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General
Drugs
of Abuse

Use, Abuse and Detection of OxyContin

Answers for life.

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Syva has been a leading developer and manufacturer of drugs-of-abuse tests for more than 30 years.

Now part of Siemens Healthcare Diagnostics, Syva® boasts a long and successful track record in drugs-of-abuse testing, and leads the industry in the production of enzyme immunoassays. In addition to drugs-of-abuse assays, Syva has been a key player in the development and manufacture of therapeutic drug monitoring assays.

Syva products are sold in more than 45 countries worldwide.

Introduction

In response to the recent reports of abuse of OxyContin® (a proprietary slow-release formulation of oxycodone hydrochloride marketed by Purdue Pharma, Stamford, CT), Siemens Healthcare Diagnostics is providing information on the pharmacology and pharmacokinetics of OxyContin in relation to other opiates and the use of immunoassays to detect use and abuse.

Basics

Opiates is a class of drugs composed not only of naturally occurring compounds but also semisynthetic derivatives of such natural compounds.

Refer to Figure 1 for the chemical structures of various compounds in the opiate family. Morphine and codeine are naturally occurring opiate products found in the poppy plant, *Papaver Somniferum*. Semisynthetic derivatives of these natural products (eg, heroin and oxycodone) are also members of the opiate family. Other compounds such as fentanyl, meperidine (Demerol®), and methadone are structurally unrelated to opiates but have similar pharmacological profiles. These are classified as narcotic analgesics. All opiate-based drugs have similar pharmacological profiles; however, they differ slightly in their potency.

Other Opiates

Several other synthetic narcotic analgesic members of the opiate family exist; they, too, have high abuse potential and have similar pharmacological properties that differ mainly in potency. Examples include:

- Oxymorphone (Numorphan®)—for use postoperatively in pain relief and available in limited amounts on the street—the drug is about 10 times more potent than morphine and about 14 times more potent than oxycodone. A metabolite of oxycodone, it apparently makes little contribution to the pharmacological effects after oxycodone administration due to low plasma concentrations.
- Hydromorphone (Dilaudid®)—for relief from moderate to severe pain as well as for coughs—the drug is about 8 times more potent than morphine. Abused in the 1970s, the drug is also a metabolite of hydrocodone (Vicodin®, Lorcet®).
- Hydrocodone (Vicodin, Lorcet, Lortabs®)—for use as an analgesic and for its anti-tussive properties—the drug is about 6 times more potent than codeine.

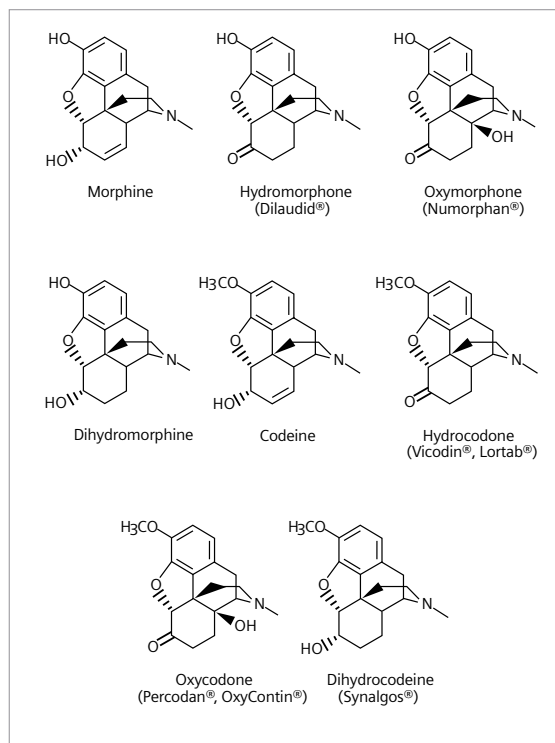


Figure 1: Chemical Structures of Compounds in the Opiate Family

About OxyContin and Oxycodone

OxyContin is a proprietary slow-release formulation of oxycodone hydrochloride and has been prescribed for use in the management of moderate to severe pain. Oxycodone is a semi-synthetic narcotic analgesic classified by the Drug Enforcement Agency as a Schedule II controlled substance (ie, the drug has approved clinical uses but also has high abuse potential). The potential for addiction is similar to morphine. The FDA cleared OxyContin for marketing by Purdue Pharma, Stamford, CT, in January 1996, but oxycodone has been available since 1915.

