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## Oxycodone: Recognition And Pharmacogenomics

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**O**xycodone, a narcotic analgesic, is a semi-synthetic opioid agonist with a potential for abuse similar to that of morphine. Opioid agonists are prescribed for their analgesic properties. Other medications in this class include morphine, codeine, hydromorphone, hydrocodone, methadone, propoxyphene, and fentanyl.

Oxycodone is recommended for the treatment of moderate to severe pain, chronic pain, or terminal cancer pain. It produces intense euphoria, relaxation, and sedation. Its analgesic properties are similar to those of morphine. The primary adverse (toxic) effect is respiratory depression, but others include apnea, respiratory arrest, circulatory depression, hypotension, and shock.

Oxycodone is available in immediate-release and controlled-release formulations, either as a single entity or in combination. Brand names for single entity oxycodone hydrochloride formulations include the immediate-release formulations OxyFast, OxyIR, Roxicodone, and Percolone. The controlled-release formulation is OxyContin. Combination immediate-release formulations containing oxycodone hydrochloride with acetaminophen include Percocet, Tylox, Roxicet, and Endocet. Formulations containing oxycodone hydrochloride and oxycodone terephthalate with aspirin include Percodan and Endodan.

### Pharmacokinetics

The usual adult dose of oxycodone hydrochloride is 2.5–5 mg every 6 hours, although patients with severe pain may take 10–30 mg every 4 hours (1). Controlled-release oxycodone is taken every 12 hours; clinical studies have not been done on more frequent dosing (2). Dosages may be adjusted every day or two as steady-state plasma concentrations are usually reached in 24–36 hours.

Oxycodone is well-absorbed, with an oral bioavailability of 60–87%. The absorption half-life for the immediate-release formulation is 0.4 hours, whereas for the controlled-release formulation, it is 0.6 hours for the first phase and 6.9 hours for the second phase (2). Peak plasma oxycodone concentrations in 12 patients receiving a 10-mg oral dose of immediate-release oxycodone averaged 0.030 mg/L at 0.8–2.5 hours post dose (1). Peak plasma oxycodone concentrations in 28 adults given a single 20-mg controlled-release oral dose averaged 0.023 mg/L at 3.2 hours. Peak concentrations for a single 40-mg or 80-mg controlled-release dose averaged 0.039 and 0.099 mg/L, respectively (1).

### Metabolism

Oxycodone is metabolized to noroxycodone, which is a relatively inactive metabolite, and to oxymorphone, which is also a potent narcotic analgesic, although present in the blood only in low concentrations after oxycodone administration. The formation of oxymorphone is mediated by cytochrome P450 2D6. From 33–61% of a single dose of oxycodone is excreted in the urine within 24 hours as unconjugated oxycodone (13–19%), conjugated oxycodone (7–29%), conjugated oxymorphone (13–14%), and noroxycodone (unknown amount) (1). In pharmacokinetic studies, after repeated dosing in normal volunteers, the elimination half-life of oxycodone following the administration of Oxycontin was 4.5 hours compared with 3.2 hours for immediate-release oxycodone (2).

Published pharmacokinetic studies show that plasma oxycodone concentrations are generally less than 100 µg/L. Blood or plasma oxycodone concen-

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## Oxycodone

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trations following prolonged administration are not known. Fatal concentrations involving oxycodone and at least one other depressant drug have been reported at 600 µg/L or higher in postmortem blood (3). However, oxycodone concentrations as low as 100 µg/L in conjunction with elevated concentrations of antidepressants or certain other prescription drugs can cause death (4).

In a recent study by the Milwaukee County medical examiner's office from January 2000 to March 2002, there were 46 cases in which oxycodone was identified as part of a comprehensive toxicology screen and quantified (5). In 15 of these cases, oxycodone was considered to be a contributory factor in the cause of death, and oxycodone values ranged from 160 µg/L to 2070 µg/L. In 11 of these cases, the cause of death was listed as mixed drug toxicity and in four it was oxycodone overdose. The manner of death was nine accidental, three suicide, and three undetermined. Other drugs were identified in 14 of these cases and included: seven diazepam, four diphenhydramine, four alcohol, three acetaminophen, three hydrocodone, two venlafaxine, two nortriptyline, and one each of cocaine, clonazepam, cyclobenzaprine, meperidine, methadone, amitriptyline, carisoprodol, meprobamate, citalopram, fentanyl, tramadol, and phenytoin.

