For Practitioner

Pharmacodynamic and Pharmacokinetic Interactions of Class III Antiarrhythmic Drugs

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ABSTRACT Summary The desirable and undesirable effects of a drug are generally related to its concentration at the sites of action, which in turn is related to the amount administered (dose) and to the drug's absorption, distribution, metabolism, and/or excretion, and also drug–drug interactions. The class III antiarrhythmic drugs include amiodarone, sotalol, bretylium, dofetilide, ibutilide and azimilide. Class III antiarrhythmic drugs may interact with other drugs by two major processes: pharmacodynamic and pharmacokinetic interactions. In this review are described the interaction between classes III of antiarrhythmic drugs and other classes antiarrhythmics.

KEY WORDS *antiarrhythmic drugs,*

Introduction

The desirable and undesirable effects of a drug are generally related to its concentration at the sites of action, which in turn is related to the amount administered (dose) and to the drug's absorption, distribution, metabolism, and/or excretion, and also drug–drug interactions.

Drug interactions represent an important and widely under recognized source of medication errors. An interaction is said to occur when the effects of one drug are changed by the presence of another drug(s), food, drink or an environmental chemical. When a therapeutic combination could lead to an unexpected change in the condition of the patient, this would be described as an interaction of potential clinical significance (1). Drug interactions can arise in numerous ways; such as pharmacodynamic interaction, in which receptor effects of different agents interacts to produce synergy or antagonism of drug effects. In pharmacokinetic interaction, the blood levels of given agents may be raised or lowered based on the type of interaction (1).

Most cardiac patients who have cardiac arrhythmias and are treated by antiarrhythmic agents will receive other cardiovascular drugs to treat coexistent problems, for example heart failure, angina or hypertension. Two antiarrhythmic drugs may be simultaneously prescribed to these patients in the search for better efficacy and fewer side effects. In all cases, complex pharmacodynamic and pharmacokinetic drug interactions are likely to occur (2)

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, azimilide and sotalol. These agents are effective for the management of various types of cardiac arrhythmias both atrial and ventricular in origin (3).

Class III antiarrhythmic drugs may interact with other drugs by two major processes: pharmacodynamic and pharmacokinetic interactions (3).

Combinations of anti-arrhythmic drugs are often employed to treat patients with refractory and life-threatening arrhythmias. The combination of a class 1 and a class 3 agent is particularly attractive, since these drugs act principally on different phases of the action potential.

Amiodarone

The use of amiodarone in conjunction with other antiarrhythmic agents generally should be reserved for patients with life-threatening arrhythmias who do not respond completely to either a single antiarrhythmic agent or amiodarone alone. When combination therapy with amiodarone is employed, it is generally recommended that dosage of the currently administered antiarrhythmic agent(s) be reduced by 30–50% several days after initiation of amiodarone therapy, since the onset of amiodarone's antiarrhythmic effect may be delayed (4).

Atypical ventricular tachycardia (torsades de pointes) has been reported rarely when amiodarone was administered concomitantly with various antiarrhythmic agents, including disopyramide, mexiletine, propafenone, and quinidine (3,12,13). Pending further accumulation of data, amiodarone should be used with caution when administered concomitantly with other antiarrhythmic agents, particularly class IA antiarrhythmic agents (4).

Serum quinidine concentrations may increase following initiation of amiodarone therapy in patients currently receiving quinidine, with subsequent toxicity occurring in some patients. Administration of amiodarone hydrochloride (1200 mg daily for 5–7 days then reduced to 600 mg daily) to a limited number of patients receiving quinidine gluconate or sulfate (average dose of about 3 g daily) resulted in an increase in serum quinidine concentrations of about 33%. Serum quinidine concentrations may begin to increase within a couple days after initiation of amiodarone therapy (4).

