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Cytochrome P450-2D6 Genotype Definition May Improve Therapy for Paroxysmal Atrial Fibrillation: A Case of Syncope Following "Pill-in-the-Pocket" Quinidine plus Propafenone

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Abstract

Classes 1A, 1C and III anti-arrhythmics may be ineffective or induce adverse events including potentially fatal arrhythmias when administered in recommended doses. Serum levels of these medications vary widely during conventional dosing due in large part to variations in cytochrome P450-2D6 isoenzyme activity which metabolizes most antiarrhythmics in addition to over 25% of other commonly prescribed medications. 2D6 activity is also profoundly inhibited by some antiarrhythmics and other commonly used medications and varies widely between the individuals of all populations, a pattern which has resulted in separation of subjects into 4 phenotypes and genotypes consisting of poor metabolizers (PM), intermediate metabolizers (IM), efficient metabolizers (EM), and ultra-rapid metabolizers (UM). Patients with a phenotype PM classification almost universally are also genotype PM due to the possession of two inactive 2D6 alleles, with this PM pattern often inducing supratherapeutic and toxic antiarrhythmic blood levels during conventional antiarrhythmic therapy. UM individuals have supranormal levels of 2D6 activity often created by the presence of 3 or more active alleles which often induce subtherapeutic and ineffective drug levels during antiarrhythmic administration in conventional doses.

We searched for evidence relating Cytochrome P450-2D6 phenotypes or genotypes to antiarrhythmic metabolism in order to judge whether this analysis might contribute to improved safety and effectiveness of antiarrhythmic medications commonly utilized in the treatment of atrial fibrillation. The available evidence strongly supported these possibilities.

We also describe a patient in whom knowledge of his IM/PM CYP2D6 genotype might have prevented the only episode of syncope and myocardial stunning which developed during his 28 years of "Pill-in-a-Pocket" therapy.

Case Report

An 81-year-old marathon runner-internist developed syncope followed by myocardial stunning two hours after conversion to normal sinus rhythm and 4 hours after adding a single 150mg dose of propafenone to 650mg of quinidine gluconate which he had ingested 3 hours earlier. Cardiac isoenzyme, electrolyte, CBC, TSH and EKG were normal. Echocardiogram one week later revealed left ventricular hypertrophy with an enlarged left atrium typical of men with habitual endurance-associated atrial fibrillation. Over the previous 24 years he had successfully converted more than 100 episodes of PAF with PIP oral quinidine sulfate (200mg-600mg) or quinidine gluconate (650-975mg) without utilizing other cardiac, anti-arrhythmic, or anti-coagulation therapy. Several months after we published his adverse event[37] CYP2D6 analysis demonstrated alleles 4 and 41, identifying him as an IM/PM 2D6-deficient subject.

Within the next year, he successfully converted episodes of PAF on 2 occasions with 100mg of oral flecainide, but both were accompanied by mildly symptomatic EKG-documented atrial flutter with 2/1 AV block and a ventricular rate of 120-140 beats per minute. He continued to reject non-quinidine therapy for his PAF because of the absence of studies documenting their safety and effectiveness in the treatment of atrial fibrillation in endurance athletes, and their potential for impairing his ventricular function. Following his return to PPI quinidine, over the next 3 years more than 60 additional mildly symptomatic episodes of PAF were successfully converted within 4-8 hours by utilizing 200-600mg of oral quinidine sulfate while continuing his daily exercise and other activities without interruption.

Introduction

Each of the commonly prescribed antiarrhythmics is metabolized by the Cytochrome P450 2D6 (CYP2D6) (2D6) isoenzyme system with several of them also inhibiting this system. CYP2D6 also metabolizes 25% of other commonly used medications and is inhibited by others, some of which are listed in Table 1.

Antiarrhythmic drugs may be either ineffective or induce unwanted symptoms including potentially fatal arrhythmias when administered in conventional doses for paroxysmal atrial

Disclosures:
None.