A search of the National Library of Medicine's MEDLINE database indicated only two citations that specifically referenced OxyContin; however 309 references to oxycodone appeared, and 31 out of the 309 references specifically addressed substance abuse.

OxyContin is available in several dosage levels: 10-, 20-, 40-, 80-, and 160-mg slow-release tablets for oral consumption. The 10-, 20- and 40-mg formulations were first marketed in 1996; the 80-mg formulation was made available in 1997; and the 160-mg formulation in July 2000. The 80- and 160-mg tablets are for use with only opiate-tolerant patients. These pills are marked and colored as follows:

- 10 on one side, OC on the other side, round, white
- 20 on one side, OC on the other side, round, pink
- 40 on one side, OC on the other side, round, yellow/tan
- 80 on one side, OC on the other side, round, green gray
- 160 on one side, OC on the other side, oval caplet, blue

The front portion of the Physicians' Desk Reference presents color photographs of the pills. Available as bottles of 100 pills or as 25 individual dosages on a card, the pills have been designed for oral consumption and slow release. The body rapidly absorbs a portion of the drug in the stomach for rapid onset of action (~1 hour), then additional drug becomes absorbed in the small intestine over another 12-hour period. However, a person can greatly increase the potential for abuse and toxicity by chewing the pills, grinding the pills and

snorting the powder, or by dissolving the pills and injecting the solution. In fact, the package insert information (also presented in the Physicians' Desk Reference) specifically warns in boldface capital letters against chewing or crushing the tablets due to the rapid release and absorption of potentially toxic doses of oxycodone.

Purdue Pharma also sells an immediate release formulation of oxycodone called OxyIR[®], which is a 5-mg dose intended for dosing every 6 hours. In addition, Purdue Frederick markets a slow-release formulation of morphine sulfate, MS Contin[®], in varying dosage strengths from 15—200 mg.

Several proprietary and generic formulations of oxycodone are available from various manufacturers. These formulations include oxycodone as the hydrochloride and/or terephthalate salts:

- Percolone[®] (5 mg): Dosing 10–30 mg/4 hrs as needed, manufactured by Endo Labs
- Roxicodone[®] (5, 15, 30 mg): Dosing 10–30 mg/4 hrs as needed, manufactured by Roxane

Oxycodone can also be compounded with other analgesics, such as acetaminophen or aspirin:

- Percocet[®] (oxycodone [2.5–10 mg] with acetaminophen [325–650 mg]), 1 tablet/6 hrs), manufactured by Endo Labs
- Percodan[®] (oxycodone [2.5–5 mg] with aspirin [325 mg]), 1 tablet/6 hrs), manufactured by Endo Labs
- Roxicet[®] (oxycodone [5 mg] with acetaminophen [325–500 mg]), manufactured by Roxane
- Tylox[®] (oxycodone [5 mg] with acetaminophen [500 mg]), 1 tablet/6 hrs as needed), manufactured by Ortho-McNeil

A recent article in Forbes Magazine (2/5/01) noted that 2000 OxyContin sales increased 77% to \$957 million (therefore a larger selling drug than Viagra®). Further detailed information about OxyContin (including press releases on Purdue Pharma's steps to address abuse of OxyContin) is available at Purdue Pharma's website, www.purduepharma.com. Additional information is also available at their associated website: www.partnersagainstpain.com, which also has the complete package insert on OxyContin at: www.partnersagainstpain.com/html/pi/ppi/pi_ppi2.htm.

Clinical Use

Oxycodone is an analgesic for treating moderate to severe pain, for example, in cancer patients. The drug acts like other opiates by binding to opiate receptors in the brain and spinal cord. Although a few other opiates and opiate antagonists are approved for use in treating addictive disorders, oxycodone has no approved use in treating addiction.

Therapy

The recommended starting dose of OxyContin for an opiate-naive patient is 10 mg every 12 hours, and the regimen can be titrated upwards as clinically necessary. The regimen for immediate release formulations of oxycodone is typically 10–30 mg every 4 hours as needed. The higher-level dosage forms available (ie, 80 and 160 mg formulations) are reserved only for patients already tolerant to the effects of opiates due to ongoing use.

