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TOXICOLOGY SCREENING: A REVIEW

by Aaron Cooper, PharmD

Soucre: QuickMedical

Introduction

Toxicology screening is a tool frequently used in the initial evaluation of poisoned patients. It is also commonly used in the community setting by employers and in court-mandated drug testing programs. At-home test kits have become increasingly popular, further underscoring the need for all healthcare practitioners to be cognizant of toxicology screen methodology and interpretation considerations. In an acute overdose, the results of preliminary screens may be used to reconcile a patient's presenting symptoms or toxidrome with available exposure history. This rarely alters the management of the patient, but when patients withhold exposure information for fear of consequences, in a show of defiance, or because of CNS depression, toxicology screens can prove valuable.

A common pitfall involves placing undue emphasis on toxicology screen results without considering the limitations of the information they convey. Appreciation of the significance of toxicology screen results, including knowing when to interpret a positive or negative result with caution is important.

Terminology

Sensitivity of a test is the probability that it will accurately detect the specified drug or substance when it is truly present at a specified concentration (i.e., 100% sensitivity accurately identifies all samples within testing limits that contain the targeted substance). Highly sensitive tests have a low false negative rate. **Specificity** is the probability that a test will not detect the drug or substance when it is truly absent or below a specified concentration (i.e., 100% specificity accurately identifies all samples that do not contain the targeted substance). Tests with high specificity are associated with a low false-positive rate and are typically used to rule-in a diagnosis. A **false-positive** result is the detection of the targeted drug or substance which is absent or at concentrations below the assay cutoff. A **false-negative** result is the lack of detection of a substance where the substance is present above the appropriate assay cutoffs or has been diluted below the cutoff concentration by an adulterant. **Screening tests** are used to detect the presence of drugs or drug classes, generally by using immunoassay techniques. They are usually qualitative, although quantitative assays are available for some substances such as acetaminophen and salicylate. Confirmation tests generally have a high degree of specificity.

Toxicology Testing Methodology

Urine and blood screens are used to test for the presence of both legal

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POISON PEARL

GHB, GBL, 1,4B

Mike Mallin, MD
Emergency Medicine Resident

Gamma-hydroxybutyric acid (GHB) entered the street drug market as a supplement for body-builders in the late 1980s and its sale and manufacturing were banned in 1990. GHB and its precursors gamma butyrolactone (GBL and 1,4-butanediol (1,4B) arrived on "club drug" scene and in dietary supplements (GBL and 1,4B) in the mid 1990's. GHB was sold over the internet and recipes for home manufacture of GHB were also available on the internet. Overdoses poured into emergency departments across the country, until the federal government made GHB a Schedule I substance in 2000. Some states also banned the precursors.

Toxicity of GHB, GBL, and 1,4B includes CNS depression, amnesia, euphoria, coma, hypotonia, bradycardia, Cheyne-Stokes respiration, nausea, and vomiting, ataxia, urinary incontinence or urgency, seizure-like activity, and hypothermia. Patients are often obtunded and may need intubation for airway protection. Patients often awaken abruptly and are agitated. Bradycardia is typically responsive to atropine. Antidotes such as naloxone, flumazenil, and physostigmine are not effective for reversal of CNS depression. In addition, physostigmine may worsen bradycardia. Treatment remains supportive.(1)

Diagnosis of GHB or precursor ingestion is difficult

(cont. on pg. 3)

POISON PREVENTION PACKAGING ACT

What is a child-resistant package?

It is a package that is significantly difficult for young children to open. The rule states that no more than 20 of 100 children aged 4 years and under should be able to open the container within 10 minutes. Child-resistant does not mean "childproof". Most children can eventually open these containers. It also states that 90% of adult panelists, aged 50-70, must be able to open the container within 5 minutes on the first try and in 1 minute on subsequent attempts.