In the study of Kim A Saal et al (1984) serum levels of quinidine or procainamide were measured in patients who had amiodarone added to their antiarrhythmic regimen. Eleven of 11 patients had an increase in the serum quinidine level, and 11 of 12 other patients had an increase in the serum procainamide level. The dose requirement to maintain a stable plasma level of quinidine or procainamide decreased by 37 % and 20 %, respectively. Clinical toxicity occasionally occurred with the increase in serum levels of quinidine and procalnamide, and the dose of these drugs should be decreased when amiodarone is administered concurrently (5). Quinidine clearance is reduced by amiodarone, and plasma concentrations of quinidine may increase by 32% when administered concurrently (6). Amiodarone may increase the serum concentration of quinidine along with an increase in QT prolongation in patients treated with amiodarone who are already receiving quinidine. (7). The dose of the second antiarrhythmic agent probably should be reduced by 50%.

The mechanism of the interaction is not fully established, but it has been suggested that amiodarone may inhibit hepatic clearance or decrease renal clearance of quinidine and/or displace quinidine from tissue- and/or protein-binding sites. Although not clearly established, combination therapy with amiodarone and quinidine may also cause marked QT prolongation, predisposing patients to atypical ventricular tachycardia (torsades de pointes). It is generally recommended that quinidine dosage be reduced by 33–50% when amiodarone therapy is initiated in patients currently receiving quinidine or that quinidine therapy be discontinued. Serum quinidine concentrations should be monitored carefully and quinidine dosage reduced as necessary in patients receiving concomitant amiodarone and quinidine therapy; patients should be observed closely for signs of toxicity, including QT prolongation

Flecainide and amiodarone are antiarrhythmic agents with dissimilar electrophysiologic and pharmacokinetic properties. Each is known to be efficacious in suppressing various cardiac arrhythmias and their use in combination may, in some cases, have an enhanced antiarrhythmic effect (8). In the study of Shea P. et al plasma flecainide concentrations adjusted for daily dosage increased by an average of about 60% (range: 5–190%) when amiodarone therapy was initiated in a limited number of patients receiving flecainide (8). Although the mechanism(s) of this interaction is not known, it has been suggested that amiodarone may inhibit the hepatic metabolism and/or decrease the renal clearance of flecainide (8). It is recommended that the dosage of flecainide be reduced by 30–50% several days after initiation of amiodarone therapy; subsequently, the patient and plasma flecainide concentrations should be monitored closely and flecainide dosage adjusted as necessary.

Concomitant use of amiodarone and procainamide may result in increased plasma procainamide and *N*-acetylprocainamide (NAPA) concentrations and subsequent toxicity. In a limited number of patients receiving 2–6 g of procainamide hydrochloride daily, initiation of amiodarone hydrochloride (1200 mg daily for 5–7 days and then 600 mg daily) increased plasma procainamide and NAPA concentrations by about 55 and 33%, respectively, during the first week of amiodarone therapy (4). The exact mechanism(s) has not been elucidated, but it has been suggested that amiodarone may decrease the renal clearance of procainamide or NAPA and/or inhibit the hepatic metabolism of procainamide. Liu LL et al (9) examined the effect of amiodarone on the disposition of procainamide in the rat to determine the mechanism of a reported interaction between amiodarone and procainamide and to determine the effect of amiodarone on drug acetylation. Neither the renal clearance of procainamide nor N-acetylprocainamide was altered by amiodarone pretreatment. These data suggest that amiodarone interacts with procainamide by reduction of an alternate pathway of elimination, possibly oxidative metabolism (10). In addition to a pharmacokinetic interaction, additive electrophysiologic effects, including increased QT_c and QRS intervals, occur during concomitant use; adverse electrophysiologic effects (e.g., acceleration of ventricular tachycardia) may also occur (8). Pending further accumulation of data, it is recommended that procainamide dosage be reduced by 20–33% when amiodarone therapy is initiated in patients currently receiving

procainamide or that procainamide therapy be discontinued. Some experts do not recommend routine use of the combination of procainamide and amiodarone, and suggest expert consultation (8).

Amiodarone and mexiletine have a beneficial pharmacodynamic interaction with an increase in antiarrhythmic efficacy but no information is available concerning their relative influence on drug plasma concentration (13).

