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Potentially Significant Drug Interactions of Class III Antiarrhythmic Drugs

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Abstract

Class III antiarrhythmic drugs, especially amiodarone (a broad-spectrum antiarrhythmic agent), have gained popularity for use in clinical practice in recent years. Other class III antiarrhythmic drugs include bretylium, dofetilide, ibutilide and sotalol. These agents are effective for the management of various types of cardiac arrhythmias both atrial and ventricular in origin.

Class III antiarrhythmic drugs may interact with other drugs by two major processes: pharmacodynamic and pharmacokinetic interactions. The pharmacodynamic interaction occurs when the pharmacological effects of the object drug are stimulated or inhibited by the precipitant drug. Pharmacokinetic interactions can result from the interference of drug absorption, metabolism and/or elimination of the object drug by the precipitant drug.

Among the class III antiarrhythmic drugs, amiodarone has been reported to be involved in a significant number of drug interactions. It is mainly metabolised by cytochrome P450 (CYP)3A4 and it is a potent inhibitor of CYP1A2, 2C9, 2D6 and 3A4. In addition, amiodarone may interact with other drugs (such as digoxin) via the inhibition of the P-glycoprotein membrane transporter system, a recently described pharmacokinetic mechanism of drug interactions.

Bretylium is not metabolised; it is excreted unchanged in the urine. Therefore the interactions between bretylium and other drugs (including other antiarrhythmic drugs) is primarily through the pharmacodynamic mechanism.

Dofetilide is metabolised by CYP3A4 and excreted by the renal cation transport system. Drugs that inhibit CYP3A4 (such as erythromycin) and/or the renal transport system (such as triamterene) may interact with dofetilide.

It appears that the potential for pharmacokinetic interactions between ibutilide and other drugs is low. This is because ibutilide is not metabolised by CYP3A4 or CYP2D6. However, ibutilide may significantly interact with other drugs by a pharmacodynamic mechanism.

Sotalol is primarily excreted unchanged in the urine. The potential for drug interactions due to hepatic enzyme induction or inhibition appears to be less

likely. However, a number of drugs (such as digoxin) have been reported to interact with sotalol pharmacodynamically.

If concurrent use of a class III antiarrhythmic agent and another drug cannot be avoided or no published studies for that particular drug interaction are available, caution should be exercised and close monitoring of the patient should be performed in order to avoid or minimise the risks associated with a possible adverse drug interaction.

Clinically significant drug interactions involving class III antiarrhythmic drugs can result in important problems in clinical practice. According to the Vaughan Williams classification system, antiarrhythmic drugs are categorised into four classes based on their similar electrophysiological properties.[1] Some of the class III agents include amiodarone, bretylium, dofetilide, ibutilide and sotalol. Based on clinical evidence, class III antiarrhythmic drugs have recently gained popularity for use in the management of various cardiac arrhythmias; this applies particularly to amiodarone, which is considered to be a broad-spectrum antiarrhythmic agent. Numerous drugs have been reported to significantly interact with these antiarrhythmic agents.

Knowledge about the nature and mechanisms of drug interactions would allow early recognition, monitoring and possible prevention of adverse outcomes. This knowledge would also help to avoid healthcare costs associated with managing patients who develop drug toxicity or have inadequate therapeutic responses resulting from drug interactions. The purpose of this review is to enhance and update the knowledge of clinicians about the potential drug interactions of class III antiarrhythmic agents, so that the interactions can be recognised early and thus, adverse outcomes due to these interactions can be prevented or properly managed. Drug interactions of the other three antiarrhythmic drug classes appear to have been relatively well documented (readers are referred to several publications[2-4]). Most of the evidence presented in this review, regarding drug interactions of class III antiarrhythmic agents, is from case reports in humans.

1. Mechanisms of Drug Interactions

Some interactions can be serious or even fatal, as in the case of amiodarone and warfarin, where serious bleeding complications may occur.[5,6] Other drug interactions may be insignificant or theoretical, such as the interaction between captopril and probenecid, where the renal clearance of captopril may be reduced, resulting in increased serum captopril concentrations.[7,8] However, no significant changes in blood pressure and other clinical findings have been noted in patients with concurrent administration of captopril and probenecid.[7] Drugs can interact with each other in numerous ways; however, to simplify the discussion, drug interaction processes can be classified into two general categories: pharmacodynamic and pharmacokinetic interactions.[9]

Pharmacodynamic interactions occur when the pharmacological effects of an object drug are altered or influenced by the action of a precipitant drug.[10] This type of drug interaction does not involve any changes in pharmacokinetic properties of the object drug. For example, the interaction between warfarin and vitamin K can be categorised as a pharmacodynamic interaction.[11] The decreased hypoprothrombinaemic effect of warfarin is due to the increase in vitamin K availability for the conversion of vitamin K-dependent clotting factors from inactive to active forms.[11]

A pharmacokinetic interaction is characterised by interference with drug kinetic parameters such as absorption, metabolism, distribution and excretion. The interaction between erythromycin and theophylline has been described as a pharmacokinetic interaction because erythromycin can inhibit hepatic metabolism of theophylline, thereby increasing serum theophylline concentrations.[12] Recently, a type of pharmacokinetic interaction through induction or inhibition of the P-glycoprotein system has been described.[13]

P-glycoprotein is a membrane transporter, which plays a role in drug biotransformation processes.[14] It is a cell membrane protein that transports various drug substrates. This membrane transporter system is widely distributed in human tissues such as intestinal epithelium, liver, renal tubules and the blood-brain barrier.[15] Also, the P-glycoprotein transport system is suggested to be a cause of multidrug resistance in cancer tissues. It has been reported that the P-glycoprotein in neoplastic tissues may act as an export pump that transports the drugs out of the tissues or cells, resulting in decreased intracellular concentrations of numerous anticancer drugs.[16] Although not as well established, recently, the P-glycoprotein system has been implicated as a possible cause of HIV resistance to antiretroviral agents.[17] The P-glycoprotein system appears to play an important role in drug-drug interactions. Drugs that inhibit or induce P-glycoprotein will increase or decrease the bioavailability of other drugs that are substrates of this membrane transporter system.[13,15]

The potentially significant drug interactions of class III antiarrhythmic drugs, including mechanisms, onset, severity and management or recommendations, are summarised in table I.

