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Hydrocodone and Fentanyl Abuse Is Growing Problem

By Jeri D. Roper-Miller

Opioid analgesics are commonly prescribed for pain management in the United States. Although prescription painkillers such as oxycodone and methadone have been highly publicized in recent years, there are other opioids that are less recognized but used and abused as or more often. Growing use, both licit and illicit, of hydrocodone and fentanyl makes these opioids of particular interest to governmental regulatory agencies, clinicians, and clinical and forensic toxicologists alike.

Opioids can be diverted for illicit use through “doctor shopping,” altered or fraudulent prescriptions, malpractice of physicians and pharmacists, and theft. The Office of Diversion Control of the Drug Enforcement Administration (DEA) has placed both hydrocodone and fentanyl on its “Drugs and Chemicals of Concern” list, which includes 26 agents (1). In 2005, the Drug Abuse Warning Network (DAWN) estimated that 42,491 of 495,732 (8.6%) emergency room visits resulted from hydrocodone combination products, and 8,000 (1.6%) resulted from fentanyl combination products. Hydrocodone was associated with more reported emergency room visits than any other pharmaceutical opioid, and fentanyl ranked fifth among reported opioids (2).

Hydrocodone

Hydrocodone (4,5 α -epoxy-3-methoxy-17-methyl-morphinan-6-one tartrate [1:1], hydrate [2:5], dihydrocodeinone) is a semi-synthetic analgesic and antitussive opioid derived from codeine. Available in the form of capsules, tablets, and elixirs, it is marketed as Lortab, Vicodin, and over 200 generic brands.

Although bulk or single ingredient formulations are listed under Schedule II of the 1970 Controlled

Substances Act, multi-ingredient medications are currently available under the less stringent rules of Schedules III and IV, depending on the hydrocodone concentration. However, the DEA is considering moving all hydrocodone products into Schedule II to assist in reducing abuse and trafficking.

Dangers of hydrocodone abuse include a high risk of addiction and tolerance, which promotes increased use. Hydrocodone was first reported to produce euphoria and habituation symptoms in 1923 and dependence and addiction in 1961 (1).

Hydrocodone is the most frequently prescribed opiate in the United States, with more than 124 million prescriptions dispensed in 2005. In addition to legitimate prescriptions last year, DEA’s System to Retrieve Information from Drug Evidence, a multi-system database of investigations and drug analyses throughout the law enforcement community worldwide, reported submission of approximately 1,100 capsules, 7,400 grams, and 22,000 milliliters of hydrocodone-containing evidence among its 590 exhibits analyzed. Similarly, almost 20,000 exhibits of hydrocodone made it the most frequently encountered opioid pharmaceutical among drug evidence submitted to the National Forensic Laboratory Information System.

Escalating deaths have been reported by many death investigation and poison control systems (1). For example, North Carolina’s Office of the Chief Medical Examiner reported increased hydrocodone deaths in every year from 2000 to 2004 (Table 1) (3).

While the analgesic pills are available in 5-mg and 10-mg doses, hydrocodone cough syrups contain 2.5-mg to 5-mg doses, usually in combination with

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Case Report: Overdose from Deliberate Duragesic Misuse

By Jeri D. Ropero-Miller and Ruth E. Winecker

During a 15-year period from 1990 to 2004, the North Carolina Office of the Chief Medical Examiner (NC-OCME) investigated almost 200 deaths in which the cause of death included fentanyl toxicity. During this time the annual cases of fentanyl toxicity increased from none in 1990 to 53 in 2004. The total annual cases investigated by NC-OCME during this period ranged from 7806 to 8827 (1). In the last five years alone, the number of fentanyl-related deaths increased by more than 300% (Figure 1).

The misuse of fentanyl (Duragesic) transdermal patches, either inadvertently or deliberately, is a recurring finding at NC-OCME. This case report describes the deliberate misuse of a fentanyl patch, resulting in a fatality.

A 44-year-old Caucasian male was found by his wife propped up in bed. He had a belt around his arm and appeared to be asleep. There was drug paraphernalia on the bed and nightstand, including remnants of a fentanyl patch, kitchen knives and a spoon, a lighter, and a hypodermic syringe. Investi-

gators found additional drug paraphernalia in another location in the house, including a beer can transformed into a smoking pipe, a ballpoint pen, and several glass crack pipes.

