Rational use of toxicology testing in children
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The majority of all patients with poison exposures in the United States are children. The evaluation and management of poisoned patients may be aided by the use of laboratory assays, ranging from basic assessments not uniquely indicated for the poisoned patient to highly sophisticated laboratory tests with very specific indications. Literature concerning poisoning in pregnant patients is evaluated and recommendations regarding the utility of pregnancy testing in poisoned females are discussed. Recent studies evaluating the use of toxicology testing in pediatrics have concluded that the use of comprehensive toxicology screening in pediatric patients is costly and does not affect the medical management of most poisoned patients. The utility of focused quantitative serum assays to determine serum levels of particular poisons is reviewed. Toxicology tests used for detection of drugs of abuse, with a particular focus on the capabilities and limitations of such tests, are discussed. The potential pitfalls that occur when toxicology tests are obtained indiscriminately, are misapplied, or are misunderstood are analyzed. Hair sampling as nonemergent toxicology testing for drugs of abuse is discussed. Curr Opin Pediatr 2001, 13:183–188 © 2001 Lippincott Williams & Wilkins, Inc.

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Abbreviation
TS toxicology screening

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Most patients with poison exposures in the United States are children. Toxicology testing may be a necessary or adjunctive component of management of a child with a suspected or known poisonous exposure. This review examines laboratory testing for suspected or known cases of poisoning in children. The laboratory tests available, the indications for such tests, situations in which they are helpful, and their limitations and pitfalls are discussed in this article. Conclusions are drawn regarding the rational use of laboratory testing for poisoned children.

Initial evaluation and adjunctive investigations in the poisoned patient

In the poisoned patient, after appropriate initial stabilization, there may be a role for laboratory testing. The most crucial initial laboratory investigations are basic assessments not uniquely indicated for the poisoned patient (Table 1). A poison control center should be contacted in all cases of poisoning, for consultation regarding management and to assist in the maintenance of vital epidemiologic data.

The most generally indicated laboratory test for such patients is determination of their blood glucose level. Of the deleterious effects of poisons, hypoglycemia is the most easily detected and treatable. Any patient with altered mental status or the potential to develop hypoglycemia from a poisoning should have a bedside blood glucose assessment.

An electrocardiogram is indicated for any patient potentially poisoned with a substance capable of inducing cardiac dysrhythmia, any patient with an intentional overdose taken with intent of self-harm, and any unresponsive patient. Several poisons cause recognizable electrocardiogram changes that may aid in diagnosis and management. These include tricyclic antidepressants, phenothiazines, antidysrhythmics, calcium channel antagonists, β-blockers, digoxin, and lithium.

Pulse oximetry is indicated for any poisoned patient with altered mental status or exposure to poisons capable of producing respiratory compromise or metabolic compromise of oxygen-carrying capacity, such as methemoglobinemia. Hemoglobin co-oximetry can quantify concentrations of carboxyhemoglobin, methemoglobin, and sulfhemoglobin.

Serum chemistry tests with resultant calculation of an anion gap and blood gas assessment can be used in cases
of poisonings by unknown agents or poisoning with agents known to cause a high anion gap metabolic acido-
sis. These "MUDPILES" poisons include salicylates,
ethanol, ethylene glycol, methanol, isoniazid, and iron.
Measuring the serum osmolality can be used to calculate
the osmolality gap when considering the possibility of a
toxic alcohol ingestion. (Osmolality Gap =
Osmolality_{measured} - Osmolality_{calculated}).

Quantification of acetaminophen concentration as well
as focused toxicology laboratory testing may also be
indicated. Several recent publications presented possi-
bile alternatives to the standard practice of assessing
the serum acetaminophen concentrations of patients
with potential acetaminophen ingestions [1–3]. No alter-
native method of evaluation of such cases has been
demonstrated to be safe and effective. Determination
of the serum acetaminophen concentration with subse-
quent plotting on the Rumack-Matthew nomogram
should still be a routine step in the assessment of any
polydrug ingestion or ingestion with intent for self-
harms, as acetaminophen is a common coingestant.

