CYP2D6 Genotype Information to Guide Pimozide Treatment in Adult and Pediatric Patients: Basis for the US Food and Drug Administration's New Dosing Recommendations

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ABSTRACT

Objective: The occurrence of pimozide-induced arrhythmias is concentration dependent. Hence, it is important for prescribers to consider causes of increased pimozide exposure. This article summarizes the US Food and Drug Administration's (FDA's) review of drug interaction and pharmacogenomic studies and discusses pharmacokinetic simulations we performed to develop new cytochrome P450 2D6 (CYP2D6) genotype–guided dosing recommendations for pimozide.

Method: Pharmacokinetic parameters by CYP2D6 genotype were derived from a published single-dose pharmacogenomic study of pimozide. We simulated what pimozide exposures would result from a multiple-dose scenario in different CYP2D6 genotype groups: extensive, intermediate, and poor metabolizers. The maximum dose for poor metabolizers was defined as the dose that would not exceed pimozide concentrations following 10 mg daily in extensive metabolizers and intermediate metabolizers (the current maximum dose in an unselected population).

Results: Dose-ranging analyses revealed that 4 mg daily in CYP2D6 poor metabolizers was the maximum dose that would not result in plasma concentrations in excess of those observed in extensive metabolizer and intermediate metabolizer patients receiving 10 mg daily. CYP2D6 genotyping is now consequently recommended in the pimozide product label before exceeding 4 mg of pimozide daily in adults or 0.05 mg/kg/d in children. Previously, dose adjustment was recommended every 3 days to achieve the desired clinical response for all patients. The label was modified to subsequently reflect that pimozide doses should not be increased earlier than 14 days in patients who are known CYP2D6 poor metabolizers.

Conclusions: Given the risk of increased pimozide concentrations and longer time to steady state in CYP2D6 poor metabolizers, the FDA has revised the pimozide label to provide clinicians with clearer dosing, titration, and genotype testing recommendations. The new information is intended to enhance therapeutic individualization of pimozide in pediatric and adult patients.

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Pimozide and haloperidol are the only 2 US Food and Drug Administration (FDA)–approved therapies for treatment of Tourette's syndrome. Pimozide is an oral dopamine antagonist that was first approved by the FDA in 1984 for the suppression of motor and phonic tics in patients with Tourette's syndrome who have failed to respond satisfactorily to standard treatment. Pimozide interacts with the delayed rectifier potassium channel and prolongs the QT interval.[1–3] Published studies[4–9] confirm that QT prolongation events are observed following pimozide administration at the higher end of the recommended dose range (ie, above 5 mg). Cases of sudden cardiac death have been reported in patients receiving pimozide.[10,11] Ten of 13 deaths may have been attributed to excessive doses in 1 report.[12]

Pimozide is metabolized in the liver, primarily by cytochrome P450 (CYP) 3A4 and, to a lesser degree, by CYP1A2. Previously, in vitro data suggested that CYP2D6 did not play a significant role in the metabolism of pimozide.[13] Data from in vivo drug interaction studies now suggest that CYP2D6 plays an important role in the metabolism of pimozide. In a drug-drug interaction study,[14] coadministration of a weak CYP2D6 inhibitor (sertraline) significantly increased pimozide exposure by 37%. Coadministration of potent CYP2D6 inhibitors could significantly increase pimozide exposure; hence, labels for multiple drugs known to inhibit CYP2D6 (eg, paroxetine, fluoxetine) now bear contraindications for concomitant use with pimozide. Until recently, the pimozide label did not reflect this potential for interactions with many commonly used CYP2D6 inhibitors.

