REVIEW ARTICLE

Drug Safety 2000 Dec; 23 (6): 509-532
0114-5916/00/0012-0509/$20.00/0

Antiarrhythmic Agents
Drug Interactions of Clinical Significance

Toby C. Trujillo[1] and *Paul E. Nolan*[2,3]

1 Department of Pharmacy Practice, Massachusetts College of Pharmacy and Health Sciences, Boston, Massachusetts, USA
2 Department of Pharmacy Practice and Science, College of Pharmacy, The University of Arizona, Tucson, Arizona, USA
3 Sarver Heart Center, The University of Arizona, Tucson, Arizona, USA

Contents

Abstract

The management of cardiac arrhythmias has grown more complex in recent years. Despite the recent focus on nonpharmacological therapy, most clinical arrhythmias are treated with existing antiarrhythmics. Because of the narrow therapeutic index of antiarrhythmic agents, potential drug interactions with other medications are of major clinical importance.

As most antiarrhythmics are metabolised via the cytochrome P450 enzyme system, pharmacokinetic interactions constitute the majority of clinically significant interactions seen with these agents. Antiarrhythmics may be substrates, inducers or inhibitors of cytochrome P450 enzymes, and many of these metabolic interactions have been characterised. However, many potential interactions have not,

and knowledge of how antiarrhythmic agents are metabolised by the cytochrome P450 enzyme system may allow clinicians to predict potential interactions.

Drug interactions with Vaughn-Williams Class II (β-blockers) and Class IV (calcium antagonists) agents have previously been reviewed and are not discussed here. Class I agents, which primarily block fast sodium channels and slow conduction velocity, include quinidine, procainamide, disopyramide, lidocaine (lignocaine), mexiletine, flecainide and propafenone. All of these agents except procainamide are metabolised via the cytochrome P450 system and are involved in a number of drug-drug interactions, including over 20 different interactions with quinidine. Quinidine has been observed to inhibit the metabolism of digoxin, tricyclic antidepressants and codeine. Furthermore, cimetidine, azole antifungals and calcium antagonists can significantly inhibit the metabolism of quinidine. Procainamide is excreted via active tubular secretion, which may be inhibited by cimetidine and trimethoprim. Other Class I agents may affect the disposition of warfarin, theophylline and tricyclic antidepressants. Many of these interactions can significantly affect efficacy and/or toxicity.

Of the Class III antiarrhythmics, amiodarone is involved in a significant number of interactions since it is a potent inhibitor of several cytochrome P450 enzymes. It can significantly impair the metabolism of digoxin, theophylline and warfarin. Dosages of digoxin and warfarin should empirically be decreased by one-half when amiodarone therapy is added.

In addition to pharmacokinetic interactions, many reports describe the use of antiarrhythmic drug combinations for the treatment of arrhythmias. By combining antiarrhythmic drugs and utilising additive electrophysiological/pharmacodynamic effects, antiarrhythmic efficacy may be improved and toxicity reduced.

As medication regimens grow more complex with the aging population, knowledge of existing and potential drug-drug interactions becomes vital for clinicians to optimise drug therapy for every patient.

In recent years the management of cardiac arrhythmias has become more complex. For example, routine use of antiarrhythmic drug therapy to eliminate asymptomatic ventricular premature depolarisations or nonsustained ventricular tachycardia following acute myocardial infarction is no longer considered the standard of practice.[1] Consequently, the use of nonpharmacological therapy for arrhythmias continues to expand, such as the use of radiofrequency catheter ablation in the management of junctional tachycardias[2] and the insertion of automatic implantable cardioverter-defibrillators (AICDs) for treatment of inducible sustained ventricular tachycardia or ventricular fibrillation.[3,4]

Despite these technological advances, most clinial arrhythmias can be diagnosed with electrocardiography (ECG) and treated with available pharmacological therapy. Antiarrhythmic agents are commonly prescribed for patients with recurrent paroxysmal or chronic atrial fibrillation.[5] In addition, antiarrhythmic drugs are used in the treatment[6] or prophylaxis[6,7] of atrial arrhythmias following cardiothoracic surgery. Furthermore, antiarrhythmics are commonly used in conjunction with AICDs.[3,4] These drugs are also used in patients with obstructive hypertrophic cardiomyopathy[8] as well as in patients with heart failure secondary to systolic dysfunction.[9]

Therefore, given the not uncommon use of antiarrhythmic drugs in patients with a variety of arrhythmias and related conditions, the awareness of potential drug interactions is especially important, since these agents often have a narrow therapeutic index. Small increases or decreases in the serum concentrations of antiarrhythmics can lead to therapeutic failure or toxicity. However, not all drug in-

teractions are clinically significant. Therefore, in this review a comprehensive discussion of known drug interactions relating to antiarrhythmic therapy is provided, but the interactions are also discussed in terms of their likelihood and clinical significance.

1. General Aspects of Drug Interactions

A drug interaction is defined as a reaction between 2 or more drugs that acts to enhance or inhibit the predicted response. An interaction between 2 or more agents may be either beneficial or harmful, depending on the desired outcome. Generally drug interactions can be divided into 2 subgroups. The first are pharmacokinetic interactions, where one drug can interfere with the absorption, distribution, metabolism or excretion of another. Absorption of a drug may be altered by changing the rate or extent of uptake. Drug distribution may be altered by changes in blood flow or protein binding. Metabolism of a drug may be altered by either inhibition or induction of the responsible enzyme(s). Elimination of a drug may be altered by inhibition of active secretion in the kidneys.[10]

The second group are pharmacodynamic interactions. With these the clinical response to a given drug is either enhanced or inhibited without a change in pharmacokinetic parameters. This may occur in patients taking 2 agents that produce similar pharmacological effects. An example would be 2 drugs that prolong ventricular refractoriness and lengthen the QT interval, thereby increasing the likelihood for torsade de pointes.[10] Favourable or desirable pharmacodynamic interactions also may result through the combination of antiarrhythmic drugs with different but complementary or additive electrophysiological properties.[11] Examples of each, respectively, are the combination of quinidine plus mexiletine in the treatment of ventricular arrhythmias[12] or the combination of digoxin plus a β-adrenergic blocking drug to slow the ventricular response in patients with atrial fibrillation.[13]

1.1 Drug Metabolism: Types of Metabolic Reactions

Humans metabolise drugs and other xenobiotics through phase I or phase II reactions. Phase I reactions (oxidation, reduction or hydrolysis) convert the parent drug to a more water-soluble metabolite, which may retain significant pharmacological activity. Phase II reactions typically involve coupling the parent drug with an endogenous substance (e.g. glucuronic acid, acetic acid, inorganic sulphate), which results in an inactive compound.[10,14]

1.2 Cytochrome P450 Enzymes

Cytochrome P450 (CYP) enzymes are a large group of haem-containing compounds that are primarily responsible for carrying out phase I reactions in humans. Approximately 33 types of human enzymes in 14 families have been identified. Of these 33, approximately 20 are involved in the transformation of xenobiotics in humans. CYP enzymes are classified into families (1, 2, 3, etc.) and subfamilies (A, B, C, etc.) based on the degree of homology in their respective amino acid sequences. These enzymes are most commonly found in the liver but can also be identified in other tissues (gastrointestinal tract, lungs and brain).[10,14-16]

A particular drug entity can be a substrate, inducer or inhibitor of any particular CYP enzyme. Typically, drugs are substrates for more than 1 CYP enzyme. Furthermore, a drug may inhibit or induce the activity of a specific isozyme that is not involved in its own metabolism. Interest in CYP enzymes has greatly increased in recent years as more drug entities metabolised by this enzyme system are approved for use. As the number of potential drug interactions increases with the release of these new entities, knowledge of CYP metabolism may allow for prediction of significant drug interactions and avoidance of an adverse event.

1.3 Genetic Variation among the Cytochrome P450 Enzymes

A few specific CYP enzymes are found in altered forms because of the existence of different alleles

which control their expression. In terms of drug metabolism, the polymorphism seen with CYP2D6 is the most studied and clinically relevant. Approximately 3 to 10% of Caucasians and 0 to 2% of Asians and African-Americans have low or no activity of the enzyme and are known as 'poor metabolisers'. Another common polymorphism involves CYP2C19. About 3 to 5% of Caucasians, 18 to 23% of Asians and 5% of African-Americans possess little to no activity of this enzyme.[10,14-16] Patients who are poor metabolisers generally require a lower dose to produce a desired therapeutic effect. However, the opposite may be true if the clinical effect of a particular medication is associated with an active metabolite.

This genetic polymorphism complicates the evaluation of potential drug interactions involving agents metabolised by CYP2D6 or CYP2C19. In persons who are 'extensive metabolisers' of a particular agent, coadministration of a drug that inhibits its metabolism through either CYP2D6 or CYP2C19 will essentially convert that patient to being a poor metaboliser, possibly necessitating a dosage reduction. The same clinical situation in a patient who is a poor metaboliser often does not result in increased blood concentrations of the object drug, and no adjustment may be necessary.[17,13]

Extensive metabolisers appear to be more at risk for developing drug interactions than slow metabolisers, given that most patients would be expected to be extensive metabolisers and that for most drugs it is the parent drug rather than a metabolite that has the greatest pharmacological activity. Examples of antiarrhythmics metabolised by CYP2D6 where the activity of the parent exceeds that of the metabolite(s) include mexiletine, flecainide and the β-blockers propranolol and metoprolol. For propafenone the parent and major metabolite generated by CYP2D6 metabolism are approximately equally active; thus, inhibition of this enzyme by another drug should result in no change in pharmacological activity. Thus, for antiarrhythmic agents, routine screening for CYP2D6 metabolic phenotype appears unnecessary.[17-18]

2. Classification of Antiarrhythmic Agents

The Vaughn-Williams[19] classification of antiarrhythmic drugs has been used for the greater part of the last 2 decades. Recently this classification system has been criticised for being incomplete, oversimplified and not useful for clinical practice. Because of these concerns, a new classification system was developed.[20] This system is based on the differential effects of antiarrhythmic drugs on channels, receptors and transmembrane pumps. It may be more appropriate for clinical practice, as it takes into consideration the arrhythmia mechanism and attempts to identify targeted drug therapy. However, this has not become a clinical reality. Therefore, in

Table I. Vaughn Williams classification of antiarrhythmic agents[19]

Class	Action	Drugs
1	Sodium channel blockade	
1A	Moderate phase 0 depression	Quinidine, procainamide, disopyramide
1B	Minimal phase 0 depression	Lidocaine (lignocaine), mexiletine
1C	Marked phase 0 depression	Flecainide, propafenone
2	β-Adrenergic blockade	
	Slow sinoatrial node firing and atrioventricular node conduction	Metoprolol, atenolol, propranolol, etc.
3	Potassium channel blockade	
	Prolonged repolarisation	Amiodarone, sotalol, bretylium, dofetilide, ibutilide
4	Calcium channel blockade	
	Slow atrioventricular nodal conduction	Verapamil, diltiazem
Other	Variable	
		Digitalis glycosides, adenosine, atropine

Table II. Antiarrhythmic agents that are substrates or inhibitors of cytochrome P450 (CYP) enzymes[14,15]

CYP enzyme	Substrate	Inhibitor
CYP1A2	Lidocaine (lignocaine)	Lidocaine
	Mexiletine	Mexiletine
	Propafenone	
CYP2B6	Lidocaine	
CYP2C9		Amiodarone
CYP2D6	Flecainide	Amiodarone
	Mexiletine	Flecainide
	Propafenone	Propafenone
		Quinidine
CYP3A4	Amiodarone	Quinidine
	Disopyramide	
	Lidocaine	
	Propafenone	
	Quinidine	

regard to the organisation of this review, the Vaughn-Williams classification is used (table I). However, the focus of the review is limited principally to Class I and Class III agents, along with adenosine, since drug interactions for Class II (β-blockers) and Class IV (calcium antagonists) agents as well as for digitalis glycosides have recently been reviewed.[21-23]

As previously discussed, a number of antiarrhythmic agents are substrates and inhibitors of CYP enzymes (table II).[14,15] These relationships are integral in understanding the mechanism of many currently known drug-drug interactions involving antiarrhythmic agents. Furthermore, the significance of these relationships will increase as new medications become available and the elderly population continues to increase. With the growing number of new medications being approved and limited healthcare resources, significant drug-drug interactions may not have been discovered before a drug comes to the market. In the following sections the currently known drug-drug interactions of antiarrhythmic agents are discussed. However, our current understanding of the breadth and scope of antiarrhythmic agent drug interactions is likely to be limited. The ability to predict potential interactions based on the CYP profile of antiarrhythmics and other drugs is likely to become increasingly clinically relevant. An excellent review and synopsis of the currently known medications that are substrates, inducers or inhibitors of CYP enzymes is provided by Rendic and Di Carlo.[14]

3. Pharmacokinetic Interactions of Antiarrhythmic Agents

3.1 Quinidine

Quinidine has been observed to take part in numerous drug-drug interactions. A complete list can be found in table III. Some of the more prominent interactions are discussed below.