His wife informed investigators that he habitually abused drugs. His current practice was to scrape the contents of a fentanyl patch onto a spoon and reduce it to a liquid to inject intravenously. Sometimes he also used cocaine during his drug abuse sessions.

Autopsy findings

Autopsy findings were insignificant other than pulmonary edema and passive hyperemia. The findings of excess blood pooling and fluid buildup in the lungs are associated with decreased blood outflow caused by cardiorespiratory shutdown, a fatal event occurring with an opioid overdose. In addition, the toxicological investigation confirmed the following drug analytes to be present in the decedent's aortic blood: fentanyl at 6.0 $\mu\text{g/L}$ and cocaine analytes, benzoylecgonine and ecgonine methyl ester, at 2.3 and 0.38 mg/L, respectively. The medical examiner ruled the decedent's death an accidental fentanyl overdose and the presence of cocaine was listed as a contributory finding.

Taken correctly, the highest prescribed Durage-

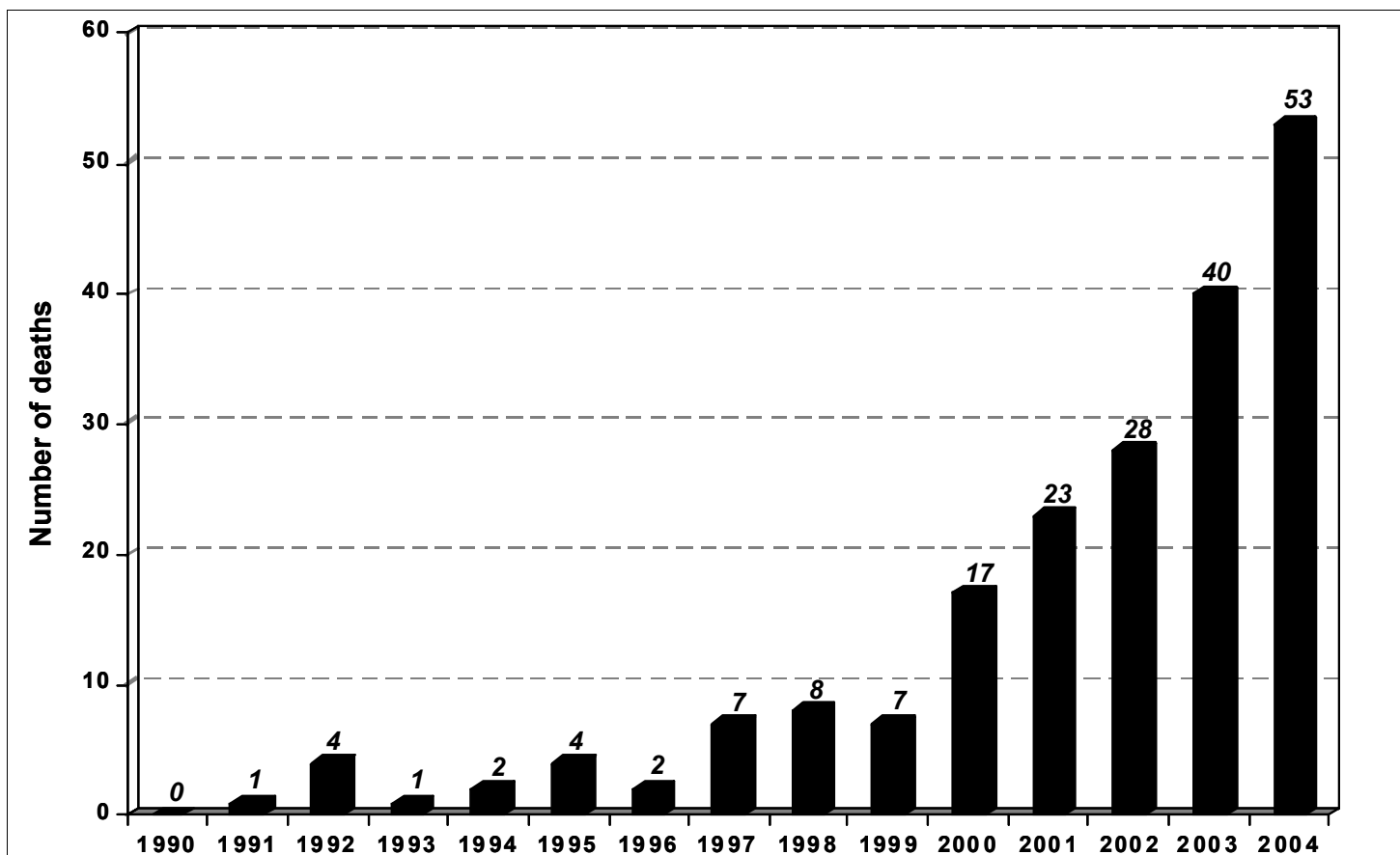


Figure 1. Fentanyl Deaths Investigated by the North Carolina OCME During a 15-Year Period

sic system dose is 100 µg/hr. Clinical studies performed by the manufacturer (Janssen Pharmaceutical) demonstrated that, after the first 72-hour application to reach steady-state, the mean maximal serum concentration ranged from 1.3 to 3.7 µg/L (2). A fatality involving an individual who smoked the contents of a transdermal fentanyl patch had a blood concentration of 6.1 µg/L (3).

Lunn et al. reported that patients given high-dose fentanyl anesthesia for coronary artery surgery lost consciousness at an average plasma fentanyl concentration of 34 µg/L (4). The anesthetic protocol brought the patients to a peak plasma concentration of 50 µg/L by an intravenous infusion rate of 75 µg/kg (5250 µg/70 kg) over a 15-minute period. Furthermore, in seven fatalities following self-administered intravenous injections of fentanyl, the reported blood concentrations ranged from 3.0 µg/L to 28 µg/L (with an average of 8.3 µg/L) (3). Given that the observed whole blood to plasma ratio for fentanyl approximates 1.0 (5), Lunn's reported antemortem serum and plasma concentrations are comparable to the postmortem concentrations reported in this case. Intravenous administration of fentanyl at these blood concentrations should be done only under the direct observation of an anesthesiologist.