Cytochrome P450 2D6 is known to be genetically variable. Genetic variants that result in poor metabolism of CYP2D6 substrates are present in approximately 6%–10% of whites, 2% of Asians, and 10% of African Americans.[15] Poor metabolizers are virtually unable to metabolize drugs that are predominantly CYP2D6 substrates. Pharmacogenomic studies have confirmed that CYP2D6 is an important pathway for pimozide metabolism and that genetic poor metabolism affects pimozide clearance to the same extent as CYP2D6 inhibitors.[16]

The occurrence of pimozide-induced arrhythmias is concentration dependent.[17] Hence, it is important for prescribers to consider causes of increased pimozide concentrations. The FDA recently revised the pimozide label to address drug-drug and gene-drug interactions with pimozide that result in high pimozide exposures, which can increase the risk for arrhythmic events. We used pharmacokinetic simulation to determine appropriate dose adjustments in adult and pediatric patients who are CYP2D6 poor metabolizers. This article summarizes the FDA's review of drug interaction and pharmacogenomic studies and discusses our pharmacokinetic simulation used to characterize

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Clinical Points

- Cytochrome P450 2D6 (CYP2D6) poor metabolizers are at an increased risk for QT prolongation at standard doses of pimozide because of higher drug concentrations.
- People who are CYP2D6 poor metabolizers should not receive more than 4 mg of pimozide daily if adults or 0.05 mg/kg daily (up to 4 mg daily) if children.
- Clinicians can refer to the US Food and Drug Administration pimozide label for new guidance on dosing, titration, and CYP2D6 status testing recommendations.

dose-exposure relationships, determine genotype-guided dosing and titration recommendations, and identify pimozide doses above which genotyping should be performed.

METHOD

In order to determine the influence of CYP2D6 genetic variation on pimozide drug concentrations and identify optimal dosing strategies, pharmacokinetic parameters were derived from a single-dose pharmacokinetic/pharmacogenomic study submitted to the FDA. This study[16] was conducted in 32 healthy volunteers, and subjects received a 2-mg dose of pimozide followed by periodic plasma sampling over 120 hours. The CYP2D6 genotype was determined in each subject. The single-dose pharmacokinetic parameters derived from this study and used in the pharmacokinetic simulation models can be found in Table 1. We used these parameters to simulate pimozide exposures that would result from a multiple-dose (ie, chronic use) scenario in different CYP2D6 genotype groups (extensive metabolizers, intermediate metabolizers, and poor metabolizers; Berkeley Madonna, Version 8.3 [University of California, Berkeley]).

The maximum recommended dose of pimozide for this indication in an unselected population (ie, the "average" patient without consideration of CYP2D6 metabolizer status) is 10 mg daily in adults or 0.2 mg/kg/d in children (up to 10 mg daily). We determined what pimozide drug concentrations would result from administration of 10 mg daily to CYP2D6 extensive metabolizers and intermediate metabolizers and set this concentration as the "not-to-exceed" exposure threshold for poor metabolizers. We then derived a maximum dose up to which pimozide could be safely administered in all patients before CYP2D6 testing would be warranted. This maximum-dose threshold was defined as the dose that would result in pimozide drug concentrations in poor metabolizers that would not exceed concentrations resulting from 10 mg daily in extensive metabolizers and intermediate metabolizers. Results were extrapolated to children, assuming a weight-based dose for a 70-kg adult.

Given the QT prolongation risk associated with high pimozide exposures, the following aspects of dosing were determined based on our analyses, which served as the basis for the recent pimozide label update (dated September 27, 2011)[18]: (1) dose threshold above which CYP2D6 genotyping should be considered, (2) initial dosing and maximal dose limits in patients known to be CYP2D6 poor metabolizers, and (3) dose titration intervals in patients known to be CYP2D6 poor metabolizers.

