Why There Is No Cookbook Approach to Palliative Care: Implications of the P450 Enzyme System

Kim K. Kuebler, MN, RN, ANP-CS, James Varga, MBA, PharmBS, and Ronald A. Mihelic, PharmD

Integrating palliative interventions throughout the clinical course of patients’ cancer treatment experience promotes quality of life. As defined and updated by the World Health Organization (2002), “palliative care . . . provides relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychological and spiritual” (p. 10). Palliative care interventions should be considered throughout patients’ disease trajectory and not reserved for the imminently dying or performed within a time-defined framework, such as at the end of life (Davis, Walsh, Le-Grand, & Lagman, 2003; Last Acts, 2002; Sepulveda, Marlin, Grand, & Lagman, 2003; Davis, 2003). This article is intended to provide oncology nurses with a basic understanding of the P450 enzyme system as its relevancy to nursing practice. However, oncology nurses providing palliative symptom management must have a working knowledge of the P450 enzyme system to recognize the variability that exists among individual medication reactions or why a “cookbook approach” to symptom management is not always effective and appropriate. This article describes the variations associated with medication metabolism with reference to ethnic differences. Having a basic understanding of the P450 enzyme system and, more specifically, the CYP2D6 influence on the metabolism of common medications used in palliative symptom management can help to prevent medication toxicity or underdosing, which interferes with patients’ quality of life.

Key Words: cytochrome P-450 enzyme system, pharmacokinetics, palliative care

A plethora of literature describes the impact of the P450 enzyme system, but this information is limited regarding its relevancy to nursing practice. However, oncology nurses providing palliative symptom management must recognize the variability that exists among individual medication reactions or why a “cookbook approach” to symptom management is not always effective and appropriate. This article describes the variations associated with medication metabolism with reference to ethnic differences. Having a basic understanding of the P450 enzyme system and, more specifically, the CYP2D6 influence on the metabolism of common medications used in palliative symptom management can help to prevent medication toxicity or underdosing, which interferes with patients’ quality of life.

Drug Interactions

Patients with advanced cancer receive an average of five or more medications at any given time for symptom relief. Polypharmacy increases the risk of adverse drug interactions (Davis & Homsi, 2001). Drug interactions generally fall into two categories: pharmacodynamic or pharmacokinetic.

Pharmacodynamic interactions are related to a drug’s mechanism of action on physiologic function. Drug interactions of this type frequently involve competition at a specific receptor site or neuronal pathway. Drug metabolism may remain unaltered. For example, a common pharmacodynamic drug-to-drug interaction may involve the concomitant use of an antimuscarinic drug (anticholinergic) and a prokinetic drug (antacid). When these drugs are prescribed together, the final pathway for the prokinetic drug (e.g., metoclopramide) is cholinergic. A drug with anticholinergic properties (e.g., diphenhydramine) may block the same receptor or pathway of metoclopramide; ultimately, this competition will diminish the

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therapeutic benefit of the prokinetic drug (Tucker, 2000).

Pharmacokinetics is the movement of drugs within biologic systems (Johnson, Newkirk, & White, 1999). Pharmacokinetic interactions are related to absorption, distribution, biotransformation, or excretion of a drug. Patient variables that affect a drug’s pharmacokinetics include disease state, age, race, diet, and other drugs being given concurrently. Absorption and distribution have long been associated with drug interactions. More recently, attention has focused on drug biotransformation and the role of enzymes that metabolize drugs in the liver and other sites. The cytochrome P450 (CYP450) system is a major enzyme system responsible for drug metabolism. As the P450 system has become elucidated further, the potential for predicting pharmacokinetic drug interactions has increased accordingly (Twycross, Wilcock, Charlestown, & Dickman, 2002; Wolf & Smith, 1999). A pharmacokinetic interaction involving the CYP450 enzyme pathway occurs, for example, when warfarin and cimetidine are given concomitantly. Warfarin is metabolized principally by the CYP2C9 enzyme, and cimetidine is a known inhibitor of many CYP450 enzymes, including CYP2C9. When cimetidine is given in addition to warfarin therapy, warfarin levels may increase dramatically, placing patients at an increased risk of bleeding.

