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Amiodarone-Digoxin Interaction: Clinical Significance, Time Course of Development, Potential Pharmacokinetic Mechanisms and Therapeutic Implications

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Administration of amiodarone (600 to 1,600 mg/day) to 28 patients during long-term digoxin therapy (0.25 ± 0.05 mg/day) increased serum digoxin level from 0.97 ± 0.45 to 1.98 ± 0.84 ng/ml ($p < 0.001$). Gastrointestinal side effects occurred in nine patients, central nervous system reactions occurred in five and cardiovascular reactions occurred in four. Pharmacokinetic studies in six patients with a 1 mg intravenous digoxin dose before and during amiodarone therapy increased serum digoxin level at 30 minutes from 8.59 ± 1.68 to 10.07 ± 1.70 ng/ml ($p < 0.05$). Amiodarone caused a 31% prolongation of digoxin elimination half-life from 49.5 ± 8.8 to 65.0 ± 28.8 hours, but the increase in half-life was not statistically significant. Total body clearance was reduced significantly (29%, $p < 0.05$) from 2.05 ± 0.76 to 1.46 ± 0.64 ml/min per kg. Nonrenal clearance also showed a significant decrease (33%, $p < 0.05$) from 1.20 ± 0.46 to 0.80 ± 0.30 ml/min per kg. The renal clearance decreased by 22% and the volume of distribution decreased by 11% after amiodarone therapy, but these changes were not significant. The data show that the mechanism of digoxin-amiodarone interaction is multifactorial and emphasize the need for close monitoring of serum digoxin levels and clinical features during concurrent digoxin-amiodarone therapy.

Disorders of cardiac rhythm requiring antiarrhythmic therapy generally develop in patients with heart disease often with impaired ventricular performance for which cardiac glycosides are frequently prescribed. Thus, concomitant therapy with antiarrhythmic drugs and digitalis in many patients is not unusual. For this reason, pharmacokinetic interactions between cardiac glycosides and antiarrhythmic compounds are of more than theoretical importance. Antiarrhythmic agents and digoxin exert distinct electrophysiologic effects on the heart, which, in combination, may lead to potentially deleterious effects on cardiac rhythm and conduction. The above interaction can also result in adverse reactions of extracardiac origin. In particular, unexpected increases in serum digoxin concentrations supervene as a result of a pharmacokinetic interaction. Such an interaction has already been demonstrated with digoxin and quinidine (1–4) and digoxin and verapamil (5).

Our own preliminary studies (6) and those of others (7–11) have indicated that an important interaction between amiodarone and therapeutic doses of digoxin can induce side effects that may closely mimic those of toxic doses of amiodarone. This study was undertaken to quantify the magnitude of the increase in serum digoxin levels induced by amiodarone, determine the time course of such an increase and explore the possible pharmacokinetic mechanisms mediating the observed interaction relative to its clinical significance.

Methods

Study group. Twenty-eight patients receiving maintenance doses of digoxin were given amiodarone for the control of refractory tachyarrhythmias. Maintenance doses of digoxin had been constant for at least 2 weeks. In addition,

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in six other patients possible pharmacokinetic mechanisms were explored. In these six patients, single intravenous injections of digoxin (in accordance with the protocol outlined later) were given before and after amiodarone treatment. Concomitant oral digoxin was *not* given during the entire period of study. Of the total 34 patients constituting the study group, 32 were men and 2 were women; 20 had coronary artery disease, 11 had cardiomyopathy, 2 had atrial septal defect and 1 had valvular heart disease. All 34 had normal renal function with clinically stable cardiovascular hemodynamics. No patients were given other antiarrhythmic agents concomitantly, nor did they receive other medications known to interact with cardiac glycosides. The mean age of the patients was 59 years (range 43 to 84).

Protocol. *Study of magnitude of increase in serum digoxin levels induced by amiodarone.* Trough levels of serum digoxin were obtained before and after 1 week of continuous amiodarone treatment in 28 patients treated with maintenance doses of digoxin. The mean (± SD) daily dose of digoxin for the study group was 0.25 ± 0.05 mg. The dose of amiodarone varied between 600 to 1,800 mg/day. The data were collected retrospectively in 16 patients and prospectively in 12. All 28 patients were given digoxin for left ventricular failure (n = 14), control of supraventricular tachyarrhythmias (n = 9) and both indications (n = 5).