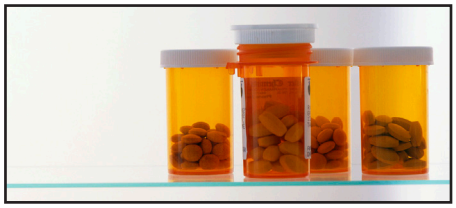
Did you know that the Poison Prevention Packaging Act (PPPA) of 1970 requires certain products to be packaged in child-resistant packaging?

The purpose is to protect children under five years old from poisonings and deaths that occur when they open containers of hazardous products, and eat or drink the contents. The current law incorporates numerous amendments to the original Act. While the original closures kept children out, many older people had so much trouble opening them they either left the caps off or put their medication in non-child resistant containers, posing more of a danger.

What products require child-resistant packaging?

Specific products customarily used in and around the home that require this special packaging include:

- Chemical and cosmetic products such as furniture polish, lighter fluid, lamp oil, paint solvents, methyl alcohol, ethylene glycol, home permanent wave neutralizers
- Mouthwash with >3 grams of ethanol per bottle
- Drugs and dietary supplements such as aspirin, acetaminophen, prescription drugs, products with >250 mg of iron, products with >5 mg lidocaine, and many over-the-counter medicines.



Research has shown that child-resistant packaging has markedly reduced pediatric poisonings and subsequent fatalities. As amendments have been made to the original PPPA, child-resistant containers still remain an effective method to protect children, while increasing the ease with which older adults can access medications. To access further details, visit: http://www.cpsc.gov/BUSINFO/pppainfo.html.

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Toxicology Screening: A Review

and illicit substances. Urine is the most popular medium to screen for drugs of abuse. Urine screening is only valuable for drugs that are excreted either changed (metabolites and conjugates) or unchanged in the urine. It is time dependent according to the amount of time it takes for the targeted substance to be present in the urine at detectable concentrations. Blood (serum) is used most often for quantitative screening of substances where a concentration may be useful in management of the patient, such as salicylate, acetaminophen and ethylene glycol. Confirmatory testing utilizes blood and urine, as well as many other biological fluids and tissues. The choice of the sample type depends on the type of testing needed (clinical or forensic); what the targeted substance is and its duration and detectability in the sample type.

Historically, thin layer chromatography (TLC) was used to screen for the presence of toxic substances in the urine. Its advantages include the ability to screen for multiple substances and their metabolites simultaneously utilizing a series of detection techniques. However, TLC has limitations in an acute care situation because it can usually only detect substances in high concentrations, requires hours to process and interpretation is dependent on the experience of the laboratory professional.

Current testing methods utilize immunoassay and other technologies that provide greater sensitivity and specificity and easier interpretation. Enzyme multiplied immunoassay technique (EMIT), fluorescent polarization immunoassay (FPIA), radioimmunoassay (RIA), and latex agglutination immunoassay (LAI) techniques use polyclonal and monoclonal antibodies to detect the presence of targeted substances. Polyclonal antibodies have lower specificity, can detect more drug substances and have more cross-reactivity with metabolites resulting in false positive results. Polyclonal antibodies are used mostly in drug class assays, whereas monoclonal antibodies are use in specific assays. Monoclonal antibodies detect fewer drugs resulting in higher specificity for the substance of choice. The sensitivity of the assays is dependant on the antibody and its ability to accurately detect low concentrations resulting in varying lower end cutoffs for individual assays. Immunoassay screens offer the benefit of a rapid and reproducible result and simplified interpretation. All STAT urine and serum drug screens and most therapeutic drug monitoring performed onsite in Utah hospitals utilize immunoassay technology.

Confirmation assays verify positive screening results and use a variety of chromatographic techniques that use many types of instruments and detectors. Confirmation techniques are more expensive because they are more labor intensive with higher instrumentation costs. Generally, the turn-around-time for a result is longer due to extensive sample preparation when compared with immunoassay techniques. Therefore, confirmation results are not usually received in time in order to affect patient care in acute situations. Most hospitals in Utah do not have the capability to confirm their positive screen results resulting in the transfer of the specimen to a regional specialty laboratory for processing. Rarely are positive screening tests confirmed in the hospital setting, with the exception of child endangerment situations.

