Cardiol

NEWER ANTIARRHYTHMIC AGENTS

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We go to gain a little patch of ground

That hath in it no profit but the name.

SHAKESPEARE: *Hamlet* IV,IV,18

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MEDICAL GRAND ROUNDS

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Therapy for the chronic suppression of ventricular arrhythmias has been very limited until recently. Chronic oral therapy has been limited to one subclass of antiarrhythmic agents. The purpose of this discussion is to focus on the latest four agents to become available and the three classes of antiarrhythmic agents that they represent. This discussion will be a clinical discussion of these agents, their usefulness, their side effects, and their clinical problems. Before discussing these clinical aspects, a short review of the classification systems and the basic electrophysiology of these agents is in order to better understand the relationships between the drugs and possible interactions that might occur.

Classification of Antiarrhythmic Agents Since 1970 Vaughn Williams has described and revised probably the best classification system of antiarrhythmic agents which is shown in Table I.[1-6] Modifications of this classification and additional information have been supplied by the work of several other investigators including Bigger, Gettes, Hoffman, and Rosen.[7-10]

Table I
Classification of Antiarrhythmic Agents[11-13]

Class	Action	Agents
I	Local anesthetic effect Slows inward Na movement	
I-A	Depresses phase 0 Slows conduction Prolongs repolarization	quinidine procainamide disopyramide
I-B	Depresses phase 0 in abnormal fibers, not in normal Shortens repolarization	lidocaine phenytoin tocainide mexiletine *ethmozin*
I-C	Markedly depresses phase 0 Markedly slows conduction Little effect on repolarization	flecainide *lorcainide* *encainide* *propafenone* *indecainide*
II	Beta adrenergic blockade	propranolol
III	Prolongs repolarization	bretylium amiodarone *sotalol* *N-acetylprocainamide* *clofilium*
IV	Calcium channel blockade	verapamil diltiazem

Drugs listed in *italics* are drugs which show some promise of being marketed within the next three years.

Class I agents are agents which possess local anesthetic properties upon the cell membrane. These agents slow the inward movement of sodium into the cell

during phase 0 of the action potential (depolarization of the cell). There are three distinct subtypes or classes within the Class I agents. The three subtypes vary as to their effects both on phase 0 and repolarization. Phase 0 is depressed or slowed with I-A agents. With I-B agents, phase 0 is only slightly effected in normal fibers; however, in abnormal fibers phase 0 is depressed or slowed. With I-C agents, there is marked slowing of phase 0. When the action potential duration is examined, I-A agents cause prolongation, I-B agents cause shortening, and I-C agents have little effect. Conduction is generally not affected by I-B agents, is slowed by I-A agents, and is markedly slowed by I-C agents. Class II antiarrhythmic agents are those which have beta adrenergic blocking activity. The beta blocking agents vary in their antiarrhythmic properties. Propranolol, for example, has some quinidine-like membrane activity which is seen in varying degrees with other beta adrenergic blocking agents. Agents with intrinsic sympathomimetic activity may not be as effective an antiarrhythmic agent as those which do not possess this activity. Sotalol, an experimental agent in this country, also has some Class III effects of prolonging repolarization. Class III agents prolong the action potential duration while not affecting phase 0 or the rate of depolarization of the cell membrane. Class IV agents are calcium channel blockers. It should be noted that there is marked variance between calcium channel blockers as far as their antiarrhythmic effects are concerned. Nifedipine has very little antiarrhythmic effect, while verapamil has the most. This classification is based on experimental data from isolated strips. In the intact individual, there may be variations of these effects on different parts of the heart.[1-18]

The Class I Agents

Electrophysiology The basic electrophysiologic effects of the Class I drugs in normal cardiac tissue are summarized in many texts. The electrophysiologic effects of Class I drugs on various cardiac tissues which are of more obvious clinical significance are summarized in Table II.

Table II
Electrophysiologic Effects of Class I Agents on Cardiac Tissues[13]

Cardiac Tissue	Parameter	I-A	I-B	I-C
Sinus node	sinus node recovery time	↑	0	↑
Atrium	Conduction	↑	0	↑↑
	ERP	↑↑	0	↑
AV node	Conduction	0	0	0
	ERP			
	Normal	0	0	0
	Antegrade fast path	-	-	0
	Retrograde fast path	↑	-	↑↑
His-Purkinje	Conduction	↑	0	↑↑
	ERP			
	Antegrade	↑	↓	-
	Retrograde	↑	-	-
Ventricle	Conduction	↑	0	↑↑
	ERP	↑	0	↑

Table II (contd.)
Electrophysiologic Effects of Class I Agents on Cardiac Tissues[13]

Cardiac Tissue	Parameter	I-A	I-B	I-C
Accessory AV pathway	Conduction			
	Antegrade	↑	0	↑↑
	Retrograde	↑	0	↑↑
	ERP			
	Antegrade	↑	↑	↑↑
	Retrograde	↑	0	↑↑

ERP = effective refractory period
↑ = increase, ↑↑ = marked increase, ↓ = decrease, 0 = unchanged,
- = not known

As can be seen, I-A agents increase conduction time and the effective refractory period in all tissues except the AV node, as do the I-C agents. The I-B agents do not affect either conduction or refractory period greatly. Though the direct effects of agents are shown in this chart, the net effects may vary. For example, many antiarrhythmic agents have a vagolytic effect which will speed the sinus node and may increase conduction in the AV node.[13]

The effects of these agents on the mechanisms of arrhythmias is very similar, though their electrophysiologic characteristics vary. Automaticity, the inherent characteristic of a pacemaker cell to fire itself, is suppressed by all three types of Class I agents. All three types of Class I agents can prevent reentry by converting unidirectional block to bidirectional block. Only the I-B agents may also prevent reentry by breaking the unidirectional block. Hence, the major methods by which these agents prevent arrhythmias is very similar.

Electrocardiographic Findings The effect of these agents on the electrocardiogram is shown in Table III.

Table III
Effects of Class I Agents on Scalar and His Electrocardiograms[13]

Intervals	I-A	I-B	I-C
AH	↑↓	0	↑
HV	↑	0	↑↑
PR	0	0	↑
QRS	↑	0	↑↑
QT	↑↑	0	↑
JT	↑↑	0	0

↑ = increase, ↑↑ = marked increase, ↓ = decrease,
↑↓ = increase or decrease, 0 = no change

The PR interval is normally only affected by I-C agents. The QRS interval is markedly increased by I-C agents and may increase with I-A agents. The QT and JT intervals are markedly increased by I-A agents; the QT may be prolonged by I-C agents. I-B agents usually do not cause any measurable changes on the electrocardiogram.[13]

Tocainide (Tonocard)

Pharmacology of Tocainide Tocainide is a primary amine derivative of lidocaine, which was synthesized in a search for an oral analog of lidocaine which was not degraded during the first pass after absorption.[19,20] Tocainide is a Class I-B agent.[21] As a Class I-B agent, it affects slightly the rate of rise of depolarization, phase 0, and shortens the action potential duration and refractory period of Purkinje fibers.[21] It has little effect on the sinus node in the majority of patients, with various studies showing between a 1% decrease and a 4% increase in heart rate.[22-25] Sinus node recovery time was increased in one-half of the patients in one study.[26] The atria are not generally affected by tocainide. The response of the AV node to tocainide has been variable. A few patients have shown an increase in the A-H time of the His electrocardiogram, while most patients have shown no change.[26-28] A few patients have been reported as showing AV block after tocainide.[29] In our own series we have seen two patients who developed second degree block on tocainide, though the majority of patients showed no changes in PR intervals. The effects on the ventricles have not shown any increases in the QRS intervals.[26,30] The effect of tocainide on the QT interval has been variable. Some series have shown shortening of the QT interval[30,31], while other studies have not shown an effect on the QT intervals.[28,32]

Tocainide is almost completely absorbed, with a peak effect from one to one and one-half hours after ingestion orally.[17,33,34] After the initial phase, the serum half life is about 11 hours.[33] Peak absorption is affected by food, with a meal lowering the peak level by as much as 40%; however, total absorption is unaffected.[33] This factor is important when one tries to avoid side effects which occur mostly at peak drug levels. The metabolites of tocainide do not appear to have any antiarrhythmic activity.[35] About one-half of the drug is excreted unmetabolized by the kidneys, while the rest is metabolized to a glucuronide in the liver prior to excretion by the kidneys.[36] Though the normal terminal phase half life of tocainide is about 11 hours, it has been shown to be prolonged in different states. The presence of chronic arrhythmias and left ventricular dysfunction have been shown to increase the half life to from 13.5 to 19 hours.[17,37,38] Renal failure has been shown to increase the half life to 22.3 hours.[39] About 25% of the body stores of tocainide is cleared with one hemodialysis run.[39] Liver disease may also affect the half life, though this has not been proven. In our series one patient became unconscious after three days of therapy and remained unconscious for eight hours. This patient had bad liver disease and responded to cessation of the drug; unfortunately, drug blood levels were not available at the time. The therapeutic dose range of tocainide is 3 to 10 µg/ml. Toxicity is frequently found above 10 µg/ml.[17,37,38,40-44]

Efficacy of Tocainide Tocainide has been studied with animal models, with open label studies in patients with arrhythmias, and with a few placebo-controlled trials. There have also been several comparative trials between tocainide and other antiarrhythmic agents. In animal models, tocainide has been shown to increase the ventricular fibrillation threshold by 28, 53, and 71% at low, medium, and high doses of tocainide.[45] A summary of some of the trials in humans with ventricular arrhythmias is summarized in Table IV.