2. Interactions with Amiodarone

Amiodarone is considered to be a broad-spectrum antiarrhythmic drug because it has mechanisms of action of all antiarrhythmic drug classes.[19-21] Amiodarone is metabolised by cytochrome P450 (CYP)3A4, and it is an inhibitor of CYP1A2, 2C9, 2D6 and 3A4 (or 3A3/4).[22] It is also an inhibitor of the P-glycoprotein system.[13] The inducers, inhibitors and substrates of CYP3A4 and the P-glycoprotein system are summarised in table II and table III, respectively. The following section describes significant interactions between amiodarone and other drugs.

2.1 β-Adrenoceptor Antagonists

Leor et al.[23] reported severe sinus bradycardia in a 64-year-old woman with hypertrophic cardiomyopathy when metoprolol (a β-adrenoceptor antagonist [β-blocker]) was co-administered with amiodarone. Bradycardia occurred 3 hours after the first dose of metoprolol (100mg once daily) that was given with amiodarone 1200mg daily. The cardiac adverse effect responded to intravenous isoprenaline (isoproterenol) but was resistant to intravenous atropine (two doses of 1mg each). Bradycardia completely subsided within 24 hours after the discontinuation of metoprolol. The mechanism of interaction is unclear, however, an additive β-adrenoceptor blocking effect was suggested. Also, it is possible that, in this case, bradycardia might be mainly caused by the negative chronotropic effect of metoprolol. In a subgroup analysis of a pooled database from two randomised clinical trials, the European Amiodarone Myocardial Infarction Trial (EMIAT) and the Canadian Amiodarone Myocardial Infarction Trial (CAMIAT), the unadjusted and adjusted relative risks for all-cause mortality were lower for patients receiving β-blockers and amiodarone than for those without β-blockers, and those with β-blockers alone, and those with neither amiodarone nor β-blockers.[24] The interaction was significant for the endpoints of cardiac death ($p = 0.05$) and arrhythmic death or resuscitated cardiac arrest ($p = 0.03$). The investigators did not find the use of combination therapy with a β-blocker and ami-

Table I. Onsets, mechanisms, adverse effects and management of important interactions of class III antiarrhythmic drugs[18]

Antiarrhythmic (or object) drug	Precipitant drug	Onset of interaction	Mechanism of interaction	Adverse effect(s)	Management/ recommendations
Amiodarone	β-Adrenoceptor antagonists	Rapid	↑ cardiac effects	Significant bradycardia	Monitor cardiac function (especially HR)
	Bile-acid sequestrant	Rapid	↓ bioavailability of amiodarone	↓ effects of amiodarone	Give amiodarone 2h before, or 4h after, bile-acid sequestrant
	Cisapride	Rapid	↑ effects on QT interval	↑ cardiac arrhythmia potential	Concurrent use is contraindicated
	Cyclosporin	Delayed	↓ cyclosporin metabolism	↑ cyclosporin toxicity	Monitor serum cyclosporin concentrations and adjust its dose as needed
	Digoxin	Delayed	Inhibits P-glycoprotein	↑ digoxin toxicity	Monitor serum digoxin concentrations and adjust its dose as needed
	Dofetilide	Delayed	↑ cardiac effects	QT prolongation	Class III drugs should be withheld at least 3 half-lives prior to dofetilide administration[a]
	Dolasetron	Delayed	↑ effects on QT interval	QT prolongation	Cardiac function should be closely monitored; ondansetron may be substituted
	Flecainide	Delayed	↓ flecainide metabolism	↑ cardiac arrhythmia potential	Monitor serum flecainide concentrations; may ↓ the dose of flecainide by 50%; monitor cardiac arrhythmias
	Fluoroquinolones[b]	Delayed	↑ effects on QT interval	↑ cardiac arrhythmia potential	Avoid concurrent use; use other antimicrobial
	Fosphenytoin (and phenytoin)	Delayed	↓ phenytoin metabolism and ↑ amiodarone metabolism	↑ phenytoin toxicity and ↓ amiodarone effectiveness	Monitor serum phenytoin concentrations and adjust its dosage accordingly; monitor amiodarone clinical responses
	Lidocaine	Rapid	↓ lidocaine clearance	↑ lidocaine toxicity	Monitor serum lidocaine concentrations and cardiac/CNS adverse events; adjust lidocaine dose as needed
	Procainamide	Rapid	↓ procainamide clearance	↑ procainamide toxicity	Monitor serum procainamide concentrations and its cardiac toxicity; may ↓ procainamide dose by 20%
	Protease inhibitors[c]	Delayed	↓ amiodarone metabolism	↑ amiodarone toxicity	Monitor signs/symptoms of amiodarone adverse events (e.g. ↓ HR and BP), serum amiodarone concentrations; adjust amiodarone dose as needed

