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Changes in the Product Label for Pimozide Illustrate Both the Promises and the Challenges of Personalized Medicine

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The article by Rogers and colleagues,[1] viewed alone, is an important addition to the literature. When viewed within a historical context, it provides an excellent example of the changes being wrought by advances made in personalized medicine, by which I mean (1) our growing knowledge of the biological variance among patients and (2) our ability to improve the safety, tolerability, and efficacy of specific treatments for specific patients by adjusting drug and dose selection based on knowledge of such variance. This commentary will discuss both of these perspectives.

In their article, Rogers and colleagues[1] from the US Food and Drug Administration (FDA) present data that improve our understanding of the role that genetically determined differences in cytochrome P450 (CYP) 2D6 enzyme function plays in determining the clearance of pimozide. These data resulted in the most recent change to the product label for pimozide made jointly by the FDA and the drug manufacturer. These changes affected the following sections: (1) Clinical Pharmacology-Metabolism and Pharmacokinetics; (2) Contraindications, Precautions-Drug Interactions; (3) Dosage and Administration sections; and (4) the addition of a new subsection under Precautions entitled Pharmacogenomics.

The biotransformation of pimozide—as a necessary step in its eventual clearance from the body—is mediated by both CYP3A4 and CYP2D6. While CYP3A4 is the major pathway, CYP2D6 also contributes to a clinically meaningful degree. Deficiency in the CYP2D6 drug metabolizing pathway can occur either because of genetics (a trait phenomenon) or because of concomitant administration of a substantial CYP2D6 inhibitor (a state phenomenon). The second phenomenon is also called *phenoconversion* because the individual may be genetically normal in terms of CYP2D6 function (ie, a CYP2D6 extensive metabolizer) but functionally behaves as if he or she is genetically deficient in this enzyme (ie, a CYP2D6 poor metabolizer). As discussed later in this commentary, phenoconversion is a more common cause of CYP2D6 poor metabolizer status than is genetics.

Whether this enzyme deficiency is due to genetics or the presence of an inhibitor, CYP2D6 poor metabolizers will develop higher systemic concentrations of pimozide and greater pimozide-induced QT (commonly reported as QTc, which is heart-rate corrected) prolongation than will CYP2D6 extensive metabolizers despite their being on the same dose of pimozide.[1] The reason for the differential outcome between the 2 groups is that pimozide, in a concentration-dependent fashion, inhibits potassium (K^+) channels encoded by the human ether-a-go-go-related gene (hERG).[2,3] These channels are responsible for cardiac repolarization via the rapid component of the delayed rectifier potassium current (I_{Kr}) in myocytes.[4] The pimozide-induced QT prolongation in turn can produce fatal ventricular arrhythmias such as torsades de pointes.[5]

The article by Rogers and colleagues[1] documents that CYP2D6 poor metabolizers (about 5%–10% of the US population, particularly those who are descendants of northern Europeans) develop plasma pimozide concentrations 2–2.5 times higher than those that occur in CYP2D6 extensive metabolizers (the majority of the US population), despite both groups receiving the same dose of pimozide. Hence, CYP2D6 poor metabolizers are at increased risk of developing a pimozide-induced arrhythmia if they receive the same dose as CYP2D6 extensive metabolizers. Moreover, the FDA considers that risk to be excessive at concentrations above those usually achieved in extensive metabolizers taking 10 mg/d. Parenthetically, plasma concentration of pimozide is being used as a surrogate for the risk of developing clinically meaningful pimozide-induced QT prolongation by the FDA and the manufacturer.

On the basis of these data and rationale, the new product label dosing guidance for pimozide is as follows: start at a dose of 0.05 mg/kg, preferably taken once daily at bedtime. If the patient is a known CYP2D6 extensive metabolizer and is not on a substantial CYP2D6 inhibitor, the dose may be increased every third day to a maximum of 0.2 mg/kg/d, not to exceed a maximum of 10 mg/d. If the CYP2D6 status is not known, then CYP2D6 genotyping should be done before deciding to increase the dose above 0.05 mg/kg/d, which is the maximum dose for anyone who is a CYP2D6 poor metabolizer either because of genetics or because of the coadministration of a substantial CYP2D6 inhibitor.

The current product label does not address what to do in the case of patients who are CYP2D6 intermediate metabolizers or ultrarapid metabolizers. It would seem prudent to be cautious when dosing in intermediate metabolizers and perhaps to use pimozide plasma concentrations to guide dosing adjustment. Such patients will most likely need lower pimozide doses to achieve concentrations comparable to those achieved in CYP2D6 extensive metabolizers on 0.2 mg/kg/d up to a maximum of 10 mg/d. CYP2D6 ultrarapid metabolizers would be expected to achieve concentrations below

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those achieved in CYP2D6 extensive metabolizers. Nevertheless, prescribers may choose to not exceed the maximum pimozide doses in the pimozide product label until specific language is added to cover CYP2D6 ultrarapid metabolizers. As a caveat, the FDA stopped short of recommending that all patients be genotyped before taking pimozide.