Complications
CNS
tremor 45%
Paresth 15%
Dizz 10%
confusion 15%

N & V 45% - 20% discontinued.
Brady-Heart Blk 7%
Night sweats 20%

Table IV
Efficacy of Tocainide

Author	# Patients	# Responding (%)	Ave. Reduction*
Winkle[17]	15	11 (73%)	91%
McDevitt[37]	8	most	
Woosley[41] **	12	8 (67%)	83%
Winkle[46] ***	17	9 (53%)	
Ryan[47] ***	30	13 (43%)	88%
LeWinter[42]	10	7 (70%)	
Podrid[48] ***	120	55 (46%)	
Haffajee[29] ***	21	14 (67%)	

* of those reported as responding ** placebo controlled trial *** resistant to other antiarrhythmic agents

Winkle[17] showed a reduction of greater than 70% decrease in the number of PVCs in 73% of patients. The dose needed to give a greater than 70% reduction was 1200 mg/day in eight patients and 1800 mg/day in three patients. McDevitt[37] showed that most patients had a greater than 60% reduction in the number of PVCs. Woosley[41] showed that two-thirds of the patients had a greater than 75% reduction in the number of PVCs in a placebo-controlled trial. Winkle,[46] in a second study, revealed that they were successful in controlling 53% of patients in a compassionate trial; 12 of 17 patients had recurrent ventricular tachycardia, and all patients were resistant to all I-A antiarrhythmic agents. Of the non-responders, three died and the other five showed no response. Of the nine responders, seven remained well controlled for from two to 27 months. Ryan[47] showed that only 43% of his patients had a greater than 75% reduction in the number of PVCs; all patients were resistant to other antiarrhythmic therapy. Eight of Ryan's patients had ventricular tachycardia which was abolished on tocainide. LeWinter[42] showed a 70% reduction in PVCs. Podrid and Lown,[48] in the biggest series, reported a 46% success rate. All of Podrid's patients were resistant to conventional therapy. Success in Podrid's study was defined as no ventricular tachycardia, a 90% decrease in the presence of ventricular couplets, and a 50% decrease in the number of PVCs. In Podrid's series 34 patients were followed long term. Three of these patients had sudden death, one died of congestive heart failure, one had recurrence of ventricular tachycardia, and four had intolerable side effects that caused cessation of the drug. Haffajee[29] reported a two-thirds reduction in the patients resistant to other drugs. Young[49] reported the results of the compassionate trial, reporting that 71% of the patients initially responded to tocainide and that 89% of the responders did well long term. In our own series, we treated 20 patients with recurrent ventricular tachycardia that was resistant to I-A antiarrhythmic agents. We were able to abolish the ventricular tachycardia in 18 of 20 patients. Of the 18 patients in which we obtained control, five had sudden death while on the drug over a six and one-half year period. One patient had

sudden death, 24 hours after stopping the drug, because "he wanted to die." Six patients were discontinued due to side effects. The remaining six patients remain well controlled and have been followed to date from four and one-half to eight years.

In studies of intravenous tocainide, Morganroth[50] revealed that 28 of 32 (87%) responded to intravenous tocainide after open heart surgery. Maloney[31] also showed that intravenous tocainide was effective in 11 of 15 patients (73%).

Several studies have been reported in patients with an acute myocardial infarction. Nyquist[25] compared tracings on patients with an acute myocardial infarction for one hour before and one hour after an intravenous dose of tocainide. They found there were seven episodes of ventricular tachycardia before tocainide; one episode after tocainide. They also reported that nine patients had PVCs before and two patients had PVCs after tocainide. One problem with this study is time; as the "after" was always later, it would be expected that there would be less arrhythmias. Ryden[51] and Campbell[52] reported placebo-controlled randomized trials in 112 and 559 patients respectively. In both trials the ventricular ectopy was reduced by tocainide; however, there was no difference in the incidence of ventricular fibrillation or mortality.

Comparison of Tocainide with Other Agents Another way of looking at efficacy is to compare the effect of two drugs in a randomized manner. A number of such studies has been performed. There have been two trials reported comparing lidocaine to tocainide plus a multicenter trial that has yet to be reported. In seven patients who were compared with intravenous lidocaine and tocainide in the same patients, tocainide was more effective in one, lidocaine in four, and they were equal in two patients.[37] Morganroth[50] compared the response of 67 patients after open heart surgery. With lidocaine, 27 of 35 patients (77%) responded; while with tocainide, 28 of 32 patients (88%) responded. In a multicenter trial that has not yet been reported, 24 patients studied in Dallas showed similar responses to both lidocaine and tocainide in patients with complex ectopy. Three studies have compared procainamide and tocainide.[53,55] One study used intravenous medications, while the other two used oral medications. The efficacy was similar between the intraveous drugs. When given orally, procainamide 4500 mg/day was similar in effect to tocainide 1800 mg/day. In the other study 3500 mg/day of procainamide was as effective as 1800 mg/day of tocainide but more effective than 1200 mg/day of tocainide. In two comparison trials with quinidine, there was similar efficacy of quinidine and tocainide.[56,57]

Adverse Reactions to Tocainide Adverse reactions that are minor are quite common with tocainide. Serious adverse reactions that could lead to death or hospitalization are rare. The most common side effects are central nervous system or gastrointestinal in nature. In some series these have been reported as high as 70%.[47] The most common side effect is tremulousness that has been reported in more than half of the patients.[46] In our own series, 45% of the patients reported tremors. When you compare signatures over the six and one-half years of our study, you find that three-fourths of the patients have a deterioration of their signature caused by a fine tremor. Other CNS side effects include paresthesias, dizziness, disorientation, anxiety, and confusion (particularly in the elderly). Gastrointestinal side effects have been reported in 25% of patients.[29] In our own series we have seen nausea

and abdominal discomfort at times in about 45% of our patients; 20% of our patients had to be discontinued due to nausea and vomiting. This can be minimized by taking the medication with food or antacids. As mentioned earlier, the total absorption of tocainide is not affected by food, though the peak blood level is blunted by 40%. Hence, food will minimize the neurologic side effects as well as lessen the nausea. Constipation also occurs with tocainide. There are virtually no cardiovascular side effects that have been reported. The hemodynamic effects of tocainide include a slight vasoconstriction in the arterial systems, but this is probably not clinically important.[22-25,52,58] Tocainide, like all antiarrhythmic agents, has a myocardial depressant quality; however, this is mild and is usually seen in very high doses. This depressant effect is about the same magnitude as is seen with quinidine and procainamide, and it is not clinically important.[22-24,30,43,46,59-61] There is some evidence that concomitant use with beta blockers may have a depressant effect on the myocardium.[62] Second degree heart block was precipitated in two of our patients; this has also rarely been reported, according to the package insert. About 20% of patients will complain of night sweats and hot and cold sensations.[46] Reversible interstitial pneumonitis has been rarely reported with tocainide.[63,64] Rarely rash and pericarditis have been seen. We had one case of thrombocytopenia that developed with the use of tocainide. Proarrhythmic effects have been reported and will be discussed later.[65]

Combination of Tocainide with Other Agents There is little published information about the combination of tocainide with other antiarrhythmic agents.[20] In our own series we have had several patients who were successfully controlled by the combination of tocainide with another antiarrhythmic agent when neither agent could control the arrhythmia by itself. These combinations included quinidine in two cases, procainamide in one case, amiodarone in one case, and flecainide in one case. Hence, tocainide appears to have an additive effect to other antiarrhythmic agents; however, this has never been systematically studied.

Doses for Tocainide The dose of tocainide is 1200 to 1800 mg/day, occasionally as high as 2400 mg/day, divided into two or three doses. Giving the drug in three doses with meals often reduces the side effects. The drug should be begun at 400 mg TID and titrate up at two to three day intervals.

Mexiletine (Mexitil)

Pharmacology of Mexiletine Mexiletine, like tocainide, has a structure similar to lidocaine. Unlike lidocaine, however, it is not broken down on first pass, due to a side chain that interferes with metabolism by the liver.[66-68] The drug was originally synthesized in an effort to alter preludin, in order to make a more effective anoretic agent. However, the compound did not have anoretic properties, but it did have antiarrhythmic properties.[69] The agent belongs to the Class I-B group of antiarrhythmic agents such as tocainide.[66] Like other Class I agents, it has local anesthetic properties and has a depressant effect on slow Na^+ channels.[66,70-72] Like other I-B agents, mexiletine slightly slows the rate of rise of depolarization, phase 0; while it shortens the action potential duration and repolarization in the Purkinje fibers.[66,71,73-77] The effect of mexiletine on the sinus node is variable. Mexiletine appears to have

little effect on the normal sinus node.[78-83] In about 2% of patients marked slowing of the sinus node may occur, occasionally leading to sinus arrest with junctional or ventricular escapes.[84-92] In our series we have seen three patients with marked slowing and two patients who went into slow junctional or ventricular rhythms. An acceleration of heart rate has also been reported.[93] We have seen two patients with marked acceleration of the sinus node, including one patient who had a dose dependent increase in heart rate from 75 to 120; this was reproducible on several attempts to titrate up or down the dose of mexiletine. The atria tended to show a slight decrease in the atrial refractory period, but there was little other effect.[73,93,94] The effect on the AV node has been quite variable. Several studies have suggested that the conduction time and refractory period in the AV node was either increased, decreased, or unchanged.[78-81,93] Generally, there is no effect of mexiletine on the PR interval, the A-H time or the H-V time, However, like tocainide, an occasional case of complete heart block has been reported.[94] The QRS interval is generally not changed by mexiletine except at very high dose.[83,84,95-97] The QT interval also is not affected by mexiletine.[98]

Mexiletine is more than 90% absorbed and has a peak blood level in one and one-half to four hours.[99-101] The serum half life varies from ten hours in normals to 17 hours in patients with acute myocardial infarction.[99,101] The peak plasma level can be altered by both food, which slows absorption, and narcotics, which slows gastric emptying.[103] There are several metabolites of mexiletine, and all of these metabolites appear to be inactive.[104] A variable amount of the drug can be found in the urine. Generally, the amount of the drug found in the urine is between 8 and 14%.[99,105] The amount is dependent upon pH of the urine, and if the urine becomes alkalotic there is a marked decrease in renal excretion.[77,106,107] Liver dysfunction probably will increase the half life.[108] Renal dysfunction also has been shown to prolong the half life of the drug.[109] The plasma levels of mexiletine which appear to be therapeutic range from 0.7 to 2.8 μg/ml.[110]

Efficacy of Mexiletine Mexiletine has been studied extensively using many different techniques. Mexiletine has been studied in different animal models. In humans, mexiletine has been studied by electrophysiologic testing (programmed electrical stimulation or PES), double blind placebo controlled trials, open label trials, double blind trials with other antiarrhythmic agents, and by compassionate protocols. The studies in animals have shown that mexiletine is an effective antiarrhythmic agent in arrhythmias induced by coronary artery occlusion and by ouabain induced arrhythmias.[66,67,111,112] Ventricular fibrillation threshold was increased by 100% in a dog model.[113] In one animal study, mexiletine was more potent than either procainamide or phenytoin in dogs with ouabain induced arrhythmias.[111]

Unlike tocainide, mexiletine has been extensively studied using programmed electrical stimulation (PES). Before reviewing the data from PES, a short discussion concerning PES is in order. PES has been used extensively to study several drugs over the last few years. However, there are certain problems with PES. PES is predominantly reported in patients with sustained ventricular tachycardia who are resistant to four or five other antiarrhythmic drugs. Hence, PES patients are highly selected and are an unusual subset of patients. Anecdotal discussions at scientific meetings have suggested that both I-A and I-B antiarrhythmic agents are are only about 20-30% successful in abolishing ventricular tachycardia in response to PES. However, patients

often do not have spontaneous arrhythmias while they do show sustained tachycardia in response to PES. It is clear that patients whose ventricular tachycardia in response to PES is abolished have a better survival rate than those patients who do not show abolition. Yet, the survival is better, even in those who are not completely controlled, than the untreated condition. The relationship of the response to PES in patients with sustained ventricular tachycardia to those with non-sustained ventricular tachycardia or complex ectopy is not clear. Table V shows the effect of mexiletine in patients studied by PES.