### New era of oxycodone abuse

Because of its highly effective opiate-like effects, oxycodone has a very high abuse potential. OxyContin, the controlled-release formulation, was developed by Purdue Pharma and approved by the Food and Drug Administration in December 1995. It was initially prescribed in 10-, 20-, 40-, 80-, and 160-mg tablets, but recently the distribution of the 160-mg tablet was discontinued as part of Purdue Pharma's ongoing effort to address the problem of diversion and abuse.

OxyContin tablets provide controlled-release of oxycodone over 12 hours using the manufacturer's AcroContin drug-delivery system. This system allows for a biphasic drug-absorption pattern with initial rapid release of oxycodone from the tablet surface followed by slow release by dissolution through the tablet matrix (6).

According to the package insert warning section, OxyContin is indicated for the management of moderate to severe pain when an around-the-clock analgesic is needed for an extended period and should not be used as a prn (as needed) analgesic.

The 80-mg and 160-mg tablets are recommended for use only in opioid tolerant patients. For effective sustained-release, the tablets must be swallowed whole (2).

The treatment goal when OxyContin is used for the management of moderate to severe pain is dosing to effectively control pain with two or fewer rescue doses per day. Rescue medications suggested for use with OxyContin are immediate-release opiate formulations (including oxycodone) alone or in combination with acetaminophen, aspirin, or other non-steroidal anti-inflammatory drugs.

Oxycontin's strength, duration of action, and known dosages are the reasons the drug is attractive to both abusers and legitimate users. The controlled release of the drug can be negated by chewing or crushing the tablets, which results in the rapid release and absorption of what could be a potentially fatal dose. Abusers tend to use OxyContin in one of three ways: chewing the tablets; crushing the tablets, then snorting the powder; or crushing the tablets, then dissolving the powder in water for intravenous injection. Currently, Purdue Pharma is developing a reformulated version that contains an opioid antagonist to reduce the abuse potential if the pill is chewed or crushed (7). The company estimates that it will take at least four years to complete the clinical development of an abuse-resistant product.

### DAWN and other reports

According to an Office of National Drug Control Policy fact sheet, in 1998 an estimated 1.6 million Americans used prescription pain relievers for non-medical reasons for the first time. According to the 1999 National Household Survey on Drug Abuse by the Substance Abuse and Mental Health Services Administration (SAMHSA), about 4 million Americans reported current use of prescription drugs for non-medical purposes (8). The three classes of prescription drugs most commonly abused in order of frequency were opioids (including oxycodone), sedatives and tranquilizers, and stimulants. The survey also showed that approximately 9% of the U.S. population (19.9 million people) used pain relievers illegally in their lifetime.

Recent reports by the Drug Abuse Warning Network (DAWN) indicate that oxycodone abuse has risen significantly, as indicated by an increase in oxycodone mentions from emergency department and medical examiner reports. From 1999 to 2000, DAWN emergency department mentions of prescription drugs containing oxycodone increased 68% (from 6,429 to 10,825), and mentions of drugs containing hydrocodone increased 31% (from 14,639 to 19,221) (9). According to the 2000 Annual Report of

the American Association of Poison Control Centers Toxic Exposure Surveillance System, analgesics, such as oxycodone, are the primary substance in 30% of all reported fatalities (10).

The U.S. Department of Justice Drug Enforcement Administration (DEA) recently solicited medical examiner reports on oxycodone-related deaths for 2000 and 2001 (11). Of the 949 complete medical examiner reports on oxycodone-associated deaths, 146 deaths were identified as "OxyContin-verified" (pills in stomach, at scene, or on person) and 318 were labeled "OxyContin-likely" (defined as oxycodone positive, with no acetaminophen or salicylate detected). This data suggests that almost half (49%) of all oxycodone deaths may have been related to OxyContin, although only 15% of all oxycodone-positive toxicology reports were actually confirmed to be OxyContin.