Potency

Though oxycodone is approximately equivalent to morphine in its potency, it provides a longer analgesic action and causes less hallucinations than morphine. Oxycodone is about 6 times more potent than codeine and is slightly more potent

than hydrocodone (Vicodin®); however, it has only about one-quarter the potency of hydromorphone Dilaudid®).

Oxycodone is 10 times more potent than the non-opiate synthetic narcotic analgesic, meperidine (Demerol®).

One distinction of oxycodone is its relatively high oral bioavailability—the amount of intact drug actually reaching the circulation after oral administration. Oral administration of drugs can result in significant losses in the physiological availability of the drug as it passes through the liver after absorption from the gastrointestinal tract. Therefore, the higher the percentage of bioavailability, the better the absorption of drug into the body. The liver can metabolize a significant portion of drug before it is available to the general circulation. One reason why oxycodone is preferred to morphine in oral administration is that the bioavailability of oxycodone is 60% of its intramuscular bioavailability; oral morphine is only 19–30%.

Effects

Oxycodone has pharmacological and side effects such as analgesia, euphoria, sedation, and relaxation, which are similar to effects from other opiate receptor agonists such as morphine, codeine, hydrocodone, and hydromorphone. Drowsiness occurs about 30 minutes after oral dosing; however, after intravenous dosing, lightheadedness and dizziness occur almost immediately, followed by drowsiness within 30 minutes. Adverse effects include reduced gastrointestinal motility (constipation), nausea, dizziness, lightheadedness, pruritis (itching), vomiting, headache, dry mouth, and sweating. Serious adverse effects include hypotension, but most seriously—respiratory depression at higher dosing levels, especially when used in combination with alcohol or other central nervous system depressants. Death from respiratory depression can occur when taking opiates along with other depressants such as alcohol, benzodiazepine, or barbiturate sedatives.

A readily observable clinical sign of oxycodone and other opiate use is miosis (constriction of pupils). Severe overdose situations may lead to mydriasis (dilation of the pupils) due to hypoxia (lack of oxygen from respiratory depression).

When tolerance to the effects of oxycodone develops at higher doses and prolonged use, the effects observed are markedly dependent on the history of opiate use for each individual. Therefore, the therapeutic dose of opiates should be tailored to the response of each individual. Withdrawal is observed in physically dependent patients after abrupt cessation. Withdrawal symptoms include restlessness, agitation, tears, runny nose, perspiration, chills, and mydriasis. The treatment for oxycodone overdose includes maintaining an open airway and the use of opiate antagonists (eg, naloxone or nalmefene). Antagonists, however, should be used cautiously in known opiate tolerant subjects, lest a sudden complete withdrawal occur.

Abuse

Recently, news reports have been profiling a rash of deaths from OxyContin abuse. The news reports include thefts of the drug from pharmacies, illegal prescriptions by physicians, and abuses by students. Public response has manifested in summit meetings of local, state, and federal authorities, as well as calls for removal of the drug from the market. Purdue Pharma continues to issue press releases that indicate its actions to help address the diversion and abuse of OxyContin. Such actions include physicians using tamper-resistant pads, schools offering continuing education medical programs, and funds for studying the limits on prescription drug diversion.

Forbes Magazine reports that OxyContin sells on the street for about \$1 per milligram, which is about 10 times the prescription cost. The Drug Abuse Warning Network (DAWN), sponsored by the Substance Abuse and Mental Health Services Administration (SAMHSA), currently surveys about 500 hospital

emergency rooms in 21 metropolitan and other areas around the country and reports on the incidence of various drugs in these same emergency room visits. Recent DAWN data on opiate abuse, published in the Journal of the American Medical Association (Joranson et al.), indicates 3,000–4,000 mentions each year for oxycodone (3 to 5 times as much as for morphine abuse) between 1990 and 1996. Reports for all opiates were 30–35,000 mentions each year, representing 3–5% of all mentions. DAWN data is available at the SAMHSA's website, www.samhsa.gov/OAS/p0000018.htm

The Community Epidemiology Working Group, a network of researchers from major metropolitan areas of the United States and selected foreign countries that meets semi-annually to discuss the current epidemiology of drug abuse, reported the following oxycodone statistics at their December 2000 meeting in San Francisco:

- 3,400 mentions in 1993
- 3,400 mentions in 1995
- 4,800 mentions in 1997
- 6,400 mentions in 1999

Refer to the National Institute on Drug Abuse (NIDA) web site, www.drugabuse.gov/CEWG/AdvancedRep/1200ADV/1200adv.html for additional information.