Table V
Efficacy of Mexiletine as Shown by PES

Author	# Patients	# Controlled (%)	Refractory to Other Drugs
Seipel[93]	13	3 (23%)	?
DiMarco[114]	35	13 (37%)	yes
Palileo[115]	24	0 (0%)	yes
Westveer[116]	21	4 (19%)	?
Manz[117]	30	3 (10%)	yes
Waspe[98]	33	3 (9%)	yes

Seipel reported that mexiletine abolished PES inducible ventricular tachycardia in only 23% of patients tested; however, it did control spontaneous ventricular tachycardia in these patients.[93] DiMarco revealed that 37% of patients had PES induced VT controlled in patients who were resistant to other drugs; seven additional patients were improved, though they were not controlled.[114] Palileo reported on 24 patients with refractory ventricular tachycardia; all patients had inducible ventricular tachycardia on quinidine, procainamide, and disopyramide; four patients had spontaneous VT on mexiletine, and the other 20 patients were inducible but the rate was slower in nine patients.[115] Westveer revealed that PES induced VT was controlled in 19% of patients, while five patients either had an increase in the ventricular tachycardia rate or had ventricular fibrillation. In complex PVC's without sustained ventricular tachycardia, six of seven patients were controlled.[116] Manz showed a 10% control rate in patients with sustained ventricular tachycardia resistant to other drugs.[117] Finally, Waspe showed control in only 9% of patients but showed that the cycle length (time between two beats) increased from 270 msec to 313 msec, thereby slowing the rate of the ventricular tachycardia.[98] It is easy to become discouraged about the efficacy of mexiletine by looking at this PES data. However, the selection of patients must be remembered. In addition, similar patients studied with tocainide and I-A agents have shown equally poor results when tested by PES in patients with recurrent sustained ventricular tachycardia.

Evaluation of patients using techniques other than PES have shown results similar to other antiarrhythmic agents. Table VI shows the results of several studies.

Table VI
Efficacy of Mexiletine

Author	Route	# Patients	# Controlled (%)	Placebo	Ave. Reduction
Talbot[118]	IV	43	31 (72%)	no	
	PO	16	12 (75%)	no	
(post MI)	IV	35	29 (83%)	no	
Talbot[119]	PO	24	23 (96%)	no	
Durme[120]	PO			yes	26-99%
Ekelund[121]	PO	19	10 (53%)	yes	
Koch[122]	PO	10	10 (100%)	no	
Esser[123]	IV	58	51 (88%)	no	
Posse[124]	PO	96	69 (72%)	no	
Heger[125]	PO	15		yes	66%
Podrid[96]	PO	108			
single dose		88	57 (65%)	no	
2-3 days		79	51 (65%)	no	
Podrid[110]	PO	267	158 (59%)	no	
long term		97	74 (76%)	no	
Duff[126]	PO	21	17 (81%)	no	

Table VI-a
Efficacy of Mexiletine (Prophylactic Studies in AMI)

Author	Agent	# Patients	Deaths	VF(Pts)	VT(Pts)	VT(Episodes)
Merx[127]	mex	29			3	
	pla	28			6	
Campbell[103]	mex	44	3	1	13	27
	pla	53	0	2	30	200
Bell[128]	mex	72	"less arrhythmias"			
	pla	85	"more deaths"			

mex = mexiletine, pla = placebo

In 1973 Talbot reported a number of patients studied with both intravenous and oral mexiletine.[118] In patients with acute ventricular arrhythmias, 72% were completely controlled with intravenous mexiletine and nine additional patients were partially controlled; in patients with chronic ventricular arrhythmias, 75% were controlled.[118] Talbot also reported that in patients with acute myocardial infarction 63% had greater than 95% suppression of ventricular arrhythmias and an additional 20% had between 75 and 95% suppression of the arrhythmias.[118] In a later study Talbot reported that 79% of his patients had complete suppression of arrhythmias, with an additional 17% having greater than 75% suppression; all ventricular tachycardia was abolished in this study.[119] Durme, in a placebo controlled trial, showed that PVC count reductions of 26 to 99% occurred when oral mexiletine was compared to placebo.[120] Ekelund, in a placebo controlled trial, showed that 53% of patients had greater than a 75% reduction in arrhythmias as compared to placebo.[121] Koch studied ten patients with arrhythmias during an exercise test or in the recovery period from exercise; mexiletine abolished the arrhythmias in these patients.[122] Esser, in an intravenous study, showed that 88% of the serious arrhythmias were controlled with intravenous mexiletine and nine of 11 patients with ventricular tachycardia were converted. Esser also gave mexiletine to 19 patients with ventricular fibrillation, and all could be cardioverted after administration of mexiletine.[123] Posse revealed that 72% of his patients had complete suppression.[124] Heger reported that there was a 66% reduction in ventricular arrhythmias in his patients; two patients had greater than 90% reduction, but 11 had less than 50% reduction.[125] Podrid has the largest reported series of patients.[96,110] In 88 patients given a single oral dose of mexiletine, 65% of patients had suppression of arrhythmias at rest and 58% had suppression with exercise. Suppression in Podrid's two series are defined as no ventricular tachycardia, greater than 90% suppression of couplets, and greater than 50% suppression of PVCs.[96] In patients treated with two to three days of oral mexiletine, 65% were controlled at rest and 66% were controlled with exercise.[96] Thirty-one patients were followed long term only on mexiletine with good results.[96] In a larger series of 267 patients, Podrid showed that 59% were controlled; also, 74 of 97 patients were controlled long term with a yearly reoccurrence rate of ventricular tachycardia of only 3.5%.[110] Duff revealed 81% of patients had reductions of ventricular arrhythmias; however, only three were completely controlled and ten still had ventricular tachycardia.[126] Three double blind placebo controlled trials have been reported in the early stages of acute myocardial infarction. Merx showed that ventricular tachycardia was less frequent after mexiletine.[127] Campbell reported less ventricular fibrillation and less ventricular tachycardia after mexiletine as compared to placebo; however, there were three deaths in the mexiletine group and none in the placebo group. It was felt that the deaths were not related to mexiletine or arrhythmias.[103] In another study Bell reported less arrhythmias and less deaths with mexiletine, but this study is seriously flawed, and the differences are not significant.[128]

In our own series of patients treated with mexiletine, Dr. Robert Rude and I have found that mexiletine has been an effective drug in some patients. We studied 107 patients with refractory ventricular tachycardia and followed these patients for up to five years. Of the 107 patients, 44 (41%) had sustained ventricular tachycardia, with 28 of these patients requiring cardioversion. Sixty-three (59%) of the patients had non-sustained ventricular

tachycardia. Of the patients 78 were men and 29 were women. Seventy-eight patients had coronary artery disease, 19 had cardiomyopathy, four had valvular disease, and the remaining six had other forms of heart disease or no disease. Eighty-three (78%) patients were tried on mexiletine because they had side effects on I-A agents. Twenty-five patients (23%) were tried on mexiletine because I-A agents were ineffective; these patients had non-sustained ventricular tachycardia. Nineteen patients (18%) had demonstrated torsade de pointes on I-A agents, and four patients had developed very long QT intervals without evidence of torsade de pointes. Initially, we found excellent results in the hospital. Ninety-one of our patients (85%) had control of their arrhythmia. Control in our series was defined as no ventricular tachycardia, greater than 90% reduction in couplets, and greater than 70% reduction in PVCs. It should be noted that only three patients showed any couplets at all on mexiletine, and the interval between the two PVCs had been lengthened. Thirteen patients (12%) were not controlled by mexiletine. Three patients (3%) were not controlled at the highest dose they could tolerate (due to side effects), but they appeared to have improvement. Over the first year of followup, there were 18 deaths (17%). Of these deaths only four deaths (4%) were sudden death, with ventricular tachycardia being proven in one and ventricular fibrillation in another. Six of the deaths were due to refractory congestive heart failure, with no evidence of arrhythmias. Two patients died in shock after acute myocardial infarctions. Two patients died in respiratory failure due to severe pulmonary disease. Two patients died of amiodarone toxicity. One patient died from post-operative hemorrhage, and one patient died from a stroke. Hence, in the first year, the incidence of sudden death was 4%; however, 13% of patients died due to the seriousness of their other problems. It is known that many patients with recurrent ventricular tachycardia have severe ventricular dysfunction, and a high death rate would be predicted. Excluding the deaths, thirteen patients (12%) who had no side effects but were controlled initially, had recurrences of their arrhythmias and the mexiletine was no longer effective. Over the first year eight patients (7%) had to be discontinued due to side effects. Six patients (6%) became ineffective at the highest tolerated dose. Thus, initially, the drug was effective in 85%. In the 85% in whom it was initially successful, 55% remained well controlled after one year and 23% had arrhythmias or sudden death. Fifty patients were followed for two years. During the second year there were five deaths (10%). One death was sudden, three patients died of congestive heart failure, and one patient died of cancer. Two patients (4%) developed side effects. In none of the surviving patients did the drug become ineffective during the second year. Nineteen patients were treated for three years. During the third year there were no deaths, and none of the patients showed ineffectiveness of the drug. One patient during the third year had to be discontinued due to side effects (5%). Seven patients have been followed for over four years; there have been no recurrences of arrhythmias, deaths, or side effects in these patients. The results by indication are shown in Table VII.

Table VII
Five Year Efficacy of Mexiletine (by Indication)

Indication	I-A Effective But Side Effects	I-A Ineffective	Torsade de Pointes
Number patients	83	25	25
Sudden deaths (%)	2 (2%)	1 (4%)	2 (8%)
All deaths (%)	17 (20%)	5 (20%)	7 (28%)
Not effective (%)	8 (10%)	4 (16%)	0 (0%)
Stopped - side effects	9 (11%)	1 (4%)	1 (4%)
Not effective/tolerated dose	6 (7%)	0 (0%)	0 (0%)

As can be seen from this table, mexiletine was very effective when used in the manner that was used in this study. It proved very effective when a I-A agent had been effective but had to be discontinued. It was effective in torsade de pointes and prolonged QT syndromes. It was also effective in non-sustained ventricular tachycardia when a I-A was ineffective. It should be noted that when a I-A agent was ineffective and the patient had sustained ventricular tachycardia, we did not use a I-B agent except in three patients who had such severe ventricular dysfunction that it was felt that flecainide and/or amiodarone was contraindicated. Two of these three patients died of congestive heart failure on mexiletine. This selection of patients may explain in part why our patients did better than several reported series.

