Review article

Benefits of Implementing Oral Fluid Testing for Opioid Pain Management Compliance

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An increasing number of adults are treated for chronic pain, making the risk of opioid misuse much greater. One of the primary compliance strategies in pain management is drug testing. Drug testing ensures that patients properly take prescribed medications and can identify aberrant behaviors such as illicit drug use. Urine is the preferred matrix for drug testing in pain management compliance but has many drawbacks. Patient care is often negatively impacted due to the collection process and the difficulties that can occur in the elderly and disabled. Although new test methods for urine drug testing have advanced, preparation methods can still be lengthy, and sample tampering is a common element that continues to affect the accuracy of results.

Oral fluid testing is a viable method with several advantages when compared to urine testing. Results are easier to interpret, collection methods remove barriers and avoid sample tampering, and technical procedures are less cumbersome. Despite the few limitations associated with oral fluid testing, laboratories implementing oral fluid testing can offer better results using a streamlined preparation method, with the most significant impact being the elimination of sample tampering. Implementing oral fluid testing can be considered a positive contribution to compliance monitoring in pain management.

Keywords: Pain management, compliance, oral fluid, opioids.

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Introduction

Pain management compliance measures have increased exponential concurrently with the global opioid crisis. According to the Centers for Disease Control and Prevention (CDC) an increasing number of adults are being treated for chronic pain.[1] Common opioids prescribed for chronic pain include morphine, hydromorphone, hydrocodone, oxycodone, methadone, fentanyl, and buprenorphine. The misuse of these opioids is more prevalent in chronic pain patients putting them at an increased risk of developing opioid use disorder (OUD).[2, 3] Drug testing is a valuable component for monitoring the compliance of prescribed medications. While drug testing supports compliance measures, it can also identify therapeutic failures and detect potential drug interactions.[4] Since patients are at high risk of misuse, illicit drugs such as heroin, methamphetamine, cocaine, and ecstasy are often considered for testing.

Traditionally, urine has been the matrix of choice for detecting opioids and illicit drugs. However, oral fluid has emerged as an alternative matrix. Physiological differences between urine and saliva allow laboratories to improve efficiency using preparation methods requiring a small sample size.[5] In addition, oral fluid presents a practical option for streamlining the laboratory's drug testing workflow.[6, 7] Oral fluid provides an additional advantage by solving the challenge of adulteration commonly seen with urine samples. Compared to urine, oral fluid offers better patient care by providing a safer and less invasive collection method. Implementing oral fluid to detect opioids for pain management compliance improves sample integrity, simplifies workflow, and improves patient care.

Urine Testing

Hepatic and Renal Physiology in Drug Metabolism

Drug metabolism and excretion occur primarily in the liver and kidneys. There are two general ways drugs are metabolized and excreted. One way is the excretion of the drug in the intact form, and another is metabolism by biotransformation, followed by excretion.[8] The method of metabolizing drugs depends on whether the drug is hydrophilic or hydrophobic. Hydrophilic drugs are directly excreted through the renal pathway, while hydrophobic drugs must undergo metabolic modification through the liver before excretion.[8, 9]

The opioids commonly prescribed for pain are a combination of hydrophilic and hydrophobic drugs, including morphine, hydromorphone, hydrocodone, oxycodone, methadone, fentanyl, and buprenorphine. While the opioids are tested for compliance, illicit drugs such as 6-acetylmorphine, *d*-methamphetamine, cocaine, and 3, 4-Methylenedioxy-methamphetamine are often tested since chronic pain patients have been known to use them in conjunction with prescribed medication.[2] In addition to detecting the parent drug, drug metabolites are highly concentrated in the urine and are often measured to ensure the ingestion of the appropriate dose of medication.[10] Table 1 summarizes the parent drugs, associated metabolites, and commonly tested illicit drugs. When including the detection for metabolites, the half-life of most opioids is one to four days, except buprenorphine, which can be detected up to 10 days.[11]

