

Utilizing the Laboratory in the Poisoned Patient

David L. Eldridge, MD, MA^a,
Christopher P. Holstege, MD^{b,*}

^a*Department of Pediatrics, Brody School of Medicine,
East Carolina University, Greenville, NC, USA*

^b*Division of Medical Toxicology, Departments of Emergency Medicine and Pediatrics,
University of Virginia, Charlottesville, VA, USA*

When evaluating an intoxicated patient, there is no substitute for a thorough history and physical examination. Numerous medical shows on television depict a universal *toxicology screen* that automatically determines the agent causing a patient's symptoms. Samples cannot be simply "sent to the lab," however, with the correct diagnosis to a clinical mystery returning on a computer printout. Clues from a patient's physical examination are generally more likely to be helpful than a "shotgun" laboratory approach that involves indiscriminate testing of blood or urine for multiple agents.

When used appropriately, diagnostic tests may be helpful in the management of an intoxicated patient. When a specific toxin or class of toxins is suspected, requesting qualitative or quantitative levels may be appropriate. The National Academy of Clinical Biochemistry published recommendations for the use of laboratory tests in the evaluation of poisoned patients [1]. Among their recommendations was a list of diagnostic serum tests described as necessary to support a hospital's emergency department (Box 1). This is an excellent list of diagnostic studies that are generally widely available for application in the emergency department.

In a suicidal patient, whose history is generally unreliable, or in an unresponsive patient, for whom no history is available, the clinician may gain further clues as to the cause of a poisoning by responsible diagnostic

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* Corresponding author. University of Virginia Health System, PO Box 800774, Charlottesville, VA 22908-0774.

E-mail address: ch2xf@virginia.edu (C.P. Holstege).

Box 1. Stat quantitative serum toxicology assays to support an emergency department

Acetaminophen
Lithium
Salicylate
Co-oximetry (carboxyhemoglobin, methemoglobin)
Theophylline
Valproic acid
Carbamazepine
Digoxin
Phenobarbital
Iron
Ethanol
Methanol
Ethylene glycol

Data from Wu AH, McKay C, Broussard LA, et al. National Academy of Clinical Biochemistry Laboratory Medicine practice guidelines: recommendations for the use of laboratory tests to support poisoned patients who present to the emergency department. Clin Chem 2003;49:357-79.

testing. This article examines the role of common diagnostic tests in the evaluation of a poisoned patient.

Salicylates

Salicylates are readily available in numerous over-the-counter products. In any patient with history of salicylate ingestion or possessing characteristic signs or symptoms of salicylate poisoning, a serum salicylate level should be obtained. Early identification of salicylate toxicity can be life saving.

After acute salicylate overdose, patients may develop nausea, vomiting, abdominal pain, tinnitus, tachypnea, oliguria, and altered mental status ranging from lethargy to coma [2]. Chronic intoxication can manifest in a similar fashion as acute intoxication, but chronic intoxication typically is more insidious and often misdiagnosed [3]. In all overdoses, a thorough review of the patient's medications is vital.

Several medications have been documented to cause false-positive salicylate levels in commonly used salicylate assays. The most well documented of these is the nonsteroidal anti-inflammatory drug diflunisal (Dolobid) [4,5]. In toxic and therapeutic doses, the presence of diflunisal has caused false-positive serum salicylate levels [6-8]. Another possible important consideration in the interpretation of salicylate levels is the presence of

hyperbilirubinemia. Hyperbilirubinemia in term and preterm infants may lead to positive serum salicylate levels in certain fluorescence assays [9].

Interpretation of salicylate levels as a guide for clinical management decisions can be difficult. Perhaps the most well-known attempt at using salicylate levels to predict the severity of salicylate toxicity was the nomogram developed by Done [10]. After examining the clinical symptoms and the salicylate levels in patients who had a single acute overdose, Done created a nomogram that predicted severity of poisoning based on the salicylate level drawn at a given time from ingestion. This tool, however well intentioned, had significant limitations. Because the original development of this nomogram was based on only 38 pediatric patients, its utility for acute adult overdoses is unknown. One of the assumptions allowing the creation of this nomogram was that salicylates are eliminated by first-order kinetics. It since has been well established that some of the pathways for the elimination of salicylates become saturated in overdose and follow zero order kinetics [11]. One study showed that there was significant disagreement between the clinical severity predicted by the nomogram and the severity judged by physicians [12]. The authors no longer recommend its use in the management of a salicylate-poisoned patient.