Sinus bradycardia was observed in a patient receiving oral amiodarone who was given lidocaine for local anesthesia. Seizures associated with increased lidocaine concentrations were observed in one patient receiving concomitant iv amiodarone therapy (4).

The study of T. Morgera et al (14) suggest that best candidates for this type of pharmacologic association may be patients without ischemic heart disease and severe left ventricular dysfunction, who continue to present recurrences of ventricular tachycardia despite treatment with amiodarone. In these cases an inhospital pharmacological evaluation, using continuous electrocardiographic monitoring, levels of the drug in the plasma, and serial electropharmacologic studies, is required. Two types of response have a predictive value: the impossibility of inducing sustained ventricular tachycardia at programmed electrical stimulation, which identifies protection against spontaneous relapses of ventricular tachycardia, and an easy initiation of spontaneous and induced ventricular tachycardias, which indicates failure of the dosage of propafenone tested.

Amiodarone and its main metabolite, desethylamiodarone, accumulate in multiple tissues, including the liver. Amiodarone is metabolized by the CYP3A4 enzymes. Previous studies have demonstrated that amiodarone and especially desethylamiodarone are inhibitors of the hepatic cytochrome P450 (CYP) 2D6, which metabolizes – beta blockers, such as metoprolol, carvedilol, and propranolol (11).

Amiodarone may increase plasma concentrations of hepatically metabolized beta-blockers and calcium channel blockers. Amiodarone is inhibitor of CYP 2D6, CYP 1A2, CYP 2C9, CYP 3A4, 5,7(6).

Phenytoin, by inducing CYP3A4, has been reported to enhance amiodarone metabolism and decrease plasma concentrations by as much as 49% (14). On the other hand, amiodarone inhibits CYP2C9, thus inhibiting phenytoin metabolism, resulting in doubling plasma phenytoin levels (6).

Another type of drug interaction is that between two classes of drugs that have similar effects. Amiodarone has sympathetic blocking activity but is not a competitive antagonist of the beta-adrenergic receptors. Amiodarone decreases sinus node automaticity and prolongs the refractory period of the atrioventricular (AV) node. In patients with sinus bradycardia, sick sinus syndrome, or partial AV block, either amiodarone, a beta-blocking drug, or certain calcium antagonists (e.g., verapamil and diltiazem) can further slow the sinus rate or worsen AV block. The combination can have additive effects, occasionally with adverse consequences. For example, Derrida et al. described a patient who had a rapid ventricular response to atrial flutter even with amiodarone and digitalis therapy. After one dose of propranolol given by mouth, the patient had cardiac arrest (15). The ECG showed complete absence of ventricular activity. Fortunately the patient responded to isoproterenol infusion. Another patient with an acute myocardial infarction was given amiodarone intravenously because of continued pain. When the pain persisted for 24 hours, amiodarone was discontinued, and he received two doses of oral propranolol. One and one-half hours later he developed marked bradycardia that was soon followed by ventricular fibrillation, successfully treated with electrical defibrillation. Amiodarone should be used with caution with beta-blocking drugs or calcium antagonists, particularly if there is suspicion of underlying dysfunction of the sinus node, such as bradycardia or sick sinus syndrome, or if there is partial AV block. It would be prudent to exercise the same caution with verapamil and diltiazem (15).

Recent data from a variety of clinical trial outcomes suggest that both amiodarone and beta-blockers have pharmacologic properties that might be additive or even synergistic in the control of disorders of cardiac rhythm leading to a prolongation in overall survival. However, such a possibility has not been examined in a critical fashion in prospectively designed, controlled randomized clinical trials, although the vindication of such a possibility has wide clinical implications. Nevertheless, the available data are compelling. As indicated in the above discussion, as a class, beta-blockers exert a range of effects that stem from their ability to competitively block beta-adrenergic receptors. The net outcome is the lowering of heart rate and blood pressure associated with the prevention of acute myocardial infarction, and in the reduction of sudden death and prolongation of overall survival. Indeed, no other class of therapeutic agents has been shown to reduce total mortality in such a consistent