While the abuse of OxyContin appears as a recent phenomenon; oxycodone abuse has been well-documented with several studies and publications. For example, a study from Australia (Drummer, et al) in 1994 reported nine deaths involving oxycodone, with several reports associated with other depressants (ie, alcohol, benzodiazepines).

Pharmacokinetics

The primary pharmacological effects of oxycodone are due to the parent drug. The formulation of OxyContin provides an initial rapid release of sufficient drug for an early onset of action as well as a continued slow release of the drug over a 12-hour period. After oral dosing, the time to reach peak blood levels is about 2 to 3 hours.

The half-life of oxycodone is about 4.5 hours, compared to the half-life of morphine, which is 1.5 to 2 hours. [Note: Half-life is the time required for half of the parent drug to be eliminated from the body.] Immediate-release oxycodone shows a slightly more rapid elimination half-life than OxyContin. The liver metabolizes oxycodone to several metabolites, mainly noroxycodone through N-demethylation, and oxymorphone through O-demethylation, and their glucuronide conjugates. [Note: Conjugates is defined as the attachment of the sugar glucuronic acid to the molecules, which enhances water solubility and elimination in urine.]

Administered oxycodone and its metabolites, oxymorphone and noroxycodone (as conjugated and unconjugated forms), are recovered in urine as parent drugs. Studies of the drug metabolites in urine show that 19% of the dose is free oxycodone, 50% is conjugated oxycodone, and <14% is conjugated oxymorphone. No free oxymorphone exists, and noroxycodone is present in both free and conjugated forms.

Data plots demonstrate that oxycodone levels exceed metabolite oxymorphone levels for about 6 to 24 hours post-dose. Afterwards, oxymorphone levels equal or exceed parent oxycodone levels.

Three Summaries of Pharmacokinetic Studies

Pöhiä R, et al. The Pharmacokinetics and Metabolism of Oxycodone after Intramuscular and Oral Administration to Healthy Subjects. *Br J Clin Pharmacol*. 1992;33(6):617.

Nine subjects receive 10 mg oxycodone intramuscularly and 20 mg oxycodone orally. Both free and conjugated oxycodone comprise 8–14% of the original dose recovered from 24-hour urine samples. Though the report does not detail the concentrations of each compound, scientists recovered the following:

Free oxycodone	1,000 µg
Conjugated oxycodone	500 µg
Free noroxycodone	1,000–2,000 µg
Conjugated noroxymorphone	500 µg
Conjugated oxymorphone	1,000 µg

However, because typical 24-hour urine volumes are 1–2 liters, one would expect free oxycodone levels to average about 500–1,000 ng/mL. This study also reports that participants attain maximum blood levels of oxycodone within 1 hour after an intramuscular injection; the elimination half-life of the drug is 5 hours. The report further notes that the noroxycodone levels are higher after oral dosing compared to intramuscular dosing. This indicates the role of firstpass metabolism in the liver in generating this metabolite. When orally ingested, the body absorbs a drug partially through the stomach, but primarily through the small intestine. The drug circulates to the liver, where significant metabolism may occur before the drug can reach general circulation and display its pharmacological effects. OxyContin displays relatively high oral bioavailability; therefore, low overall presystemic clearance or first-pass metabolism occurs.

Leow K, et al. Comparative Oxycodone Pharmacokinetics in Humans After Intravenous, Oral, and Rectal Administration. Ther Drug Monitor. 1992;14:479.

Forty-eight subjects receive 5 mg oxycodone intravenously (IV), 10 mg orally, and 30 mg rectally. The average elimination half-life of the drug takes 5.5 hours, and the lag time between oral absorption and pharmacological effects is 30 minutes. After IV administration, results only demonstrate 50% bioavailability by extravascular routes of administration. Participants attain peak blood levels of the drug 8 minutes after the IV dose, 1.5 hours after the oral dose, and 3 hours after the rectal dose. The report does not state drug concentration levels.

Kaiko R, et al. Pharmacokinetic-Pharmacodynamic Relationships of Controlled-Release Oxycodone. Clin Pharmacol Ther. 1996;59:52.

