect of oral digoxin on sodium excretion, renin-angiotensin-aldosterone system and blood pressure in normotensive subjects

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Summary: The effect of digoxin (0.25 mg t.d.s.) given orally for 5 days, on sodium excretion, plasma renin activity, plasma aldosterone and blood pressure has been studied in 6 normotensive subjects, on a constant sodium intake. Average serum digoxin level measured in 5 subjects on the 5th day of treatment was in the upper range of the therapeutic level (1.92 ± 0.3 nmol/l). Red cell sodium content increased from 9.75 ± 1.2 mmol/l of cells in the control period to 15.3 ± 1.7 mmol/l of cells on the 5th day of digoxin treatment when measured in 4 of the 6 subjects. In spite of this evidence of inhibition of the red cell sodium pump, there was no detectable change in sodium excretion, blood pressure, plasma renin activity and aldosterone.

Introduction

Digoxin and ouabain are known to cause a natriuresis when given intra-arterially or intravenously in animals and in men (Farber *et al.*, 1951; Hyman *et al.*, 1956; Hook, 1969), to increase vascular reactivity of isolated arterial preparations (Flaim & DiPette, 1979; Mikkelsen *et al.*, 1979), to increase sympathetic activity *in vitro* (Toda, 1980; Aarhus *et al.*, 1983) and to cause inhibition of renin secretion both *in vitro* (Churchill, 1979) and *in vivo* (Covit *et al.*, 1983). We, therefore, investigated the effects of digoxin given orally for 5 days to normotensive subjects, on sodium excretion, blood pressure, plasma renin activity and aldosterone.

Patients and methods

Six healthy, normotensive male volunteers were studied over 3 weeks as outpatients after a few days of observation in the blood pressure unit; the mean age was 21.3 ± 0.33 years. The average supine blood pressure was $111/65 \pm 5/5$ mm Hg. During the whole study subjects were on a fixed normal sodium intake of 120 mmol/day and potassium intake of 80 mmol/day. All food and drink was provided by the metabolic kitchen. After a 1 week control period, subjects were given an oral loading dose of digoxin (Lanoxin) 0.50 mg in the morning and thereafter 0.25 mg t.d.s.

for 5 days; a further week's control period was continued on a fixed sodium intake after stopping digoxin. Informed consent was obtained from each subject and the study protocol was approved by Charing Cross Hospital Ethical Committee. During the study, subjects were seen in the Blood Pressure Unit every day for blood pressure, pulse rate and weight measurements. All subjects were told not to take vigorous exercise. Daily 24 hour urines were collected for the measurement of sodium and potassium excretion. Blood was taken during each period for measurement of electrolytes, creatinine, urea, plasma renin activity and aldosterone. In the first week and on the 5th day of the experimental period on digoxin, red blood cell sodium content was measured in 4 of the 6 subjects; serum digoxin levels were measured at the end of the experimental period in 5 subjects. Subjects were seen daily between 10.00 hours and 12.00 hours by the same nurse, in the same room. Blood pressure was measured in the same arm by nurses using semi-automatic ultrasound sphygmomanometers (Arteriosonde) (George *et al.*, 1975) with attached recorders. The measurements were therefore free from observer bias. Supine and standing blood pressures were the means of 5 readings taken at 1–2 minute intervals with the subjects in the corresponding position; supine pressures were measured before standing pressures. Pulse rate was measured on a Cambridge 3048 pulse monitor. Subjects were carefully instructed on how to collect 24 hour

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specimens of urine. Blood samples were taken without stasis after the subject had been sitting upright for 10 minutes. Plasma renin activity (Roulston & MacGregor, 1978) and aldosterone (James & Wilson, 1976) were measured by radioimmunoassay. Serum digoxin was measured by radioimmunoassay using a kit with ¹²⁵I-digoxin (The Radiochemical Centre, Amersham, Buckinghamshire). All results are reported as means ± s.e.m. Because of the small number of subjects Wilcoxon's rank sum test was carried out for the statistical evaluation as described by Colton (1974).

Results

Average serum digoxin level measured on the 5th day of oral treatment in 5 subjects was in the upper range of the therapeutic levels showing a mean value of 1.92 ± 0.33 nmol/l and red cell sodium content, measured in 4 subjects, increased from 9.75 ± 1.21 to 15.30 ± 1.70 mmol/l of cells (Table I).

During the one-week control period before digoxin was given, mean 24 hour urinary sodium excretion was 117 ± 6 mmol. There was a small but non-significant increase in sodium excretion on the first day of digitalization (137 ± 10 mmol of sodium/24 hour). However, during the 5 days of digoxin treatment there was no detectable change in sodium balance, mean 24 hour urinary sodium excretion being 118 ± 7 mmol (Figure 1). In the week following digoxin, mean 24 hour urinary sodium was 126 ± 8 mmol. Digoxin treatment did not produce any significant change in potassium excretion; mean 24 hour urinary potassium excretion before digoxin was 76.9 ± 3.5 mmol, 83.1 ± 5 mmol during digoxin treatment and 76.8 ± 5 mmol following digoxin (Figure 1). Plasma renin activity before treatment was 2.33 ± 0.65 ng/ml/hour, on the 5th day of digoxin was 2.84 ± 0.47 ng/ml/hour and on the 3rd day of the control week after stopping digoxin was 3.04 ± 0.64 ng/ml/hour. Plasma aldosterone did not change during the study: before treatment it was 486 ± 89 pmol/l, on the 5th day of digoxin treatment 451 ± 74 pmol/l and on the 3rd day of the control period after digoxin 397 ± 62 pmol/l.