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Table 1: Commonly Utilized Medications Whose Effectiveness & Safety Can Be Modified By Cyp2d6

Drugs Inhibiting 2D6	Drugs Metabolized by 2D6
Anti-arrhythmias	**Anti-arrhythmias**
quinidine	flecainide
propafenone*	propafenone*
amiodarone	carvedilol
flecainide	metoprolol
	propranolol
	amiodarone
Opioids	Opioids
methadone	methadone
	oxycodone
	hydrocodone
	tramadol
	codeine
Anti-depressants & Psychotropics	**Anti-depressants & Psychotropics**
fluvoxamine	fluoxetine
sertraline	amitriptyline
paroxetine	paroxetine
citalopram	citalopram
haloperidol	haloperidol
resperdal	resperdal
zolpidem	zolpidem
Gastrointestinal	**Anti-histamines**
cimetidine	loratadine
ranitidine	diphenhydramine
Anti-virals	**Others**
Various	tamoxifen

*First metabolite possessing additional anti-arrhythmic activity only present in significant concentrations following oral administration due to "first pass" metabolism.

fibrillation (PAF).[1-5] Over a decade ago Jazwinski-Tarnawaka et al,[6] demonstrated that the widely varied responses to oral propafenone in patients with atrial fibrillation were closely associated with their 2D6 phenotype, and speculated that measurement of 2D6 activity before drug administration might help in selecting most-appropriate anti-arrhythmic doses. The intensity of this activity had previously been standardized by utilizing probe analysis techniques to classify individuals into 4 phenotypes; poor metabolizers (PM), intermediate metabolizers (IM), efficient metabolizers (EM) or ultra-rapid metabolizers (UM). Martinez-Selles et al[7] subsequently demonstrated more frequent adverse events (AE's) among those patients who were 2D6 deficient during treatment with propafenone or flecainide suggesting to them and others [8-9] that 2D6 genotype or phenotype analysis might assist antiarrhythmic selection and dose titration.

More recently, a potential for contributions to improved safety and effectiveness of anti-arrhythmic therapy by identification of 2D6 status has repeatedly been suggested[1,3,9,10] and Samer et al[11] have presented and endorsed the updated CYP-associated recommendations formulated by the Pharmacogenomics Working Group (PWG) of the Royal Dutch Pharmacists Association for diminished dosing of multiple medications in CYP2D6-deficient patients, including those for metoprolol, propafenone, flecainide, and carvedilol which have reproduced in Table 2.

Multiple observations support the possibility of improved safety and effectiveness for anti-arrhythmic drugs by analyzing patient 2D6 phenotypes or genotypes. These include reports of severe arrhythmias or supratherapeutic plasma levels during anti-arrhythmic use in genetically 2D6-defecient patients,[12-26] similar observations in patients of unknown 2D6 status but who developed AE's during concurrent consumption of antiarrhythmics and medications which utilize or inhibit 2D6 activity,[25-33] ineffective therapy and subtherapeutic antiarrhythmic plasma levels in patients with unusually high 2D6 activity[6,18,21,22] and a high frequency of severe AE's during "Pill-in-a-Pocket" (PIP) therapy among patients of unknown genetic and metabolic 2D6 status receiving propafenone[25,34,35] a medication which is metabolized by 2D6 while also inhibiting its activity.[36] These events are referenced in Table 3. Our investigation was untaken in order to evaluate the potential value of 2D6 genotype analysis in improving the safety and effectiveness of antiarrhythmic therapy and to report a patient whose genetic 2D6 deficiency was identified after we had reported syncope and myocardial stunning following his first combined use of quinidine and propafenone in the "Pill-in-the-Pocket" (PIP) treatment of his paroxysmal atrial fibrillation.[37]

Material and Methods

PubMed Searches of multiple related subjects including atrial fibrillation treatment and prevention, antiarrhythmics, Cytochrome P450-2D6 phenotypes and genotypes, syncope, pro-arrhythmias, Pill-in-a-Pocket therapy. Informed consent was obtained from our patient.

Genotype Analysis

The frequency of adverse events occurring in clinical practice which reflect supratherapeutic antiarrhythmic blood levels induced during 2D6 deficiency has not been established nor has that of inadequate responses to antiarrhythmic therapy resulting from subtherapeutic antiarrhythmic levels in patients with excessive 2D6 activity. These

Table 2: Therapeutic Recommendations for Selected Cardiovasular Drugs Based on CYP2D6 Genotype/Phenotype*

DRUG	2D6 Phenotype	Recommendation
METOPROLOL and PROPAFENONE	PM	Dose reduction by 70-75% or alternative drug, record ECG, monitor plasma concentration
	IM	Dose recution by 50% or alternative drug
	UM	Alternative drug or titration to a maximum of 250% of the normal metoprolol dose; insufficient data to allow propafenone dose adjustment calculation but adjust to plasma concentration, record ECG or select alternative drug
FLECAINIDE	PM	Dose reduction by 50%, record ECG, monitor plasma concentration
	IM	Dose reduction by 25%, record ECG, monitor plasma concentration
	UM	Dose reduction and monitor plasma concentration or select alternative drug (e.g. sotalol, disopyramide, quinidine, amiodarone)
CARVEDILOL	PM	No recommendation at this time
	IM	No recommendation at this time
	UM	No recommendation at this time

