DRUG INTERACTIONS INVOLVING DIGITALIS GLYCOSIDES

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INTRODUCTION

Digitalis glycosides are still among the most frequently administered cardiac drugs. Since most patients who take these drugs continue to take them for many years, there is ample opportunity for interactions, some of which are of considerable clinical importance.

The most widely prescribed cardiac glycosides are digoxin, digitoxin and ouabain. Digoxin and digitoxin are most commonly administered orally but may be given parenterally; ouabain must be given intravenously and is usually reserved for emergency situations. The pharmacological effects produced by these drugs involve direct stimulation of myocardial contractility and complex effects on automaticity and conduction of cardiac impulses. Direct myocardial effects are thought to be due to the ability of these drugs to inhibit membrane (Na+, K+) –ATPase, with resultant increases in myocardial cell sodium concentration and in calcium concentration around the contractile element (Smith et al., 1973). Although relatively little is known about the other sites of digitalis action, such as autonomic nuclei in the brain stem, it seems likely that all digitalis glycosides share the capacity to activate specific receptors. Hence, all digitalis glycosides will interact in a similar manner with drugs which alter the pharmacologic sequelae of digitalis receptor activation (pharmacodynamic interactions).

Individual digitalis glycosides, however, have unique pharmacokinetic interactions with other drugs owing to differences in the way that the body handles them. Intestinal absorption of digoxin is incomplete, is highly dependent upon formulation characteristics and probably varies considerably between individuals. Less than 25% is bound to plasma proteins, the apparent volume of distribution is large, it is largely eliminated in the urine as unchanged drug with its elimination rate correlating with measurement of renal function, and it has a plasma half-life of about 35 hours in patients with normal renal function. By contrast, digitoxin is completely absorbed from the intestine, is 97% protein-bound, has a much smaller volume of distribution and is eliminated much more slowly (mainly by hepatic metabolism) with an average plasma half-life of between 7 and 9 days. Pharmacokinetic interactions are far less important with ouabain, since it is only given intravenously and rarely in continuous fashion.

PHARMACOKINETIC INTERACTIONS

Interference with Absorption

Antacids: Concurrent administration of aluminum hydroxide, magnesium hydroxide or magnesium trisilicate liquid antacids will reduce by about 25% the absorption of digoxin given in tablet form (Brown et al., 1976). In vitro studies have demonstrated that magnesium trisilicate has a higher binding affinity for digoxin than aluminum or calcium salts or other salts of magnesium (Thompson, 1973; Khalil, 1974), but mechanisms other than adsorption must apply to the in vivo situation since the extent to which these preparations depress digoxin absorption is so similar. Altered gut motility and (since calcium carbonate tablets do not decrease digoxin absorption) the acid neutralizing capacity of antacids also cannot fully explain the interaction. Brown, Spector and Juhl (1980) postulate that liquid antacids physically coat digoxin tablets and thus interfere with proper dissolution of the tablets in the gut. As one would expect if this postulate were true, antacid tablet formulations do not significantly lower steady state plasma digoxin levels (Vohringer, et al., 1976). For patients that require both digoxin and liquid antacids on a chronic basis, it is probably wise to separate their times of administration by at least 2 hours; tablet antacid formulations may help avoid such inconvenience. Digoxin absorption is less affected when administered in capsules, which have an advantage over tablets when concurrent liquid antacid administration is necessary (Allen et al., 1981).

Kaolin and pectin: Commonly used anti-diarrheal preparations containing kaolin and pectin strongly adsorb digoxin (Binnion, 1973), and a reduction of about 40% in urinary recovery of orally administered digoxin has been demonstrated in normal volunteers given kaolin-pectin concurrently (Brown et al., 1976). Since physical adsorption underlies this interaction, the relative times of drug administration are critical in determining the extent to which digoxin absorption will be impaired. Albert et al. (1978) showed a mean 62% decrease in extent of digoxin absorbed when a concentrated kaolin-pectin suspension was given concurrently with digoxin, a 20% decrease when the kaolin-pectin was given 2 hours before digoxin, and no change at all if the kaolin-pectin was given 2 hours after digoxin. As with liquid antacids, concurrently administered kaolin-pectin causes less reduction in digoxin bioavailability when digoxin capsules are used instead of tablets (Allen et al., 1981). It

is not known whether chronic treatment with kaolin-pectin influences steady-state digoxin concentration, but it seems advisable to separate daily drug administrations by at least 2 hours.