Interpreting Results—Proceed With Caution

False-positive results are more likely to occur with screening tests that don't have a high degree of specificity. False-negative results are most commonly seen with toxicology screens that don't have a high degree of sensitivity or if an adulterant is present in the sample. A common cause of a false positive *(cont. on pg. 3)*

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Toxicology Screening: A Review

toxicology screen following an overdose is the presence of substance(s) that cross-reacts with the monoclonal or polyclonal antibodies. A positive or negative drug screen may seem like reliable information, however, a positive drug of abuse screen does not tell you specifics of when, what, and how much drug was ingested. Most drugs of abuse are detectable for 1 – 2 days in the urine and chronic use of benzodiazepines remain detectable for 30 days. (1) In addition, a positive drug screen cannot differentiate the pattern of use (chronic abuser vs. experimenter vs. therapeutic user).

Similarly, a negative result must be interpreted in the context of time sensitivity. For instance, an abuser of controlled substance may test negative if it has been more than two days since their last use. A negative screen may also result when the concentration present in the patient is below the threshold for detection of the assay or if an adulterant is present. For tests used in the Emergency Department, the threshold may be set to detect an overdose and not therapeutic use. This varies by manufacturer and medical institution. Some hospitals in Utah use urine screening tests that detect therapeutic concentrations of benzodiazepines. Others use tests that require high concentrations and usually only detect the older benzodiazepines like diazepam. In addition, many drugs are not detectable on toxicology screens, such as cardiovascular drugs. Determining the presence of opioids and amphetamines can be difficult. Opioid class screens are susceptible to false-positive results due to numerous sources of cross-reactivity. Opioids are also susceptible to false-negative results. For instance, a recent study on substance abuse showed that 63% of GC-MS confirmed opioid-positive participants had tested negative with an initial urine toxicology screen.(2) Another important consideration in result interpretation is the possibility of legal use of medications. In the above cited study, 91% of positive amphetamine class screens verified by GC-MS were explained by legal use of prescription amphetamines and over-the-counter cold medications. There are immunoassays specific for methamphetamine that will not cross-react with OTC stimulant amines.

(cont. from pg. 1)

GHB, GBL, 1,4B

as there is no readily available laboratory test. In the past several years, very few cases involving GHB have been reported to Utah Poison Control Center. However, since GHB is now Schedule 1, an alternative is to make the GHB at home or to take a precursor. Some consider 1,4B the new GHB. It is metabolized by alcohol dehydrogenase in the liver to GHB. The onset of effects is delayed by its metabolism to GHB, but it eventually creates similar symptoms and effects as GHB. Currently 1,4B is not federally controlled and is only scheduled in 5 states. It is legal in Utah and readily available over the Internet.

Reference

1. Shannon M, Quang LS. Gamma-hydroxybutyrate, gamma-butyrolactone, and 1,4-butanediol: a case report and review of the literature. Pediatr Emerg Care. 2000;16(6):435-40.

Table 1. Common Agents Contributing to a False-Positive Immunoassay Screen[1]

Substance tested via immunoassay	Potential agents causing false-positive result
Amphetamines	Bupropion Chlorpromazine Desipramine Ephedrine Labetalol MDMA Phentermine Phenylephrine Promethazine Pseudoephedrine Ranitidine Trazodone
Benzodiazepines	Sertraline
Cannabinoids	NSAIDs Proton pump inhibitor
Methadone	Diphenhydramine Verapamil and metabolites
Opiates & Opioids	Dextromethorphan Poppy seeds Quinolones Rifampin
Phencyclidine	Dextromethorphan Diphenhydramine Doxylamine Ibuprofen Imipramine Ketamine Tramadol Venlafaxine
Tricyclic Antidepressants	Carbamazepine Chlorpromazine Cyclobenzaprine Diphenhydramine Promethazine Quetiapine

Cross Reacting Substances

Decades of drug screen usage have produced lengthy lists of substances that have the potential to cross-react with commercial immunoassays. (Table 1) The potential for a substance to cross-react varies based on the manufacturer design of the screen, the specificity and sensitivity of the antibody, the concentration of the *(cont. on pg. 4)*

ACTIVATED CHARCOAL

Matt Dawson, MD
Emergency Medicine Resident

Activated charcoal has been used since 1550 BC by the ancient Egyptians. However, even after 3500 years of experience and multiple studies, there still not a definitive answer to if and when to administer activated charcoal.

