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EFFECT OF QUINIDINE ON PLASMA CONCENTRATION AND RENAL CLEARANCE OF DIGOXIN. A CLINICALLY IMPORTANT DRUG INTERACTION

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1 Thirty patients on maintenance digoxin therapy and admitted for cardioversion of atrial fibrillation were closely monitored with regard to plasma levels of digoxin and quinidine.

2 Seventeen of these patients were kept on maintenance digoxin therapy. After an initial lag period of 6 to 18 h after the addition of quinidine their digoxin levels started to increase and had increased by between 20 and 330% after 3 days on quinidine. Side-effects attributed to the raised digoxin concentration occurred in 6 of these patients.

3 As studied in 5 of these 17 patients the renal clearance of digoxin decreased markedly when quinidine was added to the therapy. There was also a slight but significant reduction in creatinine clearance ($n = 4$).

4 In 13 patients digoxin was discontinued 36 h prior to the first quinidine dose. Also in these patients digoxin plasma levels increased significantly.

5 It is concluded that quinidine causes an unpredictably large increase in plasma digoxin and that this effect is probably at least initially to a large part due to a redistribution of digoxin in the body. The relative contributions of re-distribution and impaired renal clearance of digoxin to the increase in digoxin steady-state levels are presently unknown.

6 It is recommended that close monitoring of digoxin concentration and appropriate reduction of the maintenance dose is undertaken when quinidine is to be given to patients on digitalis therapy.

Introduction

Syncope is a not uncommon side effect during treatment of atrial fibrillation with quinidine and usually appears during the first two days of therapy (Kerth, Selzer, Keyani & Gerbode, 1964; Castellanos, Lemberg, Gilmore & Johnson, 1965; Gilbert & Cuddy, 1965; Bjerkelund & Skåland, 1967; Derweduwen, Enderle, deGeest, Polis, Vancrombreucq & Joossens, 1969; Ejvinsson, 1978a). Short periods of ventricular tachycardia or ventricular fibrillation have been suggested as the mechanism of this side effect (Kerth *et al.*, 1964; Castellanos *et al.*, 1965; Gilbert & Cuddy, 1965; Bjerkelund & Skåland, 1967; Derweduwen *et al.*, 1969; Ejvinsson, 1978a). A literature survey suggests that many patients who develop quinidine syncope are simultaneously treated with digoxin (Ejvinsson, 1978a). Studies in this hospital pointed out the possibility that a pharmacokinetic drug interaction between quinidine and digoxin may partially explain this side-effect. It was found that the plasma digoxin levels increased when quinidine was added to the therapy (Ejvinsson, 1977, 1978a, 1978b). This finding has been independently confirmed by other investigators (Leahey, Reifell, Drusin, Heissenbuttel, Lovejoy & Bigger, 1978). This report deals with our present knowledge about this unexpected drug interaction.

Methods

Patients and procedures

The patient material was made up by 30 patients admitted for cardioversion of atrial fibrillation. All of them had been on digoxin therapy in unchanged dose administered once daily for at least 4 weeks. In the majority of the patients digoxin steady state was documented within 3 weeks prior to admission by analyses of at least two digoxin samples several days apart.

All patients were on warfarin during 3 weeks or

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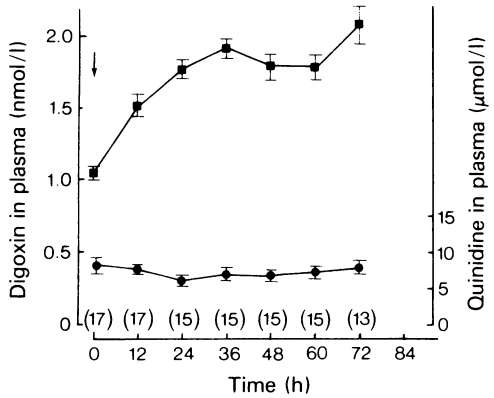

Figure 1 Mean ± s.e. mean digoxin (■) and quinidine (●) concentrations in plasma in patients with maintained digoxin therapy. The first quinidine dose is given at time zero (arrow). Number of patients still on quinidine indicated in brackets.

more before admission and had achieved therapeutically desirable prothrombin levels prior to admission. Most patients were also treated with other drugs, mainly diuretics and potassium. These medications were kept unchanged throughout the investigation. All patients were normokalemic and had normal serum values of thyroxine and triiodothyronine.