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Table I. Contd

Antiarrhythmic (or object) drug	Precipitant drug	Onset of interaction	Mechanism of interaction	Adverse effect(s)	Management/ recommendations
	Quinidine	Rapid	↑ effects on QT interval	↑ cardiac arrhythmia potential	Monitor serum quinidine and cardiac arrhythmias; may ↓ quinidine dose by 40% after the addition of amiodarone to quinidine
	Warfarin	Delayed	↓ warfarin metabolism	↑ risk of bleeding	Monitor international normalised ratio closely and adjust warfarin dose accordingly; may ↓ warfarin dose by 25% empirically
Bretylium	Drugs prolonging QT interval[d]	Probably rapid	↑ effects on QT interval	QT prolongation	Avoid concurrent use if possible; monitor cardiac arrhythmias
Dofetilide	Cimetidine	Delayed	Inhibits dofetilide renal tubular secretion	↑ risk of cardiac arrhythmia	Avoid concurrent use; use other antiulcer agents such as a PPI
	Cisapride	Rapid	↑ effects on QT interval	QT prolongation (↑ cardiac arrhythmias)	Coadministration is contraindicated
	Drugs prolonging QT interval[d]	Probably rapid	↑ effects on QT interval	QT prolongation (↑ cardiac arrhythmias)	Avoid concurrent use if possible; monitor cardiac arrhythmias
	Drugs inhibiting renal cation transport system[e]	Delayed	Inhibits dofetilide renal transport system	↑ risk of cardiac arrhythmia	Avoid concurrent use; monitor dofetilide adverse effects (i.e. cardiac arrhythmias)
	Megestrol	Delayed	Inhibits dofetilide renal transport system	↑ risk of cardiac arrhythmias	Coadministration is contraindicated
	Prochlorperazine	Delayed	Inhibits dofetilide renal transport system	↑ risk of cardiac arrhythmias	Coadministration is contraindicated
	Trimethoprim (including cotrimoxazole [trimethoprim/ sulfamethoxazole])	Delayed	Inhibits dofetilide renal transport system	↑ risk of cardiac arrhythmias	Coadministration is contraindicated
	Verapamil	Rapid	Inhibits dofetilide metabolism	↑ risk of cardiac arrhythmias (especially TdP)	Coadministration is contraindicated
Ibutilide	Amiodarone	Rapid	↑ atrial and ventricular refractoriness	↑ risk of cardiac arrhythmias	Avoid concurrent use; amiodarone should not be given within 4h of ibutilide infusion
	Cisapride	Rapid	↑ effects on QT interval	↑ risk of cardiac arrhythmias	Concurrent use is not recommended

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Table I. Contd

Antiarrhythmic (or object) drug	Precipitant drug	Onset of interaction	Mechanism of interaction	Adverse effect(s)	Management/ recommendations
	Class IA and class III antiarrhythmic drugs[f]	Rapid	Additive cardiac effects	↑ risk of cardiac arrhythmias	Withhold the other drug for at least 5 half-lives prior to ibutilide infusion, or other drug should not be given within 4h of ibutilide infusion[g]
	Drugs prolonging QT interval	Rapid	↑ effects on QT interval	QT prolongation (↑ risk of cardiac arrhythmias)	Avoid concurrent use; use other alternative if available, or monitor the patient closely for cardiac adverse effects if there is no alternative
Sotalol	α_1-Adrenoceptor antagonists	Rapid	Suppression of β-mediated compensatory increases in heart rate	↑ hypotensive effect	Monitor BP closely, use lowest possible initial dose of α_1-adrenoceptor antagonist
	Class IA and class III antiarrhythmic drugs	Rapid	Additive cardiac effects	↑ risk of cardiac arrhythmias	Concurrent use is not recommended; also withhold the drug for at least 3 half-lives prior to sotalol initiation[h]
	Digoxin	Delayed	Additive cardiac effects, possibly ↑ digoxin bioavailability	↑ bradycardic effect	Monitor ECG and serum digoxin concentrations; adjust dose accordingly
	Dihydropyridine calcium antagonists	Rapid	Additive cardiovascular effects	↑ hypotensive effects	Monitor BP and cardiac function, especially in patients predisposed to HF
	Drugs prolonging QT interval	Rapid	↑ effects on QT interval	QT prolongation (↑ risk of cardiac arrhythmias)	Avoid concurrent use; use other alternative if available, or monitor the patient closely for cardiac adverse effects if there is no alternative

a The manufacturer of dofetilide recommends that class I and other class III antiarrhythmic drugs should be withheld for 3 half-lives before dofetilide initiation. However, this may not be applicable for amiodarone, since it has a very long terminal half-life (mean half-life of approximately 53 days).

b Including gatifloxacin, grepafloxacin, moxifloxacin and sparfloxacin.

c Including amprenavir, indinavir, nelfinavir and ritonavir.

d Including bepridil, dolasetron, itraconazole, ketoconazole, tricyclic antidepressants, phenothiazines, pimozide and ziprasidone.

e Including megestrol, prochlorperazine, thioridazine and trimethoprim (also the combination drug cotrimoxazole).

f Including quinidine, disopyramide and procainamide (class IA) and amiodarone, bretylium, dofetilide, ibutilide and sotalol (class III).

g The manufacturer of ibutilide recommends that class I and class III antiarrhythmic agents should be withheld for 5 half-lives before or 4 hours after ibutilide administration. However, this may not be applicable for amiodarone, since it has a very long terminal half-life (mean half-life of approximately 53 days).

h It is recommended that class I and class III antiarrhythmic agents should be withheld for at least 3 half-lives prior to sotalol initiation. However, this may not be applicable for amiodarone, since it has a very long terminal half-life (mean half-life of approximately 53 days).