One of the problems with determining "does charcoal improve patient outcomes" is that it has been considered the standard of care for so long that most studies focus on how it compares to other decontamination strategies. One area where there is some good evidence for treatment is acetaminophen poisoning. Buckley and collegues[1] showed that by giving activated charcoal you can reduce the need for acetylcysteine therapy and subsequent hospital admission. Other than this study, the evidence for improved outcomes is lacking.

There are reasons to not give charcoal as there are rare reports of pulmonary aspiration and death from charcoal administration. Patients unable to protect their airway, with potential GI perforation (e.g., caustics), or when the drug is known not to bind to charcoal (e.g. iron, lithium) should not receive charcoal.

The American Academy of Clinical Toxicology[2] recommends that charcoal not be administered "routinely" in the management of poisoned patients. It can be considered for patients that present less than 1 hour after exposure or perhaps longer in patients ingesting drugs with delayed absorption (e.g., aspirin, anticonvulsants).

Soucre: Paddock Laboratories, Inc.

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1. Buckley NA, Whyte IM, O'Connell DL, Dawson AH, Activated charcoal reduces the need for N-acetylcysteine treatment after acetaminophen (paracetamol) overdose. J Toxicol Clin Toxicol. 1999;37(6):753-7

2. Chyka PA, Seger D. Position statement: single-dose activated charcoal. American Academy of Clinical Toxicology; European Association of Poisons Centres and Clinical Toxicologists. J Toxicol Clin Toxicol. 1997;35(7):721-41.

(cont. from pg. 3)

potential cross-reacting substance and the chemical similarity of the cross reacting substance to the target. Cross-reactions occur with varying degrees of predictability. For example, high doses of diphenhydramine cross-react to produce a false-positive TCA screen with certain screening tests. Thus, a positive TCA level can be often be discounted in cases of known diphenhydramine overdose. Other cross-reactants trigger false-positives with such rarity that the positive result is discounted only after searching literature for a few case studies.

Cross-reactions are often explained by two substances having similar chemical structures (i.e., quetiapine and tricyclic antidepressant assays).(3)

Conclusion

Drug screen results can be a useful source of information in the evaluation of a potentially toxic patient when the patient is unable to provide an accurate history. When deciding on treatments for a toxic or poisoned patient, it is important to pay the most attention to the patient's signs and symptoms, and use drug screen results as supplementary information. Understanding the strengths and limitations of different screening methods and possible cross-reacting substances will help clinicians accurately interpret test results and appropriately treat the patient.

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2. Levy S, et al. Results of Random Drug Testing in an Adolescent Substance Abuse Program. Pediatrics 2007;119(4):e843-e848.
3. Caravati EM, et al. Quetiapine Cross-Reactivity With Plasma Tricyclic-Antidepressant Immunoassays. Ann Pharmacother 2005;39:1446-1449.

MEET THE UPCC STAFF

KAREN THOMAS, PHARMD

started at the Utah Poison Control Center in 2006 as a pharmacy student intern. Karen graduated from the University of Utah with her B.S. in Chemistry in 2004 and her PharmD in 2008. People are truly concerned when they call a poison center, and Karen loves the fact that you can generally spend less than 5 minutes on the phone and put all of those worries to rest. Karen had the unique opportunity to pursue a PhD in Pharmacology and Toxicology concurrently with her PharmD and hopes to wrap up her thesis research within the next year. When Karen is not at work or school, she enjoys spending time with her husband, cooking, and backyard bird watching with her cats. Karen's favorite poison topics include venomous animals and toxic alcohols.

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