2018

Opioids Metabolism

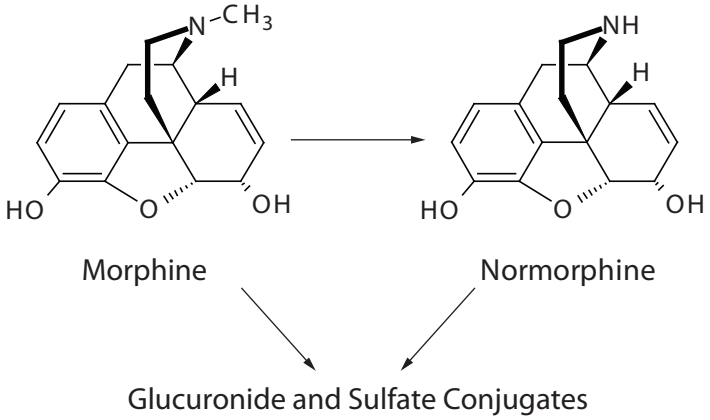
This is the third of a four-part Drug Testing Matters series on opioids.

Metabolism

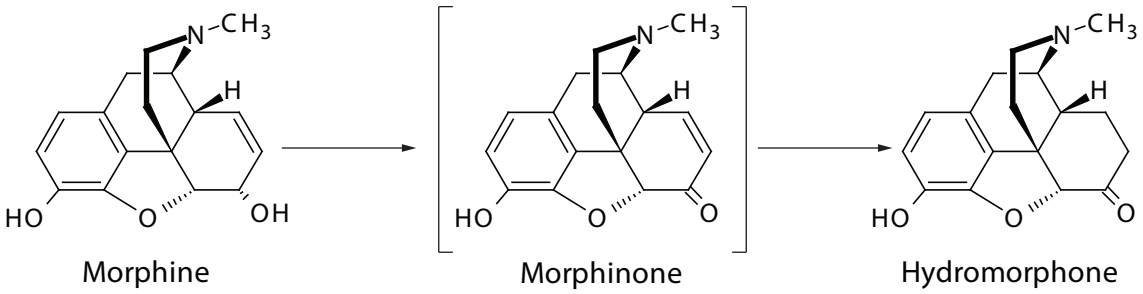
Opioids undergo phase I oxidation/reduction reactions catalyzed by cytochrome P450 (CYP) enzymes exposing or modifying functional groups. The opioid metabolites formed from phase I biotransformation and parent compounds with the appropriate functional groups undergo phase II conjugation reactions, such as glucuronidation and sulfation. The pharmacokinetics of prescription opioids have been reviewed recently (1).

Note: The term "free" is sometimes used to describe unconjugated drugs and metabolites, although "free" technically refers to those compounds that are not protein bound. For the purpose of clarity, the term "free" in this article is used to describe unconjugated drugs and metabolites.

