

Toxicology News

March 2000

An AACC Educational Newsletter for Toxicology Laboratories

Interferences Can Cause Spurious Screening Results

By Jimmie L. Valentine

Immunoassays depend on competitive binding. The analyte to be measured and a known quantity of labeled analyte compete to bind with an antibody produced to the analyte or its hapten (a conjugated form of the analyte). The extent to which the analyte binds with the antibody is measured in a number of different ways, such as spectrophotometrically, visually by aid of some colored reaction, or by latex agglutination.

Because immunoassays are based on detection of this competitive step, any substance or situation that either alters the binding of the target analyte to the detection antibody or interferes with the detection mechanism is referred to as an interference and has the potential to change the result.

A substance that interferes with an immunoassay can be from an exogenous or endogenous source. An example of an exogenous interference is an adulterant purposefully added to the urine specimen to mask a potentially positive result. Table 1 lists some potential urine immunoassay test interferences.

Table 1. Potential Urine Immunoassay Interferences

Endogenous

Proteinuria, glucose, bilirubin, nitrates, pH, ketones, urobilinogen, blood, leukocytes, bacteria, fungi

Exogenous

Drugs, drug metabolites, herbal products, foods, vitamins

Adulterants

Bleach, drain cleaners (NaOH), nitrites, salts (NaCl, KCl), commercial products sold for adulteration, assay antibodies

Enzyme assays, like immunoassays, rely on a competitive interaction—the competition between the analyte and an enzyme. For most enzyme assays, the detection step depends on a cofactor that changes oxidation state, a change that can be measured spectrophotometrically or through a visual color change. Both exogenous and endogenous substances can interfere with the result either by disrupting the competitive reaction through interacting with the enzyme or by possessing a chromophoric character that interferes with the detection step.

Endogenous interferences

Urine drug tests can be affected by the physical or disease state of an individual. A variety of diseases or pathological infections can lead to presence in a urine specimen of the endogenous interferences listed in Table 1 either individually or in certain combinations.

For example, diabetics excrete glucose into their urine, and fermentation can occur during prolonged storage to produce various amounts of ethanol. This was demonstrated in diabetic patients with glycosuria and symptoms of genitourinary candidiasis (1). After three days of room-temperature storage, the levels of ethanol began to increase, reaching 1.5–10 mg/dL after 20 days. Another study (2) found a similar result with somewhat higher levels of 3.6–232.7 mg/dL in diabetic patients. This latter study, however, demonstrated that only specimens containing yeast produced the ethanol. The obvious effect on an

Continued on page 5

Inside...

LSD Presents Challenges	2
Change in Accreditation Cycle.....	7
On-Line Toxicology Certificate	7
False-Positive BDP Result?	8

LSD Remains a Mysterious And Challenging Drug

By Sarah Kerrigan

Lysergic acid diethylamide (LSD) is derived from ergot, a sugary excretion of the fungus *Claviceps purpurea*, which grows on rye and other grains. The source of mass poisonings (ergotism) in the Middle Ages, ergot contains alkaloids with medicinal properties on record since the 16th century, when they were used by European midwives to precipitate childbirth. Today, ergotamine's vasoconstrictive properties are used to treat migraine headaches.

Research into ergot alkaloids commenced in the early 1900s at Sandoz Laboratories in Switzerland. In 1943, in an endeavor to discover a new analeptic drug, Albert Hofmann repeated an earlier synthesis of lysergic acid diethylamide from ergonovine. He unexpectedly discovered the unusual psychotropic effects of LSD: "The surroundings had changed in a strange way, and had become luminous, more expressive. I perceived an uninterrupted stream of fantastic pictures, with an intense kaleidoscope play of colors...."