Pregnancy testing of the poisoned patient
For females of childbearing age who present after self-
poisoning, determination of pregnancy status is a wide-
spread practice. This is often done in an attempt to iden-
tify unwanted pregnancy as a potential motive for the
attempted self-harm or with the notion that stresses of
pregnancy increase the likelihood of attempting self-harm.

The literature suggests that pregnant women are not
more likely to attempt self-harm by poisoning and, in
fact, are probably less likely to do so. The largest
published study of the timing and consequences of
suicide attempts in women clearly refutes myths regard-
ing pregnancy and poisoning. Specifically, an 8-year
prospective study by Czeizel et al. [4•] reports that of
22,969 females aged 16 to 50 years hospitalized after
attempted suicide by self-poisoning, only 2.8% of
women were pregnant, and only 0.0004% had an unrec-
nognized pregnancy. A prospective study by Perrone
and Hoffman [5] of women aged 12 to 30 years having
taken an intentional overdose reports that 11.6% are pregnant,
which is statistically equivalent to the percentage of all
females presenting for care. Epidemiologic data by
Weiss [6] regarding pregnancy-associated hospitaliza-
tions in Pennsylvania demonstrated poisoning as the
most common reason for injury-associated hospitaliza-
tion in all women aged 15 to 44 years, constituting
32.6% of hospital admissions. For pregnant patients,
only 16% of such admissions resulted from poisonings.

Clear indications for pregnancy testing in the poisoned
patient are cases that will be managed uniquely or
differently in a pregnant patient. These include
exposure to poisons that are managed differently in a preg-
nant versus non-pregnant patient, such as carbon
monoxide or methotrexate, and exposures that would
warrant counseling regarding fetal loss or malforma-
tion, such as hormones, retinoids, antineoplastic
agents, anticonvulsants, and coumarins. Performing a
pregnancy test on an adolescent female requires her
consent. If obtained, the medical indication or neces-
sity of pregnancy testing should be clearly understood
and documented.

Focused quantitative drug assays
Very precise quantitative assays are used to measure
the concentration of a particular drug. Colloquially
called "levels," they are used to detect a toxic concen-
tration of drug. Substances for which assays are used are
given in Table 2.

Determination of drug levels is the most useful type of
assay used to manage poisoned patients. For many
poisons, the clinical effects and toxicity correlate with
the serum level of drug. In such cases, management is
often dependent on the data provided by quantitative
assays. Examples of specific management interventions
are performing hemodialysis, hemoperfusion, or chela-
tion therapy based on the presence of a toxic serum
concentration of a particular poison.

Toxicology screening of the poisoned patient
Any review of laboratory evaluation of poisoned
patients would be incomplete without a discussion of
toxicology screening (TS). Defining "toxicology
screening" is problematic, because there is no stan-
dard definition of what constitutes TS. Generally
speaking, a "tox screen" usually involves qualitative
detection of specific drugs in the urine or blood, or
both. The term is often used to denote laboratory
detection of several commonly abused drugs or their
metabolites including amphetamines, barbiturates,
benzodiazepines, cocaine, marijuana, opioids, and
phenylcyclidine (Table 3). Some laboratories can
perform highly specific assays for hundreds of drugs
on urine and blood specimens. Which drugs are assayed for varies considerably among health care facilities and may include pharmaceutical drugs as well as abused substances. It is important for the pediatric health care provider to understand what specific testing is done at their facility.

Recent literature has confirmed the conclusions of older literature, which is that neither comprehensive TS nor drug of abuse screening of poisoned patients significantly influences their clinical management. This is not surprising when one understands that these tests are generally incapable of providing useful information for the acute management of a potentially poisoned patient.

In a retrospective study of all comprehensive emergency department TS performed in pediatric patients, 463 cases were reviewed by Belsan and Simon [76]. In this study, TS was comprehensive and tested for more than 350 toxins, including acetaminophen, salicylates, ethanol, drugs of abuse, antidepressants, anticonvulsants, antipsychotics, narcotics, stimulants, antiarrhythmics, anesthetics, antihypertensives, antibiotics, and miscellaneous other toxins. Of 234 positive screening tests, 3% of screening tests (7 of 234) were positive without a documented suspicion of an exposure. These cases involved three antiarrhythmics, one tricyclic antidepressant, and three drugs of abuse. In these cases, detection of these specific drugs did not result in a change in medical management and can be interpreted as not affecting the patient's clinical outcome. The costs of such screening tests—$88,433 total, or $2,315 per patient—seem exorbitant considering that none of this expenditure had an impact on clinical management or outcome.