Morphine

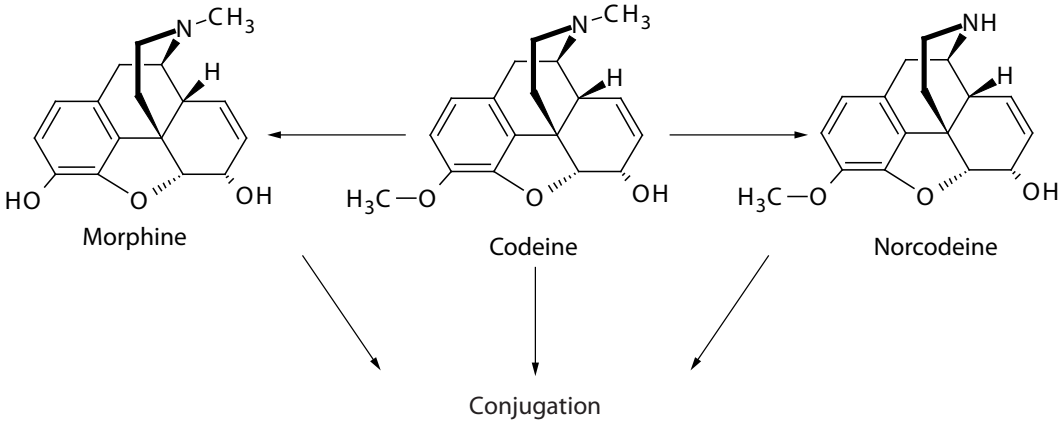


Morphine undergoes extensive phase II conjugation via glucuronidation and sulfation. The conjugate morphine-3-glucuronide accounts for approximately 75% of a dose of morphine, while unconjugated morphine accounts for approximately 10% of the dose (2). Roughly 5% of a dose of morphine undergoes phase I N-demethylation to normorphine (2), primarily via CYP3A4 and, to a lesser extent, CYP2C8 (3). Normorphine subsequently undergoes conjugation to form glucuronide and sulfate conjugates accounting for about 4% of the dose, with free normorphine representing approximately 1% of the dose (2). Trace amounts of morphine-6-glucuronide, morphine-3-ethereal sulfate, and morphine-3,6-diglucuronide are also formed during the biotransformation of morphine (2,4). The aspects of the metabolism of morphine and other opioids applicable to oral fluid drug and drug metabolite testing have been reviewed recently (5). The use of metabolites in hair to distinguish between opioid use and passive exposure has been presented (6). Although the glucuronides of morphine are substantially more polar than the parent drug and its unconjugated metabolites, the glucuronides of morphine and other opiates, such as codeine, hydromorphone, and oxymorphone (*vide infra*), have been demonstrated in the hair of individuals using these drugs (7).

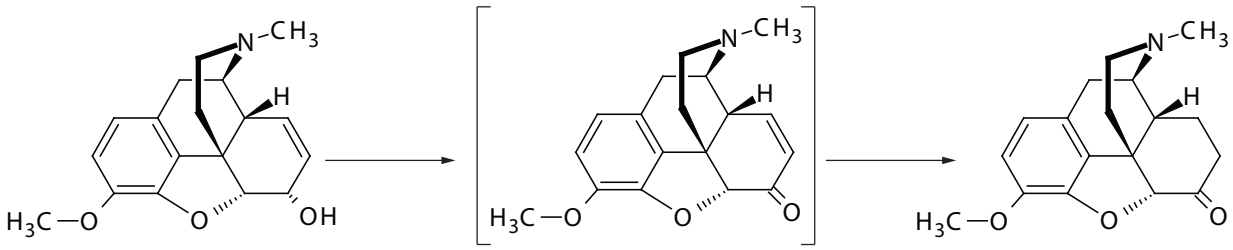


A minor metabolic pathway of morphine to hydromorphone has been reported in pain patients chronically treated with morphine (8). It has been postulated that morphinone is an intermediate prior to the formation of hydromorphone from morphine in this minor metabolic pathway (8).

