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Phenoconversion: Drug-Drug-Gene Interactions

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Abstract
Based on the extensive, poor, intermediate and ultrarapid phenotypes of patients, inferences may be made relative to drug metabolism, ultimately leading to changes in therapeutic drug choice or dosing. Phenoconversion is a phenomenon that occurs when an individual's drug metabolizing capacity is altered due to the combination of a drug-drug interaction and a drug-gene interaction. Phenoconversion can affect pharmacokinetics as well as pharmacodynamics. Some examples of phenoconversions include amiodarone-warfarin, duloxetine-codeine, rifampin-clopidogrel, and rifampin-warfarin. Pharmacists must consider phenoconversion in cases of multi-drug therapy.

Introduction/Background

Pharmacogenomics (PGx), in relation to drug metabolism, stems from the basics of the human genome itself. It begins with the genotype (specific inherited alleles, forms of a gene), which, along with other factors, leads to the phenotype (expression of the individual gene via physical traits or physiological functions).[1] Relative to the deoxyribonucleic acid (DNA) code are polymorphisms, which are genetic mutations found in more than 1 percent of the population. Most often these mutations are single base substitutions known as single nucleotide polymorphisms (SNPs).[1] With SNPs, resulting variant genes and subsequent expressions are what define an individual's inherent capabilities, such as those related to drug metabolism. Based on the occurrence of SNPs and other mutations, some individuals will have "normal" protein function, while others may not.[2] Some of the proteins of interest function to metabolize drugs, therefore when their function is altered or absent, two aspects of drug metabolism can change dramatically the extent of drug metabolism and the rate of drug metabolism. In general, a "wild-type" allele (normal gene) will code for the typical or normal enzyme, and an individual with this type of allele would be considered an extensive (normal) metabolizer (EM; NM) of drugs which are substrates for the enzyme. In contrast, individuals may receive variant alleles, which result in metabolism phenotypes of poor (PM), intermediate (IM), or ultrarapid (UM). Based on these phenotypes, inferences may be made relative to drug metabolism, ultimately leading to changes in therapeutic drug choice or dosing (e.g., choice of antiplatelet medication or alteration of dose for a chemotherapeutic agent).[2,3]

Pharmacogenomics as explained above has had greater uptake in recent years, resulting in more proactive genetic testing occurring prior to drug administration in an attempt to decrease or avoid adverse drug reactions that are linked to variant alleles. However, while PGx is starting to be applied in practice today, the problem of phenoconversion has presented itself as another piece of the puzzle. Phenoconversion is an alteration in an individual's drug metabolizing capacity due to the combination of a drug-drug interaction and a drug-gene interaction. In other words, an individual's phenotype is transformed as a consequence of a drug-drug-gene interaction (DDGI) (e.g., an IM being converted to a PM). One of the interactions, the drug-drug interaction, is familiar to pharmacists since individuals are often put on multidrug therapies that may lead to additive effects or possible toxicities either by synergistic or antagonistic mechanisms. The drug-gene interaction component of phenoconversion is described by the previously discussed definition of pharmacogenomics and different metabolic "intrinsic" (inherited) phenotypes.[1-3] The consequence of a DDGI is altered pharmacodynamics and/or pharmacokinetics. Pharmacodynamic (PD) interactions occur when one drug alters the response to another drug through alteration in drug receptors without the influence of a change in drug concentration. Pharmacokinetic (PK) interactions occur when a drug interferes with the absorption, distribution, metabolism and/or excretion (ADME) of another drug, here altering the concentration of the original drug.[3] Either one of these situations can create phenoconversion, but ultimately an individual's genotype will no longer match their predicted phenotype. A DDGI occurs when the first drug is given to an individual with altered drug metabolism due to a variant genotype (drug-gene interaction) followed by an additional drug that alters the PD or PK of the first drug (drug-drug interaction). Now, instead of a drug-gene interaction alone or a drug-drug interaction alone, we must consider a DDGI, and this phenoconversion can result in increased or decreased drug concentrations with subsequent adverse effects or therapeutic failures, respectively. The following are individual examples of phenoconversion.