A second prospective study by Belsan et al. [81] evaluated pediatric patients who presented to the emergency department after suspected drug ingestion. The study relied on treating physicians to document whether the TS affected the patient's management. The specific circumstances of some of these cases are not clear. TS was influential on patient management when it involved quantitative assays such as acetaminophen, salicylates, phenytoin, and carbamazepine. The study concluded that assessment of quantitative serum levels of certain drugs, such as acetaminophen, anticonvulsants, and salicylates, played a role in patient management. Qualitative screening, or the ordering of extensive assessment for the more than 500 other toxins tested for, was not demonstrated to have a similar effect or role in patient management.

Sugarman et al. [91] published a retrospective review of TS obtained on pediatric patients in an emergency department that drew similar conclusions. Unfortunately, this study does not specify what substances were assayed for with TS. Of 338 patients who had TS in a pediatric

Table 2. Useful quantitative drug assays

<table>
<thead>
<tr>
<th>Drug/group</th>
<th>What is detected</th>
<th>False-positive result</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td>Amphetamine</td>
<td>Many cough/cold preparations containing ephedrine, pseudoephedrine, phenylpropanolamine and other similar drugs</td>
<td>Typically may not detect methamphetamine, or MDMA (ecstasy), which are more commonly abused than amphetamine</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>(carbamazepine, phenytoin, valproic acid)</td>
<td>Some NSAIDS</td>
<td>Barbbiturates are infrequently abused by pediatric patients</td>
</tr>
<tr>
<td>Barbbiturates</td>
<td>Barbbiturate</td>
<td>Some NSAIDS</td>
<td>Does not usually detect alprazolam (Xanax), lorazepam (Ativan), or midazolam (Versed)</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Oxazepam, a benzodiazepine metabolite</td>
<td>Some NSAIDS</td>
<td>Very sensitive and specific test</td>
</tr>
<tr>
<td>Cocaine</td>
<td>Benzoylecgonine, a cocaine metabolite</td>
<td>Tea made from coca leaves</td>
<td></td>
</tr>
<tr>
<td>Marijuana</td>
<td>Tetrahydrocannabinol, an active ingredient in marijuana</td>
<td>NSAIDS in the past</td>
<td></td>
</tr>
<tr>
<td>Opioids</td>
<td>Morphone, a metabolite of heroin and many opioids</td>
<td>Poppy seeds, rifapin</td>
<td>Does not detect many synthetic opioids such as fentanyl and meperidine</td>
</tr>
<tr>
<td>Phencyclidine (PCP)</td>
<td>Phencyclidine</td>
<td>Dextromethorphan, diphenhydramine, doxylamine, ketamine</td>
<td></td>
</tr>
</tbody>
</table>

NSAID, nonsteroidal anti-inflammatory drug.
emergency department, 22 patients had an unexpected positive result. Three of these patients had an alteration in medical management based on their unexpected results: One had a focused quantitative serum assay that resulted in a change in medical management; one received medical treatment for tricyclic antidepressant poisoning, which should have been suspected due to wide complex ventricular tachydysrhythmia and seizure; and the third patient received therapy that was probably not indicated, specifically urine alkalization for tricyclic antidepressant exposure without report of tachycardia or prolongation of her QRS interval. The authors’ appropriate conclusions were that comprehensive TS rarely alters the medical management of patients, and physicians should re-evaluate their practice of ordering such tests.

A significant consideration regarding TS involves the use of point-of-care assays. Such tests are typically similar to a urine dipstick, requiring no technical expertise to perform. Although these bedside tests are intended for use by health care providers without specific laboratory training, their use by untrained individuals may give inconsistent and unreliable results [10]. Additionally, many of these bedside tests perform significantly less well than asserted by the manufacturer [11].