Using salicylate levels to guide management must be done cautiously and only in conjunction with careful evaluation of a patient's clinical status. One group of investigators examined 97 patients who experienced significant exposures to salicylate. In this study, patients who did not survive the ingestion and patients with reasonably high serum levels (≥ 70 mg/dL) were included [13]. Although toxic levels alone were of poor prognostic value, the investigators identified certain clinical findings that predicted a poor prognosis, including pulmonary edema, fever, coma, and acidosis.

The absorptive phase of salicylates can be unpredictable (either delayed or erratic) owing to bezoar formation, enteric-coated product, gastric outlet obstruction, and pylorospasm [3]. A level drawn soon after the original ingestion may not reflect the potential peak concentration. Initial serial levels should be performed every 2 hours while monitoring the patient clinically. When the levels begin to decline, and the patient's clinical status is improved, levels can be performed less frequently.

The units reported with each level should be documented before management decisions are made. Laboratories alternatively may report levels in terms of milligrams per deciliter and milligrams per liter. This is an important distinction that involves a 10-fold difference in concentration and is infamous for causing confusion. In the extreme cases of these miscommunications, hemodialysis has been ordered for patients thought to have astronomically high salicylate levels that are later proved to be nontoxic [14].

The need to screen all intentional overdose patients for salicylates also is debated. One case review of 737 toxicology screening tests in a year revealed only 31 positive for salicylates (4.2%) [15]. There was no mention in this study of clinical symptoms in any of the patients. Two studies by a group in

Hong Kong further examined the role of salicylate screenings in acutely poisoned patients. In a retrospective study by Chan and colleagues [16], charts were reviewed on 347 patients who had a salicylate level performed. In 264 of these patients (76%), there was no clinical suspicion of salicylate poisoning. Only 3 of the 264 patients (1%) had elevated serum salicylate levels. This study gave no specific details of the clinical presentation of these three patients, only that they did not have typical symptoms of salicylism. The authors concluded that routine screening was unnecessary and should be restricted to only patients truly suspected of having salicylate toxicity. In a follow-up study [17], the same group looked at the practice of serum salicylate screening at their institution after educating their colleagues to their previous study's findings. In this study, they reviewed the discharge summaries of all acutely poisoned patients in a 6-month period who had received a serum salicylate level (total 196 patients). In 88% (172 patients) of the cases, there was no clinical suspicion of salicylate toxicity; only 3 of these patients (1.7%) had an elevated level. None of the three patients had symptoms clearly indicating salicylate toxicity. Their conclusion was that "indiscriminate" measurements of plasma salicylate levels in acutely poisoned patients were unjustified. In the United States, investigators in San Francisco performed a retrospective 2-year chart review ($n = 1820$) to question the necessity of universal screening for salicylates in patients with suicidal ingestion or altered mental status [18]. The authors found 155 patients (8.5%) with detectable levels (> 1 mg/dL). Of these, 111 (6%) had histories negative for salicylate ingestion. Only three of these patients had a significant degree of toxicity. The three patients all presented with significant altered mental status and large anion gaps. These three patients represented only 0.16% of the 1820 patients of whom salicylate levels had been obtained. The authors concluded that universal screening for salicylate poisoning in this population was neither cost-effective nor indicated.