Determination of time course of increase in serum digoxin levels induced by amiodarone. Five patients who had received a constant dose of digoxin for more than 2 weeks and in whom amiodarone therapy was considered appropriate for the control of refractory ventricular arrhythmias were admitted to the special diagnostic and treatment unit for the initiation of therapy and for blood collection for serum levels of digoxin and amiodarone on the day before and on days 2,4,6,10 and 16 of amiodarone treatment. Both digoxin and amiodarone were given at the same time each day. Blood was drawn every morning, before the administration of the drug in all patients.

Pharmacokinetic studies. These were carried out in six patients (five with ventricular and one with supraventricular tachyarrhythmias) who gave informed consent; they were admitted to the special diagnostic and treatment unit after the initial screen tests revealed normal renal function. On the first day of the study, all six patients were given a 1.0 mg intravenous dose of digoxin over a period of 10 to 20 minutes. Blood samples for digoxin levels were collected before the intravenous dose and at specific times thereafter for 96 hours after the intravenous digoxin infusion. Twenty-four hour urine collections (two aliquots each of 12 hours) were obtained daily for 4 days after the intravenous digoxin administration. Commencing on the fifth day, each patient received 1,600 mg/day of amiodarone for 2 weeks. After this period, each subject received a second intravenous dose (1.0 mg) of digoxin, again over a period of 10 to 20 minutes. Blood and urine samples were obtained in a manner identical to that described for the control period. Serum samples were analyzed to determine the concentrations of digoxin, creatinine and amiodarone; urine was analyzed for digoxin and creatinine.

Analytical methods. Serum and urine concentrations of digoxin were determined by radioimmunoassay (12) using a RIANEN digoxin (iodine-125) RIA kit (New England Nuclear Corp.). Serum levels of amiodarone were determined by a recent high performance liquid chromatographic method (13) standardized in our laboratory (14). Serum and urinary creatinine levels were determined by the Technicon autoanalyser. Creatinine clearances in the absence and presence of amiodarone were calculated using pooled data from the 4 day urine collections.

Data analysis and statistics. Pharmacokinetic variables were calculated by standard conventional techniques (15). For each patient, serum digoxin concentration versus time data were individually fitted to a multiexponential equation by means of a nonlinear regression computer program and SAAM analysis. The renal clearance of digoxin was calculated by dividing the amount of digoxin excreted in the urine over the 4 days after the intravenous dose of the drug by the area under the plasma concentration time curve for the same period.

The data were analyzed by the Student's *t* test for paired variables and mean values are presented with 1 standard deviation.

Results

Digoxin levels after amiodarone (Fig. 1 and 2). In nearly all the 28 patients, substantial increases in serum levels of digoxin were produced after 1 to 3 weeks of amiodarone administration. The serum digoxin levels before and during amiodarone treatment are shown in Figure 1. The mean increase of 104% (from 0.97 ± 0.48 to 1.98 ± 0.84 ng/ml) for the entire group was statistically significant ($p < 0.001$). These changes occurred without a change in the dose of digoxin (mean 0.25 ± 0.05 mg/day); the mean dose of amiodarone was 1,251 ± 335 mg/day administered for a mean of 13.3 ± 5.3 days (range 7 to 21).

The time course of increases in serum digoxin concentration induced by amiodarone concomitantly in five patients who had already been on a constant dose of digoxin alone for 4 weeks is shown in Figure 2. The serum digoxin level increase was parallel with the observed increases in the levels of serum amiodarone, although the changes in the levels of the latter demonstrated considerable variability as indicated by large standard deviations. The increase in the levels of digoxin induced by amiodarone was apparent within 1 to 2 days of concomitant therapy. However, at a constant dose of both drugs, new steady state in the levels of serum digoxin was not attained even after 2 weeks of the combination regimen. The development of side effects or im-