Table 1. Commonly Prescribed Opioids and Associated Metabolites

Drug	*Metabolites*
Morphine	Hydromorphone
Hydrocodone	Hydromorphone, Norhydrocodone & Dihydrocodeine
Oxycodone	Noroxycodone & Oxymorphone
Methadone	EDDP
Fentanyl	Norfentanyl & Hydroxynorfentanyl
Buprenorphine	Nobuprenorphine
6-MAM	Morphine
Methamphetamine	None
Cocaine	Benzoylecgonine
MDMA	MDA

Sample Collection, Transport, and Storage

Sample collection, transport and storage requirements are essential components for the proper detection of opioids and drug metabolites. The collection of the urine sample does not require a unique device. Urine samples are typically collected in a single-use plastic container with the option of a temperature gauge on the outside of the cup or container.[12, 13] The minimum sample volume can be up to 30mL and stored for a limited time, depending on the laboratory's established stability requirements.[13] The collection is generally unobserved in a restroom facility within the clinic, and can create additional patient challenges. Challenges for urine collection are notable in elderly or disabled patients. Physical and mental disabilities should be considered when initiating collection from patients with cognitive impairment who may be at risk for falling due to gait instability.[14, 15]

Instrumentation

Gas chromatography-mass spectrometry (GC-MS) or liquid chromatography-mass spectrometry (LC-MS) are commonly used for urine confirmation testing.[7, 10] Both instruments separate and identify molecules based on the structure and chemical properties.[10, 16] GC separates the molecules in the gas or vapor phase. LC separates molecules based on affinity, absorption, partition, ion exchange, or size exclusion while in solution.[12] Although GC-MS is considered the gold standard in confirmatory testing, LC-MS is typically preferred due to its high selectivity, sensitivity, and decreased drug interferences.[10, 17]

Despite the preferred qualities of LC-MS, sample hydrolysis pretreatment is required to remove matrix interferences and extract drug targets.[17] Hydrolysis of the sample breaks-down drug-glucuronide conjugates, extending the detection window of quickly metabolized drugs.[18] Hydrophobic opioids, such as morphine, undergo glucuronidation. As such, this is an essential step in identifying the metabolism of the parent compound. Quality control is required to verify the hydrolysis activity using control samples containing known amounts of drug-glucuronide conjugates. Laboratories can produce a control material by purchasing the drug-glucuronide conjugates, morphine-6ß-D-glucuronide, and buprenorphine-3ß-D-glucuronide from manufacturers such as Cerilliant (Round Rock, TX) or Lipomed (Cambridge, MA). These standards come in either 1.0 mg/mL or 100 µg/mL. Each standard requires dilution with a certified negative urine matrix until the desired target concentration is achieved. Laboratories may also purchase control material from vendors such as Utak (Valencia, CA). Custom-made control material can be designed to meet a desired concentration and comes ready to use.

Additional considerations in confirmatory urine testing includes limitations and interferences that can complicate the interpretation of results. The variation in the enzyme activity of cytochrome P450 (CYP450) in some patients may reduce or increase drug metabolism.[8] Since CYP450 enzymes are heavily responsible for metabolizing opioids, gene mutations or drug interferences may prohibit accurate interpretations. One example of drug interference is the commonly prescribed anti-depressant fluoxetine. Fluoxetine inhibits CYP450 enzymes responsible for the metabolic process of opioids.[19]

Workflow

Although the laboratory may select a robust LC-MS system, the turn-around time of the testing largely depends on the steps in sample preparation and the LC-MS method design to achieve sensitivity and good peak performance. Glucuronide metabolism requires enzymatic hydrolysis in the sample preparation affecting time from sample collection to result or turn-around time. There are different ways to hydrolyze the sample. One way is to purchase a genetically modified enzyme, such as IMCSzyme® (IMCS, Inc., Irmo, SC), marketed to hydrolyze the sample faster than traditional methods. Laboratories may hydrolyze the sample using ß-glucuronidase from different sources such as *Patella vulgate, Helix pomatia,*

Escherichia coli, bovine liver, or abalone.[20] In addition to the hydrolysis method, different extraction techniques in sample preparation are also available, such as solid-phase extraction (SPE) or liquid-to-liquid extraction (LLE). SPE is considered a simple process with a short extraction time and uses less solvent, while LLE demonstrates a high recovery rate for opioids such as buprenorphine.[17]

