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(54) **USE OF CYP2D6 INHIBITORS IN COMBINATION THERAPIES**

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(57) **ABSTRACT**

This invention relates to the use of a CYP2D6 inhibitor in combination with a drug having CYP2D6 catalyzed metabolism, wherein the drug and the CYP2D6 inhibitor are not the same compound; and pharmaceutical compositions for said use.

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USE OF CYP2D6 INHIBITORS IN COMBINATION THERAPIES

BACKGROUND

[0001] This invention relates to the use of a CYP2D6 inhibitor in combination with a drug having CYP2D6 catalyzed metabolism in order to improve the drug's pharmacokinetic profile.

[0002] The clearance of drugs in humans can occur by several mechanisms, such as metabolism, excretion in urine, excretion in bile, etc. Despite the many types of clearance mechanisms, a large proportion of drugs are eliminated in humans via hepatic metabolism. Hepatic metabolism can consist of oxidative (e.g., hydroxylation, heteroatom dealkylation) and conjugative (e.g., glucuronidation, acetylation) reactions. Again, despite the many possibilities of types of metabolic reactions, a preponderance of drugs are metabolized via oxidative pathways. Thus, the primary route of clearance of a vast majority of drugs is oxidative hepatic metabolism.

[0003] Of the enzymes involved in the oxidative metabolism of drugs, the cytochrome P-450 (CYP) superfamily of enzymes are major contributors. CYP constitutes a class of over 200 enzymes that are able to catalyze a variety of types of oxidative reactions (via a hypothesized common reaction mechanism) on a wide range of xenobiotic substrate structures. In humans, the CYP catalyzed metabolism of most drugs is carried out by one of five isoforms: CYP1A2, CYP2C19, CYP2C9, CYP2D6, and CYP3A4, with the latter three being the most important of these enzymes.

[0004] Of all of the known human CYP isoforms, the most highly developed knowledge base of substrate specificity is for CYP2D6. This isoform is almost exclusively involved in the oxidative metabolism of lipophilic amine drugs. Well known CYP2D6 substrates include neuroleptics, type 1C antiarrhythmics, β -blockers, antidepressants (tricyclic antidepressants, selective serotonin reuptake inhibitors and monoamine oxidase inhibitors), and others such as codeine and dextromethorphan. This apparent specificity for amines as substrates is hypothesized to arise from the presence of an acidic amino acid residue in the substrate binding site. This residue can form an ionic interaction with amine substrates while positioning sites for oxidation in propinquity to the reactive iron center of the heme of CYP. Structure activity relationships for CYP2D6 and the metabolism of amines have led to the development of a predictive model for this enzyme which states that the position of oxidation of a CYP2D6 substrate is 5 to 7 Å from the basic amine nitrogen. Some additional steric requirements are also hypothesized.

[0005] Many compounds for which the major clearance mechanism in humans is CYP2D6 mediated oxidative biotransformation commonly exhibit one or more detrimental characteristics with regard to human pharmacokinetics. These characteristics are: (1) wide disparity in exposure between individuals possessing and lacking a copy of the CYP2D6 gene ("extensive and poor metabolizers"); (2) high inter-individual variability in exposure among extensive metabolizers; (3) propensity for supraproportional dose-exposure relationships; (4) frequent drug-drug interactions; and (5) short half-lives and poor oral bioavailability due to extensive first-pass hepatic clearance.

[0006] While not all CYP2D6 substrates possess these characteristics, most CYP2D6 substrates are subject to one or more.

[0007] In the mid-1980s observations were made concerning the disparity in exposure to drugs in a small subset of the population. In some cases, the high exposures observed in the minority of individuals were also associated with adverse reactions. These observations led to the discovery of the CYP2D6 genetic polymorphism. The CYP2D6 gene is absent in 5-10% of the Caucasian population (referred to as poor metabolizers or PM's). Such individuals can be distinguished from the rest of the population (extensive metabolizers or EM's) by an examination of genotype through restriction fragment length polymorphism analysis or through determination of phenotype by measurement of the urinary dextrophan/dextromethorphan ratio after administration of the latter compound. When population histograms of exposure to prototypical CYP2D6-cleared compounds are constructed, a bimodal distribution is observed. For example, the mean terminal phase half-life of propafenone, a well known CYP2D6 cleared compound, is 5.5 hours in extensive metabolizers, but is 17.2 hours in poor metabolizers. EM-PM differences are typically exacerbated upon oral administration of CYP2D6 cleared compounds due to wide disparities in first-pass extraction. Propafenone exposure after oral administration is 4.2-fold greater in PM's vs. EM's. Thus, CYP2D6 cleared compounds can be subject to increased incidences of adverse effects, due to elevated systemic exposures observed in PM's.