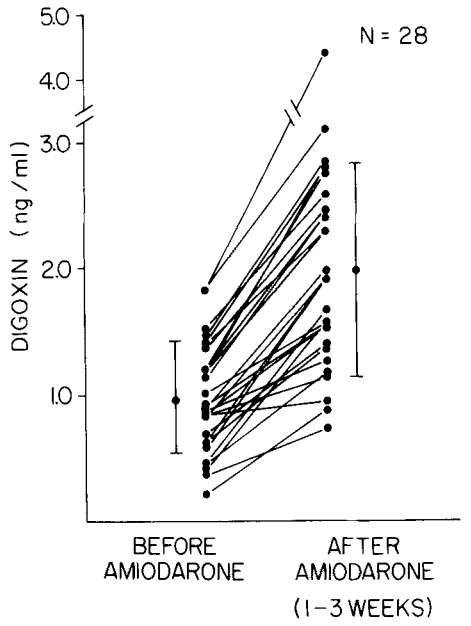


Figure 1. Changes in steady state serum digoxin concentrations induced by the concomitant administration of amiodarone (600 to 1,600 mg/day; mean 1,251 ± 335) for 7 to 21 days (mean 13.3 ± 5.3). Each **closed circle** represents a value from one patient. The **vertical bars** indicate standard deviations from the mean values. Amiodarone increased digoxin levels in all patients.

pending toxicity precluded more protracted observations at a constant dosage regimen of the two drugs.

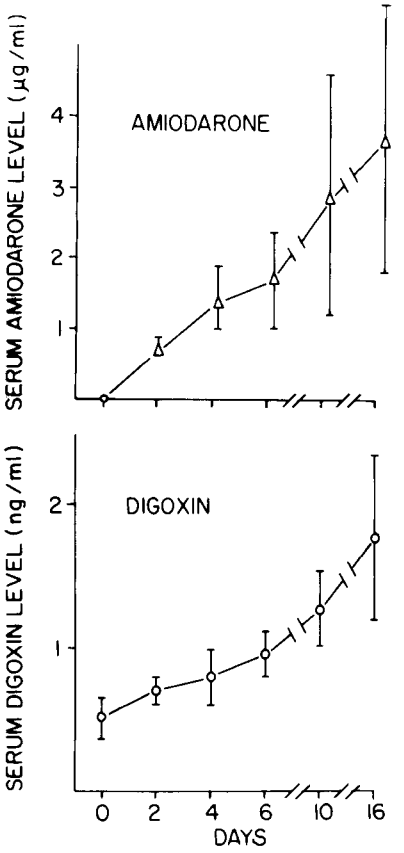
Side effects (Table 1). The side effects observed (Table 1) were closely correlated with the increases of serum digoxin levels into the toxic range (2.67 ± 0.64 ng/ml). Despite the high levels of serum digoxin in patients who developed side effects, digitalis-toxic tachyarrhythmias were not encountered except in one patient who had an episode of ventricular fibrillation at a time when the serum digoxin level was 2.8 ng/ml and potassium was 2.2 mEq/liter. The adverse effects disappeared in all patients within 3 days after discontinuation or reduction of digoxin dose.

Pharmacokinetic variables (Table 2). Amiodarone had no effect on either the serum levels of creatinine or on the creatinine clearances in six patients in whom detailed pharmacokinetic studies were carried out. Table 2 summarizes the pharmacokinetic values derived from the analysis of the serum and urinary concentrations of digoxin. The elimination half-life of digoxin was prolonged by 31% from 49.5 ± 8.8 to 65.0 ± 28.8 hours after amiodarone, but the increase was not statistically significant. There was an increase in the half-life of digoxin in all patients except in Patient 3 whose decreased from 51.0 to 40.7 hours. Values for the volume of central compartment (V_c) and volume of distribution (V_d) after amiodarone were not significantly altered after amiodarone. There was a consistent decrease in digoxin total body clearance after amiodarone administration in all patients. Thus, mean total body clearance decreased significantly (29%, $p < 0.05$) from 2.05 ± 0.76 to 1.46 ± 0.64 ml/min per kg. The renal clearance of digoxin was not affected significantly by amiodarone therapy. The nonrenal clearance, however, showed a significant decrease (33%, $p < 0.05$) from 1.20 ± 0.46 to 0.80 ± 0.30 ml/min per kg. Digoxin concentrations were higher in all six patients when digoxin was given during amiodarone administration as compared with those under control conditions. The mean concentration measured at 30 minutes after digoxin injection increased from 8.6 ± 1.7 to 10.1 ± 1.7 ng/ml ($p < 0.05$).

