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PHARMACOKINETICS OF DIGOXIN IN PATIENTS SUBJECTED TO THE QUINIDINE-DIGOXIN INTERACTION

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1 This study was designed to evaluate pharmacokinetically the digoxin-quinidine interaction in patients with atrial fibrillation.

2 Five patients on maintenance digoxin therapy were given [^{3}H]-digoxin as a single i.v. dose before and during quinidine therapy and the elimination of [^{3}H]-digoxin from plasma and excretion in urine were determined.

3 The mean steady state plasma concentration of digoxin increased from 0.7 to 1.3 nmol/l after quinidine administration.

4 The apparent volume of distribution of digoxin decreased on the average 38%. Renal clearance and the total body clearance of digoxin decreased 51 and 56 % respectively (mean values). Also non renal clearance was reduced. The fraction of digoxin excreted unmetabolised in urine did not change during quinidine treatment. The mean elimination half life of digoxin increased from 49 to 72 h during quinidine.

5 In two patients the DC-shock did not cause a conversion to sinus rhythm. However, the quinidine induced changes in the pharmacokinetics of digoxin in these patients did not differ from the others.

6 Quinidine appears to decrease the amount of digoxin distributed to body tissue(s). In addition, the reduction of renal clearance of digoxin and the observed unchanged clearance of creatinine suggests an inhibition of the renal secretion of digoxin.

Introduction

Since the unexpected discovery that quinidine causes a marked increase in the steady-state plasma concentration of digoxin (Ejvinsson, 1977; Kaufman 1978; Ejvinsson 1978; Leahey, Reiffel, Drusin, Heissenbuttel, Lovejoy & Bigger, 1978; Doering & König, 1978) work has progressed to clarify the underlying mechanisms. It was shown that quinidine also exerts this effect in patients where digoxin maintenance therapy was discontinued 2 days before quinidine treatment suggesting redistribution as a mechanism (Leahey *et al.*, 1978; Dahlqvist, Ejvinsson & Schenck-Gustafsson, 1980). Preliminary reports from experimental studies have given further support for this explanation. Quinidine reduced the number of binding sites of digitalis in beef heart membrane Straub, Kane, Bissett & Doherty, 1978) and reduced canine skeletal and heart muscle levels of digoxin while plasma and brain levels increased (Doherty, Straub, Bissett, Kane, deSoyza & Murphy, 1979). Redistribution was reported by Hager, Fenster, Mayersohn, Perrier, Graves, Marcus & Goldman (1979) in six human subjects given single i.v. doses of digoxin before and during quinidine administration. These authors found a reduction in the apparent volume of distribution together with decreased total and renal clearances of digoxin but no change in elimination half-life. Interestingly, the reduction in renal digoxin clearance was not accompanied by any change in creatinine clearance in agreement with a previous observation (Hooymans & Merkus, 1978). The present study was undertaken to explore the pharmacokinetic background of the quinidine-digoxin interaction in the relevant patient group. The use of a tracer dose of radioactively labelled digoxin enabled us to simultaneously determine the pharmacokinetic parameters of digoxin as well as the changes in plasma digoxin levels.

Methods

Patients and procedures

Five patients with atrial fibrillation scheduled for cardio-conversion to sinus rhythm gave their informed consent to participate in the study. They were between 44 and 67 years of age (mean 58 years). All had been receiving maintenance digoxin therapy for at least 1 month and therapeutic doses of warfarin for

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at least 3 weeks. During the hospital stay for introduction of anticoagulant therapy, steady-state concentrations of digoxin in plasma were determined. Doses were adjusted to maintain levels less than 1 nmol/l. Four patients received 0.25 mg and one 0.375 mg digoxin daily. Three patients received a diuretic (frusemide or hydrochlorothiazide) and one also verapamil. These medications were kept unchanged throughout the study. The patients had normal blood chemistry including thyroid hormone levels. Renal function tests including clearance of endogenous creatinine were normal. The heart volumes did not exceed 600 ml/m^2 body surface area. Two patients had mitral valvular disease (1, 2), one patient had intermittent claudication and diabetes mellitus (5), the fourth patient had had a previous myocardial infarction (4). The fifth patient appeared healthy except for his atrial fibrillation (3). This investigation was approved by the ethical committee of the hospital.