Cholestyramine and colestipol: Although only small changes were noted in earlier studies (Hall et al., 1977; Brown et al., 1978), Brown et al. have convincingly demonstrated that cholestyramine interferes with digoxin absorption; more so when it is given simultaneously with digoxin and at higher dosages (Brown et al., 1979). They noted distinct variations in the response of any given individual to the effect of cholestyramine, presumed the interaction to be due to physical binding of digoxin to cholestyramine, and suggested that twice daily cholestyramine dosing (8 hours before and after digoxin administration) could minimize the interaction.

The effect of cholestyramine on digitoxin handling may be even more significant. Although this may to some extent reflect the greater binding affinity for digitoxin (Caldwell et al., 1970), a more important factor is the greater enterohepatic circulation of digitoxin (Caldwell et al., 1971). By preventing reabsorption, cholestyramine increases the elimination rate and reduces serum concentrations of digitoxin. In a parallel study in groups of 7 subjects, the plasma half-life of digitoxin was 11.5 days in a control group and 6.6 days in the group receiving cholestyramine (Perrier et al., 1977).

The relative effects of cholestyramine and colestipol remain uncertain. Colestipol has a lower binding affinity for digitoxin in aqueous solutions, but it has a higher affinity in duodenal fluid (Bazzano et al., 1972). One study has shown no significant shortening by colestipol of digitoxin plasma half-life (Van Bever et al., 1976), but conflicting results are reported (Bazzano et al., 1971). Payne et al. (1981) report successful enhancement of digoxin elimination when colestipol was given every six hours to digoxin-toxic patients.

Sulphasalazine, neomycin and para-aminosalicyclic acid (PAS): Previous administration of 2 to 6 g sulphasalazine daily for 6 days was demonstrated to reduce absorption of a single orally administered dose of digoxin by about 20% (Juhl et al., 1976). Large doses of neomycin inhibit both the rate and extent of digoxin absorption when concurrently administered, and a 28% reduction in steady-state plasma digoxin levels was demonstrated in 5 subjects who took the two drugs together for nine days (Lindenbaum et al., 1976). PAS also depresses digoxin absorption, and it is interesting that this effect is accompanied by a sig-

nificant reduction in D-xylose absorption (Brown et a., 1979). It is thought that alteration of gut wall absorptive processes (perhaps structural as well as functional changes) by these antimicrobials explains their interference with glycoside absorption. Cytotoxic agents used in cancer chemotherapy may reduce digoxin absorption by a similar mechanism (Kuhlman et al., 1981).

Other Drugs. Other drugs which may inhibit digoxin absorption under certain circumstances include activated charcoal (Hartel et al., 1973) and phenytoin (Lahiri et al., 1974). Fiber, whether it be from dietary sources or from drugs such as psyllium hydrophilic mucilloid, can also decrease digoxin absorption (Brown et al., 1980; Brown et al., 1979). In general, drugs which inhibit digoxin absorption may be responsible for unanticipated loss of therapeutic effect. Conversely, patients who are digitalized while taking one of the above drugs may develop evidence of toxicity when concurrent drug treatment is stopped.

About 10% of patients given digoxin convert the drug (presumably by action of gastrointestinal bacteria)to cardioinactive digoxin reduction products. Such patients, when given antibiotics that change enteric flora, may experience marked rises in serum digoxin concentration (Lindenbaum et al., 1981).

Altered Bowel Motility

Metoclopramide and propantheline: Manninen et al. (1973) showed a reduction of steady-state digoxin levels by metoclopramide and an increase in levels with propantheline. While this supports the inviting concept of digoxin absorption varying inversely with gastrointestinal mobility, it is important to note that digoxin tablets of low dissolution rate were used in this study and that formulations from which digoxin is released relatively quickly have replaced such tablets in most parts of the world. With better quality tablets it has been demonstrated that metoclopramide and propantheline cause no clinically important interaction (Johnson et al., 1978).

Altered Protein Binding

Little digoxin is bound to plasma proteins, so altered binding is not an important mechanism of interaction. Digitoxin, on the other hand, is extensively bound to serum albumin, but the binding affinity is strong

and displacement is not readily obtained. High concentrations of phenylbutazone, warfarin, clofibrate, sulfonamides and tolbutamide are capable of displacing digitoxin from albumin, but this seems to be of no clinical significance since therapeutic concentrations of these agents showed little effect (Solomon et al., 1971).

Heparin given during hemodialysis releases large quantities of free fatty acids into the circulation. The clinical relevance of the resultant alteration of digitoxin binding to albumin has not been determined (Storstein, 1977).