Twenty-eight subjects receive a single 20 mg dose. Scientists note maximum blood levels of OxyContin after 3 to 4 hours, and they note pharmacological effects after 1 to 2 hours. Such effects last about 12 hours, but with some effects apparent up to 24 hours post-dose. Plasma oxycodone levels are about 2 times noroxycodone levels and about 20 times oxymorphone levels. Scientists consider the metabolite noroxycodone to have very weak pharmacological effect. Similarly, they find oxymorphone in plasma, and because its level is quite low, scientists also state that its level contributes little to oxycodone's pharmacological effects. As in the previous study, the report does not mention drug concentration levels.

Four Summaries of Studies on Oxycodone Levels in Urine

Baselt R and Stewart C. Determination of Oxycodone and a Major Metabolite in Urine by Electron-Capture GLC. J Anal Toxicol. 1978;2:107.

Two subjects receive oral doses of 5 mg oxycodone and 24 hours later, the subjects submit urine specimens for analysis. Analyses of each urine sample recover 61% and 33% of the administered dose. Free oxycodone amounts to 19% and 13% of the original dose; the concentrations are 640 ng/mL and 400 ng/mL. Conjugated oxycodone amounts to 29% and 7% of the original dose; the concentrations are 960 ng/mL and 200 ng/mL. Conjugated oxymorphone amounts to 13% and 14% of the dose; the concentrations are 420 ng/mL and 430 ng/mL. The samples do not contain free oxymorphone.

Weinstein S and Gaylord J. Determination of Oxycodone in Plasma and Identification of a Major Metabolite. J Pharm Sci. 1979;68(4):527.

The urine levels of oxycodone and noroxycodone from a single subject, who had been taking a very high dose of oxycodone (700 mg/day), were 12,900 ng/mL and 18,300 ng/mL, respectively.

Pöhiä R, et al. The Pharmacokinetics and Metabolism of Oxycodone after Intramuscular and Oral Administration to Healthy Subjects. Br J Clin Pharmacol. 1992;33(6):617.

Nine subjects receive 10 mg oxycodone intramuscularly and 20 mg orally. Scientists collect urine samples after 24 hours and analytical results show that 8–14% of the dose is free and conjugated oxycodone; the elimination half-life was 5 hours. Free oxycodone represents 5–8% of the dose; conjugated oxycodone represents 2–6% of the dose.

Smith M, et al. Forensic Drug Testing of Opiates. VI. Urine Testing for Hydromorphone, Hydrocodone, Oxymorphone, and Oxycodone with Commercial Opiate Immunoassays and Gas Chromatography-Mass Spectrometry. J Anal Toxicol. 1995;19:18.

Two heroin users receive 10 mg or 20 mg oxycodone intramuscularly, and scientists evaluate the users' urine samples for oxycodone and its metabolites using the EMIT® d.a.u.® Opiate Assay. Tables 1 and 2 summarize the peak drug levels in urine after the administration of 10 mg and 20mg, respectively.

Drug	Subject 1	Subject 2
Oxycodone	~2,500 ng/mL, @ 5-9 hr	~750 ng/mL, @ 3-9 hr
Oxymorphone	~1,900 ng/mL, @ 5-9 hr	~1,000 ng/mL, @ 4-9 hr

Table 1: GC/MS Peak Drug Urine Levels 10 mg Post-Dose Administration

The EMIT d.a.u. Opiate Assay results are ~280 ng/mL @ 5 to 9 hours and ~150 ng/mL @ 4 to 9 hours for the two subjects.

Drug	Subject 1	Subject 2
Oxycodone	~2,500-10,000 ng/mL, @ 3-9 hr	~600-800 ng/mL, @ 2-9 hr
Oxymorphone	~2,500-5,000 ng/mL, @ 3-9 hr	~1,000-2,000 ng/mL, @ 2-8 hr

Table 2: GC/MS Peak Drug Urine Levels 20 mg Post-Dose Administration

The EMIT d.a.u. Opiate Assay results at the 300 ng/mL cutoff demonstrate positive test results at 3 to 9 hours post-dose.

Pharmacogenetics/Drug Abuse

The Addiction Research Foundation finds genetic differences in the levels and functions of particular liver enzymes that are responsible for metabolizing oxycodone and other opiates. The results of the study show that, in general, 4-10% of Caucasians are poor oxycodone metabolizers; however, results

show no poor metabolizers among opiate abusers. The Foundation attributes "protective effects" as the reason for the under-representation of poor metabolizers among drug abusers. Subjects are not able to effectively metabolize certain opiates to more active or potent metabolites.

