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LA THÈSE A ÉTÉ
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A Study to Determine the
Effect of Disopyramide on
The Serum Digoxin Concentration

A Thesis Presented to
The School of Graduate Studies
of
The University of Ottawa
by Michael Gerard Tierney, B.Sc. Phm.

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I. Introduction

A drug interaction has been defined as the sequelae attending the simultaneous use of two or more drugs.¹ An interaction can result in enhanced or diminished drug effect and may be therapeutically advantageous or harmful.

Despite the large number of drug interactions reported in the medical literature, many are poorly substantiated and/or not well studied. Consequently, prescribers may be unsure of the clinical significance of many drug interactions.

Previous work^{2,3,4} has indicated that the incidence of drug - drug interactions is probably quite low and yet it is recognized that those drug interactions which do occur can pose a serious threat to a patient's health. When a clinical study of a drug interaction is considered, the following aspects deserve attention:

a) drug interactions can only be accurately assessed for drugs whose pharmacological effects can be clinically measured and/or when drug concentrations in the blood or plasma are measurable and reflect clinical efficacy and toxicity.

- b) drugs with a narrow therapeutic index deserve primary consideration since small changes in their activity will either diminish their efficacy or enhance their toxicity.
- c) new therapeutic agents which have not born the test of years of clinical experience may be more likely to demonstrate new and unsuspected drug interactions.

Digoxin is a drug whose narrow therapeutic index is well recognized. The incidence of digitalis toxicity in clinical practice is reported to range from eight to 30% with death due to cardiac toxicity occurring in three to 21% of intoxicated patients.⁵ Due to the dangers of alterations in digoxin's therapeutic efficacy or toxicity, it is important that drugs which are commonly co-administered with digoxin be studied to assess their potential to interact with digoxin.

II. Literature Review

a) Digoxin

The digitalis glycosides are a group of drugs that have been used in the treatment of cardiac disorders for several centuries.⁶ Of the available glycosides, digoxin is presently the most widely used as a therapeutic agent, and this thesis will deal primarily with digoxin.

The structural formula of digoxin is shown in Figure 1.

Chemically, digoxin occurs in crystal form or as a white powder. It is almost insoluble in water, dehydrated alcohol and ether.⁷

i) Pharmacology

With respect to the basic pharmacological actions of digoxin and other digitalis glycosides, perhaps the most notable is the positive inotropic effect. The precise mechanism, at the cellular level, of this effect is not well understood. Mechanisms which have been excluded are augmented contractility via catecholamine release, increased catecholamine sensitivity and any effect on the contractile proteins.⁵ Much work has been done on the effect of

digitalis on transmembrane ion fluxes and on the sarcolemmal enzyme, sodium, potassium adenosine triphosphatase ($\text{Na}^+, \text{K}^+ \text{-ATPase}$). Associated with inhibition of $\text{Na}^+, \text{K}^+ \text{-ATPase}$ is an increase in the sodium concentration and a decrease in potassium concentration within the cell. As well, digitalis induced inotropy is associated with an increase in the intracellular concentration of calcium which is proposed to mediate the positive inotropic effect.⁸ The most widely accepted mechanism is that the digitalis induced inhibition of $\text{Na}^+, \text{K}^+ \text{-ATPase}$ is the initial step in a cascade of sequences that ultimately leads to an increase in intracellular calcium and thus an inotropic response.^{5, 9, 10} Smith and Haber⁵ have summarized evidence in support of this theory:

- i) $\text{Na}^+, \text{K}^+ \text{-ATPase}$ is inhibited by cardioactive but not by inactive digitalis glycosides.
- ii) Interspecies cardiac sensitivity to the digitalis glycosides parallels the ability of the glycosides to inhibit $\text{Na}^+, \text{K}^+ \text{-ATPase}$ in that species.
- iii) Interventions (eg. hypothermia, decreased pH, increased extracellular potassium concentration) which reduce the inotropic effect of digitalis also reduce the ability of digitalis to inhibit $\text{Na}^+, \text{K}^+ \text{-ATPase}$.
- iv) A chemically distinct group of compounds, the erythrophilum alkaloids, are capable of producing both an inotropic

response and inhibition of Na^+ , K^+ -ATPase.

However, not all investigators agree with the link between Na^+ , K^+ -ATPase inhibition and the positive inotropic effect of digoxin. Okita¹¹ has reviewed several of his experiments in which he has been able to dissociate these two effects of digitalis. He proposes that there are two digitalis receptors on the sarcolemmal membrane-one which is associated with the positive inotropic effect and has weak binding affinities and rapid association/dissociation kinetics and another which mediates the inhibition of Na^+ , K^+ -ATPase which has stronger binding affinities and slower association/dissociation kinetics.

Electrophysiologically, digitalis exerts a number of effects both via a direct effect and also by an enhancement of vagal tone.^{5,8} In certain cases, the net effect will be dependent on pre-existing vagal tone. Within the atria, digitalis causes a direct decrease in the conduction velocity and an increase in the refractory period but indirectly, via the vagomimetic effect, causes an increase in conduction velocity and a decrease in the refractory period. In the atrioventricular node, the direct and indirect effects of digitalis act in the same direction to cause a decrease in conduction velocity and an increase in the refractory period.

The direct effect of digitalis causes an enhancement of automaticity in the His-Purkinje system at doses larger than those required for both the inotropic effect and for the effect on the atrioventricular node.

Another pharmacological effect of digitalis is one of vasoconstriction in both arterial and venous beds.^{5,8} In man, the degree of this effect will depend on the basal hemodynamic status. In a subject with congestive heart failure, digitalis may actually produce vasodilation secondary to a withdrawal of excessive sympathetic tone. The other extreme is the healthy subject in whom a digitalis induced vasoconstriction can increase afterload and thus paradoxically negate any positive inotropic effect.

ii) Pharmacokinetics

The pharmacokinetics of digoxin have been well studied to date and the information gained has been used in an attempt to improve the understanding of digoxin dosing. The following section will deal with the absorption, distribution, metabolism and excretion of digoxin as well as some of the factors which can alter the pharmacokinetics of the drug.

The disposition of digoxin is not dose dependent and is best characterized by a two compartment model.¹²

The oral route of administration is the most commonly used for digoxin. When given in the fasting state as an alcoholic elixir, serum levels peak in 45 to 60 minutes and this peak is delayed by approximately 30 minutes when the drug is given in tablet form.¹² The relative bioavailability of the elixir is approximately 85% and that of the oral tablet approximately 60 to 75%.¹² In the early 1970's, problems in the bioavailability of some digoxin tablets were discovered but since that time the problems have been corrected by regulations governing the formulation and bioavailability characteristics of digoxin products.¹³ Digoxin can be given by intramuscular injection but this is quite painful and the rate of absorption may be slower than when given orally.¹²

After absorption, digoxin is distributed from the blood to tissues in a process which is termed the alpha (α) distribution phase. With the measurement of serial serum digoxin concentrations (SDC) after a dose, this phase is evident for approximately three to four hours after an intravenous dose and six to eight hours after an oral dose.¹² Digoxin is preferentially distributed to certain tissues with the highest tissue to serum ratios being attained in the heart, kidney, liver and pancreas. The tissue to serum ratio in skeletal muscle is relatively low compared to the aforementioned tissues but skeletal muscle is the major depot for digoxin in man owing to its

proportionately larger size.¹² Several studies have examined the ratio between myocardial and serum digoxin concentrations. Although some studies have demonstrated little variability in this ratio^{14,15} this is not the rule.¹⁶ A number of factors may be able to account for the differences between results and these include differences in sampling time after a dose of digoxin, differences in the anatomical section of the heart sampled and the effect of various diseases on the ratio. Plasma protein binding of digoxin is not an important determinant of digoxin distribution as only 20 to 25% of the drug is bound to plasma proteins.

Digoxin is largely excreted as the unchanged drug and therefore metabolic processes do not play a significant role in the elimination of the drug in subjects with normal renal function. The major metabolites are mono- and bis-digoxigenin digitoxide and digoxigenin.¹² Biliary excretion also plays a role in the excretion of digoxin and approximately 30% of an intravenous dose is excreted through the biliary route in the first 24 hours.¹⁷ It is estimated that much of this is in the form of the unchanged drug which is available for reabsorption into the systemic circulation. Using radiolabelled digoxin, 45 to 55% of the radioactivity recovered in the stool is in the form of the unchanged drug while the rest is in the form of metabolites.¹⁸ Jelliffe¹⁹ has estimated that 14% of an intravenous dose

is excreted daily by non-renal mechanisms.

In subjects with normal renal function, digoxin is largely excreted unchanged in the urine. With respect to renal mechanisms involved in the elimination of digoxin it has been proposed by Risler et al²⁰ that glomerular filtration is the principal mechanism at play whereas Steiness²¹ has presented evidence that tubular secretion accounts for 50% of digoxin appearing in the urine. A linear relationship exists between the total body clearance of digoxin and creatinine clearance.^{22,23}

Several disease states have been found to alter the pharmacokinetics of digoxin. The absorption of oral digoxin may be decreased in certain malabsorption syndromes²⁴ but this may be due to the type of oral dosage form used rather than impaired absorption of the digoxin molecule itself.^{25,26} The thyroid status of an individual also appears to affect the pharmacokinetics of digoxin in that serum digoxin levels are generally higher than expected in hypothyroid subjects and lower than expected in hyperthyroid subjects.^{27,28} However, the clinical relevance of these findings remain controversial.²⁹ Finally, in renal dysfunction, not only is the expected decrease in digoxin clearance observed but a decrease in the volume of distribution has been described, resulting in a further increase in the serum digoxin concentration.^{22,30}

iii) Therapeutic Indications

Clinically, digoxin is used in the treatment of heart failure and certain atrial dysrhythmias. For these indications the positive inotropic effect of digoxin and its effects on the atrioventricular node are taken advantage of, respectively.

iv) Clinical Toxicity

As mentioned previously, the incidence of digitalis toxicity has been found to vary from eight to 30%.⁵ Reasons for the large variability in this incidence may be attributed to the following : criteria for selection of patients, distribution of the risk factors predisposing to toxicity in the population studied, the definition of digitalis toxicity, the methods used to detect toxicity and the duration of observation of the patients. A review of four prospective studies on hospitalized patients taking a digitalis glycoside reveals a range in the incidence of toxicity from 13 to 27% with a mean of 22%.^{31, 32, 33, 34}

The manifestations of digitalis toxicity in man involve the gastrointestinal tract, the central nervous system and the heart. The precise mechanisms underlying digitalis induced toxicity are not entirely clear. It is felt that the gastrointestinal and central nervous system manifestations are due to central effects while the cardiac toxicity has

previously been explained by extension of the basic electrophysiologic effects of digoxin.⁵ More recently, another mechanism for digitalis induced cardiac arrhythmias has been proposed³⁵ - the induction of oscillatory afterpotentials in the specialized conducting system of the heart (and in the myocardium under certain circumstances) during diastolic depolarization.

Digitalis toxicity can manifest itself through either cardiac or extracardiac signs and/or symptoms. Perhaps the best report on the extracardiac side effects of digitalis intoxication is that of Lely and Van Enter³⁶ who observed 179 patients with manifestations of digitalis toxicity due to an error in the formulation of digoxin tablets (the tablets contained 0.20 mg. of digitoxin plus 0.05 mg of digoxin instead of 0.25 mg of digoxin). The incidence of the various extracardiac complaints were as follows : acute fatigue in 95%; complaints of visual disturbances such as hazy vision or altered colour perception in 95%; diminished muscular strength in 82%; nausea in 81%; anorexia in 80%; psychic complaints such as bad dreams, restlessness, agitation or pseudohallucinations in 65%; headache in 45%; diarrhea in 41% and vomiting in 40%. Death due to intoxication was believed to have occurred in six of the patients. Unfortunately, continuous electrocardiographic monitoring was not available and therefore it was not possible for the authors to reliably comment on the incidence of various cardiac disturbances.

Chung³⁷ reviewed 726 cases of digitalis induced cardiac rhythm disturbances in order to determine which were most commonly associated with digitalis intoxication. The most common arrhythmias were premature ventricular contractions (PVC's) which occurred in 53.9% of patients while 25.4% of patients had bigeminal rhythms and 18% had multifocal PVC's. These were followed by atrio-ventricular (AV) nodal tachycardia (18.5%), AV dissociation (17.5%), second degree AV block (16.8%), first degree AV block (14.1%), atrial tachycardia (14.1%), ventricular tachycardia (11.9%), complete heart block (11.2%) and a wide variety of less common arrhythmias each occurring in less than 10% of the patients. This is consistent with the review by Smith and Haber⁵ who stated:

There are no unequivocal electrocardiographic features that distinguish digitalis toxic rhythms from those due to intrinsic cardiac disease, although rhythms combining features of increased automaticity of ectopic pacemakers with impaired conduction, such as paroxysmal atrial tachycardia with atrioventricular dissociation and an accelerated atrioventricular junctional pacemaker are very strongly suggestive of a digitalis toxic rhythm.

Lely and Van Enter³⁶ described anorexia and nausea as often being the first signs of digitalis intoxication. However, as mentioned earlier, electrocardiographic monitoring was not done during the early stages of toxicity. Church et al³⁸ intentionally overdosed 30 subjects a total of 85 times with three different digitalis glycosides.

All were dosed until the earliest signs of toxicity. Gastrointestinal complaints were among the earliest manifestations in 60% of the subjects while cardiac arrhythmias were among the earliest signs in 50% of patients. There were no obvious differences between the three glycoside preparations tested with respect to the spectrum of adverse effects.

v) Factors Predisposing to Toxicity

There have been a large number of clinical and experimental studies which have sought to identify factors which predispose to the development of digitalis toxicity.