Altered Metabolism

Since it is more extensively metabolized than is digoxin, digitoxin is more likely to interact with agents which alter drug metabolizing enzyme systems. Both phenylbutazone and phenytoin have been demonstrated to decrease steady-state digitoxin levels, presumably via hepatic enzyme induction (Solomon et al., 1971). Phenobarbital, in doses of 180 to 240 mg/day for 8 to 12 weeks, significantly decreases plasma half-life and steady-state concentration of digitoxin and enhances the urinary excretion of digoxin and other digitoxin metabolites (Solomon et al., 1972). Rifampin, another enzyme inducer, can also substantially reduce plasma digitoxin levels by increasing rate of elimination (Peters et al., 1974); a similar interaction has been postulated for rifampin and digoxin (Novi et al., 1980). Because of rifampin's ability to dramatically decrease the elimination half-life of quinidine (Ahmad et al., 1979; Twum-Barima et al., 1981), patients stabilized on digoxin and quinidine may have an abrupt reduction of serum quinidine and (perhaps secondarily) digoxin concentrations when rifampin is added to the regimen. Cimetidine may potentiate the digitoxin-quinidine interaction (see below), raising serum levels of both drugs by an unclear mechanism (Polish et al., 1981). Finally, spironolactone may enhance the rate of metabolic degradation and reduce the elimination half-life of digitoxin (Wirth et al., 1976).

Since drugs which alter enzyme systems have such variable effects between individual patients, general suggestions regarding changes in glycoside dosages are not possible. Careful clinical observation and plasma glycoside levels are indicated in patients beginning or ending a course of treatment with any of the above drugs.

Altered Urinary Excretion

Drugs which alter glomerular filtration rate should be expected to cause a similar change in the renal clearance of digoxin. Changes in urinary volume seem unimportant; potent "loop" diuretics such as furosemide do not enhance urinary elimination of digitalis glycosides (Brown et al., 1976; Tilstone et al., 1977).

Altered Distribution and Clearance

Quinidine: The digoxin-quinidine interaction, consisting of significant and sustained elevations of the serum digoxin concentrations (SDC) when quinidine is co-administered, was first described in the late 1970's (Doering, 1979; Leahey et al., 1978; Ejvinsson, 1978). Since each drug by itself can cause toxic symptoms, the interaction was obscured clinically for many years until the widespread use of serum digoxin levels forced its recognition (Doherty, 1982; Bigger et al., 1982; Bigger, 1982). A flood of investigations followed in an attempt to elucidate the mechanisms of the interaction and its clinical importance.

Several retrospective (Doering, 1979; Leahey et al., 1978; Ejvinsson, 1978) and prospective (Pederson et al., 1980; Leahey et al., 1980; Mungall et al., 1980; Dahlqvist et al., 1980) studies have confirmed an interaction incidence of 90% or more in patients exposed to the drug combination. The magnitude of the SDC increase is variable, but most patients exhibit a two or three-fold rise (Coering, 1979; Leahey et al., 1978; Ejvinsson, 1978; Friedman et al., 1982; Leahey et al., 1981; Schenck-Gustafsson et al., 1981). The facts that some patients will show no elevation of SDC, and that in others the magnitude of the increase is variable, may relate to the quinidine dosage used. While the data are conflicting (the association between quinidine serum levels and magnitude of SDC rise was strong in some studies (Manolas et al., 1980; Powell et al., 1980) and unapparent in others (Dahlqvist et al., 1980; Friedman et al., 1982; Schenck-Gustafsson et al., 1981)), Bussey (1982) attempts reconciliation by suggesting that the magnitude of SDC increase correlates with serum quinidine concentration at low levels but plateaus as the latter approaches 2.3 μg/ml.

The SDC will usually rise significantly within 24 hours of starting quinidine and this initial elevation is due primarily to alteration in the volume of distribution of digoxin (see below). How long the SDC con-

tinues to rise seems to depend on whether or not a quinidine loading dose was used and the extent to which the elimination half-life and tissue distribution of digoxin are altered (see below). In some studies, new steady-state digoxin levels were achieved within 3-5 days after starting quinidine (Doering, 1979; Mungall et al., 1980; Dahlqvist et al., 1980; Leahey et al., 1981). However, others have shown SDC to be still rising at 7 (Fenster et al., 1980) and 9 days (Pedersen et al., 1980), although the rate of rise was not as rapid as it had been in the first five days. An approximation of steady-state SDC may be attained within a few days if a quinidine loading dose is used, but the time to true steady-state level will vary with digoxin half-life of elimination and may take 14 or more days. Renal dysfunction would presumably lengthen the time course of the interaction. There is no evidence that SDC eventually falls if quinidine therapy is sustained.