An important caveat to the preceding discussion relates to the use of TS in cases of suspected child abuse or neglect. For patients incapable of using drugs of abuse voluntarily (which would now be considered under 8 to 10 years of age) and in cases of malicious poisoning, laboratory assays might be helpful in diagnosing and confirming the medical condition, especially as forensic evidence. In addition, when young children present with altered mental status or change in behavior that cannot be easily explained by the parent or caregiver, this type of TS may be necessary to confirm the suspicion of a malicious exposure. The general admonishment against the use of such laboratory tests does not apply in these instances.

Assays capable of detecting numerous various poisons may seemingly provide a formidable diagnostic armamentarium. There is a tremendous appeal to the idea that TS can allow clinicians to make toxicologic diagnoses. This idea, however, is in part the basis for the widespread misunderstanding of TS, as described subsequently.

**Negative toxicology screening results**

Negative TS results tend to be unhelpful clinically because of the limited capability of screens to detect some drugs and the limited window of time after which exposure to a drug will be detectable by TS. One problem with TS is that many assays do not detect all drugs in their specific class. For example, benzodiazepine screening typically detects oxazepam, which is a common metabolite of most benzodiazepines. However, because use of lorazepam (Ativan, Wyeth-Ayerst Laboratories, Philadelphia, PA) and alprazolam (Xanax, Pharmacia & Upjohn, Kalamazoo, MI) do not result in oxazepam metabolites, exposure to these benzodiazepines will not be detected by most benzodiazepine screening. Amphetamine screening tests may not detect more commonly abused amphetamines such as methamphetamine or MDMA (ecstasy), and opioid screening may not detect synthetic opioids such as methadone or fentanyl. Furthermore, many clinically relevant drugs of abuse, such as gamma hydroxybutyrate (GHB), ketamine, flunitrazepam (Rohypnol), and lysergic acid diethylamide (LSD), are not assayed for by routine drug-of-abuse screening tests.

Any TS assay only reflects the presence or absence of drugs or metabolites at or above a threshold concentration at the time of the assay. It does not exclude the presence of drug or metabolite; it only concludes that the substance assayed was not present in a minimum threshold quantity. This is understood by savvy drug users who know to abstain from using drugs for a particular period of time before submitting a sample for drug testing. In such cases, negative TS may be misinterpreted as meaning that the patient has not used the drugs tested for. A negative result only means that the drug in question has not been used recently enough to cause a positive result. Therefore, a negative result can easily be misinterpreted as meaning that no toxin or drug present, when actually it only means that the particular toxins or metabolites assayed were not detected.

**Positive toxicology screening results**

A major pitfall of positive TS relates to its extreme sensitivity, lack of specificity, and failure to give quantitative information. Due to poor specificity, many substances can cause interference and cross-react with various drug-of-abuse screening assays. Over-the-counter cough and cold preparations are well described as causing positive results for amphetamines and phencyclidine (PCP), coca tea may result in positive cocaine screening test results, and poppy seeds may cause a positive result in screening test for opioids.

Regarding sensitivity of TS, these tests were never intended for use in determining that there is a clinically significant quantity of drug in poisoned patients. Government and industry have established the standards of TS assays for drugs of abuse, for the purposes of detecting casual drug use in employees. From the standpoint of an employer who wants to detect casual drug use, a screening assay should be very sensitive in detecting trace amounts of drugs that may have been used in preceding days. Routinely assayed drugs of abuse,
including amphetamines, benzodiazepines, cocaine, opioids, and phencyclidine, are typically detectable for several days after exposure. Barbiturates, methadone, and marijuana may be detected for much longer periods. Trace amounts of drug will not cause clinically significant symptoms. Qualitative detection without quantitative data may be both unhelpful and misleading when such results are applied clinically.