[0008] Regardless of the genetic polymorphism, a high degree of interindividual variability exists in the exposure to CYP2D6 cleared compounds among those individuals considered to be extensive metabolizers. While a reason for this variability is not presently known, it does not appear to be due to an increase in CYP2D6 gene copy number (although one such genotype has been reported in the literature in Sweden), nor does it appear to be due to environmental factors as this CYP isoform has never been demonstrated to be inducible. An example of this variability phenomenon is demonstrated by the exposure to the antidepressant agent imipramine and its metabolite desipramine, which demonstrates a 20-fold range of steady state plasma concentrations after oral administration. For compounds with wide therapeutic indices, this variability may not be problematic. However, if the therapeutic index for a CYP2D6 cleared compound approaches 10, increased incidences of adverse effects are likely to be observed.

[0009] Metabolic clearance is a potentially saturable process. The intrinsic clearance (Cl'_{int} , the ability of an organ to clear a compound without constraints imposed by organ blood flow or plasma protein binding) is a function of Michaelis-Menten parameters:

$$\frac{1}{\text{oral exposure}} \propto Cl'_{int} = \frac{V_{max}}{K_M + [S]}$$

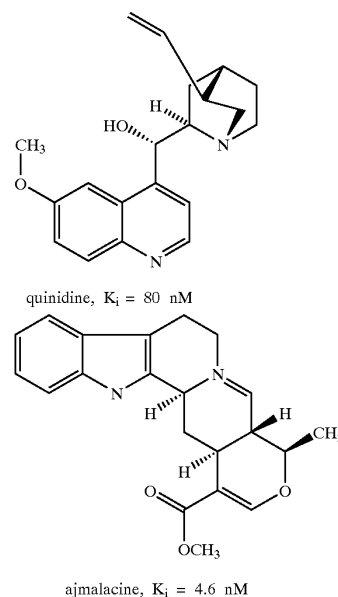
[0010] where both V_{max} and K_M are fixed constants and $[S]$ represents the concentration of the drug in the clearing organ. For most drugs, concentrations of drug typically attained in vivo are well below the K_M and thus the denominator of the above expression degenerates to a constant

value of K_M . However, for many CYP2D6 catalyzed reactions, K_M values are typically low. This is hypothesized to be due to the strong (relative to other CYP enzymes) ionic bond formation between cationic amine substrates and an anionic amino acid in the substrate binding site of CYP2D6. Thus for compounds cleared by CYP2D6, drug concentrations can approach and exceed K_M values resulting in intrinsic clearance values that decrease with increasing drug concentration. Since drug concentration is related to dose, clearance is observed to decrease with increasing dose. With decreases in clearance with increases in dose, exposure is thus observed to increase in a supraproportional manner with increasing dose. Such a relationship has been described in the scientific literature for the CYP2D6 cleared compounds propafenone and paroxetine. Interestingly, this phenomenon is not observed in poor metabolizers, since the CYP2D6 isoform is not present in these individuals.

[0011] The parameter K_M is a complex function of enzymatic rate constants that, for CYP, has a strong component of substrate binding rate constants. The potential exists that competitive inhibition of the metabolism of one drug can occur via catalytically competent substrate binding of a second drug. Since the K_M for CYP enzymes are closely related to binding constants, they approximate K_i values in many cases. For CYP2D6, low K_M values for typical substrates can also result in low K_i values for these same substrates as competitive inhibitors. Low K_i values reflect a greater potential to result in drug-drug interactions, since lower concentrations and doses of drug are adequate to exhibit inhibition. Thus, the potential for drug-drug interactions is a more likely concern with CYP2D6 substrates than other CYP substrates, due to the greater binding affinities of the former. Thus, since K_i values typically track K_M values, the potential for drug-drug interactions usually go hand-in-hand with the potential for supraproportional dose-exposure relationships.