A decrease in apparent volume of distribution (Vd) of digoxin and a decreased rate of digoxin elimination are the accepted mechanisms by which concurrently administered quinidine raises SDC. As a result, quinidine decreases total body clearance (TBC) of digoxin, the extent variably reported as ranging from 36 to 64% (Leahey et al., 1981; Schenck-Gustafsson et al., 1981; Steiness et al., 1980; Hager et al., 1981; Ochs et al., 1981; Hager et al., 1979). The SDC rise is not artifactual, several groups having shown non-interference of quinidine with the radioimmunoassay of digoxin (Ejvinsson, 1978; Hager et al., 1979). The possibility of quinidine enhancing digoxin absorption has also been examined (Doering, 1979; Hager et al., 1981; Chen et al., 1980) and found insignificant.

The first evidence for a quinidine-induced reduction in Vd of digoxin was provided by Leahey et al. (1978), who showed that SDC continued rising for 36 hours after quinidine was given and digoxin dosing had ceased. Dahlqvist et al. (1980) confirmed this and other studies have documented a 30-40% decrease in apparent Vd when quinidine was co-administered (Schenck-Gustafsson et al., 1981; Hager et al., 1981; Hager et al., 1979). Some studies did not find a significant change in digoxin Vd (Steiness et al., 1980; Ochs et al., 1981), but Leahey et al. (1981) point out that the magnitude of Vd decrease may be dependent on the attainment of adequate quinidine levels (8 of their patients with quinidine levels > 1.9 μg/ml had a mean decrease in Vd of 30% while the Vd decreased only 7% in 7 patients with quinidine concentrations > 1.9).

It seems well established that quinidine decreases the renal clearance of digoxin (Leahey et al., 1978; Pedersen et al., 1980; Mungall et al., 1980; Leahey et al., 1981; Schenck-Gustafsson et al., 1981; Steiner et al., 1980; Ochs et al., 1981; Hager et al., 1979; Leahey et al., 1979; Hooymans et al., 1978). Since creatinine clearance remained stable in many of the patients studied, decreased renal clearance seems to be due primarily to an inhibition of renal tubular secretion. Studies in animals provide support for this hypothesis (Gibson et al., 1980; Kaplinsky et al., 1980). The degree to which renal clearance is decreased is probably about 30 to 50%, and may be dependent on serum quinidine concentration. Leahey et al. (1981) showed that mean renal clearance decreased by 32% in patients on 800 mg/day of quinidine and by 54% when the quinidine dose was doubled. The proportion of digoxin excreted by the kidneys that is due to tubular secretion is about 50% under normal circumstances (Steiness, 1974), but may increase (and thus be subject to more inhibition by quinidine) in patients with congestive heart failure receiving vasodilators (Cogan et al., 1981).

The non-renal clearance of digoxin, vaguely understood to consist of hepatic metabolism plus biliary and intestinal secretion, has also been consistently found to decrease when quinidine is co-administered (Leahey et al., 1981; Schenck-Gustafsson et al., 1981; Steineess et al., 1980; Ochs et al., 1981; Hager et al., 1979). This mechanism may explain the quinidine-induced elevation of SDC seen in patients with renal failure (Doering et al., 1982; Hirschberg et al., 1981). The degree to which non-renal clearance is decreased is variable and does not appear to correlate with differences in serum quinidine concentration.

It should be stressed that increased steady-state plasma digoxin concentrations might not be associated with increased risk of toxicity or enhanced therapeutic effect as the usual relationship between SDC level and effect may be altered. Attempts to clarify this issue have looked at changes in digoxin tissue levels, changes in receptor site binding, non-invasive tests of cardiac function and clinical observations.

Animal data regarding the displacement of tissue digoxin by quinidine are conflicting, although a decrease in myocardial to serum concentration ratio and an increase in brain stem concentration of digoxin have been suggested (Bigger, 1982). Schenck-Gustaffson et al.(1981) document a decrease in skeletal muscle to serum digoxin concentration ratio in cardiac patients on maintenance quinidine, but they did not look at cardiac muscle. Bussey (1982), however, points out that the

issue of myocardial tissue level alterations may be relatively insignificant. He cites the work of Coltart et al. (1972) showing no correlation between serum and left ventricular tissue concentrations in patients on maintenance digoxin, and of Weintraub and Lasagna (1973) showing that postmorten SDC correlated well with toxicity while left ventricular concentrations and serum-to-tissue ratios did not.