In 1947 Sandoz marketed LSD under the tradename Delysid. It was anticipated that LSD would enhance understanding of psychiatric illness, particularly schizophrenia, psychoses, neuroses, sexual dysfunction, and alcoholism. Recreational use of LSD became pandemic during the 1960s and is largely responsible for the notoriety of the drug. LSD was widely used in the United States as a psychotherapeutic agent until 1965, when its use was restricted by an amendment of the Narcotics Act. At present there are no accepted medicinal uses of LSD, which is classified under Schedule I of the federal Controlled Substances Act.

Recreational use

Recreational use of LSD-like substances dates back more than 2,000 years. It is believed that *kykeon*, the holy potion of the ancient Eleusinians, contained lysergic acid amide and lysergic acid hydroxyethylamide. The same alkaloids are present in *ololiuqui*, a sacred drug of the Mexican Indians that contains seeds of *Convolvulaceae* of the morning glory family.

According to the 1998 National Household Survey on Drug Abuse, there were an estimated 1.1 million new hallucinogen users in 1997, nearly twice the average annual number during the 1980s. The rate of initiation among youths aged 12–17 years

more than doubled between 1991 and 1995 but has remained stable since 1995. Despite the dramatic increase in first-time use among youths in the past decade, overall rates of use among this age group remain comparatively low. Approximately 7.9% of the U.S. population over the age of 12 have reported using LSD during their lifetime. The 18–25 age group reported the highest rate of use in 1998 (14.0%) followed by 26–34 (10.6%), >35 (6.5%), and 12–17 (4.2%).

Demographic data suggests that the typical LSD user is a middle-class Caucasian male attending high school or college. Use of the drug is more prevalent in the suburbs than the inner city, and its popularity appears to be somewhat regionalized.

LSD is manufactured primarily in the western United States, where it remains relatively inexpensive and popular. Other pockets of LSD use exist, particularly in regions where the "rave" scene is popular.

LSD synthesized in clandestine laboratories can be available as a powder, tablet, or gelatin squares (window panes), or impregnated into blotting paper, sugar cubes, or postage stamps. Most commonly, an LSD solution is sprayed onto blotting paper, which is dried, perforated, and printed with colorful icons. Street names include acid, microdot, white lightning, red dragon, and green dragon. Doses are typically 50–300 μg and can cost as little as \$3 to \$5. The average street dose is about 100 μg , but doses as low as 20 μg can produce long-lasting pharmacologic effects.

Chemistry and psychopharmacology

LSD is a semi-synthetic derivative of the naturally occurring ergot alkaloids. It shares the tetracyclic framework common to this class of drugs. LSD contains two chiral carbon atoms. Of the four stereoisomers, only d-LSD is a potent hallucinogen. The l- and iso- analogs are pharmacologically inactive. A basic drug (pKa 7.8), LSD undergoes photodecomposition to lumi-LSD under certain conditions of light and pH.

The word hallucinogen is derived from the Latin word *alucinari*, which means to wander in mind. These substances produce alterations in perception, cognition, and mood in the presence of an otherwise clear sensorium. LSD is reported to produce synesthesia, or a blending of the senses, for example, the sensation of smelling a color or tasting a sound. The user's expectations and environment can govern the overall "quality" of the experience or trip.

Classical hallucinogenic agents can be broadly

sub-divided into two groups: indolylalkylamines and phenylalkylamines. Both classes share structural similarity to the neurotransmitter serotonin (5-HT). Structural features such as the indolethyl nucleus of LSD and psilocybin and the phenethylamine nucleus of mescaline and ecstasy (MDMA) are depicted in Figure 1. The potency and effects of LSD are compared with those of other psychoactive substances in Table 1.

Pharmacodynamics

LSD modifies serotonin neurotransmission; its interaction with this family of 5-HT receptors is complex. The exact mode of action that accounts for the peripheral, cognitive, and affective distortions remains unknown. The cross-tolerance that exists among LSD, psilocybin, and mescaline suggests that their modes of action are related. There is a good correlation between hallucinogenic activity and the affinity of both indolylalkylamines and phenylalkylamines for 5-HT₂ receptors. Large numbers of these receptors are found in the noradrenergic locus coeruleus and the cerebral cortex, accounting in part for the prominent perceptual and cognitive effects of the drug. LSD exerts a selective inhibitory effect on the brain's raphe system by cessation of the spontaneous firing of serotonin-containing neurons of the dorsal and raphe nuclei. Glutamatergic transmission in the cerebral cortex may also play an important role in the psychomimetic effects of the drug.