3.1.1 Azole Antifungal Agents (Ketoconazole, Itraconazole)

In healthy volunteers, itraconazole was noted to increase peak plasma concentrations of quinidine 1.6-fold and increase the area under the plasma concentration-time curve (AUC) by 2.4-fold. The effect appears to be mediated through inhibition of CYP3A4 and decreased renal clearance of quinidine.[37] Concurrent administration of ketoconazole in a patient taking quinidine led to an increase in serum quinidine concentrations and half-life (25 hours). Additional research is warranted to document the incidence and potential clinical consequences of this interaction.[37]

3.1.2 Calcium Antagonists

The effect of various calcium antagonists on the pharmacokinetics of quinidine is variable with respect to the occurrence and direction of the potential change. Nifedipine may decrease plasma concentrations of quinidine,[40-43] although other studies have shown no effect.[45-47] The mechanism for the decrease is unknown. Additionally, quinidine may lead to increases in nifedipine concentrations.[44]

Several reports have demonstrated that both diltiazem and verapamil may lead to an increase in quinidine plasma concentrations. However, as with nifedipine, other reports have not confirmed the occurrence of a pharmacokinetic interaction between these agents.[48-53] The joint administration of verapamil and quinidine may also produce hypotension, bradycardia and atrioventricular (AV) block, and patients should be monitored for the occurrence of these potential adverse effects.

Table III. Drug interactions with quinidine

Agent	Interaction	Management
Antiarrhythmics		
Amiodarone[24-26]	↑ in serum quinidine concentrations may occur	Monitor for quinidine toxicity
Disopyramide[27]	Slight ↑ in disopyramide concentrations	Monitor for disopyramide toxicity
Flecainide[28]	↑ in $t_{1/2}$ of flecainide has been observed	Monitor for flecainide toxicity
Mexiletine[29]	↑ in serum mexiletine concentrations	Monitor for mexiletine toxicity
Procainamide[30]	Possible ↑ in $t_{1/2}$ of procainamide	Monitor procainamide concentrations and adjust dosage as necessary
Propafenone[31-33]	↑ in plasma propafenone concentrations in extensive metabolisers	Monitor for propafenone toxicity
Antibacterials/antifungals		
Ciprofloxacin/metronidazole[34]	May ↑ plasma quinidine concentrations	Monitor for quinidine toxicity
Erythromycin/clarithromycin[14,35,36]	May ↑ plasma quinidine concentrations	Monitor for quinidine toxicity
Itraconazole/ketoconazole[37,38]	↑ in plasma quinidine concentrations	Monitor for quinidine toxicity
Calcium antagonists		
Mibefradil[39]	Mild ↑ in plasma quinidine concentrations	Monitor for quinidine toxicity
Nifedipine[40-47]	Possible ↑ in plasma nifedipine concentrations	Monitor for nifedipine toxicity
	Possible ↓ in plasma quinidine concentrations	May need to increase quinidine dosage to maintain effect
Verapamil/diltiazem[48-53]	↑ in plasma quinidine concentrations in some patients	Monitor for quinidine toxicity
Enzyme inducers		
Phenytoin, phenobarbital (phenobarbitone), rifampicin (rifampin) and carbamazepine[54-60]	↓ in plasma quinidine concentrations	Monitor quinidine concentrations and adjust dosage as necessary
Other		
Anticholinesterases/skeletal muscle relaxants[61-62]	Prolonged neuromuscular blockade may be seen	
Cimetidine[63-67]	↑ in plasma quinidine concentrations in some patients	Monitor for quinidine toxicity
Codeine[68,69]	↓ in analgesic effect	Use alternative analgesic
Dextromethorphan[70]	↑ in plasma dextromethorphan concentrations may be seen	Clinical significance unknown
Digoxin[71-76]	↑ in plasma digoxin concentrations	Decrease digoxin dosage by half
Propranolol/metoprolol[77-80]	May ↓ metabolism of β-blocker and ↑ degree of β-blockade	Monitor for increased β-blocker effects
Sucralfate[81]	May ↓ plasma quinidine concentrations	Monitor for therapeutic effect
Tricyclic antidepressants (desipramine, imipramine)[82,83]	↑ in plasma concentrations of antidepressant	Monitor antidepressant plasma concentrations and adjust dosage accordingly
Fluvoxamine[84]	↓ in quinidine clearance	Monitor for quinidine toxicity
Warfarin[85-87]	↑ in warfarin effect may be seen	Monitor INR
Urinary alkalinisers (acetazolamide, antacids)[88-90]	Possible ↑ in serum quinidine concentrations due to ↓ in renal excretion	Monitor for quinidine toxicity

INR = International Normalised Ratio; **$t_{1/2}$** = half-life; ↑ = increase; ↓ = decrease.

3.1.3 Cimetidine

Several studies have shown that cimetidine administration leads to an approximately 33% reduction in the oral clearance of quinidine and a 20% increase in serum quinidine concentrations. This appears to be due to inhibition of the renal tubular secretion of the parent drug, but not of its metabolites. The effects of quinidine on the ECG were en-

hanced when cimetidine and quinidine were coadministered.[63-67]

3.1.4 Codeine

Codeine requires CYP2D6 for conversion to morphine, the active moiety, for its analgesic effect to take place. In patients who are extensive metabolisers, quinidine administration may decrease the analgesic effect of codeine by inhibiting the conversion of codeine to morphine by CYP2D6. Increased doses or an alternative analgesic agent may be tried.[68,69]

3.1.5 Digoxin

Marked increases in plasma digoxin concentrations (up to 300%) have been observed, and the magnitude of increase is directly related to quinidine plasma concentrations. Empirically decreasing the digoxin dose by one-half at the onset of therapy is recommended. Quinidine appears to decrease both the renal (up to 50%) and nonrenal (up to 65%, mean 42%) clearance of digoxin. Quinidine also appears to displace digoxin from nonspecific tissue-binding sites, decreasing the volume of distribution of digoxin by 40%, which leads to an almost immediate rise in digoxin concentrations.[71-74] The clinical consequences of this interaction in terms of an increased inotropic effect from digoxin is difficult to determine given the negative inotropic effects of quinidine. The electrophysiological actions of the 2 drugs may also be additive.[75] Quinidine may also potentially interfere with absorption of digoxin from the gastrointestinal tract.[76]

3.1.6 Inducers of Cytochrome P450 (Phenytoin, Phenobarbital (Phenobarbitone) and Rifampicin (Rifampin))

Plasma concentrations of quinidine can be significantly decreased by these agents. Three case reports document an increase in quinidine requirements during concomitant phenytoin therapy. Furthermore, in 2 healthy volunteers, quinidine half-life decreased by 50%, and quinidine AUC decreased by 60%, after 2 weeks of phenytoin therapy.[54,55] Rifampicin administration in 1 study led to a 3-fold reduction in the mean elimination half-life and an almost 6-fold reduction in the AUC for quinidine.[56] Several case reports have demonstrated the clinical significance of this interaction, often leading to drug failure with quinidine.[57,58] Several case reports have documented the effect of phenobarbital coadministration with quinidine. Generally, serum quinidine concentrations have decreased with an approximate 50% decrease in half-life.[54,59,60]

3.1.7 Warfarin

Marked potentiation of warfarin effect can be seen in some patients. However, a controlled study with quinidine has never been done and there are mixed results from case reports, with either enhanced anticoagulation[85] or even reduced anticoagulation.[86] International Normalised Ratio (INR) should be monitored and warfarin dosage adjusted as necessary.[87]

3.2 Procainamide

3.2.1 Amiodarone

Plasma concentrations of procainamide and *N*-acetyl-procainamide (NAPA) may be increased. Procainamide concentrations should be monitored and dose adjusted as necessary. Amiodarone decreases clearance and increases elimination half-life of procainamide, and the 2 agents may produce additive electrophysiological effects.[91,92]

3.2.2 Antibacterials

In 10 healthy male volunteers, trimethoprim administration resulted in an increase of the AUC of procainamide and NAPA by 39 and 25%, respectively. A second study found increases of 63 and 52%, respectively. The oral plasma clearance of procainamide was decreased by 32%. The presumed mechanism is decreased renal tubular secretion of procainamide by competitive inhibition with trimethoprim.[93,94]

In 9 healthy volunteers, administration of ofloxacin resulted in 27 and 21% increases in the AUC and peak plasma concentration of procainamide. Plasma clearance of procainamide decreased by an average of 22%. NAPA pharmacokinetics were not altered. The proposed mechanism is a decrease in the renal tubular secretion by ofloxacin.[95]

3.2.3 β-Blockers

Propranolol has been reported to increase the elimination half-life of procainamide by 56%. However,

another study found no interaction between procainamide and metoprolol. Close monitoring of procainamide concentrations is recommended with concurrent administration of propranolol.[96]

3.2.4 H_2 Antagonists

Cimetidine may increase plasma concentrations of procainamide and NAPA, probably as a result of inhibition of active tubular secretion in the kidney. Cimetidine administration has increased procainamide concentrations by 36% and prolonged elimination half-life by 25%.[97-99]

Several reports have demonstrated that ranitidine may lead to a small but significant (14%) increase in the AUC of procainamide. This was due to an observed decrease in renal and hepatic clearance, and this effect was dose-dependent.[100,101] However, other reports have documented no interaction between the 2 agents.[99,102] Because there is no consensus on the potential existence or incidence of this interaction, close monitoring of procainamide concentrations is indicated if ranitidine is coadministered.

3.3 Disopyramide

3.3.1 Anticholinergic Agents

There is a pharmacodynamic interaction with worsening anticholinergic effects. Monitoring should be undertaken for the occurrence of adverse events and dosage modified if necessary.[103]

3.3.2 β-Blockers

When disopyramide and β-blockers are given together, severe bradycardia, asystole and heart failure have been observed.[104,105] Atenolol has been observed to decrease clearance of disopyramide by about 15%, resulting in increased plasma concentrations.[106]

3.3.3 Inducers of Cytochrome P450

The elimination half-life and AUC of disopyramide were decreased by 44.5 and 59%, respectively, after administration of rifampicin. Plasma concentrations were also noted to decrease.[107,108] Phenytoin administration has also been observed to produce a decrease in disopyramide serum concentrations, with an increase in the major metabolite of disopyramide (mono-*N*-dealkyldisopyramide, MND).[107,109-111] MND has some antiarrhythmic activity, but greater anticholinergic effects than the parent compound. Because of the pharmacology of MND, the clinical significance of this interaction is unknown.