The diagnosis of salicylate poisoning based solely on clinical examination is not without pitfalls. Although large, acute ingestions usually can be detected through history and clinical symptoms, chronic salicylate toxicity can be more difficult to diagnose. Numerous cases have been reported pertaining to a delayed or mistaken diagnosis in the face of significant salicylate toxicity. In these cases, patients presented with nonspecific symptoms, such as fever, abdominal pain, and encephalopathy, and subsequently were misdiagnosed with surgical abdomen, myocardial infarction, sepsis, encephalitis, and alcoholic ketoacidosis [3,19–21]. One study revealed that a delayed diagnosis (at times 72 hours) of chronic salicylate poisoning is associated with higher morbidity and mortality rates compared with poisoning diagnosed on admission [22]. Another study looking at salicylate-related fatalities in Ontario revealed that symptoms and signs of salicylate poisoning apparently were missed even in patients who were alert on presentation [23]. The "classic" finding of ototoxicity was found by one group of investigators to be neither sensitive nor specific for serum salicylate concentration [24]. Characteristic

laboratory findings also may not be reliable. Although a wide anion gap metabolic acidosis with respiratory alkalosis often is encountered in association with salicylate poisoning, one case series of 20 elderly patients with chronic salicylate poisoning revealed that 35% of these patients presented with a normal anion gap and PCO_2 [25]. In another study performed by Baer and colleagues [26], 52.8% of patients with history of acute salicylate toxicity and a serum bicarbonate > 20 mEq/L had salicylate levels > 30 mg/dL. Because products containing salicylates are readily available, clinical effects of salicylate toxicity are nonspecific, and a lack of metabolic acidosis does not rule out the potential for salicylate toxicity, clinicians should have a low threshold for obtaining serum salicylate levels.

Acetaminophen

An acetaminophen level drawn after a single, acute overdose is one of the few examples where a diagnostic laboratory result, by itself and independent of clinical findings, can be used to make treatment decisions. An area of some controversy is whether acetaminophen screening should be performed on all intentional overdose patients. One of the most worrisome aspects of acetaminophen poisoning is that initial clinical symptoms may be vague (eg, nausea, vomiting, abdominal pain) or even absent in the first 24 hours [27]. This possible delay in diagnosis is particularly problematic because the antidote, *N*-acetyl cysteine, has been shown to be most effective when initiated within the first 8 hours [28]. Ashbourne and colleagues [29] performed one of the first formal studies looking at the issue of universal acetaminophen screening. This prospective study examined acetaminophen levels in 486 patients with intentional drug ingestion. In this study population, only 7 of 486 patients (1.4%) had no history or clinical symptoms suggesting acetaminophen overdose and had a clinically significant acetaminophen level (> 10 mg/L within 8 hours of ingestion). Only one of these patients had a potentially hepatotoxic level. In their study group overall, Ashbourne and colleagues [29] found that about 1 in 70 patients with an intentional drug overdose who presented to their urban emergency department had an unrecognized acetaminophen overdose, and about 1 in 500 of these patients had a potentially hepatotoxic acetaminophen level. These authors further concluded that, even considering this relatively low yield, the low cost of serum acetaminophen levels might justify screening patients with a history of overdose, considering that acetaminophen has a vague clinical presentation and an effective antidote.

Chan and colleagues [30] sought to assess the value of acetaminophen screening by retrospectively examining the records of 294 patients admitted to their general wards for a variety of acute poisonings. Only 86 of these patients were truly suspected of ingesting acetaminophen, and 8 of them did have plasma levels that were toxic. The remaining 208 patients were screened for acetaminophen, but had no history of acetaminophen ingestion. In this

group, 60 had no detectable level, and the remaining 148 had levels that were nontoxic. No potentially serious acetaminophen ingestion was missed by clinical suspicion alone. The authors concluded that a thorough history and physical examination were vital, and that routine plasma acetaminophen screening was not indicated.

Sporer and Khayam-Bashi [18] in San Francisco retrospectively looked at 1820 patients presenting to their emergency department with either altered mental status or suicidal ingestion. At their facility, it was protocol to obtain acetaminophen levels in all patients with this presentation. They found 175 patients (9.6%) with detectable serum acetaminophen levels $> 1 \mu\text{g/mL}$. Most of these patients ($n = 120$) had given a history of acetaminophen ingestion. Of the remaining patients ($n = 55$), only 5 (0.3%) had what was regarded by the investigators to be a “potentially toxic level” (levels $> 50 \mu\text{g/mL}$). Even with these relatively high levels, none of the patients required *N*-acetyl cysteine when their levels were compared with the Rumack-Matthew nomogram, and all did well. Still, the authors noted these cases missed by history alone. Considering even this relatively small number, Sporer and Khayam-Bashi [18] recommended screening all patients with suicidal ingestion and patients with altered mental status in whom ingestion was suspected.