The presence of hypokalemia has been implicated as a predisposing factor to digitalis toxicity.⁵ This has been supported by a large number of experimental studies 39,40,41 and Prindle et al⁴² have shown that depletion of extracellular potassium causes an increase in the myocardial concentration of digoxin thus providing a potential mechanism for the interaction. Surprisingly, most of the epidemiological studies of digitalis toxicity do not support the experimental results.^{32,33,34,43,44}

The study by Shapiro et al³¹ did find the incidence of hypokalemia to be greater in the digitalis toxic group versus control and the discrepancy in results may be due to the statistical analysis used. Shapiro and colleagues used a Chi Squared test whereas the other studies compared the means of serum potassium in the toxic versus non-toxic group.

The role of the serum magnesium concentration as a

predisposing factor to digitalis toxicity has not been as well studied as serum potassium. However, similar to potassium, there is some experimental evidence^{45,46} which indicates that hypomagnesemia plays a role in digitalis toxicity although epidemiologic studies have failed to substantiate this claim.^{33,47,48}

Hypercalcemia has been reported to enhance digitalis toxicity. This was well studied and reviewed by Nola et al⁴⁹ who found that only in the presence of marked hypercalcemia (serum calcium greater than 15 mEq/L) was the toxicity of acetylstrophanthidin enhanced in dogs. Thus, the clinical relevance of the digitalis-calcium interaction is obscure since it would be very rare to encounter such a high serum calcium concentration in the clinical setting.

Digitalis toxicity has also been reported to be enhanced in the presence of hypoxemia. This has been substantiated in experimental studies^{50,51} but results from epidemiological studies are conflicting.^{34,44} There is some evidence to suggest that this discrepancy may be due to the fact that digitalis toxicity is only enhanced by acute but not chronic hypoxemia.⁵²

Finally the severity of the underlying heart disease has been reported to affect the development of digitalis toxicity. Experimentally it has been shown that stretching of the heart enhances digitalis induced increases in automaticity⁵³ and this is supported by two

epidemiological studies^{32,33} which found digitalis toxicity to be increased in patients with more advanced heart failure. Unfortunately, it is not known if this is due to higher doses of digitalis being used in this population.

vi) Serum Digoxin Concentration (SDC)

With the study of the pharmacokinetics of digoxin came the realization that the serum concentration of the drug correlated with the dose and there were also reports of a correlation existing between the serum concentration and the myocardial concentration of digoxin. Therefore, assays were developed to measure the serum digoxin concentration with the expectation that such a measurement could be used to monitor the dose requirements, efficacy and toxicity of the drug. Several methods have been developed to measure the concentration of digoxin in the blood⁵⁴ but, of these, the radioimmunoassay is the most widely used.

Attempts have been made to correlate the SDC with digoxin's beneficial effects - both inotropic and chronotropic. In vitro, Lee et al⁵⁵ have found a good correlation between the dose of acetylstrophanthidin and the positive inotropic response. In vivo, some investigators have found a significant correlation between the SDC and measurements of myocardial contractility such as systolic time intervals^{56, 57} and echocardiographically determined parameters.⁵⁸ However, others have found no

correlation.^{59,60} With respect to the use of digoxin in slowing the ventricular response in subjects with atrial fibrillation, there is also controversy. There have been studies reporting a correlation between the SDC and the slowing of the ventricular response^{61,62} but these have been disputed.⁶³ In summary, there may be a rough correlation between the SDC and the therapeutic effects of digoxin but such a correlation could be affected by many other factors such as the pre-existing degree of impairment of the myocardium, the electrolyte status of the subject and the presence of other disease states.

A large number of studies have examined the ability of the SDC to distinguish between digoxin toxic and non-toxic patients. In 1976, Ingelfinger and Goldman⁶⁴ critically reviewed 23 studies which investigated the relationship between the SDC and the presence of digoxin toxicity. Of these studies, they chose five whose study design came the closest to matching their requirements for the ideal study. The results of these studies are summarized in Table 1.

Thus, of these studies, only three demonstrated higher mean SDC in the toxic versus non-toxic group.

Until recently however, no studies on digoxin toxicity have met all of Ingelfinger and Goldman's criteria for a well designed study.⁶⁴ The basic deficit in the previous studies, including all five mentioned above, was that the studies did not include a control population of symptomatic

but non-toxic subjects. This group would be identified as those whose signs and/or symptoms of digoxin toxicity did not disappear with discontinuation of the drug. This was deemed crucial by Ingelfinger and Goldman as it would help determine if the SDC aided the clinician in distinguishing between toxic and non-toxic patients when this could not be done on clinical grounds alone. Two recent studies ^{33,34} have included this criteria in their design.

Bernabei et al³³ examined consecutive electrocardiograms and selected those of digitalized patients whose electrocardiogram exhibited arrhythmias consistent with digoxin toxicity. In all of these patients a SDC was measured and the digoxin discontinued. If the arrhythmia completely disappeared the patient was classified as toxic (n = 76). The mean SDC was 2.88 ± 1.89 ng/mL in the toxic group versus 1.00 ± 0.61 ng/mL in the non-toxic group ($p < 0.0001$). Within the toxic group there were nine cases where the SDC was less than 2.0 ng/mL and these were considered to be false negatives (38%). In the non-toxic group there were two cases where the SDC was greater than 2.0 ng/mL and these were considered to be false positives (2.6%). Of 17 cases where the SDC was greater than 2.0 ng/mL only two were false positives and therefore the authors concluded that the SDC has a good rate of predictive accuracy for toxicity (88%). However, in view of the fact that the false negative rate was 38%, it was concluded that the SDC had a poor sensitivity

rate (62%).

Arnim et al.³⁴ performed a similar study in which they consecutively identified 206 patients taking digoxin with manifestations, both cardiac and extracardiac, of digoxin toxicity. All patients had digoxin withdrawn for one week and those whose manifestations disappeared were considered to be digoxin toxic ($n = 81$). The SDC in the group with suspected digoxin toxicity was 1.61 ± 1.22 ng/mL compared with 2.06 ± 1.46 in the 81 patients with confirmed digoxin toxicity ($p < 0.01$). At a SDC of 3.0 ng/mL or greater, the ability of the SDC to predict digoxin toxicity was 70% and this decreased to 57% for a SDC of 1.5 ng/mL.

In summary, these studies indicate that the SDC cannot be used alone in identifying digoxin toxicity. Other factors such as the patients serum electrolytes, state of renal function and underlying pathologic conditions must also be considered. However, it does appear that the SDC is an additional piece of information that, if used wisely, can help to guide the physician in managing a patient's digoxin therapy.

vii) Drugs Which Affect the SDC

A number of drugs have been studied to evaluate their potential to alter the SDC via a pharmacokinetic drug interaction. This can occur by altering the absorption, distribution or clearance of digoxin.

Studies performed on the ability of various drugs to alter the oral bioavailability of digoxin are, in certain cases, difficult to interpret due to the doses of the two drugs used, the formulation of digoxin used, the timing of administration of the drugs and whether the study was a single or multiple dose study. The bioavailability of oral digoxin has been shown to be significantly reduced by magnesium hydroxide, aluminium hydroxide, magnesium trisilicate and kaolin-pectin⁶⁷; sulfasalazine⁶⁸; neomycin⁶⁹ and metoclopramide⁷⁰. Cholestyramine has also been shown to decrease the absorption of digoxin in one study⁷¹ but not another⁷². This discrepancy may be due to differences in the timing of the cholestyramine doses relative to the digoxin doses. Propantheline has been shown to increase the bioavailability of oral digoxin when given in tablet form but to have no effect on the bioavailability of the digoxin elixir.⁷⁰

A number of studies, with varying results, have examined the effect of furosemide on the clearance of digoxin. Tsutsumi et al⁷³ reported that furosemide decreases the renal clearance of digoxin while McAllister and colleagues⁷⁴ report that furosemide increased the urinary excretion of digoxin. In both studies no change in the SDC occurred. Three other studies^{75, 76, 77} failed to show any effect of furosemide on either the renal clearance of digoxin or the SDC. Thus furosemide would seem to have

little potential to alter the SDC. Spironolactone has been shown to decrease the renal clearance of digoxin with consequent increases in the SDC.⁷⁸

Recently, considerable attention has focused on the digoxin-quinidine interaction. Although most of the research in this area was not published until 1978, Gold et al⁷⁹ in 1932 were the first to report on the potential hazards of administering digitalis with quinidine. In 1977, the Boston Collaborative Drug Surveillance Program reported their findings on adverse reactions induced by quinidine.⁸⁰

They noted that adverse reactions occurred in 13% of patients receiving a digitalis-quinidine combination.

Ejvinsson⁸¹ published the initial report on the ability of quinidine to cause an increase in the SDC. The 12 patients in this study showed an increase in the mean SDC from 0.85 ng/mL before quinidine was given to 1.6 ng/mL while taking both digoxin and quinidine. The possibility of quinidine interfering with the digoxin assay was ruled out but no alternative mechanism for the interaction was offered.

Two subsequent reports^{82,83} substantiated the findings of Ejvinsson. Leahey et al⁸² reported the results of a retrospective study in which the SDC rose in 25 of 27 patients when quinidine was added to digoxin therapy. The mean SDC more than doubled when quinidine was added. A number of adverse reactions such as nausea, vomiting,

anorexia and ventricular arrhythmias were noted to occur after the addition of quinidine but a causal relationship between these reactions and the increase in the SDC could not be established. It was noted in several patients that the rise in SDC occurred within 24 hours of the addition of quinidine and it was therefore suggested that the underlying mechanism behind the interaction was a displacement of digoxin from tissue binding sites by quinidine. The brief report of Hooymans and Merkus⁸³ suggested another mechanism behind the interaction. In three patients, they noted that the renal clearance of digoxin was decreased when quinidine was co-administered with digoxin.

The report by Straub et al⁸⁴ supports the contention raised by Leahey's group that the increased SDC is secondary to quinidine displacing digoxin from tissue binding sites. Quinidine was shown to displace ouabain from beef heart membrane $\text{Na}^+, \text{K}^+ - \text{ATPase}$ and Scatchard plots indicated that quinidine did not affect the digoxin-membrane dissociation constant but did decrease the number of binding sites.

Several subsequent studies have attempted to elucidate the underlying mechanisms of this pharmacokinetic interaction. Hager et al⁸⁵ examined the effects of quinidine administration on the pharmacokinetics of a single intravenous dose of digoxin in six subjects. The administration of quinidine caused a 35% decrease in the

total body clearance of digoxin (from 3.08 ± 0.54 to 1.96 ± 0.37 mL/min/kg). The renal clearance of digoxin was decreased from 1.64 ± 0.60 to 1.09 ± 0.24 mL/min/kg ($p < 0.05$) and the apparent volume of distribution decreased from 10.87 ± 3.81 to 7.35 ± 0.79 L/kg ($p < 0.05$) in the presence of quinidine.

Steiness et al⁸⁶ reported that quinidine also significantly decreases the extrarenal clearance of digoxin but, in contrast to the study by Hager and colleagues, could not demonstrate any quinidine induced changes in the volume of distribution of digoxin. The two studies were very similar in design with the exception of the dose of quinidine used; the study by Steiness et al used half the dose used by Hager et al. This raises the possibility that perhaps quinidine decreases the volume of distribution of digoxin in a dose-dependent manner.

Data presented by Doering⁸⁷ also indicate that the degree of elevation of the SDC by quinidine may be a function of the quinidine dose. Unfortunately, these data were not subjected to statistical analysis. However, Manolas et al⁸⁸ have reported a significant positive correlation between the plasma quinidine concentration and the degree of increase in the SDC.

Doering⁸⁷ also studied the effect of quinidine on the binding of digoxin to lamb sarcolemmal membrane and, in contrast to the earlier report by Straub et al⁸⁴, could not detect any quinidine induced displacement of digoxin.

However, in a subsequent communication,⁸⁹ Straub pointed out that, in his work, the sarcolemmal membrane was preincubated with quinidine. This was not done in the experiment by Doering and it was admitted that this could have affected his results.⁹⁰

Work done by Dahqvist et al⁹¹ has elaborated further on the interaction. Although they noted a trend towards a dose-related effect of quinidine on the SDC, statistical analysis failed to reveal a significant correlation between the serum concentration of quinidine and the degree of elevation of the SDC. As early as six hours after the addition of quinidine to patients maintained on digoxin, there was a mean increase in the SDC of 46%. After 72 hours, the SDC had risen a mean of 116%. Furthermore, in patients whose digoxin had been discontinued for 36 hours before the addition of quinidine, a significant increase of 22% was still noted in the SDC 12 hours after quinidine therapy was initiated.

Thus, the clinical studies on the pharmacokinetics of the digoxin-quinidine interaction have indicated that the interaction occurs in approximately 90% of subjects on the combination. On the average, quinidine appears to increase the SDC by approximately twofold but on examination of the data it is apparent that there is a large amount of interindividual variation. The rise in the SDC seems to start soon after the addition of quinidine but it is not

maximal until approximately one week. This is consistent with both a quinidine induced decrease in the volume of distribution and clearance of digoxin. The question which has not yet been adequately answered is whether the increase seen in the SDC is correlated with an increase in the pharmacological effects of digoxin (both efficacious and toxic).

Many of the studies previously mentioned have cited examples of cases where the increase in the SDC has been associated with digoxin toxicity, usually manifested by gastrointestinal complaints. However, these can be misleading as the toxic effects of quinidine, especially those on the gastrointestinal tract, can mimic those of digoxin. Two papers do provide evidence of the increased SDC being associated with cardiac signs of digoxin toxicity. Leahey et al⁹² reported on three cases where a quinidine induced increase in the SDC was associated with typical cardiac manifestations of digoxin toxicity. Another report from Leahey's group⁹³ demonstrated that the increase in the SDC was associated with a prolongation of the P-R interval on the electrocardiogram.

In contrast to these reports, Steiness et al⁹⁴ have reported decreased cardiac effects of digoxin when quinidine is combined with digoxin in healthy subjects. Using the pre-ejection index, determined from systolic time intervals, as an index of digoxin's inotropic effect, a typical

positive inotropic response was observed when digoxin was given alone but this was negated when quinidine was combined with digoxin. Similar results have also been reported by Hirsh et al.⁹⁴

To summarize, quinidine causes an increase in the SDC but it is not yet clear if this increase is associated with increased digoxin toxicity and/or diminished digoxin mediated increases in myocardial contractility. In any case, the use of quinidine in patients taking digoxin may be detrimental to the patient's health. Thus, it seems preferable to choose another antiarrhythmic drug over quinidine if the patient is also to receive digoxin.