The decedent's blood concentration was twice the highest concentration that could be attained through the appropriate use of the Duragesic system, even at its highest dosage, and consistent with other reported deaths involving deliberate misuse by self-administered fentanyl. Postmortem redistribution was not investigated with analyses of alternate specimens for this investigation.

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Hydrocodone and Fentanyl

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acetaminophen, ibuprofen, and/or antihistamines. Doses can be taken every four to six hours, but should not exceed 45 grams in a 24-hour period. Hydrocodone has an analgesic potency similar to or greater than that of oral morphine and an antitussive potency six times that of codeine (4).

Hydrocodone metabolism

Hydrocodone is quickly absorbed through the gastrointestinal tract and exhibits a high rate of first-pass metabolism. It has low affinity for plasma proteins (25%) and moderate to high distribution throughout the body. The pharmacokinetic profile of hydrocodone is summarized in Table 2 (5).

It is predominantly metabolized to more polar metabolites via hepatic demethylation and conjugation. Hydrocodone is metabolized to hydromorphone by demethylation of the 6-methoxy group, catalyzed by enzymatic cytochrome P450 2D6. Reduction of the 6-keto group of the parent and major metabolite yields hydrocodol and hydromorphol, respectively. Both of these metabolites exist as stereoisomers. N-demethylation to norhydrocodone and conjugation also occur. Unconjugated metabolites are pharmacologically active.

A 72-hour urine collection following a single dose resulted in 26% elimination with the following urinary profile: parent (12%), norhydrocodone (5%), conjugated hydromorphone (4%), hydrocodol (3%), and conjugated hydromorphol (0.1%). Urine concentrations of total hydromorphone average 10% of the parent concentration. Reported drug concentrations for various body fluids are given in Table 3 (4,6).