Comparison of Mexiletine to Other Agents Another way to evaluate the efficacy of mexiletine is to compare it to other antiarrhythmic agents. First, in comparisons with lidocaine, Campbell reported that of 191 patients with ventricular arrhythmias, 35 could not be controlled with 100 mg bolus of lidocaine followed by a lidocaine drip. Twenty-four of these nonresponders were controlled with mexiletine.[84] Two other comparative studies between lidocaine and mexiletine showed that mexiletine was as good as or better than lidocaine, though the doses of lidocaine were suboptimal in some studies.[129-131] In a double blind trial between quinidine and mexiletine, Fenster found a 70% or greater decrease in PVCs measured by Holter monitoring in seven of 13 patients (54%) on mexiletine and eight of 13 patients (62%) on quinidine.[132] Duff reported similar findings in ventricular tachycardia when quinidine was compared to mexiletine (35% control on quinidine and 41% control on mexiletine in 17 patients compared).[126] Singh, in a comparison of quinidine and mexiletine, showed that PVCs were decreased by 70% or more in 18 of 26 patients (69%) with mexiletine and in 16 of 23 patients (70%) with quinidine; ventricular tachycardia was controlled in eight of 11 patients (73%) with mexiletine and five of seven patients (71%) with quinidine.[133] In one crossover study by Ekelund between mexiletine (600 mg/day) and procainamide (3000 to 4500 mg/day), mexiletine reduced the number of PVCs by 75% while procainamide reduced the number of PVCs by 54% (not significant).[121] Jewitt showed that 600 mg/day of mexiletine for two weeks reduced the number of PVCs by more than 75% in 11 of 20 patients (55%), while 4500 mg/day of procainamide reduced the PVCs in 12 of 20 patients (60%).[134]

Campbell, in a parallel study between mexiletine 750 mg/day, procainamide 3000 mg/day, and placebo, showed both drugs reduced serious arrhythmias as compared to placebo.[135] Nademanee, in another parallel study, revealed that mexiletine was effective in 43% while procainamide was effective in only 19%.[136] Three crossover trials between disopyramide and mexiletine showed that the two drugs were equally effective.[120,137,138] Nademanee reported that in refractory ventricular tachycardia amiodarone was far more effective than mexiletine.[139] In two crossover trials with beta blocking agents, mexiletine was shown to be more effective than atenolol or tolamolol.[125,134]

Adverse Reactions to Mexiletine Like all other antiarrhythmic agents, side effects present a major problem. Side effects from our series are shown in Table VIII.

Table VIII
Side Effects of Mexiletine

Side effect	Total Incidence (%)	Caused Discontinuation (%)
Central Nervous System	47%	5%
Dizzy, weak	28%	3%
Tremors	24%	0%
Fear	1%	1%
Headache	1%	1%
Nausea/vomiting	28%	5%
Allergy	2%	1%
Tachycardia	3%	1%
Bradycardia/escapes	3%	0%
Positive ANA	9%	0%
Polycythemia vera	1%	0%

Neurological side effects have been reported in a number of series. The most common are dizziness and tremors.[140,141] Ataxia, nystagmus, confusion, convulsions, blurred vision, and diplopia have been reported.[141-143] The fine tremor of the hand is common and can be readily seen if you compare signatures of the patient before and during therapy with mexiletine. Tremors and dizziness are the most commonly reported side effects in several series.[119]

Gastrointestinal side effects are also common complaints of patients on mexiletine.[73,103,127] Many patients will describe intermittent nausea and/or vomiting, though this is usually self-limited. A few patients develop intolerable nausea or vomiting and therapy must be discontinued. Many

patients, however, will tolerate mexiletine for a period of time and then develop a gastroenteritis that does not clear. A short course of cimetidine may help this transient problem, though cimetidine does elevate the mexiletine blood level by 40%, presumably by reducing hepatic elimination.[144] Though cimetidine elevates the blood level of mexiletine, our experience has not shown any side effects from this elevation of the blood level with two to four week courses of therapy with cimetidine. Antacids also must frequently be given. Antacids do decrease the maximal serum concentration of mexiletine but not its bioavailability, though one study contradicts this.[100,145] Another gastrointestinal symptom is a feeling that the pill is stuck in the mid-esophagus and is burning. Most of these symptoms can be reduced if mexiletine is taken with food and a large amount of fluids to wash it down, diluting its caustic effects.

Cardiovascular side effects with mexiletine have also been reported. Sinus bradycardia, sinus arrest, and conduction disturbances have been reported.[124] If a patient develops a slow escape rhythm, hypotension may develop. Three percent of our patients showed a bradycardia. One patient in our series developed a dose dependent tachycardia that was clearly related to mexiletine, as the dose was titrated up and down on several occasions and the heart rate paralleled the dose. Two other patients may have developed tachycardia in our series, but this is not clear. Congestive heart failure is a possibility with mexiletine, as it has a slight negative inotropic effect; but this effect is less than that seen with procainamide or disopyramide.[146,147]

Cutaneous side effects with a rash have been reported.[140] In our own series we have seen an allergic rash in two patients. One patient has been controlled with occasional antihistamines, while the other patient had to be discontinued.

Ten patients in our series developed positive ANA determinations. All ten patients had developed clinical lupus in response to procainamide therapy. In all ten the ANA had returned to normal, but the AHA rose again after prolonged therapy with mexiletine. None of the patients has developed clinical evidence of lupus, though one patient has developed titers of 1:1280. One patient developed what is felt to be polycythemia vera; this could be secondary to mexiletine, but due to the patient's condition it was elected not to stop the mexiletine but to treat the patient for polycythemia vera.

Drug Interactions with Mexiletine Several drugs that delay gastric emptying have been shown to delay peak blood levels of mexiletine including narcotics, atropine, antiemetic drugs, and antacids.[100,145,148-150] Cimetidine, as stated previously, may elevate the plasma level of mexiletine by as much as 40%.[144] One patient developed seizures when given lidocaine on top of chronic mexiletine therapy.[151] Phenytoin and rifampin can both lower the plasma level of mexiletine.[152,153] As stated previously a rise in urine pH can markedly diminish renal excretion and raise the blood level by 50%.[77,106,107] Cigarette smoking can also lower plasma concentrations of mexiletine.[154]

Several different combinations of mexiletine with other antiarrhythmic agents have been shown to be of benefit where neither drug alone was effective. One small series suggested a benefit of the combination of quinidine with mexiletine and suggested that the doses of both might be

reduced.[126] In our own series, we found the combination of quinidine and mexiletine more effective than either drug alone in nine patients. We also found that the combination of mexiletine with procainamide to be more effective than either drug alone in 11 patients. The combination of disopyramide with mexiletine has been shown to be of benefit in four patients in the literature and in two patients in our series.[137] Two series with 13 patients have reported the efficacy and safety of the combination of amiodarone with mexiletine.[155,156] We have used the combination of amiodarone with mexiletine in three patients with increased effectiveness. Beta blockers have also been shown to potentiate the effect of mexiletine.[99,157-159] In our series three patients had an improvement of arrhythmia control by adding a beta blocker to mexiletine; 29 other patients were on beta blocking agents for angina or hypertension, and these were continued during therapy with mexiletine.

Doses for Mexiletine The dose of mexiletine varies from 100 mg every eight hours to 400 mg every six hours. An occasional patient will respond to as low as 50 mg every 12 hours. The usual dose is between 150 mg every eight hours and 300 mg every eight hours. Few patients can tolerate above 300 mg every eight hours. The dose should start at 100 or 150 mg every eight hours and titrate to a higher dose at two to three day intervals.

Comparisons of Tocainide and Mexiletine

There is little information about the comparisons between tocainide and mexiletine. One series with each drug reported by Podrid and Lown[48,110] used identical criteria for patients treated with tocainide and mexiletine. In both of these series the same criteria for efficacy was used; the criteria was complete abolition of ventricular tachycardia, 90% suppression of couplets, and 50% reduction in the number of PVCs. Using these criteria, tocainide controlled 46% of 120 patients and mexiletine 59% of 267 patients. In our own series the efficacy of tocainide and mexiletine was almost identical using the same criteria for therapy. Hence, the two drugs seem to be similarly effective. The differences between studies reflect differences in methodology and patient selection. In our own series tocainide had more side effects than mexiletine. We stopped tocainide for intolerable side effects in 30% of patients, and mexiletine was stopped for side effects in 11% of patients. Tocainide caused more vomiting, while it appeared that mexiletine was slightly better tolerated by the gastrointestinal system. However, this could represent better therapy with mexiletine, as we were more likely to use cimetidine if there were gastrointestinal upset.

Lidocaine can be used to predict the success of tocainide or mexiletine. Two series reported the predictive capability of lidocaine for tocainide. In patients who responded to lidocaine, 78% and 63% of the patients were controlled by tocainide, while of those not responding to lidocaine, only 17% responded to tocainide.[48,160] Of those responding to lidocaine, all responded to mexiletine; however, 24 of 35 resistant to lidocaine did respond to mexiletine.[84,129] In one study, mexiletine and tocainide were equally effective; however half of the patients who responded to one drug did not respond to the other and vice versa.[161]

Flecainide (Tambocor)

Pharmacology of Flecainide Flecainide is a fluorinated local anesthetic analog of procainamide.[162] Flecainide is the first of a new class of antiarrhythmic agents, I-C, to be released in the United States. Several other Class I-C agents are under development, including lorcainide, encainide, indecainide and propafenone.[163] Flecainide causes a marked prolongation of the rate of rise of the depolarization wave, phase 0.[164] Flecainide shortens the action potential duration and effective refractory period in Purkinje fibers but prolongs them in ventricular muscle.[164] In the majority of the studies, flecainide had little or no effect on the sinus node or the sinus node recovery time. However, with sinus node dysfunction, flecainide has been shown to slow sinus rate and markedly prolong sinus node recovery time.[165-171] Flecainide slows intraatrial conduction and the refractory period of the atria.[168] The effects of flecainide on the AV node are quite marked. Flecainide markedly slows conduction, both antegrade and retrograde. Marked prolongation of the A-H time, the H-V time, the PR interval, and the QRS interval have been reported.[172-174] The QT interval is slightly prolonged, but this prolongation is mainly due to prolongation of the QRS interval, as there is no prolongation of the JT interval (end of the S wave to the end of the T wave).[175] The QRS may be widened by 10 to 47% with therapeutic blood levels of flecainide.[174,176]