Since the investigation of the digoxin-quinidine interaction a number of other drugs have been reported to increase the SDC. However, these have not yet been substantiated in a controlled clinical setting. In an animal model, quinine, acetylsalicylic acid, ibuprofen and indomethacin have been reported to significantly increase the SDC.⁹⁵ There are also brief reports which suggest that verapamil⁹⁶ and diazepam⁹⁷ can also increase the SDC.

b) Disopyramide

Disopyramide is a compound which is most often classified as a type 1 antiarrhythmic drug and, as such, its electrophysiological properties most closely resemble those

of quinidine and procainamide.

Disopyramide is structurally unrelated to other antiarrhythmic agents. It has a molecular weight of 339.5 and is insoluble in water but is soluble in dilute acid or organic solvents. The phosphate salt is soluble in water.

i) Pharmacology

In vivo, perhaps the most impressive pharmacologic actions of disopyramide are its antiarrhythmic and anticholinergic properties. Traditionally, it has been believed that the type 1 antiarrhythmics exerted their activity via a membrane stabilizing or local anesthetic effect. However, there is some controversy regarding the ability of disopyramide to act as a local anesthetic. One study⁹⁸, using an in vivo preparation, reported that disopyramide possessed local anesthetic activity roughly equal to that of lidocaine whereas another study⁹⁹ showed that both disopyramide and its major metabolite, mono-N-dealkyl disopyramide, had little effect on the conduction velocity along an in vitro preparation of rat sciatic nerve. The anticholinergic effects seen with the clinical use of the drug may in fact be due to mono-N-dealkyl disopyramide as it was shown to be 24 times as potent as disopyramide in antagonizing acetylcholine induced contractions of an isolated guinea pig ileum preparation.⁹⁸ In the same preparation; atropine was

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shown to be 1200 times as potent compared to disopyramide.

In vitro studies on animal preparations have demonstrated that disopyramide possesses the following dose dependent electrophysiological effects: within the atria an increase in the resting potential and action potential duration and decreases in the action potential amplitude and rate of rise of phase 0¹⁰⁰; within the Purkinje system disopyramide induces decreases in the slope of phase 4 diastolic depolarization, the action potential amplitude, the rate of rise of phase 0 and the conduction velocity while increases in the action potential duration and the refractory period are seen.^{101,102} In the isolated rabbit heart, disopyramide decreases the conduction velocity through the atrioventricular node.¹⁰³ Due to the anticholinergic effects of the drug, however, a somewhat different picture may be seen in vivo. For example, Ross et al¹⁰⁴ found that in cardiac patients, the administration of disopyramide had no effect on atrioventricular nodal function, sinus node recovery time was shortened and the refractory periods in the atria and ventricles were prolonged. The importance of the anticholinergic effects of disopyramide was elegantly demonstrated by Birkhead and Williams¹⁰⁵ who studied the electrophysiologic effects of the drug in man before and after the administration of atropine. After atropine administration, the effects seen were similar to those

described in the in vitro experiments mentioned above. Thus the electrophysiologic effects of disopyramide in man are not entirely predictable and will depend to some extent on the basal vagal tone. The electrophysiologic effects of disopyramide also seem to be partially dependent on the extracellular potassium concentration. When cardiac tissue is perfused with a low concentration of potassium versus one with a normal physiologic concentration, the electrophysiologic effects of disopyramide are less marked.^{102,106}

During myocardial ischemia, the refractory period in the ischemic part of the heart is decreased relative to surrounding healthy tissue. This has the potential to predispose to re-entrant arrhythmias. Two studies^{106,107}, have now shown that although disopyramide increases the refractory period in both healthy and ischemic tissue, the effect on ischemic tissue is more marked thus reducing the disparity in refractory periods and converting a unidirectional block pattern to a bidirectional block. One of the possible explanations for this disparity of disopyramide's effects is the fact that the extracellular potassium levels are increased in ischemic myocardium thus facilitating the disopyramide-induced increase in refractory period.¹⁰⁷ Experimentally, disopyramide has been shown to be active against both atrial and ventricular arrhythmias produced by aconitine, digitalis and ischemia.^{108,109,110}

The hemodynamic effects produced in man by intravenous disopyramide include a significant reduction in cardiac output, an increase in the pulmonary capillary wedge pressure, a decrease in stroke volume and variable effects on mean arterial pressure.^{111,112,113}

The negative inotropic effect of disopyramide appears to be most marked in patients with pre-existing ventricular dysfunction.^{111,114} There have been few comparative studies of the hemodynamic effects of disopyramide versus other type I antiarrhythmic drugs. Compared with quinidine, disopyramide has been reported to produce a more pronounced negative inotropic effect in dogs.^{115,116}

Disopyramide has also been reported to cause an increase in peripheral vascular resistance^{115,117} - an effect which could contribute to the depression of left ventricular function. This vasoconstrictive effect of disopyramide has also been reported to occur in the coronary circulation.^{116,118} In contrast to disopyramide, mono-N-dealkyl disopyramide has been reported to possess a positive inotropic effect in isolated guinea pig atria.⁹⁹

There has been very little work done to date on the hemodynamic changes induced by the chronic administration of disopyramide. Recently, Cathcart-Rake et al¹¹⁹ examined this in healthy men. Using echocardiography and

systolic time intervals, significant decreases in the ejection fraction and increases in PEP/LVET (pre-ejection period divided by left ventricular ejection time) occurred after a single 200mg oral dose of disopyramide but after one week of disopyramide 200mg every six hours, there were no significant changes in these parameters. The combination of disopyramide and propranolol produced neither additive nor synergistic hemodynamic effects.

ii) Pharmacokinetics

Following an oral dose of disopyramide in healthy subjects, serum concentrations peak in approximately one to two hours with maximal levels reported as 1.5ug/mL following a 3mg/kg dose and 3.0ug/mL after a 6mg/kg dose.¹²⁰

Following an intravenous bolus dose of disopyramide, the plasma concentration-time profile can be characterized by a two compartment model. The alpha phase half-life is approximately three minutes while the half-life of the beta phase is roughly five to six hours.¹²⁰

With respect to the elimination of the drug in subjects with normal renal function 50 to 60% of a dose is excreted via the kidneys as the unchanged drug with the remainder being metabolized.^{120, 121} The major metabolite is the mono-N-dealkyl derivative which is excreted by the kidneys. A recent report¹²² suggests that some individuals accumulate the metabolite to a much greater

extent than others. The clinical significance of this finding has yet to be determined. As well, a study¹²³ in rats has indicated that the dealkylation of disopyramide may be induced by phenobarbital and that perhaps disopyramide can induce its own metabolism.

Disopyramide exhibits concentration-dependent plasma protein binding.^{124,125,126} Data from Chien et al¹²⁷ indicate that albumin is the major protein which binds disopyramide but Piafsky¹²⁸ has recently reported that disopyramide also binds to alpha-1 acid glycoprotein. Meffin et al¹²⁵ undertook an extensive analysis of the effect of this concentration dependent binding on the disposition of disopyramide. They reported that at total drug concentrations of 2ug/mL approximately 80% of the disopyramide would be bound to plasma proteins whereas at a total drug concentration of 6ug/mL only 60% of the drug in plasma would be protein bound. A pharmacokinetic analysis of their data showed that if the concentration-dependent plasma protein binding of disopyramide was taken into account then there was a linear relationship between the dose given and the serum levels observed. The authors conclude that due to a relatively large interindividual variation in the free fraction at various drug concentrations, the use of total disopyramide serum levels is an unreliable guide to dosing the drug in the clinical situation.

It has been suggested that the range of disopyramide serum levels associated with antiarrhythmic effects is from two to five ug/mL¹²⁹; however, this has not been well established. Rationale for the use of disopyramide serum concentrations has partially come from some animal work. In the rat, Karim et al¹³⁰ have shown that the kinetics of the uptake and elimination of disopyramide from the myocardium is similar to serum. Patterson et al¹³¹ have shown a relatively constant ratio, at steady state, of the concentration of disopyramide in myocardium to serum (approximately four to one). However, caution must be used in the extrapolation of animal data to man due to interspecies differences in protein binding. For example, Karim et al¹³² demonstrated that the dog does not display concentration-dependent plasma protein binding over the serum concentration range of zero to ten ug/mL. At these total drug concentrations in the dog, approximately 20% of the drug was bound to plasma proteins. In man, there have been no studies which have systematically related disopyramide serum concentrations with efficacy of arrhythmia control. Nonetheless, observations have been made; Benditt and colleagues¹³³ noted that in only one of eight patients with arrhythmia control was the disopyramide serum concentration less than 3ug/mL. However, in many patients with serum concentrations greater than 3ug/mL, disopyramide failed to produce arrhythmia control. Niarchos¹³⁴

measured disopyramide serum concentrations at the time of arrhythmia conversion and observed a mean effective serum concentration of 3.7ug/mL with a range of 2.8 to 7.5 ug/mL. In summary, there is not a great deal of experimental evidence to indicate that disopyramide serum concentrations are useful in monitoring the antiarrhythmic effects of the drug. The individual patient's free fraction of disopyramide, the serum potassium concentration and perhaps the underlying pathogenesis of the arrhythmia are factors which can alter the relationship between the serum concentration of disopyramide and its antiarrhythmic effect.

Much of the human pharmacokinetic work done with disopyramide has been done in healthy subjects but there is some evidence that important pharmacokinetic alterations do occur in certain disease states. In patients having experienced an acute myocardial infarction it has been found that the peak serum levels of disopyramide after an oral dose are lower than would be expected and it has been postulated that this is due to decreased absorption and/or an increased distribution of the drug.^{135,136} Ilett et al¹³⁷ reported that the mean disopyramide serum half-life in patients with an acute myocardial infarction was 38 and 24 hours for 400 and 800mg/day dosing regimes respectively. This report is in contrast to the studies of Ward et al¹³⁵ and Oksanen et al¹³⁶ which reported half lives of seven and 8.3 hours respectively. Possible

explanations for these discrepancies might be that the study by Ilett et al¹³⁷ used only two points on the serum concentration time curve to calculate half-life. Blood was drawn at three hours after an oral dose and this could be before the elimination phase as two reports have described a plateau in serum concentrations after the peak.^{120,124} In patients with renal dysfunction, disopyramide clearance is reduced but there is some argument as to how severe the renal dysfunction must be before a significant reduction in the clearance of the drug occurs. One report¹³⁸ suggests that reduction of dose is required only when the creatinine clearance is less than 25mL/min while another¹³⁹ reports that the clearance of disopyramide is altered at creatinine clearances less than 60mL/min. The manufacturer of disopyramide recommends dosage adjustment in patients with a creatinine clearance of less than 40mL/min¹⁴⁰ which is consistent with the report of Shen et al.¹⁴¹

iii) Clinical Efficacy

Presently, disopyramide is officially indicated to be used only for the treatment of ventricular arrhythmias and many studies support its efficacy for this indication.^{133,142,143,144,145} The usefulness of disopyramide in the treatment of atrial arrhythmias has not

been well studied ~~to date~~. Luoma et al¹⁴⁶ report that disopyramide was successful 42% of the time in converting atrial fibrillation or flutter to normal sinus rhythm while the success rate in supraventricular tachycardia was 68%. Mizgala and Huvelle¹⁴⁵ report a success rate of 22% against a variety of atrial arrhythmias. A study by Hartel et al¹⁴⁷ reports that disopyramide may be useful for the prevention of recurrence of atrial fibrillation after cardioversion.

iv) Clinical Toxicity

The most common problems associated with the use of disopyramide are due to the anticholinergic effects of the drug. Reactions and their incidences have been reported as follows:¹⁴⁰

dry mouth	42 %
urinary hesitancy	16 %
constipation	9 %
blurred vision	7 %
urinary retention	2 %
dry eyes	0.6 %

A variety of other non-specific adverse effects have been listed by the manufacturer and include gastrointestinal upset, fatigue, muscle weakness, headache, depression, impotence, insomnia, metallic taste in the mouth, and, rarely, allergic skin reactions. In addition more serious adverse reactions have been reported such as congestive heart failure, heartblock, hypotension, cardiovascular collapse,

bradycardia, cardiac arrest and ventricular arrhythmias including ventricular fibrillation. Although a causal relationship was not definitely established, disopyramide has been associated with reports of cholestatic hepatitis,^{148, 149} agranulocytosis,¹⁵⁰ and central nervous system reactions such as hallucinations, agitation and delusions.^{151, 152}

A recent article by Podrid et al¹¹⁴ examined the potential of disopyramide to induce congestive heart failure. Their results indicate that 55% of patients with a prior history of congestive heart failure will suffer an exacerbation of this problem while on disopyramide therapy whereas only two of 78 patients without a history of congestive heart failure developed this complication during treatment.

III. Rationale for Study

At times it is necessary that digoxin be used simultaneously with an antiarrhythmic agent. Of the available antiarrhythmic drugs, the most appropriate to use with digoxin is open to debate:

- i) Procainamide is an antiarrhythmic agent whose limitations include that it must be dosed frequently (at least every three to four hours) due to its short half-life and that it is reported to cause a lupus-like syndrome in up to 29% of patients on long term therapy.¹⁵³
- ii) Propranolol has the ability to pharmacologically interact with digoxin due to its negative inotropic effect and impairment of conduction in the atrioventricular node.
- iii) Lidocaine can only be administered parenterally which precludes its long term use.
- iv) Phenytoin has not been established as a reliable antiarrhythmic agent except in cases of digitalis toxicity.¹⁵⁴

- v) Quinidine has a high rate of adverse effects (approximately 30%) due to gastrointestinal effects¹⁵⁵ and has been shown to cause significant increases in the SDC.
- vi) Disopyramide is the most recently released oral antiarrhythmic drug which might be considered as a drug which can be used in combination with digoxin.