[0012] As mentioned above, clearance is related to the term V_{max}/K_M . For compounds with similar V_{max} values, the lower the value for K_M , the higher the clearance. Since many CYP2D6 substrates have very low K_M values, these compounds, as a class, are more likely to exhibit high hepatic clearance in vivo. High hepatic clearance results in shorter half-lives. It also results in greater first-pass hepatic extraction which can result in low oral bioavailabilities. This point is represented by the compounds (7S,9S)-2-(2-pyrimidyl)-7-(succinamidomethyl)-prehydro-1H-pyrido-[1,2-a]pyrazine ("sunipetron") (K_M of about 1 μ M, human half-life of about 1 hour), (2S,3S)-2-phenyl-3-(2-methoxyphenyl)-methylaminopiperidine (K_M of about 1 μ M, human half-life of about 4.7 hours), (1S,2S)-1-(4-hydroxyphenyl)-2-(4-hydroxy-4-phenylpiperidin-1-yl)-1-propanol (K_M of about 3-4 μ M, human half-life of about 3-4 hours), and (2S,3S)-2-phenyl-3-(2-methoxy-5-trifluoromethoxyphenyl)-methylamino-piperidine (K_M of about: 1 μ M, human half-life of about 8 hours), all of which are CYP2D6 substrates. The former two compounds have K_M values in the 1 μ M range. The human half-lives for these two compounds are 1.1 and 4.7 hours, and human oral bioavailability values for these two compounds are 4.6 and 1.0%, respectively. The clearance values for the former two compounds, measured after intravenous administration to humans, are in the range of blood-flow limiting values, suggesting that hepatic extraction exceeds 90%.

[0013] There are several compounds known to inhibit CYP2D6 reactions, either by 'pure' inhibition or by acting as competitive substrates. Unlike many other CYP enzymes, there are some potent inhibitors known for CYP2D6. Again, it is believed that the ionic interaction between the cationic amine group of the inhibitor and the anionic amino acid residue of CYP2D6 is at least partially responsible for the potency of CYP2D6 inhibitors. Two examples of potent CYP2D6 inhibitors are quinidine and ajmalacine:



[0014] Quinidine represents a commonly utilized antiarrhythmic agent whereas ajmalacine is a less well-known natural product with vasodilation activity. Since quinidine is a commonly administered substance, drug interaction studies have been conducted in vivo for this drug and CYP2D6 cleared compounds. Quinidine has the effect of converting an extensive metabolizer to the poor metabolizer phenotype via inhibition of CYP2D6.

[0015] In addition, extracts of St. John's wort have recently been found to contain constituent substances that exhibit CYP inhibitory activity, including inhibition of CYP2D6. Examples of constituent substances of St. John's extract that exhibit CYP inhibitory activity are hyperforin, 13, 118-biapigenin, hypericin, and quercetin. Other unidentified components also exhibit CYP inhibitory activity.

[0016] For CYP2D6 cleared compounds, the problem that is frequently focused on is the disparity in the exposures between extensive and poor metabolizers and the high variability demonstrated by the extensive metabolizers. However, what is commonly overlooked is the fact that these compounds typically have very satisfactory pharmacokinetics in the poor metabolizers. In subjects lacking the CYP2D6 enzyme, CYP2D6 cleared compounds: (1) typically have long $t_{1/2}$ values and high oral bioavailability and (2) do not exhibit supraproportional dose-exposure relationships. By lacking the CYP2D6 enzyme, the variability of drug expo-

tures in poor metabolizers is no greater than variabilities exhibited by non-CYP2D6 cleared compounds. Although attempts have been made to link poor metabolizer status with proclivity to various pathological states, a definitive cause-effect relationship has yet to be established. Thus, since poor metabolizers represent a normal and healthy segment of the population, it is not anticipated that converting extensive metabolizers to poor metabolizers via administration of a specific CYP2D6 inhibitor would result in any untoward effects related to inhibition of this enzyme.