Selective 5-HT₂ antagonists may prove useful in the treatment of adverse reactions or "bad trips." Although not yet approved by the Food and Drug Administration for this purpose, cyproheptadine, clozapine, and risperidone may become valuable for combating unpleasant electrophysiological and behavioral effects of LSD.

Pharmacology and toxicology

LSD is readily absorbed after oral administration, after which it undergoes rapid and extensive biotransformation in the liver to inactive metabolites. Less than 1% of LSD is eliminated unchanged in urine ($T_{1/2}$ 3–4 hours). N-Demethylation, N-de-ethylation, aromatic hydroxylation, and oxidation in the 2-position have been reported. As a result of the low dose of drug and rapid biotransformation, concentrations of LSD in biological fluids are typically in the low- to sub-ng/mL range, which poses a considerable analytical challenge. More than 80% of the drug is bound to plasma proteins, and the volume of distribution is low (0.28 L/kg).

Despite its potent hallucinogenic activity, LSD has surprisingly low acute toxicity. A fatal dose is estimated to be approximately 0.2 mg/kg, which is equivalent to about 140 normal street doses in an average male. Plasma concentrations in excess of 1 ng/mL have been associated with toxic effects, although doses up to 10 mg have been administered with complete recovery. Only one death has been

Figure 1. Structural Similarities Among Hallucinogens of the Indolylalkylamine and Phenylalkylamine Types

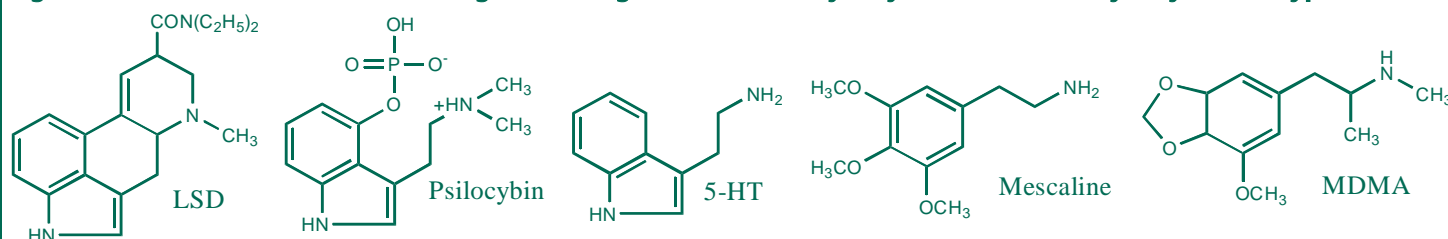


Table 1. Common Hallucinogens and their Properties

Drug	Classification	Source	Route	Typical dose	Duration of effect
LSD	Indolylalkylamine	Semi-synthetic (from <i>Claviceps purpurea</i>)	Oral	100 µg	6–12 hours
Psilocybin	Indolylalkylamine	Mushroom <i>Psilocybe</i>	Oral	4–6 mg (5–10 g dried mushrooms)	4–6 hours
Mescaline	Phenylalkylamine	Peyote cactus <i>Lophophora williamsii</i>	Oral	200–400 mg (4–6 cactus buttons)	10–12 hours
MDMA	Phenylalkylamine	Synthetic	Oral	80–150 mg	4–6 hours

directly attributed to acute LSD toxicity. Most LSD-related fatalities are the result of suicide or accidents while under the influence. According to the 1998 year-end report from the Drug Abuse Warning Network, the total number of emergency department mentions of LSD increased 30% from 3,846 in 1991 to 4,982 in 1998.