Validity Testing

In addition to sample hydrolysis and sample preparation methods in mind, the laboratory must consider the validity of the sample. Patients use adulteration techniques to conceal aberrant medication-taking behaviors.[2, 21] There are various sample tampering methods, such as diluting, and substituting using manufactured and household products. "Spiking" is another form of adulteration in which individuals dissolve prescribed medication into the sample to simulate a positive result.[22] Dilution is accomplished by overhydrating to reduce the chance of detecting targeted drugs, while substitution replaces the sample with synthetic urine or one obtained from another person.[21, 23, 24] Although some patients aim to alter the sample to hide drug misuse, some patients may unintentionally dilute the urine by drinking excessive water to stimulate urination. The chemicals from manufactured and household products used to adulterate the sample interfere with drug detection and are commonly made up of acids, alkalis, oxidizing agents, or surfactants.[24]

Automated chemistry methods are used to determine the validity of urine specimens. Validity tests can include urine creatinine, specific gravity, and pH. Assays that detect invalidity are assessed by observing the acceptability criteria expected in human urine. Urine creatinine concentrations should be between 80-200 mg/dL, specific gravity in the range of 1.003-1.035, and pH within 4.7-7.8.[25] Validity assay methods use colorimetric reactions measured by absorbance.

Validity results indicate if a urine sample is clean or adulterated. The Substance Abuse and Mental Health Services Administration (SAMHSA) offers guidelines for acceptability parameters for validity testing based on creatinine and specific gravity, as summarized in Table 2. SAMHSA is a sector of the U.S. Department of Health and Human Services that develops measures to support overdose prevention. Forensic laboratories use SAMHSA's acceptability parameters for validity testing and can be implemented in clinical laboratories.

Table 2. SAMHSA Classifications of Validity

Classification	Creatinine	Specific Gravity
Dilute	≥ 2 and < 20	> 1.0010 and <1.0030
Substituted	< 2	≤ 1.0010
Substituted	< 2	≥ 1.020
Invalid	< 2	> 1.0010 and < 1.020
Invalid	≥ 2	≤ 1.0010

An additional measure to aid in determining validity or to rule out "spiking" is to observe the drug metabolites. For example, the confirmatory results of patients taking buprenorphine as prescribed should indicate hepatic metabolism from the parent drug, buprenorphine, to the metabolite, norbuprenorphine. The presence of norbuprenorphine suggests that the patient did not "spike" the sample with the medication at collection. Alternatively, the metabolite would be absent if the patient did "spike" the sample. Therefore, it can be helpful to monitor the concentration of norbuprenorphine in patients prescribed buprenorphine.[22, 26]

Further, observing the presence of naloxone has been used to confirm the ingestion of buprenorphine. Some buprenorphine formulas, such as the medication branded Suboxone® (Indivior, Inc., North Chesterfield, VA) or Zubsolv® (Orexo US, Inc., Morristown, NJ), contain naloxone. Naloxone is an opioid antagonist used to reverse opioid overdose. Naloxone could be considered a validity measure that ensures the patient has ingested the medication as directed. Although this may be a helpful aid in validating the sample, it is not reliable. Other drugs, such as naloxegol (brand

name Movantik™), commonly prescribed for opioid-induced constipation, may cause a false positive. A false positive could occur since naloxol is a derivative of naloxone, and the drug's manufacturing process can leave impurities.[27]

When considering validity testing of urine samples, the cost per test increases. While the cost for urine confirmation testing may be similar to the testing of other matrixes, validity testing should be added to the total cost per test.

Oral Fluid

Oral Physiology and Drug Metabolism

Saliva is a filtrate of plasma by way of diffusion. Saliva contains cellular debris, secretions, and other residues expressed from the salivary glands in the oral cavity.[28] The passive diffusion of drugs from the blood through the salivary glands depends mainly on the pH of the saliva. Other factors include whether the drug is lipid-soluble, the percentage of the bound proteins, and the method by which the drug is administered.[6, 28] Opioids are weakly basic in pKa and have a low percentage of bound protein. Opioids also have a lower molecular weight which causes the parent drug to be present at higher concentrations in the oral fluid. Since oral fluid does not require the drug to undergo metabolism before excretion, the detection window or half-life is shorter, ranging from less than 1 hour to 48 hours.[5] The sample collection time should be relatively close to when the patient was administered the drug.

