Toxicologic Aspects of Heroin Substitution Treatment

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Summary: Heroin abuse is an international problem with which all countries must continually cope. Many countries have implemented heroin substitution therapy as an effective means of decreasing illicit heroin use, crime, HIV risk, and death, and in improving employment and social adjustment. Although methadone is the most commonly used medication for heroin substitution, other agonists in current use include levolimethadyl acetate (LAAM), buprenorphine, and pharmaceutical-grade heroin. This report reviews toxicologic issues that arise in these programs. A broad array of testing methodologies are available that allow selection of on-site testing or laboratory-based methodology. Urine specimens may be monitored for nonprescribed drugs on a qualitative or semiquantitative basis. Methods for differentiating opiate sources by urinalysis have been proposed to distinguish poppy seed consumption from heroin abuse and for distinguishing pharmaceutical-grade heroin from illicit heroin. Therapeutic drug monitoring for methadone in plasma continues to be evaluated for use in establishing adequate dosing and detecting diversion, and new methods have been devised for measurement of the optical isomers of methadone in plasma. Biologic specimens, in addition to plasma and urine, have been evaluated for use in drug monitoring, including sweat, hair, and oral fluid, with promising results. Overall, the many recent developments in testing methodology provide more effective means to assess patients in heroin substitution programs and should contribute to improvements in public health.

Key Words: Heroin—Methadone—Levolimethadyl acetate—Urinalysis.

Opioid-based substitution therapy for treatment of heroin dependence has been in practice in some countries for more than 40 years and is considered by many to be the most efficacious form of treatment. Replacement of heroin, a short-acting euphoriant, with methadone or other opioids that have significantly longer durations of action and are given by less-euphorogenic (noninjection) routes provides a number of therapeutic benefits. Steady-state maintenance therapy produces continuous occupancy of brain opioid receptors, thereby preventing the discomfort of withdrawal. Other benefits include elimination of needle use, suppression of heroin craving, and gradual normalization of lifestyle. A somewhat different approach to substitution therapy has been attempted in some countries in which subjects are provided pharmaceutical-grade heroin for injection as replacement for illicit heroin. Great Britain has used this approach in a small proportion of patients for some time; more recently, Switzerland has initiated a heroin maintenance program with some success (1).

Many toxicologic issues have arisen in spite of and (in some cases) as a result of these different forms of heroin substitution treatment. For example, the continued misuse of drugs by patients in opioid-maintenance treatment programs can be significant. Differentiating illicit heroin from prescribed heroin or from poppy seed consumption can be problematic. Urinalysis remains the standard methodology for monitoring drug use, but recent improvements can add to its effectiveness in practice. In addition, many new technologic advances have been made with alternate matrices testing in recent years, and their use is being evaluated for treatment monitoring.
Treatment specialists continue to debate whether a therapeutic drug monitoring (TDM) approach for methadone maintenance provides an accurate means of evaluating whether proper therapeutic doses are being administered. This report provides an overview of many of the toxicologic issues that arise in heroin substitution treatment.

PREVALENCE AND COST OF HEROIN AND OTHER DRUG ABUSE

Drug abuse remains a significant source of economic and social problems. For example, in the United States, where extensive survey data are available, the economic costs of drug abuse were estimated to be more than $97 billion in 1992 (the latest year for which data were available) (2). Estimates from the 1999 National Household Survey on Drug Abuse showed that 14.8 million persons used an illicit drug in the month before being interviewed in the United States, and 3.6 million were dependent on an illicit drug (3). Heroin use affects a relatively small proportion of drug users, although this fact belies the overall impact on its users. Lifetime prevalence of heroin use in 1999 was estimated at 3.0 million (1.4% of Americans), compared with 87.7 million (39.7%) for any illicit drug use. The number of current heroin users (those reporting use in the last month) was estimated to be 200,000; of those, 35% were dependent, the highest rate for any specific drug (3). Heroin use is associated with significant rates of complications and death (4–8). For example, 8.2% (9/110) of individuals died in the year after dropping out of methadone maintenance treatment programs (six from heroin overdose) compared with only 1% (4/397) of individuals in a similar cohort who remained in treatment (9).