Peak effects of LSD are observed within 30 to 90 minutes, declining after four to six hours. Users often report altered perception, distortions in body image, and depersonalization. Symptoms can progress to sympathomimetic, parasymphomimetic, and neuromuscular effects. Pharmacologic and behavioral effects are summarized in Table 2.

Adverse multiple drug interactions have been reported. Risk of seizure increases when LSD is used in combination with fluoxetine and lithium. Selective serotonin re-uptake inhibitors are also reported to increase the likelihood of flashbacks or hallucinatory episodes.

Flashbacks and perception disorder

A flashback is a transitory or episodic recurrence of imagery long after the acute effects of the drug have worn off. Post-hallucinogen perception disorder is a condition involving persistent recurrence of this imagery. The etiology of each phenomenon is unknown. Post-hallucinogen perception disorder, which has been reported after one-time use, can produce extreme anxiety, panic, phobia, and depression.

Table 2. Pharmacologic and Behavioral Effects of LSD

Physiological

Lacrimation, tremor, mydriasis, dizziness, headache, ataxia, hypertension, tachycardia, vomiting, hyperthermia, numbness, piloerection, paralysis, hyperglycemia

Psychological

Restlessness, anxiety, panic, depression, paranoia, perceptual distortions, delusions, hallucinations, visual illusions

Psychiatric

Flashbacks, exacerbation of pre-existing psychiatric illness, post-hallucinogen perceptual disorder, prolonged psychotic reactions, behavior-induced trauma

Tolerance and withdrawal

There are no withdrawal effects associated with LSD, although tolerance develops rapidly following three or four daily doses. Doses as high as 800 μg can be taken by a tolerant user. Tolerance disappears about four days following cessation of drug use.

Treatment

In an emergency room setting, LSD intoxication can be difficult to differentiate from stimulant drug overdose or psychosis. Distinguishing among hallucinogens is particularly difficult because many psychedelic drugs produce similar symptoms and there is no rapid screening test. Therefore, diagnosis of LSD intoxication is often based on clinical signs. Toxicological analysis can confirm the presence of LSD, but results are seldom available within the time frame of the intoxication.

Overdoses or "bad trips" are treated conservatively in a medical setting, due to the relatively low toxicity of the drug. Supportive care, reassurance, and reduction of sensory stimuli are commonly used. Relaxation or "talking down" may be used in combination with a sedative drug such as diazepam.

Drug-induced psychotic reactions or personality disorganization can be prolonged and severe. Antipsychotic medications such as haloperidol may be required together with either residential care or outpatient counseling. Concurrent use of LSD and phenothiazines should be avoided due to reduced seizure threshold and increased extrapyramidal side effects. A combination of psychotherapy, anxiolytics, and neuroleptic drugs are used for the management of flashbacks and post-hallucinogen perception disorder.

SUGGESTED READING

1. Baselt RC, ed. Disposition of toxic drugs and chemicals in man, 5th ed. Foster City, California: Chemical Toxicology Institute, 2000.
2. Ellenhorn MJ. Ellenhorn's medical toxicology: diagnosis and treatment of human poisoning, 2nd ed. Baltimore, Maryland: Williams and Wilkins, 1997.
3. Jenkins AJ. Hallucinogens. In: Levine B, ed. Principles of forensic toxicology. Washington: AACC Press, 1999:286-308.

Sarah Kerrigan, PhD, is a forensic toxicologist at the California Department of Justice, Bureau of Forensic Services Toxicology Laboratory, in Sacramento and a member of the editorial board of Clinical and Forensic Toxicology News.

Immunoassay Interferences

Continued from page 1

enzyme test for urinary alcohol would be a positive for alcohol due to the interference by endogenously secreted glucose that was subsequently fermented to ethanol. For this reason, many laboratories that perform urine ethanol enzyme assays perform a glucose assay, a yeast assay, or both on any specimens positive for ethanol.