Sample Collection, Transport, and Storage

The collection of oral fluid can be performed by passive drool, expectoration, and commercial devices.[28, 29] The passive drool collection technique is the non-stimulated pooling of saliva collected into a container. Expectoration is a collection method in which the patient spits into the container. The passive drool and expectoration collection methods provide an initial also referred to as a neat sample free of diluents.[28] One benefit of collecting neat fluid is the ability to split a single collection into two samples if needed.[5] Commercial devices generally use a swab to absorb the saliva from the oral cavity, and a transport container with a buffer that stabilizes and preserves the sample for testing. Swab with transport containers are available from many manufacturers and are more popular with patients and collectors due to the ease of handling. Commercial swabs are more sanitary than passive and expectoration collection methods.

One of the main advantages of oral fluid is the ease of collection and provides improved patient care. All patients have a safer and more private experience and significantly easier for the elderly and disabled populations. Medical personnel collect the oral fluid in a safe, controlled environment such as the exam room or designated collection area. Furthermore, the sample volume requirement is typically only 1 mL, adding to the benefits of an oral collection.[28] The small sample volume requirement is beneficial for patients with kidney dysfunction that are not unable to produce a sample size to meet that of urine.

Although there are benefits to oral collection, there are limitations for some patients. An attempt to collect saliva may be difficult for those suffering from conditions causing xerostomia.[29] Xerostomia, or hyposalivation or "dry mouth," is when the salivary gland fails to produce adequate saliva. The condition is common in patients with autoimmune disorders such as Sjögren's syndrome. Additionally, medications and anxiety can also cause hyposalivation.[30] Though the sample volume required is low, patients with the condition may still have difficulty collecting the minimum saliva volume.

Collecting the sample is vital to achieving accurate results. With commercial devices, the procedure must be performed according to the manufacturer's instructions. Pre-analytical failures such as not allowing the volume-adequacy indicator to change color or insuring the patient's mouth is free of foreign debris can contribute to test and result interferences.[28]

Instrumentation

The instrumentation for oral fluid testing is GC-MS or LC-MS.[7, 10] Oral fluid requires high-sensitivity instrumentation to detect low concentrations making the LC-MS the preferred instrumentation. Compared to GC-MS, LC-MS methods have high specificity and the robustness necessary for oral fluid testing.[28] When developing a preparation method, pre-treatment of the sample may be necessary for commercial devices that contain a buffer. However, since oral fluid captures larger concentrations of the parent drug in the free fraction form, the sample does not require a hydrolysis phase eliminating the need for quality control materials containing drug-glucuronide conjugates.

Despite the robustness associated with GC-MS, some limitations and interferences remain including the pH of patient saliva, improper collection procedures, and environmental exposures. The normal range of pH in saliva is between 5.8 and 6.8.[31] Patients with increased saliva pH due to stimulation of the salivary flow can decrease the drug concentrations.[7, 32] One of the methods utilized to stimulate salivary flow is sucking on citric-acid candy. This method can increase the salivary pH more than other methods, such as chewing on paraffin. Since there is no consensus on whether pH can be normalized, paraffin is preferred if salivary flow must be stimulated for collection.

Workflow

An additional pre-analytical consideration is the sample preparation method. While SPE or LLE methods are successful preparation techniques for oral fluid testing, laboratory workflow can be reduced with an effective dilute-and-shoot (DnS) sample preparation method. The DnS approach is a simple dilution of the oral fluid by adding LC/MS-grade water (1:4, *v:v*) before injecting it into the instrument for analysis.[33, 34]

Another consideration in the workflow and the absence of extensive drug metabolism in oral fluid is that many metabolites may not be required for testing. Since the parent drug is most concentrated in oral fluid, laboratories can consider eliminating metabolite testing from the method. With fewer drug analytes requiring analysis, run time is reduced, decreasing the turn-around time for the method.