The terms "OxyContin-verified" and "OxyContin-likely" indicated that OxyContin was or may have been the source of the oxycodone detected and was not necessarily the cause of death. The findings also showed that the majority of cases were due to polydrug toxicities. Other drugs detected in combination with oxycodone included another opioid (40%), benzodiazepine (40%), antidepressants (30%), alcohol (19%), cocaine and metabolites (15%), and antihistamines or cold medications (14%). The DEA also acknowledged that the extreme media reports of "hundreds of deaths" attributed to OxyContin could not be verified. Two recently published articles on medical examiner's toxicology results also found polydrug toxicities in most deaths in which oxycodone was detected (5, 12).

### Los Angeles study

A six-year study at the Los Angeles County coroner's toxicology laboratory detected oxycodone in 67 cases (12). Thirty-six of these cases involved OxyContin, as shown either by medication history or the identification of pills collected from gastric contents, and 24 of those cases occurred in the past two years. Of the 36 OxyContin cases, intact tablets were found in 15. Some of the pills collected from gastric contents were "ghost pills," which are seemingly intact but drug-free tablets that resemble undigested pills. In this study, intact pills and gastric contents were analyzed for detection and quantification of oxycodone.

This study demonstrated that in most cases the intact pills were clearly marked for easy identification of OxyContin; the analysis of recovered OxyContin tablets from some cases revealed little or no oxycodone; and the gastric concentrations of oxycodone were less than expected in comparison to the

number of tablets remaining in the stomach. The authors suggested that because OxyContin is a controlled-release formulation and the tablets are not meant to dissolve, it is not possible to correlate the number of pills recovered from the stomach to inappropriate drug use.

### Analytical methods

Most clinical and forensic laboratories use commercially available immunoassay kits to screen for opiates. However, commercial opiate class immunoassay kits were designed for detection of morphine and codeine, but not hydromorphone, hydrocodone, or oxycodone. Studies have addressed the problems associated with antibody cross-reactivity in opiate immunoassays. Cone et al. studied the apparent sensitivity and cross-reactivity of opiates with four commercial opiate urine immunoassays: TDx Opiates (Abbott Laboratories); Coat-A-Count Morphine (Diagnostic Products Corporation); Abuscreen Radioimmunoassay for Morphine (Roche Diagnostic Systems); and Emit d.a.u. Opiate Assay (Syva Company) (13).

In this study, each of the 6-keto-opioid compounds had concentration-dependent cross-reactivities with antibodies used in the immunoassays, and each had the potential to produce positive urine screening results. However, responses were reduced in all assays in the presence of oxycodone and oxymorphone.

Smith et al., in a later study of the same opiate immunoassays, administered single doses of the 6-keto-opioids including oxycodone to human subjects, then collected periodic urine samples (14). This study demonstrated that oxycodone was detectable by TDx and Emit d.a.u. opiate assays for 6–24 hours. However, the quantitative responses from these assays expressed as ng/mL of morphine equivalents were substantially lower than those found by gas chromatography/mass spectrometry determinations. Generally, opiate immunoassays displayed lower sensitivities for 6-keto-opioids, and could fail to detect low to moderate levels of oxycodone and its metabolite oxymorphone. Also, the immunoassays' lower sensitivity and greater cross-reactivity, combined with higher potency of oxycodone relative to morphine, reduce the probability of detection in urine after therapeutic use. As a result, opiate immunoassays are not well-suited for monitoring therapeutic use, compliance, or abuse of oxycodone.

Clinicians and other users of laboratory services may draw improper conclusions if they are unaware that these opiate screening methods may not reliably detect oxycodone use. Patients who test

“negative” for oxycodone with an immunoassay may be wrongfully accused of diverting their prescription drugs to others. To alleviate this problem, an immunoassay designed for the detection of oxycodone or oxycodone/oxymorphone should be used. Recently, Immunalysis Corporation (San Dimas, California) and Neogen Corporation (Lexington, Kentucky) have developed such immunoassays. These immunoassays can also be adapted for the detection of oxycodone in other biological fluids, such as blood. Increased assay sensitivity and detection can be achieved by adjusting the threshold concentration used to distinguish between positive and negative results (15).