* Developed by The Pharmacogenetics Working Groups of The Royal Dutch Pharmacysts Association modified by Samer et al (S17)

Table 3: Antiarrhytmic Toxicities In Cyp2d6 Deficient Patients And Diminished Effectiveness In Those With Cyp2d6 Excess

Supratherapeutic Antiarrhythmic Blood Levels or Clinical Toxicity * In Genetically CYP2D6 Deficient Patients.
Flecainide (7, 10, 16)
Propafenone (6, 12-14)
Metoprolol (15, 18-23)
Supratherapeutic Antiarrhythmic Blood Levels or Clinical Toxicity* During co-administration with 2D6 Substrate or Inhibiting Drugs.
Flecainide (16, 24, 33)
Propafenone (17, 25, 26, 28, 29, 36)
Quinidine (28, 31, 36)
Carvedilol (25, 26)
Metoprolol (17, 27, 30, 32)
Subtherapeutic Antiarrhythmic Blood Levels or Active Fibrillation In UM Patients during Conventional Antiarrhythmic Dosing.
Propafenone (6)
Metoprolol (18, 21)

*Severe Arrhythmias, Syncope, or Other Cardiovascular Symptoms.

phenomena, however, may be much more frequent than have been recognized, since both are prominent during administration of antiarrhythmics to small groups of patients of known 2D6 status[6,7,10,12-33] and few patients who developed AE's during antiarrhythmic use in other settings have had their 2D6 status identified as a possible contributing factor. More widespread identification of 2D6 genotypes and phenotypes should better define these frequencies and assist in determining whether either analysis is justified to assist in selection of the safest and most effective antiarrhythmic use.

CYP2D6 activity varies widely within all populations which have been examined, with these variations related to the large variety of combinations of its more than 70 alleles,[11,38,39] which differ greatly in their functionality and sometimes in their numbers present in individual patients. The distribution of the alleles also varies widely between populations [38] creating associated differences in average 2D6 activity between them.

The 2D6 enzyme activity of individuals with identical 2D6 alleles may differ by more than 20-fold, and sometimes by as much as 1,000-fold for some allele combinations, a pattern illustrated in Figures 1 and 2. Factors contributing to this variation are not well understood, but may reflect variations in gene expression, modification of this expression by other genes, or the activity of back-up enzyme systems, resulting in some individuals manifesting ultra-rapid metabolism without apparent gene duplication. This pattern of wide variations prevents clear definition of subjects into UM, EM, and IM genotypes, in spite of nearly universal genotypic definition of PM individuals[9,11] and the definition of the apparent minority UM patients whose status results from more than two active 2D6 alleles.

In early studies, 2D6 phenotypes were identified by determining the metabolic ratio (MR) of an appropriate probe drug known to be largely metabolized by 2D6, with sparteine dextromethorphan, or debrisoquine most frequently utilized for this measurement. MR's were determined by comparing blood and urine concentrations of a probe and its first metabolite at predetermined intervals following a single dose administration, and MR's for each substrate utilized to define PM, IM, EM, and UM status. This process is expensive, time consuming for patients and technicians, and yields results which are often inconsistent between laboratories and independent observations, varying widely with the co-administration of many medications, averaging 30% lower in women and 25% lower after age 70 ,[10]with much of the variation remaining unexplained.

More recently, CYP2D6 activity has been estimated almost exclusively by genotype analysis because of its consistency, requiring only one lifetime determination, its requirement of a single laboratory visit, lower expense and more quickly available values. It consistently identifies PM individuals, and those individuals whose UM status is reflected by the presence of 3 or more active genes but does not identify individuals specifically as UM, EM, or IM.[11]

Poor metabolizers (PM) are almost exclusively characterized by 2 null alleles, each demonstrating no significant 2D6 activity, a pattern present in 5-10% of Caucasians, 2-20% of persons of African descent, 1-2% of Asians, as well as in some patients with partially defective alleles whose activity has been markedly inhibited by other factors. These pre genetics remain unmeasured in many smaller ethnic groups. Genotyping confirms PM status in over 98% of patients who are phenotypically PM.[11, 38, 39]