Discussion

Cause of amiodarone-induced reduced digoxin clearance. These results confirm and extend our own preliminary observations (6) as well as those of others (7–11) that steady state serum digoxin concentrations increase by at

Figure 2. Time course of increase in serum digoxin (**circles**) and serum amiodarone (**triangles**) levels in five patients given fixed doses of digoxin and amiodarone for 16 days (after they had been receiving the same dose of digoxin alone for the previous 4 weeks). The data shown are mean values ± standard deviation. Despite a fixed dose of amiodarone, serum levels continue to increase over the period of observation; during this period, serum digoxin levels are augmented, the initial increment being apparent by day 2.



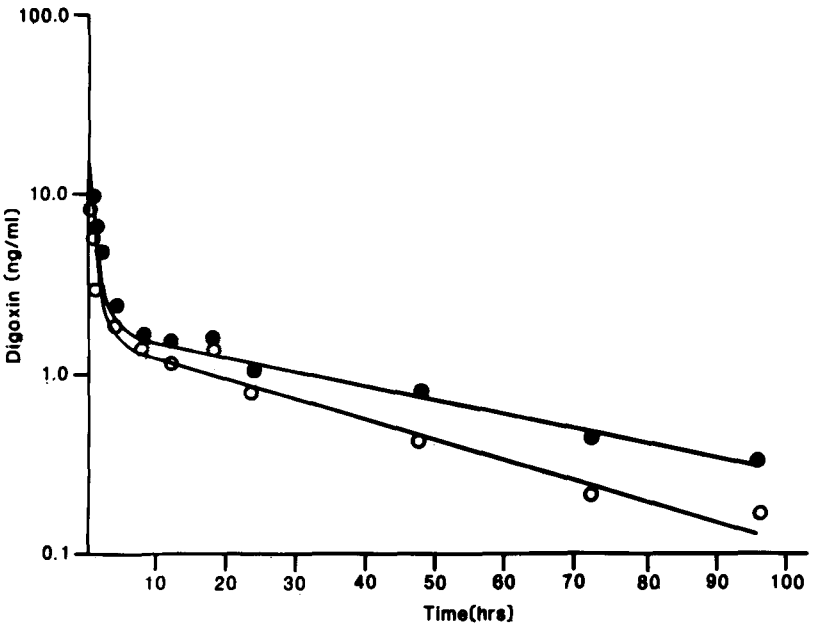


Figure 3. Case 2. Semilogarithmic plot of the serum digoxin concentration as a function of time after the intravenous administration of digoxin before (**open circles**) and during (**closed circles**) amiodarone therapy. The **lines** represent the best nonlinear regression computer fit to the data.

least 100% when therapy with 600 to 1,600 mg of amiodarone is initiated and maintained for 1 week or longer. Furthermore, our pharmacokinetic data show that amiodarone reduces the body clearance of digoxin during concurrent therapy by 29% ($p < 0.05$). If we assume steady state conditions during long-term therapy, this would mean a 29% increase in serum digoxin concentrations. However, the increases in serum digoxin levels after amiodarone administration observed by us and others (6–11) are much greater than those caused by impaired body clearance. Thus, there may be other factors involved in amiodarone-digoxin interaction. The significant (33%) reduction in nonrenal clearance would indicate that the metabolism of digoxin by liver or gut, or both, is modified by amiodarone treatment. Such a reduction in extrarenal clearance has been reported for quinidine-digoxin interaction (16). The renal clearance of digoxin decreased by 22% for the whole group, which was not statistically significant. The creatinine clearance was not affected by amiodarone treatment in all of the six patients, suggesting that glomerular filtration rate was not altered during concurrent therapy. However, it is known that digoxin is eliminated by tubular secretion (17) and the diminution in renal clearance may, in part, be explained by this phenomenon. One other mechanism that may contribute to the elevated serum digoxin levels with amiodarone is the displacement from tissue binding sites (especially myocardium) by amiodarone, similar to that reported for quinidine-digoxin interaction (18,19). This phenomenon may be a direct effect of amiodarone or may be mediated through thyroid hormones, the metabolism of which is altered during long-term amiodarone therapy (20,21). In addition, it is known that the electrophysiologic and pharmacologic effects of amiodarone in the heart are similar to those in hypothyroidism (20).