Protein in urine specimens has been shown to produce false-positive results. For example, post-mortem urine specimens from decedents with proteinuria and lactic aciduria produced false-positive results when tested by the EMIT drugs-of-abuse assays. The false-positive results were shown to be caused by the presence of lactate dehydrogenase, lactate, and protein (3).

Blood or leukocytes in urine could also bind drugs and perhaps lead to false-positive results. Blood or leukocytes could also interfere with the detection step by adding color. Both bilirubin and urobilinogen have chromophoric traits that could produce false-positive results by interfering with the detection step.

Bacteria and fungi in a urine specimen can present a potential for interference, especially in specimens stored for an extended time at room temperature. Just as yeast can use glucose as a substrate to produce ethanol in a stored specimen, other fungi or bacteria can use other substrates to continue their metabolic pathways.

Many such organisms produce acidic metabolic by-products that can interfere with immunoassays by altering the urinary pH. Most manufacturers of drug immunoassays specify that urine pH must be within a given range to obtain correct results. For example, EMIT's manufacturer specifies that urine specimens should be in the pH range of 5–8; specimens outside this range should be adjusted with either 1 mol/L HCl or 1 mol/L NaOH before the assay is run.

Urinary pH is typically between 5–6 but can be altered in pathological states or by the ingestion of various foods. Cranberry juice, for example, contains enough benzoic acid to produce a decidedly acidic urine specimen. Alterations of the urine pH outside the manufacturer's specified limits could result in a false-negative result.

Exogenous interferences

Most manufacturers of enzyme assays and immunoassays provide an extensive list of drugs that have been evaluated for cross-reaction to the

antibodies in their products. Such a list is always a starting point for an investigation if one suspects a drug-related cross-reaction has caused a false-positive result. However, it should be remembered that the manufacturer has probably evaluated parent drugs but not their metabolites. Depending upon the phenotypic characteristics of the person being tested, little or none of the parent drug may be excreted into the urine. Therefore, the manufacturer's list may not be a comprehensive tool for determining whether a cross-reaction has occurred. For this reason, reports are constantly being published in the literature suggesting that various drugs and/or their metabolites have caused an interference with an enzyme assay or immunoassay. Table 2 is a compilation of interferences found by searching MedLine using the combined key words "immunoassay" and "interference."

Herbal products and natural pharmaceuticals are now being widely promoted for their health benefits. The effect that these products, often prepared by crude methods, will have on drug tests is not yet fully known. Street lore and now the Internet have promoted the use of many herbal products to interfere with drug tests. Scientific studies to

Table 2. Drug Interferences in Urine Immunoassays Reported via MedLine Since 1990

Drug Test	Interfering Drug (type of therapeutic action)
LSD	Ambroxol (mucolytic)
Opiates	Rifampicin (antibiotic) Ofloxacin (quinolone antibiotic) Perazine (antipsychotic) Tolmetin (anti-inflammatory)
Amphetamines	Buflomedil (vasodilator) Perazine (antipsychotic) Chlorpromazine metabolites (psychotropic) Several other psychotropics Tolmetin (anti-inflammatory) Bupropion (antidepressant)
Cannabinoids	Tolmetin (anti-inflammatory)
Benzodiazepines	Tolmetin, fenoprofen, flurbiprofen, indomethacin, ketoprofen (anti-inflammatories) Oxaprozin (anti-inflammatory)
Cocaine metabolite	Salicylic acid (aspirin metabolite)

For specific references related to this table, contact Joanna Grimes at AACC by e-mail <jgrimes@aacc.org>; by phone, 202-835-8740 or 800-892-1400; or by fax, 202-833-4568.

validate such claimed interferences have not been widely performed and because of the proliferation of such products, the scientific community cannot claim knowledge of their effects.

One study evaluated the *in vitro* effects of 50 herbal drinks added directly to samples tested by fluorescence polarization immunoassay and thin-layer chromatography assays (4). This limited study demonstrated no effect of the various products on the tests. However, the diuretic effect of such products along with the copious amounts of water that some suggest be ingested with such products may dilute the drug in urine below a screening cutoff. Also, this *in vitro* study did not examine any potential interference metabolites that might be produced by *in vivo* use of such herbal products.