Supine and standing blood pressures which were measured daily throughout the study showed no significant changes (Figure 2). On the day before the administration of digoxin average supine blood pressure was 117/63 ± 4/2 mm Hg, by the end of the digoxin treatment it was 119/67 ± 6/3 mm Hg and one week after stopping digoxin it was 116/62 ± 5/4 mm Hg. Heart rate gradually fell during the study from 71 ± 5 before the administration of digoxin to 60 ± 4 beats/minute on the 4th day of digoxin treatment. On the third day after stopping digoxin heart rate was 71 ± 4 beats/minute and, for the group,

Table I Serum digoxin levels on the 5th day and red cells sodium content measured before and after 5 days of oral treatment with digoxin in normotensive subjects (n.d. = not determined).

Subject number	Serum digoxin (nmol/l)	Red cells sodium	
		Pre-treatment (mmol/l cells)	5th day
1	2.7	7.8	14.5
2	2.2	n.d.	15.5
3	2.3	9.1	13.2
4	1.6	8.8	11.6
5	n.d.	13.3	21.9
6	0.8	n.d.	n.d.

remained steady thereafter.

No changes in body weight, plasma sodium and potassium, urea and creatinine were observed during the study. One subject on the last day of digoxin treatment complained of some nausea and yellow vision. There were no other reported side effects and all subjects completed the study.

Discussion

Several studies have demonstrated the extracardiac effects of infused glycosides (Farber *et al.*, 1951; Hyman *et al.*, 1956; Hook, 1969; Covit *et al.*, 1983).

Figure 1 Average daily urinary sodium and potassium excretion (± s.e.m.) in the six normal subjects 7 days before, 5 days of and 7 days after digoxin treatment. Dotted lines represent the estimated daily intake.

Figure 2 Average daily supine (□) and standing (▨) systolic and diastolic blood pressure ($\pm$ s.e.m.) in the six normal subjects 7 days before, 5 days of and 7 days after digoxin treatment.

Strickler & Kessler, 1961; Mason & Braunwald, 1964; Williams *et al.*, 1958; Robinson *et al.*, 1983), but there is little information on the extracardiac effects of digitalis glycosides given orally to normal man.

In our study, a high dose of digoxin given orally for 5 days to normotensive subjects did not change sodium excretion. Furthermore, there was no detectable change in plasma renin activity, plasma aldosterone or blood pressure, in spite of the fact that during the study, on average, serum digoxin levels after 5 days of treatment were in the therapeutic range and there was a marked increase in red cell sodium content by the 5th day of digoxin treatment, presumably indicating inhibition of Na^+ - K^+ -ATPase in these red cells (Gill & Solomon, 1959; Glynn, 1964; Morgan *et al.*, 1980).

The natriuretic effects of glycosides have only been demonstrated in animals and man following intra-arterial or intravenous injection. Hook (1969) infused ouabain at a high dose in dog's renal arteries and measured either sodium excretion *in vivo* or Na^+ - K^+ -ATPase activity in slices of kidney *in vitro*. He found a dose-related natriuresis and, concomitantly, a dose-related depression of Na^+ - K^+ -ATPase obtained from the renal cortex, supporting the view that inhibition of renal Na^+ - K^+ -ATPase could be responsible for the natriuretic response that was seen.

Hyman *et al.* (1956) injected digoxin directly into one renal artery of a dog and observed an increase in water and sodium excretion from the injected kidney. Strickler & Kessler (1961) injected several cardiac glycosides into one renal artery of dogs, but found that only certain cardiac glycosides caused a natriuresis. They suggested that the beta-lactone ring was essential

for the natriuretic response. In man, Farber *et al.* (1951) demonstrated a prompt and considerable natriuresis following intravenous digoxin infusion in patients with congestive heart failure and suggested that digoxin might act in heart failure by its effect on renal tubular sodium excretion. In normotensive subjects the results were not so clearcut and there appeared to be no significant increase in sodium excretion. More recently, Guthrie (1984) showed no change in urinary sodium excretion following oral digoxin treatment for 4 days in normotensive subjects although, unlike our study, sodium intake was not controlled and it is difficult therefore to draw definite conclusions.

In our study cumulative urinary sodium excretion during the 5 days of digoxin treatment did not differ significantly from the sodium excretion before and after digoxin. Digoxin is likely to have been still present in the control period after stopping the drug as it has a reported mean half-life of approximately 40 hours (Kelman *et al.*, 1980). Nevertheless this would seem unlikely to affect our results as neither urinary sodium, potassium or blood pressure showed any significant change throughout the entire study.

Ouabain is known *in vitro* to inhibit renin release (Churchill, 1979) and Covit *et al.* (1983) have recently demonstrated an acute inhibitory effect of digoxin on plasma renin activity when given intravenously in patients with congestive heart failure. However, Guthrie (1984) in his study with oral digoxin showed, like us, no changes in plasma renin activity or plasma aldosterone.

Intravenous ouabain infusion in normotensive subjects causes an increase in peripheral resistance and

blood pressure (Mason & Braunwald, 1964; Williams *et al.*, 1958). Furthermore, Guthrie (1984) showed no change in blood pressure with oral digoxin but did show an increased blood pressure response to both noradrenaline infusion and angiotensin II infusion after 4 days of digoxin, strongly suggesting an increase in the sensitivity of arteriolar vascular smooth muscle cells to agonists after inhibition of the sodium pump. Robinson *et al.* (1983) infused intra-arterial ouabain into the forearm of normotensive subjects and were able to reproduce the depressed response to potassium infusion which is found in patients with essential hypertension, suggesting that this abnormal response to potassium infusion in essential hypertension is likely to be due to inhibition of the sodium pump. Our

finding that oral digoxin for 5 days does not alter blood pressure does not, therefore, exclude the role of cardiac glycosides in altering the reactivity of arteriolar smooth muscle cells or the potential effect of endogenous sodium transport inhibitors over a longer period in regulating blood pressure.

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