3.3.4 Macrolide Antibacterials

Erythromycin may inhibit the metabolism of disopyramide, leading to increased plasma concentrations and a toxic response. In 2 patients who were stabilised on disopyramide, erythromycin administration led to QT prolongation and polymorphic ventricular tachycardia. Close monitoring of the ECG is recommended when this combination is used.[112]

Concomitant administration of clarithromycin and disopyramide in a 59-year-old man led to significant increases in disopyramide plasma concentrations and hypoglycaemia. The authors postulated that elevated disopyramide plasma concentrations, possibly resulting from decreased clearance with the administration of clarithromycin, enhanced insulin secretion.[113]

3.3.5 HIV Protease Inhibitors

Protease inhibitors (indinavir, nelfinavir, ritonavir and saquinavir) have recently become available for the treatment of HIV infection. These agents are potent inhibitors of CYP3A4, and concomitant administration with disopyramide was observed to result in a >3-fold increase in AUC. Close monitoring for disopyramide toxicity is warranted if these drugs are to be coadministered.[15]

3.3.6 H_2 Antagonists

Coadministration of cimetidine and disopyramide to healthy volunteers led to significant elevations in maximum plasma concentrations and AUC for disopyramide. No effect was observed on the pharmacokinetics of disopyramide with coadministration of ranitidine.[114]

3.4 Lidocaine (Lignocaine)

3.4.1 Amiodarone

In patients receiving amiodarone, the addition of lidocaine does not appear to influence the phar-

macokinetics of either agent.[115] However, when amiodarone treatment is started in patients who are on a lidocaine infusion, there is a decrease in lidocaine clearance, possibly resulting in toxic lidocaine concentrations. This is probably due to the ability of amiodarone to inhibit CYP3A4.[116]

3.4.2 β-Blockers

Numerous reports document toxicity when propranolol is coadministered with lidocaine. Propranolol has been shown to decrease lidocaine clearance secondary to decreased hepatic blood flow. Subsequently, elevated lidocaine concentrations have been associated with CNS toxicity (lethargy, confusion).[117-120]

This interaction also should be expected with other β-blockers, since most appear to decrease hepatic blood flow. However, this effect may be more pronounced with the nonselective agents with or without additional α-adrenergic blocking effects.[121,122] Monitoring of lidocaine concentrations is recommended and dosage adjustment as necessary.[117-120]

3.4.3 Cimetidine

Lidocaine disposition is significantly affected by changes in hepatic blood flow.[123] Plasma concentrations of lidocaine may be increased when cimetidine is coadministered because of a decrease in hepatic blood flow. Monitoring of lidocaine concentrations and dosage adjustment if necessary is recommended. Conversely, an alternative H_2 antagonist may be used to avoid an increase in lidocaine concentrations.[124-126]

3.4.4 Inducers of Cytochrome P450

Decreased plasma concentrations of lidocaine may be seen when lidocaine is coadministered with CYP enzyme inducers. Rifampicin administration has been shown to increase the rate of lidocaine metabolism in cultured human hepatocytes. Clearance of lidocaine was increased approximately 100%, presumably through induction of CYP enzymes.[127,128]

3.4.5 HIV Protease Inhibitors

As with disopyramide, the AUC of lidocaine may be increased by >3-fold if there is concomitant administration of a protease inhibitor. Close monitoring of lidocaine concentrations is warranted.[15]

3.4.6 Suxamethonium (Succinylcholine)

Experimental studies in humans and animals have reported that lidocaine may prolong the time of suxamethonium-induced neuromuscular blockade and therefore cause prolongation of respiratory depression. The exact mechanism for this is unknown. Close monitoring of patients receiving both agents is warranted.[129,130]

3.5 Mexiletine

A complete list of drug-drug interactions involving mexiletine is given in table IV. A few of the better known interactions are discussed below.

Table IV. Drug interactions with mexiletine

Agent	Interaction	Management
Enzyme inducers [phenytoin, phenobarbital (phenobarbitone), rifampicin (rifampin)][131,132]	↓ in plasma mexiletine concentrations with a loss of efficacy	Monitor for mexiletine efficacy and adjust dosage as needed
Ritonavir[15]	↑ in plasma mexiletine concentrations due to inhibition of CYP2D6	Monitor for mexiletine toxicity
Amiodarone[15]	↑ in plasma mexiletine concentrations due to inhibition of CYP2D6	Monitor for mexiletine toxicity
Quinidine[15]	↑ in plasma mexiletine concentrations due to inhibition of CYP2D6	Monitor for mexiletine toxicity
Theophylline[133-140]	↑ in plasma theophylline concentrations	Monitor theophylline concentrations and adjust dosage as needed
Selective serotonin reuptake inhibitors[141]	↑ in plasma mexiletine concentrations due to inhibition of CYP2D6	Monitor for mexiletine toxicity

CYP = cytochrome P450; ↑ = increase; ↓ = decrease.

3.5.1 Inducers of Cytochrome P450

Rifampicin coadministration resulted in a 51% increase in total body clearance and 41% decrease in the elimination half-life of mexiletine.[131] Similarly, phenytoin coadministration resulted in a 55% decrease in AUC and a 51% decrease in the elimination half-life of mexiletine.[132] The postulated mechanism is induction of the CYP2D6-mediated metabolism of mexiletine.

3.5.2 Theophylline

Several cases of increased plasma concentrations of theophylline have been reported.[133-136] Typically, the serum theophylline concentration is doubled when mexiletine is added. In a randomised crossover study in 12 healthy volunteers, theophylline concentrations increased by 58% and clearance decreased by 43%.[137] A reduction in the *N*-demethyl metabolite of theophylline has been demonstrated, indicating that mexiletine inhibits the CYP1A2 metabolism of theophylline.[138-140]

3.6 Flecainide

3.6.1 Amiodarone

In 12 healthy volunteers, addition of amiodarone led to an increase in plasma concentrations of flecainide. Some investigators have advocated an empirical decrease in the flecainide dose by half.[142,143] The ability of amiodarone to inhibit CYP2D6 appears to be a likely explanation for the decrease in flecainide metabolism.[142,143]

3.6.2 Cimetidine

Concomitant administration of cimetidine to healthy volunteers resulted in a decrease in the clearance and increase in the half-life of flecainide. However, information on this interaction is limited and further investigation is warranted.[144]

3.6.3 Cigarette Smoking

A meta-analysis of several studies investigating the effect of smoking on flecainide pharmacokinetics concluded that, overall, smoking may lead to decreased plasma concentrations of flecainide, possibly as a result of enhanced hepatic metabolism.[145]

3.6.4 Digoxin

A small but significant (15%) increase in the serum digoxin concentration has been noted after administration of flecainide. Close monitoring of digoxin concentrations is warranted when these 2 agents are coadministered.[146-148]

3.6.5 Selective Serotonin Reuptake Inhibitors

Concomitant administration may produce an increase in plasma concentrations of flecainide, possibly due to inhibition of CYP2D6 metabolism. Although an empirical dosage reduction of flecainide has not been clinically investigated, because of the potential proarrythmic consequences a reduction of the flecainide dosage may be warranted.[141]

3.6.6 Urinary Alkalinisers

Excretion of flecainide in the kidney is a pH-dependent process. In 2 studies involving healthy adults, alkalinisation of the urine led to an increase in the elimination half-life and decrease in the urinary excretion of flecainide. However, there was a high degree of interindividual variability, and the clinical significance of this interaction is unknown.[149,150]

3.7 Propafenone

Table V presents a complete list of known drug-drug interactions involving propafenone. A few of the more clinically relevant interactions are discussed below.

3.7.1 Digoxin

An increase in serum digoxin concentrations occurs in over 80% of patients. Postulated mechanisms include a decrease in the volume of distribution and in nonrenal clearance of digoxin.[154,155] Plasma digoxin concentrations should be monitored and dosage adjusted accordingly. An approximate 25% decrease in the digoxin dosage may be initiated if propafenone therapy is indicated.

3.7.2 Rifampicin

Administration of rifampicin to a 42-year-old patient maintained on propafenone for ventricular arrhythmias resulted in a decrease in serum propafenone concentrations with a concomitant recurrence of the disease. Upon discontinuation of rifam-

Table V. Drug interactions with propafenone

Agent	Interaction	Management
Amiodarone[15]	Possible ↑ in serum propafenone concentrations	Monitor for propafenone toxicity
β-Blockers[151]	Pharmacodynamic interaction with ↑ in β-blocking activity	Monitor heart rate and blood pressure
Cyclosporin[152]	Possible ↑ in cyclosporin concentrations	Monitor cyclosporin concentrations
Cimetidine[15,153]	↑ in propafenone concentrations (50-75%)	Monitor for propafenone toxicity
Digoxin[154,155]	↑ in serum digoxin concentrations	Empirical 25% decrease in digoxin dosage at onset of propafenone therapy
Enzyme inducers [rifampicin (rifampin), phenobarbital (phenobarbitone), phenytoin][156,157]	Possible ↓ in serum propafenone concentrations with loss of efficacy	Monitor for propafenone efficacy
Quinidine[15]	Possible ↑ in serum propafenone concentrations	Monitor for propafenone toxicity
Selective serotonin reuptake inhibitors[148]	Possible ↑ in serum propafenone concentrations	Monitor for propafenone toxicity
Theophylline[158,159]	Possible ↑ in serum theophylline concentrations	Closely monitor theophylline concentrations
Warfarin[160]	↑ in warfarin effect	Monitor INR

INR = International Normalised Ratio; ↑ = increase; ↓ = decrease.

picin, propafenone serum concentrations returned to previous values and no further arrhythmias were noted.[156] An additional report demonstrated that rifampicin increases the metabolism of both propafenone and its main metabolite, 5-hydroxypropafenone.[157]

3.7.3 Warfarin

In healthy volunteers, propafenone administration resulted in a 38% increase in steady-state warfarin concentration. The prothrombin-time ratio was increased approximately 30% in these individuals. INR should be monitored when propafenone is initiated or discontinued.[160]

3.8 Sotalol

In healthy volunteers, administration of magnesium hydroxide (1200mg) and aluminium oxide (1800mg) resulted in a decrease in serum sotalol concentrations, presumably by decreased absorption of sotalol. Separation of the 2 drugs by 2 hours was sufficient to avoid the interaction.[161]

3.9 Amiodarone

A complete list of known drug-drug interactions involving amiodarone is presented in table VI. Some of the better described interactions are discussed below.

3.9.1 Digoxin

Marked elevation of digoxin concentrations (up to 100%) within the first 2 days of administration has been seen. The increase in digoxin serum concentrations stabilises only after 2 weeks of concomitant administration. The magnitude of increase is directly proportional to the dosage and plasma concentration of amiodarone.[168-171] Amiodarone appears to decrease both the renal and nonrenal clearance of digoxin.[172] An empirical decrease of digoxin dosage by half at the onset of amiodarone therapy is recommended to avoid toxicity.[173]

3.9.2 Phenytoin

Increased plasma concentrations of phenytoin (2-fold or greater) can be observed. Phenytoin concentrations should be monitored and dosage adjusted accordingly. The inhibition of phenytoin metabolism by amiodarone appears to be mediated through inhibition of CYP2C9.[177-179] Conversely, phenytoin administration may lead to a decrease in steady-state amiodarone concentrations and an increase in desethyl-amiodarone concentrations. The clinical

significance of this interaction needs to be investigated.[180]

3.9.3 Warfarin

Marked potentiation of warfarin effect is seen. An empirical decrease in the warfarin dosage by half at the onset of amiodarone therapy is recommended. Inhibition of CYP2C9 and CYP1A2 appears to be the mechanism for decreased clearance (approximately 65%) of the (*S*)- and (*R*)-enantiomers of warfarin by amiodarone. An increase in the free fraction of warfarin is also seen. The magnitude of the interaction appears to be dependent on the dosage of amiodarone.[182-186]

3.10 Ibutilide

Ibutilide is a pure Class III antiarrhythmic recently approved in the US for the acute conversion of atrial fibrillation and atrial flutter. Although the metabolism of ibutilide appears to be hepatic, studies have shown that it does not involve CYP2D6 or CYP3A4.[187] No significant drug interactions for ibutilide have yet been identified.

3.11 Dofetilide

Dofetilide is a new Class III antiarrhythmic agent that has recently been approved in the US for the conversion and maintenance of sinus rhythm in patients with atrial fibrillation and flutter. The drug is mainly eliminated unchanged in the kidney via the cationic transport system, and drugs that inhibit this process will lead to increased dofetilide plasma concentrations. Cimetidine, ketoconazole, trimethoprim, prochlorperazine and megestrol all inhibit the cationic transport system in the kidney and should not be administered to patients receiving dofetilide. In addition, verapamil increases plasma concentrations of dofetilide by increasing its oral absorption, and should also be avoided in patients taking dofetilide.[188]

3.12 Adenosine

3.12.1 Other Agents that Slow Atrioventricular Conduction (β-Blockers, Digoxin, Diltiazem and Verapamil)

Concomitant administration may result in significant AV block.[189] Verapamil has been observed to significantly reduce the dose of adenosine required to produce AV block.[190]

3.12.2 Dipyridamole

The pharmacological effect of dipyridamole or adenosine may be potentiated by each other, leading to profound bradycardia and chest pain upon concurrent administration.[191-194]

Table VI. Drug interactions with amiodarone

Agent	Interaction	Management
β-Blockers[162]	Pharmacodynamic interaction that may produce bradycardia and heart block	Monitor for excessive β-blockade
Calcium antagonists (verapamil, diltiazem)[162-164]	Pharmacodynamic interaction that may produce bradycardia and heart block	Monitor for conduction defects
Cyclosporin[165-167]	Possible ↑ in cyclosporin concentrations and toxicity	Monitor cyclosporin concentrations closely
Digoxin[168-173]	Doubling of the serum digoxin concentration	Empirically decrease digoxin dosage by half at onset of therapy
Fentanyl[174-176]	Combination has resulted in hypotension and sinus arrest	Monitor for adverse haemodynamic effects
Phenytoin[177-180]	↑ in phenytoin serum concentrations, possible ↓ in amiodarone concentrations	Monitor phenytoin concentrations and adjust dosage as needed. Monitor for amiodarone toxicity
Theophylline[181]	Possible ↑ in theophylline concentrations	Monitor theophylline concentrations
Warfarin[182-186]	↑ in warfarin effect	Empirically decrease warfarin dosage by half at onset of therapy

↑ = increase; ↓ = decrease.