Two weeks before the planned DC-shock, the patients were admitted to the hospital and given a single i.v. dose of [^{3}H]-digoxin (9 μg digoxin; 200 μCi). Tritium activity in plasma was analysed after 15, 30, 45, 60 and 90 min, 2, 4, 6, 10, 24 h and then less frequently for 8 days and in urine for 2 to 3 days in 24 h urine collections. Plasma digoxin levels prior to the daily dose were determined by radio-immunoassay. Two weeks later the patients were readmitted to the hospital. Quinidine therapy started with an oral loading dose of quinidine sulphate (approximately 0.1 g/10 kg body-weight) (Collste & Nordlander 1979) followed by daily maintenance doses of 0.6 g × 2 given as Kinidin Durules (AB Hässle, subsidiary of AB Astra, Gothenburg, Sweden). After one day on quinidine another i.v. dose of [^{3}H]-digoxin was given, blood and urine sampling and analyses were performed as before. Quinidine levels in plasma were determined before dose for four days.

None of the patients was converted to sinus rhythm by quinidine alone and therefore all were exposed to DC-shock within the next 24 h. Although sinus rhythm was not achieved in two of the patients (1 and 5) the quinidine therapy was continued for another week.

Materials

The 12-α-[^{3}H]-digoxin (17.5 Ci/mmol) was purchased from New England Nuclear Inc., Boston, Massachussets. Absence of radiochemical impurities was asertained by thin layer radiochromatography as well as by high pressure liquid chromatography (see below). A saline solution of the labelled drug was tested for sterility and the absence of pyrogens, then sealed in glass ampoules. These tests were kindly performed by the National Bacteriological Laboratory and AB Kabi-Vitrum, Stockholm.

Digoxin, dihydrodigoxin, digoxigenin-bis-digitoxoside, digoxigenin-mono-digitoxoside, digoxigenin and dihydrodigoxigenin were purchased from Boehringer Mannheim GmbH, Mannheim, West Germany.

Laboratory methods

Concentrations of digoxin in plasma and urine (after dilution) were determined by radioimmunoassay with ^{125}I-labelled glycoside (Clinical Assay Gammacoat, Travenol Labs., Inc., Cambridge, Massachussetts). Measured plasma concentrations below 0.5 nmol/l were not considered in the data analysis. Quinidine concentrations in plasma were determined by the method of Cramér & Isaksson (1963). [^{3}H]-digoxin in urine was separated from its metabolites (except dihydrodigoxin) by a high pressure liquid chromatographic method (Erni & Frei, 1977).

The radioactivity in plasma and urine was determined by liquid scintillation counting with corrections for quenching by the internal standard technique. Severely haemolysed samples were discarded. Only samples containing at least 25 counts/min more than the background radioactivity were considered in the data analysis.

Determination of creatinine in serum and urine were performed spectrophotometrically by the department of Clinical Chemistry of the hospital (Bartel, Böhmer & Heierli, 1972). Creatinine in serum was also determined by mass spectrometry (Björkhem, Blomstrand & Öhman, 1977).

Data analysis

The total area under the plasma concentration versus time curve (AUC) for [^{3}H]-digoxin was obtained by the trapezoidal rule and addition of the calculated residual area (C_{last}/β) and used for the calculation of the apparent volume of distribution ($V_{d(area)}$ = Dose/AUC·β). The slope of the terminal disposition phase (β) was calculated from the plasma concentration v time curve beginning 24 h after the dose. Renal clearance was determined from the relation: 24 h urine excretion of [^{3}H]-digoxin/24 h plasma AUC of [^{3}H]-digoxin. Total body clearance was obtained from the relation Dose/AUC.

The [^{3}H]-digoxin concentrations in plasma were fitted to the best triexponential equation (Kramer, Lewis, Cobb, Forester, Visconti, Wanke, Boxenbaum & Reuning, 1974) by a nonlinear regression computer program. The volume of the central compartment (V_c), the volume of distribution at steady-state ($V_{d_{ss}}$), the rate constant for elimination from the central compartment (k_{10}) and the rate constants for distri-

bution between central and peripheral compartments (k_{12} k_{21} k_{13} and k_{31}) were then calculated according to conventional techniques (Gibaldi & Perrier 1975).

