

Med-Psych Drug-Drug Interactions Update

Pharmacokinetic Drug Interactions of Morphine, Codeine, and Their Derivatives: Theory and Clinical Reality, Part II

SCOTT C. ARMSTRONG, M.D.

KELLY L. COZZA, M.D.

Pharmacokinetic drug-drug interactions with codeine, dihydrocodeine, hydrocodone, oxycodone, and buprenorphine are reviewed in this column. These compounds have a very similar chemical structure to morphine. Unlike morphine, which is metabolized chiefly through conjugation reactions with uridine diphosphate glucuronosyl transferase (UGT) enzymes, these five drugs are metabolized both through oxidative reactions by the cytochrome P450 (CYP450) enzyme and conjugation by UGT enzymes. There is controversy as to whether codeine, dihydrocodeine, and hydrocodone are actually prodrugs requiring activation by the CYP450 2D6 enzyme or UGT enzymes. Oxycodone and buprenorphine, however, are clearly not prodrugs and are metabolized by the CYP450 2D6 and 3A4 enzymes, respectively. Knowledge of this metabolism assists in the understanding for the potential of drug-drug interactions with these drugs. This understanding is important so that clinicians can choose the proper dosages for analgesia and anticipate potential drug-drug interactions.

(Psychosomatics 2003; 44:515–520)

The narcotic analgesics can be categorized into three groups. Two of the groups are synthetic chemicals: phenylpiperidines (e.g., meperidine [Demerol®] and fentanyl) and pseudopiperidines (e.g., methadone and propoxyphene [Darvon®]). The third group is related to the naturally occurring alkaloids from the seeds of the poppy plant. These natural opium derivatives include heroin, morphine, and codeine. Semi-synthetic derivatives from this group include hydromorphone (Dilaudid®), oxymorphone (Numorphan®), hydrocodone (Vicodin® and others), oxycodone (OxyContin®, Percocet®, and others), dihydrocodeine, and buprenorphine (Buprenex®, Subutex®, or Suboxone®).

This article is the second of a two-part series. In part I, the pharmacokinetic properties of morphine and its closely related semi-synthetic congeners, hydromorphone and oxymorphone, were reviewed.¹ In this column, we will review the metabolism and pharmacokinetic drug-drug interaction profiles of codeine and related compounds (dihydrocodeine, hydrocodone, and oxycodone) as well as buprenorphine. These drugs also have the potential for

pharmacodynamic drug interactions, but these interactions will not be discussed in this article.

To better understand the metabolism of these drugs, which are all closely related to morphine, it helps to appreciate the chemical structure of morphine (Figure 1).

The 3 and 6 carbon atoms along with the 17 nitrogen (N) position are the three sites that have various substitutions of ester (–OCX₂), hydroxyl (–OH), keto (=O), methyl (–CH₃), or multiple carbon groups that create other natural or synthetic opiate drugs. Morphine has hydroxyl

Dr. Armstrong is the Co-Medical Director, Center for Geriatric Psychiatry, Tuality Forest Grove Hospital, Forest Grove, Ore., and Associate Professor of Psychiatry, Oregon Health Sciences University, Portland, Ore. Dr. Cozza is the staff psychiatrist for the Infectious Disease Service, Department of Medicine, Walter Reed Army Medical Center, Washington, D.C., and Assistant Professor of Psychiatry, Uniformed Services University of the Health Sciences, Bethesda, Md. Address correspondence to Dr. Armstrong, Tuality Forest Grove Hospital, 1809 Maple St., Forest Grove, OR 97116; scott.armstrong@tuality.org (e-mail).

The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

Copyright © 2003 The Academy of Psychosomatic Medicine.

groups at the 3 and 6 carbons and a methyl group at the 17 (N) position. Other alterations in the basic morphine structure that may occur in order to create semi-synthetic compounds include: a single bond between carbon 7 and 8, an -OH group added to 14, no oxygen between 4 and 5, and a bridge between 6 and 14.

The 3, 6, and 17 positions are also the primary areas of oxidative cytochrome P450 (CYP450) metabolism. The 3 and 6 positions are often referred to as the "O" site and "N" sites, respectively, with regard to oxidative metabolism (based on the planar proximity of the 3 carbon to the oxygen atom and the 6 carbon to the nitrogen atom of a separate ring). The literature can be confusing, however, as the 17 position is also at times referred to as the "N" position. Incidentally, the 3 and 6 positions are also the main sites for conjugation with glucuronic acid by various uridine diphosphate glucuronosyl transferase (UGT) enzymes. This makes some intuitive sense, since the CYP450 enzymes prepare the drug for a "handle" to allow for the conjugation reactions.

