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Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for *CYP2D6* Genotype and Use of Ondansetron and Tropisetron

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CONFLICT OF INTEREST

All other authors declare no conflicts of interest.

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Abstract

5-hydroxytryptamine type 3 (5-HT_3) receptor antagonists are used in the prevention of chemotherapy- induced, radiation-induced and postoperative nausea and vomiting. *CYP2D6* polymorphisms can influence the metabolism of some of these drugs (i.e. ondansetron and tropisetron) thereby affecting drug efficacy. We summarize evidence from the published literature supporting these associations and provide therapeutic recommendations for ondansetron and tropisetron based on *CYP2D6* genotype (updates at www.pharmgkb.org).

Keywords

pharmacogenetics; CPIC; ondansetron; tropisetron; dolasetron; palonosetron; 5-hydroxytryptamine type 3 antagonists; CYP2D6; granisetron

INTRODUCTION

The purpose of this guideline is to provide information to allow the interpretation of clinical *CYP2D6* genotype tests so that the results can be used to guide use of the 5-hydroxytryptamine type 3 (5-HT_3) receptor antagonists, ondansetron and tropisetron. Detailed guidelines for use of ondansetron and tropisetron as well as analyses of cost effectiveness, are beyond the scope of this document. CPIC guidelines are periodically updated at https://cpicpgx.org/guidelines/ and http://www.pharmgkb.org.

FOCUSED LITERATURE REVIEW

A systematic literature review focused on *CYP2D6* genotype and ondansetron, granisetron, tropisetron, palonosetron, and ramosetron use was conducted (details in Supplement).

GENE: CYP2D6

CYP2D6 is highly polymorphic with over 100 known allelic variants and subvariants identified (http://www.cypalleles.ki.se/cyp2d6.htm; ***CYP2D6* Allele Definition** Table (1)). *CYP2D6* alleles have been extensively studied in multiple geographically, racially, and ethnically diverse groups and significant differences in allele frequencies have been observed (***CYP2D6* Frequency** Table (1)). The most commonly reported alleles are categorized into functional groups as follows: Normal function (e.g., *CYP2D6*1* and **2*), decreased function (e.g., *CYP2D6*9*, **10*, and **41*), and no function (e.g., *CYP2D6*3–*6*) (2, 3). Because *CYP2D6* is subject to deletions, gene duplications or multiplications, many clinical laboratories also report copy number variations. *CYP2D6*5* represents a gene deletion (no function allele) whereas gene duplications and multiplications are denoted by "xN" (e.g. *CYP2D6*1xN* with xN representing the number of *CYP2D6* gene copies).

Alleles carrying two or more normal function gene copies are categorized as alleles with increased function.

The combination of alleles is used to determine a patient's diplotype. Each functional group is assigned an activity value ranging from 0 to 1 (e.g. 0 for no, 0.5 for decreased and 1.0 for normal function) (3). Supplemental Table S1 describes the activity score values assigned to selected alleles. If an allele contains multiple copies of a functional gene, the value is multiplied by the number of copies present. Thus, the *CYP2D6* activity score is the sum of the values assigned to each allele, which typically ranges from 0 to 3.0 but may exceed 3.0 in rare cases (3).

The CYP2D6 activity score relates to the phenotype classification system as follows (***CYP2D6* Allele Definition** Table (1)): patients with an activity score of 0 are poor metabolizers (PMs), those with a score of 0.5 are considered intermediate metabolizers (IMs), and those with a score of 1.0, 1.5 or 2.0 represent normal metabolizers (NMs). Patients with a score >2.0 are classified as ultrarapid metabolizers (UMs). It should be noted that reference laboratories providing clinical *CYP2D6* genotyping may use varying methods to assign phenotypes. Therefore, it is advisable to note a patient's *CYP2D6* diplotype and to calculate an activity score before making therapeutic decisions about ondansetron or tropisetron therapy.