3.12.3 Methylxanthines

A potential pharmacological interaction between adenosine and methylxanthines (theophylline and caffeine) has been demonstrated in healthy volunteers. Methylxanthines in general antagonise the cardiovascular effects of adenosine. Studies examining the effect of methylxanthines on adenosine did not assess the potential effect on large doses of adenosine (6 to 12mg) used for termination of re-entrant supraventricular tachycardias. However, patients taking methylxanthines may need an increase in adenosine dose to achieve an acceptable response.[195-197]

4. Pharmacodynamic Interactions of Antiarrhythmic Agents

In addition to the pharmacokinetic interactions discussed in section 3, many reports describe the use of antiarrhythmic drug combinations for the treatment of either ventricular or supraventricular arrhythmias.[11] In general, drugs from different antiarrhythmic classes or subclasses are used in combination. By combining antiarrhythmic drugs with different but complementary or additive electrophysiological/pharmacodynamic effects, antiarrhythmic efficacy may be improved and toxicity reduced. The latter may especially be evident if lower doses of each of the antiarrhythmic agents can be prescribed, since many adverse effects are dose- or concentration-related.

4.1 Class IA plus Class IB Combinations

Several studies have examined the effectiveness of Class IA plus Class IB antiarrhythmic drug combinations in the treatment of ventricular arrhythmias. The electrophysiological rationale for these combinations is as follows.[11,198,199] Class IA agents bind to the open sodium channel, manifest intermediate onset and offset binding kinetics with the channel, increase refractoriness and markedly prolong the action potential duration. The latter 2 effects are due to the sodium channel blocking effects, which delay recovery of the sodium channel for subsequent depolarisation, as well as to blockade of the repolarising, rapidly activating, outwardly rectifying potassium current. On the other hand, Class IB agents bind to the inactivated sodium channel and exhibit fast onset and offset binding kinetics with the sodium channel, particularly in ischaemic tissue, but have minimal effects on or may shorten the action potential duration, especially in healthy nonischaemic cardiac tissue. The sodium channel blockade by both Class IA and IB antiarrhythmics is use dependent, whereas the potassium channel blocking effect of Class IA drugs is reverse-use dependent. Therefore, by combining a Class IA agent with a Class IB agent, a re-entrant ventricular arrhythmia may be abolished via additive sodium channel blockade, as prolongation of the action potential by the Class IA agent should permit increased sodium channel binding of the Class IB agent, thereby decreasing conduction velocity and increasing refractoriness at faster heart rates (i.e. during the period of the tachycardia). In addition, the combination may limit the Class IA-induced prolongation of refractoriness (i.e. prolongation of the QT or QT_c interval) at slower heart rates (i.e. during sinus rhythm) and, therefore, diminish the risk for proarrhythmia such as torsade de pointes.

The combination of a Class IA agent and mexiletine has been studied extensively, with conflicting results, in patients with ventricular arrhythmias. Studies have shown that the combination of quinidine plus mexiletine, generally in reduced doses of each, when compared with full doses of either drug alone had the following effects:

- reduced frequency of ventricular premature complexes (VPCs)[12,200] or nonsustained ventricular tachycardia[201] as determined by Holter monitoring
- decreased inducibility of sustained ventricular tachycardia, increased ventricular refractory period or increased cycle length of the tachycardia (i.e. slowed the rate of the tachycardia) during programmed electrophysiological testing[202,203]
- limited quinidine-induced increase in QT_c interval[12,201]
- generally resulted in fewer adverse effects necessitating discontinuance of antiarrhythmic therapy.[12,201]

Furthermore, the combination of quinidine plus mexiletine did not further depress ventricular function in patients with mild to moderate left ventricular dysfunction (i.e. mean left ventricular ejection fraction 36 ± 19%) and ventricular tachyarrhythmias.[204] Similar reductions in VPCs, nonsustained ventricular tachycardia and dose-related adverse effects have been reported for the combination of reduced doses of both mexiletine and disopyramide as compared with full doses of either mexiletine or disopyramide alone.[203] However, it has not been convincingly reported that the combination of disopyramide plus mexiletine is superior with respect to noninducibility of ventricular tachycardia when 1 drug is ineffective.

Conversely, other investigators have reported no differences in recurrence rates of ventricular arrhythmia as assessed by Holter monitoring in patients receiving a Class IA agent plus mexiletine versus mexiletine alone.[205,206] Also, the addition of mexiletine to procainamide did not result in enhanced noninducibility of sustained ventricular tachycardia compared with procainamide alone.[207] In an attempt to reconcile the conflicting observations surrounding the use of combined Class IA and IB therapy, Foster and colleagues[208] reported that selected electrophysiological and clinical variables were predictive of a higher probability of noninducibility to the combination of a Class IB (predominantly mexiletine) and a Class IA agent when compared with a Class IA agent alone.[208] These variables included: baseline ejection fraction greater than 40%; inducibility of ventricular fibrillation rather than ventricular tachycardia during the baseline, drug-free electrophysiological study; and marked prolongation of ventricular refractoriness as well as shortening of the QRS interval with combination therapy. Khalighi and coworkers[209] have also reported that the presence of congestive heart failure resulted in a poor response (i.e. 8% noninducibility rate of sustained ventricular tachycardia) to Class IA/Class IB combination therapy.[209]

Therefore, in summary, despite theoretical and actual electrophysiological benefits, combination therapy with a Class IA and Class IB drug would not ordinarily be expected to decrease the frequency of sustained ventricular tachycardia and associated mortality, particularly in the setting of left ventricular dysfunction.[208,209] However, the combination may be useful for decreasing episodes of symptomatic, nonsustained ventricular tachycardia, although there are no long term, randomised studies that prospectively assess the effects of the combination on survival. In addition, β-blockers and Class III agents such as sotalol, amiodarone or, potentially, dofetilide would be likely to be superior choices.[210]

4.2 Class IB plus Class IC Combinations

The electrophysiological reasoning for combining Class IB and IC antiarrhythmics is similar to that for the combination of Class IA and IB agents. Class IC drugs bind to the activated and perhaps inactivated sodium channel with very slow rates of dissociation.[198,211,212] The addition of a Class IB drug may further suppress conduction, particularly at faster heart rates, as would occur during episodes of ventricular tachycardia, but without affecting action potential duration during sinus rhythm.

Clinical studies have examined the combination of mexiletine with either flecainide[211] or propafenone,[212] with similar findings. The combinations were unlikely to render sustained ventricular tachycardia noninducible. Nonetheless, the rate of induced tachycardia was slower and haemodynamically tolerated. When combining the proarrhythmic and noninducibility results from both studies, however, the effects of combination antiarrhythmic therapy were negligible, as approximately the same number of patients had arrhythmia aggravation as had the tachycardia rendered noninducible. Therefore, the combination of Class IB and IC antiarrhythmics appears to offer very little benefit to patients with sustained ventricular tachycardia. Furthermore, results from the Cardiac Arrhythmia Suppression Trial (CAST) would be likely to discourage clinicians from using the combination in patients with symptomatic or asymptomatic nonsustained ventricular tachycardia.[1,210]

4.3 Combinations with Class II Antiarrhythmics

β-Adrenergic stimulation produces the following important electrophysiological effects:

- shortens the ventricular action potential duration and refractory period via increases in the slowly activating component of the delayed rectifier current (I_{Ks}), the chloride current (I_{Cl}) and the sodium-potassium (Na-K) pump current
- augments ventricular conduction by increasing the fast inward sodium current (I_{Na})
- promotes automaticity by increasing both the slow inward calcium current (I_{Ca}) and the pacemaker current (I_f)
- enhances atrioventricular nodal conduction, largely by increasing I_{Ca}.[213]

Consequently, increases in circulating catecholamines seen during mild to moderate physical exercise can reverse the electrophysiological effects of Class IA drugs such as quinidine, pure Class III drugs such as sematilide and digitalis glycosides.[213] In contrast, it appears that β-adrenergic stimulation only partially reverses the Class III effects of amiodarone and to a lesser extent sotalol, probably as a consequence of noncompetitive and competitive β-adrenergic blockade, respectively.[213] Therefore, β-blockers (i.e. Class II antiarrhythmics) may have important effects in modulating the electrophysiological actions of other antiarrhythmics, particularly in the setting of increased sympathetic activity.

4.3.1 Class I and Class II Combination Therapy

Combined therapy with Class I agents and either a nonselective[214] or cardioselective[215] β-blocker resulted in a higher incidence of noninducibility of sustained ventricular tachycardia as compared with Class I antiarrhythmic therapy alone. In addition, Meyerburg and associates have reported that the coadministration of propranolol eliminated the proarrhythmic effects of flecainide and encainide in 4 patients, for whom the Class IC agents had previously been effective in preventing induction of sustained ventricular tachycardia.[216] Perhaps the most convincing evidence for combining β-blockers with Class I antiarrhythmics in the treatment of potentially or actually life-threatening ventricular arrhythmias comes from retrospective subgroup analyses of the CAST[217] and the Electrophysiologic Study Versus Electrocardiographic Monitoring (ESVEM) trials,[218] respectively. In CAST there was a significant reduction in sudden death for patients treated with Class IC drugs plus β-blockers when compared with patients who received Class IC agents alone.[217] In ESVEM, although the rate of arrhythmia recurrence was lower in patients given sotalol than in those receiving Class I agents with or without a β-blocker, mortality was similar in the sotalol group and the Class I subgroup receiving concomitant β-blockers. Mortality, however, was greater in the Class I subgroup that was not taking concomitant β-blockers.

4.3.2 Class II and Class III Combination Therapy

Although amiodarone has noncompetitive β-blocking effects, β-adrenergic stimulation can partially reverse the effects of amiodarone, which prolongs the ventricular action potential duration and effective refractory period, ventricular tachycardia cycle length and QRS interval.[213] With respect to clinical trials, pooled post-hoc analysis of 2 studies of the use of amiodarone after acute myocardial infarction – the European Myocardial Infarct Amiodarone Trial (EMIAT) and the Canadian Amiodarone Infarction Arrhythmia Trial (CAMIAT) – revealed that the combination of amiodarone and β-blockade significantly lowered the incidence of cardiac and arrhythmic death and resuscitated cardiac arrest after acute myocardial infarction as compared with amiodarone alone.[219]

4.3.3 Class II and Digoxin Combination Therapy

For decreasing ventricular rate in the treatment of atrial fibrillation, digoxin has the longest accumulated experience.[13] The mechanism of action of digoxin on the AV node is indirect via parasympathetic augmentation. By way of the muscarinic type 2 (M_2) receptor, a major effect of parasympathetic stimulation is to antagonise adrenergic effects by inhibiting adenylate cyclase, thereby decreasing I_{Ca}, I_f and I_K.[20] The effects on I_{Ca} and I_K are largely responsible for depressing AV nodal conduction. However, the major limitation in the use of digoxin

for controlling the ventricular rate in atrial fibrillation is its poor control of exercise rates, during which parasympathetic tone is decreased and sympathetic tone is increased.[13] Therefore, combination of digoxin with a β-blocker should result in additive effects on slowing AV nodal conduction, particularly during periods of increased sympathetic tone such as exercise. In fact, studies have reported a substantial decrease in ventricular rates both at rest and during exertion when using β-blockers in combination with digoxin in patients with atrial fibrillation.[13] However, in selected patients, such as the elderly, it may be preferable to use β-blockers with intrinsic sympathomimetic (partial agonist) activity to reduce the risk of nocturnal bradycardia and pauses.[220,221]

4.4 Combinations with Class III Antiarrhythmics

Compared with Class I drugs, the use of Class III agents in the prevention of ventricular tachyarrhythmias and atrial fibrillation has been increasing. For the prevention of ventricular tachycardia, Class I antiarrhythmics have been relatively ineffective and have an increased risk for proarrhythmia and mortality, particularly in patients with concurrent heart failure.[222] With respect to preventing recurrences of atrial fibrillation, the comparative efficacy of Class I and Class III agents has appeared similar, particularly in patients without structural heart disease.[223] However, the increased risk for proarrhythmia in patients with structural heart disease associated with the use of Class I agents has resulted in the rationale for using Class III antiarrhythmics as first-line agents in various patient subgroups.[223] Nevertheless, Class III antiarrhythmics have been ineffective in many patients and each of the existing oral agents, amiodarone and sotalol, has adverse effects.[222,223] Therefore, investigators have assessed the antiarrhythmic effects of these 2 Class III drugs in combination with other agents.