Table 1. Pimozide Pharmacokinetic Parameters[a]

Parameter	Estimate
Clearance/bioavailability, L/h	
CYP2D6 extensive metabolizer	54.9
CYP2D6 intermediate metabolizer	35.8
CYP2D6 poor metabolizer	14.7
Volume of central compartment/bioavailability, L	1,240 × (weight [kg]/70)
Volume of peripheral compartment/bioavailability, L	1,040 × (weight [kg]/70)
Intercompartment clearance/bioavailability, L/h	69.2
Absorption rate constant, 1/h	0.68
Lag time, h	1.14

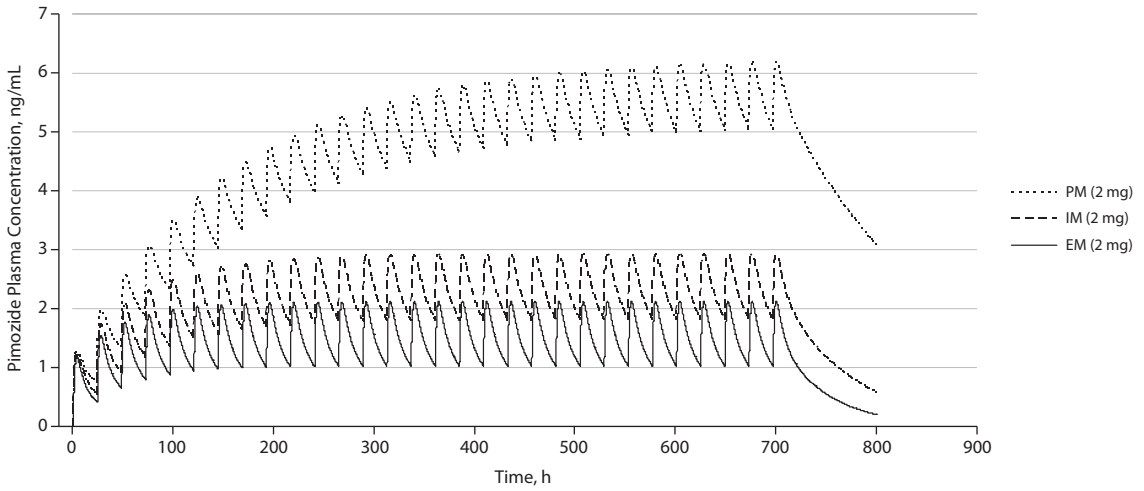
[a]Data from Nucci et al.[16]
Abbreviation: CYP2D6 = cytochrome P450 2D6.

RESULTS

Simulated chronic dosing at 2 mg daily in CYP2D6 poor metabolizers resulted in both higher exposures and a longer time to achieve steady-state concentrations compared to extensive metabolizers and intermediate metabolizers (Figure 1). Specifically, under a multiple-dose scenario, after 30 days, CYP2D6 poor metabolizers had a 3.7- and 2.4-fold greater area under the curve and a 2.9- and 2.1-fold greater maximal drug concentration (C_{max}) compared to extensive metabolizers and intermediate metabolizers, respectively. This level of exposure is similar to that seen with concomitant CYP2D6 inhibitor use. We consequently performed exposure-matching analyses to derive a dose that would mitigate the excessive exposures in CYP2D6 poor metabolizers.