Hydrocodone analysis

Analysis of hydrocodone can be accomplished by directed testing or by assays that handle opioids as a class. Most screening immunoassays have sufficient cross-reactivity with hydrocodone and its metabolites to detect the presence of the drug. Presumptive positive specimens are treated by a basic extraction by solid-phase or liquid-liquid protocols following the hydrolysis

Table 1. Opioid Deaths Reported by the North Carolina Office of the Chief Medical Examiner from 2000 to 2004

Year	Fentanyl	Heroin	Hydrocodone	Methadone	Morphine ¹	Oxycodone	Total Cases
2000	17	27	13	85	44	42	7806
2001	23	35	17	101	45	48	8059
2002	28	44	28	190	47	54	8211
2003	40	51	35	247	60	54	8670
2004	53	45	34	263	55	58	8827

¹Morphine deaths include deaths in which the actual agent may have been heroin.

Table 2. Pharmacokinetic Profiles of Hydrocodone and Fentanyl

Drug	Half-life (hr)	Volume of distribution (L/kg)	Duration of analgesia (hr)	Plasma protein binding (%)	Routes of administration	Addiction/abuse liability
Hydrocodone	3.4–8.8	3.3–4.7	3–5	25	Oral	Moderate
Fentanyl	3–12	3–8	0.5–1.0	79	IM/IV/T/TM	High

IV, intravenous; IM, intramuscular; T, transdermal; TM, transmucosal (5)

step. An acidic or enzymatic hydrolysis step is needed to release the glucuronide conjugates for analysis of total hydrocodone. Final extracts are most commonly derivatized with trimethyl silylation (TMS), trifluoroacetylation (TFA), or pentafluoropropionylation (PFP) reagents for improved chromatography.

Hydrocodone is a keto-analog of codeine and is susceptible to tautomerization when solvents donate protons to the keto group to form enols, resulting in mono- and di- derivatives, hence, inaccurate quantitation. To prevent enolization, hydroxylamine or methoxyamine-pyridine can be added prior to extraction to convert the keto moieties to oxime derivatives. Gas chromatography/mass spectrometry (GC/MS) is the most common confirmatory technique. Common ions for underivatized hydrocodone are 299, 242, 185, and 228, while TMS derivative ions are 297, 386, 371, and 229 (7, 8).

Fentanyl

Introduced to the United States in 1963 as an

Table 3. Hydrocodone Concentrations in Body Fluids

	Dose (mg)	Concentration (mg/L)	Peak time (hr)
Therapeutic (serum)	5.0	0.002–0.011	1.5
Therapeutic (serum)	10.0	0.007–0.024	1.5
Therapeutic (urine)	10.0	2.5–2.9	4.3–6.7
Toxic (blood)		0.13–0.19	
Lethal (blood)	100 (minimum)	1.4 (0.13–7.0) N = 11	
Lethal (blood) single-agent overdose		0.53 (0.12–1.6) N = 17	

intravenous anesthetic/analgesic, fentanyl (N-phenyl-N-[1-2-phenylethyl-4-piperidyl] propanamide) is a synthetic opioid with a phenylpiperidine structure similar to that of meperidine. Sublimaze is a fentanyl citrate injectable solution, with each milliliter containing 50 µg of drug. Its rapid onset and short duration of action make it attractive as a supplement for general anesthesia and pre-operative and immediate post-operative use. Typical doses are 50 µg to 100 µg, but can be as high as 200 µg (4, 9).

In 1990, Janssen Pharmaceutical introduced a transdermal system (Duragesic) in the form of a clear patch that can provide continuous delivery of fentanyl for 72 hours, the typical time to reach a steady-state concentration in the blood. Transdermal doses range from 2.5 mg to 10 mg, and are used for chronic pain management. In 1999, a transmucosal lozenge form (Actiq) was released for management of breakthrough pain in cancer and other debilitating illnesses. A typical dose of Actiq is 200 µg to 1600 µg delivered in 15 minutes. Approximately 200 times more potent than morphine, fentanyl could be used only under the direct supervision of a health professional in a hospital setting prior to these two preparations (6). Fentanyl concentrations in biological fluids are listed in Table 4.

Fentanyl is a full µ (mu) receptor agonist, responsible for central nervous system euphoria, supraspinal analgesia, respiratory depression, miosis, reduced gastrointestinal motility, and physical tolerance and dependence. The development of tolerance begins with the first dose but remains clinically insignificant until two to three weeks of chronic use. To minimize tolerance, fentanyl should be titrated to the desired dose.