After an oral loading dose of quinidine sulphate (0.6–0.8 g depending on body weight) (Collste & Nordlander, 1979) maintenance doses of quinidine were given as Kinidin Durules (each tablet containing 250 mg quinidine bisulphate, equivalent to 200 mg quinidine sulphate), three tablets twice daily. Unless sinus rhythm was achieved during the first day (this occurred in approximately 40% of the patients) DC shock was performed.

Venous blood samples for drug analyses were taken 12-hourly (12 and 24 h after each dose of digoxin) in heparinized Venoject® tubes over at least 3 days after starting quinidine treatment.

Group I

In 17 patients digoxin therapy was maintained during the quinidine treatment. Data from 12 of these patients have been published in preliminary reports (Ejvinsson, 1977, 1978b). In two of the patients quinidine treatment had to be discontinued after 12 h due to ventricular tachycardia and/or ventricular fibrillation.

Five patients were followed more closely with frequent blood samples for drug analyses during the first 12 h after addition of quinidine and with 24 h urine collections 1 to 2 days prior to quinidine and 1 to 3 (in one case up to 6) days after starting quinidine treatment.

Group II

In 13 patients digoxin treatment was discontinued 36 h prior to the institution of quinidine.

Analytical techniques

Digoxin concentrations in plasma were determined by radioimmunoassay (Schwarz–Mann, Orangeburg, New York and Clinical Assay-Gammacoat, Travenol Labs., Inc., Cambridge, Massachusetts). After suitable dilution of urine samples and preparation of digoxin standards in urine the same analytical technique was employed for the assay of urine digoxin levels.

For plasma digoxin analysis the s.d. for duplicate determinations averaged 0.12 nmol/l and for repeat determinations (day-to-day variation) 0.19 nmol/l.

Appropriate control experiments were conducted which excluded the possibility of interference from quinidine or quinidine metabolites in the digoxin measurements. Thus, addition of quinidine *in vitro* to a final average blood concentration of 5 μmol/l to blood samples from two patients on monotherapy with digoxin did not affect the measured concentrations of digoxin in plasma. Furthermore, addition of digoxin *in vitro* to serum samples from one group of patients on quinidine alone and from one group without any drug therapy did not result in any differences in the concentrations of digoxin measured in these samples. Original data are available on request.

Quinidine concentrations in plasma were determined by the method of Cramèr & Isaksson (1963).

Determinations of creatinine in serum and urine were performed by a routine spectrophotometric technique by the department of clinical chemistry at the hospital (Bartels, Böhmer & Heierli, 1972).

Renal clearances of digoxin and creatinine were calculated from the 24 h urinary excretions and the mid-interval plasma levels of these compounds.

Results

Digoxin therapy maintained

After addition of quinidine to the group of 17 patients on maintenance digoxin treatment, the plasma digoxin concentration rose gradually in all (Figure 1). The interindividual variation however was large. After a lag period of at least 6 h the mean increase amounted to 46% (range −9 to 122) after 12 h; 70% (range 23 to 150) after 24 h; 90% (range 14 to 317) after 48 h and 116% (range 17 to 333) after 72 h. The quinidine levels on the other hand were in most cases reasonably constant from one h after the loading dose and onwards (Figure 1). There

seemed to be a larger rise in plasma digoxin in patients with higher steady-state quinidine levels (Table I) but statistical analysis failed to show a significant correlation between the steady-state levels of quinidine and the percentage or absolute increase in digoxin concentrations.

Seven of the 17 patients converted spontaneously to sinus rhythm on quinidine. There was no difference in the degree of increase in serum digoxin between this group and the patients who received a DC shock.

The rise in plasma digoxin was accompanied by symptoms suggestive of digitalis side effects in 6 out of these 17 patients (Table 2). These symptoms occurred at plasma digoxin levels between 2.0 and 4.6 nmol/l (median value 2.9 nmol/l) and disappeared after reducing the dose of digoxin (4 cases) or quinidine (2 cases).