Paired *t*-test was used for the statistical evaluation of treatment effects. *P* values above 0.05 are indicated as non-significant (NS).

Results

The plasma digoxin levels increased about two-fold after quinidine was administered (Table 1). The mean quinidine levels varied from 7.3 to 13.1 μmol/l (Table 1). None of the patients suffered from adverse reactions except for moderate gastro-intenstinal reactions (nausea, diarrhea) immediately after the oral loading dose of quinidine.

The concentrations of [^{3}H]-digoxin in plasma for one patient (no. 3) before and after quinidine are shown in Figure 1 along with the computer predicted decay curves derived from the data points. The plasma levels of [^{3}H]-digoxin at all time points were higher during quinidine treatment. Furthermore the terminal slope of the disappearance curve was less steep during quinidine, i.e. the elimination half-life of digoxin was prolonged.

The results from the pharmacokinetic analysis from all five patients are shown in Table 2 and Table 3. The mean (± s.d.) apparent volume of distribution ($V_{d(area)}$) of digoxin was significantly ($P < 0.01$) decreased from 11.1 ± 2.8 l/kg before to 6.8 ± 1.0 l/kg during quinidine administration (Table 2). The mean decrease was 38 per cent. The calculated volume of distribution at steady state (V_{dss}) and the volume of the central compartment (V_c) also decreased in all patients ($P < 0.01$ and $P < 0.05$ respectively, Table 2). No consistent changes were observed in the rate constants for distribution (k_{12} k_{21} k_{13} k_{31}) of digoxin between the central and peripheral compartments (Table 2).

The mean (± s.d.) elimination half-life of digoxin increased significantly ($P < 0.01$) from 49 ± 5.9 to 72 ± 8.0 h (Table 3). The rate constant for elimination from the central compartment (K_{10}) was approximately halved in all patients by quinidine.

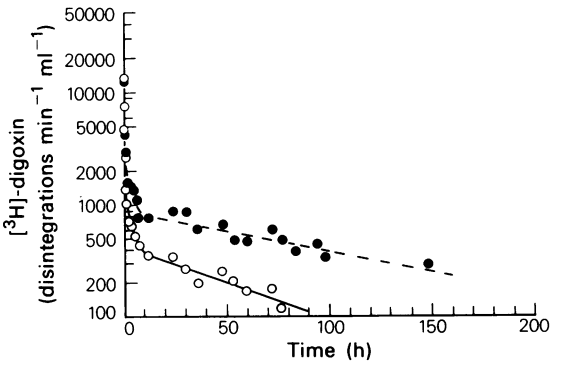

Figure 1 Concentration of [^{3}H]-digoxin in plasma after a single i.v. dose before quinidine treatment (○) and during quinidine treatment (●) in patient 3. The computer predicted decay curves best fitting the data are indicated by the lines.

The mean (± s.d.) total body clearance decreaseed ($P < 0.01$) from 188 ± 26 to 83 ± 16 ml/min (Table 3). The mean decrease was 56%. The mean renal clearance of [^{3}H]-digoxin decreased ($P < 0.01$) from 130 ± 32 to 62 ± 10 ml/min. The mean decrease was 51%. The difference between the total body clearance and the renal clearance, the non-renal clearance, was initially 51 ± 30 ml/min and was reduced to 21 ± 14 ml/min during quinidine treatment.

There was no apparent correlations between the plasma quinidine levels and the magnitude of the changes in digoxin pharmacokinetic parameters.

The mean (± s.d.) clearance of endogenous creatinine was 115 ± 25 ml/min before quinidine and 103 ± 14 ml/min during quinidine treatment. These figures were not statistically different.