Thus, disopyramide may be a suitable antiarrhythmic to use in combination with digoxin. However, before this can be recommended, it is necessary to study the potential for disopyramide to interact (either pharmacologically or pharmacokinetically) with digoxin.

This thesis deals with the potential for disopyramide to interact with digoxin and attempts to answer two basic questions, the second being conditional on the first:

- 1) Does disopyramide induce alterations in the SDC in cardiac patients?
- 2) If so, then are these changes reflective of changes in digoxin's efficacy and/or toxicity?

IV. METHODOLOGY

This study was carried out at the University of Ottawa Cardiac Unit at the Ottawa Civic Hospital under the medical supervision of Dr. D.S. Beanlands. Subjects entered into the study were medical inpatients at the time of entry. Upon entry into the study, informed consent was obtained (Appendix 1).

Patients entered into the study were of two types:

- Type I: those initially receiving both digoxin (Lanóxin, Burroughs Wellcome Ltd.) and disopyramide (Rythmodan, Roussel (Canada) Ltd.) and in whom the disopyramide was subsequently discontinued as decided by the medical staff.
- Type II: those who were receiving digoxin and in whom the decision was made to initiate disopyramide therapy

Patients were entered into the study on a consecutive basis in accordance with the inclusion and exclusion criteria outlined below. The cardiologists and cardiology house staff at the Cardiac Unit were sensitized to the nature of study and were asked to alert the co-ordinator of the study (M.T.) regarding any potential subjects. In addition, all cardiology patients in the Unit had their drug therapy screened on a regular basis to assess their eligibility for the study.

For each patient entered into the study, the study period was broken down into two phases - one when the patient was receiving both digoxin and disopyramide and another when the patient was not receiving disopyramide but was receiving digoxin. For example, for Type I patients baseline data were collected while the patient was receiving both drugs (timepoint 1) and subsequent data were collected on two additional occasions - at a point in time greater than two but less than five days after the discontinuation of disopyramide (timepoint 2) and again at a time when it was estimated that at least 3.3 half-lives of digoxin had elapsed since the discontinuation of disopyramide (timepoint 3). Data collections were at similar times for Type II patients as indicated in Figure 3. For Type I patients, the duration of disopyramide therapy ranged from five days to several months.

At each timepoint, data reflective of digoxin efficacy and/or toxicity were measured and collected. The following parameters were measured at all 3 timepoints.

a) Serum Digoxin Concentration (SDC)

The SDC was measured at the Biochemistry Laboratories, Ottawa Civic Hospital using the Digi-Tab radioimmunoassay kit of Nuclear Medical Laboratories, Inc., Dallas, Texas.

Blood for assay was drawn by direct venipuncture 20

hours after the previous dose of digoxin, centrifuged and the plasma removed. Blood for determination of SDC was regularly drawn at 0800 while the digoxin doses were given at 1200 hours. At times the plasma was frozen at -20°C for up to two days before assay.

The radioimmunoassay of digoxin was done in duplicate for each sample and was carried out according to the following procedure:

- i) 400 uL of Digoxin $-^{125}\text{I}$ reagent was dispersed into a plastic tube to serve as the total count tube.
- ii) In a plastic tube, 400 uL of digoxin $-^{125}\text{I}$ reagent was mixed vigoursly with 50 uL of the patient's serum.
- iii) To this tube, 400 uL of digoxin antisera (rabbit) was added, mixed vigoursly and allowed to stand for 25 to 35 minutes.
- iv) A charcoal adsorbent tablet was added to the tube, the tube capped, mixed by shaking for approximately five seconds and then mixed continuously by gentle inversion for 30 seconds.
- v) The tube was then centrifuged at 2500 rpm for ten minutes and the supernatant discarded.
- vi) The radioactivity present in the charcoal adsorbent was then determined by a Beckman Gamma 4,000 counter (Irvine, California) and

interpolated onto a standard curve using a Beckman DP 5,000 computer and teletype (Irvine, California).

The reproducibility of the assay was tested on every day the assay was run (generally Monday, Wednesday and Friday) and analysis of the accuracy of the assay performed monthly. These data are displayed in Appendix II.

b) Functional Classification of Dyspnea

The patient's ability to perform physical exercise before the onset of fatigue or dyspnea was used to subjectively assess the degree of heart failure. Assessment was done by questioning the patient and/or observation of the patient during physical activity. The rating scale used was that of the New York Heart Association¹⁵⁶ (NYHA) as shown below.

Class I - Patients with congestive heart failure but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue or dyspnea.

Class II - Patients with congestive heart failure causing slight limitation of physical activity. They are comfortable at rest. Ordinary activity causes fatigue or dyspnea.

Class III - Patients with congestive heart failure which causes marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue or dyspnea.

Class IV - Patients with congestive heart failure which results in inability to perform any physical activity without discomfort. Symptoms are present at rest.

c) Extracardiac Digoxin Toxicity Score

Signs and/or symptoms indicative of the extracardiac manifestations of digoxin toxicity were elicited from the patient by the co-ordinator. This was done by means of a scoring system devised to subjectively evaluate extracardiac digoxin toxicity (Appendix III). This scoring system was devised by the investigators for this study.

d) Serum Biochemistry

At each timepoint during the study, the patient had blood drawn for the determination of serum creatinine, potassium, sodium and blood urea nitrogen. This was carried out by the Biochemistry Laboratories, Ottawa Civic Hospital.

The following data were collected at the first two timepoints only.

e) Continuous Electrocardiographic Monitoring

Continuous electrocardiographic monitoring was done by means of a Holter monitor (Electrocardiocorder Model 445A, Avionics Biomedical Division, Los Angeles, California) which continuously recorded two leads of the patients electrocardiogram for a period of 12 to 24 hours. The cardiograms were recorded on Avionics Recording tape at a tape speed of 3.75 inches/min.

In preparation for attachment of the recorder, the patient's chest was shaved, swabbed with alcohol, gently rubbed with sandpaper and lubricated silver electrodes were placed in the following positions: one each over the second intercostal space in the midclavicular lines (limb leads), one placed approximately two inches to the right of the midabdominal line and approximately two inches below the right costal margin (Lewis lead), one placed approximately three inches to the right of the Lewis lead and one placed in the fifth intercostal space in the left midaxillary line

(V5). The electrodes were taped securely into place and attached to the monitor.

While being monitored, the patient was asked to keep a diary of any unusual signs or symptoms such as palpitations, shortness of breath, chest pains, light headedness, etc. If such a symptom occurred, the patient was asked to record the time and symptom in the diary as well as to depress a button on the monitor which would mark the tape.

The tapes were read with the use of an Avionics Electrocardioscanner Model 660A (Avionics Biomedical Division, Los Angeles, California) at 120 times real time. The Electrocardioscanner was operated by a technician of the Non-Invasive Laboratory, Cardiac Unit, Ottawa Civic Hospital in such a way that the scanner was programmed to detect arrhythmias if there was a greater than 20% difference in the amplitude or width of a QRS complex, compared with the patient's normal QRS complex, or if the complex was premature by more than 20% as compared to the preceding R-R interval. The Electroscanner could provide printouts of the electrocardiogram at the discretion of the technician or the physician supervising the reading of the tapes.

f) Chest X - ray

An upright posterior-anterior chest X-ray of each patient was taken by the Radiology Department, Cardiac Unit, Ottawa Civic Hospital. From the X-ray, the cardiothoracic ratio (CTR) was measured by dividing the maximal transverse

diameter of the heart by the maximal transverse diameter of the lung field above the diaphragm.

g) Electrocardiographic Intervals

The P-R and rate corrected QT (QTc) intervals were measured from either the Holter monitor records or from a 12 - lead electrocardiogram.

h) Echocardiogram

When possible, an M-mode echocardiogram was performed at the first two timepoints in order to assess left ventricular function. The echocardiogram was done by a trained technician of the Non-Invasive Laboratory, Ottawa Civic Hospital using an Ekosector I (Smith Kline Instruments Inc., Sunnyvale, California) with a KB Aerotech QSA 22DL transducer (frequency 2.25 megahertz, beam diameter 13mm, focal length three to 12cm). The image was recorded on an Ekoline 21 Recorder at a paper speed of 50mm per second using Echograph Recording Paper, Extra Thin.

Measurements were made with the patient in the supine position with a left oblique orientation. With the transducer perpendicular to the chest wall, the mitral valve was visualized and then a scan of the left ventricle from the aorta to the apex was made.

All echocardiograms were read by a cardiologist, blinded to the study drugs, and the following parameters

indicative of left ventricular function were measured:

- a) End diastolic diameter (Dd) - was measured as the distance between the septal and endocardial echo at the peak of the R wave recorded from a simultaneous electrocardiogram.
- b) End systolic diameter (Ds) - was measured at the point of least perpendicular separation of the endocardial surfaces.
- c) Percent Left ventricular ejection fraction (%EF) - was calculated as follows:

$$\%EF = \frac{Dd^3 - Ds^3}{Dd^3} \times 100\%$$

- d) The mean velocity of circumferential fiber shortening (Vcf) was calculated as follows:

$$Vcf = \frac{Dd - Ds}{Dd \times dt}$$

dt = duration of minor axis shortening as measured from onset to peak posterior wall movement.

A representative echocardiogram tracing is presented in Appendix IV.

i) Serum Disopyramide Concentration

Serum was analyzed for disopyramide concentration at the Drug Research Laboratories, Health Protection Branch using a high pressure liquid chromatographic assay.

To a 1.0 ml. plasma sample was added 0.5 mL of an aqueous solution of p-chlorodisopyramide (4 ug/mL). The

contents were mixed (Vortex Genie, Fisher Scientific Co., Ottawa) for 15 seconds before adding 0.1 mL of concentrated ammonium hydroxide and 6.0 mL of diethylether. Disopyramide, mono-N-dealkyl disopyramide and the internal standard, p-chlorodisopyramide, were extracted into the ethereal phase by centrifugation following shaking on a rotary mixer (Roto-Rack, Fisher Scientific Co., Ottawa) for 15 minutes. The organic layer (5.0 mL) was transferred to a conical tube containing 0.2 mL of an aqueous acetic acid solution 0.1M. The contents were mixed for five minutes and centrifuged for five minutes. Aliquots of the aqueous layer (25 to 100 uL) were submitted for chromatography.

A high pressure liquid chromatographic system was assembled from an Altex model 110A pump (Beckman Instruments Inc., Ottawa), a Waters model U6K injector (Waters Scientific Ltd., Mississauga), a Waters ultra violet detector operated at 254nm and an Altex UltraspHERE ODS 5um stainless steel column. The degassed mobile phase was pumped at a flow rate of 2.0 ml per minute (2000 psi) at room temperature. The mobile phase was a solution consisting of 9 per cent aqueous 0.05M acetic acid, 13.5% aqueous .05 M ammonium formate, 22.5 per cent distilled water and 55 per cent acetonitrile.

Peak height ratios were calculated by dividing the height of the peak due to the drug or the metabolite by the height of the peak due to the internal standard. Calibration curves were assembled from the results of spiked control

plasma by plotting the peak height ratios against the concentration of the drug or metabolite.

The overall mean relative standard deviations for disopyramide and mono-N-dealkyl disopyramide were 3.0 and 4.8 per cent over concentration ranges of 0.50 to 4.00 and 0.125 to 3.00 ug/mL respectively.

Patients were included in the study based on the following criteria:

- i) All patients were at least 18 years of age
- ii) Informed consent was obtained (Appendix 1)
- iii) Upon entry into the study, all patients were inpatients at the Ottawa Civic Hospital.
- iv) All patients were assessed to be at or within 15% of steady-state with respect to the SDC. This was assessed by the patients drug therapy history and/or with the use of pharmacokinetic parameters as described by Jelliffe.¹⁹

By using Jelliffe's formula,

$$\% \text{ digoxin removed daily} = \frac{\text{Creatinine Clearance}}{5} + 14,$$

a serum half-life for digoxin could be calculated. The creatinine clearance was estimated using the nomogram of Siersbaek-Nielsen¹⁵⁷ (Appendix V). Based on the calculated half-life of digoxin in any one particular patient, it could then be determined how long it would take for that patient to reach 90% of steady state if the drug was being given as a regular maintenance dose (after 3.3 half lives of maintenance therapy, 90% of steady state has been reached.) If the patient was given a partial loading dose prior to entry into the study, the assessment of steady state

was done by comparing the amount of drug remaining in the body (calculated per Jelliffe¹⁹) to the amount of drug that would ultimately be in the body considering the maintenance dose the patient was receiving. This latter amount was calculated by the formula,

$$\text{Average Amount in body at steady state} = \frac{F \times D}{k \times T}$$

where

F = relative bioavailability of digoxin

D = maintenance dose of digoxin

k = elimination rate constant = $\frac{0.693}{t_{1/2}}$

T = dosing interval.

With all calculations, the oral bioavailability of the digoxin tablet was assumed to be 70%.

Patients were excluded from the study based on the following criteria:

- i) Patients with moderate to severe or variable renal function were excluded. Any patient having a serum creatinine of greater than 2.5 mg/dL and or a blood urea nitrogen greater than 45 mg/dL and/or an estimated creatinine clearance of less than 35 mL/min during the study period was excluded. As well, patients who exhibited a greater than 25% variation in serum creatinine around the mean of at least two determinations during the study period were arbitrarily defined as having variable renal function and were excluded from the study.
- ii) Patients who demonstrated non-compliance with either their digoxin or disopyramide therapy were excluded.

Compliance was assessed with the use of nursing records for inpatients and, for outpatients a medication calender (Appendix VI) and patient interview were used. If there was any indication of a missed dose of digoxin, or if there was greater than 10% non-compliance with disopyramide, the patient was excluded.

iii) Patients whose drug therapy was altered in such a way as to possibly have altered the SDC were excluded. The following drugs could not have been initiated, discontinued or had their dosing régimes changed during the study period: antacids, kaolin-pectin mixtures, quinidine, cholestyramine, sulfasalazine, neomycin and spironolactone.

v) Type II patients who required disopyramide therapy urgently and for whom there was not enough time to collect data at the first timepoint were excluded.