Genetic Test Interpretation

Clinical laboratories rarely sequence through the *CYP2D6* gene or interrogate every known variant position. Instead, they typically test for variants that are used to determine high frequency allele haplotypes using the star-allele (*) nomenclature system, found at The Human Cytochrome P450 (CYP) Allele Nomenclature Database (http://www.cypalleles.ki.se). Supplemental Table S1 and tables found on the PharmGKB website (1) contains a list of *CYP2D6* alleles, the specific combination of variants that can be used to determine the allele, functional status, and frequency across major ethnic populations as reported in the literature.

Genetic test results are reported as diplotypes, or the combination of the maternal and paternal alleles (e.g. *CYP2D6*1/*2*). Phenotypes are assigned based on the reported *CYP2D6* diplotype, as summarized in Table 1.

The limitations of genetic testing as described here include: (1) rare variants are often not detected; (2) known star (*) alleles not tested for will not be reported, and instead, the patient will be reported as a **1* and 3) tests are not designed to detect unknown or *de novo* variants. Supplemental Data (Genetic Test Interpretation Section) contains additional information regarding *CYP2D6* genetic test interpretation and phenotype assignment.

Available Genetic Test Options

See Supplementary material and www.ncbi.nlm.nih.gov/gtr/ for more information on commercially available clinical testing options.

Incidental findings

Currently, there are no diseases or conditions which have been consistently linked to variation in the *CYP2D6* gene independently of drug metabolism and response.

Other considerations

Not applicable

DRUGS: ONDANSETRON AND TROPISETRON

Background

Ondansetron and tropisetron, highly specific and selective members of the 5-HT_3 receptor antagonists, are used in the prevention of chemotherapy- induced, radiation-induced and postoperative nausea and vomiting (4). 5-HT_3 receptor antagonists suppress nausea and vomiting by selectively binding to 5-HT_3 receptors both centrally and peripherally, thereby preventing serotonin-mediated emetogenic signaling and exhibit a steep dose-response curve (5–7). The 5-HT_3 receptor antagonist class is the cornerstone of prophylactic therapy for moderately to highly emetogenic chemotherapy and radiotherapy (8). All of the medications in this class have been shown to be effective in the prevention of nausea and vomiting; the main differences between these drugs are due variation in pharmacokinetic and pharmacodynamics considerations. 5-HT_3 receptor antagonists are generally well tolerated. Mild headache, constipation and transient elevations in liver enzymes are common side effects. Ondansetron has also been associated with cardiac adverse events such as QTc prolongation (8) (see *Other Considerations* section).

Ondansetron is metabolized to four inactive metabolites by multiple cytochrome P450 enzymes, including CYP3A4, CYP1A2, and CYP2D6, followed by glucuronide conjugation to metabolites not clinically relevant for pharmacologic activity (9, 10). Tropisetron is extensively metabolized by CYP2D6 to inactive metabolites and further conjugated to glucuronides and sulfates (10, 11). Other 5-HT_3 receptor antagonists including dolasetron, palonosetron, and ramosetron are also metabolized via multiple cytochrome P450 enzymes (12–14). CYP3A4 is majorly involved in the demethylation of granisetron to 9'-desmethylgranisetron (15) whereas CYP1A1 is preferentially responsible for the formation of 7-hydroxygranisetron, the main metabolite of granisetron (16).

Linking genetic variability to variability in drug-related phenotypes

There is evidence linking the *CYP2D6* genotype with phenotypic variability in efficacy of ondansetron and tropisetron (see Supplemental Table S2). Application of a grading system to evidence linking *CYP2D6* genotypic variations to phenotypic variability in response to these two drugs indicates an acceptable quality of evidence (Supplemental Table S2). This body of evidence, rather than randomized clinical trials involving pharmacogenetic testing, provides the basis for the ondansetron dosing recommendations in Table 2. Although the evidence to support this recommendation is limited, the recommendation is supported by the quality of these studies, the evidence to support increased metabolism of ondansetron and tropisetron (and many other CYP2D6 substrates) in CYP2D6 ultrarapid metabolizers (17) and the fact that there are suitable alternatives to ondansetron and tropisetron that are not

affected by metabolism by CYP2D6 (4, 18). Although other CYP enzymes contribute to ondansetron metabolism, there are substantial data to support a major role of CYP2D6 in the metabolism of ondansetron (9, 10, 12).