Table 1 Effect of quinidine on plasma concentration of digoxin

Patient number	*Digoxin concentration (nmol/l)* *prior to quinidine*[1]	*on quinidine*[2]	*Quinidine concentration*[3] *(μmol/l)*
1	0.63	1.2	10.6 ± 0.5
2	0.65	1.4	9.5 ± 1.0
3	0.80	1.7	11.0 ± 1.8
4	0.65	1.1	13.1 ± 4.1
5	0.58	0.9	7.3 ± 3.3
Mean	0.66	1.26	10.3
s.d	0.08	0.30	2.1
	$P < 0.01$		

[1] Mean values from 2 to 4 samples
[2] Sample taken after 4 days on quinidine
[3] Mean ± s.d. of first 4 days

Table 2 Pharmacokinetic values for digoxin disposition prior to and during quinidine therapy

Patient number	$V_{d(area)}$ (l/kg) no Q	on Q	V_{dss} (l/kg) no Q	on Q	V_c (l/kg) no Q	on Q	k_{12} (h^{-1}) no Q	on Q	k_{21} (h^{-1}) no Q	on Q	k_{13} (h^{-1}) no Q	on Q	k_{31} (h^{-1}) no Q	on Q
1	8.5	6.2	7.5	5.5	0.85	0.47	0.59	0.76	0.36	0.27	0.73	0.53	0.12	0.07
2	14.4	8.4	12.2	8.2	0.72	0.66	0.65	1.14	0.62	0.71	1.49	1.19	0.10	0.12
3	13.6	7.1	11.3	6.5	0.46	0.25	1.30	0.82	0.69	0.54	1.63	1.62	0.08	0.07
4	8.7	6.0	8.5	5.2	0.52	0.44	1.02	0.65	0.32	0.23	0.56	0.47	0.05	0.06
5	10.3	6.3	10.9	6.0	0.67	0.49	0.89	0.81	0.39	0.31	0.66	0.93	0.05	0.11
Mean	11.1	6.8	10.1	6.3	0.64	0.46	0.89	0.84	0.48	0.41	1.02	0.95	0.08	0.09
s.d	±2.8	±1.0	±2.0	±1.2	±0.16	±0.15	±0.29	±0.18	±0.17	±0.21	±0.51	±0.48	±0.03	±0.03
	$P < 0.01$		$P < 0.01$		$P < 0.05$		NS		NS		NS		NS	

Q Quinidine treatment
$V_{d(area)}$ The volume of distribution calculated from the area under the plasma concentration *v* time curve
V_{dss} The volume of distribution at steady state
V_c The volume of the central compartment
k_{12} The rate constant of distribution from central to 'shallow' tissue compartment
k_{21} The rate constant of distribution from 'shallow' tissue compartment to central compartment
k_{13} The rate constant of distribution from central to 'deep' tissue compartment
k_{31} The rate constant of distribution from 'deep' tissue compartment to central compartment

Table 3 Pharmacokinetic values for digoxin disposition prior to and during quinidine therapy

Patient number	$T_{½}\beta$ (h) no Q	on Q	k_{10} (h^{-1}) no Q	on Q	Cl_{tot} (ml/min) no Q	on Q	Cl_r (ml/min) no Q	on Q
1	41	71	0.19	0.08	179	74	91	47
2	51	60	0.26	0.14	196	108	147	75
3	46	78	0.45	0.24	205	64	160	65
4	55	69	0.22	0.10	147	82	99	64
5	64	80	0.18	0.11	214	87	151	58
Mean	49	72	0.26	0.14	188	83	130	62
s.d.	±5.9	±8.0	±0.11	±0.065	±26	±16	±32	±10
	$P<0.01$		$P < 0.01$		$P < 0.01$		$P < 0.01$	

Q Quinidine treatment
$T_{½}\beta$ The elimination half-life
k_{10} The rate constant of elimination from the central compartment
Cl_{tot} The total body clearance of digoxin
Cl_r The renal clearance of digoxin (mean values from 2 to 3 days)

Chromatographic analyses of urine were performed for [^{3}H]-digoxin and its metabolites (dihydrodigoxin, digoxigenin-bis-digitoxoside, digoxigenin-mono-digitoxoside, digoxigenin and dihydrodigoxigenin). The analyses showed that 87 ± 5% (mean ± s.d.) of the activity consisted of digoxin (including dihydrodigoxin) before and 81 ± 5% during quinidine treatment. These percentages did not differ statistically.

In two patients (nos. 1 and 5) the DC-shock did not cause a conversion to sinus rhythm. However, the quinidine induced changes in the pharmacokinetics of digoxin in these patients did not differ from the others.