[0017] This invention relates to the coformulation or combined use of a CYP2D6 inhibitor and a CYP2D6 cleared compound. Thus, instead of avoiding a drug-drug interaction, this invention involves developing such an interaction intentionally in order to improve the pharmacokinetics of therapeutically useful, but pharmacokinetically flawed compounds. Such an approach is analogous to the utilization of sustained-release formulations to enhance the pharmacokinetics of drugs. However, instead of modulating drug elimination via input rate limitation, this approach seeks to do the same by modulating the elimination rate directly. Furthermore, in addition to lengthening half-life, a CYP2D6 inhibitor would enhance oral exposure due to a suppression of hepatic first-pass extraction.

SUMMARY OF THE INVENTION

[0018] This invention relates to a method of administering a drug for which the major clearance mechanism in humans is CYP2D6 mediated oxidative biotransformation (also referred to throughout this document as a "Therapeutic Drug"), or a pharmaceutically acceptable salt thereof, in combination with a CYP2D6 inhibitor, or a pharmaceutically acceptable salt thereof, to a human in need of the intended pharmaceutical activity of such drug, wherein the Therapeutic Drug and the CYP2D6 inhibitor are not the same compound. The above method is hereinafter referred to as the "Combination Method".

[0019] This invention also relates to the Combination Method, wherein the drug for which the major clearance mechanism in humans is CYP2D6 mediated oxidative biotransformation is a selective serotonin reuptake inhibitor containing a primary, secondary or tertiary alkylamine moiety (e.g., sertraline or fluoxetine).

[0020] This invention also relates to the Combination Method, wherein the drug for which the major clearance mechanism in humans is CYP2D6 mediated oxidative biotransformation is an NMDA (N-methyl-D-aspartate) receptor antagonist containing a primary, secondary or tertiary alkylamine moiety.

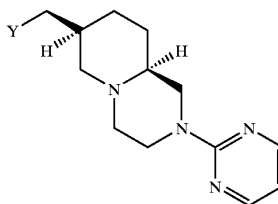
[0021] This invention also relates to the Combination Method, wherein the drug for which the major clearance mechanism in humans is CYP2D6 mediated oxidative biotransformation is a neurokinin-1 (NK-1) receptor antagonist containing a primary, secondary or tertiary alkylamine moiety.

[0022] This invention also relates to the Combination Method, wherein the drug for which the major clearance mechanism in humans is CYP2D6 mediated oxidative biotransformation is a tricyclic antidepressant containing a primary, secondary or tertiary alkylamine moiety (e.g., desipramine, imipramine or clomipramine).

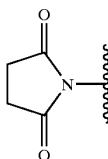
[0023] A preferred embodiment of this invention relates to the Combination Method, wherein the drug for which the major clearance mechanism in humans is CYP2D6 mediated oxidative biotransformation, is (2S,3S)-2-phenyl-3-(2-methoxy-5-trifluoromethoxyphenyl)methylamino-piperidine or a pharmaceutically acceptable salt thereof.

[0024] A preferred embodiment of this invention relates to the Combination Method, wherein the drug for which the major clearance mechanism in humans is CYP2D6 mediated oxidative biotransformation, is sunipetron or a pharmaceutically acceptable salt thereof.

[0025] Sunipetron has the following structure



[0026] wherein Y is a group of the formula



[0027] Another preferred embodiment of this invention relates to the Combination Method, wherein the drug for which the major clearance mechanism in humans is CYP2D6 mediated oxidative biotransformation is (1S,2S)-1-(4-hydroxyphenyl)-2-(4-hydroxy-4-phenylpiperidin-1-yl)-1-propanol or a pharmaceutically acceptable salt thereof.