For all patients, results obtained at timepoints 2 and 3 were statistically compared to those obtained at timepoint 1. Type I and Type II patients were analyzed separately. With the exception of the results of the NYHA functional classification of dyspnea and the extracardiac digoxin toxicity score, the statistical test employed was the Students t-test for paired data. For the above mentioned exceptions, the Wilcoxon signed rank test was employed. Regression analysis was employed when appropriate using the least squares linear regression method.

IV. RESULTS

Twenty patients were entered into the study during the time period of July 7, 1979 to July 30, 1980. Of these, there were seven dropouts leaving 13 patients to be included in the analysis of results. General patient data is given in Table I. Of the patients included in the results, seven were of Type I and six of Type II.

Patients were dropped from the study for a variety of reasons as outlined below. Patient 1 had his digoxin withheld for a day during the study due to the suspicion that the digoxin may have been contributing to the ventricular arrhythmias the patient was experiencing. Patient 8 was a Type I patient in whom the ventricular arrhythmias worsened when the disopyramide was stopped and the decision was then made to reinstitute disopyramide therapy. Patient 10 voluntarily withdrew from the study after experiencing a poor night's sleep while connected to the Holter monitor. Patient 13 voluntarily withdrew from the study after suffering an exacerbation of his illness. This was judged not to be related to the digoxin or disopyramide. Patient 14 died during the course of the study and is therefore not included in the analysis. He was a 69 year old male suffering from

severe congestive heart failure and atrial flutter. An attempt to control the ventricular response to his atrial flutter was made with digoxin therapy. The serum digoxin concentration was 2.7 ng/mL. Disopyramide 100 mg four times daily was then started with the hope to revert the patient to normal sinus rhythm. The patient had received a total of 700 mg before he was found pulseless in his room. An attempted resuscitation was unsuccessful. A postmortem autopsy was not available and therefore the cause of death could not be established although the most likely causes would be either a ventricular arrhythmia or a pulmonary embolus. Patient 15 had to be withdrawn from the study due to an error made in the assessment of the patient's total body stores of digoxin. It was originally thought that the patient was at steady state when in fact he was not. Patient 16 had to be withdrawn from the study due to the return of ventricular arrhythmias after the disopyramide was stopped.

In two patients (no.7 and 9) it was not possible to obtain data at all three timepoints and, for these patients only data from these first two timepoints are included. Patient 7 had his dose of digoxin increased from 0.125 mg daily to 0.25 mg daily after the second timepoint and therefore data was not collected subsequent to the dosage increase. Patient 9 had his digoxin discontinued after the second timepoint.

All patients had their serum creatinine and blood urea

nitrogen (BUN) measured at least twice and, in most cases, three times during the study period. These values plus the estimated creatinine clearance are displayed in Table II. It was not necessary to exclude any patients from the study because of impaired or variable renal function based on the definitions given in the methodology.

During the study, a large number of other drugs were administered to the patients (Table III). However, none of these drugs were judged to have the potential to interfere with the primary objective of the study.

For that part of the study while the subjects were inpatients, medications were administered by the nursing staff and compliance with medication regimes during this period was assessed to be 100% for both digoxin and disopyramide. In those patients who were discharged home prior to the termination of the study, patient compliance was assessed by having the patient maintain a medication calendar and by conducting an interview with the patient at timepoint 3. Seven of the 13 patients (2,3,6,11,12,18,20) spent part of the study as outpatients. All outpatients were judged to have 100% compliance with their digoxin therapy. Four of the seven outpatients were Type II patients and therefore were also taking disopyramide. Compliance with disopyramide was judged to be excellent although patient 11 missed four doses during her outpatient phase (11 days).

All but three patients had been taking digoxin for

prolonged periods of time prior to entry into the study and were thus judged to be at steady state with respect to their SDC. For three patients (11,17,18) a pharmacokinetic assessment was necessary to estimate the proximity to steady state prior to entry into the study.

Patient 11 was digitalized by oral doses of 0.5mg daily for three consecutive days followed by a maintenance dose of 0.25mg daily. Based on an estimated creatinine clearance of 90ml/min, it was calculated that 32% of the drug would be removed from the body daily. This is consistent with a serum half-life of 1.8 days or an elimination rate constant of 0.385 days⁻¹. From this information, the steady state total body stores at an oral dose of 0.25mg daily could be calculated:

$$\begin{aligned}\text{Total body stores} &= \frac{F \times D}{k \times T} \\ &= \frac{0.70 \times 0.25}{0.385 \times 1} \\ &= 0.455 \text{ mg}\end{aligned}$$

Knowing that 32% of the digoxin in the body is eliminated daily, it is possible to calculate how much digoxin was in the body at the first timepoint (ie. after three daily doses of 0.5mg). This was calculated to be 0.510mg and therefore, at timepoint 1, patient 11 was at 112% ($\frac{0.510}{0.455} \times 100\%$) of

her eventual steady state.

Patient 17 had been taking 0.125mg of digoxin daily prior to hospitalization. Upon hospitalization, the patient

was given extra doses of digoxin (0.625mg intravenous and 0.25mg oral) on the first two days and subsequently maintained on 0.25mg daily. Timepoint 1 was on the third day of the new maintenance regime. Based on an oral regime of 0.25mg daily, the predicted steady state total body stores of digoxin would be 0.556mg whereas based on the patient's drug history it was calculated that the total body stores were 0.54mg at timepoint 1. Thus this patient was assessed to be at 97% of his ultimate steady state.

Patient 18 had been taking 0.25mg of digoxin daily prior to hospitalization. Upon hospitalization, this regime was held for five days and then reinstituted at a dose of 0.125mg daily which continued for five more days before timepoint 1. On an oral maintenance dose of 0.125mg daily, the calculated total body stores at steady state would be 0.315mg. Based on the drug history the total body stores at timepoint 1 would be 0.276mg. Therefore, at timepoint 1, this patient was at 88% of his ultimate steady state.

a) Serum Digoxin Concentration

For all patients included in the results, a SDC was measured at each timepoint. Using timepoint 1 as the baseline, changes in the SDC occurring during the course of the study are illustrated in Tables IV and V for Type I and Type II patients respectively. Statistical analysis for both types of patients revealed that there was no significant changes in the SDC when measurements from timepoints 2 and 3

were separately compared with measurements from timepoint 1.

A plot of the change in the SDC versus the change in estimated creatinine clearance failed to reveal a significant relationship.

b) Functional Classification of Dyspnea

Tables VI and VII show the changes in the NYHA functional classification of dyspnea from timepoint 1 to timepoints 2 and 3. It is readily apparent that there were few patients who had any change in their degree of congestive heart failure as assessed by this method. Patient 5 was suffering from severe congestive heart failure upon entry into the study and this necessitated an increase in his dose of furosemide from 40 to 80mg daily. Subsequent to the discontinuation of disopyramide, the patient's heart failure improved somewhat enabling the dose of furosemide to be reduced to the previous level of 40mg daily. Patient 17 suffered a marked exacerbation of his congestive heart failure on the third day of the study, two days after the initiation of disopyramide therapy. This was controlled with an initial intravenous dose of furosemide followed by a doubling of the daily oral dose of furosemide to 80mg daily. Patients 2 and 20 both demonstrated a slightly improved functional classification at timepoint 3 compared with

timepoint 1.

c) Extracardiac Digoxin Toxicity Score

Questioning of the patients to elicit subjective symptoms indicative of digoxin toxicity was performed in all patients at all timepoints. Thus, this routine was performed a total of 37 times during the study. On all but seven occasions, the scores were zero. Patient 9 complained of blurred vision at timepoint 1 (score = 1), a complaint which disappeared after the discontinuation of disopyramide. Patient 2 complained of anorexia (score = 1) at timepoints 2 and 3 although this problem was not elicited at timepoint 1 before disopyramide therapy was initiated. No important changes in the SDC coincided with this symptom. Patient 4 complained of muscle weakness (score = 1) at timepoint 2 but at no other time during the study. There was not a significant change in the SDC at timepoint 2 in this patient. Patient 6 had symptoms of anorexia and muscle weakness (score = 3) at timepoint 1. These had disappeared by timepoint 2 and were not associated with any major elevation of the SDC at timepoint 1 relative to timepoint 2. Patient 11 complained of nausea and muscle weakness (score = 2) at timepoint 1, had a score of zero at timepoint 2 and had symptoms of nausea, anorexia and muscle weakness (score = 3) at timepoint 3. This patient had a fall in her SDC of approximately 0.3ng/mL from timepoint 1 to timepoints 2 and 3.

d) Continuous Electrocardiographic Monitoring

All but two patients (no. 17 and 20) had continuous electrocardiographic monitoring performed at timepoints 1 and 2. For patients 17 and 20, monitoring was not available due to mechanical problems with the monitors. In addition, although patient 18 was monitored, results are not available as the tapes were accidentally erased before they could be read.

The duration of monitoring was 20.8 ± 2.4 hours (mean $\pm$ standard error of mean, $n = 20$). Tables VIII and IX show the number of ventricular ectopic beats per hour (VEB/hr) recorded at timepoints 1 and 2 for Type I and Type II patients respectively. For both types of patients, there were no significant differences with respect to the frequency of VEB's when comparing timepoint 1 to timepoint 2. It is readily apparent that there was a large amount of interindividual variation with this measurement. Qualitative descriptions of the types of arrhythmias recorded on the tapes are listed in Tables X and XI.

e) Cardiothoracic Ratio

The cardiothoracic ratio was measured from the posterior-anterior chest X-ray at timepoints 1 and 2 in all patients but patient 2. Results are shown in Tables XII and XIII for Type I and Type II patients respectively. There were no significant changes in either group of patients.

f) PR Interval

When possible, the PR interval was measured from the patient's electrocardiogram at timepoints 1 and 2. This was not possible in the following patients: patients 17 and 19 were in atrial fibrillation and patients 2 and 18 had pacemakers which prevented the determination of the PR interval. Results are shown in Tables XIV and XV. Significant prolongation of the PR interval occurred in both types of patients when the patients were receiving the digoxin-disopyramide combination as opposed to digoxin.

g) Echocardiographic Results

Unfortunately, it was not possible for all patients in the study to have serial echocardiograms at timepoints 1 and 2. Five of the 13 patients did not have echocardiograms done due to a lack of availability of equipment. Also, in three patients who did have echocardiograms done, the procedure was technically difficult and the recordings were not of sufficient quality to allow for measurement of the various parameters. Therefore, adequate data were obtained from only five patients. The results are shown in Tables XVI and XVII.

The number of patients involved in this part of the study was not large enough to permit statistical analysis. Both Type I patients showed a small increase in both the EF and Vcf (indicative of a positive inotropic effect) upon

discontinuation of the disopyramide. Upon addition of disopyramide to the Type II patients, a negative inotropic effect was seen in patients 17 and 18 while patient 11 showed a slight absolute increase in the EF and Vcf.

h) Q-Tc Interval

The rate corrected Q-T interval (Q-Tc) was calculated for each patient at each of the first two timepoints in the study in order to ascertain that disopyramide was exerting a pharmacological effect. Results are shown in Tables XVIII and XIX. The discontinuation of disopyramide was associated with a significant decrease in the QTc interval. However, no significant change was observed in Type II patients.

i) Disopyramide Serum Concentration

All patients except for numbers 19 and 20 had serum samples analyzed for disopyramide concentration. Results are shown in Table XX.

V. Discussion

This study was carried out in an attempt to determine if disopyramide could induce a significant alteration in the SDC of patients maintained on digoxin therapy and, given such an alteration, how these changes in the SDC would affect the pharmacological activity of digoxin. The need for such a study became apparent on reviewing the available oral antiarrhythmic options suitable to use in combination with digoxin; also there is accumulating evidence suggesting that a large number of drugs have the potential to induce significant alterations in the SDC.

The results of this study indicate that disopyramide does not induce changes in the SDC. As a result, no correlations could be made between changes in the SDC and changes in a number of measurements used to assess the efficacy and toxicity of digoxin. Generally, there were few significant alterations in any of these measurements as is further discussed below.

It must be realized that this study does not rule out the possibility of disopyramide inducing subtle changes in the pharmacokinetics of digoxin. A more systematic pharmacokinetic analysis involving multiple serum levels and

measurements of the urinary excretion of digoxin and its metabolites would be needed to rule out disopyramide induced changes in digoxin kinetics. Nonetheless, this study does show that disopyramide does not affect the serum digoxin concentration to any significant degree.

Therefore, from a viewpoint which considers digoxin toxicity alone, the combination of digoxin and disopyramide can be deemed to be a safe one. Such a viewpoint, of course, does not consider the risks of inherent digoxin and/or disopyramide toxicity.

The results of this study are in general agreement with those of other investigators. Since the initiation of this study, two reports have appeared in the literature which deal with the same basic question.

Leahey et al.⁹³ studied the effects of quinidine, procainamide, mexiletine and disopyramide on the SDC. Ten patients on maintenance digoxin therapy had disopyramide added to their drug therapy regime and SDC's were measured before and after the initiation of disopyramide. In addition, 24 hour continuous electrocardiographic monitoring was obtained while the patients were receiving the digoxin and disopyramide. The initiation of disopyramide therapy failed to have any effect on the SDC, there was no worsening of arrhythmias and there was no change in the PR interval. Therefore, their results are similar to those reported in

this study with the exception that this study found a significant increase in the PR interval when the combination of disopyramide and digoxin was being given compared with the administration of digoxin alone. There are several differences between the two studies:

- i) The study of Leahey et al⁹³ included only those patients in whom disopyramide therapy was added to maintenance digoxin therapy (equivalent to Type II patients).
- ii) In the study by Leahey et al⁹³, the second SDC was apparently measured after a steady state blood level of disopyramide was assumed to have been reached. If disopyramide did affect the clearance of digoxin without affecting the volume of distribution then maximal effects on the SDC would not be expected to occur until a new steady-state blood level of digoxin had been reached. This would occur after the second SDC was measured.
- iii) Leahey et al⁹³ used only electrocardiographic parameters in an attempt to detect any changes in the pharmacologic effects of digoxin.