Fentanyl also acts on the κ (kappa) receptors (spinal analgesia, sedation, sleep, and shared actions of the µ receptor) and δ (delta) receptors (dysphoria,

delusion, respiratory depression, and vasomotor stimulation). Unlike other opioids, fentanyl does not cause histamine release and has minimal depressant effects on the heart. Use of fentanyl in coronary surgery is popular for this reason.

Fentanyl distribution

In addition to the previously mentioned routes of diversion, fentanyl theft has been reported from nursing homes and other long-term care facilities. Street names include Apache, China girl, China white, dance fever, friend, goodfella, jackpot, lollipop, murder 8, perc-o-pop, tango and cash, and TNT. Fentanyl patches are sold at prices ranging from \$10 to \$100 per patch, while lozenges are typically sold at \$20–25 per unit or \$450 per carton (24 units). Pricing depends on the dose of the unit and geographical area. Used fentanyl patches are also sold on the streets because they still contain appreciable fentanyl concentrations after a 72-hour use.

There is evidence of large illegal distribution rings selling fentanyl products along with other opioid pharmaceuticals. Recently, clandestine production and distribution of fentanyl powder and tablets (MDMA and OxyContin mimics) have also surfaced (1). In the first half of 2006, clandestinely produced fentanyl was identified in heroin samples,

leading to more than 100 overdoses and deaths in heroin addicts in Illinois, Michigan, Pennsylvania, Maryland, and New Jersey (1).

Federal agencies are noticing increased use of fentanyl, and several new reports have indicated greater fentanyl abuse. With 285 fentanyl drug items analyzed in 2005, according to the National Forensic Laboratory Information System, fentanyl does not represent a large number of evidence exhibits; however, fentanyl drug cases expressed as a percentage of the total narcotic analgesic cases increased from 0.21% in 2001 to 0.55% in 2005. On July 15, 2005, the Food and Drug Administration issued safety warnings and reiterated guidelines for the proper use of fentanyl products.

Fentanyl is a highly lipophilic drug that easily crosses the blood brain barrier. Its peak effects are experienced within minutes and its duration of action is 30 to 60 minutes (9). Other pharmacokinetic properties are listed in Table 2.

Fentanyl metabolism

Fentanyl is extensively metabolized by hepatic biotransformation. When administered as a lozenge for oral transmucosal absorption, hepatic and intestinal first-pass metabolism occurs and oral bioavailability is approximately 50% (4,10). The major metabolic pathway involves liver microsomal cytochrome P450 3A4, which catalyzes fentanyl dealkylation to norfentanyl. To a lesser extent (50%), duodenal microsomes also catalyze fentanyl metabolism to norfentanyl (10). Other minor fentanyl metabolites include hydroxylated forms of the parent and nor-metabolite and despropionylfentanyl.

Norfentanyl is the predominant metabolite found in urine, accounting for 26–55% of a single intravenous dose. It can be detected in the urine for up to three days at concentrations of 0.2 to 1.3 µg/L, while parent drug and minor metabolites can be detected for approximately 24 hours (4). Less than 10% of a fentanyl dose is recovered in the feces (6).

Toxicity of fentanyl is similar to that of other opioids. Symptoms include respiratory depression, apnea, seizures, muscle rigidity, and coma. The muscle rigidity caused by fentanyl is more marked than that of other opioids. Other than this, fentanyl has a favorable side-effect profile compared with other opioids such as morphine and meperidine. It causes less sedation, less respiratory depression, and rare nausea and vomiting. In addition, it causes less hypotension because it does not cause histamine release or much preload reduction.