### Chromatographic methods

Chromatographic methods for oxycodone detection include thin-layer chromatography (TLC), liquid chromatography (LC), automated liquid chromatography, liquid chromatography/mass spectrometry (LC/MS), gas chromatography (GC), and gas chromatography/mass spectrometry (GC/MS). Of these numerous techniques, gas or liquid chromatography coupled with mass spectrometry using selective ion monitoring (SIM) should be used for confirmation.

The Toxi-Lab A TLC drug detection system has been used for the detection of oxycodone in urine specimens. However, with its detection limit of 1.0 mg/L, the assay may not detect the therapeutic use of oxycodone. However, Gobar et al. used TLC at a lower detection limit of 300 µg/L with confirmation by GC/MS at a detection limit of 300 µg/L for successful detection of oxycodone in urine specimens from pain management patients (16).

Oxycodone can also be detected in biological fluids using GC with flame ionization or nitrogen-phosphorus detection. Subsequent confirmation by GC/MS in the full scan mode shows principle mass spectral peaks at  $m/z$  315, 230, 70, 258, and 140. Hydrolyzing urine specimens with beta-glucuronidase prior to analysis is effective in increasing the recovery of oxycodone from the specimen (17). However, routine broad-spectrum chromatography blood screens may lack the sensitivity necessary for detection of oxycodone levels seen in blood after occasional or therapeutic use. Using GC/MS with selective ion monitoring for principal ions increases assay sensitivity to detection limits of 10–20 µg/L (5). At these detection limits, oxycodone therapeutic use, compliance, and abuse can be monitored.

With the rise in prescription opioid abuse, mainly of hydrocodone and oxycodone, and the concurrent use of more than one opioid, as is seen in pain management treatment programs, a single assay

capable of detecting and quantifying morphine, 6-acetylmorphine, codeine, and keto-opioids (including hydromorphone, hydrocodone, oxycodone, and oxymorphone) would be beneficial.

Problems with GC/MS methods used for the determination of multiple opioids in a single assay include instability of derivatives, poor conditions for chromatography including unsuitable ions and abundances, formation of multiple derivatives, inadequate recovery, and co-elution or interference by other opiates due to incomplete derivatization or side reactions (18–22).

The choice of derivatization agents to be used in the GC/MS analysis of opioids is one of the most important factors determining the accuracy and precision of the method. Derivatization agents that can be used include acetic anhydride, bis(trimethylsilyl) trifluoroacetamide (BSTFA) with 1% trimethylchlorosilane (TMCS), heptafluorobutyric anhydride, pentafluoropropionic anhydride, and N-methyl-bis(trifluoroacetamide) (MBFTA) (18–22).

Recently, several groups have investigated the use of oxime-TMS derivatization for the simultaneous detection of codeine, morphine, and keto-analytes in urine (23–25). This derivatization resulted in reduced interference from other opioids, short analysis time, and acceptable assay precision and accuracy. A recent study demonstrated the adaptation of this method for use with blood or alternative biological matrices (26). In this study, the simultaneous quantitation of seven opioids (morphine, codeine, 6-acetylmorphine, hydromorphone, hydrocodone, oxycodone, and oxymorphone) in blood and alternative matrices could be achieved. Prior to extraction, specimens were subjected to a methanolic deproteinization step followed by initial derivatization with hydroxylamine to convert the keto moieties to oxime derivatives, thereby preventing enolization and production of multiple analyte peaks. After extraction, BSTFA with 1% TMCS was used for the second derivatization step. This resulted in increased analyte recovery and acceptable chromatography for detection of opioids when biological matrices other than urine were analyzed.