BP = blood pressure; **HF** = heart failure; **HR** = heart rate; **PPI** = proton pump inhibitor; **TdP** = torsade de pointes. ↑ indicates increase; ↓ indicates decrease.

Table II. Drugs that may potentially pharmacokinetically interact with class III antiarrhythmic agents via cytochrome P450 3A4 enzyme[22]

Inducers	Carbamazepine, ethosuximide, phenobarbital (phenobarbitone), phenytoin, primidone, rifabutin, rifampicin (rifampin)
Inhibitors	Amiodarone, clarithromycin, erythromycin, fluconazole, fluoxetine, fluvoxamine, grapefruit juice, indinavir, itraconazole, ketoconazole, metronidazole, miconazole, nefazodone, nelfinavir, norfloxacin, quinine, ritonavir, saquinavir, sertraline, zafirlukast
Substrates	Alfentanil, alprazolam, amiodarone, atorvastatin, busulfan, cannabinoids, carbamazepine, cisapride, clomipramine, clonazepam, cocaine, cyclobenzaprine, cyclophosphamide, cyclosporin, dapsone, dextromethorphan, diltiazem, disopyramide, dronabinol, erythromycin, felodipine, indinavir, ketoconazole, losartan, lovastatin, midazolam, navelbine, nefazodone, nelfinavir, nicardipine, nifedipine, nimodipine, nisoldipine, ondansetron, paclitaxel, quinidine, quinine, ritonavir, saquinavir, sertraline, tacrolimus, tamoxifen, triazolam, verapamil, vinblastine, vincristine, *R*-warfarin, zileuton

odarone to be a clinical problem; in fact, they suggested that, in such patients, a β-blocker should be used as an adjunct to amiodarone therapy and be continued, if possible, in patients receiving amiodarone therapy.[24] However, more studies are warranted to further investigate and/or confirm the interaction between these two drugs.

2.2 Bile-Acid Sequestrants

A significant decrease in gastrointestinal absorption of amiodarone was reported when it was coadministered with a bile-acid sequestrant, cholestyramine.[25] The bile-acid sequestrant can bind amiodarone and decrease its availability for gastrointestinal absorption. It is possible that other bile-acid sequestrants (such as colestipol) may interact with amiodarone in the same manner.

2.3 Calcium Channel Antagonists

Significant bradycardia or worsening of atrioventricular block may occur with the concurrent use of amiodarone and a calcium channel antagonist. Sinus arrest was reported in a 61-year-old woman with congestive heart failure who was receiving amiodarone and diltiazem concomitantly.[26] The possible mechanism of this interaction is the additive calcium channel blocking effect. Other calcium channel antagonists, especially verapamil, may interact significantly with amiodarone by the same or a similar mechanism.[27,28]

2.4 Cisapride

Serious cardiac arrhythmias, such as ventricular tachycardia, fibrillation, torsade de pointes and QT prolongation, have been reported with cisapride therapy.[29] Because of life-threatening cardiac ar-

Table III. Drugs that may potentially pharmacokinetically interact with class III antirhythmic agents via the P-glycoprotein system[13]

Inducers: decrease bioavailability of substrates	Amiodarone[a], bromocriptine, chlorambucil, cisplatin, colchicine, cyclosporin[a], daunorubicin, diltiazem, doxorubicin, erythromycin, etoposide, fluorouracil, hydroxyurea (hydroxycarbamide), methotrexate, midazolam, mitoxantrone, nicardipine, nifedipine, phenobarbital (phenobarbitone), phenytoin, rifampicin (rifampin), sirolimus, St. John's wort, tacrolimus, tamoxifen, verapamil[a], vinblastine, vincristine, yohimbine
Inhibitors: increase bioavailability of substrates	Amiodarone,[a] atorvastatin, bepridil, clarithromycin, cyclosporin,[a] diltiazem, dipyridamole, disulfiram, erythromycin, felodipine, itraconazole, ketoconazole, nicardipine, nitrendipine, quinidine, quinine, ritonavir, sirolimus, tacrolimus, tamoxifen, verapamil,[a] vinblastine
Substrates	Amitriptyline, amprenavir, chlorambucil, cimetidine, cisplatin, colchicine, cyclosporin, cytarabine, daunorubicin, digoxin, doxorubicin, erythromycin, etoposide, fentanyl, fluorouracil, hydroxyurea, indinavir, itraconazole, losartan, methadone, methotrexate, nelfinavir, nortriptyline, ondansetron, paclitaxel, phenytoin, quinidine, ritonavir, saquinavir, sparfloxacin, tacrolimus, tamoxifen, topotecan, verapamil, vinblastine, vincristine

a An inducer or inhibitor depending on the nature of a substrate.

rhythmias and death, this prokinetic drug was recently removed from the US market. It can only be obtained directly from the manufacturer through a limited-access protocol. All class III antiarrhythmic drugs, including amiodarone, may prolong the QT interval and precipitate cardiac arrhythmias.[30] Therefore, the concurrent use of cisapride and amiodarone is contraindicated.