**Implications of the P450 Enzyme System**

Nurses must have an appreciation of the CYP450 system and its role in drug metabolism and recognize that genetic variability does exist within this system. This patient variability has the potential to affect drug metabolism and cause drug interactions (Wolf & Smith, 1999). Ideally, this knowledge should influence clinical practice and therapeutic decision making. In reality, knowledge regarding the CYP450 system and patient variability, although not new, has had limited impact on therapeutic decision making (Tucker, 2000). Reliance on “cookbook” prescribing and algorithms may potentiate existing problems, thus inadvertently affecting the practice of best care.

Many drugs can be classified as CYP enzyme substrates, inhibitors, or inducers. A substrate is a drug that is biotransformed by an enzyme, and an enzyme inhibitor is a drug that blocks the activity of a particular enzyme, thereby restricting the biotransformation of another drug. Conversely, a drug that promotes the upregulation of a particular enzyme and encourages the biotransformation of another drug is an enzyme inducer. Although inhibitors and inducers do not necessarily trigger clinically significant drug interactions with substrates, caution should be exercised when prescribing two known drugs that, when combined, may perpetuate a drug interaction (see Tables 1–3).

With that in mind, if a drug interaction is to occur, patients who are rapid metabolizers may be undertreated. Alternatively, patients who are poor metabolizers may be over-treated because metabolism of the parent drug to an inactive compound may not occur. In this instance, accumulation may lead to supratherapeutic or toxic levels of a drug (Bernard & Bruera, 2000; Green et al., 2000; Tucker, 2000).

The CYP450 system consists of more than 20 families of enzymes that are located primarily in the hepatocytes of the liver and mucosal tract (Tucker, 2000). Although these enzymes catalyze many of the same reactions, they may be differentiated by slight variations in their physical properties (Twycross et al., 2002). The function of these enzymes is the metabolism of endogenous compounds (e.g., corticosteroids, lipids, prostaglandins, hormones) as well as the detoxification of prescribed medications (Davis & Homsi, 2001; Tucker). Approximately 56% of the 315 different commonly used medications in the United States undergo some form of biotransformation by CYP enzymes (Bertz & Granneman, 1997). In addition, many drugs are metabolized by more than one enzyme. The most important enzyme families in drug metabolism are CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 (Shen, Kunze, & Thummel, 1997).

### Ethnic Differences and Variability in Drug Metabolism

Since the late 1990s, genetically expressed polymorphisms have been found to be responsible for much of the variation in patient drug metabolism; 481 genes have been identified, which code for 74 unique family types or enzymes and represent a 40% variability of the CYP system in the general population (Bertz & Granneman, 1997; Davis & Homsi, 2001). In particular, polymorphism has been found in the CYP2D6 family, which primarily metabolizes most of the medications used in palliative care (Bernard & Bruera, 2000; Davis & Homsi; Twycross et al., 2002). The CYP2D6 enzyme was discovered in the early 1990s and originally was called debrisoquine hydroxylase (Bertz & Granneman; Shen et al., 1997; Tucker, 2000). Although CYP2D6 accounts for only 2%–5% of the total hepatic P450 enzymes, it metabolizes 25% of the

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### Table 1. Examples of Cytochrome P450 Substrates

<table>
<thead>
<tr>
<th>ENZYME</th>
<th>DRUGS BIOTRANSFORMED BY THESE ENZYMES</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A2</td>
<td>Amitriptyline, cyclobenzapine, imipramine, mirtazapine, olanzapine, propranolol, theophylline</td>
</tr>
<tr>
<td>2C9</td>
<td>Amitriptyline, celecoxib, diclofenac, ibuprofen, imipramine, losartan, naproxen, phenytoin</td>
</tr>
<tr>
<td>2C19</td>
<td>Amitriptyline, citralopram, diazepam, imipramine, lansoprazole, omeprazole, phenytoin</td>
</tr>
<tr>
<td>2D6</td>
<td>Chlorpromazine, codeine, d-methorphan, haloperidol, oxycodone, selective serotonin reuptake inhibitors, tricyclics</td>
</tr>
<tr>
<td>3A4</td>
<td>Alprazolam, azoles, carbamazapine, diazepam, fentanyl, prednisone, zolpidem</td>
</tr>
</tbody>
</table>

*Note. Based on information from Bernard & Bruera, 2000, Johnson et al., 1999, Lacy et al., 2003.*