Similar genetic differences exist in the conversion of codeine to morphine, and such differences may provide another reason for the ineffectiveness of codeine for pain relief in some patients. However, note that a 1996 pharmacokinetic study of slow-release oxycodone (refer to Kaiko, et al) attributes little pharmacological effect to the oxymorphone metabolite.

Urine Tests to Detect Use and Abuse

Because opiate receptors in the body recognize close structural similarities among molecular structures of the opiate family, comparable pharmacological effects occur. Although opiate immunoassay antibodies primarily recognize the molecular shapes of morphine and codeine, current immunoassay cross-reactivity to the hydro-opiate derivatives (e.g., hydromorphone and hydrocodone) is high, and, as such, provides an advantageous opportunity to detect use and abuse. On the other hand, the cross-reactivity to the oxyderivatives (e.g., oxymorphone and oxycodone) is much lower.

Indeed, research in 1995 demonstrates positive EMIT d.a.u. Assay test results for up to 9 hours after a 20 mg intramuscular oxycodone dose. In another study, scientists spike urine specimens with oxycodone or oxymorphone at various levels and test the samples using commercial opiate immunoassays, including the EMIT d.a.u. Assay. The EMIT d.a.u. Assay results show low cross-reactivity percentages to oxycodone and oxymorphone, relative to the target analyte of morphine. Because therapeutic doses of these drugs are low (due to their higher potency than morphine), the authors conclude that detection of use would be low, unless doses are at abuse levels. Results show that the cross-reactivity of the EMIT d.a.u. Assay to oxycodone is about 3.4%.

A specimen containing 1,000 ng/mL oxycodone yields an assay response comparable to a sample containing 100 ng/mL morphine; a specimen containing 5,000 ng/mL yields a response of about 260 ng/mL morphine; and a specimen containing 10,000 ng/mL yields an assay response of about 340 ng/mL morphine. Using an EMIT d.a.u. Assay at the 300 ng/mL cutoff, therefore, one would expect positive results from specimens containing oxycodone levels of 5,000–10,000 ng/mL. The cross-reactivity to oxymorphone, a metabolite of oxycodone, was less than for oxycodone at ~1.2%. Thus, a specimen spiked with 10,000 ng/mL oxymorphone gave an EMIT d.a.u. Assay response of ~130 ng/mL morphine.

In a subsequent 1995 study of commercial opiate immunoassays performed by the same research group using an EMIT d.a.u. immunoassay on actual clinical specimens, two (2) heroin users were given 10 mg or 20 mg of oxycodone intramuscularly. Table 3 summarizes results observed; positive urine drug test results were obtained for 3 to 9 hours after 20 mg post-dose.

Subject 1		
Drug	10 mg	20 mg
Oxycodone	~2,500 ng/mL @ 5–9 hr	~2,500–10,000 ng/mL @ 3–9 hr
Oxymorphone	~1,900 ng/mL @ 5–9 hr	~2,500–5,000 ng/mL @ 3–9 hr
Subject 2		
Drug	10 mg	20 mg
Oxycodone	~750 ng/mL @ 3–9 hr	~600–800 ng/mL @ 2–9 hr
Oxymorphone	~1,000 ng/mL @ 4–9 hr	~1,000–2,000 ng/mL @ 2–8 hr

Table 3: Summary of 1995 Study on Urine Specimens from Two Heroin Users

After a 10 mg dose on the two subjects, the EMIT d.a.u. Assay gave responses of ~280 ng/mL (just below the cutoff) @ 5 to 9 hrs, and ~150 ng/mL @ 4 to 9 hrs. After a 20 mg dose on the two subjects,

the EMIT d.a.u. Assay gave responses of ~270–400 ng/mL @ 3 to 9 hrs, and ~150 ng/mL @ 2 to 24 hrs. The results essentially showed that one of the subjects presented positive EMIT d.a.u. test results for up to 9 hrs after a 20 mg dose.

Table 4 summarizes the cross-reactivity levels of oxycodone and oxymorphone required to produce a positive result on the various Syva opiate immunoassays. The table also presents the cross-reactivity levels observed in actual clinical studies.