Decreased antiemetic effect (i.e. vomiting) of ondansetron and tropisetron when used for postoperative or chemotherapy-induced nausea and vomiting has been observed in CYP2D6 ultrarapid metabolizers (19, 20). Candiotti et al. genotyped 250 female patients undergoing general anesthesia who received 4 mg ondansetron 30 minutes before extubation (19). CYP2D6 ultrarapid metabolizers had the highest incidence of vomiting (45%) as compared to normal metabolizers (15%) (19). However, there was no difference in the incidence of vomiting between in CYP2D6 intermediate and poor metabolizers as compared to normal metabolizers. In addition, Kaiser *et al.* found similar results in patients (n=270) receiving tropisetron or ondansetron for chemotherapy-induced nausea and vomiting (20). The evidence review yielded no studies describing any substantial impact of CYP2D6 poor metabolizer status on ondansetron adverse events; however, one study reports that CYP2D6 poor metabolizers treated with ondansetron had the fewest episodes of vomiting (20). Although CYP2D6 poor metabolizers had higher serum concentrations of tropisetron than all other patients measured six hours after administration, no dose reduction is recommended per FDA labeling (20).

Dosage Recommendations/Therapeutic Recommendations

Table 2 summarizes the therapeutic recommendations for ondansetron and tropisetron based on CYP2D6 phenotype. Gene duplication has been shown to be associated with higher metabolism and clearance of ondansetron resulting in lower area under the plasma concentration-time curve (17, 21). This translates clinically into a decreased response to ondansetron and tropisetron, specifically increased risk of vomiting in CYP2D6 ultrarapid metabolizers (19, 20). If *CYP2D6* genotype is known, alternative 5-HT_3 receptor antagonist antiemetics not metabolized by CYP2D6 (e.g., granisetron) should be considered in CYP2D6 ultrarapid metabolizers. Although dolasetron, palonosetron, and ramosetron are also metabolized by CYP2D6 (Supplemental Table S3), limited evidence is available regarding the utilization of *CYP2D6* genetic variation to guide use of these drugs.

The strength of this recommendation is based on the evidence provided in Supplemental Table S2 and the availability of suitable antiemetics not metabolized by CYP2D6. Currently, there are limited published data to support a recommendation in CYP2D6 intermediate and poor metabolizers. Of note, the prescribing information for intravenous Zofran® states, based on unpublished data, that the pharmacokinetics of intravenous ondansetron did not differ between CYP2D6 poor metabolizers and CYP2D6 normal metabolizers (22).

At the time of this writing, there are no data available on CYP2D6 genotype's effects on ondansetron or tropisetron response in pediatric patient populations, although there is no reason to suspect that *CYP2D6* genetic variation will affect this drug's metabolism differently in children compared to adults. Because CYP2D6 catalytic activity in neonates (less than one month old) depends strongly on developmental aspects (23), the impact of CYP2D6 in this patient population might be different than adults or older children.