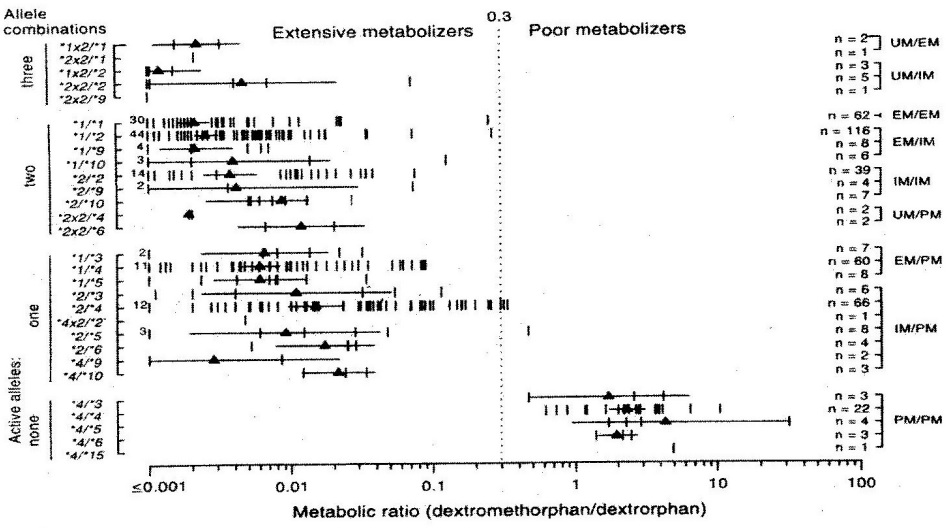

Figure 1: CYP2D6 phenotypes versus CYP2D6 allele combinations from 456 dextromethorphan-tested subjects. Horizontal lines and triangles indicate 95% confidence intervals and means of MR values (from Sachse et al) (39).

Ultra-metabolizers (UM) often manifest more than 2 active 2D6 alleles due to genetic duplications or multiple duplications of active genes but may also manifest only two unusually active alleles. The presence of this pattern in larger numbers of those tested with dextromethorphan than with debrisoquine suggests that similar differences may be likely to occur in the metabolism of other drugs in patients with identical 2D6 allele pairs. UM activity is present in 1-2% of Caucasians, 1-2% of Swedes, 6-10% of Southern Europeans, 20% of Saudi Arabians, and 29% of Ethiopians.[11]

Patients who are not clearly PM or UM, usually demonstrate 2 alleles, at least one of which is fully or partially active and are classified genotypically as EM and phenotypically as EM or IM, categories which are present in 60-85% of Caucasians.

Intermediate metabolizers (IM) have either 1 null allele or 2 partially defective alleles. IM individuals compose 10-15% of Caucasians, up to 30% of Africans and up to 50% of Asians, many of whom have 2 copies of the partially defective 10 allele, lowering their recommended and appropriate doses of 2D6-metabolized medications. Relationships between 2D6 phenotypes and genotypes are illustrated by the pioneering studies of Sache et al[39] illustrated in Figures 1 and 2, which were extended and confirmed by McElroy et al.[9]

Sache et al[39] determined the 2D6 genotypes of 589 unrelated German volunteers, ages 19 through 91, and compared them with their phenotypes determined using a dextromethorphan probe in 456 (Figure 1) and debrisoquine probe in 133 (Figure 2). In the 42 phenotype PM subjects as well as in these combined groups, 41 had two null (inactive) alleles, and the other only one inactive allele, with this subject not available for confirmation of either his phenotype or genotype. Their observations demonstrate almost complete confirmation of phenotype PM subjects by genotyping. McElroy et al[9] subsequently added data from 220 additional subjects who had undergone dextromethorphan phenotyping to 336 of those studied by Saches et al, and similarly reported over 98% confirmation of PM phenotypes by a genotype analysis.

Propafenone

Propafenone, a class IC antiarrhythmic is both a substrate for and strong inhibitor of 2D6 activity, contributing to drug-drug interactions with carvedilol,[26] metoprolol,[17] and quinidine[28,29] as well as with many non-cardiac drugs. These interactions as well as its negative inotropic effect limit its use in patients with significant heart disease, and may have contributed to its participation in almost all the serious arrhythmias developing in outpatients receiving PIP therapy,[25, 34, 35] nincluding that of the patient we report.