Codeine

Codeine is very similar in structure to morphine. It simply adds a methyl group on the 3-carbon hydroxyl group of morphine (from an -OH to a -OCH₃). Indeed, codeine is found naturally along with morphine in the poppy seed. Therefore it is not semi-synthetic, although it can be easily manufactured.

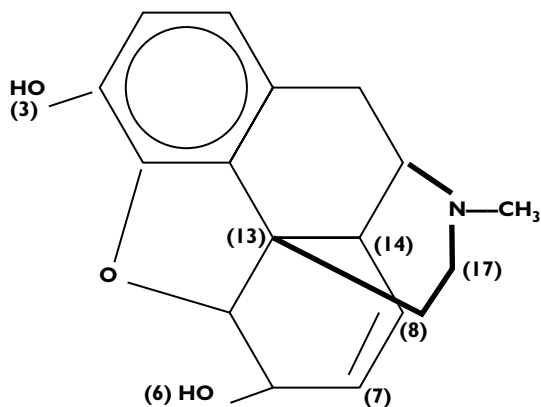
Codeine is a weak analgesic with a weak affinity to the μ receptor, 300 times less than morphine.² In 1948, Sanfilippo,³ identified that codeine is metabolized to morphine. Because of this, up until recently, it had generally been accepted that codeine's conversion to morphine is the

main reason for codeine's analgesic properties. In the early 1990s, several studies indicated that the CYP450 2D6 enzyme was responsible for the conversion of codeine to morphine.^{4,5} One of these studies⁵ also showed that within a laboratory pain model, either inhibition of 2D6 by a competitive inhibitor (quinidine in this study) or a poor 2D6 metabolism phenotype would decrease the amount of morphine measured and the subjective ratings of analgesia.

However, despite the case reports that would follow these studies, some researchers have had difficulty accepting that codeine's conversion to morphine by 2D6 is the reason for its efficacy as an analgesic. The main problem with this supposition is that very little of the total dose of codeine is actually metabolized by 2D6 into morphine. Indeed, the range has been between 0.5%⁶ to 2-3%.⁷ Generally, these studies and others have shown that 80% of codeine is actually directly glucuronidated by UGT 2B7 to codeine-6-glucuronide (C6G), 5% or less is metabolized to morphine by 2D6, and the rest is metabolized by the CYP450 3A4 enzyme into norcodeine, a compound that is inactive as an analgesic. The products of codeine's metabolism from both 2D6 and 3A4 are quickly glucuronidated, with the 2D6/morphine product going to morphine-6-glucuronide (M6G), an active analgesic, and morphine-3-glucuronide (M3G).¹

With this in mind, several more detailed studies have been done in an attempt to prove or disprove the theory that codeine's analgesic properties are due to its conversion to morphine by 2D6. Persson et al.,⁸ in a study of patient-controlled analgesia, reported that two patients had a poor postoperative pain relief response with codeine. Both patients had very low levels of morphine, and it was determined that one had poor 2D6 metabolism. However, this was a very small study (N = 11) and did not answer why one patient had low morphine levels despite normal 2D6 activity. A larger study, by Poulsen et al.,⁹ included 81 patients. They were postoperative patients hospitalized for minor surgical procedures that used spinal anesthesia (e.g., hernia repairs, varicose veins). These patients then received codeine as their postoperative analgesic drug. It had been predetermined that 66 patients had normal 2D6 activity and that eight had poor 2D6 metabolism. Samples from the remaining seven patients were either lost or indeterminate. In 22 patients—including all eight with poor 2D6 metabolism—the serum concentrations of both morphine and M6G were below detectable levels. Sum ratings of pain by patients with low, but not necessarily undetectable, morphine/M6G levels did differ from those patients with higher levels of morphine/M6G. However, the differences

FIGURE 1. The Chemical Structure of Morphine



in the pain ratings did not differ between the two phenotypes ($p=0.60$). Indeed, there were 14 patients with normal 2D6 metabolism with low morphine/M6G levels.