Diet and dietary supplements may produce interferences in two potential ways. First, consumption of large quantities of some foods may alter the urinary pH. The acidic effects of cranberry juice were noted above. Another example would be meat products, which can result in urinary excretion of large quantities of purines and pyrimidines that make the pH more basic. Second, some spices and food additives impart color to urine. Some vitamins can also affect the color of specimens collected within eight hours of a large dose. Because most enzyme assays and immunoassays depend on spectrophotometric or visual color detection, the potential for false-positive results exists. This potential has not been widely appreciated or studied.

Adulteration interference

From the earliest days of workplace drug testing, some test subjects have attempted to produce false-negative results by adding various substances to their urine specimens. One of the first things test program administrators learned was the need to exclude a source of water and liquid soap from the collection site to prevent dilution of the specimen. Then temperature strips were added to collection cups to prevent the substitution of someone else's urine.

Over the years, people have adulterated urine specimens with virtually every type of household product. Two of the most commonly used products are bleach and drain cleaners. Bleach both alters the urine pH and has the potential to oxidize some drugs. Drain cleaners make the urine decidedly basic. Common table salts, both sodium and potassium chloride, can affect the antibody binding characteristics to produce a false-negative result.

More recently, there have been reports of test subjects placing sodium nitrite crystals under their

fingernails and stirring the specimens with their fingers to dissolve the crystals. Nitrites could produce false-negative results by oxidizing any drugs present.

Internet sales of products to provide a negative test proliferate on a nearly daily basis. To keep abreast of such products and the claims for them, laboratorians can use the key words "urine test" in any Internet search engine to access these sites. While most of these products were designed to interfere with the initial screening test, some are designed to interfere with the GC-MS confirmation test. Most of those designed to interfere with the screening tests simply alter the urine pH. One study found that adulterated urine specimens would produce false-negative results in fluorescence polarization immunoassays for most drugs of abuse (5).

One other type of potential adulterant that might have some limited use has been reported (6). In this study, excess antibody used to assay for cocaine metabolite was added to urine specimens containing benzoylecgonine. Those specimens then tested negative for cocaine metabolite. The authors speculated that because no adulteration test is performed for drug-specific antibody this finding might have implications for a forensic drug-testing program. The likelihood of drug-specific antibody getting into the commercial adulteration market is remote but possible in a profit-driven Internet market.

Conclusion

Both false-negative and false-positive results are to be expected with urine enzyme assays and immunoassays. One reason such results are to be expected is the competitive-binding basis of the assays; that is, many endogenous and exogenous substances can affect the competition for the enzyme or antibody binding sites. Another reason is the detection methodologies used in the tests are susceptible to variations due to chromophoric endogenous and exogenous substances. In clinical settings, most erroneous results in enzyme assays and immunoassays are caused by interferences from disease processes or therapeutic drugs. In the drugs-of-abuse applications of these assays, interferences may also come from deliberate adulteration of the specimen.

REFERENCES

1. Alexander WD, Wills PD, Eldred N. Urinary ethanol and diabetes mellitus. *Diab Med* 1988;5:463-4.
2. Saady JJ, Poklis A, Dalton HP. Production of urinary ethanol after sample collection. *J Forensic Sci* 1993;38:1467-71.

3. Sloop G, Hall M, Simmons GT, Robinson CA. False-positive postmortem EMIT drugs-of-abuse assay due to lactate dehydrogenase and lactate in urine. *J Anal Toxicol* 1995;19:554-6.
4. Winek CL, Elzein EO, Wahba WW, Feldman JA. Interference of herbal drinks with urinalysis for drugs of abuse. *J Anal Toxicol* 1993;17: 246-7.
5. Schwarzhoff R, Cody JT. The effects of adulterating agents on FPIA analysis of urine for drugs of abuse. *J Anal Toxicol* 1993;17:14-7.
6. Critchfield GC, Wilkins DG, Loughmiller DL, Davis BW, Rollins DE. Antibody-mediated interference of a homogenous immunoassay. *J Anal Toxicol* 1993;17:69-72.