The most concerning pitfall of TS is the misinterpretation of a positive assay. Altered mental status is often the impetus for clinicians to perform TS. A positive TS assay cannot be used solely to explain altered mental status for several reasons. First, a positive screening result does not confirm that a drug is present in any clinically meaningful quantity. Also, it cannot rule out the existence of other concerning, treatable causes of altered mental status such as intracranial hemorrhage, cerebrovascular accident, meningitis, encephalitis, or a metabolic disturbance. For this reason, the results of drug-of-abuse screening should not prevent the diagnostic evaluation of altered mental status, neurologic abnormality, or another medical disease process. TS cannot be expected to assist in the acute management of patients. The misinterpretation or misapplication of the test results may result in the misdiagnosis of patients. Thus, it is important to consider all possible etiologies of a clinical presentation and to evaluate for those conditions that may require specific interventions and use TS as an adjunctive diagnostic to help confirm a diagnosis.

Considerations of nonemergent use of toxicology screens

The focus of this discussion relates to the use of TS in the urgent or emergent medical care of pediatric patients. For forensic purposes or for the rare instances of nonemergent screening, which is typically drug-of-abuse screening, other methods of TS, particularly hair sampling, may provide relevant information. Hair sampling for TS is an excellent tool because as a hair grows, traces of drugs present in the body at a given time are incorporated into that hair. Thus a hair is essentially a “diary” of drug exposure, providing a chronologic reference correlated with the areas of the hair strand that contain drug. This analysis can differentiate between one-time exposure and repeated drug use. Abstinence from drug use just before to the test, which is the method by which drug users can “pass” urine or blood drug tests, is not an issue when hair is sampled [12*]. Hair testing results are not relevant to the urgent or emergent management of poisoning but can be used to confirm drug exposures for forensic purposes, such as assessing neonates for prenatal exposure to drugs of abuse, for detecting malicious drug exposure, or for determining the extent and duration of drug abuse in the rare instances such testing is indicated.

In this era of increased acknowledgment of patient rights, including the rights of minor patients, TS has many ramifications. As such, obtaining a drug-of-abuse screening assay should be approached with appropriate care and caution. First and foremost, the best interests of the patient as well as the rights of the patient should guide the clinician caring for poisoned patients.

An issue related to drug-of-abuse testing involves the repercussions of testing. Since the social repercussions of positive drug-of-abuse screening are significant, the patient capable of or suspected of voluntarily using substances of abuse has a right to be informed of a clinician’s desire to perform such a test, and assent or consent should be obtained. Any case in which a patient requires urgent or emergent medical care is potentially a situation in which the desire of that patient may be overridden to give the patient life-sparing or life-sustaining care. It would be a particularly exceptional scenario in which drug-of-abuse screening against a patient’s will would be justified under such a clause. The American Academy of Pediatrics’ policy statement clearly iterates that only in exceptional cases should patients be tested unknowingly or against their will [13].

Conclusions

Laboratory testing may aid in the diagnosis and management of poisoned patients. There are no laboratory assays that should be ordered reflexively in every poisoned patient, but rather the indicated tests should be performed based on the type of poisoning and clinical status of the patient. Routine TS, particularly for drugs of abuse, has repeatedly been demonstrated to be unhelpful in the management of poisoned patients. Focused, quantitative assessment of specific poisons such as salicylates, acetaminophen, and anticonvulsants, for which quantitative serum levels assist in management, is the most helpful type of toxicology laboratory testing. A lack of understanding of the capabilities, limitations, and indications for laboratory testing frequently results in the ordering of unnecessary and unhelpful laboratory tests. Understanding available laboratory assays and how these tests can and cannot assist in diagnosis and management should allow the clinician to rationally use toxicology tests.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:
• Of special interest
** Of outstanding interest


4 Czeizel AE, Timar L, Susanaszy E: Timing of suicide attempts by self-poisoning during pregnancy and pregnancy outcomes. 1999, 65:39–45. The largest study evaluating suicide attempts by women, this debunks myths regarding suicide attempts and pregnancy: specifically, the long-held myth that unwanted pregnancy is a motivating factor in self-poisoning and that emotional lability of unrecognized pregnancy is a risk factor for self harm by poisoning.


A prospective study of comprehensive toxicology testing in the pediatric emergency patient confirming the results of Belson’s retrospective study, specifically that comprehensive toxicology testing in suspected or actual poisoning does not influence patient management, although focused quantitative assays (“levels”) could be helpful in some instances.