2.5 Cyclosporin

Increased cyclosporin concentrations may result when amiodarone is used concurrently with cyclosporin therapy. Nicolau et al.[31] reported a more than 50% decrease in cyclosporin clearance in a 47-year-old man with heart transplantation after receiving 44 days of amiodarone coadministration (from days 303 to 347 after transplantation). Before the addition of amiodarone, his cyclosporin clearance had remained stable. Upon discontinuation of amiodarone, cyclosporin clearance in this patient rapidly returned to baseline values. An increase in cyclosporin bioavailability by inhibition of gastrointestinal mucosa CYP (extrahepatic CYP3A4) or an amiodarone-induced decrease in gastric emptying was suggested as a mechanism of the interaction between these two drugs. The authors indicated that the rapid rise in cyclosporin clearance was difficult to explain because of the slow elimination of amiodarone from the human body.[32] However, they suggested that the rapid increase in cyclosporin clearance in their patient was probably due to the absence of the exposure of gastrointestinal mucosa to amiodarone upon its discontinuation. This could prevent the inhibition of CYP3A4 in the gastrointestinal mucosa and an increase in amiodarone bioavailability.

2.6 Digoxin

A significant increase in serum digoxin concentrations has been reported in patients receiving digoxin and amiodarone concurrently.[33,34] The suggested mechanism of this interaction is due to decreased renal and nonrenal clearance of digoxin. Inhibition of the P-glycoprotein system in the gastrointestinal tract, resulting in increased digoxin bioavailability, may also be occurring.[13]

Nademanee et al.[34] reported an increase in mean serum digoxin concentrations from 0.97 to 1.98 μg/L after the addition of oral amiodarone (600–1600mg daily) in 28 patients who were receiving long-term digoxin therapy. CNS, cardiovascular and gastrointestinal toxicities developed in four, five and nine patients, respectively. Increased serum digoxin concentrations were evident 1–3 weeks after amiodarone was instituted.

Maragno et al.[35] suggested an increase in digoxin bioavailability as the possible mechanism of this drug interaction. The suggested mechanism was based on the coadministration of digoxin and amiodarone in six healthy volunteers. Oral digoxin 0.5mg was given to the study participants prior to and at the end of a 7-day period of oral amiodarone (200mg three times daily) therapy. Serum digoxin concentrations and area under the serum concentration-time curve were significantly elevated in four of six individuals, but renal clearance remained unchanged.

Santostasi et al.[36] found no significant changes in digoxin pharmacokinetics following intravenous administration of digoxin and oral amiodarone. These investigators suggested that the most relevant mechanism of digoxin and amiodarone interaction was the increased oral digoxin bioavailability due to inhibition of the P-glycoprotein system. In addition, it has been reported that digoxin does undergo enterohepatic recycling.[37] After entering the enterocyte, digoxin may be absorbed directly into the systemic circulation, or secreted back into the lumen of the small intestine by P-glycoprotein, and then reabsorbed at a distal site of the small intestine. The enterohepatic recycling may increase the mean digoxin residence time in the intestinal lumen. This

then may cause more digoxin to be available for reabsorption, which may further increase serum digoxin concentrations.[38]

2.7 Fosphenytoin/Phenytoin

Fosphenytoin is a prodrug of phenytoin. Concurrent use of amiodarone and fosphenytoin may result in a significant increase (2–3-fold) in serum phenytoin concentrations.[39,40] Nolan et al.[41] reported that serum amiodarone concentrations were decreased by more than 30% in 2–3 weeks after phenytoin initiation. Adverse effects from the interaction may include signs of phenytoin toxicity such as nystagmus, tremor, ataxia, somnolence and hyperreflexia. In addition, decreased antiarrhythmic effects of amiodarone may occur.

2.8 Other Antiarrhythmic Drugs

2.8.1 Dofetilide

The concomitant use of dofetilide and amiodarone is not recommended because dofetilide has been shown to prolong corrected QT intervals.[42] Thus, a pharmacodynamic interaction may occur when these two drugs are used concurrently, which may result in QT prolongation, torsade de pointes and cardiac arrest.

2.8.2 Flecainide

Coadministration of amiodarone and flecainide (a class IA antiarrhythmic agent) has resulted in up to a 2-fold increase in plasma flecainide concentrations.[43] Funck-Brentano et al.[44] conducted a three-period crossover study in 12 healthy volunteers. The dosages of oral flecainide were 50 and 100mg twice daily in the first and second periods. In the third period, participants received oral flecainide 50mg plus amiodarone 200mg twice daily. The concurrent use of amiodarone and flecainide resulted in increased mean peak plasma concentrations of flecainide compared with flecainide alone (192 vs 180 μg/L; $p < 0.05$ in seven individuals and 282 vs 226 μg/L; $p < 0.05$ in five individuals). Additionally, an increase in QRS duration was observed in all participants. The investigators indicated that the increase in QRS duration was attributed to the increased plasma flecainide concentrations that were probably caused by amiodarone coadministration.

2.8.3 Ibutilide

Amiodarone should not be given with, or within 4 hours of, ibutilide injection because this drug combination causes significant QT prolongation that may result in serious cardiac arrhythmias.[45]

2.8.4 Lidocaine

There have been two case reports describing a decrease in lidocaine clearance when lidocaine has been given concomitantly with amiodarone.[46,47] Keidar et al.[46] reported severe bradycardia with a long sinus arrest in a 64-year-old man who was receiving oral amiodarone (600mg daily) after intravenous administration of lidocaine. Siegmund et al.[47] also reported the development of seizure activity in a 71-year-old man after concomitant therapy with lidocaine and amiodarone. The authors suggested that the seizure was due to a decrease in lidocaine metabolism, which resulted in increased serum lidocaine concentrations.

