Metabolism and Disposition of Prescription Opioids: A Review

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1042-7201/27-2/July 2015/115–145/$46.50 •

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REFERENCE: DePriest AZ, Puet BL, Holt AC, Roberts A, Cone EJ: Metabolism and disposition of prescription opioids: A review; *Forensic Sci Rev* 27:115; 2015.

ABSTRACT: Opioid analgesics are commonly prescribed for acute and chronic pain, but are subject to abuse. Consequently, toxicology testing programs are frequently implemented for both forensic and clinical applications. Understanding opioid metabolism and disposition is essential for assessing risk of toxicity and, in some cases, providing additional information regarding risk of therapeutic failure. Opioids significantly metabolized by the cytochrome P450 (CYP450) enzyme system may be subject to drug-drug interactions, including codeine, hydrocodone, oxycodone, fentanyl, meperidine, methadone, buprenorphine, and tramadol. CYP2D6 metabolism is polymorphic, and pharmacogenetic testing has been investigated for codeine, tramadol, oxycodone, and hydrocodone. CYP2B6 pharmacogenetic testing of methadone may reduce the risk of cardiac toxicity associated with the S-enantiomer. Opioids metabolized primarily by uridine 5'-diphospho-glucuronsyltransferase (UGT) enzymes include morphine, hydromorphone, dihydrocodeine, oxymorphone, levorphanol, and tapentadol. Parent and metabolite disposition is described for blood, oral fluid, and urine. Parent drug is most commonly detected in blood and oral fluid, whereas metabolites typically predominate in urine. Oral fluid/blood ratios exceed 1 for most opioids, making this an excellent alternative matrix for testing of this drug class. Metabolites of codeine, hydrocodone, and oxycodone are commercially available, and knowledge of metabolism is necessary for correct interpretation.

KEYWORDS: Blood, drug disposition, metabolism, opioids, oral fluid, pharmacokinetics, urine.

INTRODUCTION

Use of opioid analgesics is widespread in the United States, where 100 million adults reportedly suffer from chronic pain [147]. Opioids exert analgesic effects at mu (μ), delta (δ), and kappa (κ) receptors, which affect the modulation of pain within the central nervous system (CNS), peripheral neurons, ectodermal cells, and neuroendocrine and immune systems [346]. Analgesia results from diminished nociceptor excitability, reduced action potential proliferation, and decreased release of inflammatory neuropeptides at nerve terminals [303]. Mu opioid receptors (MOR) are also expressed in enteric neurons and assist with gut nociception, motility, and secretion [259]. Activation of MORs results in both the analgesic actions associated with opioid administration and major side effects, including CNS depression, drowsiness, constipation, respiratory depression, and dependence [254].

Although opioids are a mainstay of chronic pain management, their long-term safety and effectiveness have been questioned [99], as they have also contributed to a significant increase in drug-poisoning deaths [43]. Therapeutic response to opioids may be highly variable depending on the drug's potency, chemical properties, metabolism, drug disposition, and pharmaceutical dosage preparation, as well as patient-specific factors such as diet, drug ingestion, weight, genetic makeup, and disease states. Clinical management requires careful patient monitoring. Drug testing of biologic specimens such as urine, oral fluid, and blood have become commonplace in assessing compliance to long-term opioid therapy [8]. Attention has recently increased on the use of pharmacogenetic testing and evaluation of drug-drug interactions to assess risk of toxicity and improve patient outcomes [162,257]. Knowledge of opioid metabolism and disposition in biologic fluids is critical for proper patient assessment and interpretation of toxicology results.

I. MORPHINE

Morphine is the standard analgesic to which other opioids are compared. It is available in numerous dosage forms including immediate and extended-release capsules and tablets, oral solutions, suppositories, and solutions for subcutaneous, intramuscular, intravenous, epidural, or intrathecal injection. Morphine is also produced from metabolism of codeine and heroin. It follows three known metabolic pathways (glucuronidation, sulfation, and *N*-demethylation) and one uncharacterized metabolic pathway leading to formation of hydromorphone. The primary metabolism of morphine is by glucuronidation to morphine-3-glucuronide (50%) and morphine-6-glucuronide (10%), and trace amounts of morphine-3,6-diglucuronide [46,338]. The glucuronidation of morphine is accomplished by uridine 5'-diphospho-glucuronsyltransferase (UGT) enzymes in the intestine and liver [241], although UGT activity in the brain has also been described [327]. UGT2B7 is the chief enzyme involved, though to a lesser extent 1A1 and 1A8 isoforms may contribute to morphine-6-glucuronide formation and

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Anne Z. DePriest received her Doctor of Pharmacy degree from the University of South Carolina College of Pharmacy (Columbia, SC), with honors from the South Carolina Honors College, in 2002. Dr. DePriest completed a residency in pharmacy practice at The Johns Hopkins Hospital (Baltimore, MD) and an advanced practice Pain Management Traineeship with the American Society of Health-System Pharmacists at Lakeland Regional Medical Center (Lakeland, FL). Dr. DePriest is currently the senior scientist for healthcare at Aegis Sciences Corporation (Nashville, TN), a forensic reference and healthcare laboratory.

Dr. DePriest has worked with inpatient and outpatient teams during her tenure at The Johns Hopkins Hospital, as pharmacy clinic manager at a Walgreen's Health Initiative outpatient clinic located within The Ohio State University Medical Center (Columbus, OH), and most recently as a pharmacy clinical specialist at Baptist Hospital (Nashville, TN). She is a board-certified pharmacotherapy specialist and assistant faculty for the University of Tennessee College of Pharmacy (Memphis, TN), the University of Florida Department of Pharmacotherapy and Translational Research (Gainesville, FL), the University of South Carolina College of Pharmacy, Lipscomb University College of Pharmacy (Nashville, TN), and Belmont University College of Pharmacy (Nashville, TN).

Dr. DePriest specializes in pain-management toxicology, and has presented at numerous clinical and scientific meetings and published in a variety of peer-reviewed journals. She is a member of the American Academy of Forensic Sciences, the Society of Forensic Toxicologists, the American College of Clinical Pharmacy/ACCP Pain and Palliative Care Practice and Research Network, the American Society of Health-Systems Pharmacists, and the American Chemical Society.

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Presently, Dr. Cone is an employee of Pinney Associates (Bethesda, MD) and has developed a working dynamic model for assessment of abuse-deterrent formulations for the pharmaceutical industry. He is considered the lead authority on FDA approval requirements for Category 1 (in vitro laboratory tests) assessments of new pharmaceutical opioids with abuse-deterrent properties. Dr. Cone has an appointment as adjunct professor at The Johns Hopkins School of Medicine, and owns and operates a private firm, ConeChem Research, LLC (Severna Park, MD), which provides forensic toxicology and clinical consulting services to the federal government and private sector.

Dr. Cone's major research interests include the following: development of nonabusable drug products; addiction medicines and treatment; kinetics and disposition of drugs of abuse; development of accurate diagnostic drug tests, and the relationship of drug concentrations to behavior. Dr. Cone's research on the kinetics and dynamics of smoked and inhaled drugs, effects of environmental exposure to drugs of abuse, and the use of alternative specimens like oral fluid, sweat, and hair for drug testing has been recognized worldwide. Dr. Cone's work has resulted in the publication of over 300 scientific articles on the chemistry of pharmaceuticals and illicit drugs of abuse. He is among the most highly cited authors in the field of forensic toxicology. Dr. Cone has received a number of awards, including the Alan Curry Award from The International Association of Forensic Toxicologists ("for a long history of distinguished contributions to the field of forensic toxicology and to the TIAFT organization").