In a different approach, several researchers have looked at drug addiction/abuse potential as a way to demonstrate the importance of codeine's conversion to morphine. Their results have been mixed at best. Fernandes et al.¹⁰ hypothesized that patients with poor 2D6 metabolism might be at less risk for dependence on codeine because of the lack of creation of morphine, thus rendering less of a resultant "high." The study created a poor metabolism condition by adding fluoxetine or quinidine (both potent inhibitors of 2D6) along with a placebo and observed whether the addicts' codeine use would decrease. Although it was a small study, and both groups did show a 50% decrease in codeine use, there was also a 50% decrease of the use of codeine in the placebo group. Kathiramalainathan et al.¹¹ did a similar study with 12 healthy volunteers and used fixed-dose schedules of codeine to determine a favorite dose of codeine in the presence or absence of the 2D6 inhibitor quinidine. Volunteers predetermined their favorite dose of codeine (60, 120, or 180 mg). Then they received quinidine for 4 days. The use of quinidine did decrease the measured amount of morphine in the plasma in all groups. The subjective "high" in the 120-mg group also decreased with quinidine, but it curiously did not decrease the "high" effects of the 180-mg group.

An alternative hypothesis for codeine's analgesic properties has been set forth by Vree et al.¹² They postulate that it is the main metabolite of codeine created by UGT 2B7, codeine-6-glucuronide, that is responsible for most of

codeine's analgesic and μ receptor activity. This is only a hypothesis at this time and has not been demonstrated to date clinically. However, they make several compelling arguments:

1. Morphine is metabolized to M6G, and M6G is a potent analgesic itself, perhaps 50 times more than morphine.¹ Codeine's main metabolite is C6G, similar in structure to the very active μ receptor agonist M6G. Indeed, their only difference is at the 3-carbon position, with M6G having a hydroxyl (-OH) group and C6G having the ester (-OCH₃).
2. The molecular structure of morphine is rigid. Requirements for μ receptor activity appear to require the nitrogen atom, the quaternary carbon 13 group separated from the nitrogen by an ethyl chain and an -OH or ester at carbon 3. Both known active M6G and theorized C6G fit this model. Indeed, in one animal study, the 6-glucuronides of morphine, codeine, and dihydrocodeine all demonstrated proper μ , δ , and κ receptor binding properties and ratios that would indicate that they are potent analgesics.¹³
3. Although no human studies have been done to date regarding C6G's analgesic properties, Srinivasan et al.¹⁴ did show that C6G was antinociceptive in rats.

Vree et al.¹² argue that if studies would measure C6G along with other metabolites and pain measures, they would demonstrate that it is the conversion to C6G, and not the conversion of morphine, that gives codeine its an-

TABLE 1. Codeine, Dihydrocodeine, Hydrocodone, Oxycodone, and Buprenorphine Metabolism

Drug	Metabolism			Metabolites	
	P450 Enzyme	Other Enzymes	Inhibition or Induction	Toxic	Active
Codeine	10% 3A4 (to norcodeine) 5% 2D6 (to morphine)	80% + UGT2B7 (to C6G and others)	Moderate inhibition of UGT 2B7	C3G ^a	Morphine C6G ^b
Dihydrocodeine	5-10% 2D6 (to dihydromorphine) and 3A4 (to nordihydrocodeine)	85% UGT2B7	Unknown	DHC3G ^c	Dihydromorphine ^d DHC6G ^d
Hydrocodone	2D6 (to hydromorphone) and 3A4 (to norhydrocodone)	Other minor nonP450 oxidative enzymes; UGT (2D6 and 3A4 products)	Unknown	Unknown	Hydromorphone
Oxycodone	2D6 (to oxymorphone) and 3A4 (to noroxycodone)	2D6 and 3A4 product(s) by UGTs	Unknown	Unknown	Oxymorphone
Buprenorphine	3A4	3A4 product(s) further cleared by UGTs	Unknown	No	No

^aMorphine-3-glucuronide (M3G) is a CNS toxic compound. Unknown if C3G, a very similar compound, is also toxic.
^bTheorized to be the main active analgesic when codeine is used.
^cAs with C3G, unknown if DHC3G is CNS toxic.
^dMay be active analgesics.

algesic properties. Unfortunately, such studies have not been done to this date.