Another retrospective study done by Dargan and colleagues [31] examined acetaminophen screening in 411 patients presenting to the emergency department with either a history of drug overdose ($n = 296$) or loss of consciousness ($n = 115$). In the overdose group, 136 patients denied acetaminophen ingestion. All 136 of these patients had negative acetaminophen levels. In the 115 patients who presented with a loss of consciousness, 4 (3.5%) later proved to have ingested acetaminophen. All four received *N*-acetyl cysteine and recovered. The authors concluded that universal screening of patients who denied acetaminophen use was of little value, but that, in patients who were found with loss of consciousness, there was potential for missing significant acetaminophen toxicity.

More recently, in the United Kingdom, Hartington and colleagues [32] attempted to validate a clinical decision rule consisting of risk factors to help select out which overdose patients needed serum acetaminophen screening. They used risk factors that had been identified as potentially predictive of such exposure from the literature. Briefly, if the overdose patient denied ingestion of acetaminophen or acetaminophen-containing compounds, had a Glasgow Coma Scale score of 15, understood English well, and had not ingested excessive alcohol, the patient would not need an acetaminophen level drawn. With these parameters, 307 consecutive patients were evaluated in the emergency department. Clinicians obtained levels regardless, but recorded the risk factors that applied. Only 46 of the patients examined with this clinical decision rule in mind would have been excluded from having an acetaminophen level drawn. Of the total patients studied, 155 denied acetaminophen ingestion and were followed through the entire study. Only 13 of these patients had detectable acetaminophen levels, and none required

antidotal therapy. Seven of these 13 had normal Glasgow Coma Scale scores and would have been missed with the authors' clinical decision rule and with Dargan and colleagues's recommendations to check only in patients with altered mental status. A second part of the study was to test, through a questionnaire, the level of confidence physicians would require before they would use such an acetaminophen toxicity screening tool. Most physicians (83%) required a false-negative rate of 0.1% before considering using such a decision-making tool. Considering they were able to exclude only 46 of 307 patients with their clinical decision rule, Hartington and colleagues [32] estimated that the sample size of a potential study population would require more than 20,000 subjects to prove its clinical value conclusively. Considering numerous factors (no universal acetaminophen screening study possesses such statistical power, acetaminophen screen is inexpensive, and the potentially severe natural history of ingestion), the authors recommended to continue universal screening.

Osmol gap

The serum osmol gap is a common laboratory test that may be useful when evaluating poisoned patients. This test is discussed most often in the context of evaluating a patient suspected of toxic alcohol (eg, ethylene glycol, methanol, and isopropanol) intoxication. Although this test may have utility in such situations, it has many pitfalls and limitations that limit its effectiveness.

Osmotic concentrations are expressed in terms of osmolality (milliosmoles/kg of solvent [mOsm/kg]) and osmolarity (milliosmoles/liter of solution [mOsm/L]) [33,34]. This concentration can be measured by use of an osmometer, a tool that most often uses the technique of freezing point depression and is expressed in osmolality (Osm_M) [35]. A calculated serum osmolarity (Osm_C) may be obtained by numerous equations [36], involving the patient's glucose, sodium, and urea, which contribute to almost all of the normally measured osmolality [37]. One of the most commonly used of these calculations is as follows [38]:

$$\text{Osm}_C = 2[\text{Na}^+] + [\text{BUN}]/2.8 + [\text{glucose}]/18$$

The correction factors in the equation are based on the relative osmotic activity of the substance in question [33]. Assuming serum neutrality, sodium as the predominant serum cation is doubled to account for the corresponding anions. Finding the osmolarity contribution of any other osmotically active substance that is reported in mg/dL (eg, blood urea nitrogen [BUN] and glucose) is accomplished by dividing by one tenth its molecular weight in daltons [33]. For BUN, this conversion factor is 2.8, and for glucose it is 18. Similar conversion factors may be added to this equation

in an attempt to account for ethanol and the various toxic alcohols as follows:

$$\begin{aligned} \text{Osm}_C = & 2[\text{Na}^+] + [\text{BUN}]/2.8 + [\text{glucose}]/18 + [\text{ethanol}]/4.6 \\ & + [\text{methanol}]/3.2 + [\text{ethylene glycol}]/6.2 + [\text{isopropanol}]/6 \end{aligned}$$