### Table 2. Examples of Cytochrome P450 Inhibitors

<table>
<thead>
<tr>
<th>ENZYME</th>
<th>DRUGS AND FOODS THAT BLOCK THE ACTIVITY OF THESE ENZYMES</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A2</td>
<td>Cimetidine, ciprofloxacin, diltiazem, erythromycin, grapefruit juice, selective serotonin reuptake inhibitors, verapamil</td>
</tr>
<tr>
<td>2C9</td>
<td>Amiodarone, cimetidine, azoles, trimethoprim, zafirlukast, zileutin</td>
</tr>
<tr>
<td>2C19</td>
<td>Fluoxetine, fluvoxamine, ketoconazole, omeprazole</td>
</tr>
<tr>
<td>2D6</td>
<td>Amiodarone, cimetidine, haloperidol, quinidine, selective serotonin reuptake inhibitors, thiourazides, tramadol</td>
</tr>
<tr>
<td>3A4</td>
<td>Azoles, cimetidine, diltiazem, grapefruit juice, selective serotonin reuptake inhibitors, verapamil, zafirlukast, zileutin</td>
</tr>
</tbody>
</table>

*Note. Based on information from Bernard & Bruera, 2000, Johnson et al., 1999, Lacy et al., 2003.*
medications used in palliative practice (Bernard & Bruera; Davis & Homsi), most notably oxycodone (Oxycontin®, Purdue Pharma L.P., Stamford, CT). Therefore, patient analgesia and subsequent oxycodone metabolism and elimination can be influenced by the genetic variables of gender and ethnicity (Davis, 2003; Tyndale, Droll, & Sellers, 1997). Women eliminate oxycodone 25% slower than men (Kaiko et al., 1996). Moreover, as a substrate of CYP2D6, oxycodone metabolism could be changed by concurrent use of inhibitors CYP2D6 (Davis, Varga, et al., 2003; Kaiko et al.). Obviously, this would be considered a pharmacokinetic drug interaction if patient analgesia was affected. Other common medications used for symptom management and metabolized by the CYP2D6 isomer family include tricyclics, antidepressants, narcotics, selective serotonin reuptake inhibitors, beta blockers, antiarrhythmics, and analgesics (Davis & Homsi).

Researchers have identified a CYP2D6 phenotype in the general population. This population presents as poor metabolizers who may be at risk for drug interactions or toxicities (Bernard & Bruera, 2000; Davis & Homsi, 2001; Shulman & Ozdemir, 1997). The CYP2D6 poor-metabolizer phenotype is found in approximately 4%–10% of the Caucasian population and in 1%–2% of Asians (Davis & Homsi; Eichelbaum, Kroemer, & Fromm, 1997; Kaplan et al., 1997; Tyndale et al., 1997). Conversely, a phenotype for people who are ultrarapid metabolizers has been discovered. These patients have an amplification of the CYP2D6 enzyme and are able to rapidly eliminate endogenous compounds from their bodies (Davis & Homsi).

Further studies have examined the metabolic differences of medications on the CYP2D6 enzyme and have been able to denote ethnic variations that can affect the affinity of medications or their reactions based on polymorphisms or genetic variations. The explanation for the various polymorphisms is considered complex and beyond the scope of this article. However, high expression of CYP2D6 exists in individuals from Ethiopia, Saudi Arabia, and Northern Spain. These populations rapidly metabolize many medications (i.e., antidepressants and neuroleptics), making them less effective or requiring increased dosing (Davis & Homsi, 2001; WorldWide Anaesthetist, 2000).

Asians generally are not poor metabolizers, yet they have a tendency to experience lower drug metabolism activity as a result of carrying a mutant gene with a reduced substrate affinity (e.g., CYP2D6 #10) (Cai, Chen, Cai, & Zhang, 1999; Chida et al., 1999; Fukuda et al., 2000; Yoko et al., 1996).

In the African American population, CYP2D6 activity appears to be lower compared to American Caucasians (Leathart et al., 1998). Studies indicate that other unidentified factors contribute to lower CYP2D6 activity in African Americans (Bradford, Gaedigk, & Leeder, 1998; Gaedigk, Bradford, Marucci, & Leeder, 2002) (see Table 4).

