REX

Laboratory Bulletin

February 2007

UPDATES AND INFORMATION FROM REX PATHOLOGY LABORATORY

Issue Number 123

Drug Screens - Still Not Equal After All These Years

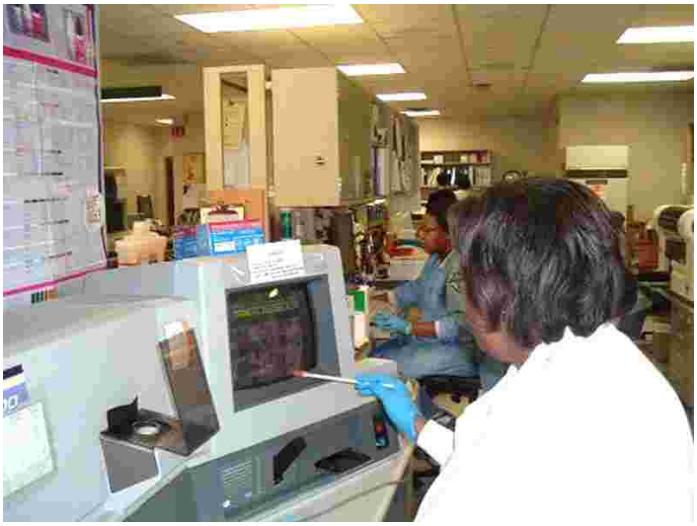
Not much has changed since our former clinical chemist, Robert B. Brainard, Ph.D., wrote an excellent article on drug screens nearly a decade ago.[1] As this topic often provokes questions or calls to the laboratory, as there have been a few changes in detection cut-offs and test profiles, and as some of you were in college at that time, a refresher article is offered below.

As the term implies, "drug screens" are designed to help determine the presence or absence of various pharmaceuticals (legal or illegal) in biologic specimens. Different screens vary in their sensitivity, utility, and comprehensiveness - depending upon the clinical setting. Recognition of these differences is helpful in selecting the appropriate test. A few general principles to keep in mind…

- Urine is the specimen of choice for most drug screens.
- "Medical" drug screens often have lower detection limits (limit of quantification or LOQ) than non-medical (e.g. employment) drug screens.
- Specific drug or drug group (e.g. opiates) assays often have a lower LOQ than more comprehensive drug screens. Thus it ALWAYS helpful to indicate suspected drug(s) and order most specific test available.
- Detection times given are an approximation for general guidance. Factors such as drug dose, chronicity of use, concurrent medications, body fat, diet, fluid consumption, activity, renal function, hepatic function, or illness can have significant impact on the detectability of selected drugs.
- While negative results are very helpful, and generally reliable, false positive results can occur on screening tests. Confirmation with a second method is highly recommended for all positive results, particularly in medicolegal or forensic settings.

Rex Urine Drug Screen

This test is offered to assist in the **immediate medical management** of patients with **acute mental status changes** in whom drug intoxication or overdose is suspected. It should not be used to screen for or monitor recreational drug use. This enzyme immunoassay is performed on urine only and tests only for the drugs (or drug classes) at the LOQ listed in the table below. More detailed information regarding the performance characteristics of the test (including interfering substances) is available on the Rex intranet "RexWebMD" by clicking on *Laboratory Services*, then *Toxicology Interferences*. This test is available 24 hours daily with an expected turnaround time of one hour. Confirmation is not available on site, and thus positive results must be interpreted in the appropriate clinical context. Positive specimens are held for one month, while negatives are held for two weeks, in case additional or confirmatory testing is desired. (Order the desired confirmatory or additional urine test as "specimen in lab" or call (919)784-4247 for assistance.)



Mayo Drug Abuse Survey (Urine), with Confirmation

This test is recommended for **medical screening** of individuals suspected of recent recreational drug use. The test, performed at Mayo Medical Laboratories, is similar to the Rex urine drug screen. It does not screen for tricyclic antidepressants, but includes a screening test for ethanol, as well as confirmation

Rex Pathology Associates, P.A.