HEROIN SUBSTITUTION THERAPY

The most effective pharmacologic approach to the treatment of opiate dependence is opiate agonist maintenance therapy, in which patients receive stable dosing at regular intervals (daily or every other day) for extended periods of time (months to years). Opiate agonist maintenance therapy has been shown to decrease the adverse consequences of heroin use, including decreasing illicit drug use, crime, HIV risk, and death and improving employment and social adjustment (4,9–15). A summary description of agonist maintenance medications is given in Table 1. Methadone and l-acetylmethadol (LAAM) are the only opiate agonists currently approved by regulatory authorities in the United States for maintenance treatment.

Characteristics that make these medications particularly useful for maintenance therapy, compared with other opioid agonists, are their long duration of action and activity via the oral route of administration. The mechanisms through which heroin substitution acts are multiple. Maintenance administration with long-acting medications attenuates the acute subjective effects of heroin and other illicit opiates through cross-tolerance and decreases the intoxication/withdrawal cycle that occurs several times daily while individuals are physically dependent on heroin (16–18). In addition, the treatment retention and physiologic stability afforded by agonist maintenance is conductive to concurrent psychosocial or behavioral therapy that can be directed at improving patient functioning and decreasing high-risk behaviors associated with the transmission of HIV. The proportion of patients receiving opioid substitution therapy in the United States has been increasing, with 14% of all patients enrolled in narcotic substitution therapy (a total of 149,030–145,610 receiving methadone and 3,420 receiving LAAM) in 811 treatment facilities in October 1998 (19).

Another medication, buprenorphine, has recently been added to the opioid substitution armamentarium. It became available for heroin substitution in France in 1996 and is nearing regulatory approval in the United States. Buprenorphine is a partial opioid agonist with

<table>
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<th>TABLE 1. Agonist maintenance medications for opioid dependence treatment</th>
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<tr>
<td><strong>Methadone</strong></td>
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<td>Dosing interval</td>
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<td>Recommended doses</td>
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<td>Initial treatment</td>
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<td>Maintenance</td>
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LAAM, l-acetylmethadol.

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pharmacodynamic effects very similar to those of typical opioid agonists such as morphine and heroin (20, 21). Buprenorphine maintenance therapy is as effective as methadone in decreasing illicit opioid use and maintaining retention in drug abuse treatment (22–24) and is effective in blocking the effects of supplemental opioids (25). Buprenorphine has a long terminal elimination half-life of 42 hours, making less than daily dosing possible (26). Unlike the prototypic opioids, however, a ceiling on the effects of sublingually administered buprenorphine has been shown, with maximal effects occurring at approximately 8 to 16 mg (21,27). This ceiling effect probably accounts for the safety of buprenorphine administration. Buprenorphine produces less respiratory depression than opioids such as morphine (28), and doses up to 32 mg (sublingual) have been administered safely to opioid-experienced, but not physically dependent, individuals (21,27). However, prolonged respiratory depression and death have been associated with combinations of buprenorphine and benzodiazepines (29–31). A product combining buprenorphine and naloxone (Suboxone) is also under development in the United States; this combination is expected to have a lower potential for diversion and misuse than buprenorphine.

**TESTING METHODOLOGY**

Monitoring prescribed and nonprescribed drug use during treatment provides valuable information for the diagnosis and management of patients. Urinalysis allows treatment specialists to determine whether the patient is compliant and whether other psychotropic drugs are being consumed. The most commonly used screening methodologies use immunologic-based assays or thin-layer chromatography (TLC), but some laboratories testing small numbers of specimens use other chromatographic methods for screening, such as gas chromatography (GC) or high-performance liquid chromatography (HPLC). Although TLC may provide more qualitative information about metabolite profiles than immunoassays, this technology often is less amenable to semiquantitation and frequently has higher detection limits.