Manolas et al⁸⁸ have recently reported the results of a study which also looked at the effect of disopyramide on the SDC. In nine patients maintained on digoxin therapy, disopyramide was added and the SDC was measured before and after the addition of disopyramide. These investigators noted that the addition of disopyramide induced a small but

statistically significant increase in the SDC from 1.3 ± 0.16 nmol/L to 1.5 ± 0.19 nmol/L ($p < 0.05$). The authors deemed this increase to be clinically insignificant. However, as there were no systematic methods used to assess digoxin efficacy and/or toxicity, this statement could not be proven. Unfortunately, it was not clear from the report at what points in time, relative to the initiation of disopyramide therapy, the blood samples were drawn for the determination of the SDC's. In addition, the blood for the determination of the SDC was always drawn six hours after a dose of digoxin. This is at a point when, after an oral dose, the alpha distribution phase is merging with the beta elimination phase. This could potentially result in more variability in the measured SDC.

The small increase in the SDC reported by Manolas et al⁸⁸ is in contrast with the results of this study. A possible explanation for this discrepancy is that the mean serum disopyramide in the study by Manolas et al was considerably higher than that reported in this study (5.5 ± 0.71 ug/ml versus 2.93 ± 1.76 ug/ml). As mentioned earlier, the anticholinergic drug propantheline has been reported to increase the SDC and thus it is possible that with higher serum levels of disopyramide a greater anticholinergic effect might be expected and this might lead to an increase in the SDC. However, other dose related mechanisms cannot be ruled out at the present time.

Nonetheless, the results of this study are generally consistent with those reported by the other two groups and indicate that disopyramide does not significantly alter the SDC and thus may be a desirable oral antiarrhythmic agent to be used in combination with digoxin.

In an attempt to account for some of the variation seen in the SDC measurements a plot was made which related the change in SDC to changes in estimated creatinine clearance. No significant relationship could be found when analysis was done using least squares linear regression. Generally, one would expect to be able to demonstrate such a relationship. Failure to do so in this study could possibly be due to the fact that the estimation of the creatinine clearance using serum creatinine is not as precise as one would desire when the serum creatinine is fluctuating. Changes in serum creatinine would lag behind changes in serum creatinine clearance just as changes in the SDC would lag behind changes in digoxin clearance. Thus, although creatinine clearance and digoxin clearance have been shown to be related, such a relationship does not necessarily hold between the SDC and the serum creatinine concentration.

The NYHA functional classification of dyspnea was incorporated into the study in an attempt to provide a clinically relevant, albeit somewhat subjective, measurement of the degree of congestive heart failure. This rating method is widely used in clinical studies whose endpoint is

the degree of congestive heart failure. Few patients demonstrated any changes in their NYHA classification and this is consistent with the lack of change in the SDC. However, one might have expected larger changes in the NYHA classification considering the number of recent reports which have focused on the negative inotropic effect of disopyramide.^{113,114,119} In this study, two patients (no. 5, no.17) had worse functional classifications while on disopyramide which could possibly have been secondary to the administration of disopyramide. With such a small number, it is difficult to determine if these patients are part of a subgroup in whom the negative inotropic effect of disopyramide is more evident.

Upon reviewing the literature on digoxin prior to the initiation of the study, it became apparent that there was no established method for recording and scoring the signs and symptoms of extracardiac digoxin toxicity. Therefore, a system had to be designed for this study and as such, suffers from the fact that it has never been previously tested to determine its sensitivity and specificity. Nonetheless, it was felt that this study had to make an attempt to monitor for extracardiac digoxin toxicity. The scoring system used was based on the description of digitalis toxicity described in the study by Lely and Van Enter.³⁶ The scoring system was used a total of 37 times during the course of the study and on 30 of these occasions the score was zero. Although

some patients developed certain symptoms consistent with extracardiac digoxin toxicity, none of these symptoms was associated with marked increases in the SDC. Therefore, it is difficult to associate these symptoms with toxicity as the symptoms of extracardiac digoxin toxicity are quite non-specific. The failure of the scoring system to elicit a greater number of positive scores could be due to either a lack of sensitivity of the scoring system or to a lack of digoxin toxicity. In view of the other results obtained by this study, the latter reason would seem more tenable. Ten of the thirteen patients underwent continuous electrocardiographic monitoring at timepoints 1 and 2 in an attempt to document any arrhythmias suggestive of digoxin toxicity. The use of this technique has been a significant advance in the documentation of arrhythmias and such monitoring should preferably be done for at least six hours although 24 hours recording is most widely recommended.¹⁵⁸

There is some controversy regarding the proper method of reporting the results of continuous electrocardiographic monitoring. Both the frequency of ectopic beats and the Lown scoring system, based on the supposed malignancy of the ectopic beats¹⁵⁹, have been used. The advantages and disadvantages of each have been recently reviewed by Winkle.¹⁵⁸ For the purpose of this thesis, it was decided that the results would be analyzed according to the

frequency of ventricular ectopics and would also be tabulated as a qualitative description of the arrhythmias.

For most Type I patients, ventricular ectopic beats (VEB's) were uncommon while the patients were receiving the digoxin-disopyramide combination and the discontinuation of disopyramide produced little change in the frequency of VEB's. The lack of difference in the frequency of VEB's from timepoint 1 to timepoint 2 supports the clinical decision that was made to discontinue the disopyramide. Patient 12 showed a somewhat paradoxical response in that a marked reduction in the frequency of VEB's was seen after discontinuation of disopyramide. Also, this patient, while receiving both disopyramide and digoxin, experienced a bout of ventricular tachycardia which was not recorded after the disopyramide was discontinued. Antiarrhythmic drugs have been noted to induce such a paradoxical response.¹⁶⁰ Patient 19, on the other hand, demonstrated a marked increase in the frequency of VEB's, including an episode of ventricular tachycardia, upon discontinuation of disopyramide. In retrospect, it can be argued that the discontinuation of disopyramide in this patient was not warranted.

All Type II patients with continuous electrocardiographic recording data demonstrated a decrease in the frequency of VEB's when disopyramide was added to their drug regimes. However, due to the large variation in

response, statistical significance was not demonstrated.

Generally, Type II patients had more frequent and more malignant arrhythmias than did Type I patients.

In neither Type I nor Type II patient were any obvious digoxin-induced arrhythmias observed; there was also no apparent relationship between changes in the SDC and changes in either the frequency or type of arrhythmias.

It is possible that patient 14 (a dropout) died during the course of the study secondary to a ventricular arrhythmia. The patient died approximately 18 hours after the institution of disopyramide therapy and thus the disopyramide could be implicated as a causative factor. Unfortunately, the cause of death was not determinable and therefore such implications are purely speculative.

The cardiothoracic ratio (CTR) was measured in all patients with the exception of patient 2. This measurement was used as another indication of cardiac failure. As the CTR can produce false enlargement,¹⁶¹ a single measurement would be of little value. Therefore, consecutive measurements were made at timepoints 1 and 2 in an attempt to detect changes in the CTR. The changes which occurred were, for the most part, small, variable and unlikely to be clinically significant. (Dr. D.S. Beanlands, personal communication).

Digoxin slows conduction through the artioventricular node and therefore the PR interval from the electrocardiogram

was used to assess this effect. As mentioned previously, disopyramide produces variable effects on atrioventricular conduction as its direct effect can cause slowing whereas the anticholinergic effect may cause an increase in conduction.

In this study, the combination of disopyramide and digoxin caused a significant prolongation of the PR interval in both Type I and II patients. It is possible that this effect could be due to the digoxin-disopyramide combination.

Further study may be warranted in this area. In this study, no patient developed a clinically significant heart block.

Echocardiography has been used in the assessment of left ventricular function^{162, 163, 164} and, in this study, two measurements were used as indicators of the inotropic state of the heart. The cardiac ejection fraction represents the fraction of the blood in the left ventricle at end diastole which is expelled from the heart during contraction. This can be calculated from an echocardiogram of the left ventricle if two basic assumptions are made:

- i) that the shape of the ventricle is a prolate ellipse and
- ii) that the walls of the left ventricle contract uniformly.

In the population studied, these assumptions cannot

necessarily be made as the presence of heart failure confers a more spherical shape to the left ventricle and patients with coronary artery disease may have significant segmental abnormalities in left ventricular contraction.^{162,164} As a result, the absolute values for the ejection fractions measured in this study may not be reliable. This is evident upon looking at the results; generally the reported ejection fractions are greater than would be expected. However, serial measurements done on the same area should provide valuable information.

Due to the small numbers of patients, no conclusions on the echocardiographic data can be made. Four of the five patients did show deterioration of left ventricular function while on disopyramide. However, in only one of these (patient 17) was a concomitant deterioration seen in the NYHA functional classification. Thus, the clinical significance of the observed changes in the EF and Vcf is not clear. The changes seen are most likely reflective of the inherent negative inotropic effect of disopyramide.

A review of this study reveals a number of areas which might be considered to be limitations.

The number of patients completing the study might be thought of as being too small. During the course of the study Leahey et al⁹³ published their data on the digoxin-disopyramide combination and these results were used to calculate the number of patients required to detect a

change in the SDC of 0.3 ng/mL with an alpha error of 5% and a beta error of 10%. It was determined that at least five patients were required for each type of patient studied (I and II). This was confirmed using the results of this study. Using the within patient variations in SDC for both types of patients, the number of subjects required for the study was determined to range from three to seven. It is possible that with the numbers used, important changes might be missed in some of the other measurements but since the change in the SDC was the prime objective, the numbers used were based on this.

Due to relatively small number of subjects entered into the study and the possibility that the sample selected does not represent the underlying population, it can be argued that non-parametric statistics should be used. This was done for the results of changes in the SDC using the Wilcoxon signed rank test, the non-parametric equivalent of the student's t test for paired data. As shown in Table XXII, disopyramide still did not significantly alter the SDC.

Enrollment of patients into the study was not random as it depended on the presence of the co-ordinator of the study. Also, the population studied was quite heterogenous as the number and severity of disease states present, the doses of digoxin and disopyramide used and the variety of other drugs

used simultaneously were quite varied. Only one of the patients was female and this same subject was the only patient under the age of forty.

Two patients (patient 7 and 9) did not complete the entire study but data from the first two timepoints were still included in the analysis.

Three patients (patients 11, 17 and 18) were assumed to be at steady state with respect to their SDC. These assumptions were based on pharmacokinetic calculations as described earlier. Due to interindividual differences in the disposition of digoxin, it is quite possible that these patients were not within 15% of steady state at the outset of the study. A more ideal method for the assessment of steady state would be to measure the SDC on two consecutive days prior to entry to the study. However, this method can be time consuming and since it was felt that most of the patients would be on regular maintenance doses of digoxin, this latter method was not used.

This study highlighted the difficulties one can encounter in trying to assess the beneficial and toxic effects of digoxin. The NYHA functional classification of dyspnea and the scoring system for extracardiac symptoms of digoxin toxicity are somewhat subjective measurements and therefore the data provided must be considered in light of this. The objective assessment of digoxin efficacy and toxicity could be an expensive undertaking and it was

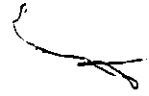
fortunate in this study to have partial access to continuous electrocardiographic recording devices and an echocardiogram. Ideally, such equipment would be available on demand for a study such as this.

The lack of availability of both equipment and of the patient's time prevented measurement of all parameters at timepoint 3. Many of the patients were outpatients at this time and as a result it would have been difficult to schedule all tests for the final timepoint. Therefore, if changes in the SDC did become evident at timepoint 3 it would have been possible to correlate these changes with only the relatively subjective assessments of digoxin efficacy and toxicity.

Examination of the serum disopyramide concentrations reveals significant interindividual variation in the results. In addition, the concentrations measured are lower than expected and were generally at the lower end of the proposed therapeutic range. This raises the question as to whether the doses of disopyramide used were pharmacologically effective. Based on the observed changes in the PR interval and QTc interval, it would seem that disopyramide was in fact exerting a pharmacological effect. Caution must be used in accepting the proposed therapeutic range as this has not been systematically tested in clinical trials.

Despite the above mentioned limitations, this study does provide an answer to the primary question which was asked. Disopyramide did not induce any significant

alterations in the SDC. Additionally, very few changes were seen in a variety of tests used to assess the efficacy and toxicity of digoxin. Trends which suggest that disopyramide may produce clinically significant heart failure and heart block in patients on digoxin were elicited. Therefore, further study will be required to determine if the digoxin-disopyramide combination can be safely used in all patients or if there are certain subgroups of patients in whom such a combination may be detrimental.