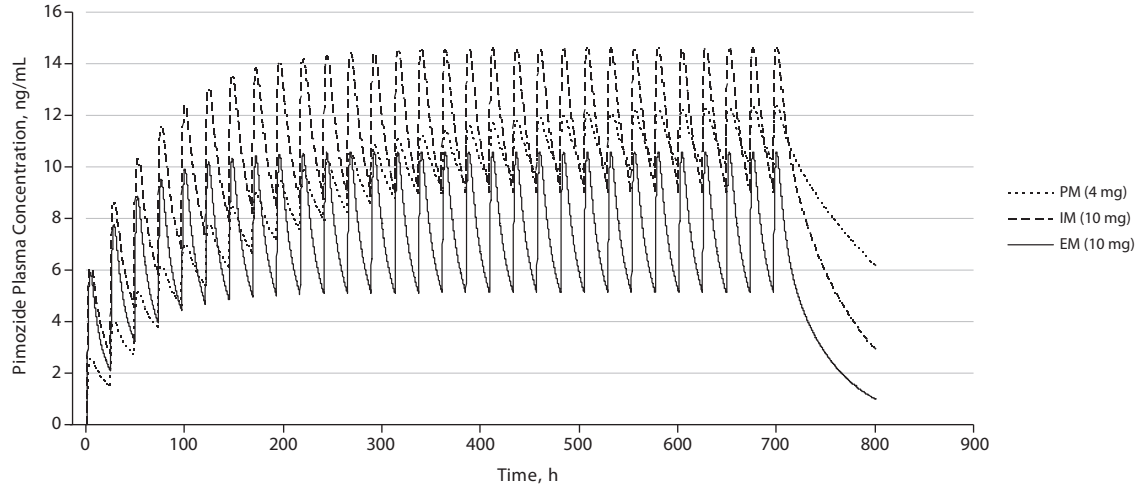
The target maximum exposure selected for normalizing exposures among genotype groups (ie, extensive metabolizers, intermediate metabolizers, and poor metabolizers) was that observed at a 10-mg daily dose in CYP2D6 extensive metabolizers and intermediate metabolizers to reflect the average maximum exposure observed in the population; the dose in poor metabolizers was not to exceed this threshold of exposure. An initial dose of 2 mg daily in CYP2D6 poor metabolizers would not exceed the maximal pimozide exposure limits. Further dose-ranging analyses revealed that a 4-mg daily dose of pimozide in the CYP2D6 poor metabolizers was the maximum dose that would not result in plasma concentrations in excess of those observed in extensive metabolizer and intermediate metabolizer patients receiving dosing at 10 mg daily (Figure 2). Hence, exceeding this dose in CYP2D6 poor metabolizers would potentially result in exposures greater than the maximal FDA-approved dose in extensive metabolizers and intermediate metabolizers. A 4-mg dose in adults roughly equates to 0.05 mg/kg/d, which was consequently set as the maximum dose for children who are poor metabolizers.

Figure 1. Simulated Pimozide Plasma Concentrations by CYP2D6 Genotype for a 2-mg Daily Dose[a]



[a]Compared to IMs and EMs, PMs have exposures that are more than twice as large and require approximately twice as long to achieve steady state.
Abbreviations: CYP2D6 = cytochrome P450 2D6, EM = CYP2D6 extensive metabolizer, IM = CYP2D6 intermediate metabolizer, PM = CYP2D6 poor metabolizer.

Figure 2. CYP2D6 Genotype Exposure Matching Analysis[a]



[a]Exposure following daily doses of the current maximum recommended dose of 10 mg was simulated for IMs and EMs. The dose was sequentially escalated for PMs to identify a dose that did not exceed the maximum exposure thresholds for IMs and EMs receiving 10 mg. The results indicate that the dose should not exceed 4 mg in PMs.
Abbreviations: CYP2D6 = cytochrome P450 2D6, EM = CYP2D6 extensive metabolizer, IM = CYP2D6 intermediate metabolizer, PM = CYP2D6 poor metabolizer.

We determined pimozide to have a half-life of approximately 61 hours in CYP2D6 poor metabolizers compared to 31 hours in extensive metabolizers. This near doubling in half-life increases the time needed to achieve steady state in CYP2D6 poor metabolizers. Steady state can be achieved in approximately 6 days in CYP2D6 extensive metabolizers, while poor metabolizers require almost 13 days to achieve steady state. Previously, the pimozide label recommended dose adjustment every 3 days to achieve the desired clinical response for all patients. By using this dose titration strategy, steady-state plasma concentrations may not be achieved before the next dose increase in poor metabolizers, resulting in inadequate time to assess whether clinical benefit has been achieved before increasing the dose and/or in excessive accumulation of pimozide in CYP2D6 poor metabolizers that could result in prolongation of the QT interval and risk for cardiac events (Figure 1).