Fentanyl is not detected by standard urine opiate immunoassays; however, specific commercial radioimmunoassays (RIA), enzyme-linked immunosorbent

Table 4. Fentanyl Concentrations in Body Fluids

	Dose (µg/kg)	Concentration (µg/L)	Peak Time (hr)
Therapeutic (serum)	2.0 (IV) (140 µg/ 70kg)	1.0–11	0.1
Therapeutic (serum)	6.4 (IV) (448 µg/ 70kg)	1.0–18	0.1
Therapeutic (plasma)	60 (IV) (4200 µg/ 70kg)	10 to >100	0.1
Therapeutic (serum)	25 µg/hr (T)	0.3–1.2	
Therapeutic (serum)	50 µg/hr (T)	0.6–1.8	
Therapeutic (serum)	100 µg/hr (T)	1.9–3.8	
Therapeutic (plasma)	800 µg (TM)	1.4–3.0	0.4
Therapeutic (urine)	50–100 µg	0.2–1.3 Norfentanyl	
Lethal (blood)	2 (minimum)	3.0 N = 112 (IV)	
Lethal (blood) single-agent overdose		8.3 (3.0–28) N = 7 (IV)	

IV, intravenous; IM, intramuscular; T, transdermal; TM, transmucosal (4,8,9)

assays, and other immunoassays are available for screening purposes. The limit of detection for commercial RIA is 0.5 µg/L. More sensitive and specific techniques are used to confirm the presence of fentanyl. Confirmatory methods include GC/MS, high-performance liquid chromatography/mass spectrometry (HPLC/MS), and tandem mass spectrometry (HPLC/MS/MS). Examples of typical ions monitored for GC/MS analysis of fentanyl include m/z 245, 146, and 189. Limits of detection for fentanyl and its metabolites (norfentanyl, despropionylfentanyl) are around 0.1 to 1.0 µg/L, depending on the confirmatory method and the amount of specimen used.

Summary

In general, opioid analgesics or prescription pain killers, when used correctly by recommended pain management guidelines, are the most effective treatment for many patients. Hydrocodone and fentanyl are two opioids whose use and abuse continue to grow dramatically and this has drawn the attention of federal agencies, clinicians, and forensic scientists alike. Both opioids have moderate to high abuse liability, dependence, and tolerance as a result of their euphoric and central nervous system effects. Hydrocodone and fentanyl share some similar pharmacokinetic characters while differing in others. Analysis of these opioids in clinical and forensic laboratories can be routine or by special request. Both require special analytical treatments (for example, hydrolysis, de-automerization, and low detection limits).

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Oral Fluid Offers Alternative Matrix for Many Applications

By Michael A. Wagner

Breath, blood, and urine are the primary samples used for the purpose of determining exposure to various agents. Oral fluid has been investigated as an alternative matrix.

The interest in oral fluid testing has been around since 1938, when Friedemann investigated the excretion of ingested alcohol in saliva (1). Many promising applications in both clinical and forensic disciplines have resulted from the investigation of oral fluid. It has been used in clinical applications to test for biomarkers for various illnesses: hormones, immunoglobulins, enzymes, viruses, and bacteria. It has also been used in therapeutic drug monitoring. Forensic applications focus on the detection of abused and therapeutic drug concentrations associated with intoxication and compliance.

For cases involving the determination of "driving while impaired" or causal relationships to accidents in the workplace, the most common matrices collected are breath, blood, urine, and recently,

oral fluid. For workplace compliance monitoring, urine samples remain the most common matrices analyzed.

Advantages and disadvantages

Each of these matrices has advantages and disadvantages with respect to ease of collection, specificity, sensitivity, and interpretative value. For example, urine provides a several-day historical perspective to drug use, but does not supply impairment information. The sample collection process can create an uncomfortable and perceived invasive environment, and samples are subject to adulteration.

Blood has the advantage of providing a perspective with respect to impairment, but sample collection is more physically invasiveness, with the risk of infectious exposure for the collector.

Oral fluid offers essentially observed, non-invasive sample collection and has the potential for supplying interpretation with respect to blood concentration and impairment with detection windows similar to blood. Oral fluid may contain higher concentrations of unbound parent drugs that are detectable for longer periods of time than in urine and blood. This increased window of detection of the parent compounds can help provide evidence as to the time of drug use (2, 3, 4).

Although the terms oral fluid and saliva are often used interchangeably, this usage is incorrect. Oral fluid represents all of the fluid in the mouth and is a complex mixture of saliva, mucosal transudate, and other substances (5). Saliva is produced from parotid, submandibular, and sublingual glands as well as smaller glands such as labial, buccal, and palatal (6).