Flecainide is completely absorbed, with essentially no first pass degradation.[177] Twenty-seven percent of the flecainide is excreted by the kidneys, both via filtration and active secretion.[177,178] There are two major metabolites that are conjugated and undergo renal excretion.[177] Alkalinization of the urine can reduce flecainide excretion from 45% to 7%.[179] The half life of flecainide varies from seven to 23 hours, with a mean of 14 hours in normal volunteers.[178] In patients with arrhythmias but no heart failure the half life is prolonged.[167,180,181] Congestive heart failure can prolong the half life to 19 hours.[182] Renal failure can prolong the half life up to 58 hours.[178] Because of the marked prolongation of the half life in some clinical states, care must be taken not to make the patient toxic and precipitate proarrhythmic effects. One patient in our series increased his serum level from 0.8 to 1.4 μg/ml following a myocardial infarction; this higher blood level precipitated an increase in the incidence and rate of the ventricular tachycardia, which disappeared when the dose of flecainide was reduced. The blood level of flecainide should be between 0.2 to 1.0 μg/ml.[163]

Efficacy of Flecainide Flecainide and some of the other I-C antiarrhythmic agents have been termed PVC killers, as they can remarkably reduce the number of PVCs that a patient has. Many patients have complete abolition of the arrhythmias, and most of the patients have greater than 90% suppression of the arrhythmias. There have been two studies using programmed electrical stimulation (PES).[183,184] Platia reported poor results with flecainide, in that PES could still induce either sustained or non-sustained ventricular tachycardia in 19 of 22 patients; only three patients (14%) could not be induced by PES.[183] Anderson reported slightly better results in 15 patients; ventricular tachycardia induced by PES was prevented in nine patients (60%).[184] In ten of Anderson's patients flecainide was continued for six months; there were two recurrences of ventricular tachycardia.[184] Better results were obtained from clinical studies as shown in Table IX.

Table IX
Efficacy of Flecainide

Author	Route	# Patients	# Responding (%)	Ave. Reduction
Hoback[185]	IV	12		93%
Somani[186]	IV	10	9 (90%)	
Klempt[187]	PO	20	20 (100%)	
Duff[180]	PO	11	11 (100%)	97%
Anderson[167]	PO	10	9 (90%)	98%
Hodges[181]	PO	11	8 (73%)	96%
Duran[170]	PO	9	8 (89%)	96%
Bender[189]	IV	40	26 (65%)	
Steinbrunn[190]	PO	8	8 (100%)	
Granrud[191]	PO	27	23 (85%)	
Wang[192]	PO	13	10 (77%)	
Zehender[193]	PO	14	12 (86%)	
Abitol[194]	IV	35	35 (100%)	100%

Hoback reported in 1978 that in 12 patients given intravenous flecainide there was a 93% reduction in ventricular arrhythmias.[185] Somani, also using intravenous flecainide, reported complete suppression of ventricular arrhythmias in 90% of patients treated.[186] Klempt reported greater than 90% suppression of arrhythmias in all 20 of the patients with oral flecainide.[187] Duff showed that there was an average 97% reduction in ventricular arrhythmias in all 11 patients given oral flecainide.[180] Nine of Duff's patients had arrhythmias resistant to at least three other agents, and eight patients had non-sustained ventricular tachycardia with none seen on flecainide; this effect persisted for 12 months.[180] Anderson revealed that there was a 98% reduction in 90% of patients treated with oral flecainide; the other patient had a 68% suppression of arrhythmias.[167] Hodges, in another oral study, reported 45% of his patients were arrhythmia free, 73% no longer had complex ectopy, and the average reduction in PVCs was 96%.[181] Duran studied nine patients who were refractory to other agents and compared flecainide to placebo; eight of nine responded with a 96% decline in multiform PVCs.[170] In Duran's series, six of eight patients with couplets had complete suppression, while the other two had greater than 90% suppression. Six of seven patients with ventricular tachycardia had complete suppression, while the remaining patient had a 91% suppression.[170] Bender, in an intravenous study, revealed that 65% of patients treated had greater than 80% suppression.[189] Steinbrunn reported that 75% of patients had greater than

90% supression, while the remaining patients had between 70 and 90% suppression.[190] Granrud showed 85% of patients treated maintained greater than 90% suppression for one year and greater than 80% suppression for the second year. Of the four patients not controlled, one had the drug discontinued for lack of effect, one had sudden death, one developed new onset congestive heart failure, and one developed right bundle branch block.[191] Wang, in 13 patients with refractory ventricular tachycardia, showed greater than 90% suppression of PVCs in 77%, with complete abolition of ventricular tachycardia.[192] Zehender revealed that 86% of patients were well controlled.[193] Abitol reported that all 35 patients had complete suppression of complex arrhythmias after a single intravenous dose of flecainide for 60 to 1440 minutes, with an average suppression for eight hours.[194] Hence, it is very apparent that flecainide gets rid of PVCs and complex ectopy. However, there is little long term data published on survival. There have been some sudden deaths reported, even with complete suppression of arrhythmia reported on Holter monitoring. In addition, the proarrhythmic effect of this drug in a small number of patients may limit its usefulness. This issue will be discussed later.

Comparison of Flecainide to Other Agents In a comparison to mexiletine, flecainide 400 mg/day was as effective as mexiletine 600 mg/day. In five patients resistant to mexiletine, flecainide was effective.[195] In a comparison with quinidine 1200 to 1600 mg/day, flecainide 400 to 600 mg/day reduced PVCs by 95%, while quinidine reduced them by 56%.[196] A randomized multicenter trial has also compared quinidine and flecainide.[197] This trial was performed in 280 patients with chronic ventricular ectopy. The patients were given placebo for one week, followed by two weeks of flecainide 400 to 600 mg/day or quinidine 1200 to 1600 mg/day, They were then given a final week of placebo. With flecainide, 85% of 118 patients had greater than 80% suppression of PVCs, while with quinidine only 57% of 110 patients showed greater than 80% suppression. Complete suppression of couplets was 70% with flecainide and 41% with quinidine. Complete suppression of ventricular tachycardia was 79% with flecainide and 55% with quinidine. In this study the PR and QRS intervals were increased by flecainide but not by quinidine. The QT interval was similarly increased by both drugs. However, with flecainide the increase was in the QRS portion. With quinidine it was in the JT portion. Side effects also varied, with flecainide producing blurred vision, dizziness, headache, and nausea; while quinidine produced diarrhea, nausea, and headache.[197]

Dr. Mark Kremers and I have used flecainide on a total of 21 patients. Nine of our patients had sustained ventricular tachycardia and were placed on flecainide. Of the nine patients with sustained ventricular tachycardia, three patients were still inducible with programmed electrical stimulation (PES); two had slow ventricular tachycardia induced, and one had a rapid ventricular tachycardia induced. Of the patients who were not inducible by PES, one had sustained ventricular tachycardia following an exercise test and then had two more episodes on the ward. Another patient who required flecainide and tocainide had an exercise test that induced ventricular tachycardia and ventricular fibrillation; another patient had sustained ventricular tachycardia two weeks later, and another patient had sudden death. Hence, in sustained ventricular tachcardia, excellent results were seen in only two patients, though we felt that the drug was of benefit in several others. We have treated five patients with non-sustained ventricular

tachycardia including one who developed several hours of sustained ventricular tachycardia on flecainide. A second patient failed to respond to flecainide. A third patient with polymorphic non-sustained ventricular tachycardia was well controlled on flecainide 100 mg TID for six months with a normal blood level of 0.8 µg/ml; the patient had an uneventful myocardial infarction, and on the sixth hospital day developed recurrent monomorphic sustained ventricular tachycardia. A flecainide level was reported as elevated at 1.4 µg/ml, and he was titrated to a lower dose of flecainide with resolution of his monomorphic ventricular tachycardia. This episode may have been induced by a decrease in ventricular function that was not clinically apparent but could have elevated his flecainide level and precipitated a proarrhythmic ventricular tachycardia. The fourth patient was poorly controlled by flecainide and had severe headaches. The fifth patient is doing well on flecainide. Six patients were treated for simple or complex ectopy without ventricular tachycardia; five have done well with almost complete resolution of the PVCs. The sixth patient was started on flecainide for simple PVCs and was referred to Dr. Kremers after three episodes of syncope. She was found to have sustained ventricular tachycardia that responded to cessation of the drug. One patient with a concealed bypass tract could not tolerate flecainide for supraventricular tachycardia. Hence, our results have shown that flecainide is great for eliminating PVCs on Holter monitoring reports; however, it is not as effective in controlling ventricular tachycardia or preventing sudden death. We feel that it is of marked benefit in some patients.

Adverse Reactions to Flecainide Adverse effects with flecainide have occurred in 15-20% of patients in one long term study.[198] Flecainide has potent negative inotropic effects; hence several cases of congestive heart failure, either induced by flecainide or aggravated by flecainide, have been reported.[192,196,197] Flecainide markedly prolongs both PR and QRS intervals up to 30% even at normal doses; this does not have the same diagnostic significance as with other agents.[167,180,181,186,199] Flecainide may aggravate sick sinus syndrome, and two cases of sinus arrest have been reported, and some evidence of increasing atrioventricular and intraventricular block have been seen.[192,196,200,201] One series reported a 6% incidence of dyspnea and chest pain.[202] Dizziness has been frequently reported with flecainide.[203] Paresthesias and unsteady gait have also been reported.[189,190,198] Several studies have reported blurring of the vision in from 20 to 45%.[170,181,188] This has been a common complaint in half of our patients. Impotence was reported in all seven male patients treated in one series.[193] We have also seen impotence in several male patients. Headache and nausea are seen in 6 to 9% of patients.[202] Mild elevation of the serum alkaline phosphatase has been reported, presumably due to altered bone metabolism induced by the release of fluoride from the flecainide.[188] The most hazardous side effect may be the proarrhythmic effect which has been reported to be as high as 20% in one series.[204] The proarrhythmic effects will be discussed later.

Drug Interactions with Flecainide Drug interactions have also been noticed with flecainide. Flecainide increases peak digoxin levels by 18% and trough levels by 24%.[205] Flecainide and propranolol appear to elevate each other's serum levels by as much as 30%, the negative inotropic effects appear to be additive, and the PR interval was prolonged more than with either drug by itself.[206] In normals, cimetidine reduced clearance of flecainide by 13

to 27%.[205] Though little information is available, the negative inotropic and atrioventricular conduction effects of several other antiarrhythmic agents, beta adrenergic blocking agents, and calcium channel blockers will probably have additive effects and may also affect each other's blood levels.[163] Care should be taken when using flecainide with any other cardioactive substance. Occasional reports have stated that a patient may benefit from combinations of flecainide with other antiarrhythmic agents, particularly amiodarone and beta blockers.[207,208] In our own series we have seen additive benefit with metoprolol and tocainide in one patient each.

