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DIGOXIN TOXICITY COMPARED WITH MYOCARDIAL DIGOXIN AND POTASSIUM CONCENTRATION

EVA STEINESS

Department of Pharmacology and Medical Department B, Rigshospitalet, University of Copenhagen, Denmark

1 Twenty-nine dogs were given digoxin (0.25 mg) by mouth twice daily for eight days. Some of them (group 1) also received diuretics and others (group 2) a mineralocorticoid. The dogs were then given an intravenous bolus injection of digoxin and plasma and cardiac muscle were analysed for digoxin and potassium.

2 In the digitalized dogs, myocardial potassium concentration decreased following the intravenous injection of either 0.05 or 0.15 mg/kg digoxin; in contrast, in those dogs given diuretics or mineralocorticoid the potassium concentration increased.

3 Ventricular arrhythmias occurred after digoxin injection (0.05 mg/kg) in the hypokalemic dogs, in those given a mineralocortocoid and in those dogs which received a toxic digoxin dose (0.15 mg/kg). No arrhythmias where seen in the control (digitalized) group.

4 Myocardial digoxin concentrations were similar in the control digitalized group and in the mineralocorticoid-treated dogs after the intravenous administration of the lower digoxin dose (0.05 mg/kg). The myocardial digoxin concentration was significantly higher in the hypokalemic group and in the group receiving the higher digoxin dose (0.15 mg/kg).

5 There was no obvious relationship between the occurrence of arrhythmias and the myocardial concentration of digoxin or potassium.

Introduction

Although digitalis toxicity is usually correlated with a high plasma concentration of the glycoside (Beller, Smith, Abelmann, Haber & Hood, 1971; Evered & Chapman, 1971; Carruthers, Kelly & MacDewitt, 1974), toxic effects may also occur in patients with normal therapeutic levels. This may be due to an increased myocardial sensitivity to the glycoside. Hypokalemia and potassium depletion may also promote toxicity, for example in patients with congestive heart failure receiving both diuretics and maintenance treatment with digitalis. This was evident in some studies (Lown & Levine, 1954; Jørgensen & Sørensen, 1970; Steiness & Olesen, 1976), whereas in others hypokalemia was not associated with toxicity (Beller *et al.*, 1971; Evered & Chapman, 1971). It is still unknown whether hypokalemia itself promotes digitalis toxicity and the aim of the present investigation was therefore to study the relationship between the myocardial uptake of digoxin, and the potassium levels in plasma and myocardium, after a non-toxic intravenous digoxin dose in digitalized dogs. Furthermore, one group of these animals was pretreated with diuretics and another group with a mineralocorticoid. The results obtained from these groups were compared with those obtained after a toxic intravenous digoxin dose in digitalized dogs. With this protocol it was possible to study the myocardial concentrations of both digoxin and potassium at a steady state, therapeutic, plasma digoxin level and at different plasma potassium levels. Furthermore, it was possible to study the acute myocardial uptake of digoxin and changes in myocardial potassium levels in the same animals.

The results suggest that arrhythmias induced by digoxin are not correlated only with total myocardial digoxin and potassium but that other mechanisms may be involved.

Methods

Twenty-nine healthy mongrel dogs (18–25 kg) were divided into four groups. All the dogs received 0.25 mg digoxin twice daily by mouth for eight days before

the study. The last digoxin dose was given not later than 12 h before the study started to ensure a steady-state equilibrium of digoxin between plasma and myocardium. Group 1: Seven of the dogs were given 80 mg furosemide (Lasix) and 10 mg bendroflumethiazide (Centyl) once daily as a supplement to the digoxin treatment. The last doses of the diuretics were given about one hour before the investigation. Group 2: Seven of the dogs were treated with 1 mg fluorhydrocortisone acetate (Florinef) daily as a supplement to digoxin. The last dose was given about one hour before investigation. Group 3 and Group 4: These dogs (15 in all) received only daily digoxin treatment before the investigation.

Experimental procedure

The dogs were anaesthetized with barbiturate (Enibomal) and, following tubocurarine (0.5 mg/kg) and pethidine (5 mg/kg) administration, intubated and connected to a Bird respirator. Anaesthesia was maintained with N_2O/O_2 (3 and 1.5 l/min) and 0.7% halothane. A left thoracotomy was performed and the pericardium incised and sutured to the chest wall. Retrograde catheterization of the left ventricle was performed from the femoral artery. The haemodynamic parameters and a standard lead of the ECG were displayed simultaneously on a Elema Schönander multichannel recorder (Mingograf 81).

A myocardial biopsy specimen weighing 200–400 mg was taken from the left ventricular wall (approx. one quarter to one third of the wall thickness) and, following haemodynamic stabilization (about 15 min), the dogs received an intravenous bolus injection of digoxin (0.05 mg/kg). The seven dogs in group 3 received a larger digoxin dose (0.15 mg/kg) whereas the eight dogs in group 4 received the same digoxin dose as those in groups 1 and 2 (0.05 mg/kg).