Jimmie L. Valentine, PhD, is professor of pediatrics and pharmacology at the University of Arkansas for Medical Sciences in Little Rock and a member of the Clinical and Forensic Toxicology News editorial advisory board.

FUDT Program Switches to Two-Year Accreditation Cycle

By Jean L. Tenuta

The College of American Pathologists' Forensic Urine Drug Testing (FUDT) program is changing from a one-year to a two-year accreditation cycle, effective in 2000.

This change is one of several steps taken to ensure timely inspection of laboratories. Last spring, three deputy commissioners were appointed to assist FUDT commissioner Wayne R. Markus in recruiting and assigning inspectors. R. H. Barry Sample handles laboratories in the east region; Michael A. Peat handles the central region; and Arthur M. Zebelman handles the west region.

The deputy commissioners also serve as faculty at one-and-a-half day inspector-training seminars, three of which were scheduled for early 2000. These seminars are designed to give inspectors a better understanding of checklist requirements, thus improving the quality and consistency of inspections and increasing the number of inspectors in the peer-review program.

Inspectors will be required to attend a training session once every three years. All CAP-accredited laboratories are required to supply an inspection team similar in size and expertise to the one required to inspect their own laboratory.

One afternoon of training will be devoted entirely to the Laboratory General checklist, which now is required for every on-site inspection, along

with the Forensic Urine Drug Testing checklist. Laboratories will be required to perform a self-inspection during the years an on-site inspection is not scheduled.

Dr. Markus will determine the laboratories to be inspected in 2000 and 2001 at the time that accreditation is granted. Laboratories that have demonstrated exemplary performance on recent inspections and proficiency testing challenges, that have been in the program for several years, and that have not had a change of scientific director are likely to be inspected in 2001. The FUDT commissioner, however, may mandate an out-of-cycle on-site inspection at any time he deems that such an inspection is necessary.

Jean L. Tenuta, MS, MBA, MT(ASCP)DLM, CLC(AMT), is a technical specialist in laboratory accreditation with the College of American Pathologists.

University of Florida to Offer Forensic Toxicology Certificate

The University of Florida will begin an Internet-based certification program in forensic toxicology in fall 2000. The program, taught by faculty with international reputations in the field of toxicology and forensic science, will be comprised of five three-credit courses designed to meet the needs of today's working professionals.

Program content will focus on general and advanced principles of toxicology, forensic toxicology, and drug metabolism, providing a strong working background in analytical techniques, pharmacokinetics, drug elimination, and toxicology. Novel features include modules in forensic pharmacology, doping control, postmortem toxicology, expert testimony, and QA/QC procedures.

Courses will be delivered via the Internet, allowing individuals to work at their own pace and within their own schedules anywhere in the world. Students can take one or more courses each semester, either as graduate credit or as non-degree continuing education. The whole certification program can be completed in as little as three semesters (12 months).

Students will be assessed by on-line tests and written projects, allowing them to attain certification without attending the University of Florida campus.

For questions or further information, e-mail the program coordinator at dwielbo@ufl.edu; visit the website at <http://grove.ufl.edu/~forensic/>; or call the UF Center for Human and Environmental Toxicology at (352) 392-4700, ext. 5500.

Ask the Experts

Q We recently had a client swear that he is not using illicit substances, yet his urine is positive for benzodiazepines. He is on the following medications: Maxzide, Covera-HS, Combivent inhaler, Avapro, Daypro, Ziagen, and Combivir. Could the metabolites of any of these drugs or combination of drugs cause a false-positive result for benzodiazepines? (Submitted by Beth Hodge, LPN, of the Maryland Division of Parole and Probation in Baltimore.)