John D. Benson, MD	(919) 784-3059	F. Catrina Reading, MD	(919) 784-3255
Timothy R. Carter, MD	(919) 784-3058	Vincent C. Smith, MD	(919) 784-3056
Stephen V. Chiavetta, MD	(919) 784-3060	John P. Sorge, MD	(919) 784-3062
Keith V. Nance, MD	(919) 784-3286	Rhonda Humphrey, Practice Manager	(919) 784-3063

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of preliminary enzyme immunoassay results with either gas chromatography-mass spectrometry (GC-MS) or gas chromatography-flame ionization detection (GC-FID). As such, the sensitivity is similar to the Rex assay, but the specificity/positive predictive value is vastly superior. The sensitivity (LOQ) is not as low in this screening test as it is in the specific drug/drug group assays. Therefore this test should **not** be ordered for **monitoring** patients **known to abuse a particular drug** or class of drug. It is not approved or appropriate for employment-related drug testing.

Urine Drug Abuse Screens - Detection Limits (Rex and Mayo)

Drug (Group)	Rex	Mayo	Detection Time*
Amphetamines	1000 ng/mL**	1000 ng/mL**	2-3 days
Barbiturates	200 ng/mL	200 ng/mL	2-15 days
Benzodiazepines	200 ng/mL	200 ng/mL	2-40 days
Cocaine	300 ng/mL **	300 ng/mL **	3-5 days
Opiates	300 ng/mL ***	300 ng/mL ***	2-3 days
Phencyclidine	25 ng/mL **	25 mg/mL **	2-3 days
Tetrahydrocannabinol (THC, Marijuana)	50 ng/mL **	20 ng/mL ***	2-60 days
Tricyclic Antidepressants	1000 ng/mL	Not detected	1-4 days
Ethanol	Not detected	300 µg/mL	12 hours

* An approximation subject to drug dosage and patient metabolism as discussed above
** Screening levels recommended by Substance Abuse and Mental Health Services Administration (SAMHSA)[2]
*** Detection level below that recommended by SAMHSA

Mayo Prescription and Over-the-Counter Drug Screen

This is the most comprehensive drug screen Mayo offers, and may be performed on urine, serum, plasma, or gastric contents. More drugs are detectable in urine specimens that serum/plasma specimens. The testing is performed by GC-MS, thus positive results are definitive. This test replaces the previous comprehensive drug screens that Mayo offered. It is **not quite as comprehensive** as the former in that it will not detect alcohol, LSD, digoxin, lithium, THC (marijuana), and some benzodiazepines, opiates and amphetamine-type stimulants.[3] Accordingly, to achieve the **broadest** (most comprehensive) testing in suspected overdose situations where there is **no clue** regarding the offending drug, I would recommend submitting a urine specimen **for both this test and the Mayo Drug Abuse Survey (with confirmation)** described above. For outpatients presenting to the laboratory with orders for "urine drug screen," we will attempt to contact the ordering physician for further clarification. If this is not possible in a timely manner, we will order both of the tests.[4]

Mayo Specific Drug/Drug Group Confirmation

These assays are the test(s) of choice for patients known to use/abuse specific drugs or class of drugs. They are more sensitive and specific than the above screening tests. They can often detect trace amounts of drug or drugs that do not cross-react well in screening tests (e.g. oxycodone).[3] The tables below provide information for selected drugs within each class. It takes seven half-lives to clear 98 percent of a drug dose. Repeated dosing will cause the drug/metabolite to accumulate, but rate of clearance remains the same.

Amphetamines

Amphetamines are rapidly cleared from blood, thus urine is the specimen of choice to screen for amphetamine use. Amphetamine, methamphetamine, and phentermine have been prescribed for weight loss. Methamphetamine is metabolized to amphetamine. If both are present in urine, methamphetamine is the primary drug. If only amphetamine is detected it is the primary drug. The presence of 3,4-methlenedioxyamphetamine (MDA) in the urine indicates use of 3,4-methylenedioxymethamphetamine (MDMA or Ecstasy). The following drugs will produce a positive result: Adderall and Benzedrine (contain amphetamine); Desoxyn and Vicks Inhaler (contain methamphetamine); and clobenzorex, famprofazone, fenethylline, fenproporex, and mefenorex (metabolized to amphetamine).[5]

Amphetamines[3]