Discussion

Quinidine therapy caused an approximately two-fold rise in the concentration of digoxin in plasma in accordance with earlier studies (Ejvinsson 1977, 1978; Leahey *et al.*, 1978; Doering & König, 1978; Dahlqvist *et al.*, 1980). In previous investigations (Leahey *et al.*, Dahlqvist *et al.*, 1980) increased digoxin levels was also observed in patients when digoxin maintenance therapy was discontinued two days prior to quinidine administration. This suggested a quinidine-induced redistribution of digoxin in the body. Recently Hager *et al.* (1979) demonstrated that quinidine reduced the apparent volume of distribution of digoxin in six subjects. In the present study of patients with atrial fibrillation the apparent volume of distribution ($V_{d(area)}$) of digoxin decreased by approximately 40 per cent during quinidine treatment. Similarly, the volume of the central compartment and the calculated volume of distribution at steady-state decreased in all patients although to a more variable degree. In contrast to $V_{d(area)}$ the terms V_c and V_{dss} are uninfluenced by the elimination rate (Gibaldi & Perrier, 1975). The quinidine-induced decrease in V_c and V_{dss} observed in the present study therefore is consistent with a true change in the distribution of digoxin. The data suggest that quinidine displaces digoxin in the central and peripheral compartments to about the same extent. No significant changes were observed in the rate constants for distribution between central and peripheral compartments. The calculated figures for these rate constants should be regarded as approximate values since they are highly dependant on a frequent early blood sampling. The degree of plasma binding of digoxin was in preliminary experiments uninfluenced by quinidine treatment (Dahlqvist *et al.*, 1980).

Both renal and nonrenal clearance of digoxin were decreased to about half their initial values during quinidine treatment. The mechanism of the decrease in nonrenal clearance of digoxin is unclear. The renal clearance of digoxin was approximately 70% of the total body clearance. This fraction was not significantly affected by the quinidine treatment. Furthermore the directly measured fraction of digoxin excreted unmetabolized before and during quinidine did not differ statistically.

Steiness and collaborators (Steiness 1974; Warldorff, Damgaard-Andersen, Heeboll-Nielsen, Gamborg-Nielsen, Moltke, Sorensen & Steiness, 1978) showed that renal elimination of digoxin occurs not only through glomerular filtration but also by tubular secretion and that this secretion is inhibited by spironolactone. In the present study the clearance of endogenous creatinine remained unchanged by quinidine treatment whereas renal digoxin clearance was markedly reduced. This is in accordance with other studies (Hager *et al.*, 1979; Hooymans *et al.*, 1978) although in one previous study (Dahlqvist *et al.*, 1980) a slight decrease in creatinine clearance by quinidine was observed. The reason for this difference is unclear but was not due to the different techniques used for serum creatinine analysis. The fact that the clearance of endogenous creatinine remained unchanged and renal clearance of digoxin greatly diminished suggests that quinidine like spironolactone inhibits the tubular secretion of digoxin.

In contrast to the data of Hager *et al.*, (1979) a significant increase was observed in the mean elimination half-life of digoxin from 49 to 72 h. The discrepancy between their results and the present study might be partly explained by the different patient materials and the fact that we were able to follow the elimination of digoxin for a longer period of time.

In this study the overall clearance of digoxin in patients with atrial fibrillation was approximately halved by quinidine administration. This is in agreement with the observed average doubling of the steady-state concentration of the glycoside. The reduction in total clearance was reflected both in renal and nonrenal clearance. Thus, this interaction appears to involve several mechanisms since the volume of distribution, clearances and the elimination rate were all decreased.

Other studies (Leahey *et al.*, 1978; Doering & König, 1978; Dahlqvist *et al.*, 1980) have indicated that quinidine-induced increases in plasma digoxin levels frequently cause side effects. In the present study adverse reactions to digoxin may have been avoided by keeping the initial digoxin steady-state levels low. In general however, if digoxin maintenance therapy is to be continued, it is recommended that the dose of digoxin is halved prior to planned quinidine therapy. The average final steady-state concentration of digoxin will then be expected to be similar to the level before quinidine treatment with the original dose of digoxin. Due to the great vari-

ation in the effect of quinidine on the plasma digoxin levels (Leahey *et al.*, 1978, Doering & König, 1978) however, it is also recommended that plasma digoxin is determined a few days later.

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