Codeine

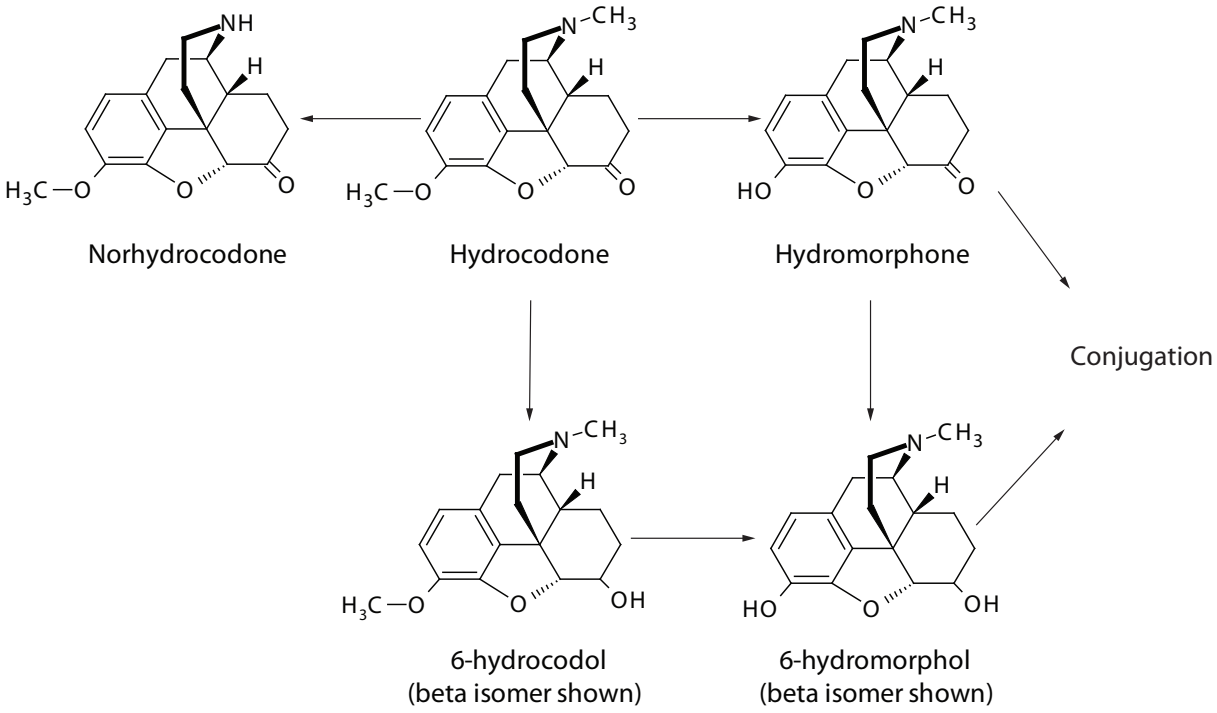


Codeine undergoes O-demethylation to morphine via CYP2D6 and N-demethylation via CYP3A4 to norcodeine. It is estimated that about 7% of Caucasians and approximately 1–3% of other ethnic groups are CYP2D6 deficient and considered poor metabolizers (9). Codeine and both phase I metabolites, morphine and norcodeine, undergo phase II glucuronide conjugation (10). Approximately 5–17% of a dose is excreted in the urine as free codeine, and 32–46% is excreted as conjugated codeine. Trace amounts of free norcodeine and morphine are detected, with 10–21% and 5–13% found in their respective conjugated forms (2).



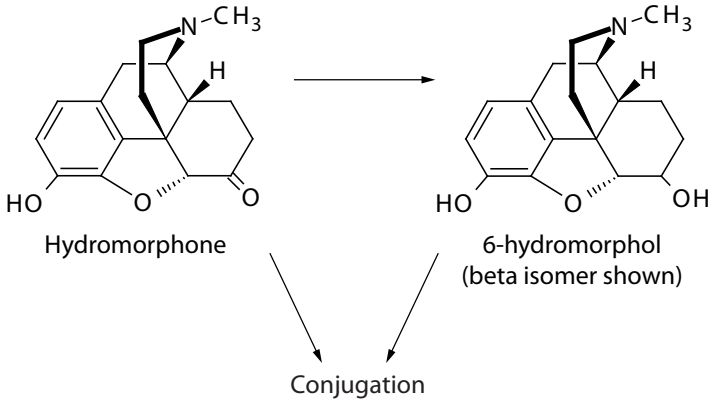
A minor metabolic pathway of codeine converting to hydrocodone has been reported by Oyler et al. after controlled codeine administration in human subjects (11). In this study, a purity check of the administered codeine was performed to rule out the presence of hydrocodone resulting from a process impurity. The metabolic pathway of this formation is poorly defined, and several possibilities, including enzymatic rearrangement of codeine or oxidation by an aldo-keto reductase enzyme, has been proposed. A third postulated pathway involves a possible codeine dehydrogenase enzyme to form the intermediate codeinone that then converts to hydrocodone, similar to the pathway proposed for the formation of hydromorphone from morphine (8). Because it has been shown that hydrocodone can be formed—up to 11%—in the urine after codeine administration, one would also expect to see trace amounts of hydrocodone metabolites, such as hydromorphone and norhydrocodone, present in the urine as well. The urine codeine metabolic pathway was further defined in pain patients in a later study by Yee *et al*. (12).