2.8.5 Procainamide

It has been reported that steady-state plasma procainamide concentrations may be increased 57% with amiodarone coadministration, resulting in procainamide toxicity, especially cardiac arrhythmias.[48] A 20% reduction in procainamide dose may be required to normalise the steady-state plasma procainamide concentrations.[48] Another report indicated that there was a 23% decrease in single-dose procainamide clearance, which resulted in a 38% increase in procainamide elimination half-life during the concurrent use of these two drugs.[49]

2.8.6 Sotalol

Sotalol monotherapy has been shown to cause prolongation of the QT interval; therefore the con-

current use of amiodarone and sotalol is not recommended.[50] An increased risk of cardiac arrest, QT prolongation and torsade de pointes may occur when sotalol is used concomitantly with amiodarone. It was suggested that class III antiarrhythmic agents, including amiodarone, should be withheld for at least three half-lives before the initiation of sotalol.

2.9 Protease Inhibitors

2.9.1 Amprenavir/Nelfinavir/Ritonavir

Amprenavir, nelfinavir and ritonavir can inhibit the metabolism of amiodarone by inhibiting CYP3A4, which may result in increased serum amiodarone concentrations with resultant cardiac toxicity.[51-53] Concomitant use of amprenavir and amiodarone is not recommended, and coadministration of nelfinavir or ritonavir with amiodarone is usually contraindicated.

2.9.2 Indinavir

Concomitant use of indinavir and amiodarone may result in a decrease in amiodarone metabolism, resulting in amiodarone toxicity. Lohman et al.[54] reported an increase in serum amiodarone concentration from 0.9 to 1.3 mg/L in a 38-year-old male after the initiation of postexposure prophylaxis of HIV regimens that included zidovudine (200mg three times daily), lamivudine (150mg twice daily) and indinavir (800mg three times daily). The increased serum amiodarone concentration did not exceed the upper limit of the therapeutic range (1–2.5 mg/L). Before the occupational HIV exposure, the patient was receiving oral amiodarone (200mg daily) for >6 months for the treatment of his paroxysmal atrial fibrillation. Although the patient did not experience any amiodarone-induced adverse effects, the authors suggested that the concurrent use of amiodarone and indinavir might lead to amiodarone toxicity in patients with higher baseline serum amiodarone concentrations. Indinavir, but not zidovudine or lamivudine, was suspected to interact with amiodarone in this patient because indinavir (but not zidovudine or lamivudine) is a significant inhibitor of hepatic CYP3A4.

2.10 Warfarin

A decrease in warfarin metabolism has been reported when amiodarone is administered concurrently. The inhibition of hepatic CYP3A4 by amiodarone may be responsible for decreased warfarin metabolism. The adverse interaction may be seen within 1–2 weeks of concomitant use and may last up to 1–3 months after amiodarone discontinuation.[55,56] A hypoprothrombinaemic effect, which may result in increased bleeding complications, may develop as a result of increased plasma warfarin concentrations.[57] Kerin et al.[55] reported a mean maximum increase of prothrombin time of 44% (range 22–108%) in eight patients after the first 2 weeks of concurrent therapy with amiodarone. The dosage of amiodarone was as follows: 5 mg/kg intravenously followed by 800mg daily for 10 days, then 200–400mg daily thereafter. These investigators also indicated that a 25–50% (average 35%) reduction in warfarin daily dose was required to reverse the prothrombin time back to baseline values (about 1.5–2 times control values). Kellett et al.[58] also reported an increased anticoagulant effect in patients who developed hyperthyroidism secondary to amiodarone therapy. The increased warfarin effect is probably due to an increase in the metabolism of various clotting factors, thus enhancing the anticoagulant effect of warfarin. A similar interaction and adverse outcomes have been reported with other oral anticoagulant products such as acenocoumarol and dicoumarol when they were used concurrently with amiodarone.[59]

Other drugs that can prolong QT or QTc intervals, including fluoroquinolones (such as gatifloxacin, moxifloxacin and sparfloxacin), dolasetron and pimozide, if possible, should not be coadministered with amiodarone.[60-64] Drugs that may cause

Table IV. Drugs that may significantly prolong the QT interval, resulting in an increased risk of proarrhythmia[30,42,45,48,51-53,65,66]

Cardiovascular drugs	Amiodarone,[a] bretylium, bepridil, disopyramide, dofetilide, ibutilide, procainamide, quinidine, sotalol
Noncardiovascular drugs	Cisapride, clarithromycin, dolasetron, droperidol, erythromycin, gatifloxacin, haloperidol, moxifloxacin, sparfloxacin, itraconazole, ketoconazole, pentamidine, phenothiazines, pimozide, quinine, tetracyclic antidepressants, tricyclic antidepressants, ziprasidone

a Amiodarone has been reported to have minimal proarrhythmic effect.[65]

significant QT prolongation are summarised in table IV.

3. Interactions with Bretylium

Bretylium is used for the treatment of ventricular dysrhythmias such as ventricular tachycardia and fibrillation. However, its effectiveness in treating ventricular dysrhythmias has been recently questioned.[67] Bretylium is excreted unchanged in the urine. Because bretylium is not metabolised, it is not subject to interactions with drugs that are hepatic enzyme inducers or inhibitors. Drugs that have been reported to interact with bretylium include agents that prolong the QT interval, which may result in torsade de pointes and cardiac arrest. Although there have been no published case reports, the concurrent use of bretylium and drugs that can prolong QT interval is usually not recommended. Based on product information, cisapride, thioridazine and ziprasidone are contraindicated in patients receiving class IA and class III antiarrhythmic agents (including bretylium).[29,68,69]

Newer class III antiarrhythmic agents have various modes of action. Dofetilide inhibits the rapid activating component of potassium current (similar to amiodarone and sotalol), whereas ibutilide and azimilide (not yet available in the US) block both the rapid and slow activating components of the potassium current.[70] There have been some promising experiments with newly developed antiarrhythmic agents that have dual or multiple mode of action (such as azimilide), which may be more effective and with a lower risk of proarrhythmia.[71] It is thought that the use of newer antiarrhythmic drugs may minimise the potential risk of proarrhythmia which may be caused by pharmacokinetic and/or pharmacodynamic interactions.