Answered by Jimmie L. Valentine

A Most manufacturers of point-of-care devices or immunoassay kits used in drug-abuse testing provide a comprehensive list of drugs that have been found to produce false-positive results. This is a starting point for attempting to explain whether a test result is a false positive. One of the drugs listed as being taken by this client, oxaprozin (trade name Daypro), is known to produce positive benzodiazepine immunoassay results (1, 2).

However, without a confirmatory assay, false-positive results from interferences are hard to document. The people being tested can find out these potential drug interferences as easily as you can, using the Internet. People can claim to have taken a drug known to interfere with the test when in fact they did not. When prescription drugs are involved, the agency administering the test has the right to ask the person to produce proof of the prescription.

In regulated workplace drug testing, the medical review officer performs the role of determining

whether a positive could have been caused by a prescription drug. In addition, regulated workplace drug testing should always include confirmation of positive immunoassay results.

Some programs, such as parole programs, do not routinely include GC-MS confirmation of positive immunoassays. In these situations, I recommend that when a person strongly denies taking a drug that is giving a positive immunoassay result, a confirmation be performed on that sample. In some cases, such as that with oxaprozin, a known interference occurs and the person's account of drugs taken coincides with the result. But the only way to be certain is to perform a confirmatory test. An agency that does not have prescription drug information as well as results from a confirmatory test should not take action based on a positive immunoassay.

REFERENCES

1. Camara PD, Audette L, Velletri K, Breitenbecher P, Rosner M, Griffiths WC. False-positive immunoassay results for urine benzodiazepines in patients receiving oxaprozin (Daypro). *Clin Chem* 1995;41:115-6.
2. Matuch-Hite T, Jones P Jr., Moriarity J. Interference of oxaprozin with benzodiazepines via enzyme immunoassay technique. *J Anal Toxicol* 1995;19:130.

Jimmie L. Valentine, PhD, is professor of pediatrics and pharmacology at the University of Arkansas College of Medicine in Little Rock and a member of the Clinical and Forensic Toxicology News editorial advisory board.

The purpose of *Clinical & Forensic Toxicology News* is to provide practical and timely information on the clinical, forensic, technical, and regulatory issues faced by toxicology laboratories.

Clinical & Forensic Toxicology News is an educational service of the forensic urine drug testing (FUDT) program. The FUDT program, cosponsored by the American Association for Clinical Chemistry and the College of American Pathologists, includes three components: FUDT accreditation, the FUDT proficiency testing survey, and this newsletter. The accreditation program is the responsibility of the CAP. The surveys are sponsored jointly by AACC and CAP. The newsletter is published quarterly by the American Association for Clinical Chemistry, Inc., 2101 L St., N.W., Suite 202, Washington, DC 20037, (800) 892-1400 or (202) 857-0717.

Clinical & Forensic Toxicology News does not accept advertising and is supported solely by its readers. Annual subscription price is \$75. Subscribers are encouraged to reproduce copy with appropriate acknowledgment of source.

Opinions expressed are those of the authors and do

Editorial Advisory Board:

Chair: Bruce A. Goldberger, PhD, University of Florida College of Medicine, Gainesville, FL, bruce-goldberger@ufl.edu

David Armbruster, PhD, Abbott Laboratories, Irving, TX, david.armbruster@abbott.com

Robert L. Fitzgerald, PhD, VA Medical Center, San Diego, CA, rfitzgerald@vapop.ucsd.edu

Donald Frederick, PhD, East Peoria, IL, dfrederick@ptpg.com

Sarah Kerrigan, PhD, California Department of Justice, Sacramento, CA, kerrigas@hcdcojnet.state.ca.us

Mark Linder, PhD, University of Louisville, Louisville, KY, mwlind01@gwise.louisville.edu

Jimmie L. Valentine, PhD, University of Arkansas College of Medicine, Little Rock, AR, ValentineJimmieL@exchange.uams.edu

Editorial Consultant: Eric Seaborg