Hydrocodone



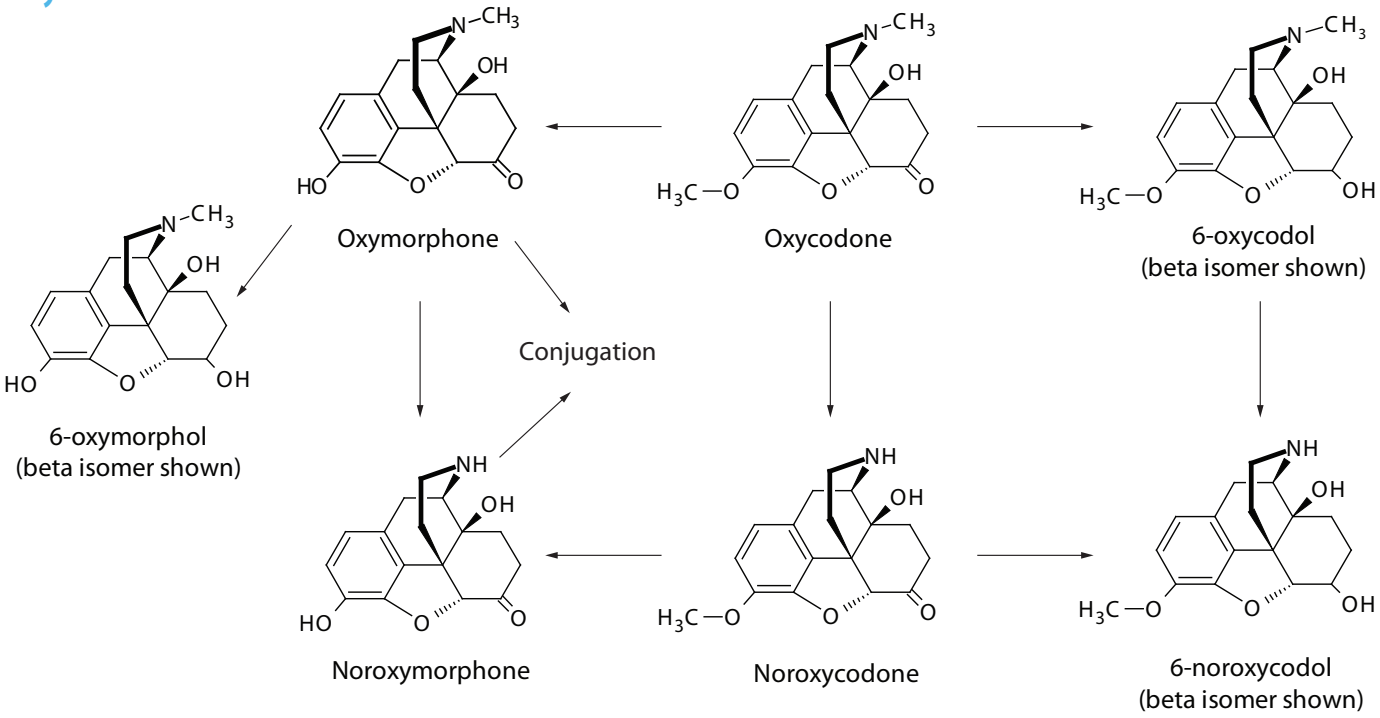
Hydrocodone undergoes O-demethylation via CYP2D6 to hydromorphone and N-demethylation, primarily through CYP3A4, to norhydrocodone (13,14). The reduction of the keto group in hydrocodone forms α- and β-hydrocodol, which O-demethylates to α- and β-hydromorphol via phase I biotransformation. In a 72-hour urine, 12% of the dose is present as unchanged hydrocodone, 5% as norhydrocodone, 4% as conjugated hydromorphone, 3% as 6-hydrocodol, and 0.1% as conjugated 6-hydromorphol (2). The pharmacokinetic parameters for hydrocodone and its metabolites norhydrocodone and dihydrocodeine in blood and oral fluid were established using a 12.1-mg total free base dose in a controlled study (15).

Hydromorphone



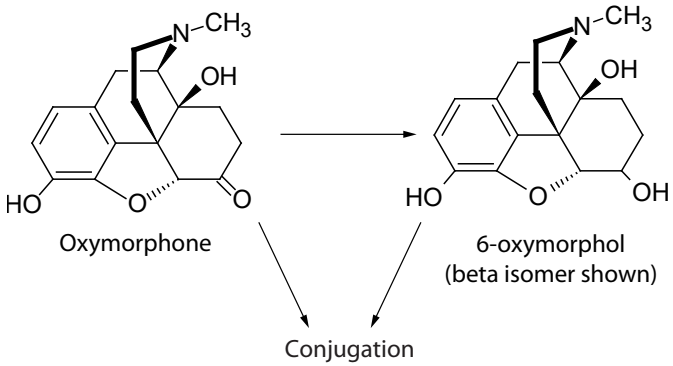
Hydromorphone undergoes extensive phase II glucuronide conjugation to form hydromorphone-3-glucuronide. Hydromorphone is also metabolized to α- and β-hydromorphol via a phase I keto reduction reaction. Approximately 30% of a dose is present in the urine as conjugated hydromorphone and 6% is excreted as free hydromorphone (2). Trace amounts of conjugated 6α- and 6β-hydromorphol were reported in the urine by Cone *et al*. (16). Following a single 8-mg dose of controlled-release hydromorphone, the urinary excretion of both total and free hydromorphone has been characterized (17).