Amiodarone and Warfarin

Warfarin is a frequently prescribed medication for anticoagulation therapy and is commonly given to patients that have atrial fibrillation, a heart valve replacement or a history of clotting for prevention of stroke and other sequelae. Warfarin is manufactured as a racemic mixture, where 50 percent exists as the S-isomer and the remainder as the R-isomer. The S-isomer, however, is almost five times more potent than the R-isomer, resulting in this form's more extensive role in warfarin's therapeutic activity.[1] As such, the cytochrome P450 enzyme that is responsible for metabolizing warfarin's S-isomer, CYP2C9, plays a significant role in determining the dose that will be required in a given patient.[1,4] Those individuals with a *1/*1 genotype are considered to be more extensive in their ability to metabolize warfarin. Individuals with some combination containing a *2 or *3 allele (e.g., *1/*2, *2/*2, *2/*3, etc.) have reduced enzyme activity, meaning that warfarin's clearance is decreased and warfarin will linger in the body for a longer time as a result of a longer half-life. A decrease in the clearance of

warfarin of approximately 30 to 40 percent can be expected when an individual has a *2 allele, with an individual who is homozygotic (*2/*2) having a greater decrease in clearance as compared to the heterozygotic individual (*1/*2). The effects of CYP2C9 allele variation on the clearance of warfarin is even more pronounced in individuals with a *3 allele, where a homozygotic individual may have a decreased clearance approaching 80 to 90 percent. The *2 and *3 alleles are most frequently found in those of European descent. These phenotypes are not categorized in the typical manner as extensive metabolizers, intermediate metabolizers, or poor metabolizers, but instead can be thought of as existing on a continuum. In this manner, a *1/*1 genotype would be comparable to an extensive metabolizer with efficient metabolism and a *3/*3 individual would resemble a poor metabolizer. Other alleles associated with decreased enzyme activity include CYP2C9*5, *6, *8, and *11, which are found most commonly in the African American population.[4] When another drug that utilizes this CYP is prescribed for a patient that is already taking warfarin, there is a potential for decreasing the enzyme's ability to metabolize warfarin, thereby resulting in a need to adjust the dose accordingly (Table 1).

In order to ensure that a patient is receiving the correct dose of warfarin for their phenotype, that patient's INR, or international normalized ratio, is monitored closely. When measuring an INR, a small collection of blood is analyzed in order to determine the amount of time it takes for that patient's blood to clot. A typical healthy individual that is not taking warfarin could expect an INR value of approximately 1, while those consuming warfarin would have higher INR values. When a patient has suffered from or is at risk of developing a clot, it is necessary to keep the INR value between 2 and 3. In individuals that have had a mechanical heart valve placed, an INR between 2.5 and 3.5 is desired. The INR must be monitored by a health care professional regularly, as many medications, foods and drinks can impact the anticoagulant effects exhibited by warfarin.[5]

For example, ML is an 80-year-old woman who has been taking warfarin for four years after she developed a deep vein thrombosis. Her INR has remained steady at 2.7 while on her prescribed dose of 3 mg daily throughout those years of use. Her genotype is *CYP2C9*2/*3*, indicating that she has decreased warfarin metabolism, thus defining a drug-gene interaction. Here, ML has a 60 percent decrease in the clearance of warfarin when compared to the normal wild-type, *1/*1 genotype.[1] While not specifically defined for CYP2C9, ML may generally be considered an intermediate metabolizer on the continuum from *1/*1 to *3/*3. Recently, ML was hospitalized to treat a ventricular arrhythmia. During this time, she was started on amiodarone.

Amiodarone also utilizes the CYP2C9 enzyme and is known to be a moderate inhibitor of this enzyme. This causes a reduction in warfarin clearance by 50 to 80 percent.[6] Enzyme inhibition is primarily caused by the metabolite, desethylamiodarone, which is a much more potent inhibitor of CYP2C9 than the parent amiodarone form. Furthermore, it has been demonstrated that the degree to which CYP2C9 is inhibited is related to the amiodarone dose that is administered.[4] Therefore, patients taking higher doses of amiodarone would experience a greater decrease in CYP2C9 function and would resultantly require a lower dose of warfarin.

In the case involving ML, phenoconversion would effectively move ML along the continuum from resembling an intermediate metabolizer to resembling a poor metabolizer.[1] Consequently, ML would have higher concentrations of warfarin in her body, thus potentiating the anticoagulant effects of her

Table 1. The *CYP2C9* "warfarin dosing continuum." The *2 and *3 variant alleles impart decreased warfarin metabolism (clearance), necessitating decreased warfarin maintenance doses.[4]

VKORC1	*CYP2C9*[a]					
	*1/*1	*1/*2	*1/*3	*2/*2	*2/*3	*3/*3
GG[b]	5-7 mg	5-7 mg	3-4 mg	3-4 mg	3-4 mg	0.5-2 mg

[a] *1 – normal CYP2C9 activity; *2 – somewhat decreased CYP2C9 activity; *3 – greatly decreased CYP2C9 activity.