Doses for Flecainide The usual dose of flecainide is 200 to 400 mg/day. Start with 100 mg every 12 hours and increase to 300 mg/day and 400 mg/day in increments of four days. Do not go above 400 mg/day without measuring blood levels. Even 300 mg/day is toxic in some patients, due to the variable half life. Patients with sustained ventricular tachycardia, ventricular dysfunction, and greater than 400 mg/day are particularly susceptible to proarrhythmic effects. The question of risk benefit is a major problem with flecainide. Clearly the patients with isolated PVCs and normal ventricular function can have their PVCs eradicated with flecainide. However, these patients are also the ones with little risk, and we may be treating a rhythm strip rather than doing anything worthwhile in these patients. Patients with poor ventricular function and sustained ventricular tachycardia are the patients with the highest risk; it is in these patients that proarrhythmic effects and sudden death may be seen.[163] Clearly, flecainide intensifies the problem of risk-benefit ratio in treating patients; and the physician must approach these patients with care.

Amiodarone (Cordarone)

Pharmacology of Amiodarone Amiodarone is an iodinated derivative of benzofuran which has 39% iodine by weight.[209] It was originally developed as antianginal agent but was found to have potent antiarrhythmic effects in 1970.[210,211] Amiodarone belongs to the Class III agents, because it prolongs the action potential duration by a mechanism other than sodium channel blockade.[209] Amiodarone is a nonselective beta adrenergic and alpha adrenergic blocking agent with direct vasodilating effects.[209] Like all the Class I agents, amiodarone slows the rate of rise of the depolarization wave, phase 0.[212] The action potential duration is prolonged; this causes prolongation of the QT interval which can be very impressively prolonged.[213,214] Amiodarone prolongs the A-H time and the H-V time. It slows conduction in all tissues and prolongs the refractory period of tissues.[214-220] Sinus node function may be affected with slowing of the sinus rate and prolongation of the sinus node recovery time.[221-224] Besides marked prolongation of the QT, amiodarone can greatly alter the T wave and cause giant U waves.[225] In one patient with good control of his arrhythmia we found that the QT was prolonged to 1000 msec with amiodarone at a heart rate of 40. The mechanism of this antiarrhythmic effect is not known, but it has been suggested that it may be due to blockade of thyroxine-dependent metabolic pathways and that mitochondrial respiratory activity that can be reversed by T3 might be involved.[226]

Amiodarone is about 50% absorbed, with a marked delay after ingestion; it can be detected after one and one half hours, and it peaks after five hours.[227-230] The time of the onset of antiarrhytmic effect is four to seven

days for atrial arrhythmias and one to four weeks for ventricular arrhythmias.[230] Rosenbaum has reported that the peak therapeutic and toxic effect is not seen for 90 to 150 days.[231] Amiodarone is a complex drug which is stored in many tissues, including fat. If a single dose is given and plasma clearance is measured, the half life is 4.6 hours.[230] Because of the fat and other tissue binding with chronic therapy, the half life is increased to five to 28 days. Though some studies have suggested in some patients that the half life is prolonged to greater than 45 days.[209,232] One patient is reported to show measurable amiodarone in his blood six months after discontinuation.[233] At an American Heart Association meeting, an English dematologist reported that he had seen three patients who still had blue skin discoloration due to deposition of amiodarone three years after discontinuation. Elimination is biphasic. There is rapid elimination from well perfused tissues and then a very slow elimination from fat and fat laden structures.[233] This biphasic elimination explains why there is a need for frequent dosing in spite of the long half life. The only known metabolite of amiodarone is desethyl amiodarone; this metabolite is probably active and has a longer half life than amiodarone.[224,233,234] There is no known excretion in the stool or urine. Small amounts of amiodarone have been detected in the tears and sweat. Therapeutic blood levels are greater than 1.0 mg/L; toxicity occurs above 2.5 mg/L.[230,235,236] Toxicity, however, does not correlate well with drug levels.[236] Nademanee has suggested that reverse T3 is better at predicting therapeutic range and toxicity; they found that therapeutic effect was seen at blood levels of reverse T3 of 55 to 100 ng/dl and toxicity occurred above 100 to 110 ng/dl.[237] Amiodarone is concentrated in many organs such as heart, skin, lungs, liver, as well as fat.[213,214,238]

A special problem with amiodarone is thyroid function. Amiodarone interferes with the normal peripheral conversion of thyroxine (T4) to triiodothyronine (T3). This causes an increase in T4 and reverse T3, with a decrease in T3.[239-243] T4 is usually increased by 10 to 20% by two weeks and usually peaks in the second month at about 25% above normal[244], though we have seen 50% elevations in patients who are clinically euthyroid. Reverse T3 levels are increased by 80% to 300%.[237,244] Amiodarone doses of 600 mg/day releases 18 mg of iodine into the patient, which is 200 times the normal daily intake of iodine.[243] The iodine can block release of T3 and T4.[242] Thyrotoxicosis and hypothyroidism can both be triggered by amiodarone; this will be discussed later.

Amiodarone has potent cardiovascular effects due to several factors. It has negative inotropic and negative chronotropic effects, due to inhibition of the beta adrenergic receptors.[212,245-247] In addition there is a direct depressant effect on the sinus node.[248] There is a direct vasodilator effect as well as alpha receptor blockade.[212,245-247] These vasodilator effects usually overcome the negative inotropic effects so that there is no deterioration in left ventricular function as measured by ejection fraction long term, though acutely ejection fraction was decreased from 54% to 44%.[249,250] Worsening of heart failure has been reported, but this is minimal, considering the degree of dysfunction in many of the patients being treated with amiodarone.[223,224,251] There is also a marked coronary vasodilator effect.[252]

Efficacy of Amiodarone The efficacy of amiodarone has been shown in several different syndromes are shown in Table X.

Table X
Efficacy of Amiodarone

Author	# Patients	Percentage Controlled					
		A.Fib	SVT	WPW	SSS	PVCs	VT-VF
Cauchier[251]	10						70%
Rosenbaum[253]	200	97%	97%	100%		90%	87%
Wellens[215]	15			60%			
Walette[254]	9		78%				
Leak[255]	16		100%	100%			
Touboul[256]	24				88%		
Brown[257]	6				100%		
Wheeler[258]	32	60%		100%	83%		86%
Moysey[259]	74	75%	82%				
Ward[260]	57			81%			56%
Haffajee[261,262]	78	86%	80%		80%	87%	75%
Heger[263]	45						67%
Podrid[264]	70	80%	88%				68%
McKenna[265]	13						77%
Nadamanee[213]	33					90%	90%
Waxman[221]	46						78%
Fogoros[266]	77						52%
Nademanee[267]	96						94%

A.fib = atrial fibrillation, SVT = paroxsymal supraventricular tachycardia, WPW = Wolfe-Parkinson-White with atrial fibrillation or PSVT, SSS = sick sinus syndrome with bradycardia-tachycardia syndrome, PVCs = complex high grade PVCs, VT-VF = ventricular tachycardia and/or fibrillation that is recurrent and refractory to drugs.

As can be seen from the chart, amiodarone has been used extensively for a number of different arrhythmias. Five series have reported results in the treatment of refractory atrial fibrillation: Rosenbaum,[253] Wheeler,[258] Moysey,[259] Haffajee,[261,262] and Podrid.[264] When these series are combined, 138 patients have been treated with amiodarone for refractory atrial fibrillation. One hundred eleven (80%) of these patients were successfully treated with amiodarone ranging in dose from 100 mg/day to 400 mg/day with the

most common dose being 200 mg/day. Amiodarone will both convert some refractory patients to sinus rhythm as well as maintain them in sinus rhythm; the remainder it will help control the rate of the atrial fibrillation. Fifteen of these patients with refractory atrial fibrillation had WPW and were well controlled in the majority of the cases. In our own series (Rude, Kremers, and Atkins), fifteen patients have had atrial fibrillation. Amiodarone was able to control the atrial fibrillation by restoring sinus rhythm in seven patients and controlling the rate in another seven.

The use of amiodarone in the treatment of refractory supraventricular tachycardia has been reported in six series, Rosenbaum,[253] Walette,[254] Leak,[255] Moysey,[259] Haffajee,[261] and Podrid.[264] In combining these series, 115 patients have been treated with amiodarone in doses ranging from 200 mg/day to 600 mg/day, with 200 mg/day and 400 mg/day being the most common dosages used. Of the 115 patients, 105 patients (91%) had their refractory supraventricular tachycardia controlled or abolished. Thirty-two of these patients had WPW. In our own series, we have treated six patients, with excellent results in five.

Amiodarone has been shown to be effective in treating both the atrial fibrillation and supraventricular tachycardia complicating the WPW syndrome. Five series have been reported: Rosenbaum,[253] Wellens,[215] Leak,[255] Wheeler,[258] and Ward.[260] Of 71 patients with WPW, 28 had atrial fibrillation and 60 had supraventricular tachycardia; control was achieved in 58 patients (82%). In our own series we have seen success in five of seven patients. However, we feel that in most cases that refractory WPW is a surgical disease today and would reserve amiodarone for very special uses when surgery cannot be performed or is unsuccessful in these patients.

Four series have reported the use of amiodarone to treat the tachycardias that occur in sick sinus syndrome: Touboul,[256] Brown,[257] Wheeler,[258] and Haffajee.[261] In these series, 41 patients were reported; success in controlling the tachycardia was see in 36 patients (88%). In these series unacceptable bradycardia was reported in three patients, but some of the patients had pacemakers. In our own series of 15 patients that fit into this category, nine have required pacemakers during their treatment with amiodarone.

The use of amiodarone in refractory high grade ventricular ectopy without tachycardia or fibrillation has been reported in three series: Rosenbaum,[253] Nadamanee,[213] and Haffajee.[261] Of 127 patients in these series, 114 patients (90%) were controlled.