fashion. It was found early that the magnitude of the benefit in this regard was the highest in patients with acute myocardial infarction having a significantly depressed left ventricular ejection fraction. Thus, as a class, beta- blockers exert a consistent beneficial effect on mortality in an exceedingly wide spectrum of disorders in which there may either be a major derangement of the autonomic nervous system, with the predominant action being the reversal of sympathetic overactivity or the attenuation of the arrhythmogenic effects of myocardial ischemia. In contrast, the effects of amiodarone in the survivors of acute myocardial infarction have been less decisive and modest despite the fact that its pharmacologic (16).

The co-administration of amiodarone and beta-blockers combines 2 different antiarrhythmic principles known to reduce mortality (e.g., postmyocardial infarction patients). In the study of Werner D. (11) on average, metoprolol plasma concentration is doubled after an amiodarone loading dose (1.2 g/day over a period of 6 days). However, the individual amount of this drug interaction depends on the CYP2D6 genotype (11).

Clinical, electrophysiological studies have shown beneficial effects, by combining amiodarone and a beta-blocker for the treatment of sustained ventricular tachyarrhythmias . Given the perceived increased risks of bradyarrhythmias or haemodynamic intolerance, these studies also confirmed the general safety and tolerability when these agents are combined, provided that a small dose of beta-blocker is used and the dose is slowly increased (18)

Amiodarone has also been reported to cause asystole and severe bradycardia when given in close proximity to propranolol.

Amiodarone reduces the density of cardiac beta-receptors, thus enhancing the effect of the beta-blocker. In addition to this pharmacodynamic effect, the CYP2D6-dependent pharmacokinetic interaction likely contributes to the clinical effects of amiodarone – metoprolol co-administration. Such an interaction may also increase the number of adverse events, such as hypotension, bradycardia, or beta-blocker intolerance (11). For example, the European Myocardial Infarct Amiodarone Trial and Canadian Amiodarone Myocardial Infarction Trial meta-analysis showed that the percentage of beta-blocker withdrawal in patients receiving beta-blockers at entry was 60% to 80% greater in the amiodarone group compared with the placebo group in Werner D. et al patients. In contrast, the large beta-blocker trials in heart failure (e.g., the Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure, Multi- center Oral Carvedilol in Heart Failure Assessment) showed a negative correlation between mortality and the use of beta-blockers (11). Thus, the inhibition of CYP2D6-mediated metoprolol metabolism by amiodarone might contribute to the survival benefits observed in studies, such as the European Myocardial Infarct Amiodarone Trial and the Canadian Amiodarone Myocardial Infarction Trial and also to the antiarrhythmic effects observed in studies, such as the Atrial Fibrillation Suppression Trial (11).

Studying the effects of combining amiodarone with various antiarrhithmic drugs on ECG of rat in acute exposure, we found the existence of pharmacodynamic interaction with desired or undesired actions on ouabain-induced arrhythmia.

Thus, the associations of amiodarone – disopyramide cancels ouabain-induced arrhythmia with total effects in twenty minutes after administration, but with marked bradycardia effects. In turn, the association between amiodarone and mexiletine did not have good effects on ouabain-induced arrhythmia. Also, the association amiodarone – atenolol either maintained arrhythmia or led to the animal dead by asystole. The antiarrhythmic effects at the same type of arrhythmia of association amiodarone – verapamil was relatively short in time and not constant.

Sotalol

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 (3).

Drugs that prolong cardiac refractoriness such as sotalol or amiodarone appear to be superior to sodium channel blocking agents, which primarily slow cardiac conduction, in preventing recurrent ventricular tachycardia or sudden death (3,4). However, prolongation of action potential duration (class III effect) is often characterized by a progressive loss of effect at higher stimulation rates, otherwise known as “reverse use dependence” The combination of low dose sotalol and a class Ia (quinidine or procainamide) agent greatly prolongs refractoriness. The magnitude of the effect increases at shorter coupling intervals. The ERP prolongation in the study of Douglas LS et al is greater than has been seen with either drug as monotherapy and probably reflects the combined effect of both drugs (19).