[b] The common VKORC1 genotype, imparting "normal" warfarin pharmacodynamics.

medication, as can be verified through an increase in her typically stable INR from 2.7 to 5.3. This places ML at an increased risk for bleeding.[4,7,8]

The original drug-gene interaction is a component of the overall interaction with the addition of amiodarone. Due to the decreased warfarin metabolism rate as a result of the DDGI, it is recommended that on the third or fourth day following amiodarone's inclusion in the patient's medication regimen, the usual warfarin dose should be decreased by one-third to one-half. In ML's situation, that means that the dose should be decreased from 3 mg daily to 1.5 to 2 mg daily. Her INR should be monitored closely during this time until stabilized.[8]

Duloxetine and Codeine

SK, an African American woman, brings a prescription for acetaminophen 300 mg/codeine phosphate 30 mg to the pharmacy because she has been having severe back pain for the past three days. Previously, as part of a pharmacy program emphasizing personalized medicine, SK provided a DNA sample via a cheek swab. The laboratory working with the pharmacy tested for many different genes related to drug metabolism; this included the gene coding for the drug metabolizing enzyme CYP2D6, for which SK had the genotype of *CYP2D6*4/*17*, indicating that SK is an intermediate metabolizer. From this genetic test, it is determined that SK may not effectively metabolize codeine to its active metabolite, morphine.[9] The doctor writes the acetaminophen 300 mg/codeine phosphate 30 mg prescription for one tablet every four hours as needed.[10] When checking the prescription, the pharmacist discovers that SK is also prescribed duloxetine for her depression. This is a potential drug-drug-gene interaction because duloxetine is a moderate inhibitor of CYP2D6 and could therefore affect the metabolism of codeine, which can result in inadequate pain relief for SK.[6]

The phenotype of the patient for the *CYP2D6* gene is determined through an activity score, which is calculated by adding the scores of the two alleles of the individual's genotype. The alleles *1, *2, *27, *33, *45, *46, *39, *48, and *53 have normal activity and are given a score of 1. Reduced function alleles include *9, *10, *17, *29, *41, *50, *54, *55, *59, *69, and *72; these alleles have an activity score of 0.5. All other, currently identified alleles are considered non-functional and have an activity score of 0.[9] Ultrarapid metabolizers of codeine have an activity score over 2, which can occur when there are more than two functional alleles present, as some individuals have two or more copies of the gene. Normal metabolizers have an activity score between 1 and 2, intermediate metabolizers have a score of 0.5, and poor metabolizers have a score of 0.[10] Table 2 summarizes these activity scores and the metabolizing function of various alleles of *CYP2D6*. SK would have an activity score of 0.5, receiving a score of 0 from the *4 allele and 0.5 from the *17 allele; her phenotype would therefore be an intermediate metabolizer.

As a moderate inhibitor of CYP2D6, duloxetine could prevent codeine from being metabolized to morphine and prevent it from having a therapeutic effect. A moderate inhibitor of a CYP enzyme is defined as causing a twofold or more increase but less than fivefold increase in area under the curve (AUC) of the enzyme's substrate.[6] In the case of SK, the duloxetine could inhibit the CYP2D6 enzyme, a product of the *17 allele, which already has reduced activity; this would inhibit codeine conversion to morphine, eliminating most of the analgesic effect provided by the medication. SK would undergo a phenoconversion from an intermediate metabolizer of codeine to a poor metabolizer if she were to take duloxetine and codeine concomitantly. For instance, her metabolism of codeine may be considered similar to someone with the *CYP2D6*4/*4* genotype, resulting in little or no therapeutic benefit because the drug is not metabolized to its active metabolite (codeine).[9]

Table 2. Examples of *CYP2D6* Variants.[a]

Function	Example Alleles (Activity score)[b]
Normal	*1[c], *2, *27, *33, *35, others (1)
Decreased	*17, *29, *41, *49, *50, others (0.5)
Lost	*3, *4, *5, *6, *7, others (0)

[a] Adapted by permission from Macmillan Publisher Ltd: Clinical Pharmacology & Therapeutics 2012;91(2):321-6, Crew et al., copyright 2012.