Multiple prospective studies suggest that the determination of 2D6 status might be helpful in selecting appropriate initial doses of propafenone for minimizing any side effects during attempted conversion of PAF and for assisting in subsequent maintenance of normal sinus rhythm.

Jazwinski-Tarnawaka et al[6] administered propafenone to 42 patients with PAF, altering drug doses based upon their blood levels, clinical responses and development of adverse effects. Initial successful control of PAF was demonstrated in 100% of 11 PM patients, 61% of 26 EM patients, and none of the 5 UM patients, with serum propafenone concentrations averaging 2-3 times higher in PM than EM patients, in spite of daily doses averaging half those in EM's.

Studies by Alboni et al[34] are compatible with 2D6 activity contributing to the inappropriate selection of patients for oral propafenone use in PIP therapy of PAF by a trial of intravenous drugs. They selected 136 patients for propafenone PIP therapy, and 74 for similar flecainide therapy after eliminating 58 of 268 potential PIP patients during hospital-monitored trial which included ingestion of one of these drugs.[34] Oral outpatient treatment with a weight-related dose of propafenone (450-600mg) successfully converted 94% of 315 episodes of PAF without significant side effects. In a subsequent outpatient[35] study following successful supervised cardioversion by their trial with intravenous propafenone, near syncope or bradyarrhythmias developed after 4 of the initial 59 initial oral doses of propafenone, resulting in termination of this second study. None of these 4 patients with bradyarrhythmias were consuming beta-blockers, and neither their genotype nor phenotype CYP status was known, but their observations would be compatible with an increased risk of bradycardia due to higher propafenone concentrations characteristic of PM patients.

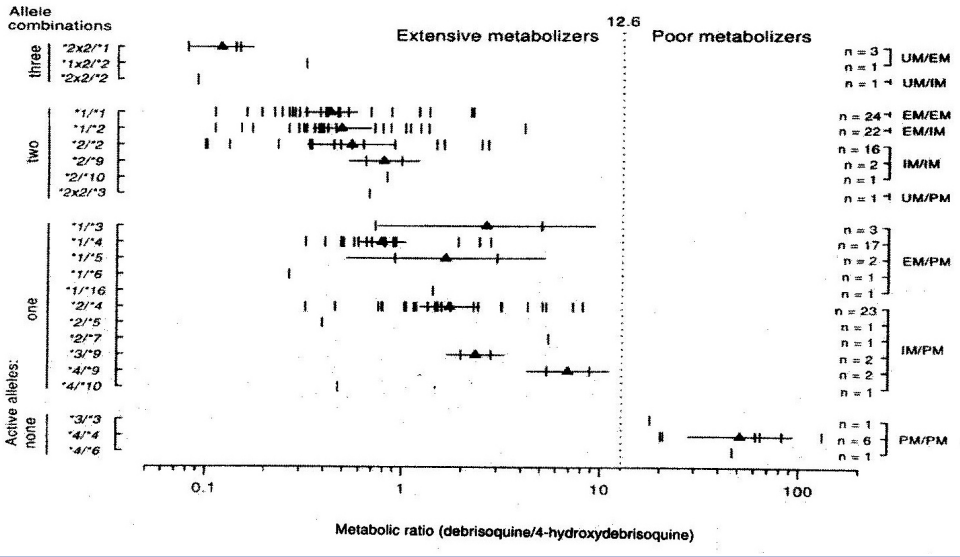

Figure 2: **CYP2D6 phenotypes versus CYP2D6 allele combinations from 133 debrisoquine-tested subjects. Horizontal lines and triangles indicate 95% confidence intervals and means of MR values (from Sachse et al) (39).**

The absence of similar arrhythmias following supervised successful conversion by the trial of intravenous propafenone suggests that the arrhythmias following its oral therapy may be related to either the increased concentration of its first metabolite 5-hydroxy propafenone induced during the "first pass" hepatic metabolism which follows oral administration and is therefore present in much lower concentrations following intravenous administration,[36] or to much higher plasma propafenone levels characteristic of PM patients in any who are 2D6 deficient.