There are currently no universally accepted or internationally recommended drug testing procedures for drug treatment programs. Some countries have specified minimum testing requirements for patients in opioid agonist maintenance. For example, in the United States, treatment providers must test patients for opiates, methadone, amphetamines, cocaine, and barbiturates on admission to their program and conduct at least eight additional random tests during the first year and at least quarterly each subsequent year of maintenance treatment. More frequent testing is required in patients who receive a 6-day supply of take-home medication. This testing regimen is the minimum required, however, and treatment programs have wide latitude in ordering urine drug testing.

The treatment center must determine the panel of screening tests used for patient assessment that best suits its needs. Regional differences in illicit drug use patterns may influence the selection of drugs to be monitored. In addition, the performance characteristics of immunoassay should be taken into consideration. Most immunoassays are not specific for a single analyte and will detect a variety of drugs within a general drug category. For example, most “opiate” immunoassays are targeted to detect morphine and morphine metabolites but also display significant cross-reactivity with other opiates such as codeine, hydrocodone, and hydromorphone if present in sufficiently high concentrations. A separate assay must also be included in the screening panel if compliance monitoring of the treatment medication is a goal of the program (e.g., methadone, LAAM, or buprenorphine).

The treatment center must also decide whether testing is to be performed on-site or if specimens will be sent to commercial or clinical laboratories. Most programs select laboratory-based testing, but there are specific advantages associated with the use of on-site test devices. On-site testing devices allow the clinic to quickly assess patients’ drug status during their visit. Numerous on-site devices are now available for detection of opiates in urine, and at least one device has been introduced for detection in oral fluid. In addition, the U.S. Department of Health and Human Services (DHHS) has developed draft guidelines for use of on-site tests in workplace drug testing programs (32).

Confirmation of positive results may or may not be required, depending on the legal requirements at the location of the treatment program and the reasons for the testing. Confirmation methods and TDM assays are exclusively laboratory-based methodologies and are generally based on chromatographic techniques. These assays must be sufficiently sensitive and specific to identify and accurately measure specific analytes at low detection levels or at designated cutoff concentrations. Gas chromatography and HPLC are often used for TDM of methadone; hyphenated chromatographic methods such as gas chromatography-mass spectrometry (GC-MS) are most often used for confirmation testing. Recently, additional methodologies such as GC-MS-MS, LC-MS,
and LC-MS-MS have been gaining popularity, particularly for alternate specimen tests (e.g., oral fluid, hair, sweat) that require very low detection limits.

**TOXICOLOGIC TESTING**

**Qualitative Versus Quantitative Urine Monitoring**

Positive urine test results may invoke a variety of clinic responses, including counseling, increased screening frequency, dose adjustments, contingency contracting, revocation of take-home privileges, and eventual discharge. Generally, urinalysis is performed in a qualitative manner in these programs; however, qualitative drug testing has some associated disadvantages compared with quantitative and semiquantitative assays. For example, if the monitoring frequency is high (i.e., thrice weekly), a single episode of drug use can result in multiple positive results. In contrast, concentration-based assays can indicate evidence of carryover from a previous drug use. Further, assessment of average concentrations across time can provide evidence of decreasing drug use despite continued positive results. Recently, Preston et al (32) reported a comparison of qualitative and semiquantitative methods for monitoring cocaine use in heroin-dependent subjects. Quantitative urinalysis was found to provide more information about patterns and frequency of illicit cocaine use during treatment than qualitative testing.

**Differentiating Opiate Sources by Urinalysis**

Positive urine test results for opiates can be obtained as a result of use of prescribed or illicit heroin, morphine, codeine, and other opiates, or by consumption of poppy seeds. Differentiating codeine use from heroin use can be problematic because codeine is partially metabolized to morphine in the body before elimination. ElSohly (33) has suggested evaluation of the codeine/morphine ratio and respective concentrations as a means of differentiation. A variety of other approaches have been suggested for differentiation of heroin use versus poppy seed ingestion. These include raising the screening and confirmation cutoff concentrations from 300 to 2000 ng/mL (DHHS workplace drug testing program guidelines), confirmation testing for 6-acetylmorphine (an intermediate metabolite for heroin), and testing for markers such as thebaine, found exclusively in poppy seeds.