[b] The activity score relates formation of metabolite to an individual's genetics, with those producing more metabolite being assigned a higher activity score.

[c] Designated as the "wild-type," and the most frequently occurring form with normal function.

If codeine is going to be used in patients taking drugs that moderately inhibit the CYP2D6 enzymes such as duloxetine, the patient should be carefully monitored to determine whether or not pain relief is adequate. There are also alternative therapy options for pain management that do not involve the CYP2D6 metabolism pathway and therefore would avoid phenoconversion due to concomitant therapy of codeine with duloxetine. Fentanyl, oxymorphone, hydromorphone and morphine are among the analgesics not metabolized by CYP2D6. Tramadol, hydrocodone and oxycodone should be avoided because they are also metabolized by CYP2D6 to their active forms and could potentially be affected by the inhibitory effects of duloxetine. In addition, there are non-opioid based pain medications such as NSAIDs and acetaminophen that do not require CYP2D6 for activation or metabolism. The choice of alternative therapy should be made based on pain severity relative to each individual.[9] In the case of SK, the pharmacist called the prescriber, who agreed to switch the prescription from acetaminophen 300 mg/codeine phosphate 30 mg to a non-opiate alternative.

Rifampin and Clopidogrel

Clopidogrel is an antiplatelet prodrug whose activation is known to be dependent upon the CYP2C19 phenotype of the given individual. For CYP2C19, there are several variant alleles that will dictate the patient's capacity for prodrug activation (metabolism) to the active metabolite. The most common form of the *CYP2C19* gene, *1, is considered the wild-type, or normal allele, and designates extensive (normal) metabolism. Therefore, an individual that is homozygous (*1/*1) would exhibit extensive metabolism of the clopidogrel prodrug into its active form. Loss of enzyme function is observed in the *2, *3, *4, *5, *6, *7, and *8 variant alleles. Of those individuals that possess a *CYP2C19* loss-of-function allele, approximately 90 percent possess the *2 allele, making it the most common variant form. When paired with the wild-type *1 in a heterozygous individual (e.g., *1/*2), the patient will be an intermediate metabolizer of clopidogrel. Homozygous individuals with decreased function alleles (e.g., *2/*2) are considered poor metabolizers. Additionally, there is one known variant allele that is associated with increased metabolic function, the *17 allele. Individuals that are heterozygous (*1/*17) or are homozygous for the *17 allele are considered ultrarapid metabolizers of clopidogrel.[1,6] It is vital that a patient's phenotype is determined prior to clopidogrel therapy, as this will determine the possibility of therapeutic success that the patient may experience. Typically, with antiplatelet therapy for coronary artery stent placement, if a patient is found to be an intermediate or poor metabolizer, other therapies should be considered due to the lack of complete conversion of the prodrug to its active form and the increased risk of adverse cardiovascular events noted in such patients.[11]

JM is a 49-year-old man who has enjoyed smoking a pack of cigarettes daily for the past 40 years. He has a maternal family history of hypertension and hyperlipidemia. Recently, JM suffered a myocardial infarction while working at his job as a prison guard. During heart catheterization, a stent was placed in two of JM's coronary arteries. JM was started on clopidogrel 75 mg daily. At the time JM started clopidogrel, a blood sample was sent for *CYP2C19* genotyping. The lab reports JM's genotype to be *CYP2C19*1/*2*, thus illustrating the drug-gene interaction. His physician, not being familiar with the genotyping data, increases the clopidogrel dose to 150 mg daily. Several months later, while attending an annual checkup required for all prison employees, JM received a positive tuberculin skin test result. After additional blood and sputum tests were conducted, it was determined that JM had latent tuberculosis, and was placed on rifampin 600 mg therapy for four months.

Rifampin is a known inducer of the CYP2C19 enzyme, and consequently causes a twentyfold increase in the metabolizing capabilities of this enzyme.[6] Therefore, when rifampin and clopidogrel are used concomitantly, the amount of prodrug that is converted to the active metabolite within the body vastly increases for the duration of the dual medication usage. Although JM's genotype remains *CYP2C19*1/*2*, thus reflecting an intermediate metabolizer, his phenotype may now more closely resemble that of a *1/*1 extensive metabolizer. With the increased dose of clopidogrel 150 mg daily being employed, and the increased metabolism of clopidogrel to its active form, higher concentrations of therapeutic metabolite will be found in JM's body. This puts JM at an increased risk of adverse drug events, including bleeding. In reality, as JM is inherently a *1/*2, intermediate metabolizer, he should receive an alternative antiplatelet drug. In this scenario, however, the physician chose to increase the dose of clopidogrel. The addition of rifampin to treat JM completes the drug-drug-gene interaction and the likely phenoconversion of JM from an intermediate to extensive metabolizer, albeit, during rifampin therapy.