Oxycodone



Oxycodone undergoes N-demethylation to noroxycodone via CYP3A4 and O-demethylation via CYP2D6 to oxymorphone (18). Noroxycodone is a relatively inactive metabolite, whereas oxymorphone is a potent analgesic. Oxymorphone is extensively conjugated. Oxycodone and noroxycodone do not exhibit significant conjugation but undergo a keto reduction to form α- and β-oxycodol and α- and β-noroxycodol, respectively (2,19). Oxymorphone metabolizes to α- and β-oxymorphol through a keto reduction and represents about 1% of the dose (19). In a 48-hour urine after a single oral dose of oxycodone, 8.0% is excreted as free oxycodone, 23.1% as free noroxycodone, 10.4% as conjugated oxymorphone, 0.3% as free oxymorphone, 8.6% as conjugated noroxymorphone, 5.6 % as free noroxymorphone, 6.0% as α-oxycodol, 1.9% asβ-oxycodol, 6.8 % as α-noroxycodol, and 1.6% as β-noroxycodol (19). The pharmacokinetics of oxycodone in oral fluid and blood have been defined in a study that employed a single 20-mg dose of OxyContin® (20). In a separate study, it was noted that oxycodone is predominant over noroxycodone in saliva (i.e., oral fluid), while the reverse is true in urine (21).

