NEWS LETTER

Pharmacotherapy Update

from the Department of Pharmacy

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Pharmacogenomics

By Jessica Dusky, Pharm.D. Candidate

Extensive research is being conducted in the area of pharmacogenomics with the hope of better understanding the role this field plays in everyday clinical practice. Traditionally, drugs are prescribed to patients based on studies assessing the "average" population; however, there are many variations in human DNA that affect responses to medications. Pharmacogenomics are being evaluated for predicting drug response based on DNA, tailoring drug therapy for the patient, and decreasing adverse drug reactions.

Single nucleotide polymorphisms (SNPs) are the genetic variation most commonly identified that can affect drug response and disease pathways in different individuals. The terms pharmacogenetics and pharmacogenomics are often used interchangeably. Pharmacogenetics are single gene variations and pharmacogenomics are multiple gene variations which cause corresponding drug responses. Genetic variations affect drug response through pharmacokinetic and pharmacodynamic interactions. Pharmacokinetics is defined as what the body does to a drug (e.g., absorption, distribution, metabolism, and excretion), while pharmacodynamics is defined as what a drug does to the body (e.g., time-dependent killing, concentration-dependent killing, and post-antibiotic effect).

In terms of pharmacokinetics, SNPs may affect both Phase I and Phase II metabolism. Phase I metabolism consists of oxidation, reduction, hydrolysis, and the cytochrome P450 (CYP450) isoenzyme system. The majority of drugs are metabolized by CYP450 3A4/5 and 2D6 isosenzymes. It is estimated that SNPs affect the CYP450 2D6 or 2C19 enzyme systems in approximately 1% of the population. Phase II metabolism involves conjugation (e.g., acetylation, glucuronidation, sulfation, and methylation).

Based on pharmacogenomics, an individual may be an extensive (normal) metabolizer (EM), poor metabolizer (PM), or ultra-extensive metabolizer (UM). Extensive metabolizers (i.e., normal metabolizers; wild type allele) have normal activity and anticipated responses to drugs are demonstrated with standard doses. Poor metabolizers have a specific CYP450 isoenzyme with decreased or no activity (two nonfunctional alleles); thus, producing increased toxicity from substrate drugs or decreased efficacy from drugs requiring activation (i.e., pro-drugs). Conversely, UMs often have gene duplication (more isoenzyme) and will experience decreased efficacy from substrate drugs or increased toxicity from prodrugs. As an example, codeine may have little or no effect in an individual who is a PM (variations to

CYP450 2D6). This is because codeine is a prodrug and requires conversion to morphine via the CYP450 2D6 to produce a clinical effect. On the other hand, UMs may experience enhanced analgesia from codeine as well as more adverse effects.

Not only can genetic variations affect Phase I metabolism, but they can also affect Phase II metabolism or conjugation reactions. Patients who are slow acetylators are at an increased risk for peripheral neuropathy from isoniazid or at an increased risk of developing systemic lupus erythematosus (SLE) from procainamide, since both of these drugs need to be acetylated for metabolism. However, patients who are fast acetylators may not respond to these medications because of increased metabolism.

Genetic polymorphisms can also affect drug receptors and signal transductions which have the potential to alter the effect of drugs on the body. Most of these pharmacodynamic interactions are not clearly understood, however, an example is the overexpression of the HER2/neu oncogene in some breast cancers. The treatment of this oncogene appears to be most beneficial with trastuzumab (Herceptin®), which specifically targets the gene overexpression.

It is important to be able to detect genetic variations in patients. Presently, there is one genotyping test approved by the Food and Drug Administration (FDA). The Roche *AmpliChip* Cytochrome P450 test determines a patient's ability to metabolize drugs through CYP450 2D6 and 2C19 isoenzymes. This test is done at a health care facility or a physician office. The Roche *AmpliChip* Cytochrome P450 test costs approximately $520 and requires an average of 8 hours to determine the results. The device to interpret the results costs over $250,000. It is important to note that this test only evaluates two CYP450 isoenzymes and does not explain in depth the specific variations. Another recent advancement in pharmacogenomics is the approval of thiopurine methyltransferase (TPMT) testing for gene variation when administering 6-mercaptopurine (6-MP). Genotyping of TPMT may help to identify patients at risk for life-threatening bone marrow suppression.

In summary, it is anticipated that specific pharmacogenomic tests will be used as a primary measure to determine the correct drug and dose for a patient, especially for medications with a narrow therapeutic index. The current approach for prescribing medications to the "average" patient will eventually move to more individualized therapy, and the end result is expected to be an improvement in drug efficacy and safety.

Proton Pump Inhibitors (PPIs) Therapeutic Interchange

Rationale: TAP Pharmaceuticals no longer has a contract for lansoprazole capsules (i.e., significant price increase), therefore, the Cleveland Clinic Hospitals have made a change in the automatic therapeutic interchange for the proton pump inhibitors (PPIs). As of January 3, 2006, the PPI on the Cleveland Clinic Formulary for **adult** patients who do not require a suspension is esomeprazole (Nexium®). All new medication orders for PPIs (e.g., lansoprazole, omeprazole, pantoprazole, and rabeprazole) for oral (PO) and intravenous (IV) administration, will be automatically converted to esomeprazole. The PPI on the Formulary for **adult** patients who require an oral suspension or nasogastric (NG) administration is lansoprazole orally-disintegrating tablets (Prevacid® SoluTab™). The reason for this is because 1) there is no recipe to compound an esomeprazole suspension, and 2) it is difficult to ensure when esomeprazole capsules are opened and placed in water that all of the pellets inside are administered to the patient (i.e., not sticking to the medicine cup or inside an oral syringe).