Studies of the effect of quinidine on binding of digoxin to (Na+, K+) –ATPase preparations have attempted to infer alterations in digoxin activity at tissue "receptor sites". It is apparent that the pharmacologic activity of digoxin could be reduced if specific binding to such receptors was inhibited regardless of total tissue or plasma concentrations of the drug. Although Straub et al. (1978) showed a reduction in ouabain binding to beef heart membrane ATPase in the presence of quinidine, two subsequent studies (Doering, 1979; Doering et al., 1981) have failed to show a similar effect. At present, it seems unlikely that quinidine interferes with digoxin binding at receptor sites. Hence increased SDC should be associated with increased (Na+, K+) –ATPase inhibition and, by inference, increased myocardial contractility.

The opposite conclusion, namely that myocardial performance may worsen despite the increased SDC caused by quinidine, is suggested by two studies using systolic time intervals as indices of cardiac performance (Steiness et al., 1980; Hirsh et al., 1980). A more recent study, however, also evaluating systolic time intervals but with perhaps less problems related to study design, concludes that the quinidine-induced SDC rise does correlate with increased cardiac effects (Belz et al., 1982). A recent study in dogs concludes that the electrophysiological changes induced by the combination of digoxin plus quinidine equalled the sum of changes induced by each drug alone (Gessman et al., 1983). Given the problems inherent in evaluating the combined effects of two drugs with at least partially opposing inotropic and electrophysiological properties, and the imprecise relationship of systolic time intervals to true ventricular performance, it must be concluded that the impact of quinidine upon the main pharmacological effects of digoxin remains uncertain.

In general, clinical studies provide some support for the hypothesis that SDC increase is associated with increased effect. Two such studies (Dahlqvist et al., 1980; Schenck-Gustafsson et al., 1981) have shown that the extent of the drug interaction had no effect on the successful conversion of atrial fibrillation to sinus rhythm. There have been re-

ports of exacerbated congestive heart failure when SDC fell following quinidine discontinuation (Moench, 1980; Leahey et al., 1979). Doering (1979) noted that cardiac failure did not develop during long-term observation of 15 consecutive patients who had their digoxin doses halved when quinidine was added to their regimen.

Support for an unchanged relationship between SDC and digoxin effect is stronger when clinical reports of enhanced digoxin toxicity are examined. There are many reports of signs and symptoms of digoxin toxicity appearing when quinidine was added to the regimen (Leahey et al., 1978; Ejvinsson, 1978; Pedersen et al., 1980; Leahey et al., 1980; Dahlqvist et al., 1980; Leahey et al., 1981; Leahey et al., 1979). Doherty (1982), in his review of 14 studies of the interaction (190 patients), calculated a 27% incidence of gastrointestinal and cardiac adverse reactions attributable to digoxin toxicity. The true incidence may be even higher since some of the studies were prospective and used relatively small dosages of digoxin. Cody (1980), in a retrospective comparison of 7,573 hospitalized patients receiving digoxin and 315 patients on both quinidine and digoxin, found that the latter group had gastrointestinal and cardiac symptoms compatible with digoxin toxicity 2.7 times more frequently. The adverse reaction rate difference was maximal two to ten days following the addition of quinidine to digoxin therapy. It seems probable that the quinidine induced increase in SDC correlates with an increased risk of digoxin toxicity. Since some aspects of digoxin toxicity may be centrally mediated however, an increased risk of toxicity does not necessarily imply enhanced inotropic efficacy.

Given the frequency and potential risks of the digoxin-quinidine interaction, what recommendations can be made regarding clinical management? The practice of halving the digoxin dose immediately upon starting quinidine, with adjustments based on clinical course and SDC seven to ten days later, has gained wide acceptance. If a loading dose of quinidine is used, it may be wise to omit digoxin administration on that day altogether (Bussey, 1982). The possibility of avoiding concomitant use of the two drugs by using afterload reducers or alternative antiarrhythmics (Manolas et al., 1980) should not be overlooked.

An early report by Ochs et al. (1980) concluded that there was no interaction between quinidine and digitoxin, but the design of that study has been roundly criticized (Melvin et al., 1981; Rollins et al., 1981; Fenster et al., 1981). Other workers have documented that digitoxin levels are raised when quinidine is co-administered (Dahlqvist

et al., 1980; Garty et al. 1981; Fenster et al., 1980). Studying the effect on digitoxin single-dose pharmacokinetics, Fenster et al. (1980) found a 29% decrease in total body clearance (due mostly to significantly decreased renal clearance) and a 49% increase in elimination half-life. In a similar study, Garty et al. (1981) found a 63% reduction in total body clearance of digitoxin and a 2.5-fold increase in elimination half-life without change in volume of distribution. The higher serum quinidine concentrations attained in the latter study may explain the greater magnitudes of observed changes. The interaction between quinidine and digitoxin may occur more slowly, but the eventual results seem approximately similar to those in the quinidine-digoxin interaction.