Deposition in oral fluid

The passage into and collection of drugs in oral fluid is governed by a number of processes. Although active transport plays a role in certain drugs, steroids, and hormones, the dominant process is passive diffusion across the lipid bilayer. Diffusion across these membranes requires the molecule to be non-ionized, lipid-soluble, and predominantly unbound. For this reason, saliva drug concentrations represent free drug plasma concentrations.

The saliva to plasma partitioning ratio is governed by the pK_a or pK_b of the acid or basic ionization constant for each drug, respectively; the pH condition of the saliva and plasma; and the fraction of protein binding ($f_{s/p}$) in plasma or saliva. Basic drugs tend to have a calculated saliva:plasma partitioning ratio >1 , yet measured values can have large differences, and even be <1 . Routes of ingestion also impact the saliva:plasma ratio. For example, smoked or snorted drugs, such as crack cocaine, heroin, methamphetamine, and marijuana, deposit in mouth

tissue, creating elevated concentrations of parent drug and a saliva:plasma ratio as high as 400. For these types of ingestions, it may take a couple of hours for saliva concentrations to begin to reflect plasma concentrations.

Oral fluid collection processes can affect the partitioning of drug from plasma to saliva. When saliva flow is stimulated, the pH rises due to the loss of carbon dioxide. In addition, a number of drugs and disease states inhibit saliva production by producing a dry mouth condition (xerostomia) (7).

Testing devices

There are two major categories of oral fluid collection/testing devices. The first, point-of-care testing (POCT) or on-site testing devices, screen by immunochromatographic methods. Oral fluid is collected and deposited into the sample well of a testing device. The oral fluid is mixed with buffered labeled antibodies and diffuses laterally along a surface containing a linear array of immobilized drugs. Competitive binding of active drug with these antibodies prevents the antibodies from reacting with drug conjugate test lines. Hence, no line indicates a positive test result. Detection is accomplished via colloidal gold, phosphor indicators, or other means (1).

International multi-center forensic studies, Roadside Testing Assessment (ROSITA) (1999–2000) and ROSITA-2 (2003–2005), have noted improvements in these testing platforms with respect to sensitivity and specificity (8); however, the technology has not reached the stability or sensitivity required for the detection of all the drugs commonly found in subjects driving under the influence.

The second platform involves collecting the subject's oral fluid in the field for analysis in the laboratory. Immunoassay screening techniques, such as enzyme-linked immunosorbent assays approved by the Food and Drug Administration or developmental homogeneous immunoassays, may be used to determine presumptive positives.

Confirmation

Confirmations are commonly performed by tandem mass spectrometry (MS) methods such as gas chromatography (GC) or liquid chromatography (LC) in formats such as GC/MS/MS or LC/MS/MS. Other analytical techniques, such as GC coupled with various detectors (flame ionization, electron capture, nitrogen phosphorus, MS) or high performance liquid chromatography with ultraviolet/visible light detection, are also used. These other techniques do not offer the same sensitivity as the MS/MS techniques. However, if one is focused on a single drug (or drugs with similar saliva partitioning ratios), has enough sample volume, and the specific drug's plasma pro-

tein binding is minimal, one may not need MSⁿ instrumentation. A noteworthy advantage of LC/MSⁿ is the potential for direct injection of the captured sample, which minimizes sample preparation time.

If the saliva concentrations of parent drugs and/or their metabolites tend to be much lower than those in serum or whole blood, MSⁿ techniques may not help. For example, THC as a parent drug does not partition well into oral fluid. Yet, apparently elevated oral fluid concentrations of THC may be detected due to oral cavity contamination. Ultimately, consistent interpretable cutoffs will need to be established as continued fieldwork incorporates law enforcement observations of impairment with drugs detected in various matrices (for example, urine and oral fluid results correlated with drug recognition experts' observations) (9).

Oral fluid detection and analysis technology has progressed to the point where the use of these types of samples may become significant. POCT or on-site platforms still need to be proven reliable in field studies. Field-captured samples supported by more rigorous laboratory testing, including confirmation testing, do provide excellent results when compared with alternate/parallel matrices. However, interpretation with respect to pharmacokinetics and pharmacodynamics requires additional foundation to be established. This progress will most certainly be made as oral fluid sample collection gains acceptance.

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