Dose Conversion Chart for PPIs for Oral Administration:

Lansoprazole to Esomeprazole

Lansoprazole (Prevacid®) 30 mg once daily = Esomeprazole (Nexium®) 40 mg once daily
Lansoprazole (Prevacid®) 30 mg twice daily = Esomeprazole (Nexium®) 40 mg twice daily
Lansoprazole (Prevacid®) 15 mg once daily = Esomeprazole (Nexium®) 20 mg once daily

Omeprazole to Esomeprazole

Omeprazole (Prilosec®) 40 mg once daily = Esomeprazole (Nexium®) 40 mg once daily

Pantoprazole to Esomeprazole

Pantoprazole (Protonix®) 40 mg once daily = Esomeprazole (Nexium®) 40 mg once daily

Rabeprazole to Esomeprazole

Rabeprazole (Aciphex®) 20 mg once daily = Esomeprazole (Nexium®) 40 mg once daily

Dose Conversion Chart for PPIs for IV Administration:

Lansoprazole IV to Esomeprazole IV

Formulary Restriction

- Regardless of the route of administration (e.g., continuous infusion [CI], IV Piggyback [IVPB], or IV Push), IV PPI use is restricted to Staff Physicians from the Department of Gastroenterology for patients with a confirmed, acute GI bleed (e.g., EGD/endoscopy) to prevent re-bleeding.
- For initiation of an IV PPI, patients must be in an ICU setting, but therapy may be continued on all nursing units.
- Based on available data in the literature, for prevention of re-bleeding in patients with an acute GI bleed, an IV bolus of a PPI followed by a CI should be used.
- IV PPI CI should be used for no longer than 72 hours (i.e., patients need to be converted to PO or NG administration as soon as possible using esomeprazole 40 mg PO or lansoprazole SoluTab™ 30 mg NG once daily).
- If patients continue to be NPO after 72 hours, then the esomeprazole CI should be converted to esomeprazole 40 mg IV Push once daily. Esomeprazole IV Push should only be dispensed for patients initiated on esomeprazole CI in the ICU who are unable to be converted to esomeprazole PO or lansoprazole SoluTab™ NG administration.
- Esomeprazole 40 mg IV = Esomeprazole 40 mg PO or Lansoprazole SoluTab™ 30 mg NG

Therapeutic Interchange Dose Conversion:
Lansoprazole (Prevacid®) 60 mg IV bolus, followed by 6 mg/hr infusion for up to 72 hours =
Esomeprazole (Nexium®) 80 mg IV bolus, followed by 8 mg/hr infusion for up to 72 hours

Dose Conversion Chart for PPIs for Oral Suspension or NG Administration:

Esomeprazole Capsules to Lansoprazole SoluTabs™

Esomeprazole (Nexium®) 40 mg once daily	= Lansoprazole (Prevacid® SoluTab™) 30 mg once daily
Esomeprazole (Nexium®) 40 mg twice daily	= Lansoprazole (Prevacid® SoluTab™) 30 mg twice daily
Esomeprazole (Nexium®) 20 mg once daily	= Lansoprazole (Prevacid® SoluTab™) 15 mg once daily

Prevacid® SoluTabs™ (orally-disintegrating tablets):
Prevacid® SoluTabs™ should not be swallowed whole or chewed. Place tablet on tongue; allow to dissolve (with or without water) until particles can be swallowed.

Prevacid® SoluTabs™ may also be administered via an oral syringe (for NG administration):

- Place the **15 mg SoluTab™** in a 5 mL oral syringe and draw up 4 mL water, *or*
- Place the **30 mg SoluTab™** in a 10 mL oral syringe and draw up 10 mL water
- Shake gently to allow for quick dispersal of SoluTab™
- After the SoluTab™ has dispersed, administer to the patient within 15 minutes
- Refill the syringe with water (2 mL for the 15 mg tablet; 4 mL for the 30 mg tablet), shake gently, and then administer any remaining contents.

Note: For the Children's Hospital, pediatric patients requiring a PPI may receive esomeprazole capsules, lansoprazole SoluTabs™, or lansoprazole IV (IV formulation is restricted).

FDA Public Health Advisory

Recently, the Food and Drug Administration (FDA) warned consumers and healthcare professionals about the risks of filling U.S. prescriptions out of the country. This particular risk involves the dispensing of the wrong medication since some FDA-approved products carry the same brand name as products marketed outside of the U.S. but contain different active ingredients. This leads to preventable pharmacy errors. The FDA has found 18 foreign drug products that use the same brand name as an FDA-approved medication but contain different active ingredients. A select group of these medications can be found in Table 1 and the remaining products can be found at **http://www.fda.gov/oc/opacom/reports/confusingnames.html**.

Table 1. Select Identical U.S. and Foreign Brand Names Associated with Different Active Ingredients

Brand Name	U.S. Active Ingredient	U.S. Indication	Foreign Active Ingredient	Foreign Indication	Foreign Country
Calan®	verapamil	Heart conditions	vinpocetine	Stroke symptoms	Japan
Flomax®	tamsulosin	Enlarged prostate	morniflumate	Anti-inflammatory	Italy
Rubex®	doxorubicin	Cancer	ascorbic acid	Vitamin C deficiency	Ireland
Urex®	methenamine	Urinary tract infections	furosemide	Water pill	Australia

Additionally, the FDA website lists similar U.S. and foreign brand names that have different active ingredients. Consumers filling U.S. prescriptions while traveling abroad or through foreign Internet pharmacies are at an increased risk of receiving products with different active ingredients, potentially adversely affecting their health.

Cleveland Clinic
Department of Pharmacy/Hb-03
Drug Information Center