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TABLE I. SERUM DIGOXIN CONCENTRATION (ng/ml)

<u>Reference</u>	<u>Toxic Patients</u>	<u>Non-Toxic Patients</u>	<u>Significance</u>
Fogelman et al ⁶⁵	n=18 1.69 + 1.29	n=76 1.41 + 1.09	ns
Beller et al ³²	n=31 2.3 + 1.6	n=96 1.0 + 0.5	p<0.005
Evered and Chapman ⁴³	n=22 3.4 + 1.2	n=86 1.4 + 0.8	p<0.001
Howard et al ⁴⁸	n=13 0.88 + 0.14	n=73 0.94 + 0.09	ns
Park et al ⁶⁶	n=21 3.8 + 0.5	n=108 1.1 + 0.1	p<0.005

TABLE II. PATIENT CHARACTERISTICS UPON ENTRY INTO STUDY

TYPE	PT. NO.	AGE (yr)	PRIMARY DIAGNOSIS	NYHA CLASS	DIGOXIN MG/DAY	DISOPYRAMIDE MG/DAY
I	3	56	MI, CHF, VA	I	0.25	450
I	5	73	MI, CHF, VA CHB	IV	0.25	600
I	7	47	MI, CHF, VA	III	0.125	400
I	9	80	CHF, VA	I	0.25	400
I	12	52	CHF, VA	I	0.25	400
I	19	65	CHF, VA, SBE	I	0.25	600
I	20	44	CHF, VA	II	0.25	600
II	2	58	CHF, VA	III	0.125	600
II	4	65	CHF, VA	II	0.25	400
II	6	64	CHF, VA	III	0.25	600
II	11	28	CHF, VA, AS, MR	III	0.25	400, 600
II	17	65	MI, CHF, SVA	II	0.25	400
II	18	70	SVA	I	0.125	400

MI - MYOCARDIAL INFARCTION
VA - VENTRICULAR ARRHYTHMIAS
SVA - ATRIAL ARRHYTHMIAS
AS - AORTIC STENOSIS
CHF - CONGESTIVE HEART FAILURE
CHB - COMPLETE HEART BLOCK
SBE - SUBACUTE BACTERIAL ENDOCARDITIS
MR - MITRAL REGURGITATION

TABLE III. MEAN VALUES FOR SERUM CREATININE, BLOOD UREA NITROGEN AND ESTIMATED CREATININE CLEARANCE DURING THE STUDY PERIOD. EXCEPT WHERE DENOTED, n=3. RANGE IN PARENTHESIS.

Type	Patient	Serum Creatinine mg/dL	Blood Urea Nitrogen mg/dL	Estimated Creatinine Clearance mL/min
I	3*	1.4(1.3 - 1.4)	20(18 - 21)	56(54 - 58)
I	5	1.5(1.3 - 1.7)	42(39 - 44)	40(35 - 48)
I	7*	1.3(1.1 - 1.5)	17(16 - 17)	79(65 - 93)
I	9	1.0(0.9 - 1.0)	25(23 - 27)	68(65 - 70)
I	12	1.4(1.2 - 1.6)	17(13 - 20)	53(45 - 60)
I	19	1.2(1.1 - 1.4)	14(11 - 16)	65(60 - 70)
I	20	1.1(0.9 - 1.3)	16(14 - 18)	65(57 - 72)
II	2*	1.7(1.6 - 1.8)	37(35 - 39)	52(48 - 55)
II	4	1.3(1.2 - 1.6)	23(21 - 25)	53(47 - 66)
II	6*	1.1(0.9 - 1.2)	11(9 - 14)	57(52 - 62)
II	11	1.0(0.9 - 1.0)	11(10 - 13)	85(82 - 90)
II	17	1.4(1.3 - 1.7)	20(17 - 26)	59(48 - 65)
II	18	1.4(1.4 - 1.5)	23(16 - 28)	49(46 - 50)

* n=2

Table IV. DRUGS OTHER THAN DIGOXIN AND DISOPYRAMIDE
ADMINISTERED DURING STUDY.

* dose increased during study

** dose decreased during study

<u>Type</u>	<u>Patient</u>	
I	3	- cholestyramine, dioctyl sodium sulfosuccinate, furosemide, flurazepam, potassium chloride
I	5	- nitroglycerin ointment, potassium chloride, heparin subcutaneous, furosemide*, isosorbide dinitrate*
I	7	- isosorbide dinitrate, indomethacin**, propranolol**
I	9	- ketoprofen, psyllium hydrophilic, oxazepam, chlorpropamide
I	12	- furosemide*, acetylsalicylic acid**
I	20	
I	19	- furosemide, potassium chloride, penicillin G, streptomycin
II	2	- furosemide, quinidine, flurazepam, spironolactone, lidocaine**
II	4	- diazepam, hydrocortisone cream*, hydrochlorothiazide*, hydrallazine*
II	6	- oxazepam, carbachol eyedrops, furosemide**, potassium chloride**, procainamide**, hydrochlorothiazide**, isosorbide dinitrate**
II	11	- ferrous sulfate**, flurazepam**
II	17	- heparin subcutaneous, potassium chloride, methyldopa, furosemide*, colchicine*, phenylbutazone**
II	18	- allopurinol, hydrochlorothiazide-triamterene**, chloral hydrate**

Table V. CHANGES IN SERUM DIGOXIN CONCENTRATION (SDC) IN TYPE I PATIENTS

PATIENT	TIMEPOINT 1 SDC NG/ML	TIMEPOINT 2 Δ SDC NG/ML	TIMEPOINT 3 Δ SDC NG/ML
3	0.75	-0.10	+0.13
5	1.84	-0.34	-0.07
7	0.55	-0.03	
9	0.95	+0.10	
12	1.13	-0.20	-0.16
19	1.08	-0.28	-0.34
20	0.83	-0.09	+0.21
MEAN ± SEM		-0.13±0.15 ns*	-0.05±0.22 ns*

* not statistically significant (t-test for paired data).

TABLE VI. CHANGES IN SERUM DIGOXIN CONCENTRATION (SDC) IN TYPE II PATIENTS

PATIENT	TIMEPOINT 1 SDC NG/ML	TIMEPOINT 2 ASDC NG/ML	TIMEPOINT 3 ΔSDC NG/ML
2	2.10	+0.05	-0.05
4	0.86	-0.04	+0.24
6	0.83	+0.03	-0.33
11	1.12	-0.03	-0.28
17	1.49	-0.28	-0.33
18	0.46	+0.02	+0.06
MEAN±SEM		-0.09±0.16 ns*	-0.12±0.24 ns*

not statistically significant (t-test for paired data)

Table VII. CHANGES IN NYHA CLASSIFICATION OF DYSPNEA IN TYPE I. PATIENTS

PATIENT	TIMEPOINT 1 CLASS	TIMEPOINT 2 ΔCLASS	TIMEPOINT 3 ΔCLASS
3	I	0	0
5	IV	-I	-I
7	III	0	
9	I	0	
12	I	0	0
19	I	0	0
20	II	0	-I

ns*

ns*

* not statistically significant (Wilcoxon signed rank test)

TABLE VIII. CHANGES IN NYHA CLASSIFICATION OF DYSPNEA IN TYPE II PATIENTS

PATIENT	TIMEPOINT 1 CLASS	TIMEPOINT 2 ΔCLASS	TIMEPOINT 3 ΔCLASS
2	III	0	-I
4	II	0	0
6	III	0	0
11	III	0	0
17	II	+II	+I
18	I	0	0

ns*

ns*

* not statistically significant (Wilcoxon signed rank test)

TABLE IX. CHANGES IN THE NUMBER OF VENTRICULAR ECTOPIC BEATS (VEB) PER HOUR. FROM TIMEPOINT 1 TO TIMEPOINT 2 IN TYPE I PATIENTS.

PATIENT	TIMEPOINT 1 VEB/HR	TIMEPOINT 2 Δ VEB/HR
3	6.4	-5.3
5	3.2	-2.2
7	0.2	+1.9
9	0.2	+4.1
12	21.4	-14.2
19	2.4	+47.0
MEAN±SEM		5.1±21.5 ns*

* not statistically significant (t-test for paired data)

TABLE X. CHANGES IN THE NUMBER OF VENTRICULAR ECTOPIC BEATS (VEB) PER HOUR IN TYPE II PATIENTS FROM TIMEPOINT 1 TO TIMEPOINT 2.

PATIENT	TIMEPOINT 1 VEB/HR	TIMEPOINT 2 Δ VEB/HR
2	290.0	-230.0
4	7.5	-1.1
6	9.2	-8.2
11	37.5	-36.1
MEAN+SEM		-68.9+108.5 ns*

* not statistically significant (t-test for paired data).

TABLE XI. ARRHYTHMIAS RECORDED ON CONTINUOUS
ELECTROCARDIOGRAPHIC MONITORING IN TYPE I
PATIENTS.

PATIENT	TIMEPOINT 1	TIMEPOINT 2
3	VEB, SVEB	VEB, SVEB
5	VEB, SVEB	VEB, SVEB, frequent sinus pauses
7	VEB, SVEB	VEB, SVEB
9	VEB, SVEB	VEB, SVEB
12	VEB, SVEB, VT	VEB, SVEB
19	VEB, AF	VEB, AF, VT

VEB = ventricular ectopic beats, SVEB = supraventricular
ectopic beats, VT = ventricular tachycardia, AF = atrial
fibrillation, PAT = paroxysmal atrial tachycardia.

TABLE XII. ARRHYTHMIAS RECORDED ON CONTINUOUS
ELECTROCARDIOGRAPHIC MONITORING IN TYPE II
PATIENTS.

PATIENT	TIMEPOINT 1	TIMEPOINT 2
2.	VEB, SVEB, couplets, triplets, VT	VEB, SVEB; couplet, triplet
4	VEB, SVEB, couplets, triplets	VEB; SVEB
6	VEB, SVEB	VEB, SVEB, PAT
11.	VEB, SVEB, VT, PAT	VEB, SVEB, VT

VEB = ventricular ectopic beats, SVEB = supraventricular
ectopic beats, VT = ventricular tachycardia, AF = atrial
fibrillation, PAT = paroxysmal atrial tachycardia.

TABLE XIII. CHANGES IN THE CARDIOTHORACIC RATIO (CTR) FROM TIMEPOINT 1 TO TIMEPOINT 2 IN TYPE I PATIENTS.

PATIENT	TIMEPOINT 1 CTR %	TIMEPOINT 2 ΔCTR %
3	52	0
5	43	-2
7	51	+3
9	52	-2
12	46	+1
19	50	+3
20	53	-1

ns*

* not statistically significantly (t-test) for paired data)

TABLE XIV. CHANGES IN THE CARDIOTHORACIC RATIO (CTR) FROM TIMEPOINT 1 AND TIMEPOINT 2 IN TYPE II PATIENTS.

PATIENT	TIMEPOINT 1 CTR %	TIMEPOINT 2 ΔCTR %
4	51	-1
6	51	0
11	44	+2
17	50	+3
18	51	-3

ns*

* not statistically significant (t-test for paired data).

TABLE XV. CHANGES IN THE PR INTERVAL (MSEC) FROM TIMEPOINT 1 TO TIMEPOINT 2 IN TYPE I PATIENTS

PATIENT	TIMEPOINT 1 PR	TIMEPOINT 2 Δ PR
3	15	0
5	18	-2
7	18	-2
9	24	0
12	22	-2
20	20	-2

$p < 0.05^*$

* t-test for paired data

TABLE XVI. CHANGES IN THE PR INTERVAL (MSEC) FROM TIMEPOINT 1 TO TIMEPOINT 2 IN TYPE II PATIENTS.

PATIENT	TIMEPOINT 1 PR	TIMEPOINT 2 Δ PR
4	18	+2
6	16	+2
11	18	+2

p < 0.05*

* t-test for paired data

Table XVII. CHANGES IN ECHOCARDIOGRAPHIC PARAMETERS FROM
TIMEPOINT 1 TO TIMEPOINT 2 IN TYPE I PATIENTS

PATIENT	TIMEPOINT 1		TIMEPOINT 2	
	EF %	Vcf	Δ EF %	Δ Vcf
19	76	1.7	+3	+0.2
20	61	1.4	+6	+0.3

EF = ejection fraction

Vcf = velocity of circumferential fibre shortening

Table XVIII. CHANGES IN ECHOCARDIOGRAPHIC PARAMETERS FROM TIMEPOINT 1 TO TIMEPOINT 2 IN TYPE II PATIENTS.

PATIENT	TIMEPOINT 1		TIMEPOINT 2	
	EF %	Vcf	Δ EF %	Δ Vcf
11	70	1.5	+1	+0.1
17	72	1.9	-5	-0.6
18	92	3.3	-3	-0.6

EF = ejection fraction

Vcf = velocity of circumferential fiber shortening
(circumferences/second)

Table XIX. CHANGE IN QTc INTERVAL (SECONDS) FROM
TIMEPOINT 1 TO TIMEPOINT 2 IN TYPE I
PATIENTS.

PATIENT	TIMEPOINT 1 QTc(sec)	TIMEPOINT 2 QTc(sec)
3	0.40	-0.02
5	0.48	-0.05
7	0.41	-0.02
9	0.40	-0.08
12	0.42	-0.07
19	0.48	-0.05
20	0.40	0.00

$p < 0.05^*$

* t-test for paired data.



Table XX. CHANGE IN QTc INTERVAL (SECONDS) FROM
TIMEPOINT 1 TO TIMEPOINT 2 IN TYPE II
PATIENTS

PATIENT	TIMEPOINT 1 QTc(sec)	TIMEPOINT 2 Δ QTc (sec)
2	0.53	+0.07
4	0.40	-0.02
6	0.47	+0.05
11	0.39	+0.03
17	0.40	-0.01
18	0.39	0.00

ns*

* not statistically significant (t-test for paired data)

Table XXI. SERUM DISOPYRAMIDE CONCENTRATION (ug/mL) IN TYPE I AND TYPE II PATIENTS.