Twelve series have reported their results in refractory, recurrent ventricular tachycardia and/or ventricular fibrillation including series by Cauchier,[251] Rosenbaum,[253] Wheeler,[258] Ward,[260] Haffajee,[261] Heger,[263] Podrid,[264] McKenna,[265] Nadamanee,[213] Waxman,[221] Fogoros,[266] and Nadamanee.[267] In these series 432 patients were treated, 320 of these patients (74%) were controlled. It should also be pointed out that many of these studies were long term studies with followups as long as five years. In these series, Heger[263] reported success in 21 of 29 patients at 30 months with ventricular tachycardia and in nine of 16 with recurrent ventricular fibrillation. There were five deaths in followup - two were sudden death, two were due to congestive heart failure, and one was due to pulmonary insufficiency. In Podrid's series,[264] ten of 41 patients died, with six deaths being sudden over two years. In Fogoros series,[266] the

success rate in drug refractory ventricular tachycardia and fibrillation was 52% at one year but only 28% at two years; this is worse than other series and could be explained by differences in patient selection or dosage. There has been one study reported by Horowitz[268] with programmed electrical stimulation (PES) in 69 patients. Twenty-two patients could not be induced on amiodarone and had no recurrences during followup, while 47 patients were inducible, and these patients had 15 recurrences during followup. Hence, amiodarone seems to be extremely effective in the most refractory patients.

Our own results are shown in Table XI.

Table XI
Efficacy of Amiodarone

	Number	Treatment Duration Average	Range
Number of patients treated	139	2.9 years	(3 days - 5 years)
Ineffective	7		
Deaths	35	5.2 mos	(3 days - 42 mos)
Died < 8 days	11	3.6 days	(3 - 8 days)
Sudden death > 8 days	12	10.3 mos	(1.5 - 42 mos)
Congestive heart failure	6	6.5 mos	(1 - 19 mos)
Pulmonary reaction	1	22 mos	
Other	5		
Discontinued	16		

The 139 patients in our study had recurrent ventricular tachycardia and/or ventricular fibrillation that was refractory to other antiarrhythmic agents. Of the 139 patients, 94 had sustained ventricular tachycardia and 45 had non-sustained ventricular tachycardia. The patients with non-sustained ventricular tachycardia were considered high risk. Thirty-one patients had had ventricular fibrillation at least once in the past. Eleven patients died before eight days of therapy. In general it takes ten days to three weeks for amiodarone to be effective in ventricular arrhythmias. Thus, these 11 deaths occurred before the drug could be expected to be effective. Of the 128 patients who lived for more than eight days, the drug was initially effective in 121 patients (95%). If you count the early deaths as failures, then the success rate initially was 87%. Twelve patients had sudden death; eight had sudden death in the first three months, one at seven months, one at 22 months, one at 31 months, and one at 42 months. Six patients died of congestive heart failure. One patient died of a pulmonary reaction. Five patients died of other causes; three of post operative complications. Sixteen patients were discontinued from amiodarone; seven of the discontinuations were due to pulmonary fibrosis or alveolitis secondary to amiodarone. One was discontinued due to amiodarone induced cirrhosis of the liver, one was

discontinued for severe myalgias, one was discontinued because of ataxia and weakness, one was discontinued for severe photosensitivity, and five were discontinued for loss of effective rhythm control. Of the 16 patients that had to be withdrawn from amiodarone, eight had sudden death within six weeks. A second antiarrhythmic agent had to be used in 27 patients either initially or had to be added later due to recurrence of the arrhythmia. Hence, if you exclude the eleven deaths before amiodarone became effective, 95% were effectively controlled on amiodarone at one month, 64% were effectively controlled at one year, 59% were controlled at two years, 55% were controlled at three years, and 55% were controlled at four years. The majority of those no longer effectively controlled were due mostly to unrelated deaths and side effect withdrawals. If you examine these data only for arrhythmia control by eliminating all deaths that were not sudden and discontinuations other than for ineffectiveness, then the control rates were 86%, 84%, 82%, and 82% for one, two, three, and four years respectively. Thus, as an arrhythmia controlling agent, amiodarone is extremely effective for long periods of time; however, many patients who require amiodarone are severely ill and will die of problems other than arrhythmias, or the side effects of amiodarone will cause late withdrawals.

Adverse Reactions to Amiodarone Amiodarone is potentially a very toxic agent. Due to its long half life, avoidance and reversal of side effects is extremely difficult. The use of blood levels of amiodarone, its metabolite desethylamiodarone, and reverse T3 have been suggested as ways of following the patient; however, none of these methods have proved reliable in preventing side effects.[230,235-237,269] The incidence of side effects have been reported as high as 100% in the literature.[266] Serious side effects that caused discontinuation have averaged between 10 and 20% with higher numbers coming from longer term studies.[220,230,248,260] Bigger has stated in a conference on this campus that he feels that side effects are related to total dose given as excretion is very slow. We would tend to agree. The percentage and type of side effects we see at one year with a 600 mg/day dose is similar to that seen at two years with 400mg/day and at three years with 200 mg/day. Hence, the goal of therapy with amiodarone is to continuously try to find the lowest dose possible; this is difficult in patients who may show their first sign of breaking through control as sudden death.

As stated previously, thyroid function is altered by amiodarone. Three tablets a day of amiodarone (600 mg) contains 18 mg of available iodine, which is 200 times the normal daily intake. This amount of iodine may suppress the thyroid in some individuals. Other individuals may develop thyrotoxicosis. In our series almost all of the patients have elevations of T4 when these are checked during the first six months of therapy. After an early peak, the T4's will slowly fall into the normal range. The incidence of thyrotoxicosis has been reported from 2 to 4%.[243,253,263,270-273] In our own series we have seen three cases of thyrotoxicosis. The thyrotoxicosis may appear after prolonged therapy as long as three years. Thyrotoxicosis is best diagnosed by directly measuring T3 levels. The T4 is spuriously elevated due to the blockage of peripheral conversion. TSH is usually, but not always, abnormal. Treatment of thyrotoxicosis may be accomplished in the usual manner with beta adrenergic blocking agents, antithyroid drugs, thyroidectomy, or withdrawal of amiodarone. Myxedema occurs in 1 to 2% of patients treated with amiodarone.[244,253,271,273] We have seen three cases of hypothyroidism in the patients we have treated. All the cases came on late and very insidiously. The signs and symptoms are those of classic myxedema. The

diagnosis of myxedema can be difficult due to the alterations in thyroid functions caused by the drug. Never try to measure a PBI (protein bound iodine) or one of the other older tests, as amiodarone contains enough iodine to destroy the assay. The T4 will be low or in the low normal range. Remember, amiodarone blocks conversion of T4 to T3; hence a low normal T4 may be seen in someone who is overtly myxedematous.

Cardiovascular side effects have also been reported frequently. As amiodarone prolongs AV conduction and slows the sinus node, it would be expected that some symptomatic sinus bradycardia as well as second and third degree heart block would be seen. This has been the case in 9 to 15% of patients in the literature.[221,251,253,274,275] In our own series, symptomatic bradycardia precipitated by amiodarone has required permanent pacemakers in 11% of our patients. Another 12% have heart rates under 45 beats per minute, though they are asymptomatic at the present time. Many patients develop gradual progressive slowing and usually become symptomatic when their rate gets down to about 35 beats per minute. Occasionally the escape rates for those in heart block are also slowed.[276,277] The combination of slow heart rate, beta adrenergic blockade, alpha adrenergic blockade, and direct vasodilatation may make some individuals hypotensive. However, this is relatively unusual and usually can be corrected by pacing the patient at a faster rate with an AV sequential pacemaker (except for those in atrial fibrillation).[278] Congestive heart failure is a potential problem due to the negative inotropic effects; however, it is not commonly seen due to the afterload and preload reduction that amiodarone also causes. In spite of the negative inotropic effects which are potent, depressed ejection fraction usually does not fall further.[250] Though we have had six deaths from congestive heart failure, all six had ejection fractions below 18% before amiodarone and they tolerated amiodarone for one, three, three, six, seven, and 19 months respectively. We have had 24 other patients with ejection fractions less than 25%; two had sudden death, three died of post operative complications after emergency surgery for mitral valve replacement, carcinoma causing obstruction, and leaking aortic aneurysm.

Though the cardiovascular and thyroid side effects are serious, the patient can usually continue amiodarone and be treated for side effects. The side effect which most commonly causes discontinuation is the syndrome of pneumonitis and pulmonary alveolar fibrosis. The literature recognizes a low incidence of pulmonary reactions usually between 2 and 6%. In our series we have seen eight definite cases of pulmonary involvement and two more presumptive cases that we are following. Several of the centers who have pooled their data suggest that the incidence is about 10 to 12% at one year on a dose of 600 mg/day, two years on a dose of 400 mg/day, or three years on a dose of 200 mg/day; it appears that this is an accumulative process that correlates with the total amount of amiodarone received rather than dose. The patient may present with pleuritic chest pain, dyspnea, fever or weakness. On chest X-ray, the appearance may be that of patchy pneumonia, pulmonary edema, or an appearance that resembles the X-ray of ARDS (adult respiratory distress syndrome). The onset can be insidious, with progressive dysnea, or may be sudden. One of our patients was seen on Tuesday and found to have a normal chest film only to return on Friday with pleuritic chest pain and be found to have "severe pulmonary edema" which turned out to be pulmonary alveolar fibrosis. Lung biopsy will show interstitial or alveolar fibropneumonitis. There is an accumulation of foamy macrophages which can be seen on biopsy or on sputum or bronchial washings. There is also a hyperplasia of type 2

pneumocytes. There is thickening of the alveolar septum. Scattered lymphocytes and granulocytes are seen with an increase in fibroblasts and collagen.[279] The patients are hypoxic, with findings of both restrictive lung disease and marked diminution of diffusion capacity. Other tests include elevations of the ESR and leukocytosis.[279] The pulmonary reaction can occur as early as one month or may appear after several years. Persons with preexisting lung disease may be more susceptible, though that is debated.[280] The treatment is withdrawal of amiodarone and treatment with steroids. The X-ray will improve over two to eight months. The steroids can usually be tapered in two months. One of our patients repeatedly varied his diffusion capacity as the level of steroids were varied. There is one case report of a patient whose pulmonary reaction abated who was then restarted on low dose amiodarone with another antiarrhythmic agent and steroids who has done well.[281]

Arrhythmogenic side effects have occurred with amiodarone and will be discussed later.

The most common side effect is the development of corneal microdeposits of the drug. These can be seen on slit lamp examination. After one year of therapy, we found them in 100% of the patients when we specifically looked for them. They do not occur in children, due to the faster lacrimal circulation.[273] Some have suggested using methyl cellulose or artificial tears to reduce the deposits, though no study has been reported. About 10% of patients will complain of blurred vision that can be aided by changing the prescription in their glasses. A few patients will see halos around lights. We have see two such cases; this is dose dependent.