On the basis of the above findings of the higher exposure and longer half-life of pimozide in CYP2D6 poor metabolizers, the label for pimozide now contains new dosing, titration, and genotype testing recommendations (Table 2).[18]

DISCUSSION

Previously, CYP2D6 was not considered a clinically relevant pathway in the metabolism of pimozide. Subsequent

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Table 2. Summary of the Recent US Food and Drug Administration Update[18] to Pimozide Drug Label[19,a]

	Children		Adults	
Variable	Original	Revised	Original	Revised
CYP2D6 genotype testing	None	At doses above 0.05 mg/kg/d	None	At doses above 4 mg/d
Starting dose	0.05 mg/kg/d	0.05 mg/kg/d	1–2 mg/d	1–2 mg/d
Titration interval	Every third day	EMs/IMs: every third day PMs: not sooner than every 14 days	Every other day	EMs/IMs: every other day PMs: not sooner than every 14 days
Maximum dose	0.2 mg/kg/d or 10 mg/d, whichever is less	EMs/IMs: 0.2 mg/kg/d or 10 mg/d, whichever is less PMs: 0.05 mg/kg/d	0.2 mg/kg/d or 10 mg/d, whichever is less	EMs/IMs: 0.2 mg/kg/d or 10 mg/d, whichever is less PMs: 4 mg/d

[a]Maximum doses in children should not exceed the maximum adult doses.
Abbreviations: CYP2D6 = cytochrome P450 2D6, EM = CYP2D6 extensive metabolizer, IM = CYP2D6 intermediate metabolizer, PM = CYP2D6 poor metabolizer.

drug-drug interaction studies with both sertraline (a weak CYP2D6 inhibitor) and paroxetine (a strong CYP2D6 inhibitor) led to clinically significant increases in exposures to pimozide. The results of these studies prompted the FDA to contraindicate use of these agents with pimozide because alternative drugs that do not inhibit CYP2D6 are available. A pharmacogenomic study[16] suggested that CYP2D6 poor metabolizers had pimozide concentrations that were as high as those seen with paroxetine. Rather than contraindicate the use of pimozide in all CYP2D6 poor metabolizers, the FDA chose to simulate exposures to generate a genotype-specific dose recommendation for these individuals. Consequently, the FDA revised the pimozide label to include recommendations[18] for CYP2D6 genotyping and dosing of pimozide for patients with Tourette's syndrome based on integrative clinical pharmacokinetic, pharmacometric, and pharmacogenetic analyses.

Genetic- or drug-induced CYP2D6 poor metabolizer status is associated with high exposures to pimozide, which may increase the risk for QT prolongation. Contraindicating pimozide in genetic CYP2D6 poor metabolizers in a manner consistent with the drug interaction labeling would require all patients to be genotyped for their CYP2D6 status and would limit treatment options for the 5%–10% of the population that are CYP2D6 poor metabolizers. Consequently, the FDA employed dose-exposure simulation to identify a dose threshold that should not be exceeded in CYP2D6 poor metabolizers, informing genotype-guided dosing recommendations. This approach has been employed with other drugs that are susceptible to polymorphic metabolism (eg, tetrabenazine for Huntington's disease, aripiprazole for schizophrenia) and may be a useful strategy to improve the safe use of much needed therapies with narrow therapeutic indices. Since numerous drugs used in psychiatric practice are metabolized by CYP2D6, similar approaches may be used to optimize dosing and treatment outcomes.

Drug names: aripiprazole (Abilify), fluoxetine (Prozac and others), haloperidol (Haldol and others), paroxetine (Paxil, Pexeva, and others), pimozide (Orap), sertraline (Zoloft and others), tetrabenazine (Xenazine).
Author affiliations: US Food and Drug Administration, Silver Spring, Maryland. Dr Gobburu is now a professor at the University of Maryland School of Pharmacy, Baltimore.
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