4.4.1 Combinations with Amiodarone

In addition to the combination of amiodarone plus β-blockers discussed in section 4.3.2, amiodarone has been combined with various Class I agents to prevent the induction of sustained ventricular tachycardia.[224,225] This combination was based on the theory that the action potential-prolonging effects of amiodarone, due largely to blockade of I_K, would be expected to allow for greater binding of the sodium channel blocking agent. As a result, conduction should be slowed and refractoriness increased.[226] Toivonen and colleagues reported that the combination of amiodarone plus either quinidine, mexiletine or encainide did not prevent induction of sustained ventricular tachycardia.[224] However, the combinations slowed the ventricular tachycardia rate in about one-third of the patients, thereby rendering them more haemodynamically stable. The combinations of amiodarone with the Class IA and IC drugs were most efficacious in this regard. In addition, ventricular refractoriness was enhanced by combination therapy, but no episodes of proarrhythmia occurred. Jung and co-workers reported similar findings with respect to the failure of combination therapy to suppress inducibility of the arrhythmia as well as slowing of the tachycardia with the amiodarone/Class IC combinations.[225] However, there were increased proarrhythmic events with the amiodarone/encainide combination. Despite the potentially beneficial antiarrhythmic and electrophysiological effects of amiodarone/Class I combination therapy, its effects on mortality have not been assessed.[226]

Amiodarone plus flecainide has also been used in combination for refractory tachyarrhythmias in infants.[227] Successful control of tachyarrhythmia was achieved in 7 of 9 (78%) of the patients and 100% of the 6 patients with supraventricular arrhythmias. No episodes of proarrhythmia were reported. Thus, in selected patients, this combination may delay or obviate the need for corrective, radiofrequency ablative or surgical interventions.

4.4.2 Combinations with Sotalol

Low doses of sotalol have been used in combination with the Class IA agents quinidine and procainamide in the management of sustained ventricular tachycardia.[228,229] For 46 patients with inducible sustained ventricular tachycardia, there was a com-

bined 83% response rate with combination therapy: in 46% of patients the tachycardia was rendered noninducible and 37% had their arrhythmia favourably modified.[228] Recurrence rates of arrhythmia tended to be much less in the responders than in patients in whom the combination failed to prevent inducibility or modification of the arrhythmia. In addition, there were no instances of torsade de pointes or other proarrhythmia in the group receiving combination therapy. The major beneficial electrophysiological effect of combination therapy with sotalol and either quinidine or procainamide appeared to result from a significant increase in ventricular refractoriness that was not reversed at faster heart rates (i.e. abolishment of reverse-use dependence) in conjunction with a minimal increase in ventricular conduction.[229]

4.5 Combinations with Class IV Antiarrhythmics

The Class IV antiarrhythmic agents, verapamil and diltiazem, work principally to reduce the inward calcium current (I_{Ca}) that produces depolarisation and propagation in sinoatrial and AV nodes. This current also contributes to the plateau phase of the action potential in atrial, ventricular and His-Purkinje cells.[20] As previously noted, β-adrenergic stimulation can augment I_{Ca}.[20]

As a consequence of their pharmacological effects, Class IV antiarrhythmics have been most useful for terminating AV nodal re-entrant tachycardias and for decreasing AV nodal conduction to slow the ventricular response in atrial fibrillation.[222] For the latter, both diltiazem and verapamil have been used in combination with digoxin to further enhance the reduction in ventricular rate.[13]

In addition, low, fixed dosages of verapamil (240 mg/day) and quinidine (480 mg/day) in combination have been used to restore sinus rhythm and prevent recurrences of atrial fibrillation.[230] This combination was as effective as amiodarone in restoring sinus rhythm (55 and 60% of patients, respectively). Thereafter, the combination maintained sinus rhythm in 60% of the initial responders for 2 years without adverse effects.[230] As serum quinidine concentrations were not measured, a combined, beneficial pharmacodynamic-pharmacokinetic interaction cannot be excluded. Larger, long term trials may be needed, however, to further clarify the role of this combination in the management of paroxysmal or chronic atrial fibrillation. Nevertheless, this combination could serve as a choice for arrhythmia suppression, particularly in the setting of reasonably preserved left ventricular function.

4.6 Overview of Antiarrhythmic Combinations

The management of ventricular tachyarrhythmias or atrial fibrillation with combinations of antiarrhythmic drugs from different classes or subclasses can be beneficial in selected patients. With respect to prevention of life-threatening ventricular tachyarrhythmias, various combinations with the Class II, β-blocking, drugs appear to offer the highest therapeutic to toxic risk ratio in comparison with other combinations.[231] For atrial fibrillation, there are insufficient long term outcome data to recommend combination therapy routinely for ventricular rate control. However, β-blockers or Class IV antiarrhythmics as single agents for ventricular rate control appear to have advantages over digoxin alone in most patients.[13]

4.7 Combinations with Noncardiac Drugs

No discussion regarding combined pharmacodynamic effects would be complete without a brief discussion of the potential additive effects of noncardiac drugs that have electrophysiological effects.[232,233] Included in table VII are medications that have been reported to have the ability to prolong repolarisation (Class III antiarrhythmic effect) and induce torsade de pointes independently in patients. Some medications, such as erythromycin or haloperidol, may produce QT prolongation at normal plasma concentrations. Others, such as astemizole or cisapride, exhibit their electrophysiological effects only at elevated plasma concentrations. There is little literature regarding the magnitude of increased risk, but using any of these medications in patients who are concomitantly taking either Class

Table VII. Noncardiac drugs that prolong repolarisation (QT interval)[232,233]

Class	Drugs
Antihistamines	Terfenadine, astemizole
Antimicrobials	Erythromycin, cotrimoxazole (trimethoprim-sulfamethoxazole), clarithromycin, azithromycin, ketoconazole, pentamidine, chloroquine, quinine
Gastrointestinal	Cisapride
Lipid lowering	Probucol
Psychotropic agents	Tricyclic antidepressants, haloperidol, phenothiazines, risperidone

Ia or Class III antiarrhythmics is likely to increase the risk of drug-induced arrhythmia due to the combined pharmacodynamic effects. If such combinations are deemed to be necessary in a given patient, clinicians should be aware of the increased potential for these adverse events and monitor the patient accordingly.

5. Conclusions

Despite an increased risk of mortality in some studies with antiarrhythmic drugs,[1] these agents continue to be used in a number of clinical settings.[2-9] Therefore, knowledge of both pharmacokinetic and pharmacodynamic interactions involving antiarrhythmic drugs is essential to optimising the pharmacological care of patients taking these medications.

References

1. Echt DS, Liebson PR, Mitchell LB, et al. Mortality and morbidity in patients receiving encainide, flecainide or placebo – the Cardiac Arrhythmia Suppression Trial. N Engl J Med 1991; 324: 781-8
2. Kuck K-H, Schlüter M. Junctional tachycardia and the role of catheter ablation. Lancet 1993; 341: 1386-91
3. Moss AJ, Hall WJ, Cannom DS, et al. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. N Engl J Med 1996; 335: 1933-40
4. The Antiarrhythmics versus Implantable Defibrillators (AVID) Investigators. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. N Engl J Med 1997; 337: 1576-83
5. Prystowsky EN, Benson W, Fuster V, et al. Management of patients with atrial fibrillation. A statement for healthcare professionals from the subcommittee on electrocardiography and electrophysiology, American Heart Association. Circulation 1996; 93: 1262-77
6. Ommen SR, Odell JA, Stanton MS. Atrial arrhythmias after cardiothoracic surgery. N Engl J Med 1997; 336: 1429-34
7. Daoud EG, Strickberger SA, Man KC, et al. Preoperative amiodarone as prophylaxis against atrial fibrillation after heart surgery. N Engl J Med 1997; 337: 1785-91
8. Sherrid MV, Pearle G, Gunsburg DZ. Mechanism of benefit of negative inotropes in obstructive hypertrophic cardiomyopathy. Circulation 1998; 97: 41-7
9. Singh BN. Amiodarone: the expanding antiarrhythmic role and how to follow a patient on chronic therapy. Clin Cardiol 1997; 20: 608-18
10. Benet LZ, Kroetz DL, Sheiner L. Pharmacokinetics: the dynamics of drug absorption, distribution, and elimination. In: Hardman JG, Limbird LE, editors. Goodman & Gillman's the pharmacologic basis of therapeutics. New York (NY): McGraw-Hill, 1996: 3-28
11. Lévy S. Combination therapy for cardiac arrhythmias. Am J Cardiol 1988; 61: 95A-101A
12. Duff HJ, Roden D, Primm RK, et al. Mexiletine in the treatment of resistant ventricular arrhythmias: enhancement of efficacy and reduction of dose-related side effects by combination with quinidine. Circulation 1983; 67: 1124-8
13. Blitzer M, Costeas C, Kassotis J, et al. Rhythm management in atrial fibrillation – with a primary emphasis on pharmacological therapy: Part 1. PACE 1998; 21: 590-602
14. Rendic S, Di Carlo FJ. Human cytochrome P450 enzymes: a status report summarizing their reactions, substrates, inducers, and inhibitors. Drug Metab Rev 1997; 29 (1 & 2): 413-580
15. Michalets EL. Update: clinically significant cytochrome P-450 drug interactions. Pharmacotherapy 1998; 18 (1): 84-112
16. Slaughter RL, Edwards DJ. Recent advances: the cytochrome P450 enzymes. Ann Pharmacother 1995; 29: 619-24
17. Lennard MS. Genetically determined adverse drug reactions involving metabolism. Drug Saf 1993; 9 (1): 60-77
18. Funck-Brentano C. Genetically determined drug interactions of antiarrhythmic drugs. Cardiology 1992; 6 Suppl. 2: 11-4
19. Vaughn Williams EM. A classification of antiarrhythmic actions reassessed after a decade of new drugs. J Clin Pharmacol 1984; 24: 129-47
20. Task Force of the Working Group of Arrhythmias of European Society of Cardiology. The Sicilian gambit: a new approach to classification of antiarrhythmic drugs based on their actions on arrhythmogenic mechanisms. Circulation 1991; 84: 1831-51
21. Blaufarb I, Pfeifer TM, Frishman WH. β-Blockers. Drug interactions of clinical significance. Drug Saf 1995; 13 (6): 359-70
22. Rosenthal T, Ezra D. Calcium antagonists. Drug interactions of clinical significance. Drug Saf 1995; 13 (3): 157-87
23. Magnani B, Malini PL. Cardiac glycosides. Drug Interactions of clinical significance. Drug Saf 1995; 12 (2): 97-109
24. Marcus FI. Drug interactions with amiodarone. Am Heart J 1983; 106: 9924-30
25. Tartini R, Kappenberger L, Steinbrunn W, et al. Dangerous interaction between amiodarone and quinidine. Lancet 1982; I (8285): 1327-9
26. Saal AK, Werner JA, Greene HL, et al. Effect of amiodarone on serum quinidine and procainamide levels. Am J Cardiol 1984; 53 (9): 1264-7
27. Baker BJ, Gammill J, Massengill J, et al. Concurrent use of quinidine and disopyramide: evaluation of serum concentrations and electrocardiographic effects. Am Heart J 1983; 105 (1): 12-5
28. Munafo A, Buclin T, Tuto D, et al. The effect of a low dose of quinidine on the disposition of flecainide in healthy volunteers. Eur J Clin Pharmacol 1992; 43 (4): 441-3