Cutaneous reactions are also commonly seen. Photosensitivity has been reported in from 3 to 57%.[244,253] In our sunny clime, we have seen some degree of photosensitivity in about 67% of patients. This photosensitivity is mild in most patients, though one-third of our patients have to use sun screen and long sleeves. Occasionally the photosensitivity is severe. One of our patients developed a reaction so severe that even exposure to fluorescent lights would cause blistering, and the inside of her mouth had blisters that were confirmed to be photosensitivity by a dermatologist. A bluish discoloration is seen in more than 35% of patients treated for more than two years.[282] The bluish discoloration is primarily in the sun-exposed areas. The earliest manifestation is a malar rash in a butterfly pattern that is a dark blue or gray. Usually the blue-gray appearance regresses with discontinuation over one to two years, though persistence at three years has been reported.[273] There is a thinning of the skin that occurs with chronic therapy. Ecchymoses appear under the skin and have an appearance identical to the changes seen in geriatric populations, complete with easy bruising and easily torn skin.

Neurologic side effects that are serious are rare. However, tremor, ataxia, proximal muscle weakness are seen in 20 to 54% of patients.[266,283] A peripheral demyelinating neuropathy can occur which is progressive and fatal. We have had two such cases confirmed at autopsy. The patients develop progressive weakness, which continues after discontinuation of the drug to the point that they can not lift themselves from bed. The two patients who had this syndrome went slowly into coma, then became hypotensive, developed electromechanical dissociation, and expired. Pathologically, these patients have demyelination of nerve fibers and have lipid containing lysosomal

inclusion bodies.[284-288] Insomnia is also commonly reported in these patients. Two patients have developed difficulty voiding due to a neurogenic type of bladder.

Gastrointestinal side effects are uncommon. Some patients will describe nausea and gastrointestinal discomfort. Fatty infiltration of the liver with elevation of hepatic enzymes is seen in about 20% of patients after one year of therapy. Constipation is a chronic problem with this drug. Hyaline cirrhosis of the liver has been reported in four cases, including one in our series. One elderly strict non-drinker, over one year of therapy, developed cirrhosis of the liver that was identical to that seen in alcoholic cirrhosis. Fifteen days after discontinuation of amiodarone, she had sudden death. At autopsy she had classic hyaline cirrhosis; on chemical studies the hyaline bodies were amiodarone. Other side effects include, hepatitis, hypercalcemia, renal toxicity, rash and erythema nodosum.[213,219,266]

Surgery and Anesthesia There is only one paper in the literature that addresses this problem stating that patients on amiodarone can be safely anesthetized.[289] However, some problems have been noted. Local anesthetics and spinal anesthesia have shown unusual responses. Most of our patients given local anesthetics have reported initial difficulty in achieving anesthesia; much higher doses had to be given to give pain relief for dental procedures. Once anesthesia is achieved, the effect is markedly prolonged. Two patients did not recover from spinal anesthesia for 48 to 72 hours. Patients have reported their jaw being numb after dental procedures for as long as one to four weeks. Ten of our patients have required general anesthesia and have done well. Three died post operatively, but these were due to the diseases that precipitated the surgery, not the anesthetic. Another unusual finding has been an unusual number of abdominal emergencies. Three patients have presented with gangrenous gall bladders, including one that was eroding into the transverse colon. Though no explanation is known and no correlation is definite, having this number of gangrenous gall bladders in 100 patients followed for an average of less than three years is highly unusual.

Drug Interactions with Amiodarone Amiodarone has been described to have major interactions with many drugs. Amiodarone interferes with the production of vitamin K dependent coagulation factors in the same was as warfarin (Coumadin).[290,291] This will markedly potentiate the effect of warfarin. It is recommended that the dose of warfarin be halved when starting amiodarone; the pro time and PTT must be followed closely. Amiodarone tends to double the serum digoxin level, digoxin should be halved, and the serum level followed closely.[292,293] Almost all patients who are receiving quinidine and procainamide will have significant elevations in the levels of those drugs.[294] One of our patients had significant elevations of disopyramide when used in combination with amiodarone and developed electromechanical dissociation. The I-B and I-C drugs have not been studied adequately in combination with amiodarone. Amiodarone will potentiate the depressant effects of beta adrenergic blocking agents and calcium channel blockers; the effects on sinus node and AV node function are additive.[295]

Combination of Amiodarone with Other Agents Amiodarone has been used with other agents, though there is little information in the literature. In our own series we have seen additive benefits of amiodarone plus quinidine in six patients, plus procainamide in 13 patients, plus disopyramide in one patient,

plus tocainide in one patient, and plus mexiletine in three patients. The QT interval can become frighteningly long in those patients in which amiodarone is combined with a I-A agent, particularly quinidine. No torsade has been seen.

Doses for Amiodarone The proper dose for amiodarone is difficult. There is a lot of disagreement in the literature. In general we have tried to load a patient for a period of time. The starting dose is 600 mg of amiodarone BID (1200 mg/day) for three days. Higher doses have caused some neurologic problems; less frequent dosing also increases neurologic side effects. After three days we continue amiodarone at 400 mg BID (800 mg/day) until the arrhythmia is under control, usually ten to 21 days. On discharge from the hospital, the dose is reduced to 200 mg TID (600 mg/day). After six weeks an attempt is made to reduce the dose to 400 mg/day. If successful, then an attempt is made to reduce the dose to 200 mg/day after about six months.

Proarrhythmic Effects

All antiarrhythmic agents have proarrhythmic effects, though the physician notices them more with certain drugs. Proarrhythmic effects include an increase in the number of PVCs, the episode of couplets, and/or the episodes of ventricular tachycardia or fibrillation; an increase in the rate or duration of the ventricular tachycardia; the appearance of a new focus or morphology of the ventricular tachycardia; and/or the appearance of a new arrhythmia. The following Table XII is modified from Velebit and Poser.[296,297]

Table XII
Incidence of Proarrhythmic Effects[296.297]

Drug	Ambulatory Monitoring	PES
Quinidine	15.4%	16.0%
Procainamide	9.1%	21.1%
Disopyramide	5.9%	4.8%
Tocainide	15.8%	4.8%
Mexiletine	7.6%	17.5%
Flecainide	7.0%*	N/A
Amiodarone	6.4%	N/A

PES = programmed electrical stimulation, * = different type of patients being studied who may be less susceptible to proarrhythmic effects.

As can be seen, there are proarrhythmic effects with all of the agents. Generally, these proarrhythmic effects are not noticed by the physician, as they are thought to be that the agent in ineffective. In the majority of cases this effect is a slight increase in frequency or in the case of

ventricular tachycardia, the rate is increased by ten to 15 beats per minute and the clinician feels that the drug is ineffective and goes to another agent. Agents that cause torsade de pointes are often recognized as being proarrhythmic.[296,297] Quinidine is the most common cause of torsade. Procainamide and disopyramide also cause torsade, but to a lesser degree. Amiodarone, tocainide, and mexiletine have one to six case reports each of torsade.[20,209,298] Flecainide has a proarrhythmic effect that is easy to identify.[170,180,181,299-301] The proarrhythmic effect is generally a long and sometimes sustained monomorphic ventricular tachycardia that is often different from the patient's underlying arrhythmia. This effect can be very protracted (hours) and be resistant to other drugs and cardioversion. Ventricular fibrillation has been reported.[301] In two major electrophysiology laboratories, the only two deaths reported have been from a proarrhythmic effect of flecainide that could not be converted. Hence, proarrhythmic effects occur with these agent; the difficult thing to judge is how often this precipitates sudden death. Therefore, prudent judgment should prevail. Do not use a I-A agent in a patient who has long QTs or has evidence of torsade de pointes. Do not use flecainide in patients with poor left ventricular dysfunction and sustained ventricular tachycardia, particularly in doses above 400 mg/day. Be cautious in the use of amiodarone in patients with a history of torsade de pointes.

Relative Efficacy and Safety

The following table was developed by Drs. Morganroth, Anderson, and Laidlaw. This author has added judgments about mexiletine.

Table XIII
Relative Efficacy and Safety of Antiarrhythmics

Drug	% Efficacy PVCs, Couplets	% Efficacy Sustained VT*	% Intolerance
Quinidine	65%	30%	25%
Procainamide	60%	25%	25%
Disopyramide	60%	25%	25%
Tocainide	50%	15%	25%
Mexiletine	55%	25%	25%
Flecainide	85%	35%	10%
Propranolol	50%	10%	15%
Amiodarone	75%	35%**	30%

* = efficacy determined by programmed electrical stimulation, ** as determined by PES - clinical experience suggests that clinical results are twice as good

As can readily be seen, none of these drugs in a panacea. However, used appropriately and wisely they add new strength to our armamentarium. If PVCs, couplets, and multiformed ventricular ectopy are being treated the relative efficacy is as follows:

Therapy for PVCs and Couplets

Most potent	flecainide
Slightly less potent	amiodarone
Less potent	high dose procainamide
Least potent	quinidine, procainamide, disopyramide, tocainide, mexiletine

If the rhythm being treated is sustained ventricular tachycardia or ventricular fibrillation the relative efficacy is as follows:

Therapy for Sustained Ventricular Tachycardia and Ventricular Fibrillation

Most potent	amiodarone
Less potent	high dose procainamide
Less potent	flecainide
Least potent	quinidine, procainamide, disopyramide, tocainide, mexiletine

High dose procainamide means doses of procainamide necessary to keep the serum procainamide level between 15 and 20 μg/ml exclusive of NAPA.

As discussed earlier, the more effective agents tend to have a higher risk and should not be the primary agents. In general start with a I-A or I-B agent, as these are the safest agents. If the first agent is ineffective, try an agent in the other class. If the second agent fails, go back to the first class. If a patient has a side effect other than torsade de pointes, try another agent in the same class. Once the agents in the I-A and I-B classes have failed, then go to a more potent agent on the appropriate list above, realizing the risk is greater; for just PVCs or couplets with normal ventricular function, the only more potent agent that I might try is flecainide. If it is felt that the benefit is worth the risk continue up the ladder until control is achieved. If a patient has a long QT before or after a I-A agent or torsade de pointes, then a I-B agent is the drug of choice. If the patient is elderly and/or has confusion, disorientation, etc., the drug of choice is quinidine as it has the least CNS effects.

Conclusion While we are far from having an ideal antiarrhythmic agent that is both highly effective and safe, there are now many drugs to choose from, so that we can tailor the therapy to the individual patient's needs. Due to the potential for harm, the risk to benefit ratio must constantly be considered. It is difficult to know what the risk to benefit ratio is with certainty, when there have never been large scale trials to fully assess the risk to benefit ratios in various classes of patients. This leaves the decision up to the prudent physician.

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