As is the case with digoxin (Mungall et al., 1980; Gibson et al. 1980) digitoxin probably alters quinidine pharmacokinetics and tends to raise serum quinidine concentrations (Garty et al., 1981). The clinical significance of this aspect of the interaction is unclear.

Quinidine-related drugs. Quinine, an optical isomer of quinidine, was found by Wandell et al. (1980) to increase digoxin elimination half-life by 32% via a decrease in non-renal clearance of 55% and a decreased total body clearance of 26%; no change in distribution volume or renal clearance was noted. Doering (1981) refutes these findings, reporting no significant quinine-induced SDC increase in a relatively uncontrolled study. Hydroxychloroquine, a semisynthetic quinine derivative, probably raises SDC (Leden, 1981).

Verapamil: Doering (1979) initially reported no interaction between verapamil and digoxin, but that conclusion may have been related to using low doses of verapamil (Klein et al., 1980). Subsequent studies have documented a significant rise in SDC when the two drugs are coadministered (Klein et al., 1982; Pedersen et al., 1982; Pedersen et al., 1981; Belz et al., 1981). Studying 49 patients with chronic atrial fibrillation on stable doses of digoxin, Klein et al. (1982) reported that verapamil induced a mean SDC increase of 72%, noted that the degree of SDC increase was dependent on the verapamil dosage, and showed that the effect developed gradually. They ruled out artifactual laboratory error as the explanation for their results and noted that renal digoxin clearance decreased significantly in three normal and six cardiac patients who showed elevation of SDC.

In a single-dose crossover study using eight normal volunteers, Pedersen et al. (1981) showed 1) no change in glomerular filtration rate;

2) a decrease in apparent central distribution volume of 23%; 3) mean decreases in non-renal digoxin clearance of 60%, in renal clearance of 20% and in total body clearance of 35% and 4) an increase in biologic half-life of approximately 20%. A subsequent study by the same group is of interest because it suggests that some verapamil-induced changes in digoxin handling are not persistent over time (Pedersen et al., 1982). In this longitudinal study of seven volunteers on constant doses of both drugs the SDC increased by about 60% in five days but gradually decreased to 30% above control by six weeks; the decrease in renal clearance seen at one week was gone by six weeks but the extrarenal interaction seemed to persist. The implication that there is a long term alteration of digoxin metabolism by verapamil needs further study.

Klein noted evidence of digoxin toxicity in seven of his 49 patients. Until more is known regarding the details of this interaction, it seems advisable to reduce digoxin dosage when adding verapamil to a patient's regimen and to follow serum levels and clinical parameters carefully over a six to eight week period.

Nifedipine: Belz et al. (1981a; 1981b) have reported that SDC increased 40 to 45% when nifedipine 30 mg/day was coadministered, and noted a decrease in renal clearance. Schwartz et al. (1982) dispute that SDC is elevated by nifedipine on the basis of their relatively uncontrolled study, but a better designed study by Pedersen et al. (1982) also tends to cast doubt on the existence of any important interaction. Studying single dose digoxin kinetics in eight healthy volunteers, they found that nifedipine produced insignificant changes in digoxin distribution volume or elimination and biologic half-life. The reasons for these conflicting findings are not apparent and further study is needed.

Other Antiarrhythmics; Amiodarone at a dose of 200 mg twice a day was reported not to alter SDC (Achilli et al., 1981). Moysey et al., (1981) however, gave amiodarone at a dose of 200 mg three times a day and noted an average SDC increase of 69% over seven days with four of their seven patients developing evidence of digoxin toxicity. Marcus and Fenster (1983) report preliminary observations confirming the interaction and estimate that SDC may double when amiodarone is coadministered. Details as to the mechanisms involved await further study. Procainamide, disopyrasmide and mexiletine appear not to interact significantly with digoxin (Leahey et al., 1980; Manolas et al., 1980).

Spironolactone, Triamterene and Amiloride; Renal tubular secretion

of digoxin can apparently be inhibited by spironolactone (Steiness 1974). In four patients and four healthy subjects who received single intravenous injections of digoxin, 100 mg spironolactone twice daily for five days was associated with increased SDC and with reductions in digoxin renal clearance and volume of distribution (Waldorff et al., 1978). The degree to which plasma digoxin is increased seems highly variable.

