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(54) **METHODS FOR THE ADMINISTRATION OF ILOPERIDONE**

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None
See application file for complete search history.

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(57) **ABSTRACT**

The present invention relates to methods for the identification of genetic polymorphisms that may be associated with a risk for QT prolongation after treatment with iloperidone and related methods of administering iloperidone to patients with such polymorphisms.

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METHODS FOR THE ADMINISTRATION OF ILOPERIDONE

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a 35 USC 371 national stage application of co-pending International Patent Application No. PCT/US2005/035526, filed Sep. 30, 2005, which claims the benefit of U.S. Provisional Application No. 60/614,798, filed Sep. 30, 2004, each of which is hereby incorporated herein.

SEQUENCE LISTING

The sequence listing contained in the electronic file titled "VAND-0002-US_SeqID__2009-07-16.txt" created Jul. 16, 2009, comprising 4 KB, is hereby incorporated herein by reference.

BACKGROUND OF THE INVENTION

Several genes associated with drug metabolism have been found to be polymorphic. As a result, the abilities of individual patients to metabolize a particular drug may vary greatly. This can prove problematic or dangerous where an increased concentration of a non-metabolized drug or its metabolites is capable of producing unwanted physiological effects.

The cytochrome P450 2D6 gene (CYP2D6), located on chromosome 22, encodes the Phase I drug metabolizing enzyme debrisoquine hydroxylase. A large number of drugs are known to be metabolized by debrisoquine hydroxylase, including many common central nervous system and cardiovascular drugs. One such drug is iloperidone (1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxyphenyl]ethanone). Iloperidone and methods for its production and use as an antipsychotic and analgesic are described in U.S. Pat. No. 5,364,866 to Strupczewski et al. The diseases and disorders that can be treated by administration of iloperidone include all forms of schizophrenia (i.e., paranoid, catatonic, disorganized, undifferentiated, and residual), schizoaffective disorders, bipolar mania/depression, cardiac arrhythmias, Tourette's Syndrome, brief psychotic disorder, delusional disorder, psychotic disorder NOS (not otherwise specified), psychotic disorder due to a general medical condition, schizophreniform disorder, and substance-induced psychotic disorder.

P88 is an active metabolite of iloperidone. See, e.g., PCT WO2003020707, which is incorporated herein by reference.

Among the unwanted physiological effects associated with an increased concentration of iloperidone or its metabolites is prolongation of the electrocardiographic QT interval.

Mutations in the CYP2D6 gene have been associated with a number of drug metabolism-related phenotypes. These include the ultra rapid metabolizer (UM), extensive metabolizer (EM), intermediate metabolizer (IM), and poor metabolizer (PM) phenotypes. Where a particular drug is capable of producing unwanted physiological effects in its metabolized or non-metabolized forms, it is desirable to determine whether a patient is a poor metabolizer of the drug prior to its administration.

A number of references are directed toward the identification of CYP2D6 mutations and their corresponding phenotypes. For example, United States Patent Application Publication No. 2003/0083485 to Milos et al. describes a novel

variant prior to the administration of a drug. United States Patent Application Publication No. 2004/0072235 to Dawson describes a primer set useful in identifying variants of the CYP2D6 gene. Similarly, United States Patent Application Publication No. 2004/0091909 to Huang describes methods for screening an individual for variants in the CYP2D6 gene and other cytochrome P450 genes and tailoring the individual's drug therapy according to his or her phenotypic profile. Finally, United States Patent Application Publication No. 2004/0096874 to Neville et al. describes methods for identifying cytochrome P450 variants.

SUMMARY OF THE INVENTION

The present invention comprises the discovery that treatment of a patient, who has lower CYP2D6 activity than a normal person, with a drug that is pre-disposed to cause QT prolongation and is metabolized by the CYP2D6 enzyme, can be accomplishing more safely by administering a lower dose of the drug than would be administered to a person who has normal CYP2D6 enzyme activity. Such drugs include, for example, dolasetron, paroxetine, venlafaxin, and iloperidone. Patients who have lower than normal CYP2D6 activity are herein referred to as CYP2D6 Poor Metabolizers.

This invention also relates to methods for the identification of genetic polymorphisms that may be associated with a risk for QT prolongation after treatment with compounds metabolized by the CYP2D6 enzyme, particularly iloperidone or an active metabolite thereof or a pharmaceutically acceptable salt of either (including, e.g., solvates, polymorphs, hydrates, and stereoisomers thereof), and related methods of administering these compounds to individuals with such polymorphisms.