### Pharmacogenetics

Previous studies failed to examine the role that pharmacogenetics may have in oxycodone toxicity. Pharmacogenomics is the study of the link between an individual's genotype and that individual's ability to metabolize a foreign compound (27). Most xenobiotics, including therapeutic drugs, are metabolized by cytochromes P450 (*CYP*) to some extent. Mutations in *CYP* genes can cause altered drug metabolism and lead to therapeutic failure and toxicity by

altering the blood concentration of the pharmacologically active drug (28). Among the P450 subfamilies, *CYP2D6* plays a critical role in determining the response to 25% of all medications, including oxycodone (29). *CYP2D6* is polymorphic and is responsible for the metabolism of oxycodone to oxymorphone. *CYP2D6* polymorphisms can be categorized into four groups: ultrarapid metabolizers, who possess multiple copies of the *CYP2D6* gene; extensive metabolizers, who have a single wild-type copy of the *CYP2D6* gene; intermediate metabolizers, who exhibit decreased enzymatic activity; and poor metabolizers, who have no detectable activity (30). Although most people are extensive metabolizers, 5–10% of Caucasians and 1–4% of most other ethnic groups are poor metabolizers and risk toxic effects if they receive the routine clinical dose (31).

As a result, poor drug metabolism due to *CYP2D6* deficiency may play a significant role in oxycodone toxicity. Therefore, postmortem drug concentrations of oxycodone should be interpreted in conjunction with the medical history, death scene investigation, autopsy findings, postmortem interval, and pharmacogenomics.

A recent study from the Milwaukee County medical examiner's office examined the potential role that pharmacogenomics might play in oxycodone deaths (5). This study found a higher prevalence of poor and intermediate metabolizers in the oxycodone-related deaths compared with a control group. The following case illustrates how the application of pharmacogenomics in forensic toxicology may help provide a rational basis for the understanding of oxycodone fatalities.

### Case study

A 49-year-old white male was last seen alive at 8:15 a.m. by his roommate when she left for work. After returning home that evening, she went to check on him at about 8:00 p.m. Upon discovering him lying unresponsive in his bed, she contacted authorities. His medical history included treatment for recurrent depression, post-traumatic stress disorder, chronic lower back pain, and polysubstance abuse (alcohol and opiate addiction). As part of his outpatient psychiatric treatment, the decedent was prescribed the antidepressants venlafaxine, mirtazapine, and risperidol with gabapentin or naproxen for pain. He was also seeing various doctors who had prescribed Percodan, Percocet, and Oxycontin for treatment of chronic lower back pain. His history also included previous overdose attempts.

Medication vials recovered from the scene included naproxen, Neurontin (gabapentin), amoxicillin, and Oxycontin. These medications were in order

except for the Oxycontin prescription for 60 10-mg tablets with instructions to take one tablet twice daily. Only 12 of the 60 Oxycontin tablets remained from the prescription that was filled the previous day. A comprehensive toxicology screen was performed on urine, gastric, and blood specimens collected at autopsy. Venlafaxine, mirtazapine, oxycodone, caffeine, and nicotine were detected in the urine specimen. Oxycodone was the only analyte detected in the gastric and blood specimens. Toxicological analysis of subclavian blood detected an elevated level of oxycodone (0.437 mg/L). Nineteen intact 10-mg Oxycontin tablets were recovered from the gastric contents.

The autopsy showed hepatic cirrhosis and atherosclerotic heart disease. Since the decedent had a medical history of chronic lower back pain and surgery for which he was prescribed oxycodone, he was not opioid naive. In addition, the decedent was an alcoholic. Because the postmortem interval was less than 24 hours and subclavian blood was used, the elevated concentration of oxycodone was not due to postmortem redistribution.

A molecular autopsy (pharmacogenomic assessment of *CYP2D6*) showed that the individual was homozygous for the \*4 mutation. As a result, this individual lacked any *CYP2D6* activity and would be a poor metabolizer of oxycodone. The cause of death was certified as oxycodone overdose and manner accidental. This determination was made from the following case information: absence of a suicide note from the scene investigation, recent history of prescription pain medication abuse, elevated blood oxycodone level, presence of 10-mg Oxycontin tablets in gastric contents, poor metabolizer phenotype conferred by *CYP2D6* deficiency, and impaired metabolism due to hepatic cirrhosis.