Recommendations for Incidental Findings

Not applicable

Other considerations

The syndrome of congenital prolongation of the QT interval of the electrocardiogram (LQTS) is associated with a risk of potentially fatal polymorphic ventricular tachycardia, which is commonly referred to as torsades de pointes. Drugs that prolong the QT interval, such as ondansetron, should generally be avoided in patients with this diagnosis, as well as in those patients considered to be borderline. In September 2011, the FDA issued a safety communication reporting a change to the medication label by adding a warning to avoid ondansetron use in patients with congenital long QT syndrome (http://www.fda.gov/Drugs/DrugSafety/ucm271913.htm). The alert also recommended ECG monitoring for patients with electrolyte abnormalities, congestive heart failure, bradyarrhythmias, or patients taking concomitant medications that prolong the QT interval. In June 2012, the FDA issued another safety communication reporting changes to the ondansetron label regarding intravenous dosing (http://www.fda.gov/Drugs/DrugSafety/ucm310190.htm). This alert recommended that no single intravenous dose should exceed 16mg. The alert noted new evidence suggesting that QT prolongation is dose dependent. Therefore, in patients for whom genetic testing indicates intermediate or poor CYP2D6 metabolism, potentially elevated blood levels of ondansetron would suggest these patients might be at an even greater risk for torsades de pointes even with the 16 mg maximum dose (24, 25). However, there are no clinical data demonstrating greater QT prolongation in CYP2D6 poor metabolizers.

CYP2D6 genetic variants do not account for all variation observed for ondansetron or tropisetron response. In addition to specific patients factors (such as smokers vs. nonsmokers, male vs. female), other genes have been implicated in the response to ondansetron including the adenosine triphosphate-binding cassette subfamily B member 1 (*ABCB1*) gene (26, 27) and the genes for the serotonin 5-HT_3A and 5-HT_3B receptors (18, 27, 28). Genetic variation in *CYP3A5* has been found to influence concentrations of R-ondansetron; however, to date, there is no data to support how *CYP3A5* variation impacts antiemetic efficacy in individuals taking ondansetron and tropisetron (17). However, one study has found that variation in *CYP3A5* and *CYP1A1* impact systemic clearance and exposure of granisetron in pregnant women (29). Additional studies are needed to elucidate the role of variation in these genes in antiemetic therapy.

Implementation resources for this guideline

The guideline supplement contains resources that can be used within electronic health records (EHRs) to assist clinicians in applying genetic information to patient care for the purpose of drug therapy optimization (see *Resources to incorporate pharmacogenetics into an electronic health record with clinical decision support* sections of supplement). Clinical implementation resources include cross-references for drug and gene names to widely-used terminologies and standardized nomenclature systems, workflow diagrams, a table that translates genotype test results into a predicted phenotype with genetic test interpretation, and example text for documentation in the EHR and point-of-care alerts.

POTENTIAL BENEFITS AND RISKS FOR THE PATIENT

The potential benefit of using *CYP2D6* genotype to guide ondansetron and tropisetron use is that patients with genotypes that are associated with a decreased response (e.g., CYP2D6 ultrarapid metabolizers) may be identified and alternative antiemetics administered. At this time, the evidence does not justify increasing the dose in CYP2D6 ultrarapid metabolizers because dose adjustments based on CYP2D6 ultrarapid metabolism have not been studied and a detailed recommendation of dosing for the different CYP2D6 phenotypes is missing. Additionally, there is a single IV dose maximum of 16 mg in the FDA labeling which might prevent increases in dosing in certain situations. *CYP2D6* genotyping is reliable when performed in qualified laboratories (e.g., CLIA-certified). However, as with any laboratory test, a possible risk to patients is an error in genotyping or phenotype prediction, along with the presence of a rare genomic variant not tested for, which could have long-term adverse health implications for patients.

CAVEATS: APPROPRIATE USE AND/OR POTENTIAL MISUSE OF GENETIC TESTS

Rare *CYP2D6* variants may not be included in the genotype test used and patients with rare variants may be assigned a "wild-type" (*CYP2D6**1) genotype by default. Thus, an assigned “wild-type” allele could potentially harbor a no or decreased function variant. Furthermore, it is important that the genetic testing platform includes testing for gene copy number to identify CYP2D6 ultrarapid metabolizers. Caution should be used regarding molecular diagnostics of *CYP2D6* gene copy number variation since commercially available genotyping results may differ between diagnostic laboratories depending on assay design. Like all diagnostic tests, *CYP2D6* genotype is one of multiple pieces of information that clinicians should consider when making their therapeutic choice for each patient. Furthermore, there are several other factors that cause potential uncertainty in the genotyping results and phenotype predictions. These are discussed in detail in the Supplementary Data online.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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TABLE 1