It is known that spironolactone or its metabolites may cross-react with the digoxin binding antibody that is used in some commercially available digoxin radioimmunoassay kits and that false apparent elevations of SDC may be produced (Lichey et al., 1977). It appears that digoxin assays using sheep antibodies are less likely to be affected than are assays using rabbit antibodies, but identification of a general type of assay which will definitely not be affected is not yet possible (Horn, 1982). Although the magnitude of falsely elevated SDC is usually small, it is difficult to predict. The cross reactivity of spironolactone with digoxin should be determined in each individual laboratory by assaying plasma from subjects taking spironolactone but not digitalis.

Studies of the influence of spironolactone on digitoxin have been conflicting, with both increases and decreases in digitoxin half-life being reported (Wirth et al., 1976; Carruthers et al., 1979).

Amiloride apparently increases tubular secretion of digoxin and decreases its non-renal clearance with a net result of slightly decreased total body clearance and slightly increased SDC (Waldorff et al., 1981). The opposite effects of spironolactone and amiloride on digoxin tubular secretion may be related to the fact that spironolactone decreases, and amiloride increases, tubular cell potassium. Hypokalemia has been reported to reduce digoxin tubular secretion in patients with diuretic-induced potassium deficiency (Steiner, 1978).

It is claimed that triamterene may decrease renal tubular secretion of digoxin (Pedersen et al., 1980; Steiness, 1974), but supporting data were not presented.

Vasodilators; Cogan et al. (1981) report that the total renal clearance of digoxin increased by about 50% when vasodilators were administered to patients with congestive heart failure. They used short term urine collections and single blood samples to calculate clearance in eight patients before and after intravenous administration of hydralazine and nitroprusside. No change in glomerular filtration rate was noted, so an increase in tubular secretory clearance may result from an increase in renal blood flow.

PHARMACODYNAMIC INTERACTIONS

In this group of interactions, altered pharmacological effects do not result from changes in plasma drug concentrations. While it is possible that an interacting drug may alter the affinity of a digitalis glycoside for its specific tissue membrane binding site, interference with the pharmacological sequelae of binding to receptors is probably more common. Drugs interacting by this latter mechanism will presumably do so with any of the digitalis glycosides.

Drugs Inducing Hypokalemia

It is possible that drug-induced hypokalemia enhances the cardiac effects of digitalis glycosides, although conflicting evidence has been reported. Lower doses of digitalis glycosides were needed to induce arrhythmias when potassium depletion was produced by desoxycorticosterone acetate in dogs (Zeeman et al., 1954), by glucose and insulin infusions in dogs (Hall et al., 1977), and by a combination of a low potassium diet and daily furosemide in dogs (Gelbert et al., 1976). By contrast, Binnion (1975) found no increase in digoxin sensitivity in dogs when either acute or chronic hypokalemia was induced.

It appears that the risk of increased sensitivity to digitalis may relate to the rate at which serum potassium falls. The relative importance of reduction in serum potassium compared to total body potassium is uncertain, but a proportionally greater reduction in extracellular potassium is usual (Wilkinson et al., 1975) and the resulting gradient across the myocardial cell membrane probably enhances automaticity and depresses atrioventricular conduction. The mechanism of increased myocardial sensitivity remains controversial, with increased myocardial digoxin uptake during hypokalemia being demonstrated by Hall et al.,(1977) but not by Marcus et al.,(1971). The effect of hypokalemia on renal tubular secretion of digoxin has been discussed above.

Hypokalemia must be severe before it induces arrhythmias in the absence of digitalis (Strauss et al., 1953; Curry et al., 1976), but one can infer from data such as that from Steiness and Olesen (1976) that the arrhythmogenic threshold is lowered when digitalis therapy and moderate hypokalemia coexist.

The risk of digitalis cardiotoxicity must, then, be considered greater in patients receiving thiazides, furosemide, bumetanide, ethacrynic acid and chlorthalidone, all of which can produce marked reductions in

serum potassium. Mineralocorticoids, amphotericin, carbenoxolone and lithium may have similar effects. Although many clinicians do not think it necessary to routinely correct moderate hypokalemia in patients receiving such drugs chronically, it would appear imperative to do so in those who are concurrently taking digitalis glycosides.