Siddoway et al[14] compared propafenone metabolism in 6 PM and 22 EM patients, with PM subjects demonstrating drug half-lives 3 times longer (P<.01), plasma levels 2.3 times higher (P<.001), and central nervous system adverse events 4.8 times more frequently. Moike et al[13] reported syncope and toxic propafenone blood levels in an elderly PM woman receiving 450mg daily. They then undertook a protocol-driven study in 160 patients evaluating relationships between propafenone use and CYP2D6 status in the prevention of atrial fibrillation during the week following cardiac surgery [12] 37 of those receiving propafenone and 45 receiving placebo completed their study. Propafenone levels were strongly related to 2D6 genotypes with plasma levels in 4 PM, 4 IM, 26 EM, and 3 UM subjects of 1200ng/mL, 600ng/mL, 25ng/mL and 15ng/mL after receiving 150mg of propafenone every 8 hours for 5 post-surgical days. 21% of 37 (57%) patients were, however, also receiving beta-blockers in unreported doses, and the independent contributions by beta-blockers and propafenone to propafenone blood levels, arrhythmias and other AE were not analyzed. Although propafenone use was associated with diminished frequency of post-operative atrial tachycardias in this setting, the frequency of bradycardia and other drug-related complications was double that in subjects receiving placebo therapy, and patients with 2D6 deficient alleles more often required drug discontinuation because of arrhythmias or other adverse events than in patients receiving placebo.

High levels of propafenone during conventional propafenone dosing may be greatly augmented by the concurrent administration of quinidine which independently inhibits 2D6 activity, as well as by PM status.[29] O'Hara et al[28] randomized 102 patients receiving 400mg of propafenone daily to receive either 200 mg of quinidine daily or a placebo. Tripling of plasma propafenone concentrations and lowering the levels of 5-hydroxypropafenone during co-administration of the drugs, without increasing evidence of adverse events[28] and with better control of PAF over the following year closely related to the higher propafenone blood levels. In a small independent study in healthy volunteers, administration of quinidine 150mg daily to 7 EM subjects [29] receiving propafenone 150mg 3 times daily doubled propafenone levels while not altering those levels in 2 PM subjects.[29] These observations suggest that raising propafenone levels while inhibiting formation of 5- hydroxypropafenone by increasing 2D6 inhibition during co-administration of another 2D6 inhibitor might aid PAF control without any potential increase in risks which might be associated with greater 5-hydroxypropafenone levels.

Flecainide

Flecainide, a class 1C anti-arrhythmic both requires 2D6 for its metabolism and weakly inhibits 2D6 activity. Its use is limited in patients with heart disease by its negative inotropic effects and by its production of potentially fatal pro-arrhythmias including Torsade-de-Pointes,.[2,38] It has been associated with many drug-drug interactions when administered with medications which also independently inhibit 2D6 metabolism including quinidine,[24]and paroxetine.[16] Oral flecainide clearance was lower in IM than EM subjects among 50 Japanese patients with supraventricular tachycardias (P<.05)[10] as well as 24% lower in women and 30% lower in subjects over age 70, patterns compatible with the lower 2D6 activity in these two groups. Flecainide concentrations were increased by 13.8% in 5 EM volunteers (P<.05) by co-administration of quinidine 50mg 4 times daily, while levels in 2PM subjects remain unchanged during quinidine use.[24] Diminished initial flecainide dosing is recommending in PM patients by the PWG (Table 2).

Flecainide concentrations are increased by an average of 60% soon after the addition of amiodarone therapy,[34] a 2D6 inhibitor, resulting in a recommended decrease in flecainide doses by up to 50% with the onset of amiodarone therapy in order to maintain therapeutic flecainide blood levels.

Quinidine

Quinidine is a powerful inhibitor of 2D6 activity[19] but is mainly metabolized by CYP3A4 rather than 2D6. Currently it is not routinely recommended for chronic arrhythmia control because of its gastrointestinal side effects and multiple reports of associated pro-arrhythmias, a 1-3% frequency of Torsade-de-Pointes and increased rates of mortality.[39,40] These AE's developed, however, during utilizing of quinidine sulfate in daily doses of 800-1600mg, or its equivalent, and increasingly frequent recent studies which often utilize lower doses of quinidine have often not confirmed an increased frequency of either pro-arrhythmias or mortality,[41-50]and several studies have demonstrated a safety and effectiveness similar to that of other antiarrhythmics in the conversion and control of PAF[44, 45,46]with or without concurrent use of verapamil.[42,47] These have resulted in recommendations for its subsequent use by some.[49,50] We are unaware of reports of the PIP use of quinidine other than that in the patient we report.