Drug/Metabolite	Clearance (t1/2)(hours)	Urine Concentration (ng/mL)	Detection Time* (days)	LOQ (ng/mL)
Amphetamine	7-34	50-30000	2-3	50
Methamphetamine	6-15	500-30000	2-3	500
3,4-methlenedioxy-amphetamine	4-6	50-2000	1-2	50
Phentermine	19-24	500-30000	3-4	50
Ephedrine/pseudoephedrine	2-10	NA**	1-3	NA**
Phenylpoanolamine	3-4.4	NA**	1-3	NA**

* An approximation subject to drug dosage and patient metabolism as discussed above
** NA = not available, not quantitated

Barbiturates

Serum assays are available for many barbiturates, and are preferred for situations in which patients are known to be receiving a specific drug. Urine is the specimen of choice for confirming a suspected barbiturate overdose or abuse, where the specific drug is unknown.

Barbiturates[3]

Drug	Clearance (t1/2) (hours)	Urine Concentration (ng/mL)	Detection Time* (days)	LOQ (ng/mL)
Phenobarbital	80-120	2000-30000	10-15	100
Amobarbital	10-40	500-2000	2-3	100
Butabarbital	35-50	500-3500	5-7	100
Mephobarbital	10-70	500-5000	2-3	100
Butalbital	35-88	500-3000	5-7	100
Pentobarbital	15-50	500-5000	2-3	100
Secobarbital	15-40	500-5000	2-3	100
Thiopental	8-10	500-5000	2-3	100

* An approximation subject to drug dosage and patient metabolism as discussed above

Benzodiazepines

Serum assays are available for selected benzodiazepines, but levels may not correlate with observed levels of sedation. Urine is the specimen of choice for confirming a suspected benzodiazepine overdose or abuse.

Benzodiazepines[3]

Drug	Clearance (t1/2)(hours)	Urine Concentration (ng/mL)	Detection Time* (days)	LOQ (ng/mL)
Chlordiazepoxide	6-27	200-10000	5	100
Clonazepam	19-60	200-1000	10	100
Clorazepate	1-3	200-20000	15	100
Diazepam	21-37	200-6000	7-10	100
Nordiazepam	31-97	200-20000	10-20	100
Oxazepam	4-11	200-150000	10-20	100
Temazepam	5-17	200-10000	10-15	100
Lorazepam	9-19	200-5000	2-3	100
Alprazolam	6-27	200-2000	2-3	100
Flunitrazepam	9-25	50-200	3-5	50
Flurazepam	1-3	2000	2-3	100
Triazolam	1.5-5.5	200-1000	1-2	100

* An approximation subject to drug dosage and patient metabolism as discussed above

Cocaine

Cocaine is rapidly metabolized to several inactive metabolites, the principal one is benzoylecgonine. While a whole blood assay (requiring sodium fluoride anticoagulant) is available, urine is the specimen of choice for confirming recent cocaine use. The drug typically appears in urine within 10 minutes and peaks at two hours following a typical dose.

Cocaine[3]

Drug/Metabolite	Clearance (t1/2)(hours)	Urine Concentration (ng/mL)	Detection Time* (days)	LOQ (ng/mL)
Cocaine	0.7-1.5	150-30000	1	50
Benzoylecgonine	12-15	150-800000	3-5	20

* An approximation subject to drug dosage and patient metabolism as discussed above

Lysergic Acid Diethylamide (LSD)

There are no blood or serum assays for LSD. The drug typically appears in urine within 30 minutes and peaks at two hours following a typical dose. A metabolite of LSD is 2-oxo-3-hydroxy-LSD.

LSD[3]

Drug/Metabolite	Clearance (t1/2)(hours)	Urine Concentration (ng/mL)	Detection Time* (days)	LOQ (ng/mL)
LSD	3-4	0.5-2	<1	0.5
2-oxo-3-hydroxy-LSD	10-15	1-10	<5	5

* An approximation subject to drug dosage and patient metabolism as discussed above

Marijuana (Tetrahydrocannabinol, THC)

A whole blood assay (requiring sodium heparin, EDTA, or sodium fluoride anticoagulant) exists, but is not practical due to the short half-life of the drug. THC is rapidly metabolized to tetrahydrocannabinol carboxylic acid. This metabolite appears in urine within 1-4 hours after a typical dose and peaks at two days.