Four further patients developed ventricular tachycardia or ventricular fibrillation within 3 days after initiation of quinidine therapy. At that time the levels of plasma digoxin varied from 1.2 to 2.9 nmol/l and the quinidine levels from 4.0 to 12.5 μmol/l.

In four patients renal clearances of endogenous creatinine were measured 2 to 3 days before and the first 1 to 6 days on quinidine treatment. The average value for creatinine clearance before quinidine treatment was 89 ml/min (82 ml/min × 1.73 m^2). The first day on quinidine creatinine clearance decreased by 15 to 32% (mean 24%) to an average uncorrected value of 68 ml/min (Table 3). The change in creatinine clearance was statistically significant ($P < 0.05$) regardless of whether uncorrected values or bodysurface normalized values were used for the calculations. This reduction in creatinine clearance remained at follow-up investigations 6–10 months later ($P < 0.05$).

In five patients renal clearances of digoxin were measured 1 to 2 days before and the first 2 to 6 days on quinidine treatment. The effect of quinidine on renal digoxin clearance was marked (Figure 2). Before addition of quinidine renal digoxin clearance averaged 131 ml/min with a range from 83 to 165 ml/min (expressed per 1.73 m^2 body surface area the average was 121 ml/min and the range 84–150). After one to three days on quinidine, renal digoxin clearance had decreased by 57 to 84% (mean 72%) to an average of 39 ml/min (range 15 to 55 ml/min).

Digoxin therapy discontinued

In a group of 13 patients digoxin treatment was discontinued 2 days prior to the quinidine therapy.

Table 1 Quinidine plasma levels (means from 1 to 72 h) in relation to the increase in plasma digoxin 72 h after addition of quinidine.

	Mean quinidine levels (μmol/l)				
	<3.9	4.0–5.9	6.0–7.9	8.0–9.9	>10.0
Number of patients	0	6	2	2	3
% increase in plasma digoxin		17–75 (mean 44)	44 and 333	23 and 214	86–130 (mean 112)
Level increase in plasma digoxin (nmol/l)		0.2–1.0 (mean 0.47)	0.4 and 2.0	0.3 and 1.5	0.6–2.6 (mean 1.63)

Table 2 Patients on maintenance digoxin treatment with side effects reminiscent of those of digitalis after administration of quinidine (Q)[1].

Patient	*Dose of digoxin (mg/day)*	*Mean plasma conc. of digoxin prior to Q (nmol/l)*	*Plasma digoxin at side effect event (nmol/l)*	*Plasma Q at side effect event (μmol/l)*	*Duration of Q treatment prior to registration of side effects (days)*
A	0.25	1.0 ($n = 3$)	2.4	—[2]	30
B	0.37	1.8 ($n = 3$)	4.6	12	3
C	0.19	1.1 ($n = 4$)	2.0	6	40
D	0.25	1.3 ($n = 5$)	3.0	13	6
E	0.25	0.7 ($n = 4$)	3.3	14	7
F	0.13	0.8 ($n = 6$)	2.7	11	6

[1] Appearance of nausea, sedation and/or arrhythmia and AV-block I disappearing after dose reduction. (In cases B and C the dose of quinidrine was reduced and the symptoms disappeared. Concomitantly their plasma levels of digoxin decreased to 2.5 and 1.0 nmol/l respectively).
[2] Not determined.

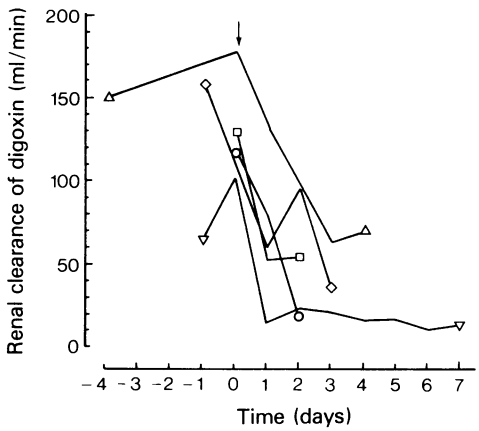

Figure 2 Renal digoxin clearances before quinidine and on quinidine therapy. Initiation of quinidine treatment indicated by arrow (day 0). Individual data (not corrected for body surface areas) from five patients shown.