	Oxycodone (ng/mL)	Oxymorphone (ng/mL)
Syva RapidTest	20,000	60,000
Syva RapidCup™	15,000	Not Tested
EMIT d.a.u. (300 ng/mL cut-off)	4,500	30,000
EMIT® II Plus® (300 ng/mL cut-off)	5,400	>20,000

Observed Urine Levels			
Dose and subjects	Oxycodone (ng/mL)	Oxymorphone (ng/mL)	Report
5 mg Oral 2 Subjects	400, 640 free	0 free	Baselt and Stewart, 1978
10 mg Intramuscular 2 Subjects	~2,500 total @ 5–9 hr ~750 total @ 3–9 hr	~1,900 total @ 5–9 hr ~1,000 total @ 4–9 hrs	Smith et al, 1995
20 mg Intramuscular 2 Subjects	2,500–10,000 total @ 3–9 hr 600–800 total @ 2–9 hr	~2,500–5,000 total @ 3–9 hr 1,000–2,000 total @ 2–8 hr	Smith et al, 1995
10 mg Intramuscular 20 mg Oral 9 Subjects	~500–1,000 (free)	Below Assay Limit	Pöhiä et al, 1992
700 mg/day 1 Subject	12,900	Not addressed	Weinstein and Gaylord, 1979

Table 4: Immunoassay and clinical study cross-reactivity data showing levels required to produce positive results

The EMIT d.a.u. and EMIT II Plus Assays have sufficient cross-reactivity to oxycodone to detect use and abuse, if testing is performed within 1 day post-dose. Note that the 1995 study by Smith, et al, demonstrated positive EMIT d.a.u. test results after a 20 mg intramuscular dose. The Syva RapidTest and Syva RapidCup have much lower cross-reactivities to oxycodone, and would require several-times higher dosing in order to generate positive test results. However, in cases of oxycodone abuse, such levels could be reached and detected.

Although noroxycodone is also a recognized urinary metabolite of oxycodone, cross-reactivity of the EMIT assays to this metabolite is apparently low. Despite the fact that no data is available, the cross-reactivity towards the conjugated forms of the metabolites is expected to be low.

Certainly, a positive test result obtained with an opiate immunoassay does not provide information on the specific opiate or opiates responsible for the positive result. Subsequent specific analyses using techniques such as the standard gas chromatography–mass spectrometry (GC/MS) aid in the determination of specific opiates. Current GC/MS laboratory procedures in widespread use for the confirmation of opiate-positive immunoassays involve only determinations for morphine, codeine, and the heroinmetabolite, 6-monoacetylmorphine (ie, current confirmation testing in federally regulated workplace testing programs performed according to the Substance Abuse and Mental Health Services Administration guidelines). However, GC/MS analysis for other members of the opiate family (including oxycodone) can be incorporated by special request into opiate confirmation testing.

Conclusions

EMIT d.a.u. and EMIT II Plus opiate immunoassays have sufficient cross-reactivity to oxycodone such that use and abuse of this drug, including the slow-release formulation of OxyContin, should be detectable, through urine testing, for several

hours to about 1 day post-dose, depending on the level of drug taken (ie, as prescribed use vs. higher-dose abuse). A 1995 clinical study demonstrated EMIT d.a.u. positive test results for up to nine hours after a 20 mg intramuscular dose of oxycodone (Smith, et al). However, the current non-instrumented devices, Syva RapidCup™ and Syva® RapidTest™, are unlikely to generate positive results, except in cases of abuse of significant amounts.

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Biography

Dr. Kadehjian is an independent biomedical consultant in Palo Alto, California, primarily lecturing and writing on the clinical, scientific, regulatory, and legal issues in drugs of abuse testing. He has provided consulting services for a wide variety of both private and public sector drug programs worldwide. He has special experience with on-site testing programs and provides oversight of the U.S. Federal Courts' on-site drug testing programs. He also serves on the faculty of the National Judicial College, lecturing on the neurobiology of addiction and drug-testing issues, and has provided nationally-broadcast live satellite television seminars for the Federal Judicial Center. An internationally recognized speaker, he has earned an Outstanding Speaker recognition from the American Association of Clinical Chemistry and has provided expert testimony in court and labor arbitration. Born and raised in Boston, he received his Bachelor's degree in Organic Chemistry from M.I.T. in 1972 and his Ph.D. in Biochemistry from Stanford University in 1977.