With regard to pharmacokinetic drug-drug interactions with codeine, it then depends on what theory is held. If one believes that codeine's analgesic properties are from its conversion by 2D6 to morphine, then inhibiting 2D6 with such drugs as bupropion, cimetidine, fluoxetine, paroxetine, quinidine, and ritonavir¹⁵—all known potent inhibitors of 2D6—will likely decrease codeine's efficacy. In addition, up to 10% of people will have a poor response to codeine because they lack normal 2D6 activity. In both circumstances, via drug inhibition or genotype, the lack of conversion of codeine to morphine by 2D6 would be the reason for the lack of efficacy of codeine. However, if one believes Vree et al.'s theory, then the metabolism by 2D6 becomes irrelevant. In this case, inhibiting UGT enzymes, likely 2B7, which converts codeine to C6G, becomes the concern. Although there are inhibitors of UGT enzymes and UGT 2B7,¹⁶ at this time there are no studies or case reports that inhibition of 2B7 alters codeine's efficacy. One in vivo study¹⁷ of 12 volunteers concomitantly using codeine and diclofenac—a drug that in vitro has been shown to inhibit codeine's glucuronidation—did not demonstrate that codeine's glucuronidation was inhibited in the presence of diclofenac.

Therefore, by what mechanism codeine is a prodrug is unclear. It may be a prodrug via CYP450 2D6 metabolism or UGT 2B7 activity or perhaps both. We believe that future studies looking at C6G and its efficacy will strongly help better delineate codeine's properties as an analgesic.

Dihydrocodeine

As the name implies, dihydrocodeine is very similar in structure to codeine. Its only difference is that it has a single bond between carbons 7 and 8 instead of a double bond. Its analgesic properties are generally considered equipotent to codeine.¹⁸ Similar to codeine, demethylation at the 3-carbon site occurs via 2D6 to create dihydromorphine.¹⁹ Nordihydrocodeine is created by 3A4 activity.²⁰ In terms of amounts of metabolites made by these enzymes, dihydrocodeine's metabolism also appears to be similar to codeine. The 2D6 *O*-demethylated compound, dihydromorphine, is a minor metabolite (<5%). The conjugated 3 and 6 metabolites make up 85% of the metabolites in the urine after a single fixed dose.²¹ It has been presumed that UGT 2B7 is largely responsible for DHC-6-glucuronide formation,²² similar to codeine's conversion to C6G.

With dihydrocodeine's metabolism so similar to co-

deine, it should come as no surprise that there is the potential for controversy as to what chemical(s) or metabolite(s) contributes to its analgesic effect. Some have proposed that 2D6's activity to create dihydromorphine is the reason for analgesia with dihydrocodeine. The best study to date to demonstrate this failed to show that dihydromorphine was responsible for dihydrocodeine's analgesia.²³ Eleven volunteers were given dihydrocodeine in the presence or in the absence of the 2D6 inhibitor quinidine. Although the production of dihydromorphine was markedly reduced with quinidine use, the perception of pain was no different if quinidine was used or not.

In another study with 10 volunteers,²⁴ the amount of dihydromorphine found in blood samples did not predict analgesia, but the parent drug, dihydrocodeine, did. Other metabolites, however, were not measured.

We are not aware if anyone has proposed that DHC6G could be a reason for dihydrocodeine's analgesia, similar to the codeine model purported by Vree et al.¹² At this time, we believe it is unclear what primarily causes dihydrocodeine's analgesic properties—parent drug, metabolites, or some combination. Therefore, drug-drug interactions or implications of the phenotypes of 2D6 or UGT enzymes will have to wait for further research.

Hydrocodone

Hydrocodone (Vicodin® when combined with acetaminophen) is similar in structure to codeine. It differs with a single bond at carbons 7 and 8 and a keto (=O) group at 6-carbon instead of a hydroxyl (-OH) group.

Hydrocodone displays weak binding capacity for the μ receptor.²⁵ The 2D6 enzyme demethylates it at the 3-carbon position into hydromorphone,²⁶ which has much stronger μ binding than hydrocodone.²⁵ The metabolism of hydromorphone was described in part I.¹ Unlike codeine and dihydrocodeine, very little of hydrocodone goes directly to glucuronidation unless it is first made into hydromorphone by 2D6.²⁷ It is unclear if some hydrocodone is metabolized by 3A4, although it is likely that some 6-carbon oxidation does occur at 3A4 to create norhydrocodone. Finally, unknown enzymes reduce the 6-carbon position to minor active metabolites.