Quinidine has also been utilized as a technique for changing genotype EM patients into phenotype PM status[51,52] in order to increase plasma concentrations of other antiarrhythmic drugs metabolized by CYP2D6, while decreasing the concentrations of their metabolites thereby enhancing the antiarrhythmic influence of the primary drug while diminishing any side effects of its metabolites, and possibly adding some additional antiarrhythmic benefit from low-dose quinidine.[28,29] Brinn et al[52] measured 2D6 phenotypes in 8 Caucasian patients ages 33-84 before and after one week of receiving quinidine sulfate 600-800mg daily for one week. Each was EM before quinidine, but became PM during quinidine therapy with MR values increasing an average of over 90-fold and MR values barely detectable (>25) in 5. Prolonged studies evaluating the effectiveness and safety of antiarrhythmic combinations in patients of defined 2D6 genotypes have not been undertaken even though low dose quinidine has been demonstrated in very small series to double[29]or triple [28] blood levels of propafenone and to increase those of flecainide.[24]

In 19 patients with PAF not responsive to propafenone 300-450mg daily, Lau et al[50] in a double-blind cross-over study increased serum propafenone concentrations by 30% by adding 150mg of quinidine daily, a change which controlled PAF in 7 (37%), without inducing more frequent gastrointestinal side effects. They subsequently maintained normal sinus rhythm in 7 of their 10 persistently refractory patients by increasing quinidine to 600mg daily while

maintaining the lower dose of propafenone without inducing apparent side effects, supporting a role for stepwise anti-arrhythmic treatment of PAF.

The onset of amiodarone therapy at 1200mg daily increases quinidine levels by an average of 33% within a few days,[31]suggesting that a decrease in quinidine dosages by 33-50% as well as monitoring of quinidine levels would be appropriate in order to diminish the risks of quinidine side effects. Whether the elevated quinidine levels following the addition of amiodarone are related to 2D6 genotype has apparently not been examined.

Amiodarone

Amiodarone is largely metabolized by CYP3A4 but moderately inhibits CYP2D6 activity,[53] modifying the concentrations of multiple co-administered drugs within a few days, including increasing the average blood levels of flecainide by 60%[34] and of quinidine by 33%,[31] changes which may be accompanied by an increased risk of adverse events unless the daily doses of these co-administered drugs are decreased by 20-50% as recommended.[31, 34]

Carvedilol

Neither of the two isomers of Carvedilol inhibits 2D6 activity, and only R-carvedilol is largely metabolized by 2D6. Severe bradyarrhythmias are less frequent in patients utilizing carvedilol than those consuming metoprolol,[54] but carvedilol likely contributed to an arrhythmia resulting in syncope in a carvedilol consumer of unknown 2D6 status 3 hours after her ingestion of a single oral 600mg PIP dose of propafenone, which had proven to be safe during multiple previous PIP ingestions,[25] her symptoms being similar to those demonstrated in the patient we report.

Commenting on this report, Boriani et al[26] recognized the possible presence of a propafenone-induced 2D6 deficiency contributing to her syncope and advised against the concurrent use of propafenone and carvedilol during PIP therapy. Adverse events in other carvedilol consumers potentially related to differences in 2D6 activity have apparently not been reported, and modification of carvedilol use based upon 2D6 genotype/phenotype differences are not currently recommended (Table 2).

Metoprolol

Metoprolol is almost exclusively metabolized by 2D6, and, like carvedilol and other beta-adrenergic blockers, does not inhibit 2D6 activity and has only limited direct antiarrhythmic activity.[55] It is frequently used, however, in conjunction with antiarrhythmic drugs for control of hypertension, angina, or tachycardia. Its blood levels, clinical effectiveness and side effects are each greatly modified by differences in 2D6 activity,[18, 20, 23, 27] with multiple adverse events described during its use in patients with PM patients,[19,22] or when co-administered with drugs which inhibit 2D6 activity including propafenone,[17] propoxyphene,[32,56] paroxetine,[27,30] or diltiazem[15] or to patients whose 2D6 activity is unknown. It is also frequently ineffective due to sub-therapeutic blood levels when administered to UM patients.[18, 22]

Plasma levels of both metoprolol and its first metabolite, alpha-hydroxy metoprolol, in 91 chronic metoprolol consumers of varied 2D6 genotypes, varied more than 100-fold 4 hours post-dose,[23] and increased 2-5 fold during inhibition of 2D6 activity induced by propafenone.[17] Metoprolol clearance was over 20 times greater in UM than PM healthy volunteers resulting in maximum plasma concentrations after a single 100mg oral dose 25% lower and exercise-induced heart rates 42% higher.[18] Among 24 patients with adverse events during metoprolol therapy, the frequency of PM status was 5 times greater than in a control population,[20] and heart rates averaged slower among with an increased risk of bradycardia (OR-3.86) among the PM patients in a group of 1,533 beta-blocker consumers .[19]