An unusual case of opiate differentiation is needed in heroin maintenance programs. In these programs, there is a need to differentiate prescribed, pharmaceutical heroin from illicit heroin that addicts might use to supplement their doses. 6-Acetylmorphine, an impurity of illicit heroin, has been identified as a potentially useful urinary biomarker for detection of illicit heroin use. O’Neal and Poklis (34) reported that 37 samples were positive for 6-acetylmorphine (concentration range 2 to 290 ng/mL) of 100 confirmed positive samples for morphine obtained from the criminal justice system. They concluded that 6-acetylmorphine detection could play an important role in detecting illicit heroin use in heroin maintenance programs.

**THERAPEUTIC DRUG MONITORING**

Monitoring methadone plasma or serum concentrations has been suggested as a means of improving patient outcome in treatment, but wide intersubject variability is known to occur. Numerous reasons account for the variability, including individual variations in enzyme levels, enzyme induction and inhibition by concomitant medications, metabolic tolerance, differences in plasma protein binding, and changes in the pH of the urinary tract (35). Lower plasma methadone concentrations have been associated with greater likelihood of abuse of nonprescribed opiates (36). A TDM approach has been suggested as a means of assessing the adequacy of methadone prescribing, monitoring compliance, and detecting illicit drug use (37). Minimum plasma trough levels of methadone in the range of 100 to 400 ng/mL have been reported to be essential for adequate maintenance (38,39). In addition to revealing unrecognized under- or overdosage, TDM has the potential to establish individual drug baselines and monitor disposition changes that may occur as a result of pregnancy, disease, and abnormal liver function.

Methadone monitoring by analysis of oral fluid (saliva) has also been proposed because of the noninvasive nature of the collection procedure. Wolff et al (40) reported obtaining a significant correlation between saliva and plasma methadone levels obtained just before daily dosing. For every 1-µg/L increase in plasma concentration, saliva concentration increased by 1.3 µg/L. In contrast, Bermejo et al (41) failed to find a significant relationship between saliva and plasma methadone concentrations in 10 methadone maintenance patients. Saliva/plasma ratios were variable and ranged from 0.6 to 7.2. Recently, Orrell et al (42) used LC-MS equipped with an enantioselective column to resolve methadone isomers in saliva and serum. They reported a lack of correlation of total methadone in saliva and plasma but found a high correlation of the optical isomer ratio (R/S) ratio measured in saliva compared with serum.
TESTING FOR METHADONE ENANTIOMERS

Methadone exists as optical isomers (R,S) of which the majority of opioid activity is associated with the R-isomer (l-methadone). Generally, the racemic (R,S) drug is prescribed in treatment, with the exception of some European countries in which R-methadone is used (43). A longer elimination half-life has been reported for R-methadone (51.7 to 61.8 hours) compared with S-methadone (31.8 to 37 hours). Stereospecific assays are now available for direct measurement of enantiomers, allowing assessment of interindividual variability in the R/S ratios of patients in treatment (43).

ALTERNATE MATRICES

Although urine is the traditional specimen tested in treatment programs, other biologic specimens have been evaluated for use in drug monitoring, including sweat, hair, and oral fluid. Several reviews have appeared that address the potential uses of sweat, hair, and oral fluid (37,44) for detection of illicit drug use. Table 2 provides a comparison of urine with alternate matrices in treatment testing. Each biologic matrix provides unique and potentially useful information in treatment monitoring. In addition, nail clippings have been reported to be a potentially useful specimen for monitoring patient compliance in methadone maintenance programs (45).

CONCLUSIONS

The number of countries that have implemented opioid substitution programs as treatment of heroin dependence is increasing. Although methadone is most commonly used, other opioids such as LAAM, buprenorphine, and pharmaceutical-grade heroin are in use. Non-prescribed drug use remains a persistent problem for patients in treatment. Monitoring compliance and non-prescribed drug use is an ongoing challenge confronting treatment programs. Technologic advances in drug testing methodology provide an array of choices to treatment specialists, including on-site testing devices, quantitative urinalysis for assessment of frequency of drug use, TDM for assessment of dose adequacy and treatment adherence, and use of alternate matrices such as sweat, hair, and saliva (oral fluid) for monitoring drug use.

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