Marijuana (Tetrahydrocannabinol)[3]

Drug/Metabolite	Clearance (t1/2)(hours)	Urine Concentration (ng/mL)	Detection Time* (days)	LOQ (ng/mL)
THC	0.5	NA**	NA**	NA**
THC carboxylic acid	24-72	15-1000	2-30	3

* An approximation subject to drug dosage and patient metabolism as discussed above
** NA = not available, not quantitated

Methadone

Serum assays are available, but correlate poorly with pharmacologic effect. In addition, there may be large interpatient variability in serum levels at the same dose. Tolerance develops in patients on chronic methadone therapy. An inactive metabolite which appears in urine in variable concentration is 2-ethylidene-1,5-dimethyl-3,3-diphenypyrrolidine (EDDP). Patients compliant with methadone therapy generally have EDDP:methadone ratios > 0.60.[3] The drug and metabolite appear in the urine within 30 minutes of a typical dose and peak at two hours.

Methadone[3]

Drug/Metabolite	Clearance (t1/2)(hours)	Urine Concentration (ng/mL)	Detection Time* (days)	LOQ (ng/mL)
Methadone	15-55	500-50000	3-7	100
EDDP	15-60	500-50000	3-7	100

* An approximation subject to drug dosage and patient metabolism as discussed above

Methaqualone

Serum levels correlate poorly with pharmacologic effect. The drug appears in the urine within 30 minutes of a typical dose and peaks at four hours.

Methaqualone[3]

Drug/Metabolite	Clearance (t1/2)(hours)	Urine Concentration (ng/mL)	Detection Time* (days)	LOQ (ng/mL)
Methaqualone	20-60	800-32000	4-6	500

* An approximation subject to drug dosage and patient metabolism as discussed above

Opiates

Opiates are drugs (natural or synthetic) that are structurally similar to morphine including codeine, hydrocodone (Vicodin), hydromorphone (Dilaudid), and oxycodone (Percodan). Heroin and codeine are metabolized to morphine. Hydrocodone is a minor metabolite of codeine. Ingestion of poppy seeds (baked goods) can also cause morphine to be excreted in the urine (up to 2000 ng/mL if large amounts are consumed). No pharmacologic effect is achieved from poppy seeds due to first pass metabolism.[3] Tolerance develops for many opiates. Serum levels for morphine and oxycodone correlate well with pharmacologic effect, if tolerance is taken into consideration. Opiates generally appear in the urine within 30 minutes of a dose and peak at two hours. Urine levels of oxycodone are highly dose dependent and can be used to monitor compliance. Opioids are drugs that affect the opiate receptor, but are not structurally related to morphine. Examples include meperidine (Demerol), loperamide, diphenoxylate, fentanyl (Sublimaze, Innovar), sufentanyl, and alfentanyl. These drugs will NOT be routinely detected by the opiates assay and require separate specific tests.

Opiates[3]

Drug/Metabolite	Clearance (t1/2)(hours)	Urine Concentration (ng/mL)	Detection Time* (days)	LOQ (ng/mL)
Morphine	1.3-6.7	300-50000	2-3	100
Codeine	1.9-3.9	300-30000	2	100
Hydrocodone	3.4-8.8	300-20000	2	100
Hydormorphone	1.5-308	300-20000	2	100
Oxycodone	4-6	300-20000	2	100
Oxymorphone	4-6	300-5000	2	100

* An approximation subject to drug dosage and patient metabolism as discussed above

Oxycodone Urine Concentration Dose/Compliance Effect[3]

Dose/Compliance	Concentration Range (ng/mL)
Questionable compliance	0-1000
20 mg bid	2000-5000
40 mg bid	5000-40000
80 mg bid	15000-100000

Phencyclidine (PCP)

Serum assays are available, but are not particularly useful. The drug appears in the urine within 10 minutes of a typical dose and peaks at two hours.

Phencyclidine (PCP)[3]

Drug	Clearance (t1/2)g/mL)	Urine Concentration (ng/mL)	Detection Time* (days)	LOQ (ng/mL)
Phencyclidine	7-46	25-200	2-3	25

* An approximation subject to drug dosage and patient metabolism as discussed above

Propoxyphene

Serum assays are available and correlate with pharmacologic effect, if a patient is known to be taking the drug. Norpropoxyphene is the major metabolite and has 25-50% of the pharmacologic effect of the parent drug. Propoxyphene appears in the urine within 30 minutes of a typical dose and peaks at two hours.