29. Broly F, Vandamme N, Caron J, et al. Single-dose quinidine treatment inhibits mexiletine oxidation in extensive metabolizers of debrisoquine. Life Sci 1991; 48: 123-8
30. Hughes B, Dyer JE, Schwartz AB. Increased procainamide plasma concentrations caused by quinidine: a new drug interaction. Am Heart J 1987; 114: 908-9
31. Klein RC, Huang SK, Marcus FI, et al. Efficacy of propafenone when used in combination with procainamide or quinidine. Am Heart J 1987; 114 (3): 551-8
32. Funck-Brentano C, Kroemer HK, Pavlou H, et al. Genetically-determined interaction between propafenone and low dose quinidine: role of active metabolites in modulating net drug effect. Br J Clin Pharmacol 1989; 27 (4): 435-44
33. Morike KE, Roden DM. Quinidine-enhanced beta-blockade during treatment with propafenone in extensive metabolizer human subjects. Clin Pharmacol Ther 1994; 55 (1): 28-34
34. Cooke CE, Sklar GE, Nappi JM. Possible pharmacokinetic interaction with quinidine: ciprofloxacin or metronidazole? Ann Pharmacother 1996; 30 (4): 364-6
35. Spinler SA, Cheng JW, Kindwall KE, et al. Possible inhibition of hepatic metabolism of quinidine by erythromycin. Clin Pharmacol Ther 1995; 57 (1): 89-94
36. Lin JC, Quasny HA. QT prolongation and development of torsades de pointes with the concomitant administration of oral erythromycin base and quinidine. Pharmacotherapy 1997; 17 (3): 626-30
37. Kaukonen KM, Olkkola KT, Neuvonen PJ. Itraconazole increases plasma concentrations of quinidine. Clin Pharmacol Ther 1997; 62: 10-7
38. McNulty RM, Lazor JA, Sketch M. Transient increase in plasma quinidine concentrations during ketoconazole-quinidine therapy. Clin Pharmacol 1989; 8 (3): 222-5
39. Posicor Product Information. Nutley (NJ): Roche Laboratories, June 1997
40. Farringer JA, Green JA, O'Rourke RA, et al. Nifedipine-induced alterations in serum quinidine concentrations. Am Heart J 1984; 108: 1570-2
41. Van Lith RM, Appleby DH. Quinidine-nifedipine interaction. Drug Intell Clin Pharmacol 1985; 19: 829-31
42. Green JA, Clementi WA, Porter C, et al. Nifedipine-quinidine interaction. Clin Pharmacol 1983; 2: 461-5
43. Munger MA, Jarvis RC, Nair R, et al. Elucidation of the nifedipine-quinidine interaction. Clin Pharmacol Ther 1989; 45: 411-6
44. Oates NS. Influence of quinidine on nifedipine plasma pharmacokinetics. Br J Pharmacol 1988; 25: 675
45. Schellens JH, Ghabrial H, van der wart H-HF, et al. Differential effects of quinidine on the disposition of nifedipine, sparteine, and mephenytoin in humans. Clin Pharmacol Ther 1991; 50: 520-8
46. Bowles SK, Reeves RA, Cardozo L, et al. Evaluation of the pharmacokinetic and pharmacodynamic interaction between quinidine and nifedipine. J Clin Pharmacol 1993; 33: 727-31
47. Bailey DG, Freeman DJ, Melendez LJ, et al. Quinidine interaction with nifedipine and felodipine: pharmacokinetic and pharmacodynamic evaluation. Clin Pharmacol Ther 1993; 53: 354-9
48. Maisel AS, Motulsky HJ, Insel PA. Hypotension after quinidine plus verapamil: possible additive competition at alpha-adrenergic receptors. N Engl J Med 1984; 312: 167-70
49. Lavoie R. The effect of verapamil on quinidine pharmacokinetics in man [abstract]. Drug Intell Clin Pharmacol 1986; 20: 457
50. Trohman RG, Estes DM, Castellanos A, et al. Increased quinidine plasma concentrations during administration of verapramil: a new quinidine-verapramil interaction. Am J Cardiol 1986; 57 (8): 706-7
51. Edwards DJ, Lavorie R, Beckman H, et al. The effect of coadministration of verapramil on the pharmacokinetics and metabolism of quinidine. Clin Pharmacol Ther 1987; 41: 68-73
52. Laganiere S, Davies RF, Carignan G, et al. Pharmacokinetic and pharmacodynamic interactions between diltiazem and quinidine. Clin Pharmacol Ther 1996; 60 (3): 255-64
53. Matera MG, De Santis D, Vacca C, et al. Quinidine-diltiazem: pharmacokinetic interaction in humans. Curr Ther Res 1986; 40: 653-6
54. Data JL, Wilkinson GR, Nies AS. Interaction of quinidine with anticonvulsant drugs. N Engl J Med 1976; 294: 699-702
55. Urbano AM. Phenytoin-quinidine interactions in a patient with recurrent ventricular tachyarrhythmias [letter]. N Engl J Med 1983; 308 (4): 225
56. Twum-Barima Y, Carruthers SG. Quinidine-rifampin interaction. N Engl J Med 1981; 304 (24): 1466-9
57. Bussey HI, Merritt GJ, Hill EG. The influence of rifampin on quinidine and digoxin. Arch Intern Med 1984; 144 (5): 1021-3
58. Schwartz A, Brown JR. Quinidine-rifampin interaction. Am Heart J 1984; 107 (4): 789-90
59. Chapron DJ, Mumford D, Pitegoff GI. Apparent quinidine-induced digoxin toxicity after withdrawal of pentobarbital: a case of sequential drug interactions. Arch Intern Med 1979; 139 (3): 363-5
60. Rodgers GC, Blackman MS. Quinidine interaction with anticonvulsants. Drug Intell Clin Pharmacol 1983; 17 (11): 819-20
61. Grogano AW. Anesthesia for atrial fibrillation. Effect of quinidine on muscle relaxation. Lancet 1963; II: 1039-40
62. Kornfeld P, Horowitz SH, Genkins G, et al. Myasthenia gravis unmasked by antiarrhythmic agents. Mt Sinai J Med 1976; 43: 10-4
63. Hardy BG, Schentag JJ. Lack of effect of cimetidine on the metabolism of quinidine: effect on renal clearance. Int J Clin Pharmacol Ther 1988; 26: 388-91
64. Fruncillo RJ, DiGregorio GJ, Soll A. Effect of cimetidine on the pharmacokinetics of quinidine and lidocaine in the rat. J Pharm Sci 1983; 72 (7): 826-8
65. Hardy BG, Zador IT, Golden L, et al. Effect of cimetidine on the pharmacokinetics and pharmacodynamics of quinidine. Am J Cardiol 1983; 52 (1): 172-5
66. Farringer JA, McWay-Hess K, Clementi WA. Cimetidine–quinidine interaction. Clin Pharmacol 1984; 3 (1): 81-3
67. Kolb KW, Garnett WR, Small RE, et al. Effect of cimetidine on quinidine clearance. Ther Drug Monitor 1984; 6 (3): 306-13
68. Sindrup SH, Brosen K, Bjerring P, et al. Codeine increases pain thresholds to copper vapor laser stimuli in extensive but not poor metabolizers of sparteine. Clin Pharmacol Ther 1990; 48 (6): 686-93
69. Sindrup SH, Arendt-Nielsen L, Brosen K, et al. The effect of quinidine on the analgesic effect of codeine. Eur J Clin Pharmacol 1992; 42 (6): 587-91
70. Zhang Y, Britto MR, Valderhaug KL, et al. Dextromethorphan: enhancing its systemic availability by way of low-dose quinidine-mediated inhibition of cytochrome P4502D6. Clin Pharmacol Ther 1992; 51 (6): 647-55
71. Leahey EB, Reiffel JA, Giradina EGV, et al. The effect of quinidine and other oral antiarrhythmic drugs on serum digoxin: a prospective study. Ann Intern Med 1980; 92: 605-8
72. Koren G, MacLeod SM. Characteristics of the digoxin-quinidine and digoxin-verapramil interactions in the rat kidney. Res Commun Chem Pathol Pharmacol 1984; 45 (1): 3-18

73. Bigger JT, Leahey EB. Quinidine and digoxin: an important interaction. Drugs 1982; 24: 229-39
74. Fichtl B, Doering W. The quinidine-digoxin interaction in perspective. Clin Pharmacokinet 1983; 8: 137-54
75. Gessman L, Danilo P, Rosen MR. An electrophysiologic study of the quinidine-digoxin interaction. J Clin Pharmacol 1983; 23: 16-23
76. Su SF, Huang JD. Inhibition of the intestinal digoxin absorption and exsorption of quinidine. Drug Metab Dispos 1996; 24 (2): 142-7
77. Zhou H-H, Anthony LB, Roden DM, et al. Quinidine reduces clearance of (+) propranolol more than (-) propranolol through marked reduction in 4-hydroxylation. Clin Pharmacol Ther 1990; 457: 686-93
78. Leemann T, Dayer P, Meyer UA. Single-dose quinidine treatment inhibits metoprolol oxidation in extensive metabolizers. Eur J Clin Pharmacol 1986; 29 (6): 739-41
79. Kessler KM, Humphries Jr WC, Black M, et al. Quinidine pharmacokinetics in patients with cirrhosis or receiving propranolol. Am Heart J 1978; 96 (5): 627-35
80. Fenster P, Perrier D, Mayersohn M, et al. Kinetic evaluation of the propranolol-quinidine combination. Clin Pharmacol Ther 1980; 27 (4): 450-3
81. Rey AM, Gums JG. Altered absorption of digoxin, sustained-release quinidine, and warfarin with sucralfate. Drug Intell Clin Pharm 1991; 25 (7-8): 745-6
82. Brosen K, Gram LF. Quinidine inhibits the 2-hydroxylation of imipramine and desipramine but not the demethylation of imipramine. Eur J Clin Pharmacol 1989; 37 (2): 155-60
83. Steiner E, Dumont E, Spina E, et al. Inhibition of desipramine 2-hydroxylation by quinidine and quinine. Clin Pharmacol Ther 1998; 43 (5): 577-81
84. Damkier, Hansen LL, Brosen K. Effect of fluvoxamine on the pharmacokinetics of quinidine. Eur J Clin Pharmacol 1999; 55 (6): 451-6
85. Gazzaninga AB, Stewart DR. Possible quinidine induced hemorrhage in a patient with warfarin sodium [letter]. N Engl J Med 1969; 280: 711
86. Sylven C, Anderson P. Evidence that disopyramide does not interact with warfarin [letter]. BMJ 1983 Apr 9; 286: 1181
87. Koch-Weser j. Quinidine-induced hypoprothrombinemic hemorrhage in patients with chronic warfarin therapy. Ann Intern Med 1968; 68: 511-7
88. Gerhardt RE, Knouss RF, Thyrum PT, et al. Quinidine excretion in aciduria and alkaluria. Ann Intern Med 1969; 71 (5): 927-33
89. Romankiewicz JA, Reidenberg M, Drayer D, et al. The noninterference of aluminum hydroxide gel with quinidine sulfate absorption: an approach to control quinidine-induced diarrhea. Am Heart J 1978; 96 (4): 518-20
90. Mauro VF, Mauro LS, Fraker Jr TD, et al. Effect of aluminum hydroxide gel on quinidine gluconate absorption. Drug Intell Clin Pharm 1990; 24 (3): 252-4
91. Windle J, Prystowsky EN, Miles WM, et al. Pharmacokinetic and electrophysiologic interactions of amiodarone and procainamide. Clin Pharmacol Ther 1987; 41 (6): 603-10
92. Saal AK, Werner JA, Greene HL, et al. Effect of amiodarone on serum quinidine and procainamide levels. Am J Cardiol 1984; 53 (9): 1264-7
93. Kosoglou T, Rocci Jr ML, Vlasses PH. Trimethoprim alters the disposition of procainamide N-acetylprocainamide. Clin Pharmacol Ther 1988; 44 (4): 467-77
94. Vlasses PH, Kosoglou T, Chase SL, et al. Trimethoprim inhibition of the renal clearance of procainamide and N-acetylprocainamide. Arch Intern Med 1989; 149 (6): 1350-3
95. Martin DE, Shen J, Griener J, et al. Effects of ofloxacin on the pharmacokinetics and pharmacodynamics of procainamide. J Clin Pharmacol 1996; 36 (1): 85-91
96. Ochs HR, Carstens G, Roberts GM, et al. Metoprolol or propranolol does not alter the kinetics of procainamide. J Cardiovasc Pharmacol 1983; 5 (3): 392-5
97. Christian DC, Meredith CG, Speeg KV. Cimetidine inhibits renal procainamide clearance. Clin Pharmacol Ther 1984; 36: 221-7
98. Bauer LA, Black D, Gensler A. Procainamide-cimetidine drug interaction in elderly male patients. J Am Geriatr Soc 1990; 38 (4): 467-9
99. Rodvold KA, Paloucek FP, Jung D, et al. Interaction of steady-state procainamide with H2-receptor antagonists cimetidine and ranitidine. Ther Drug Monit 1987; 9 (4): 378-83
100. Martin BK. Effect of ranitidine on procainamide disposition. Br J Clin Pharmacol 1985; 19 (6): 858-60
101. Somogyi A, Bochner F. Ranitidine and procainamide absorption. Br J Clin Pharmacol 1985; 20 (2): 182-3
102. Rocci Jr ML, Kosoglou T, Ferguson RK, et al. Ranitidine-induced changes in the renal and hepatic clearances of procainamide are correlated. J Pharmacol Exp Ther 1989; 248 (3): 923-8
103. Teichman SL, Fisher JD, Matos JA, et al. Disopyramide-pyridostigmine: report of a beneficial drug interaction. J Cardiovasc Pharmacol 1985; 7: 108-13
104. Wilcox RG, Hampton JR, Rowley JM. Randomised placebo controlled trial comparing oxprenolol with disopyramide phosphate in immediate treatment of suspected myocardial infarction. Lancet 1980; II: 765-9
105. Cumming AD, Robertson D. Interaction between disopyramide and practolol. BMJ 1979; 2: 1264
106. Bonde J, Bodtker S, Angelo HR, et al. Atenolol inhibits the elimination of disopyramide. Eur J Clin Pharmacol 1985; 28: 41-3
107. Aitio ML, Mansury L, Tula E, et al. The effect of enzyme induction on the metabolism of disopyramide in man. Br J Clin Pharmacol 1981; 11: 279-85
108. Staum JM. Enzyme induction: rifampin-disopyramide interaction. Drug Intell Clin Pharm 1990; 24 (7-8): 701-3
109. Aitio ML, Vuoremma T. Enhanced metabolism and diminished efficacy of disopyramide by enzyme induction. Br J Clin Pharmacol 1980; 9: 149-52
110. Kessler JM, Keys PN, Stafford RW. Disopyramide and phenytoin interaction. Br JClin Pharm 1982; 1: 263-4
111. Kapil RP, Axelson JE, Mansfield IL, et al. Disopyramide pharmacokinetics and metabolism: effects of inducers. Br J Clin Pharmacol 1987; 24: 781-91
112. Ragosta M, Weihl AC, Rosenfeld LE. Potentially fatal interaction between erythromycin and disopyramide. Am J Med 1989; 86 (4): 465-6
113. Iida H, Morita T, Suzuki E, et al. Hypoglycemia induced by interaction between clarithromycin and disopyramide. Jpn Heart J 1999; 40 (1): 91-6
114. Jou MJ, Huang SC, Kiang FM, et al. Comparison of the effects of cimetidine and ranitidine on the pharmacokinetics of disopyramide in man. J Pharm Pharmacol 1997; 49 (11): 1072-5
115. Fruncillo RJ, Kozin SH, Digregorio GJ. Effect of amiodarone on the pharmacokinetics of phenytoin, quinidine, and lidocaine in the rat. Res Commun Chem Pathol Pharmacol 1985; 50 (3): 451-4
116. Siegmund JB, Wilson JH, Imhoff TE. Amiodarone interaction with lidocaine. J Cardiovasc Pharmacol 1993; 21 (4): 513-5