### Conclusion

Overall, the prescription use of oxycodone and other opioids has increased dramatically in recent years. Along with the increased therapeutic use of opioids such as oxycodone for the treatment of moderate to severe pain, an increase in the abuse of these medications is also occurring. The increase in prescription drug abuse of oxycodone has been demonstrated by the increase in oxycodone mentions from both emergency room visits and medical examiner's reports. Also, the use of opioids such as oxycodone for pain treatment can include polydrug therapy with simultaneous use of other opioids, non-steroidal anti-inflammatory drugs, co-analgesic drugs, antidepressants, anticonvulsants, and other prescription medications. In both clinical and forensic toxicology, the detection of oxycodone may be necessary in assess-

ing oxycodone compliance, abuse, and toxicity. Oxycodone therapeutic use can be best detected using an oxycodone-specific immunoassay or a chromatographic procedure with sensitivity for detection of therapeutic levels of oxycodone, which are generally less than 100 µg/L. Although the abuse of oxycodone can result in toxicity, poor drug metabolism due to *CYP2D6* deficiency can also play a significant role. Therefore, pharmacogenomics may provide the additional information needed to explain and understand oxycodone-related toxicities and fatalities.

## References

1. Oxycodone. In: Baselt RC. Disposition of toxic drugs and chemicals in man, 6<sup>th</sup> ed. Foster City, California: Biomedical Publications, 2002:787–89.
2. OxyContin package insert. Purdue Pharma L.P. Website: [www.purduepharma.com](http://www.purduepharma.com)
3. Drummer OH, Syrjanen ML, Phelan M, Corder SM. A study of deaths involving oxycodone. *J Forensic Sci* 1994;39:1069–75.
4. Cooke AH, Holt LA, McCurdy HH. A review of oxycodone related deaths in the state of Georgia. Society of Forensic Toxicologists Annual Meeting 2001, P-21.
5. 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;26:438–47.
6. AcroContin Drug Delivery System. Purdue Pharma L.P., Stamford, Connecticut.
7. Purdue Pharma L.P. Website: [www.purduepharma.com](http://www.purduepharma.com)
8. National Institute on Drug Abuse Research Report Series: Prescription drugs—abuse and addiction. Website: [www.nida.nih.gov](http://www.nida.nih.gov)
9. New trends released for drug related emergency department visits. Substance Abuse and Mental Health Services Administration News 2001. Website: [www.samhsa.gov](http://www.samhsa.gov)
10. Litovitz TL, Klein-Schwartz W, White S, et al. Annual report of the American Association of Poison Control Centers toxic exposure surveillance system. *Am J Emerg Med* 2001;19:337–95.
11. United States Department of Justice website: [www.usdoj.gov](http://www.usdoj.gov)
12. Anderson DT, Fritz KL, Muto JJ. OxyContin: the concept of a “ghost pill” and the postmortem tissue distribution of oxycodone in 36 cases. *J Anal Toxicol* 2002;26:448–59.
13. Cone EJ, Dickerson S, Paul BD, Mitchell JM. Forensic drug testing for opiates. IV. Analytical sensitivity, specificity, and accuracy of commercial urine opiate immunoassays. *J Anal Toxicol* 1992;16:72–8.
14. Smith ML, Hughes RO, Levin B, Dickerson S, Darwin WD, Cone EJ. Forensic drug testing for opiates. VI. Urine testing for hydromorphone, hydrocodone, oxycodone, and oxycodone with commercial opiate immunoassays and gas chromatography-mass spectrometry. *J Anal Toxicol* 1995;19:18–26.
15. Hattab EM, Goldberger BA, Johannsen LM, et al. Modification of screening immunoassays to detect sub-threshold concentrations of cocaine, cannabinoids, and opiates in urine: use for detecting maternal and neonatal drug exposures. *Ann Clin Lab Sci* 2000;30:85–91.
16. Gobar AB, Wagner MA, Wong SH, Elias M, Wu A. A retrospective study of oxycodone monitoring in pain management. *J Anal Toxicol* 2001;25:377–8.
17. Huang W, Adollo W, Hearn WL. A solid phase extraction technique for the isolation and identification of opiates in urine. *J Anal Toxicol* 1992;16:307–10.
18. Paul BD, Mell LD, Mitchell JM, Irving J, Novak AJ. Simultaneous identification and quantification of codeine and morphine in urine by capillary gas chromatography and mass spectrometry. *J Anal Toxicol* 1985;9:222–6.
19. Chen BH, Taylor EH, Pappas AA. Comparison of derivatives for determination of codeine and morphine by gas chromatography/mass spectrometry. *J Anal Toxicol* 1990;14:12–7.
20. Saddy JJ, Narasimhachari N, Blanke RV. Rapid, simultaneous quantification of morphine, codeine, and hydromorphone by GC-MS. *J Anal Toxicol* 1982;6:235–7.
21. Grinstead GF. A closer look at acetyl and pentafluoropropionyl derivatives for quantitative analysis of morphine and codeine by gas chromatography/mass spectrometry. *J Anal Toxicol* 1991;15:293–8.
22. Broussard LA, Presley LC, Tanous M, Queen C. Improved gas chromatography-mass spectrometry method for the simultaneous identification and quantification of opiates in urine as propionyl and oxime derivatives. *Clin Chem* 2001;47:127–9.
23. Jones CW, Chaney G, Mastorides S. Simultaneous analysis of opiates in urine by SPE and GC-MS with stabilization of keto-opiates via conversion to oxime derivative. *J Anal Toxicol* 1997;21:86.