Like codeine and dihydrocodeine, it has been proposed that hydrocodone is a prodrug. Since oxidative products by 2D6, 3A4, and other enzymes are the primary products of hydrocodone's metabolism, and some of these products are better μ agonists than hydrocodone itself, this

proposal, in our opinion, appears more likely than for codeine or dihydrocodeine.

Unfortunately, studies that would help demonstrate that hydrocodone is a prodrug are scant, and no human studies have been done with pain models or with pain patients. Kaplan et al.²⁸ showed in a small study that poor or normal 2D6 metabolism does not predict abuse liability with hydrocodone, which might argue that hydrocodone is not a prodrug, but such a small study is hardly definitive.

Oxycodone

Oxycodone (OxyContin® and others) is similar in structure to hydrocodone, with the addition of a hydroxyl (–OH) group at the 14-carbon. Unlike codeine and hydrocodone, oxycodone is a potent analgesic in its own right.²⁹ Therefore, oxycodone is not a prodrug. There is an active metabolite, however, as 2D6 activity creates oxymorphone (Numorphan®), an active opioid analgesic.¹ This 3A4 activity appears to create inactive noroxycodone. When a 2D6 inhibitor was given with oxycodone in 10 volunteers, the amount of the 2D6 metabolite, oxymorphone, essentially disappeared, but the subjective feeling of being on oxycodone did not change.³⁰ Unfortunately, pain was not measured in this study.

Since it appears that 2D6 is major pathway for oxycodone's clearance, some have been concerned that toxicity could occur with oxycodone in patients with genetically poor 2D6 metabolism or in the constant presence of a 2D6 inhibitor, such as fluoxetine or paroxetine. Indeed, in one postmortem retrospective analysis of 15 deaths where suspected oxycodone toxicity was a cause of death, there were two, and possibly six, deaths that occurred in patients with poor 2D6 metabolism, and four of these cases helped better interpret the oxycodone toxicity.³¹ In another retrospective study involving nine deaths associated with oxycodone, the amount of oxycodone in the blood was higher than expected when used therapeutically.³² Four of the cases involved no other centrally acting drug (i.e., alcohol, benzodiazepine, stimulant, etc.). Although genetic testing was not done, in retrospect we wonder if some of these individuals either had poor 2D6 metabolism or ingested an inhibitor of 2D6 that contributed to their high oxycodone levels. The review unfortunately did not consider pharmacogenetics.

Buprenorphine

Buprenorphine (Buprenex®, Subutex®, or Suboxone®) is a potent mixed μ agonist/antagonist semi-synthetic

opioid. It differs from the morphine structure by an –OCH₃ at the 6-carbon; a single bond between the 7 and 8 carbon with a hydroxyl, triethylpropyl group on the 7 carbon; an –OH at the 14 carbon; a small 3-carbon ring at the 17-carbon site; and an endotheno bridge between the 6 and 14 carbon. It appears to be metabolized chiefly by 3A4,³³ and many of these metabolites go on through conjugation by UGTs. Drug-drug interactions are likely with this drug because of its reliance on 3A4. Indeed, the Buprenex® package insert³⁴ warns against the use of buprenorphine with 3A4 inhibitors and inducers—the former possibly creating opioid toxicity and the latter creating possible opioid withdrawal. Common 3A4 inhibitors include azole antifungals, many macrolide antibiotics, and nefazodone. Common inducers include rifampin and many antiepileptics.

Summary

Pharmacokinetic drug-drug interactions with codeine, dihydrocodeine, hydrocodone, oxycodone, and buprenorphine are likely common. However, the ability to predict these interactions is difficult. Codeine may be a prodrug, but by what mechanism(s) it is a prodrug has not been fully deduced. Some believe that CYP450 2D6 conversion of codeine to morphine is responsible for codeine's analgesia. Others believe that it is codeine's conversion by UGT 2B7 codeine to C6G that creates the analgesia. Either way, inhibition, induction, or altered enzyme genotypes could alter codeine's effectiveness. More definitive studies are needed for codeine to sort these issues in order to make more definitive predictions about its potential as a prodrug and for drug-drug interactions. Similarly, dihydrocodeine may be a prodrug through 2D6 or 2B7, but even fewer definitive studies have been done.