The present invention describes an association between genetic polymorphisms in the CYP2D6 locus, corresponding increases in the concentrations of iloperidone or its metabolites, and the effect of such increases in concentrations on corrected QT (QTc) duration relative to baseline. Any number of formulas may be employed to calculate the QTc, including, for example, the Fridericia formula (QTcF) and the Bazett formula (QTcB), among others. The present invention includes any such formula or method for calculating a QTc.

A first aspect of the invention provides a method for treating a patient with iloperidone or an active metabolite thereof or a pharmaceutically acceptable salt of either, comprising the steps of determining the patient's CYP2D6 genotype and administering to the patient an effective amount of iloperidone or an active metabolite thereof or a pharmaceutically acceptable salt of either based on the patient's CYP2D6 genotype, such that patients who are CYP2D6 poor metabolizers receive a lower dose than patients who are CYP2D6 normal metabolizers.

Another aspect of the invention provides a method for treating a patient who is a CYP2D6 poor metabolizer with iloperidone or an active metabolite thereof or a pharmaceutically acceptable salt of either, wherein the patient is administered a lower dosage than would be given to an individual who is not a CYP2D6 poor metabolizer.

Another aspect of the invention provides a method of treating a patient with iloperidone or an active metabolite thereof or a pharmaceutically acceptable salt of either comprising the steps of determining whether the patient is being administered a CYP2D6 inhibitor and reducing the dosage of drug if the patient is being administered a CYP2D6 inhibitor.

Another aspect of the invention provides a method for

or an active metabolite thereof or a pharmaceutically acceptable salt of either, determining a first concentration of at least one of iloperidone and an iloperidone metabolite in the patient's blood, administering to the patient at least one CYP2D6 inhibitor, determining a second concentration of at least one of iloperidone and an iloperidone metabolite in the patient's blood, and comparing the first and second concentrations.

Another aspect of the invention provides a method for determining whether a patient is at risk for prolongation of his or her QTc interval due to iloperidone administration comprising the step of: determining a patient's CYP2D6 metabolizer status by either determining the patient's CYP2D6 genotype or CYP2D6 phenotype. In the case that a patient is determined to be at risk for prolongation of his or her QTc interval, the dose of iloperidone administered to the patient may be reduced.

Another aspect of the invention provides a method of administering iloperidone or an active metabolite thereof, or a pharmaceutically acceptable salt of either, for the treatment of a disease or disorder in a human patient comprising the steps of determining the activity of the patient's CYP2D6 enzyme on at least one of iloperidone and its metabolites relative to the activity of a wild type CYP2D6 enzyme and reducing the dose of at least one of iloperidone and its pharmaceutically acceptable salts if the patient's CYP2D6 enzyme activity is less than that of the wild type CYP2D6.

Another aspect of the invention relates to modifying the dose and/or frequency of dosing with iloperidone or a pharmaceutically acceptable salt thereof based on the P88:P95 ratio and/or the (P88+iloperidone):P95 ratio in a blood sample of a patient being treated with iloperidone or P88, especially patients susceptible to QT prolongation or to harmful effects associated with QT prolongation.

Another aspect of the invention provides a kit for use in determining a CYP2D6 genotype of an individual, comprising a detection device, a sampling device, and instructions for use of the kit.

Another aspect of the invention provides a kit for use in determining a CYP2D6 phenotype of an individual, comprising a detection device, a collection device, and instructions for use of the kit.

Another aspect of the invention provides a kit for use in determining at least one of a P88 to P95 ratio and a P88 and iloperidone to P95 ratio in an individual, comprising a detection device, a collection device, and instructions for use of the kit.

Yet another aspect of the invention provides a method for commercializing a pharmaceutical composition comprising at least one of iloperidone, a pharmaceutically acceptable salt of iloperidone, an active metabolite of iloperidone, and a pharmaceutically acceptable salt of an active metabolite of iloperidone, said method comprising: obtaining regulatory approval of the composition by providing data to a regulatory agency demonstrating that the composition is effective in treating humans when administered in accordance with instructions to determine whether or not a patient is a CYP2D6 poor metabolizer prior to determining what dose to administer to the patient; and disseminating information concerning the use of such composition in such manner to prescribers or patients or both.

The foregoing and other features of the invention will be apparent from the following more particular description of embodiments of the invention.