Drug Inducing Hyperkalemia

There is good experimental evidence that hyperkalemia inhibits the inotropic response to digitalis (Goldman et al., 1972; Lee et al., 1977), probably by potassium competing for specific myocardial binding sites (Marcus et al., 1969; Goldman et al., 1975). This mechanism may contribute to the inhibition of digoxin-induced inotropy and reversal of digoxin electrocardiographic effects reported for amiloride (Horn, 1982; Waldorff et al., 1981). Supplemental potassium salts (and possibly triamterene) may similarly reduce the beneficial effects of digitalis on myocardial contractility.

Spironolactone may also alter the pharmacologic response to digoxin but the exact nature of the alteration remains unclear. Horn (1982) reviews a body of conflicting literature that includes reports of canrenoate (which is rapidly converted to canrenone, a spironolactone metabolite) both inhibiting and enhancing the effects of digitalis on the heart. A recent report evaluating systolic time intervals during spironolactone treatment of digitalized and non-digitalized patients with ischemic heart disease suggests a spironolactone-induced negative inotropic effect (Waldorff et al., 1982). Further study of the nature of the spironolactone-digitalis pharmacodynamic interaction and the mechanisms underlying it are clearly needed.

Calcium Salts

Although serum calcium levels exceeding 15 mEq/l have been associated with increased risk of digoxin toxicity in dogs (Nola et al., 1970), it seems unlikely that administration of calcium salts under normal clinical conditions has any important effects upon digitalis therapy.

Drugs Altering Autonomic Nervous System Activity

Many of the cardiac effects of digitalis are mediated through vagal activity, the effects of which are physiologically opposed by the sympa-

thetic nervous system. High doses of reserpine, which depletes the heart of catecholamines, may increase the susceptibility of the heart to the vagal effects of digitalis causing bradycardia or impaired atrioventricular conduction (Lown et al., 1961). Other catecholamine depleting drugs, such as guanethidine or bretylium, may have similar effects.

Similarly, beta-adrenergic receptor blocking agents reduce physiologic antagonism to the vagal effects of digitalis on the heart. The combined effects of digitalis and beta-blockers can be used to advantage in certain situations. Beta-blockers can allow the use of smaller digoxin doses to control the ventricular rate in patients with atrial fibrillation (Stock, 1966), and digitalis can be used to improve ventricular performance when beta-blockers are depressing cardiac function (Crawford et al., 1975). The dangers, however, of combined digitalis and beta-blocker therapy must always be kept in mind. Beta-blocker potentiation of digitalis-induced sinus node dysfunction or atrioventricular nodal conduction abnormalities can result in severe adverse effects on the conduction of cardiac impulses (potentially producing severe sinus bradycardia, sinus arrest, sinoatrial block or any degree of atrioventricular block).

Release of myocardial catecholamines may be involved in the genesis of the ventricular arrhythmias seen in digitalis toxicity (Becker et al., 1962; Erlij et al., 1964; Raines et al., 1968). Parenterally administered reserpine can precipitate ventricular arrhythmias in digitalized patients, presumably by causing sudden release of catecholamines (Lown et al., 1961). A similar effect to endogenous norepinephrine may be seen when beta-adrenergic stimulants are given (Becker et al., 1962), suggesting that digitalis should be given cautiously to patients receiving sympathomimetic bronchodilators. Concurrent treatment with beta blocking agents reduces the risks of digitalis-induced ventricular arrhythmias (Vaughan Williams et al., 1963; Gibson et al., 1969; Mason et al., 1971), but the risks of using beta-blockers to treat digitalis cardiotoxicity seem to outweigh the benefits (Schamroth, 1966; Stephen, 1966; Watt, 1968).

Drugs Interacting Through Other Mechanisms

Drugs which suppress cardiac arrhythmias generally reduce the risk of digitalis cardiotoxicity. In addition to the drugs usually used to treat digitalis toxicity, lidocaine and phenytoin, the anesthetic agent halo-

thane also inhibits digitalis-induced arrhythmias (Morrow et al., 1970). Phenytoin is often advocated for the treatment of digitalis-toxic rhythms because it does not reduce the inotropic effect of digitalis (Helfant et al., 1967) and it does not depress atrioventricular conduction.

Succinylcholine has been reported to induce ventricular irritability in digitalized patients (Dowdy et al., 1963). The sudden release of catecholamines, associated hypoxia or sudden shifts of potassium from inside muscle cells constitute a possible underlying mechanism.

Digitalis glycosides are useful in treating (and may be useful in reducing the risk of) cardiac failure in patients taking doxurubicin or other anthracyclines for the treatment of cancer. Digoxin has been reported to reduce the myocardial uptake of doxorubicin in paced, isolated perfused cat hearts (Somberg et al., 1978).

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