Hydrocodone is a weak μ agonist, and its primary metabolism is through 2D6, which creates a more active metabolite hydromorphone. Although few studies have been done to demonstrate this process, it is likely that inhibition/induction or poor 2D6 metabolism will alter hydrocodone's efficacy. Oxycodone is not a prodrug, since it is a potent μ agonist. It is mainly metabolized by 2D6, and there is some, albeit limited, evidence that inhibition of 2D6 or poor 2D6 metabolism can lead to toxicity of oxycodone. Finally, buprenorphine is metabolized through 3A4, and 3A4 inhibition or induction by other drugs may alter significantly the levels of buprenorphine.

References

1. Armstrong SC, Cozza KL: Pharmacokinetic drug interactions of morphine, codeine, and their derivatives: theory and clinical reality, part I. *Psychosomatics* 2003; 44:167–171
2. Pert CB, Snyder SH: Opiate receptor, demonstration in nervous tissue. *Science* 1973; 179:1101–1104
3. Sanfilippo G: Contributo sperimentale all'ipotesi della smetilazione della codeina nella organismo. I. Influence della dose sull'assuefazione all codeine. II. Assuefazione all codeine attenuata con somministrazione prolungata di morfina. *Boll Soc Italiana Biol Sper* 1948; 24:723–726
4. Sindrup SH, Brosen K, Bjerring P, Arendt-Nielsen L, Larsen U, Angelo HR, Gram LF: Codeine increases pain thresholds to copper vapour laser stimuli in extensive but not in poor metabolisers of sparteine. *Clin Pharmacol Ther* 1990; 48:686–693
5. Desmeules J, Gascon MP, Dayer P, Magistris M: Impact of environmental and genetic factors on codeine analgesia. *Eur J Clin Pharmacol* 1991; 41:23–26
6. Vree TB, Verwey-van Wissen CP: Pharmacokinetics and metabolism of codeine in humans. *Biopharm Drug Dispos* 1992; 13:445–460
7. Quiding H, Lundqvist G, Boreus LO, Bondesson U, Ohrvik J: Analgesic effect and plasma concentrations of codeine and morphine after two dose levels of codeine following oral surgery. *Eur J Clin Pharmacol* 1993; 44:319–323
8. Persson K, Sjoström S, Sigurdardottir I, Molnar V, Hammarlund-Udenaes M, Rane A: Patient-controlled analgesia (PCA) with codeine for postoperative pain relief in ten extensive metabolisers and one poor metaboliser of dextromethorphan. *Br J Clin Pharmacol* 1995; 39:182–186
9. Poulsen L, Riishede L, Brosen K, Clemensen S, Sindrup SH: Codeine in post-operative pain: study of the influence of sparteine phenotype and serum concentrations of morphine and morphine-6-glucuronide. *Eur J Clin Pharmacol* 1998; 54:451–454
10. Fernandes LC, Kilicarslan T, Kaplan HL, Tyndale RF, Sellers EM, Romach MK: Treatment of codeine dependence with inhibitors of cytochrome P450 2D6. *J Clin Psychopharmacol* 2002; 22:326–329
11. Kathiramalainathan K, Kaplan HL, Romach MK, Busto UE, Li NY, Sawe J, Tyndale RF, Sellers EM: Inhibition of cytochrome P450 2D6 modifies codeine abuse liability. *J Clin Psychopharmacol* 2000; 20:435–444
12. Vree TB, Van Dongren RT, Koopman-Kimenai PM: Codeine analgesia is due to codeine-6-glucuronide, not morphine. *Int J Clin Pract* 2000; 54:395–398
13. Mignat C, Wille U, Ziegler A: Affinity profiles of morphine, codeine, dihydrocodeine and the glucuronides at the opioid receptor subtypes. *Life Sci* 1995; 56:793–799
14. Srinivasan V, Wielbo D, Simpkins J, Karlx J, Sloan K, Tebbett I: Analgesic and immunomodulatory effects of codeine and codeine-6-glucuronide. *Pharm Res* 1996; 13:296–300
15. Cozza KL, Armstrong SC, Oesterheld JH: Concise Guide to Drug Interaction Principles for Medical Practice: Cytochrome P450s, UGTs, P-glycoproteins, 2nd edition. Arlington, Va, American Psychiatric Publishing, 2003