4. Interactions with Dofetilide

Most drugs that interact with dofetilide can be divided into three categories: drugs that prolong the QT interval, drugs that inhibit the renal cation transport system, and drugs that inhibit CYP3A4. The manufacturer recommends that dofetilide should be stopped for at least 2 days before initiating any interacting drugs.[42]

4.1 Drugs that Prolong the QT Interval

Coadministration of dofetilide and drugs that prolong the QT interval (see table IV) is not recommended. If concurrent use cannot be avoided, cautious dosage and telemetric monitoring is advised. Specifically, the manufacturer recommends withholding class I or class III antiarrhythmics for three half-lives before dofetilide initiation. In clinical trials, patients previously on amiodarone did not receive dofetilide until they had stopped taking amiodarone for 3 months or amiodarone plasma concentrations were below 0.3 mg/L.[42]

4.2 Drugs that Inhibit the Renal Cation Transport System

Drugs that inhibit tubular secretion through the cation transport system are contraindicated with dofetilide therapy. These include ketoconazole, cimetidine, trimethoprim (with or without sulfamethoxazole), prochlorperazine and megestrol. In addition, drugs that are excreted by renal cation

transport, including triamterene, amiloride and metformin, theoretically may compete with dofetilide for elimination.[42] Although the clinical significance of the renal cation transport competition (between dofetilide and triamterene or amiloride or metformin) is unknown, caution should be exercised when administering dofetilide in combination with these agents (triamterene, amiloride and metformin). In a pharmacokinetic study of 20 healthy volunteers, oral cimetidine 100 or 400mg twice daily increased maximum dofetilide concentrations by 11% and 29%, respectively, and increased the QT interval from baseline by 22% and 33%, respectively. It appeared that cimetidine reduced both renal and hepatic clearance of dofetilide. In contrast, ranitidine produced no effect on dofetilide pharmacokinetics or pharmacodynamics.[72] In patients receiving dofetilide, if acid suppression therapy is needed, ranitidine, proton pump inhibitors and antacids are recommended. Ketoconazole increases dofetilide concentrations by inhibiting both the renal cation transport system and hepatic CYP3A4. According to the manufacturer, ketoconazole 400mg daily increased maximum dofetilide concentrations by 53% in males and 97% in females; both renal and nonrenal clearance were decreased.[42]

4.3 Drugs that Inhibit Hepatic Cytochrome P450 3A4 Metabolism

Coadministration of cimetidine and ketoconazole with dofetilide is contraindicated according to the manufacturer because of the significant increase in serum dofetilide concentrations, which may result in its toxicity.[42]

4.4 Thiazide Diuretics

Thiazides reduce the renal clearance of dofetilide and lower serum potassium as well as magnesium concentrations, which may increase the risk of dofetilide toxicity. Patients receiving thiazides (or other diuretics such as furosemide, which can result in hypokalaemia and/or hypomagnesaemia) and dofetilide concurrently should be closely monitored.[42]

4.5 Verapamil

Concomitant use of verapamil and dofetilide is contraindicated. Verapamil can accelerate the rate of absorption of dofetilide and result in an increase in maximum serum dofetilide concentrations of 42%. In clinical trials, coadministration of verapamil and dofetilide was associated with a higher rate of torsade de pointes.[42]

5. Interactions with Ibutilide

Ibutilide is indicated for conversion of atrial fibrillation or atrial flutter to normal sinus rhythm. It is extensively metabolised in the liver by enzymes other than CYP3A4 and CYP2D6. Therefore, the potential for pharmacokinetic interactions with ibutilide is low. As with other class III antiarrhythmics, concurrent use with drugs that prolong the QT interval (see table IV) may theoretically increase the risk of torsade de pointes. Class IA and class III antiarrhythmics should not be given concomitantly with ibutilide because of the potential for prolonging refractoriness. The manufacturer recommends these agents be withheld for five half-lives prior to, and 4 hours after, ibutilide administration.[45]

6. Interactions with Sotalol

Sotalol is classified as a class III antiarrhythmic agent; however, it is also a nonselective beta-adrenergic blocking agent. Approximately 75% of the administered dose is excreted unchanged in the urine. It has insignificant or negligible first-pass hepatic metabolism, therefore interactions with other drugs due to hepatic enzyme induction or inhibition are less likely. The following drugs may have potentially significant interactions with sotalol:

6.1 α_1-Adrenoceptor Antagonists

The concurrent use of α_1-adrenoceptor antagonists (α_1-blockers) such as prazosin with a β-blocker such as sotalol may increase the risk of hypotensive response (or the first-dose phenomenon) of α_1-blockers.[73] The hypotensive adverse effect is more likely to develop when the α_1-blocker is added to the ongoing regimen of sotalol. However, it is less likely to cause a significant fall in blood pressure if sotalol is added to the pre-existing regimen of an α_1-blocker.[74]

6.2 Antacids

Laer et al.[75] reported that concurrent use of sotalol and an antacid (containing magnesium and aluminium compounds) can decrease sotalol bioavailability, thereby decreasing serum sotalol concentrations. In addition, these investigators found that the area under the serum concentration-time curve and the amount of sotalol excreted into the urine were decreased when sotalol was coadministered with an antacid. They indicated that the interaction could be avoided by giving the antacid 2 hours after sotalol administration.