Thus, the new pimozide product label is based on the use of plasma pimozide concentrations as a surrogate end point to minimize the risk of a serious safety concern with pimozide and incorporates genotyping recommendations as well as contraindications to the concomitant use of substantial CYP2D6 inhibitors in patients taking pimozide. Parenthetically, substantial CYP2D6 inhibitors include bupropion, fluoxetine, paroxetine, and terbinafine.[6,7] Paroxetine, for example, can phenoconvert 2 of every 3 (ie, 66%) genetic CYP2D6 extensive metabolizers to poor metabolizer status at a dose of 20 mg/d and 95% at a dose of 40 mg/d.[8]

Phenoconversion to CYP2D6 poor metabolizer status is 6 times more common than genetically determined poor metabolizer status based on a recently completed study that we did in 900 patients being treated with an antidepressant in routine clinical practice (S.H.P., unpublished data, 2010). On average, patients in that study were taking 3 drugs in addition to their antidepressant. Of this population, 4% were genotypic CYP2D6 poor metabolizers, while 24% were phenotypic poor metabolizers because of being on concomitant CYP2D6 inhibitors or substrates. This finding underscores a problem with relying solely on genetic information to characterize the CYP2D6 functional or phenotypic status of a patient. Relying on genotyping alone would lead to almost 1 of 4 patients being misclassified as extensive metabolizers when they are functionally poor metabolizers. Without taking this fact into consideration, the patient could be put on a dose of pimozide that could have potentially life-threatening consequences.

The publication of the article by Rogers et al[1] and the revision of the pimozide product label mean that prescribers of pimozide now know or should know this information and take it into account when treating someone with pimozide. To put this matter in perspective, there are now over 120 drugs (34 of these are central nervous system drugs, with the majority being psychiatric medications) with recommendations for genetic testing in their product labels.[9,10] This expansion is happening with both new approvals and already marketed drugs such as pimozide, a trend that will most likely increase as more pharmacogenomic information becomes available.

This prediction serves as a segue to the second part of this commentary, which seeks to put the dosing recommendations presented in Rogers et al[1] in perspective relative to all medications.

Pimozide originally received approval from the FDA 28 years ago.[11] That approval occurred before a number of significant advances in pharmaceutical sciences, molecular biology, and genetics. All of the following have occurred since the approval of pimozide: (1) the identification of the various CYP enzymes, (2) the ability to characterize the likely human metabolism of a drug before it is ever given to a human via the use of in vitro techniques, (3) the ability to characterize individuals in terms of their genetic status relative to CYP2D6 and some other CYP enzymes, (4) the recognition that some drugs are substantial inducers or inhibitors of specific CYP enzymes and can interact pharmacokinetically with other coadministered drugs that are dependent on those specific CYP enzymes for their biotransformation as part of the process determining their clearance from the body, (5) the identification of the hERG K^+ channels, (6) the ability to use in vitro and in vivo models of the hERG K^+ channels to study the interaction of drugs with this mechanism and thus predict the potential for causing arrhythmias via this mechanism, and (7) the potential of 2 drugs to interact via their effects on the hERG K^+ channels or related mechanisms to increase the risk of arrhythmias. This knowledge and these techniques are now part of the drug discovery and preclinical development of new drugs but were not available when pimozide was being developed in the 1970s and early 1980s.

After the approval of pimozide, these developments revealed many important aspects about the pharmacology of pimozide. Those discoveries in turn have led to 8 revisions of its product label over the last 14 years, which represent more revisions in the pimozide product label than occurred during its first 14 years on the market. In fact, the product label for pimozide has been revised 4 times in the last 3 years.

Some readers may be surprised to learn that the metabolism of many older drugs is not known nor is their potential for being either a perpetrator or victim of a CYP enzyme–mediated drug-drug interaction. The reason is that this knowledge was not available and, hence, was not required when these drugs were undergoing human testing and being approved. After these drugs have been marketed, manufacturers back-fill this knowledge only for cause. After the drugs' patents have expired, the development of this knowledge is generally dependent on grant funding, and, to my knowledge, the National Institutes of Health does not specifically earmark grant funding for such work, but the FDA may have a limited amount of such funding, as witnessed by the publication of Rogers et al.[1]

Obviously, the limitations with the older drugs discussed above also mean that this knowledge was not available when many practicing prescribers were being trained with the new drug. Continuing medical education and keeping up with product label revisions are the primary means by which such "older" prescribers keep up with such developments for drugs that they may have prescribed for years.

Even if the prescriber has a good grasp on these concepts, there is the problem of the sheer amount of data to know and the rate at which the information is increasing. That is especially true when one considers the frequency and complexity of multiple medication use in practice. The volume of data now available may well have outstripped the capacity and speed of the central processing unit of most, if not all, prescribers. That is the reason to move toward software

solutions. Unfortunately, the current ones have many limitations. A discussion of this topic is beyond the scope of this commentary.

The next century will most likely be dominated by conformational biology and bioinformatics. A major effort must be made so that the information being developed as a result of advances in molecular biology and pharmaceutical sciences can be translated into user-friendly, actionable knowledge for health care providers and their patients. That, from my perspective, is the overarching, take-home message from the article by Rogers and colleagues.[1] In the meantime, we may be in an era that represents both the best of times and the worst of times, depending on one's point of view.

Drug names: bupropion (Wellbutrin, Aplenzin, and others), fluoxetine (Prozac and others), paroxetine (Paxil, Pexeva, and others), pimozide (Orap), terbinafine (Lamisil and others).

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