16. Grancharov K, Naydenova Z, Lozeva S, Golovinsky E: Natural and synthetic inhibitors of UDP-glucuronosyltransferase. *Pharmacol Ther* 2001; 89:171–186
17. Ammon S, Marx C, Behrens C, Hofmann U, Murdter T, Griese EU, Mikus G: Diclofenac does not interact with codeine metabolism in vivo: study in healthy volunteers. *BMC Clin Pharmacol* 2002; 2:2 (<http://www.biomedcentral.com/1472-6904/2/2>)
18. Case LJ, Frederick WS: An experimental and statistical method in the study of new drugs. *Arch Int Med* 1958; 102:571–580
19. Schmidt H, Vormfelde SV, Walchner-Bonjean M, Klinder K, Freudenthaler S, Gleiter CH, Gundert-Remy U, Skopp G, Aderjan R, Fuhr U: The role of active metabolites in dihydrocodeine effects. *Int J Clin Pharmacol Ther* 2003; 41:95–106
20. Kirkwood LC, Nation RL, Somogyi AA: Characterization in the human cytochrome P450 enzymes involved in the metabolism of dihydrocodeine. *Br J Clin Pharmacol* 1997; 44:549–555
21. Balikova M, Maresova V, Habrdova V: Evaluation of urinary dihydrocodeine excretion in human by gas chromatography-mass spectrometry. *J Chromatogr B Biomed Sci Appl* 2001; 752:179–186
22. Kirkwood LC, Nation RL, Somogyi AA: Glucuronidation of dihydrocodeine by human liver microsomes and the effect of inhibitors. *Clin Exp Pharmacol Physiol* 1998; 25:266–270
23. Wilder-Smith CH, Hufschmid E, Thorman W: The visceral and somatic antinociceptive effects of dihydrocodeine and its metabolite, dihydromorphine: a cross-over study with extensive and quinidine-induced poor metabolizers. *Br J Pharmacol* 1998; 45:575–581
24. Webb JA, Rostami-Hodjegan A, Abdul-Manap R, Hofmann U, Mikus G, Kamali F: Contribution of dihydrocodeine and dihydromorphine to analgesia following dihydrocodeine administration in man: a PK-PD modeling analysis. *Br J Clin Pharmacol* 2001; 52:35–43
25. Chen ZR, Irvine RJ, Somogyi AA, Bochner F: Mu receptor binding of some commonly used opioids and their metabolites. *Life Sci* 1991; 48:2165–2171
26. Otton SV, Wu D, Joffe RT, Cheung SW, Sellers EM: Inhibition by fluoxetine of cytochrome P450 2D6 activity. *Clin Pharmacol Ther* 1993; 53:401–409
27. Cone EJ, Darwin WD, Gorodetzky CW, Tan T: Comparative metabolism of hydrocodone in man, rat, guinea pig, rabbit, and dog. *Drug Metab Dispos* 1978; 6:488–493
28. Kaplan HL, Busto UE, Baylon GJ, Cheung SW, Otton SV, Somer G, Sellers EM: Inhibition of cytochrome P450 2D6 metabolism of hydrocodone to hydromorphone does not importantly affect abuse liability. *J Pharmacol Exp Ther* 1997; 281:103–108
29. Kalso E, Vainio A, Mattila MJ, Rosenberg PH, Seppala T: Morphine and oxycodone in the management of cancer pain: plasma levels determined by chemical and radioreceptor assays. *Pharmacol Toxicol* 1990; 67:322–328
30. Heiskanen T, Olkkola KT, Kalso E: Effects of blocking CYP2D6 on the pharmacokinetics and pharmacodynamics of oxycodone. *Clin Pharmacol Ther* 1998; 64:603–611
31. Jannetto PJ, Wong SH, Gock SB, Laleli-Sahin E, Schur BC, Jentzen JM: Pharmacogenomics as molecular autopsy for postmortem forensic toxicology; genotyping cytochrome P450 2D6 for oxycodone cases. *J Anal Toxicol* 2002; 26:438–447
32. Drummer OH, Syrjanen ML, Phelan M, Corder SM: A study of deaths involving oxycodone. *J Forensic Sci* 1994; 39:1069–1075
33. Kobayashi K, Yamamoto T, Chiba K, Tani M, Shimada N, Ishizaki T, Kuroiwa Y: Human buprenorphine N-dealkylation is catalyzed by cytochrome P450 3A4. *Drug Metab Dispos* 1998; 26:818–821
34. Buprenex® (Buprenorphine hydrochloride). Hull, England, Rickett Benckiser Healthcare (UK) Ltd, July 2001