Combination antiarrhythmic drug therapy with low dose DL-sotalol plus a type I-a antiarrhythmic agent has been shown to prevent spontaneous and induced ventricular tachycardia (19).

The combination of sotalol plus quinidine procainamide appears to be highly effective in preventing modifying inducible ventricular tachycardia at electrophysiologic study. This drug combination appears effective for the long-term suppression of recurrence of sustained ventricular tachycardia. Furthermore, the combination is associated with a marked prolongation of cardiac refractoriness, which may be associated with clinical benefit. Sotalol and type I-a drugs in combination prevent recurrence of sustained ventricular tachycardia (20) Quinidine plus sotalol did not augment the risk of TdP in a canine model. In another study, the combination of sotalol and quinidine or procainamide not only prolonged the refractory period more than the single agents, but the enhancement was preserved at faster heart rates in contrast to the diminution of repolarization prolongation that occurs with sotalol alone (22). It has been suggested that adding sotalol to propafenone therapy may be useful in patients with recurrent atrial fibrillation. However, combination antiarrhythmic therapy may result in unanticipated increases in plasma concentrations and should be pursued with caution (21). Antiarrhythmic drug combinations could also diminish toxic effects. In an animal model mexiletine inhibited sotalol-induced TdP without loss of the antiarrhythmic potency in a canine infarct model (22)

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 (3).

Dofetilide is metabolized chiefly by CYP3A4 and excreted by the renal cation transport system (3). Dofetilide is a potent inhibitor of several other enzymes within the system, including 1A2, 2C9, 2D6 and 3A4 itself. It may also interact with drugs through inhibition of the P-glycoprotein membrane transporter system. Consequently it interacts pharmacokinetically with a number of drugs, including beta-blockers, calcium antagonists, digoxin, phenytoin.

Drugs that inhibit the renal transport system (such as triamterene) may interact with dofetilide. Drugs that interfere with the renal elimination of dofetilide, such as ketoconazole and cimetidine, or that increase its plasma levels, such as verapamil, cannot be co-administered with this antiarrhythmic drug (17).

Potential kinetic and dynamic interactions between the new class III antiarrhythmic dofetilide and the calcium channel blocker verapamil were determined in 12 young healthy male volunteers (23). In steady-state conditions during combination treatment, a modest increase in mean (+/- SD) peak plasma concentration of dofetilide from 2.40 +/- 0.42 to 3.43 +/- 0.71 ng x ml (-1) (43% increase, $p < 0.1$) was noted. During the combination period, for the first 4 hours, mean AUC values for dofetilide increased from 7.4 +/- 1.0 (dofetilide alone) to 9.2 +/- 1.4 ng x h x ml(-1) (26% increase, $p < 0.1$). The maximal mean increase in QT, over steady-state baseline values was 20 msec for dofetilide alone versus 26 msec during combination therapy. This relatively small interactive effect occurred only while peak plasma drug concentrations were developing at 1 to 3 hours after dosing and is probably caused by the known effect of verapamil to increase hepatic and portal blood flow. In view of this interaction and the relationship between dofetilide plasma concentration and torsade, verapamil is contraindicated in patients receiving dofetilide (23).

Ibutilide 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 (3).

Azimilide No clinically important drug interactions are expected when azimilide is co-administered with CYP 3A4 inhibitors.

If concurrent use of a class III antiarrhythmic agent and another antiarrhythmic drug, 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.

References

1. Bista D, Palaian S, Shankar PR, Prabhu MM, Paudel R, Mishra P. Understanding the essentials of drug interactions: A potential need for safe and effective use of drugs. Kathmandu University Medical Journal, 2006, Vol. 4, No. 3, Issue 15,421-430.
2. Jaillon P. Antiarrhythmic drug interactions: are they important? European Heart Journal (1987) 8 (Supplement A), 127-132
3. Yamreudeewong W, DeBisschop M, Martin LG; Lower DL. Potentially Significant Drug Interactions of Class III Antiarrhythmic Drugs Drug Safety: 2003 - Volume 26 - Issue 6 - pp 421-438
4. AHFS Drug Information. (CR) Copyright, 1959-2010, Selected Revisions February 2010. American Society of Health-System Pharmacists, Inc., 7272 Wisconsin Avenue, Bethesda, Maryland 20814.