Rifampin and Warfarin

The previous example addresses a DDGI relative to a prodrug. The following example addresses a DDGI relative to an active drug, here, warfarin.

NF, a 62-year-old African American male, is admitted to the hospital with chest pain and shortness of breath. He had a positive purified protein derivative (PPD) tuberculin skin test two months ago and, after a chest x-ray, was diagnosed with latent tuberculosis (TB); he currently takes rifampin 600 mg daily. Another chest x-ray shows that his TB had not become active, and the doctor orders a ventilation perfusion scan, which shows that the blood flow in NF's lung is low compared to the air in his lungs. The doctor suspects NF has a pulmonary embolism (PE) and orders fondaparinux sodium injections in order to treat the PE. NF is started on warfarin concomitantly with the intent of using warfarin for anticoagulation therapy beyond the hospital stay. The electronic medical record system allows access to NF's genetic testing results to be retrieved from a secure database. The data indicate that NF has a *CYP2C9*2/*3* genotype, and has the common genotype of vitamin K epoxide reductase complex subunit 1 (*VKORC1*), which is also involved in the response to warfarin. Utilizing the package label pharmacogenomic-based dosing chart, NF is started on 3 mg of warfarin daily.[4,10]

Rifampin is a moderate inducer of the CYP2C9 metabolizing enzyme and thus causes a 50 to 80 percent decrease in the AUC for drugs metabolized by CYP2C9, such as warfarin.[6] The induction of CYP2C9 increases warfarin metabolism, increasing its clearance and shortening the warfarin half-life. This can result in decreased anticoagulation effect putting the individual at risk of clot formation; sub-therapeutic warfarin concentrations can result in clot formation that can have fatal consequences for the patient. Based solely on his genotype of *CYP2C9*2/*3* resulting in a poor metabolizer-like phenotype, the daily warfarin dose of 3 mg would be considered appropriate. However, NF has latent TB and is taking rifampin. The use of rifampin has resulted in a phenoconversion in NF as it has caused an increase in the metabolism of warfarin, resulting in a clearance similar to that of an individual with a *CYP2C9*1/*1* genotype, or that of a normal metabolizer. The 3 mg dose of warfarin would probably not be sufficient in preventing blood clots in a normal metabolizer and is thus not sufficient for NF while the rifampin is increasing his metabolism of warfarin. The dose of warfarin must be guided by monitoring his INR and working to get the value into the therapeutic range.

The pharmacist in the hospital realizes that there is a drug-drug-gene interaction when verifying the warfarin order and calls the doctor in order to prevent NF from being readmitted to the hospital in the future with another blood clot. Warfarin could still be given to NF, but he would require a higher dose (5-7 mg) in order for it to be effective.[4] NF's INR is monitored during his hospital stay, and the warfarin dose increased until his INR is at a therapeutic level.

When NF finishes his course of rifampin therapy in two months, the higher dose of warfarin given previously will no longer be required. Warfarin metabolism will no longer be induced, as the rifampin will no longer be "on board." NF's warfarin dose needs to be decreased because his genotype suggests decreased metabolism as compared to a *1/*1 normal metabolizer. On the current dose and with relatively decreased metabolism, the concentration of warfarin will increase, putting NF at an increased risk for bleeding as noted by a likely supratherapeutic INR.[4] NF's INR should be closely monitored while the dose is being decreased in order to ensure he receives the correct dose.

Conclusion - What this Means for Pharmacists

The above examples depict some of the more distinct cases of phenoconversion that are already evident in practice today. They included both those which led to an increase in function of metabolic proteins and a decrease in function of metabolic proteins, but both were based on allelic differences in genetic make-up relative to concomitant drug use, or a DDGI. Therefore, phenoconversion should be considered within clinical judgment in cases of multi-drug therapy, and knowledge of drug-drug *and* drug-gene interactions is necessary to optimize therapeutic effects while minimizing or avoiding adverse drug events.

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