An example of the clinical importance of ethnic variations in metabolism is evident when using codeine. Codeine is a prodrug converted to its active form, morphine, by CYP2D6. In patients who are CYP2D6 poor metabolizers, codeine is an ineffective analgesic. Using an alternate opioid that does not require activation by CYP2D6 would be indicated (Rogers, Nafziger, & Bertino, 2002).

### Table 3. Examples of Cytochrome P450 Inducers

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Drugs, Foods, and Substances That Promote the Upregulation of These Enzymes and Encourage the Biotransformation of Other Drugs, Foods, or Substances</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A2</td>
<td>Charcoal-broiled beef, cigarette smoke, cruciferous vegetables, omeprazole, phenobarbital, phenytoin</td>
</tr>
</tbody>
</table>
| 2C9    | Carbamazepine, rifampin  
| 2C19   | Phenytoin, rifampin  
| 2D6    | None identified  
| 3A4    | Carbamazapine, dexamethasone, griseofulvin, phenobarbital, phenytoin |

Note. Based on information from Bernard & Bruera, 2000; Johnson et al., 1999; Lacy et al., 2003.

### Table 4. Prevalence of Poor Metabolizer and Ultrarapid Metabolizer Phenotype for CYP2D6

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Poor Metabolizers (%)</th>
<th>Ultrarapid Metabolizers (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caucasian</td>
<td>5–10</td>
<td>1–20</td>
</tr>
<tr>
<td>African American</td>
<td>0–20</td>
<td>2</td>
</tr>
<tr>
<td>Asian</td>
<td>1</td>
<td>0–2</td>
</tr>
<tr>
<td>Ethiopian or Saudi Arabian</td>
<td>1.8–2</td>
<td>10–20</td>
</tr>
</tbody>
</table>

Note. Based on information from Davis & Homsi, 2001; Rogers et al., 2002.

### Conclusion

Appropriate medication prescription and administration are not only skills, these interventions also can make a difference between poor and excellent symptom control. Therefore, palliative care clinicians need to possess and appreciate the patient variability that exists and the pharmacology principles that influence effective medication prescription and administration (Wolf & Smith, 1999).

Patient variability, manifested via genetic expression, must be considered when prescribing and administering medications for pain and symptom management. Other factors also should be considered when monitoring patients’ response to therapy. Factors such as gender, ethnicity, disease, and concurrent therapy will help to define patients’ unique P450 enzyme system architecture. Choice of drug therapy should be made based on this knowledge and with the assumption that the P450 system directly will affect drug metabolism and effectiveness.

Clinicians must understand pharmacodynamics, pharmacokinetics, and the potential drug interactions that may ensue. To that end, many drugs used in palliative care have been identified as CYP enzyme substrates, inducers, or inhibitors. Information describing these varied interactions must be current. As well, proactive nurses, with a good knowledge of drug interactions, may be the last line of defense against a clinically significant drug interaction before it reaches patients.

The goal of palliative drug therapy is to control, relieve, or eliminate symptoms. This can be accomplished by assessing and evaluating the interindividual responses to specific medications, keeping medication use to a minimum, and appreciating that every patient will react differently to specific medications. A cookbook approach to medication administration likely will result in ineffective symptom management for patients receiving palliative care.

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**Rapid Recap**

**Why There Is No Cookbook Approach to Palliative Care: Implications of the P450 Enzyme System**

- Polypharmacy increases the risk of adverse drug interactions.
- Pharmacodynamic drug interactions affect a drug’s mechanism of action on physiologic function.
- Pharmacokinetic drug interactions affect the absorption, distribution, biotransformation, and excretion of a drug.
- The cytochrome P450 system is a major enzyme system responsible for drug metabolism and consists of more than 20 families of enzymes that primarily are located in the hepatocytes of the liver and mucosal tract.
- Patient variability, including age, gender, ethnicity, disease, and concurrent therapy, needs to be considered when medications are prescribed and administered.
- Tailoring medication selection to each patient enhances symptom management in palliative care.

**References**


Fukuda, T., Nishida, Y., Imaoka, S., Hiroi, T., Naohara, M., Funae, Y., et al. (2000). The decrease in vivo clearance of CYP2D6 substrates by CYP2D6*10 might be caused not only by the low-expression but also by low affinity of CYP2D6. *Archives of Biochemistry and Biophysics, 380,* 303–308.