ASSIGNMENT OF LIKELY CYP2D6 PHENOTYPES BASED ON DIPLOTYPES

Likely phenotype	Activity Score	Genotypes[a]	Examples of *CYP2D6* diplotypes
CYP2D6 ultrarapid metabolizer (~1–2% of patients)[b]	> 2.0	An individual carrying duplications of functional alleles	**1/*1xN, *1/*2xN, *2/*2xN*[c]
CYP2D6 normal metabolizer (~77–92% of patients)	2.0-1.0[d]	An individual carrying two normal function alleles or two decreased function alleles or one normal function and one no function allele or one normal function and one decreased function allele or combinations of duplicated alleles that result in an activity score of 1.0 –2.0.	**1/*1, *1/*2, *1/*4, *1/*5, *1/*9, *1/*41, *2/*2, *41/*41*
CYP2D6 intermediate metabolizer (~2–11% of patients)	0.5	An individual carrying one decreased function and one no function allele	**4/*10, *4/*41, *5/*9*
CYP2D6 poor metabolizer (~5–10% of patients)	0	An individual carrying only no functional alleles	**3/*4, *4/*4, *5/*5, *5/*6*

[a] Assignment of allele function and citations for allele function can be found https://www.pharmgkb.org/page/cyp2d6RefMaterials (***CYP2D6* Allele Definition Table** and ***CYP2D6* Allele Functionality References Table (1)**).

[b] See the ***CYP2D6* Frequency Table (1)** for race-specific allele and phenotype frequencies or see Gaedigk et al (30).

[c] Where *xN* represents the number of *CYP2D6* gene copies. For individuals with *CYP2D6* duplications or multiplications, see supplemental data for additional information on how to translate diplotypes into phenotypes.

[d] Patients with an activity score of 1.0 may be classified as intermediate metabolizers by some reference laboratories.

TABLE 2

DOSING RECOMMENDATIONS FOR ONDANSETRON AND TROPISETRON BASED ON *CYP2D6* GENOTYPE

Phenotype	**Implication**	**Therapeutic Recommendation**	**Classification of Recommendation**[a]	**Consideration for alternative 5-HT_3 receptor antagonists antiemetics**[b]
CYP2D6 ultrarapid metabolizer	Increased metabolism to less active compounds when compared to normal metabolizers and is associated with decreased response to ondansetron and tropisetron (i.e. vomiting).	Select alternative drug not predominantly metabolized by CYP2D6 (i.e. granisetron).[c]	Moderate	Dolasetron, palonosetron, and ramosetron are also metabolized by CYP2D6. Limited evidence is available regarding the utilization of *CYP2D6* genetic variation to guide use of these drugs.
CYP2D6 normal metabolizer	Normal metabolism	Initiate therapy with recommended starting dose.[c]	Strong	
CYP2D6 intermediate metabolizer	Very limited data available for CYP2D6 intermediate metabolizers.	Insufficient evidence demonstrating clinical impact based on *CYP2D6* genotype. Initiate therapy with recommended starting dose.[c]	No recommendation	
CYP2D6 poor metabolizer	Very limited data available for CYP2D6 poor metabolizers.	Insufficient evidence demonstrating clinical impact based on *CYP2D6* genotype. Initiate therapy with recommended starting dose.[c]	No recommendation	

[a] Rating scheme described in the Supplement.

[b] CPIC strength of recommendation: No Recommendation. See rating scheme described in the Supplement.

[c] Drug-drug interactions and other patient characteristics (e.g., age, renal function, and liver function) should be considered when selecting alternative therapy.