6.3 Class IA and other Class III Antiarrhythmic Drugs

Because class IA and class III antiarrhythmic drugs can prolong the QT interval, the concomitant administration of sotalol with any class IA or III antiarrhythmic drugs may result in an additive QT prolongation.[50] The concurrent use of sotalol and any class IA or III antiarrhythmic agents should be avoided. It is also suggested that a class IA or III antiarrhythmic drug should be withheld for at least three half-lives before the initiation of sotalol therapy.

Warren et al.[76] reported a case of bradycardia and atrioventricular conduction block in a 72-year-old man after sotalol was added to flecainide therapy. The patient was diagnosed with nonsustained ventricular tachycardia. His ventricular arrhythmia was treated with amiodarone and flecainide (100mg twice daily). However, 3 days after taking both drugs (amiodarone and flecainide), his ventricular tachycardia became more frequent, flecainide was discontinued, and oral sotalol 40mg was started 1 hour after the last dose of flecainide. The second dose of sotalol 40mg was given to the patient 1 hour after the first dose. Three hours after the second dose of sotalol, the patient developed a cardiac arrest with unsuccessful resuscitation. It is possible that the cardiac arrest in this patient was caused by all three antiarrhythmic drugs or the additive adverse effects of these three drugs.

However, Price et al.[77] have reported recently that the combination of flecainide and sotalol can be used safely and effectively in the control of refractory supraventricular tachycardia in children aged less than 1 year. These investigators also indicated that this drug combination may help eliminate the need for radiofrequency ablation in this age group.

6.4 Clonidine

Saarimaa[78] reported a possible antagonistic effect on blood pressure in six out of ten patients who were receiving sotalol and clonidine. An increase in blood pressure occurred in these patients approximately 1 week after starting the combined therapy and lasted for approximately 7 days after one drug was discontinued. Of the remaining four patients, two had decreased blood pressure with the combination and two had no change.[78] In addition, an exaggerated rebound hypertension may occur upon abrupt cessation of clonidine in patients receiving a β-blocker.[79] This is probably due to an unopposed α stimulation. It is suggested that the β-blocker should be discontinued several days before gradually tapering the dose of clonidine.

6.5 Digoxin

Singh et al.[80] conducted a placebo-controlled study to evaluate the effect of sotalol (80–320mg daily) on digoxin therapy. These investigators reported that bradycardia was more common in patients receiving both digoxin and sotalol than in patients who received digoxin alone. Bradycardia was probably due to the additive atrioventricular inhibition. Another potential pharmacodynamic interaction is the opposing effects on cardiac contractility with digoxin exerting a positive inotropic effect and sotalol having a negative inotropic effect.

6.6 Diuretics

Among the risk factors for torsade de pointes, associated with QT prolongation, are hypokalaemia and hypomagnesaemia. Reports suggest that these adverse effects are related to diuretic-induced electrolyte loss. Monitoring and appropriate replacement of potassium and magnesium is recommended for patients on combination therapy with diuretics and sotalol.[81,82]

6.7 Drugs Prolonging the QT Interval

The risk of serious cardiac arrhythmias such as significant QT prolongation and torsade de pointes may be increased significantly with coadministration of sotalol and drugs listed in table IV.

7. Discussion

Although it may not be a direct drug-drug interaction, electrolyte abnormalities, especially hypokalaemia and hypomagnesaemia that are caused by diuretics (e.g. thiazide and loop diuretics) or other drugs (such as amphotericin B, and cisplatin), can cause patients to become more prone to proarrhythmic effects of any of the class III antiarrhythmic drugs.

The management of drug interactions is not always straightforward. Discontinuation or substitution of the offending drug may not be feasible. Therefore, clinicians should be kept abreast of knowledge related to significant drug interactions, especially with the newly approved drugs. Serious consideration and attention should be placed on drug interactions that are well established and have been documented as clinically important. These interactions can cause serious adverse consequences such as cardiac arrhythmias or arrest. Although it is beyond the scope of this review, clinicians should be aware of the potentially significant interactions between class III antiarrhythmic agents and herbal or natural products such as grapefruit juice. Grapefruit juice has been reported to interact with numerous drugs by inhibiting CYP3A4 and the P-glycoprotein transport system.[22,83] Therefore, patients should be educated and/or instructed to avoid grapefruit juice when taking drugs that are highly metabolised by CYP3A4 and/or the P-glycoprotein system (such as amiodarone).

8. Conclusion

All currently marketed antiarrhythmic drugs have the potential to cause cardiac arrhythmias because of their arrhythmogenic or proarrhythmic adverse effect. As a general rule, coadministration of any class III antiarrhythmic drug with a drug that has been reported to significantly alter the pharmacokinetics and/or pharmacodynamics of an antiarrhythmic drug should be avoided. Likewise, the concurrent use of a class III antiarrhythmic agent that may significantly affect the pharmacokinetics and/or pharmacodynamics of the other drug is not recommended. Serious adverse consequences (such as cardiac arrhythmia or severe bradycardia) may develop as a result of the interaction between a class III antiarrhythmic drug and the other drug. If concurrent use (of a class III antiarrhythmic agent and another drug) cannot be avoided or no published studies for that particular drug interaction are available, caution should be exercised and close monitor-

ing of the patient should be performed in order to avoid or minimise the risks associated with a possible adverse drug interaction.

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