Oxymorphone

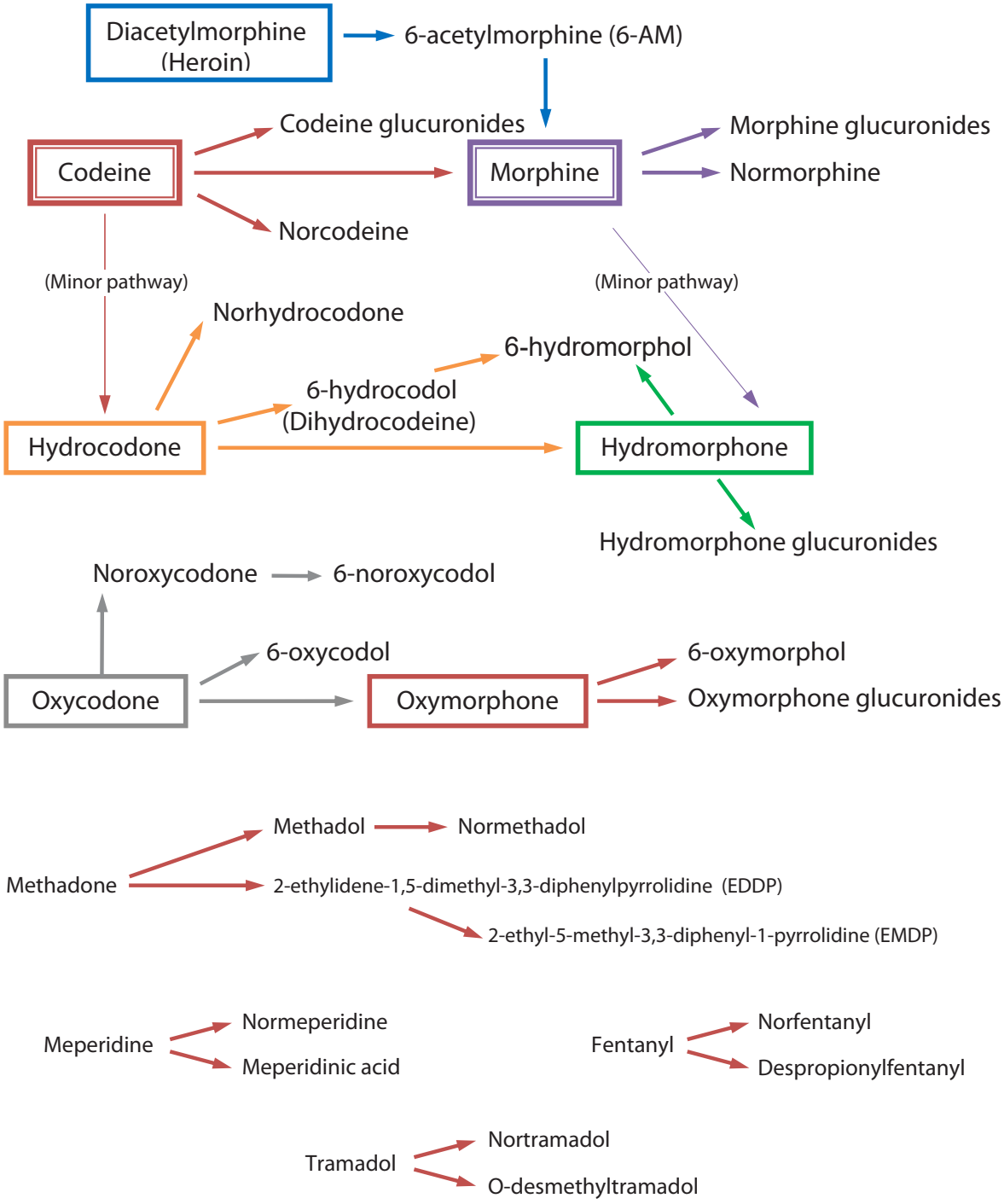


Oxymorphone is extensively metabolized via phase II conjugation to form oxymorphone glucuronide and undergoes a keto reduction to form 6-oxymorphol, which also undergoes conjugation. In a 120-hour urine, 1.9% is detected as free oxymorphone, 44% as conjugated oxymorphone, 2.9% as free and conjugated 6β-oxymorphol, and 0.1% as conjugated 6α-oxymorphol (2). Using a single 10-mg dose of Opana® ER, which is a controlled-release tablet, total and free oxymorphone and total noroxymorphone pharmacokinetics in urine have been defined (22).

The Opioid Metabolism diagram on the following page presents major metabolic pathways.

Opioids Metabolism

Opioid Metabolism



Note: This diagram shows major metabolic pathways and does not show all conjugated metabolites.

References

1. A.Z. DePriest, B.L Puet, A.C. Holt, A. Roberts, E.J. Cone, Metabolism and disposition of prescription opioids: A review, *Forensic Sci. Rev.* (27), 115-45 (2015).

2. R.C. Baselt. *Disposition of Toxic Drugs and Chemicals in Man*, 11th ed. Biomedical Publications, Seal Beach, CA, 2017.

3. D.Projean, P.E. Morin, T.M. Tu and J. Ducharme. Identification of CYP3A4 and CYP2C8 as the major cytochrome P450s responsible for morphine N-demethylation in human liver microsomes. *Xenob.*(33) 841-854 (2003).

4. S.Y. Yeh, C.W. Gorodetzky and H.A. Krebs. Isolation and Identification of Morphine 3- and 6-Glucuronides, Morphine 3,6-Diglucuronide, Morphine 3-Ethereal Sulfate, Normorphine, and Normorphine 6-Glucuronide as Morphine Metabolites in Human, *J. Pharm. Sci.* (66) 1288-1293 (1977).

5. R.M. White and C.M. Moore, Detection of Drugs and Their Metabolites in Oral Fluid, RTI Press, Research Triangle Park, NC, 2018.

6. R.M. White, Drugs in hair. Part I. Metabolisms of major drug classes, *Forensic Sci. Rev.* (29), 23-55 (2017).

7. M. Grabenauer, N.D. Bynum, K.N. Moore, R.M. White, J.M. Mitchell, E.D. Hayes, R. Flegel. Detection and quantification of codeine-6-glucuronide, hydromorphone-3-glucuronide, oxymorphone-3-glucuronide, morphine 3-glucuronide and morphine-6-glucuronide in human hair from opioid users by LC–MS-MS. Online 24 November 2017. https://doi.org/10.1093/jat/bkx086.

8. E.J. Cone, H.A. Heit, Y.H. Caplan and D. Gourlay, Evidence of Morphine Metabolism to Hydromorphone in Pain Patients Chronically Treated with Morphine, *J. Anal. Toxicol.* (30) 1-5 (2006).