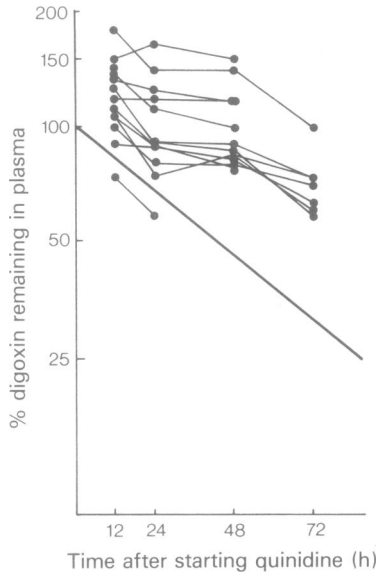

Figure 3 Digoxin in plasma in patients where digoxin therapy was discontinued 36 h prior to the first dose of quinidine. Thin lines indicate the individual patients with their digoxin concentrations expressed as percentage remaining of their level just prior to quinidine. The thick line indicates the calculated disappearance of digoxin with a biological half-life of 44 h and an unchanged volume of distribution.

Even in this group an actual increase in plasma digoxin was recorded in most patients. Thus, after 12 h on quinidine the plasma concentration of digoxin had increased by an average of 0.23 nmol/l (22%) ($P < 0.01$; paired t-test). No patients in this group developed any symptoms suggestive of digitalis intoxication. The digoxin levels were generally low. The individual percentages remaining of plasma digoxin after 12 to 72 h on quinidine were calculated, setting the pre-quinidine value to 100. For comparison, the expected disappearance of digoxin with a $T_{\frac{1}{2}}\beta$ of 44 h (Kramer, Lewis, Cobb, Forester, Visconti, Wanke, Boxenbaum & Reuning, 1974; Koup, Greenblatt, Jusko, Smith & Koch-Weser, 1975; Sheiner, Rosenberg & Marathe, 1977) was calculated (Figure 3). Of the observed values for plasma digoxin 39 out of 41 values were higher than expected from a $T_{\frac{1}{2}}$ of 44 h. This result was highly significant (binomial test). Digoxin plasma levels were not followed for a sufficiently long time period to allow an adequate estimation of the elimination rate constant during quinidine maintenance treatment.

In this group one patient developed reversible ventricular tachycardia/fibrillation. The nearest plasma digoxin level was 1.7 nmol/l and plasma quinidine at the same time was 8.2 μmol/l.

Discussion

This prospective investigation has confirmed that quinidine, as used therapeutically in patients with atrial fibrillation, raises the steady state level of digoxin in plasma. Moreover, it also significantly decreases the renal clearance of digoxin. The effect of quinidine to cause digoxin in plasma to increase during maintenance therapy was also recently reported from a retrospective study (Leahey *et al.*, 1978).

The observed pharmacokinetic drug interaction was not due to excessive concentrations of quinidine, since only a few patients had steady state plasma levels above the recommended therapeutic range (Sokolow & Ball, 1956).

In all seventeen patients with maintained digoxin therapy the plasma digoxin levels increased after addition of quinidine. The degree of increase in plasma digoxin varied several-fold between individuals and was not significantly related to the

Table 3 Endogenous creatinine clearance (ml/min, not corrected for body surface area).

		During quinidine	
Patient	*Prior to quinidine*[1]	*Day* 1	*After* 6 *to* 10 *months*[2]
1	105	89	59
2	107	73	88
3	83	69	53
4	61	42	43

[1] Mean of 2 to 3 determinations.
[2] Outpatients.

concentration of quinidine in plasma. There was a lag period up to 18 h before the increase in plasma digoxin was discernible. In contrast, the stead-state levels of quinidine regularly were attained already within one h after the loading dose.