5. Saal.A. K., Werner J.A., Greene H. L, Sears Gena K., Graham Ellen L., Effect of Amiodarone on Serum Quinidine and Procainamide Levels. Am J Cardiol 1984;53:1284-1287
6. Cheng W. M. Judy, Frishman, W. H, Aronow W. S. Updates on Cytochrome P450-Mediated Cardiovascular Drug Interactions Am J Ther 2009;16:155-63.
7. Zipes DP, Prystowsky E., Heger JJ. Amiodarone: Electrophysiologic Actions, Pharmacokinetics and Clinical Effects lACC Vol. 3. No.4 April 1984: 1059-71
8. Shea P, Lal R, Kim Sung Soon, Schechtman K, Ruffy R. Flecainide and Amiodarone Interaction J Am Coli CardioI 1986;7:1127-30
9. Liu LL, Knowlton PW, Svensson CK. Effect of amiodarone on the disposition of procainamide in the rat. J.Pharm. Sci., 1988Aug 77(8), 662-665
10. Windle J, Prystowsky EN, Miles WM, Heger JJ. Pharmacokinetic and electrophysiologic interactions of amiodarone and procainamide. Clin Pharmacol Therapy1987 Jun 41(6), 603-610
11. Werner D, Wuttke H, Fromm MF, Schaefer S, Eschenhagen T, Brune K, Werner DG, Werner U. Effect of Amiodarone on the Plasma Levels of Metoprolol Am J Cardiol 2004; 94:1319–1321
12. James MA, Papouchado M, Vann Jones J. Combined therapy with disopyramide and amiodarone: a report of 11 cases International Journal oj Cardiologs, 13 (1986) 248-252
13. Bigger JT. The interaction of mexiletine with other cardiovascular drugs. Am Heart J 1984; 107: 1079-85.
14. Morgera T, Dreas L, Humar F, Maras P, Chersevani D, Camerini F. The use of associated propafenone in patients with amiodarone-resistant ventricular tachycardia. International Journal of Cardiology, 31 (1991) 187-198
15. Marcus F.I. Drug interactions with amiodarone Am Heart J 1983. 106:924
16. Ogunyankin KO, and Bramah N. Singh BN. Mortality Reduction by Antiadrenergic Modulation of Arrhythmogenic Substrate: Significance of Combining Beta Blockers and Amiodarone Am J Cardiol 1999; 84: 76R–82R
17. Camm A.J. Safety considerations in the pharmacological management of atrial fibrillation International Journal of Cardiology 127, 2008, 299–306
18. Ghuran AV, Camm AJ Amiodarone and beta blockade - is the whole better than parts? Journal of Clinical and Basic Cardiology 2000; 3 (Issue 3), 205-207
19. Douglas Lee S, Newman D, Ham M, Dorian P. 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 –105
20. Dorian P, Newman D, Ber N , Hardy Judy, Mitchell J. RN Sotalol and type Ia drugs in combination prevent recurrence of sustainrd ventricular tachycardia. JACC Vol. 22. No. 1. July 1993:106-113.
21. Brian R. Triola,Peter R. Kowey, Antiarrhythmic Drug Therapy. Current Treatment Options in Cardiovascular Medicine 2006, 8:362–370
22. Susan Brode, 1Singh BN, Anderson KP. 1998 Sotalol Cardiac Electrophysiology Review 1998;2:211–214
23. Johnson BF, Cheng SL, Venitz J Transient kinetic and dynamic interactions between verapamil and dofetilide, a class III antiarrhythmic J Clin Pharmacol November 1, 2001 vol. 41 no. 11 1248-1256

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