In all groups myocardial biopsies were taken 10, 30 and 60 min after the intravenous administration of digoxin.

Blood samples

Heparinized venous blood was drawn for measurements of plasma concentrations of digoxin, potassium and sodium just before, and 5, 10, 15, 20, 30, 45 and 60 min after the intravenous injection of digoxin. Arterial P_{O_2}, P_{CO_2} and pH were measured before and 10, 30 and 60 min after administration of digoxin.

Analytical procedure

Plasma and myocardial concentrations of digoxin were measured in duplicate by radioimmunoassay as previously described (Steiness 1974; Steiness & Valentin 1976a). The sensitivity of the method is 0.25×10^{-9} mol/l plasma and 5×10^{-9} mol/kg tissue. The small amount of the single myocardial biopsy did not allow measurements of digoxin in subcellular fractions. Plasma potassium and sodium were determined in duplicate by flame photometry. Tissue potassium was determined in triplicate according to Valentin & Olesen (1973) and expressed in mmol/kg fat-free dried solids (standard deviations of 11 measurements from the same tissue sample were 10 mmol/kg fat free solids).

Blood gases and pH were measured with a Radiometer apparatus (Copenhagen).

Any blood loss, including sampling, was replaced with an electrolyte-containing plasma expander (Haemaccel). To replace the water loss 250 ml of isotonic glucose was given every hour.

Statistics

The statistic calculations were based on non-parametric methods (Documenta Geigy, 1970). The Wilcoxon test for paired data was used for determination of statistical significance.

For comparison between different groups the Wilcoxon test for nonpaired data was used.

Results

Arrhythmias

All the dogs were in sinus rhythm at the end of the oral digoxin treatment. Arrhythmias developed in groups 1 (in 4 out of 7), 2 (in 3 out of 7) and 3 (in 5 out of 7), 7 to 8 min after intravenous dose of digoxin. Sinus rhythm persisted in group 4 throughout the investigation. One dog in group 1 and two in group 2 developed A-V block after about 45 minutes.

Plasma digoxin

The steady state plasma digoxin concentration was significantly higher in group 1 than in groups 2, 3 and 4 ($P < 0.01$) (Table 1).

After one intravenous injection of 0.05 mg digoxin/kg, identical plasma digoxin curves were obtained in groups 1, 2 and 4, whereas in group 3 (receiving the larger digoxin dose) plasma digoxin concentrations were, as expected, significantly higher ($P < 0.01$). There were no significant differences between the plasma concentrations in the dogs which developed arrhythmias and those which did not.

Myocardial digoxin

The steady state myocardial concentration of digoxin

was significantly higher in group 1 than in groups 2, 3 and 4 ($P < 0.01$), whereas there was no difference between the concentration in groups 2, 3 and 4 (the range of values being large) (Table 2).

The concentration reached 10 min after the intravenous digoxin injection was significantly higher in group 3 ($P < 0.01$). The concentration in group 1 was significantly higher than in groups 2 and 4 ($P < 0.02$). These differences between the groups persisted throughout the study. There was no significant difference between the myocardial concentrations in the dogs developing arrhythmias and those that did not.

Electrolytes

The steady state plasma potassium was significantly lower in group 1 than in the other groups ($P < 0.01$; Table 1). No change in plasma concentration of either sodium or potassium was found following the intravenous injection of digoxin.

The myocardial potassium concentrations were virtually the same in the four groups before digoxin injection. In groups 1 and 2 the myocardial potassium concentration increased significantly after the digoxin injection ($P < 0.02$; Table 2). However, in groups 3 and 4 myocardial potassium decreased significantly and remained low. There was no difference between the concentration of potassium in plasma and myocardium in the dogs showing digitalis toxicity and those that did not.

Haemodynamics

Both left ventricular systolic and end-diastolic pressures were similar in all groups and remained unchanged. There were also no significant changes in arterial P_{O_2}, P_{CO_2} and pH in any of the groups throughout the study.

Discussion

The aim of the present study was to determine the interaction between hypokalemia and arrhythmias induced by digoxin and to compare this with the arrhythmias resulting from a digoxin overdose.