Endogenous creatinine clearance was significantly decreased during quinidine treatment. Such an effect of quinidine used therapeutically has not been reported previously. The number of patients investigated was small however ($n = 4$) and the analytical technique for creatinine determinations not completely specific. Preliminary control experiments ruled out interference by quinidine itself in the assay of serum creatinine whereas falsely high serum creatinine from quinidine metabolites still remains a possibility. Further experiments are in progress to investigate a possible adverse effect of quinidine on renal function. Hooymans & Merkus (1978) found no consistent effect of quinidine on creatinine clearance in three volunteers.

Renal excretion of unchanged drug is the major route of elimination of digoxin in man (Doherty & Perkins, 1962; Marcus, Kapadia & Kapadia, 1964; Jellife, 1968; Waldorff, Damgaard Andersen, Heebøll-Nielsen, Gamborg Nielsen, Moltke, Sørensen & Steiness, 1978). Any decrease in renal digoxin clearance therefore would be expected to give a decrease, although lesser, in the total clearance and consequently an increase in the steady-state level of digoxin during maintained treatment.

Quinidine induced a rise in plasma digoxin even in patients where digoxin therapy had been discontinued 36 h previously. This indicates that an important mechanism for this interaction is a redistribution of the body stores of digoxin with an increase of the fraction available in plasma. Thus in pharmacokinetic terms the apparent volume of distribution of digoxin should be decreased. Preliminary experiments in two patients showed the plasma protein binding of digoxin to be similar before and during quinidine therapy. Therefore, we assume that quinidine may decrease the fraction of digoxin localized in one or several tissues. It is of interest in this regard that Straub, Kane, Bissett & Doherty (1978) found quinidine to reduce the number of binding sites for ouabain on beef heart membrane Na-K-ATPase. Although the concentrations of quinidine used in their study were very high the results suggest the possibility of quinidine-induced reduction of digitalis binding to cell membranes as part of the mechanism for the increase in digoxin serum levels.

The possible effect of conversion to sinus rhythm on digoxin distribution and digoxin serum levels could not be evaluated in this study since all patients were converted to sinus rhythm. However, the interaction was recently demonstrated also in healthy volunteers (Hooymans & Merkus, 1978).

Interestingly, in the hitherto only patient studied on digitoxin maintenance therapy, quinidine approximately doubled the steady state level in plasma of this glycoside (Schenck-Gustafsson & Dahlqvist, unpublished observations). If confirmed in further patients this could provide an additional argument for a redistribution mechanism since, in contrast to the case for digoxin, renal elimination of unchanged drug makes up only a minor part of the overall elimination of digitoxin (e.g. Lukas, 1973; Storstein, 1973).

To evaluate the potential hazards of a drug interaction the prevalence of this particular drug combination also should be estimated. Figures from drug wholesales records in Sweden indicate an incidence of usage of cardiac glycosides (mainly digoxin) and quinidine of 3.1 and 0.1% respectively (National Corporation of Swedish Pharmacies. Drug statistics 1977). In the experience of our laboratory, around 70% of patients with a request for analysis of quinidine in plasma are also on digitalis (usually digoxin) therapy. According to prescription registration from the county of Jämtland in Sweden approximately 50% of patients on quinidine are also treated with digitalis glycosides (Boethius, G. personal communication). Thus, around 4000 people in Sweden are presently subjected to the pharmacokinetic drug interaction described here.

Therapeutic implications

The quinidine treatment led, in a high percentage of our cases, to subjective or ECG-recorded side effects attributed to the rise in the digoxin levels. However, a contribution of quinidine itself to these symptoms cannot be ruled out in all cases. It is recommended that when quinidine is to be given to a patient on digoxin therapy, close monitoring of the digoxin concentration and appropriate reduction of the maintenance dose should be performed.

Note

After the submission of this paper Hager, Fenster, Mayersohn, Perrier, Graves, Marcus & Goldman (1979) have published a pharmacokinetic evaluation of this interaction based on single i.v. doses of digoxin to three non-cardiac patients and three healthy volunteers. They found substantial reductions in total body clearance, renal clearance, total and central volumes of distribution of digoxin during quinidine administration but no consistent effect on the elimination half-life. Furthermore creatinine clearances were unchanged. Hager *et al.* (1979) suggest reduced tissue binding of digoxin as one explanation for the rise in serum digoxin and reduced renal secretion of digoxin as the mechanism for the decrease in renal digoxin clearance.

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