Table 1. Side Effects Attributable to Digoxin Toxicity During Digoxin-Amiodarone Combination Therapy

Side Effects	No. of Patients	Digoxin Level (ng/ml)
Gastrointestinal (anorexia, vomiting, constipation)	9	2.7 ± 0.48
Central nervous system (weakness, malaise, visual disturbances)	5	2.9 ± 1.1
Cardiac		
Sinus arrest and sinus bradycardia	3	2.2 ± 0.5
Ventricular fibrillation*	1	2.8

*Responded to potassium repletion and temporary digoxin withdrawal; subsequently well controlled on amiodarone therapy, which was initially instituted when quinidine and procainamide had failed to control recurrent ventricular fibrillation or tachycardia, or both.

Clinical implications. Whatever the mechanisms that are finally established for the elevation of the steady state serum digoxin concentrations during amiodarone therapy, the clinical significance of such an interaction deserves emphasis in view of the increasing use of amiodarone in the United States for recalcitrant ventricular tachyarrhythmias in patients with ventricular dysfunction needing glycoside therapy (22–27). We found that increases in serum digoxin concentration (on a fixed dose of digoxin) during the early loading doses of amiodarone led to a high incidence of side effects, mostly of central nervous system or gastrointestinal origin; they disappeared as the serum digoxin decreased with the adjustment of digoxin dosage. In our experience, such

Table 2. Pharmacokinetic Variables for Digoxin Disposition Before and During Amiodarone Administration

Case	Body Weight (kg)	T½(h)		V_c(1/kg)		V_d(1/kg)		Digoxin Clearance (ml/min per kg)					
								Total Body		Renal		Nonrenal	
		C	Amiod	C	Amiod	C	Amiod	C	Amiod	C	Amiod	C	Amiod
1	68	40.8	111.0	0.76	0.64	7.17	8.08	2.03	0.84	0.87	0.28	1.16	0.56
2	99	49.6	50.3	0.84	0.57	8.12	7.79	1.90	1.78	0.61	0.76	1.29	1.02
3	82	51.0	40.7	0.99	0.86	9.87	7.16	2.24	2.04	0.83	0.86	1.41	1.18
4	67	27.0	39.9	0.90	0.90	7.87	7.26	3.37	2.16	1.48	1.31	1.89	0.85
5	87	60.2	62.5	1.11	0.70	8.88	7.03	1.70	1.30	0.76	0.47	0.94	0.83
6	93	57.3	81.3	0.70	0.75	5.36	4.78	1.08	0.63	0.55	0.28	0.53	0.35
Mean		49.5	65.0	0.88	0.74	7.88	7.02	2.05	1.46	0.85	0.66	1.20	0.80
± SD		8.8	28.8	0.15	0.13	1.54	1.17	0.76	0.64	0.33	0.39	0.46	0.30
p Value*		NS		NS		NS		<0.05		NS		<0.05	

*Control versus amiodarone. Amiod = amiodarone; C = control; T½ = elimination half-life; V_c = volume of central compartment; V_d = apparent volume of distribution.

side effects (except for constipation) are rarely encountered in the first month of therapy with amiodarone, even with high doses (27). The high digoxin levels, especially in association with hypokalemia that might result from concomitant diuretic drug therapy in this context and which may have occurred in one of our patients, could lead to the early recurrence of ventricular tachyarrhythmias and might be responsible for the uncommon cases of torsade de pointes attributed to amiodarone (28).

The interaction between digoxin and amiodarone reported herein was based on observations at moderate to high doses of amiodarone given over 1 to 3 weeks. At the end of this period when digoxin doses were generally adjusted, the serum digoxin levels were still increasing at an equal rate with increases in serum levels of amiodarone at a constant dosage of the two compounds. Clearly, one might expect less profound changes at lower doses of amiodarone for a given digoxin regimen. Since loading doses of amiodarone are now commonly employed for variable periods at the start of therapy, increases in serum digoxin may reach toxic levels during this period. Furthermore, it is known that the elimination half-life of amiodarone is exceedingly variable and long (14) ranging between 15 to 65 days. Thus, cumulation of the drug as a function of time even at maintenance doses might still lead to a significant interaction that may become apparent after a lapse of varying durations of combination therapy. For these reasons, regular determination of serum digoxin concentrations with a careful surveillance of the clinical features of toxicity are indicated when digoxin and amiodarone are given as combination therapy. The need for such monitoring is clearly most urgent during the early high dose therapy with amiodarone.

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