9. J. de Leon, M.T. Susce and E. Murray-Carmichael. The AmpliChip™ CYP450 Genotyping Test: Integrating a New Clinical Tool. Mol. Diag. *Ther. 10* (3) 135-151 (2006).

10. H. He, S.D. Shay, Y. Caraco, M. Wood, and A.J.J. Wood. Simultaneous determination of codeine and seven metabolites in plasma and urine by high performance liquid chromatography and ultraviolet and electrochemical detection. *J. Chrom. B.* 708 (1) 185-193 (1998).

11. J.M. Oyler, E.J. Cone, R.E. Joseph and M.A. Huestis. Identification of Hydrocodone in Human Urine Following Controlled Codeine Administration, *J. Anal. Toxicol.* (24) 530-535 (2000).

12. D.A. Yee, R.S. Atayee, B.M. Best, J.D. Ma, Observations on the urine metabolic profile of codeine in pain patients, *J. Anal. Toxicol.* (38), 86-91 (2014).

13. H.L. Kaplan, U.E. Busto, G. J. Baylon, S. W. Cheung, S. Victoria Otton, G. Somer and E. M. Sellers. Inihibition of Cytochrome P450 2D6 Metabolism of Hydrocodone to Hydromorphone Does not Importantly Affect Abuse Liability, *J. Pharmacol. Exp. Ther.* (281) 103-108 (1997).

14. M.R. Hutchison, A. Menelaou, D. J. R. Foster, J.K. Coller and A. A. Somogyi. CYP2D6 and CYP3A4 Involvement in Primary Oxidative Metabolism of Hydrocodone by Human Liver Microsomes. *Br. J. Clin. Pharmacol.* (57) 287-297 (2003).

15. E.J. Cone, A.Z. DePriest, R. Heltsley, D.L. Black, J.M. Mitchell, C. LoDico, R. Flegel, Prescription opioids. IV. Disposition of hydrocodone in oral fluid and blood following single-dose administration, *J Anal Toxicol*., (39)510-18 (2015).

16. E.J. Cone, B.A. Phelps and C.W. Gorodetzky. Urinary excretion of hydromorphone and metabolites in humans, rats, dogs, guinea pigs and rabbits. *J. Pharm. Sci.* (66) 1709-1713 (1977).

17. A.Z. DePriest, R. Heltsley, D.L. Black, J.M. Mitchell, C. LoDico, R. Flegel, E.J. Cone, Prescription opioids, VI. Metabolism and excretion of hydromorphone in urine following controlled-release single-dose administration, *J. Anal. Toxicol.* (40) 575-82 (2016).

18. J. Gronlund, T.I. Saari, N.M. Hagelberg, P.J. Neuvonen, K.T. Olkkola and K. Laine. Exposure to oral oxycodone is increased by concomitant inhibition of CYP2D6 and 3A4 pathways, but not by inhibition of CYP2D6 alone. *Br. J. Clin. Pharmacol.* (70) 78-87 (2010).

19. B. Lalovic, E. Kharasch, C. Hoffer, L. Risser, L-Y Lie-Chen, and D.D. Shen. Pharmacokinetics and pharmacodynamics of oral oxycodone in healthy human subjects: Role of circulating active metabolites. *Clin. Pharmacol. Ther. 79* (5) 461-479 (2006).

20. E.J. Cone, A.Z. DePriest, R. Heltsley, D.L. Black, J.M. Mitchell, C. LoDico, R. Flegel, Prescription opioids, III. Disposition of oxycodone in oral fluid and blood following controlled single-dose administration, *J. Anal Toxicol.* (39)192-202(2015).

21. K.V. Moy, J.D. Ma, C.M. Morello, R.S. Atayee, B.M. Best, Monitoring oxycodone use in patients with chronic pain: Analysis of oxycodone and metabolite excretion in saliva and urine, *J. Opioid Manag.* (10) 47-56 (2014).

22. A.Z. DePriest, R. Heltsley, D.L. Black, J.M. Mitchell, C. LoDico, R. Flegel, E.J. Cone, Prescription opioids. V. Metabolism and excretion of oxymorphone in urine following controlled single-dose administration, *J. Anal. Toxicol.* (40) 566-74 (2016).

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