Fux et al[21] compared the CYP2D6 genotypes with plasma metoprolol levels in 121 patients 6 weeks after beginning treatment with doses adjusted on clinical grounds. Average plasma levels in 5 UM, (4.1%) 91 EM (75%), 21 IM (17%), and 4PM (3.3%), were .0088 ng/ml, .047 ng/ml, 0.34 ng/ml, and 1.34 ng/ml, respectively, a 152 times greater level in the 4 PM than the 5 UM patients, and cold extremities were more frequent in PM plus IM subjects than EM plus UM patients (16.0% vs 4.2%) (P=.05).

The intensity of the 2D6 inhibition of metoprolol metabolism induced by paroxetine was illustrated by Goryachkina et al[27] who administered 20mg of paroxetine daily for one week to 17 depressed genotypically EM patients who were receiving metoprolol as routine post-myocardial infarction therapy. One week after beginning paroxetine, metoprolol AUC had increased by more than 4 fold (P=.0001), metabolite AUC had decreased by 76% (P<.0001), metabolic ratios had increased from 0.9 to 26 (P<.0001), and average heart rates decreased by 13%, while bradycardia and hypotension had required a reduction in metoprolol doses in two patients. The PWC recommended that metoprolol therapy be instituted at a 50% lower dose in PM patients.

Discussion

An estimate of 2D6 activity as an aid in selecting the safest and the most effective antiarrhythmic therapy is best based up determination of each patient's 2D6 genotype by blood analysis, coupled with any modification resulting from considerations of age, sex and any influence of 2D6 activity by co-administered and potentially administered medications. Similar analysis could also be used in the dose selections of medications other than antiarrhythmics which are metabolized by 2D6 including several opioids,[32,56,57] many antidepressant and psychotropic drugs.

Less clearly justified on clinical grounds are 2D6 analyses in patients who have had an inadequate clinical response to antiarrhythmics in a setting of subtherapeutic drug blood levels during ingestion of conventional doses of 2D6-metabolized medications, in an effort to determine whether UM status presented a similar potential benefit. The uncertainties associated either of these interventions suggest that changing therapy to the use of alternate medications less intensively metabolized by 2D6 would likely be preferred.

Conclusions:

Our observations strongly support the use of 2D6 genotype analysis in a variety of clinical settings including the identification of PM patients, for whom lower initial doses of metoprolol, propafenone and flecainide are appropriate, reinforcing the recommendations of the PWG. These observations also suggest that similar precautions before antiarrhythmic use may be appropriate in patients consuming antidepressants, psychotropics or opioid drugs known to strongly inhibit 2D6 activity, as well as in patients chronically consuming antiarrhythmic drugs when a 2D6-inhiting medication is to begin.

Similarly, unusual caution should accompany the concurrent

administration of drugs such as metoprolol and propafenone, one or both of which are both metabolized by 2D6 and also inhibit its actions, caution which should be enhanced for patients whose genetic 2D6 activity is impaired.

Our observations also support identification of 2D6 status in patients being considered for PIP therapy. Flecainide may be a potentially safer PIP choice than propafenone for patients who are 2D6 PM, with identification of PM genotypes also potentially increasing the numbers of patients for whom PIP therapy may be appropriate, and identification of UM genotypes possibly identifying a few patients for whom larger than conventional doses of either flecainide or propafenone would be appropriate following their uses in inducing successful conversion without the development of supratherapeutic blood levels.

The measure of 2D6 genotypes in patients who develop or have developed adverse events during PIP propafenone or during the use of metoprolol or other medications strongly metabolized by 2D6 would help to define the frequency of these adverse events associated with PM status, and also aid in the subsequent clinical management of related patients.

Identification of 2D6 status together with measurement of plasma antiarrhythmic levels may be helpful in patients in whom conventional doses of antiarrhythmics have been ineffective in order to aid in determining whether an increased dose of administered antiarrhythmic, or change to an antiarrhythmic less actively metabolized by 2D6, would be more appropriate, as well as being useful in the selection of other medications metabolized by 2D6 in other clinical settings for these patients.

Potential benefit from the addition of medications which inhibit 2D6 activity including SSRI's or quinidine in order to enhance the effectiveness of antiarrhythmic medications in UM patients, may also be worthy of investigation.

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