[0028] Examples of other drugs for which the major clearance mechanism in humans is CYP2D6 mediated oxidative biotransformation are the following: mequitazine (*J. Pharmacol. Exp. Ther.*, 284, 437442 (1998)); tamsulosin (*Xenobiotica*, 28, 909-22 (1998)); oxybutynin (*Pharmacogen.*, 8, 449-51 (1998)); ritonavir (*Clin. PK*, 35, 275-291 (1998)); iloperidone (*J. Pharmacol. Exp. Ther.*, 286, 1285-93 (1998)); ibogaine (*Drug Metab. Dispos.*, 26, 764-8 (1998)); delavirdine (*Drug Metab. Dispos.*, 26, 631-9 (1998)); tolteridone (*Clin. Pharmacol. Ther.*, 63, 529-39 (1998)); promethazine (*Rinshoyakon*, 29, 231-38 (1998)); pimozone, *J. Pharmacol. Exp. Ther.*, 285, 428-37 (1998)); epinastine (*Res. Comm. Md. Path. Pharmacol.*, 98, 273-92 (1997)); tramadol (*Eur. J. Clin. Pharm.*, 53, 235-239 (1997)); procainamide (*Pharmacogenetics*, 7, 381-90 (1997)); methamphetamine (*Drug Metab. Dispos.*, 25, 1059-64 (1997)); tamoxifen (*Cancer Res.*, 57, 3402-06 (1997)); nicergoline (*Br. J. Pharm.*, 42, 707-11 (1996)); and fluoxetine (*Clin. Pharmacol. Ther.*, 60, 512-21 (1996)). All of the foregoing references are incorporated herein by references in their entireties.

[0029] Examples of other drugs for which the major clearance mechanism in humans is CYP2D6 mediated oxidative biotransformation, all of which are referred to, along with their respective pathways of CYP2D6 mediated oxidative biotransformation (e.g., O-demethylation, hydroxylation, etc.), by M. F. Fromm et al. in *Advanced Drug Delivery Reviews*, 27, 171-199 (1997), are the following: alprenolol, amiflamine, amitriptyline, aprindine, brofaromine, butorolol, cinnarizine, clomipramine, codeine, debrisoquine, desipramine, desmethylcitalopram, dexfenfluramine, dextromethorphan, dihydrocodine, dolasetron, encainide, ethylmorphine, flecainide, flunarizine, fluvoxamine, guanoxan, haloperidol, hydrocodone, indoramin, imipramine, maprotiline, methoxyamphetamine, methoxyphenamine, methylenedioxyamphetamine, metoprolol, mexiletine, mianserin, minaprine, procodine, nortriptyline, N-propylajmaline, ondansetron, oxycodone, paroxetine, perhexiline, perphenazine, phenformine, promethazine, propafenone, propranolol, risperidone, sparteine, thioridazine, timolol, tomoxtine, tropisetron, venlafaxine and zuclopenthixol.

[0030] Other preferred embodiments of this invention relate to the Combination Method wherein the CYP2D6 inhibitor, or pharmaceutically acceptable salt thereof, that is employed in such method is quinidine or ajmalicine or a pharmaceutically acceptable salt of one of these compounds.

[0031] Other embodiments of this invention relate to the Combination Method, wherein the CYP2D6 inhibitor, or pharmaceutically acceptable salt thereof, that is employed in such method, is selected from the following compounds and their pharmaceutically acceptable salts: sertraline (*J. Clin. Psychopharm.* 18, 55-61 (1998)); venlafaxine (*Br. J. Pharm.*, 43, 619-26 (1997)); dexmedetomidine (*DMD*, 25, 651-55 (1997)); tripenelamine, premethazine, hydroxyzine, (*Drug Metab. Dispos.*, 26, 531-39 (1998)); halofrinane and chloroquine, (*Br. J. Clin. Pharm.*, 45, 315-(1998)); and moclobemide (*Psychopharm.*, 135, 22-26 (1998)).

[0032] A further embodiment of this invention relates to the Combination Method wherein the CYP2D6 inhibitor that is employed in such method is St. John's wort or an extract or constituent thereof.

[0033] This invention also relates to a pharmaceutical composition comprising:

[0034] (a) a therapeutically effective amount of a drug for which the major clearance mechanism in humans is CYP2D6 mediated oxidative biotransformation (also referred to throughout this document as a "Therapeutic Drug"), or a pharmaceutically acceptable salt thereof;

[0035] (b) an amount of a CYP2D6 inhibitor, or a pharmaceutically acceptable salt thereof, that is effective in treating the disorder or condition for which the Therapeutic Drug referred to in (a) is intended to treat; and

[0036] (c) a pharmaceutically acceptable carrier;

[0037] wherein said drug and said CYP2D6 inhibitor are not the same compound.