Validity Testing

Validity testing is traditionally a consideration in drug testing but is not necessary when testing oral fluid for the clinical setting. SAMHSA recognizes Immunoglobulin G (IgG) and albumin as validity test markers. The antibody, IgG, and albumin, a polypeptide, are present in normal human saliva. The normal range for IgG is 0.1-1.0 mg/L, and the normal range for albumin is 0.2-0.3 mg/mL.[32, 35] If the concentrations fall below the laboratory's established limit of detection or are absent, it is an invalid sample.[12] In addition, collections are performed by clinical staff and observed and it is unlikely the sample can be manipulated or adulterated.

Another consideration is the utilization of metabolites and other compounds to support medication compliance. As with buprenorphine-prescribed patients, the parent drug can be observed independently to monitor patient compliance and adherence to the prescribed medication regime. The observation of norbuprenorphine or naloxone is unnecessary.

Discussion

The use of oral fluid in clinical toxicology is gaining momentum. In comparing oral fluid and urine testing, oral fluid is more useful to laboratories and provides a better resource for providers to treat chronic pain patients. The comparison of the physiological characteristics of urine and oral fluid is important. In oral fluid, the passive diffusion of lower-weighted opioid molecules allows the observation of the parent drug to determine drug compliance. Oral fluid is optimal for chronic pain patients because they are typically in a steady state of prescribed medications.[2] Consistent capture of the parent drug from saliva is a strong determinant of compliance.

Although the lower weight of opioid molecules improves parent drug detection, oral fluid still requires a high-sensitive instrument to measure small concentrations. GC-MS and LC-MS can be used, but LC-MS is most prevalent due to the robustness, sensitivity, and specificity required for oral fluid.[28] In addition, oral fluid does not require a hydrolysis step, a DnS preparation is the ideal method. A quick preparation method such as DnS decreases laboratory turn-around time, reducing the amount of solvents and technician time needed compared to SPE or LLE.

Despite the preferred qualities of LC-MS and effective sample preparation methods, the most significant impact of oral fluid testing is the improvement in the integrity of the sample due to preanalytical processes. Urine can be easily adulterated, but oral fluid collection ensures that the sample presented for testing is without impairment. The collection of oral fluid can be observed without interfering with a patient's privacy and significantly reduces or eliminates adulteration. It also removes the limitations associated with collecting urine specimens for patients with physical disabilities. Oral fluid does not need a particular collection environment and can be obtained using a manufactured swab and transport device.

Patient care is improved by testing oral fluid because providers are able to interpret the results more easily. The provider's ability to correctly interpret the results is essential in determining compliance. Whether providers can accurately interpret results, especially those exhibiting adulterated characteristics, is questionable. Twenty-eight percent of providers report contrasting interpretations to the laboratory.[36] Providers may assume aberrant medication-taking behaviors if the metabolite is missing and fail to consider the possibility of a CYP450 gene mutation that reduces or increases drug metabolism. The characteristics of oral fluid and the ability to eliminate adulteryation also removes providers' errors in interpretation. Oral fluid identifies the parent drug and indicates to the providers that a patient is taking the medication as prescribed.

Despite the many benefits of oral fluid testing, some limitations should be highlighted. Although determining compliance based on the parent drug is easier to interpret, it could result in the provider overlooking the potential identification of a CYP450 mutation. If the provider is knowledgeable about pharmacogenomics, the routine absence of the drug metabolite in urine would lead to further clinical diagnostics and potentially alter the patient's treatment plan. A second limitation of oral fluid testing is the collection from patients with xerostomia. Patients unable to produce saliva may have difficulty producing the minimum volume needed for testing. Salivary stimulation techniques can affect the saliva's pH, which may impact the test results.

Conclusion

The misuse of opioids is prevalent in chronic pain patients and has increased pain management compliance measures. A compliance measure such as drug testing is an element necessary in proper pain management. Oral fluid testing improves patient care due to the ability to capture the presence of prescribed, non-prescribed, and illicit drugs, and potentially aiding in reducing opioid use disorder. Oral fluid testing could be useful in testing other classes of medications, such as benzodiazepines, that are commonly prescribed in chronic pain patients. More research is needed to determine whether screening an oral fluid sample would be beneficial before definitive drug testing is required. The need for pain management compliance continues to grow, and implementing oral fluid testing provides better sample integrity, streamlined testing, and better patient care.

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