24. Broussard LA, Presley LC, Pittman T, Cluette R, Wimbish GH. Simultaneous identification and quantitation of codeine, morphine, hydrocodone, and hydromorphone in urine as trimethylsilyl and oxime derivatives by gas chromatography-mass spectrometry. *Clin Chem* 1997;43:1029–32.
25. Cremese M, Wu AHB, Cassella G, O'Conner E, Rymut K, Hill DW. Improved GC/MS analysis of opiates with use of oxime-TMS derivatives. *J Forensic Sci* 1998;43:1220–4.
26. Roper-Miller JD, Lambing MK, Winecker RE. Simultaneous quantitation of opioids in blood by GC-EI-MS analysis following deproteination, deautomerization of keto analytes, solid-phase extraction, and trimethylsilyl derivatization. *J Anal Toxicol* 2002;26:524–8.
27. Linder MW, Prough RA, Valdes R Jr. Pharmacogenetics: a laboratory tool for optimizing therapeutic efficiency. *Clin Chem* 1997;43:254–66.
28. Nebert DW, Dieter MZ. The evolution of drug metabolism. *Pharmacology* 2000;61:124–35.
29. Wolf CR, Smith G. Pharmacogenetics. *Br Med Bull* 1999;55:366–86.
30. Benet L, Kroetz D, Sheiner L. Pharmacokinetics: the dynamics of drug absorption, distribution, and elimination. In: Hardman J, Goodman G, eds. *Goodman and Gilman's the pharmacological basis of therapeutics*. New York: McGraw-Hill, 1996:3–27.
31. Sachse C, Brockmoller J, Roots I. Cytochrome P450 2D6 variants in a Caucasian population: allele frequencies and phenotypic consequences. *Am J Hum Genet* 1997;60:284–95.
32. Fraser AD, Jannetto PJ, Gock SB, Wong SH. The North American oxycodone story 2001–2002. *The International Association for Therapeutic Drug Monitoring and Clinical Toxicology Newsletter* 2002; Volume 2 Issue 1.

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## Thanks for Questionnaires

The Editorial Advisory Board of *Clinical & Forensic Toxicology News* would like to express its appreciation to subscribers who returned the questionnaire included with the December issue. Your responses are important for planning future articles. Subscribers with additional comments can send them to [cftnews@aacc.org](mailto:cftnews@aacc.org).

## Changes Urged in On-site Correction of Deficiencies

*By Wayne Markus*

During on-site inspections of laboratories in the forensic urine drug testing and laboratory accreditation programs, it has been common practice to allow the laboratory to correct deficiencies and not be cited for them. These deficiencies are generally small items that can be readily fixed.

The College of American Pathologists (CAP) Commission on Laboratory Accreditation (CLA) has supported this practice. After all, what's important is correcting the deficiency. It has been up to the inspector to decide whether to allow an on-site correction. We have no data on how often this occurs.