Propoxyphene[3]

Drug	Clearance (t1/2)g/mL)	Urine Concentration (ng/mL)	Detection Time* (days)	LOQ (ng/mL)
Propoxyphene	6-12	200-5000	3	100
Norpropoxyphene	30-36	200-10000	6-9	100

* An approximation subject to drug dosage and patient metabolism as discussed above

"Date Rape Drugs (Flunitrazepam, Gamma-Hydroxybutyrate, and Ketamine)"

Several drugs have gained notoriety due to their prevalence in "rave clubs" and their use to incapacitate unsuspecting subjects for subsequent sexual assault. These "predatory drugs" are often colorless and their presence can be masked by mixing with fruit juice, sodas or alcoholic beverages. The drugs produce feelings of euphoria and lowered sexual inhibition, while inducing amnesia or memory problems, such that a victim may not remember an attack until many hours later and may lack clarity about details important for successful prosecution. Rapid metabolism of these drugs often precludes obtaining objective confirmation of drug exposure.[6]

Flunitrazepam (Rohypnol, R-2, Mexican Valium, rophies, roofies, circles) is a short acting benzodiazepine, originally designed for short term use in treating insomnia or in preanesthetic settings. It is a pill, but can be crushed for either "snorting" or dissolving into a beverage. Within 15-20 minutes of ingestion, it produces the behavioral changes described above, including pronounced anterograde amnesia. This drug may be detected in the urine benzodiazepine confirmation assay described above.

Gamma-Hydroxybutyrate (GHB, G, Liquid Ecstasy, Scoop, Easy Lay, Georgia Home Boy, Grievous Bodily Harm, Liquid X, and Goop) occurs naturally in minute quantities in the human brain as a metabolite of gamma-aminobutyric acid (GABA). It is easily manufactured by mixing a degreasing solvent/floor stripper (gamma butyrolactone) with a drain cleaner (sodium or potassium hydroxide such as Drano). It can either be an odorless, colorless liquid or a white powder.

It is commonly mixed with alcohol and can result in hallucinations, euphoria, sexual disinhibition, muscle relaxation, amnesia, seizures, coma, and death. The drug is often undetectable in urine by 12 hours after a dose. If exposure to this compound is suspected, collect blood and urine specimens and order specific testing for "gamma-hydroxybutyrate."

Ketamine (jet, super acid, Special "K", green, K, cat Valium) is a clear white powder or colorless liquid, designed as an anesthetic/tranquilizer and often used in a veterinary setting. It has a "dissociative effect," leading to use recreationally for an "out of body" experience (K-hole) as well as a date rape drug. Serum and urine assays are available. The serum half-live is two to three hours and the drug can be detected in urine for up to two to three days.[7] If exposure to this compound is suspected, collect blood and urine specimens and order specific testing for "ketamine".

Non-Medical Drug Screens

The Laboratory offers employment related drug screens on a contractual basis for both pre-employment and reasonable cause evaluation. This involves specimen collection using chain-of-custody procedures. Specimens are referred to an outside SAMSHA approved laboratory (Quest Laboratories) for testing. For further information regarding this program, please contact Barbara Koelsch (919) 784-3048.

Medicolegal Death Investigation

The North Carolina Office of the Chief Medical Examiner (OCME) offers toxicology testing for death investigations falling into the jurisdiction of the medical examiner system.[8] The nature and scope of testing varies with the circumstances surrounding the death. Depending on the staffing and workload of the OCME Toxicology laboratory, the turnaround time for analysis can be several weeks or months.

John D. Benson, MD

References

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8. *Nance KV, Benson JD. Deaths to be reported to the medical examiner. Rex Healthcare Laboratory Bulletin. Issue 77. February 2003.*

Rex Healthcare Laboratory (919) 784-3040. Telephone extensions are: Pathologists' Direct Line (3063), Robin Ivosic (Customer Service and Outreach Manager 3053), Elaine Patterson (Core Lab and Microbiology Manager 3054), Anne Cleverly (Blood Bank and Rex Blood Services Manager 4763), Diane Young (Anatomic Pathology Manager 3888).

Client Response Center (919) 784-6000 (phone) (919) 784-6299 (fax)