117. Ochs HR, Carstens G, Greenblatt DJ. Reduction in lidocaine clearance during continuous infusion and by coadministration of propranolol. N Engl J Med 1980; 303: 373-7
118. Nies AS, Shand DG, Wilkinson GR. Altered hepatic blood flow and drug disposition. Clin Pharmacokinet 1976; 1 (2): 135-55
119. Bax NDS, Tucker GT, Lennard MS, et al. The impairment of lignocaine clearance by propranolol – major contribution from enzyme inhibition. Br J Clin Pharmacol 1985; 19: 597-603
120. Conrad KA, Byers JM, Finley PR, et al. Lidocaine elimination: effects of metoprolol and of propranolol. Clin Pharmacol Ther 1983; 33 (2): 133-8
121. Bosch J. Medical treatment of portal hypertension. Digestion 1998; 59: 547-55
122. Sekiyama T, Komeichi H, Nagano T, et al. Effects of the α-/β-blocking agent carvedilol on hepatic and systemic hemodynamics in patients with cirrhosis and portal hypertension. ArzneimittelForschung/Drug Res 1997; 47: 353-5
123. Stenson RE, Constantino RT, Harrison DC. Interrelationships of hepatic blood flow, cardiac output, and blood levels of lidocaine in man. Circulation 1971; 43: 205-11
124. Feely J, Wilkinson GR, McAllister CB, et al. Increased toxicity and reduced clearance of lidocaine by cimetidine. Ann Intern Med 1982; 96: 592-4
125. Berk SI, Gal P, Bauman JL, et al. The effect of oral cimetidine on total and unbound serum lidocaine concentration in patients with suspected myocardial infarction. Int J Cardiol 1987; 14: 91-4
126. Powell JR, Foster JR, Patterson JH, et al. Effect of duration of lidocaine infusion and route of cimetidine administration on lidocaine pharmacokinetics. Clin Pharm 1986; 5: 993-8
127. Li AP, Rasmussen A, Xu L, et al. Rifampicin induction of lidocaine metabolism in cultured human hepatocytes. J Pharmacol Exp Ther 1995; 274 (2): 673-7
128. Perucca E, Richens A. Reduction of oral bioavailability of lignocaine by induction of first pass metabolism in epileptic patients. Br J Clin Pharmacol 1979; 8 (1): 21-31
129. Bruckner J, Thomas Jr KC, Bikhazi GB, et al. Neuromuscular drug interactions of clinical importance. Anesth Analg 1980; 59 (9): 678-82
130. Fukuda S, Wakuta K, Ishikawa T, et al. Lidocaine modifies the effect of succinylcholine on muscle oxygen consumption in dogs. Anesth Analg 1987; 66 (4): 325-8
131. Pentikainen PJ, Koivula IH, Hiltunen HA. Effect of rifampicin treatment on the kinetics of mexiletine. Eur J Clin Pharmacol 1982; 23 (3): 261-6
132. Begg EJ, Chinwah PM, Webb C, et al. Enhanced metabolism of mexiletine after phenytoin administration. Br J Clin Pharmacol 1982; 14 (2): 219-23
133. Katz A, Buskila D, Sukenik S. Oral mexiletine-theophylline interaction. Int J Cardiol 1987; 17 (2): 227-8
134. Kessler KM, Interian Jr A, Cox M, et al. Proarrhythmia related to a kinetic and dynamic interaction of mexiletine and theophylline. Am Heart J 1989; 117 (4): 964-6
135. Stanley R, Comer T, Taylor JL, et al. Mexiletine-theophylline interaction. Am J Med 1989; 86 (6 Pt 1): 733-4
136. Ueno K, Miyai K, Seki T, et al. Interaction between theophylline and mexiletine. DICP 1990; 24 (5): 471-2
137. Stoysich AM, Mohiuddin SM, Destache CJ, et al. Influence of mexiletine on the pharmacokinetics of theophylline in healthy volunteers. J Clin Pharmacol 1991; 31 (4): 354-7
138. Loi CM, Wei XX, Vestal RE. Inhibition of theophylline metabolism by mexiletine in young male and female nonsmokers. Clin Pharmacol Ther 1991; 49 (5): 571-80
139. Hurwitz A, Vacek JL, Botteron GW, et al. Mexiletine effects on theophylline disposition. Clin Pharmacol Ther 1991; 50 (3): 299-307
140. Ueno K, Miyai K, Kato M, et al. Mechanism of interaction between theophylline and mexiletine. Drug Intell Clin Pharmacol 1991; 25 (7-8): 727-30
141. Nemeroff CB, DeVane L, Pollock BG. Newer antidepressants and the cytochrome P450 system. Am J Psychol 1996; 153: 311-20
142. Funck-Bretano C, Jacqz-Aigrain E, Leenhardt A, et al. Influence of amiodarone on genetically determined drug metabolism in humans. Clin Pharmacol Ther 1991; 50: 259-66
143. Funck-Bretano C, Becquemont L, Kroemer HK, et al. Variable disposition kinetics and electrocardiographic effects of flecainide during repeat dosing in humans: contribution of genetic factors, dose-dependent clearance, interaction with amiodarone. Clin Pharmacol Ther 1994; 55 (3): 256-69
144. Tjandra-Maga TB, Van Hecken A, Van Melle P, et al. Altered pharmacokinetics of oral flecainide by cimetidine. Br J Clin Pharmacol 1986; 22: 108-10
145. Holtzman JL, Weeks CE, Kvam DC, et al. Identification of drug interactions by meta-analysis of pre-marketing trials; the effect of smoking on the pharmacokinetics and dosage requirements for flecainide acetate. Clin Pharmacol Ther 1989; 46: 1-8
146. Tjandramaga TB, Verbesselt A, Hecken A, et al. Oral digoxin pharmacokinetics during multiple-dose flecainide treatment. Arch Int Pharmacodynamic Ther 1982; 260: 302-3
147. Lewis GP, Holtzman JL. Interaction of flecainide with digoxin and propranolol. Am J Cardiol 1984; 53: 52B-7B
148. Weeks C, Conrad G, Kvam D, et al. The effect of flecainide acetate, a new antiarrhythmic, on plasma digoxin level. J Clin Pharmacol 1986; 26: 27-31
149. Muhiddin KA, Johnston A, Turner P. The influence of urinary pH on flecainide excretion and its serum pharmacokinetics. Br J Clin Pharmacol 1984; 17 (4): 447-51
150. Johnston A, Warrington S, Turner P. Flecainide pharmacokinetics in healthy volunteers: the influence of urinary pH. Br J Clin Pharmacol 1985; 20 (4): 333-8
151. Kowey PR, Kirsten EB, Chau-Hwei JF, et al. Interaction between propranolol and propafenone in healthy volunteers. J Clin Pharmacol 1989; 29 (6): 512-7
152. Spes CH, Angermann CE, Horn K, et al. Ciclosporin-propafenone [letter]. Klin Wochenschr 1990; 68 (17): 872
153. Tjandra-Maga TB, Van Hecken A, Van Melle P, et al. Altered pharmacokinetics of oral flecainide by cimetidine. Br J Clin Pharmacol 1986; 22: 108-10
154. Palumbo E, Svetoni N, Casini M, et al. Digoxin-propafenone interactions: values and limitations of plasma determination of the two drugs. Antiarrhythmic effectiveness of propafenone [in Italian]. G Ital Cardiol 1986; 16: 855-62
155. Nolan PE, Marcus FI, Erstad Bl, et al. Effects of coadministration of propafenone on the pharmacokinetics of digoxin in healthy volunteer subjects. J Clin Pharmacol 1989; 29: 46-52
156. Castel JM, Cappiello E, Leopaldi D, et al. Rifampicin lowers plasma concentrations of propafenone and its antiarrhythmic effect. Br J Clin Pharmacol 1990; 30 (1): 155-6
157. Dilger K, Greiner B, Fromm MF, et al. Consequences of rifampicin treatment on propafenone disposition in extensive and poor metabolizers of CYP2D6. Pharmacogenetics 1999; 9 (5): 551-9
158. Lee BL, Dohrmann ML. Theophylline toxicity after propafenone treatment: evidence for drug interaction. Clin Pharmacol Ther 1992; 51 (3): 353-5