[0038] The above pharmaceutical composition is hereinafter referred to as the "Combination Pharmaceutical Composition".

[0039] Preferred embodiments of this invention relate to Combination Pharmaceutical Compositions wherein the drug for which the major clearance mechanism in humans is CYP2D6 mediated oxidative biotransformation, or pharmaceutically acceptable salt thereof, that is contained in such pharmaceutical composition is (2S,3S)-2-phenyl-3-(2-methoxy-5-trifluoromethoxyphenyl)methylaminopiperidine or a pharmaceutically acceptable salt thereof.

[0040] Other preferred embodiments of this invention relate to Combination Pharmaceutical Compositions wherein the drug for which the major clearance mechanism in humans is CYP2D6 mediated oxidative biotransformation, or pharmaceutically acceptable salt thereof, that is contained in such pharmaceutical composition is (1S,2S)-1-(4-hydroxyphenyl)-2-(4-hydroxy-4-phenylpiperidin-1-yl)-1-propanol or a pharmaceutically acceptable salt thereof.

[0041] Other preferred embodiments of this invention relate to Combination Pharmaceutical Compositions wherein the drug for which the major clearance mechanism in humans is CYP2D6 mediated oxidative biotransformation, or pharmaceutically acceptable salt thereof, that is contained in such pharmaceutical composition is sunipetron or a pharmaceutically acceptable salt thereof.

[0042] Other embodiments of this invention relate to Combination Pharmaceutical Compositions wherein the drug for which the major clearance mechanism in humans is CYP2D6 mediated oxidative biotransformation, or pharmaceutically acceptable salt thereof, that is contained in such compositions is selected from the following compounds and their pharmaceutically acceptable salts: mequitazine (*J. Pharmacol. Exp. Ther.*, 284, 437-442 (1998)); tamsulosin (*Xenobiotica*, 28, 909-22 (1998)); oxybutynin (*Pharmacogen.*, 8, 449-51 (1998)); ritonavir (*Clin. PK*, 35, 275-291 (1998)); iloperidone (*J. Pharmacol. Exp. Ther.*, 286, 1285-93 (1998)); ibogaine (*Drug Metab. Dispos.*, 26, 764-8 (1998)); delavirdine (*Drug Metab. Dispos.*, 26, 631-9 (1998)); tolteridone (*Clin. Pharmacol. Ther.*, 63, 529-39 (1998)); promethazine (*Rinshovakon*, 29, 231-38 (1998)); pimozide, *J. Pharmacol. Exp. Ther.*, 285, 428-37 (1998)); epinastine (*Res. Comm. Md. Path. Pharmacol.*, 98, 273-92 (1997)); tramadol (*Eur. J. Clin. Pharm.*, 53, 235-239 (1997)); procainamide (*Pharmacogenetics*, 7, 381-90 (1997)); methamphetamine (*Drug Metab. Dispos.*, 25, 1059-64 (1997)); tamoxifen (*Cancer Res.*, 57, 3402-06 (1997)); nicergoline (*Br. J. Pharm.*, 42, 707-11 (1996)); and fluoxetine (*Clin. Pharmacol. Ther.*, 60, 512-21 (1996)). All of the foregoing references are incorporated herein by references in their entireties.

[0043] Other embodiments of this invention relate to Combination Pharmaceutical Compositions wherein the drug for which the major clearance mechanism in humans is CYP2D6 mediated oxidative biotransformation, or pharmaceutically acceptable salt thereof, that is contained in such compositions is selected from the following compounds and their pharmaceutically acceptable salts, all of which are referred to, along with their respective pathways of CYP2D6 mediated oxidative biotransformation (e.g., O-demethylation, hydroxylation, etc.), by M. F. Fromm et al. in *Advanced Drug Delivery Reviews*, 27, 171-199 (1997): alprenolol, amiflamine, amitriptyline, aprindine, brofaromine, butorolol, cinnarizine, clomipramine, codeine, debrisoquine, desipramine, desmethylcitalopram, dexfenfluramine, dex-

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