One of the CLA commissioners recently experienced an inspection that caused him to question whether this on-site correction should be allowed. The inspection revealed a number of deficiencies. As the inspection continued, the laboratory produced new procedures and other corrections and presented them to the inspector requesting that the deficiencies not be cited. This pattern was repeated a number of times over the course of the inspection.

The commissioner brought the issue to the CLA for discussion and raised a number of concerns:

(1) In this situation, the inspector not only spends time determining that a deficiency exists, but then spends additional time reviewing the correction. When few deficiencies are involved, this may not be a burden, but for a larger number, it may be.

(2) A new policy or procedure may be produced and approved, but may not be implemented and the appropriate staff may not be trained.

(3) An adversarial situation could develop in which the inspector is pressured to accept a change or new policy. In the CAP program, it is the inspector's responsibility to identify and describe deficiencies. It is the commissioner's responsibility to determine whether they have been corrected. This differentiation of responsibility tends to lessen the likelihood of animosity that could develop if the inspector performed both functions.

(4) The Joint Commission on Accreditation of Healthcare Organizations (JCAHO) requires CAP to "grade" laboratories in JCAHO-accredited facilities. The removal of deficiencies may benefit the laboratory's grade. It would be unfair if an inspector at one laboratory did not allow on-site corrections, when another inspector at a competing laboratory did.

(5) There have been anecdotal reports that some laboratory directors have received financial bonuses based on the number of deficiencies. It is not CAP's

position to determine how employees are compensated, but it is easy to see that an inspector could be pressured to allow corrections in this situation.

(6) A laboratory that has sufficient staff to accomplish on-site corrections has an advantage over another with more limited resources.

(7) A final consideration is that the inspection is a snapshot of the laboratory at that moment in time. Although the CAP process emphasizes the educational aspects to both the laboratory and the inspection team, it is also regulatory. In a regulatory setting a deficiency is cited if present at the time of inspection. A comparable situation occurs when you slow a speeding automobile after going through radar. You are probably going to get a speeding ticket.

After discussion, the CLA recommended a policy of citing a deficiency and writing a note that the deficiency was corrected on site. In most instances this will serve the needs of accreditation, and formal documentation that the deficiency has been corrected will not be needed. The reviewing commissioner will have the option of accepting the inspector's note as evidence of correction.

In sum, the CLA and toxicology commissioners recommend discontinuing the practice of not citing deficiencies corrected on site. They recommend instead citing the deficiency and noting on the inspector's report that the deficiency was corrected on site.

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## CAT and SAT Plan Meeting

The California Association of Toxicologists (CAT) and the Southwestern Association of Toxicologists (SAT) will hold a joint meeting in Albuquerque, New Mexico, May 2–3.

A workshop entitled "Interpretive Toxicology: Unraveling the Mystery?" will be held May 2.

Speakers include: Steven Karch, MD (Office of the Chief Medical Examiner, San Francisco, California); Graham Jones, PhD, DABFT (Office of the Chief Medical Examiner, Edmonton, Alberta); Daniel Anderson (Los Angeles County Department of the Coroner); Barry Logan, PhD, DABFT (Washington State Patrol); Marilyn Huestis, PhD (National Institute on Drug Abuse); and Sarah Kerrigan, PhD (New Mexico Department of Health).

Both postmortem and performance toxicology issues will be addressed, with sessions including:

- Are Postmortem Blood Drug Concentrations Reliable Indicators of Toxicity?
- Postmortem Toxicology Results: They Do Usually Mean *Something*
- Cannabis Effects on Performance and Behavior
- Drugs and Driving: "What BAC is that Equivalent to?" and other Implausible Questions
- Driving under the Influence of UFOs, Demons, and the New Mexico Hot Tamale Defense: Unique Cases of Drug-Impaired Drivers

For more information and meeting registration, visit the CAT website at [www.cal-tox.org](http://www.cal-tox.org).

The purpose of *Clinical & Forensic Toxicology News* is to provide practical and timely information on the clinical, forensic, technical, and regulatory issues faced by toxicology laboratories.

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