The steady state plasma and myocardial concentrations of digoxin in group 1 was significantly higher than those of the other groups, in agreement with other observations in hypokalemic animals (Cohn, Kleiger & Harrison, 1967; Prindle, Skelton, Epstein & Markus, 1969), who suggested that hypokalemia facilitates the myocardial uptake of digoxin. This might however also be due to a reduced elimination rate (Steiness, unpublished observations). A similar

Table 1 Plasma digoxin and potassium concentrations before and after intravenous administration of digoxin in chronically digitalized dogs

Group	Plasma Conc. (nmol/l)		Steady state 0	Minutes after administration of digoxin 5	10	15	20	30	45	60
	Digoxin	Median	4.0	128	80	56	50	36	25	20
1		s.e. mean	0.57	14	11	7	5	4	4	3
$n = 7$	Potassium	Median	2.8	2.6	2.4	2.5	2.4	2.6	2.5	2.6
		s.e. mean	0.12	0.13	0.19	0.18	0.20	0.19	0.18	0.26
	Digoxin	Median	1.4	118	56	52	37	27	19	18
2		s.e. mean	0.35	29	23	12	8	6	5	3
$n = 7$	Potassium	Median	3.3	2.9	2.8	3.4	3.4	3.3	3.6	3.5
		s.e. mean	0.10	0.12	0.19	0.22	0.12	0.11	0.12	0.15
	Digoxin	Median	2.1	423	224	186	155	121	105	84
3		s.e. mean	0.32	95	68	67	15	18	10	10
$n = 7$	Potassium	Median	3.6	3.6	3.7	3.7	3.7	4.2	4.3	4.7
		s.e. mean	0.10	0.17	0.31	0.27	0.27	0.22	0.29	0.67
	Digoxin	Median	1.3	116	69	52	38	25	18	17
4		s.e. mean	0.43	10	5	4	4	3	3	2
$n = 8$	Potassium	Median	3.7	3.1	3.6	3.7	3.7	3.6	3.6	4.1
		s.e. mean	0.15	0.19	0.19	0.17	0.17	0.17	0.21	0.15

The results from Group 4 have been described previously (Steiness & Valentin 1976b). For further details see text.

tendency to increasing plasma digoxin concentration during potassium loss was recently found in digitalized patients (Steiness & Olesen, 1976).

Even though the steady state myocardial concentration was higher in group 1 than in the other groups, the increase of all myocardial digoxin concentrations from 0 to 10 min was very similar in groups 1, 2 and 4, whereas it was significantly higher in group 3. From these results it can be concluded, that hypokalemia does not seem to facilitate myocardial digoxin uptake. However, there was some correlation between myocardial digoxin concentration and the arrhythmias. On the other hand, other factors may be of importance, since arrhythmias developed in group 2 with a myocardial digoxin concentration virtually identical to that of the dogs in group 4, which were in sinus rhythm. Sinus rhythm in group 4 and the arrhythmias in group 3 were observed at decreasing myocardial potassium concentration, whereas the arrhythmias in groups 1 and 2 were observed at increasing myocardial potassium concentrations. It is, therefore, suggested that digoxin-induced arrhythmias do not depend on the myocardial concentration of potassium.

Digitalis glycosides inhibit Na^+-K^+-membrane ATPase and this results in a decrease in intracellular potassium. It has been suggested by Okita (1975) that digitalis toxicity may be secondary to the changes in the myocardial concentration of potassium. The relevant clinical situation was imitated in the present study by treating dogs (group 1) with diuretics to induce hypokalemia. A second group was treated with mineralocorticoid to mimic a hyperaldosteronic condition since, in contrast to digitalis, mineralocortocoids stimulate membrane Na^+-K^+ ATPase (Bittar & Tallitsch, 1976) resulting in an increased potassium concentration in groups 1 and 2 (interaction between digoxin and mineralocorticoid).

The potassium gradient from the tissue to the extracellular fluid increased in groups 1 and 2, but decreased in group 3 (Tables 1 and 2). Hence changes in potassium gradient seem to be without significance for digoxin toxicity. The present data therefore suggest that changes in myocardial potassium are not directly involved in the mechanisms of digoxin-induced arrhythmias.

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Table 2 Myocardial digoxin and potassium concentrations before and after intravenous administration of digoxin in chronically digitalized dogs

Group	*Myocardial Concn. (mg/kg)*		*Steady state* 0	*Minutes after intravenous digoxin* 10	30	60
	Digoxin	Median	266	487	482	592
1		s.e. mean	54	63	50	66
$n = 7$	Potassium	Median	320	325	349**	351**
		s.e. mean	14	34	39	35
	Digoxin	Median	125	308	261	303
2		s.e. mean	43	48	52	56
$n = 7$	Potassium	Median	332	382**	414**	400*
		s.e. mean	40	37	31	19
	Digoxin	Median	135	617	578	948
3		s.e. mean	13	152	108	162
$n = 7$	Potassium	Median	320	279*	294**	287*
		s.e. mean	45	41	59	30
	Digoxin	Median	60	306	250	300
4		s.e. mean	15	40	34	41
$n = 8$	Potassium	Median	369	354	350**	348**
		s.e. mean	8	10	11	12

The results from Group 5 have been described previously (Steiness & Valentin 1976b). For further details see text.

* $P < 0.05$; ** $P < 0.02$ compared with zero level.

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