DETAILED DESCRIPTION OF THE INVENTION

Data from placebo-controlled Phase III studies of iloperidone showed a Fridericia correction of QT duration (QTcF) increase of 0.1 to 8.5 msec at doses of 4-24 mg, when comparing a single ECG at baseline to a single ECG at endpoint. At lower doses of iloperidone (4 mg-16 mg) QTcF prolongation was minimal (0.1-5 msec). In the most recent study, a greater prolongation was observed when higher doses of iloperidone (20-24 mg/day) were studied. The mean change in the QTcF at doses 20-24 mg/day was 8.5 msec, and 4.6 msec in the 12-16 mg/day dose range in this study. These data suggest that treatment with iloperidone can be associated with prolongation of the QT interval similar to other drugs in this class, and that the effect may be dose sensitive in the clinical dose range.

The research leading to the present invention was designed to examine the effect of different doses of iloperidone relative to the effect of ziprasidone and quetiapine on QTc duration under carefully controlled conditions. To further evaluate the possible relationship between exposure to iloperidone and the comparators to QTc duration, reassessment after pharmacological inhibition of the principle metabolic pathways for each drug, under steady-state conditions, was also planned.

Blood samples for pharmacogenetic analysis were collected at screening. Two polymorphisms previously associated with poor metabolizing status were genotyped in the CYP2D6 locus and 251 genotypes were collected. The individual genotypes were studied for detection of association between genotype class and concentrations of iloperidone and its metabolites P88 and P95. The functional effect of the polymorphisms was also evaluated by analyzing the effect of the addition of the CYP2D6 inhibitor paroxetine on the concentrations of the parent drug and its metabolites.

The research leading to the present invention identified a significant association between CYP2D6 genotype and concentrations of P88 before the addition of inhibitors as well as the effect of this association on QTc prolongation.

Iloperidone is a substrate for two P450 enzymes; CYP2D6 and CYP3A4. Most metabolic clearance of iloperidone depends on these two enzymes. CYP2D6 catalyzes hydroxylation of the pendant acetyl group to form metabolite P94, which is converted to P95 after some additional reactions. Addition of the CYP2D6 inhibitor fluoxetine, along with iloperidone resulted in increases of the area under the curve (AUC) for iloperidone and P88 of 131% and 119% respectively. Addition of the CYP3A4 inhibitor ketoconazole in interaction studies resulted in a 38-58% increase in the concentrations of iloperidone and its main metabolites P88 and P95. P88 has a pharmacological profile including affinity for the HERG channel similar to that of iloperidone. P95 is less lipophilic and is dissimilar in its binding profile compared to iloperidone, including having very low affinity for the HERG channel. For these reasons P95 is regarded as being pharmacologically inactive.

The addition of metabolic inhibitors in this study therefore allowed for an evaluation of the effect of increasing blood-concentration of iloperidone and/or its metabolites on QT duration. More specifically, this study allowed for an evaluation of the effect of iloperidone on QTc before and after the addition of the CYP2D6 inhibitor, paroxetine, as well as before and after the addition of the CYP3A4 inhibitor, ketoconazole.

The CYP2D6 gene is highly polymorphic, with more than 70 allelic variants described so far. See, e.g., http://www.imm.ki.se/CYPalleles/cyp2d6.htm. Most embodiments of the present invention concern the two most common poly-

as CYP2D6C100T. These polymorphisms correspond to nucleotides 3465 and 1719, respectively, in GenBank sequence M33388.1 (GI:181303). The CYP2D6P34S/CYP2D6C100T polymorphism also corresponds to nucleotide 100 in GenBank mRNA sequence M20403.1 (GI:181349).

The CYP2D6G1846A polymorphism (known as the CYP2D6*4 alleles, encompassing *4A, *4B, *4C, *4D, *4E, *4F, *4G, *4H, *4J, *4K, and *4L) represents a G to A transition at the junction between intron 3 and exon 4, shifting the splice junction by one base pair, resulting in frameshift and premature termination of the protein (Kagimoto 1990, Gough 1990, Hanioka 1990). The CYP2D6P34S/CYP2D6C100T polymorphism (known as the CYP2D6*10 and CYP2D6*14 alleles) represents a C to T change that results in the substitution of a Proline at position 34 by Serine (Yokota 1993, Johansson 1994). Both of these polymorphisms have been associated with reduced enzymatic activity for different substrates (Johansson 1994, Dahl 1995, Jaanson 2002, see also review by Bertilsson 2002)

Methods

A. Samples

128 individuals consented to the pharmacogenetic study. Blood samples were collected according to the pharmacogenetics protocol and after the consent of patients. The DNA was extracted from whole blood by Covance using the PUREGENE DNA isolation kit (D-50K).