159. Spinler SA, Gammaitoni A, Charland SL, et al. Propafenone-theophylline interaction. Pharmacotherapy 1993; 13 (1): 68-71
160. Kates RE, Yee Y-G, Kirsten EB. Interaction between warfarin and propafenone in healthy volunteer subjects. Clin Pharmacol Ther 1987; 42: 305-11
161. Laer S, Neumann J, Scholz H. Interaction between sotalol and an antacid preparation. Br J Clin Pharmacol 1997; 43 (3): 269-72
162. Lesko LJ. Pharmacokinetic drug interactions with amiodarone. Clin Pharmacokinet 1989; 17 (2): 130-40
163. Marcus FI. Drug Interactions with amiodarone. Am Heart J 1983; 106: 9924-30
164. Lee TH, Friedman PL, Goldman L, et al. Sinus arrest and hypotension with combined amiodarone-diltiazem therapy. Am Heart J 1986; 109: 163-4
165. Mamprin F, Mullins P, Graham T, et al. Amiodarone-cyclosporine interaction in cardiac transplantation. Am Heart J 1992; 123 (6): 1725-6
166. Nicolau DP, Uber WE, Crumbley AJ 3rd, et al. Amiodarone-cyclosporine interaction in a heart transplant patient. J Heart Lung Transplant 1991; 11(3 Pt 1): 564-8
167. Chitwood KK, Abdul-Haqq AJ, Heim-Duthoy KL. Cyclosporine-amiodarone interaction. Ann Pharmacother 1993; 27 (5): 569-71
168. Moysey JO, Jaggarao NS, Grundy EN, et al. Amiodarone increases plasma digoxin concentrations. BMJ 1981; 282: 272
169. Furlanello E, Inama G, Ferrari M, et al. Digoxin-amiodarone: a further example of digoxin-antiarrhythmic agents interaction [in Italian]. G Ital Cardiol 1981; 11: 1725-8
170. Oetgen WJ, Sobol SM, Tri TB, et al. Amiodarone-digoxin interaction, clinical and experimental observations. Chest 1984; 86: 75-9
171. Nedemanee K, Kannan R, Hendrickson J, et al. Amiodarone-digoxin interaction: clinical significance, time course of development, potential pharmacokinetic mechanisms and therapeutic implications. J Am Coll Cardiol 11984; 4: 111-6
172. Fenster PE, White NW, Hanson CD. Pharmacokinetic evaluation of the digoxin-amiodarone interaction. J Am Coll Cardiol 1985; 5: 108-12
173. Krusteva E. Changes in the plasma levels and basic pharmacokinetic parameters of digoxin used in combination with gentamicin, amiodarone and spironolactone. Fol Med 1992; 34 (20): 24-8
174. Liberman BA, Teasdale SJ. Anaesthesia and amiodarone. Can Anaesth Soc J 1985; 32 (6): 629-38
175. Navalgund AA, Alifimoff JK, Jakymec AJ, et al. Amiodarone-induced sinus arrest successfully treated with ephedrine and isoproterenol. Anesth Analg 1986; 65 (4): 414-6
176. Koblin DD, Romanoff ME, Martin DE, et al. Anesthetic management of the patient receiving amiodarone. Anesthesiology 1987; 66 (4): 551-3
177. Nolan PE, Marcus FI, Hoyer GL, et al. Pharmacokinetics interaction between intravenous phenytoin and amiodarone in healthy volunteers. Clin Pharmacol Ther 1989; 46: 43-50
178. Nolan PE, Erstad BL, Hoyer GL, et al. Steady-state interaction between amiodarone and phenytoin in normal subjects. Am J Cardiol 1990; 65: 1252-7
179. Doecke CJ, Veronese ME, Pond SM, et al. Relationship between phenytoin and tolbutamide hydroxylations in human liver microsomes. Br J Clin Pharmacol 1991; 31: 125-30
180. Nolan Jr PE, Marcus FI, Karol MD, et al. Effect of phenytoin on the clinical pharmacokinetics of amiodarone. J Clin Pharmacol 1990; 30 (12): 1112-9
181. Soto J, Sacristan JA, Arellano F, et al. Possible theophylline-amiodarone interaction [abstract]. Drug Intell Clin Pharm 1990; 24 (11): 1115
182. Heimark LD, Wienkers L, Kunze KJ, et al. The mechanism of the interaction between amiodarone and warfarin in humans. Clin Pharmacol Ther 1992; 51: 398-407
183. O'Reilly RA, Trager WF, Rettie AE, et al. Interaction of amiodarone with racemic warfarin and its separated enantiomorphs in humans. Clin Pharmacol Ther 1987; 42: 290-4
184. Almog S, Shafran N, Halkin H, et al. Mechanism of warfarin potentiation by amiodarone: dose- and concentration-dependent inhibition of warfarin elimination. Eur J Clin Pharmacol 1985; 28: 257-61
185. Martinowitz U, Rabinowici J, Goldfarb D, et al. Interaction between warfarin sodium and amiodarone. N Engl J Med 1981; 304 (11): 671-2
186. Kerin NZ, Blevins RD, Goldman L, et al. The incidence, magnitude, and time course of the amiodarone-warfarin interaction. Arch Intern Med 1988; 148: 1779-81
187. Cropp JS, Antal EG, Talbert RL. Ibutilide: a new class III antiarrhythmic agent. Pharmacotherapy 1997; 17 (1): 1-9
188. Lenz TL, Hilleman DE. Dofetilide, a new class III antiarrhythmic agent. Pharmacotherapy 2000; 20 (7): 776-86
189. Porter RS. Adenosine: supplementary considerations about activity and use. Clin Pharm 1990; 9: 163-4
190. Lai WT, Lee CS, Wu JC, et al. Effects of verapramil, propranolol, and procainamide on adenosine-induced negative dromotropism. Am Heart J 1996; 132 (4): 76-5
191. Biaggioni I, Onrot J, Hollister AS, et al. Cardiovascular effects of adenosine infusion in man and their modulation by dipyridamole. Life Sci 1986; 39 (23): 2229-36
192. Watt AH, Bernard MS, Webster J, et al. Intravenous adenosine in the treatment of supraventricular tachycardia: a dose-ranging study and interaction with dipyridamole. Br J Clin Pharmacol 1986; 21 (2): 227-30
193. Conradson TB, Dixon CM, Clarke B, et al. Cardiovascular effects of infused adenosine in man: potentiation by dipyridamole. Acta Physiol Scand 1987; 129 (3): 387-91
194. German DC, Kredich NM, Bjornsson TD. Oral dipyridamole increases plasma adenosine levels in human beings. Clin Pharmacol Ther 1989: 45 (1): 80-4
195. Maxwell DL, Fuller RW, Conradson TB, et al. Contrasting effects of two xanthines, theophylline and enprofylline, on the cardio-respiratory stimulation of infused adenosine in man. Acta Physiol Scand 1987: 131 (3): 459-65
196. Smits P, Lenders JW, Thien T. Caffeine and theophylline attenuate adenosine-induced vasodilation in humans. Clin Pharmacol Ther 1990; 48 (4): 410-8
197. Biaggioni I, Paul S, Puckett A, et al. Caffeine and theophylline as adenosine receptor antagonists in humans. J Pharmacol Exp Ther 1991; 258 (2): 588-93
198. Campbell TJ. Subclassification of Class I antiarrhythmic drugs: enhanced relevance after CAST. Cardiovasc Drugs Ther 1992; 6: 519-28
199. Grace AA, Camm AJ. Quinidine. N Engl J Med 1998; 338: 35-45
200. Kim SG, Felder SD, Waspe LE, et al. Electrophysiologic effects and clinical efficacy of mexiletine used alone or in combination with Class IA agents for refractory recurrent ventricular tachycardias or ventricular fibrillation. Am J Cardiol 1986; 485-90
201. Giardina E-GV, Wechsler ME. Low dose quinidine-mexiletine combination therapy versus quinidine monotherapy for treat-

ment of ventricular arrhythmias. J Am Coll Cardiol 1990; 15: 1138-45
202. Greenspan AM, Speilman SR, Webb CR, et al. Efficacy of combination therapy with mexiletine and a type IA agent for inducible ventricular tachyarrhythmias secondary to coronary artery disease. Am J Cardiol 1985; 56: 277-84
203. Bonavita GJ, Pires LA, Wagshal AB, et al. Usefulness of oral quinidine-mexiletine combination therapy for sustained ventricular tachyarrhythmias as assessed by programmed electrical stimulation when quinidine monotherapy has failed. Am Heart J 1994; 127: 847-51
204. Sheldon RS, Duff HJ, Mitchell LB, et al. Effect of oral combination therapy with mexiletine and quinidine on left and right ventricular function. Am Heart J 1988; 115: 1030-6
205. Kim SG, Mercndo AD, Tam S, et al. Combination of disopyramide and mexiletine for better tolerance and additive effects for treatment of ventricular arrhythmias. J Am Coll Cardiol 1989; 13: 659-64
206. Poole JE, Werner JA, Bardy GH, et al. Intolerance and ineffectiveness of mexiletine in patients with serious ventricular arrhythmias. Am Heart J 1986; 112: 322-6
207. Widerhorn J, Sager PT, Rahimtoola SH, et al. The role of combination therapy with mexiletine and procainamide in patients with inducible sustained ventricular tachycardia refractory to intravenous procainamide. PACE 1991; 14: 420-6
208. Foster MT, Peters RW, Froman D, et al. Electrophysiologic effects and predictors of success of combination therapy with class Ia and Ib antiarrhythmic drugs for sustained ventricular arrhythmias. Am J Cardiol 1996; 78: 47-50
209. Khalighi K, Peters RW, Feliciano Z, et al. Comparison of class Ia/Ib versus Class III antiarrhythmic drugs for the suppression of inducible sustained ventricular tachycardia associated with coronary artery disease. Am J Cardiol 1997; 80: 591-4
210. Reiffel JA, Reiter MJ, Blitzer M. Antiarrhythmic drugs and devices for the management of ventricular tachyarrhythmia in ischemic heart disease. Am J Cardiol 1998; 82: 31I-40I
211. Mendes L, Podrid PJ, Fuchs T, et al. Role of combination drug therapy with a Class IC antiarrhythmic agent and mexiletine for ventricular tachycardia. J Am Coll Cardiol 1991; 17: 1396-402
212. Yeung-Lai-Wah JA, Murdock CJ, Boone J, et al. Propafenone-mexiletine combination for the treatment of sustained ventricular tachycardia. J Am Coll Cardiol 1992; 20: 547-51
213. Sager PT. Modulation of antiarrhythmic drug effects by beta-adrenergic sympathetic stimulation. Am J Cardiol 1998; 82: 20I-30I
214. Friehling TD, Lipshutz H, Marinchak RA, et al. Effectiveness of propranolol added to a Type I antiarrhythmic agent for sustained ventricular tachycardia secondary to coronary artery disease. Am J Cardiol 1990; 65: 1328-33
215. Brodsky MA, Chough SP, Allen BJ, et al. Adjuvant metoprolol improves efficacy of class I antiarrhythmic drugs in patients with inducible sustained monomorphic ventricular tachycardia. Am Heart J 1992; 124: 629-35
216. Myerburg RJ, Kessler KM, Cox MM, et al. Reversal of proarrhythmic effects of flecainide acetate and encainide hydrochloride by propranolol. Circulation 1989; 80: 1571-9
217. Kennedy HL, Brooks MM, Barker AH, et al. Beta-blocker therapy in the Cardiac Arrhythmia Suppression Trial. Am J Cardiol 1994; 74: 674-80
218. Reiffel JA, Hahn E, Hartz V, et al. Sotalol for ventricular tachyarrhythmias: beta-blocking and class III contributions, and relative efficacy versus class I drugs after prior drug failure. Am J Cardiol 1997; 79: 1048-53
219. Boissel J-P, Boutitie F, Bernard C, et al. Synergy between amiodarone and β-blockers after myocardial infarction [abstract]. Circulation 1998; Suppl. 98: 470
220. Channer KS, MacConell JT, Rees JR. β-Adrenoceptor blockers in atrial fibrillation: the importance of partial agonist activity. Br J Clin Pharmacol 1994; 37: 53-7
221. Lawson-Matthew P, McLean KA, Dent M, et al. Xamoterol improves the control of chronic atrial fibrillation in elderly patients. Age Ageing 1995; 24: 321-5
222. Van Gelder IC, Brügemann J, Crijns HJGM. Current treatment recommendations in antiarrhythmic therapy. Drugs 1998; 55: 331-46
223. Reiffel JA. Selecting an antiarrhythmic agent for atrial fibrillation should be a patient-specific, data-driven decision. Am J Cardiol 1998; 82: 72N-81N
224. Toivonen L, Kadish A, Morady F. A prospective comparison of Class IA, B, and C antiarrhythmic agents in combination with amiodarone in patients with inducible, sustained ventricular tachycardia. Circulation 1991; 84: 101-8
225. Jung W, Mletzko R, Manz M, et al. Efficacy and safety of combination therapy with amiodarone and Type I agents for treatment of inducible ventricular tachycardia. PACE 1993; 16: 778-88
226. Nademanee K. The amiodarone-class I agent combination increases refractoriness, conduction, and the number of electrophysiologic studies. But does it increase survival rate? Circulation 1991; 84: 429-31
227. Fenrich AL, Perry JC, Friedman RA. Flecainide and amiodarone: combined therapy for refractory tachyarrhythmias in infancy. J Am Coll Cardiol 1995; 25: 1195-8
228. Dorian P, Newman D, Berman N, et al. Sotalol and type IA drugs in combination prevent recurrences of sustained ventricular tachycardia. J Am Coll Cardiol 1993; 22: 106-13
229. Lee SD, Newman D, Ham M, et al. Electrophysiologic mechanisms of antiarrhythmic efficacy of a sotalol and class Ia drug combination: elimination of reverse use dependence. J Am Coll Cardiol 1997; 29: 100-5
230. Zehender M, Hohnloser S, Müller B, et al. Effects of amiodarone versus quinidine and verapamil in patients with chronic atrial fibrillation: results of a comparative study and a 2-year follow-up. J Am Coll Cardiol 1992; 19: 1054-9
231. Reiter MJ, Feiffel JA. Importance of beta blockade in the therapy of serious ventricular arrhythmias. Am J Cardiol 1998; 82: 9I-19I
232. Zipes DP, Wellens HJ. Sudden cardiac death. Circulation 1998; 98: 2334-51
233. De Ponti F, Poluzzi E, Montanaro N. QT-interval prolongation by non-cardiac drugs: lessons to be learned from recent experience. Eur J Clin Pharmacol 2000; 56: 1-18

Correspondence and offprints: Dr *Toby C. Trujillo*, Department of Pharmacy Practice, Massachusetts College of Pharmacy and Health Sciences, 179 Longwood Avenue, Boston, MA 02115, USA.
E-mail: Ttrujillo@mcp.edu