Type	Patient	Serum Disopyramide Concentration ug/mL
I	3	2.99
I	5	1.72
I	7	2.90
I	9	1.84
I	12	2.55
II	2	2.24
II	4	1.79
II	6	2.85
II	11	1.83
II	17	3.77
II	18	7.87

Table XXII. CHANGES IN SDC EVALUATED USING
WILCOXON SIGNED RANK TEST.

	n	Sum Negative Ranks	Sum Positive	p
Type I Patients				
Timepoint 2 vs. 1	7	-24.5	+3.5	>0.05
Timepoint 3 vs. 1	5	-9	+6	>0.05
Type II Patients				
Timepoint 2 vs. 1	6	-12.5	+9	>0.05
Timepoint 3 vs. 1	6	-16	+5	>0.05

Figure 1. Chemical Structure of Digoxin

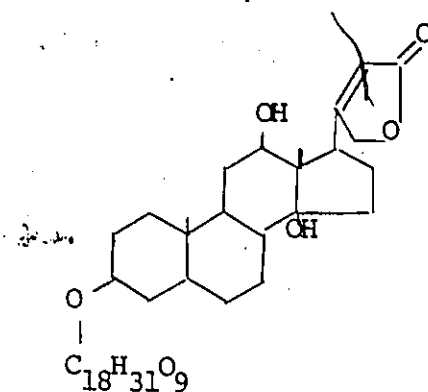


Figure 2. Chemical Structure of Disopyramide

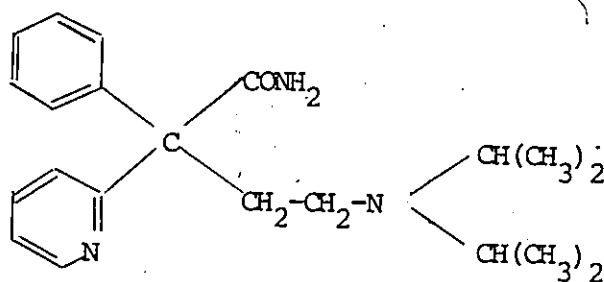
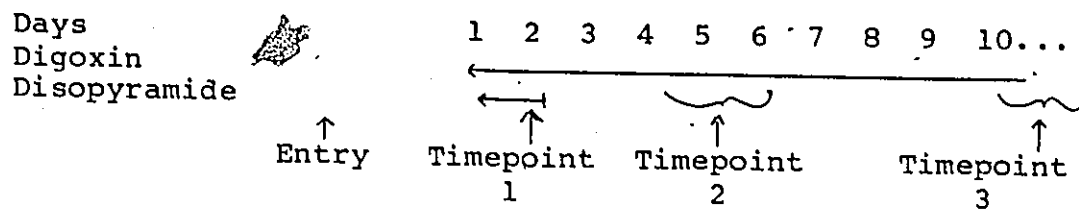
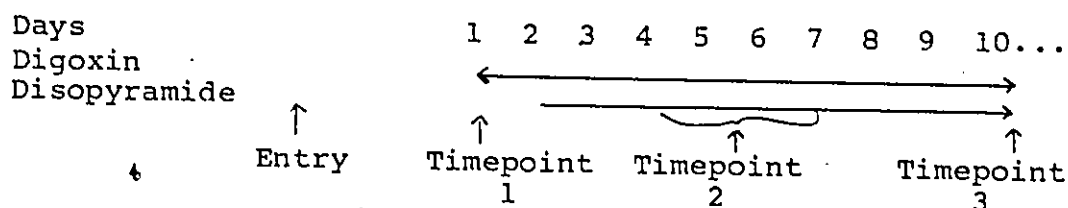


Figure 3. Time Course of Study

A) Type I Patients



B) Type II Patients



APPENDIX 1

CONSENT FORM

The Cardiac Unit of the Ottawa Civic Hospital and the Pharmacology Department of the University of Ottawa are conducting a study to examine a possible drug interaction between two drugs, digoxin and disopyramide. This study is under the supervision of Dr. D. S. Beanlands, Dr. W. M. McLean and will be coordinated by a graduate student, Mr. M. G. Tierney.

We seek your participation in this study because your physician has ordered the two drugs for you. Your assistance in this study will help us to determine for you and others how these drugs act when used together. The study will take approximately two weeks and you will be required to undergo some special tests as well as give some blood samples.

In light of this information, which I have considered and understand, I _____ agree to participate in this study to examine the possibility of a drug interaction between digoxin and disopyramide. I understand that I am free to withdraw from the study at any time without prejudice to myself.

Signature of Participant: _____

Signature of Coordinator: _____

Date: _____

Appendix II

Analysis of Digoxin Assay Accuracy

Month	Mean (ng/mL)	Standard Deviation	Coefficient of Variation
August 1979	0.97	0.05	5.3
	1.91	0.07	3.7
	2.50	0.09	3.6
September 1979	0.99	0.025	2.5
	1.94	0.05	2.6
	2.58	0.14	5.4
October 1979	0.95	0.05	5.4
	1.91	0.10	5.0
	2.58	0.16	6.3
November 1979	0.97	0.07	6.9
	1.87	0.07	3.8
	2.56	0.10	4.0
January 1980	0.30	0.08	26.7
	1.29	0.08	6.2
	3.16	0.10	31.3
February 1980	0.29	0.06	21.0
	1.27	0.10	7.5
	3.10	0.13	4.3
March 1980	0.26	0.09	34.1
	1.34	0.04	3.2
	3.26	0.19	5.7
April 1980	0.30	0.09	30.0
	1.33	0.06	4.5
	3.25	0.19	5.87
May 1980	0.79	0.04	12.2
	1.31	0.05	3.8
	3.29	0.21	0.37
June 1980	0.24	0.08	3.33
	1.31	0.06	4.6
	3.11	0.19	6.1
July 1980	0.30	0.08	26.7
	1.37	0.08	5.8
	3.12	0.16	5.12
August 1980	0.23	0.1	45.0
	1.24	0.07	5.6
	3.22	0.13	4.5

Note: Results for December 1979 are not available.

APPENDIX III

Assessment of Digoxin Toxicity

The following questions will be posed to the patient by the graduate student researcher. The questions will not be asked in a manner so as to lead the patient to an answer. Whenever possible, answers will be verified, by questioning the nurses caring for the patient. The graduate student researcher will be responsible for assigning a score to each answer and the cumulative score will be used as an index of extracardiac digoxin toxicity.

- 1) How have you been feeling during the past 24 hours? Do you have any complaints about the way you feel?

Score two points for each of the following volunteered complaints: anorexia, nausea and/or vomiting, diarrhea, muscular weakness, visual complaints, psychic disturbances.

- 2) Has your stomach been upset at all in the past day? If so, when and how badly? How has your appetite been?

Anorexia

- 0 - none
1 - less than 2 meals in past 24 hours
2 - have not eaten in past 24 hours

Nausea and/or Vomiting

- 0 - none
1 - nausea in past 24 hours
2 - vomiting in past 24 hours

Diarrhea

- 0 - none
1 - 3 loose stools in past 24 hours
2 - 3 loose stools in past 24 hours

- 3) Do you feel weak or tired?

Muscular Weakness

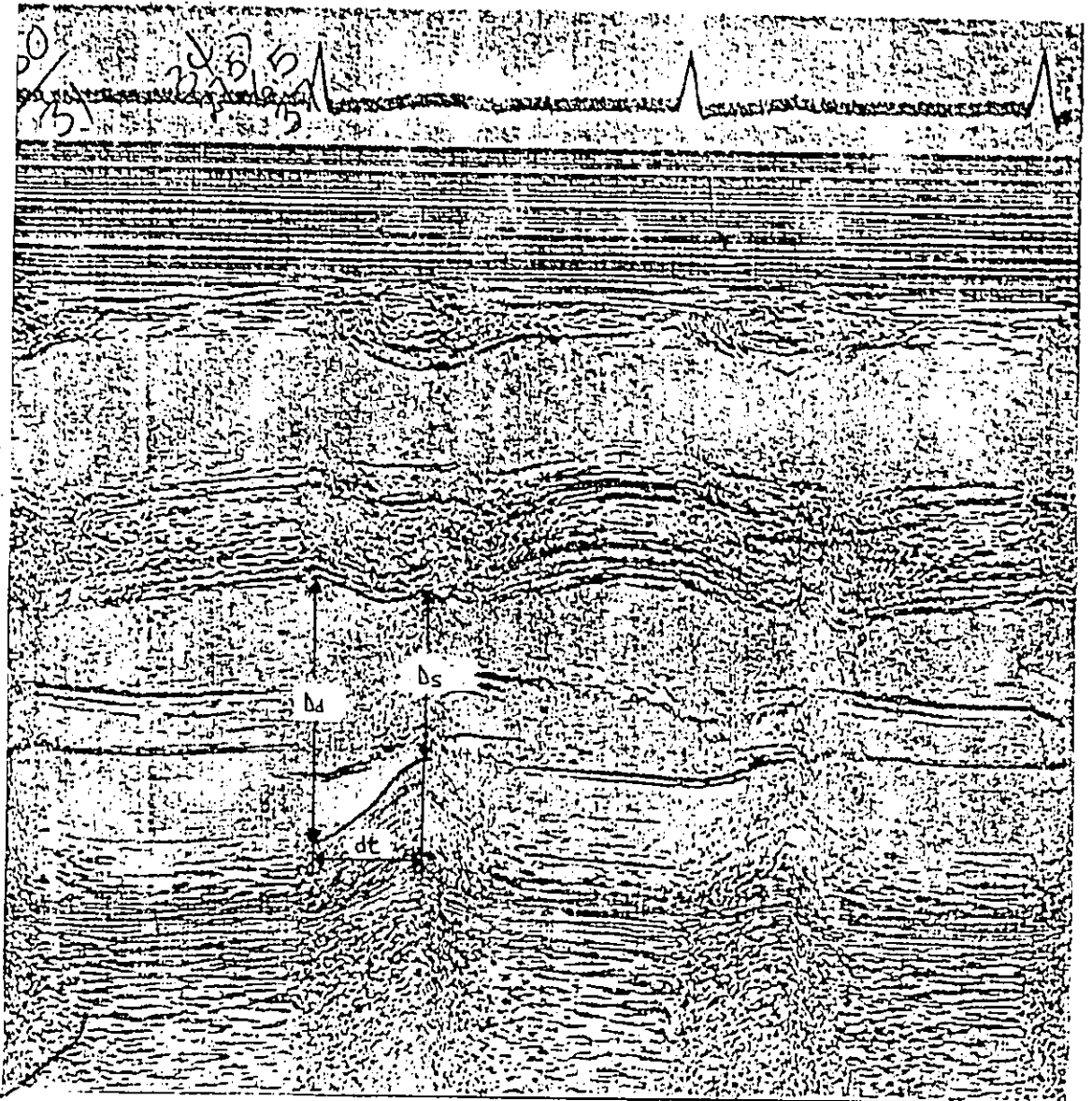
- 0 - none
- 1 - trouble walking
- 2 - too weak to get out of bed

- 4) How has your vision been?

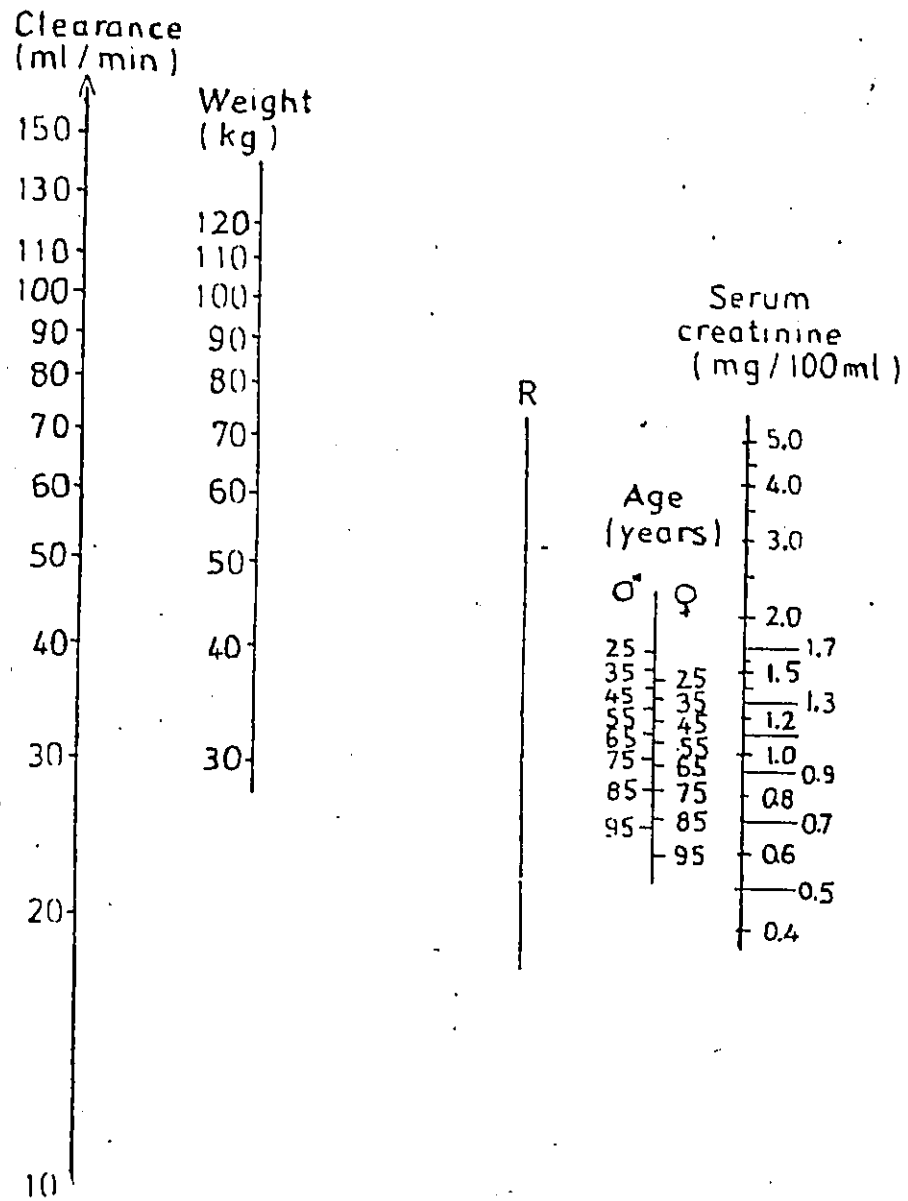
- 0 - no complaints
- 1 - hazy vision, difficulty in reading
- 2 - as in "1" plus colour disturbances

- 5) Check with nurses for signs of psychic disturbances, nightmares, hallucinations, agitation, nervousness, restlessness.

- 0 - 2 of above
- 1 - 2 or 3 of above
- 2 - 4 or 5 above



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Appendix V



Appendix VI

Mr.

Mrs. _____ . Please mark in below the time at which you take your medication. Do your best to take the pills regularly at the times indicated. Do not take your dose of digoxin on _____ until after your appointment which is at _____.

Date _____

Drug, Dose, Time
to be taken _____

Drug, Dose, Time
to be taken _____