The 128 individuals that participated were a good representation of the total sample of 165 individuals that participated in the trial. 22 of 29 total were from the iloperidone 8 mg bid group, 30 of 34 were from the iloperidone 12 mg bid group, 22 of 31 from the 24 mg qd group, 3 of 5 of the risperidone group, 28 of 33 of the ziprazidone group, and 23 of 33 of the quetiapine group.

B. Genotyping

Genotypes for the CYP2D6G1846A polymorphism were ascertained for 123 of the 128 consenting individuals, while genotypes for the CYP2D6C100T polymorphism were identified for all 128 participants. Genotyping was performed on amplified DNA fragments. The CYP2D6 genomic region was amplified using a triplex PCR strategy (Neville 2002). In brief, primers used were:

Exons 1 & 2	2D6L1F1:	CTGGGCTGGGAGCAGCCTC
	SEQ ID. 1	
	2D6L1R1:	CACTCGCTGGCCTGTTTCATGTC
	SEQ ID. 2	
Exons 3, 4, 5 & 6	2D6L2F:	CTGGAATCCGGTGTCGAAGTGG
	SEQ ID. 3	
	2D6L2R2:	CTCGGCCCCTGCACTGTTTC
	SEQ ID. 4	
Exons 7, 8 & 9	2D6L3F:	GAGGCAAGAAGGAGTGTCAGGG
	SEQ ID. 5	
	2D6L3R5B:	AGTCCTGTGGTGAGGTGACGAGG
	SEQ ID. 6	

Amplification was performed on 40-100 ng of genomic DNA using a GC-rich PCR kit (Roche Diagnostics, Mannheim, Germany) according to the manufacturer's recommendations. Thermocycling conditions were as follows: initial denaturation (3 min 95° C.), 10 cycles of 30 s of denaturation (30 s at 95° C.), annealing (30 s at 66° C.), and extension, (60 s at 72° C.) followed by 22 cycles: 30 s at 95° C., 30 s at 66° C., 60 s+5 s/cycle at 72° C. A final extension followed (7 min at 72° C.).

PCR products using the Invader® assay (Lyamichev 1999) (Third Wave Technologies, Inc) according to the manufacturer's recommendations.

The genotypes of individuals distributed among the three iloperidone groups were not significantly different (Table 1A and 1B).

TABLE 1A

Genotype frequencies by iloperidone dose class for CYP2D6C100T

Iloperidone	Genotype			
dose group	CC	CT	TT	Total
Ilo 8 mg bid	19[a]	2	1	22
Ilo 12 mg bid	23	6	1	30
Ilo 24 mg qd	15	6	1	22
Total	57	14	3	74

[a]number of individuals

TABLE 1B

Genotype frequencies by iloperidone dose class for CYP2D6G1846A

Iloperidone	Genotype			
dose group	AA	AG	GG	Total
Ilo 8 mg bid	0	3	17	20
Ilo 12 mg bid	1	6	23	30
Ilo 24 mg qd	1	5	15	21
Total	2	14	55	74

C. Statistical Analysis

The genotype effect of the two CYP2D6 polymorphisms on period 1 concentrations was evaluated using the following ANOVA model. Concentrations of iloperidone, P88, and P95 at Period 1, without inhibitor, at the time at which maximum blood concentration of the parent compound or metabolite was reached (Tmax) were used as the dependent variable, the genotypes of each polymorphism as classes and the treatment as a covariate. In order to adjust for treatment effects after the single dose of iloperidone, the 8 mg bid was coded as 8, the 12 mg bid as 12 and the 24 mg qd as 24.

The function of these polymorphisms on the degree of inhibition of the CYP2D6 enzyme was calculated from the ratio of concentrations of P88 and P95 in period 2, after the addition of the inhibitor of CYP2D6. The concentrations of iloperidone and/or its metabolites (e.g., P88 and P95) may be determined in period 1 and/or period 2 by any known or later-developed method or device, including titration.

Results and Discussion

In order to understand the functional significance of the two CYP2D6 polymorphisms on the activity of the enzyme, we examined the association of the various genotypes with the relative concentrations of the metabolites P88 and P95. It is known that P88 is degraded by CYP2D6 and that CYP2D6 is involved in the synthesis of P95. The relative amounts of P88 and P95 would therefore be controlled by the activity of the CYP2D6 enzyme. We calculated the ratio of P88/P95 before inhibition in Period 1 and at the Tmax of the two metabolites, as well as the ratio of P88/P95 in Period 2 after the addition of the CYP2D6 inhibitor paroxetine. In individuals with the wild type enzyme the concentration of P88 is

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