The difference between the measured (Osm_M) and calculated (Osm_C) is the osmol gap (OG) and depicted by the following equation [33]:

$$\text{OG} = \text{Osm}_M - \text{Osm}_C$$

One problem with this calculation is that the units are different because the measured form is in mOsm/kg, and the calculated form is in mOsm/L. This unit difference is generally not considered significant because human serum is a dilute aqueous solution with a specific gravity of 1.01, making these numbers roughly equivalent [35].

If a significant osmol gap is discovered, the difference in the two values may represent presence of foreign substances in the blood [35]. Possible causes of an elevated osmol gap are listed in **Box 2**. What constitutes a normal osmol gap is widely debated. Traditionally a normal gap has been defined as 10 mOsm/kg or less. The original source of this value is an article by Smithline and Gardner [39], which declared that this number was pure convention. Further clinical study has not shown this assumption to be correct. Glasser and colleagues [40] studied 56 healthy adults and reported that they found the normal osmol gap to range from -9 to $+5$ mOsm/kg H_2O . A study examining a pediatric emergency department population ($n = 192$) found a range from -13.5 to $+8.9$ [41]. Another study by Aabakken and colleagues [42] looked at the osmol gaps of 177 patients admitted to the emergency department and reported their range to be from -10 to $+20$ mOsm/kg H_2O . A vital point brought forth by the authors of this study is that the day-to-day coefficient of variance for their laboratory in regards to sodium was 1%. They believed this variance translated to a calculated analytical standard deviation of 9.1 mOsm in regards to osmol gap. This analytical variance alone may account for the variation found in patients' osmol gaps. Other researchers have voiced this concern that even small errors in the measurement of sodium can result in large variations of the osmol gap [41,43]. Overall, the clinician should recognize that there is likely a wide range of variability in a patient's baseline osmol gap.

There are several concerns in regard to using the osmol gap as a screening tool in the evaluation of the potentially toxic alcohol-poisoned patient. The lack of a well-established normal range is particularly problematic. A patient may present with an osmol gap of 9 mOsm—a value considered normal by the traditionally accepted normal maximum gap of 10 mOsm. If this patient had an osmol gap of -5 just before ingestion of a toxic alcohol,

Box 2. Possible causes of an elevated osmol gap*Toxic alcohols*

- Ethanol
- Isopropanol
- Methanol
- Ethylene glycol

Drugs/additives

- Isoniazide
- Mannitol
- Propylene glycol
- Glycerol
- Osmotic contrast dyes

Other chemicals

- Ethyl ether
- Acetone
- Trichloroethane

Disease/illness

- Chronic renal failure
- Lactic acidosis
- Diabetic ketoacidosis
- Alcoholic ketoacidosis
- Hyperlipidemia
- Hyperproteinemia

Data from Refs. [33,34,40,63–66].

however, the patient's osmol gap would have to have been increased by 14 mOsm to reach the new gap of 9 mOsm. If this increase was due to ethylene glycol, it would correspond to a toxic level of 86.8 mg/dL [38]. In addition, if a patient's ingestion of a toxic alcohol occurred at a time distant from the actual blood sampling, the osmotically active parent compound will have been metabolized to the acidic metabolites. The subsequent metabolites have no osmotic activity of their own, and no osmol gap would be detected [36]. Steinhart [44] reported a patient with ethylene glycol toxicity who presented with an osmol gap of 7.2 mOsm owing to delay in presentation. Darchy and colleagues [43] presented two other cases of significant ethylene glycol toxicity with osmol gaps of 4 and 7. The lack of an abnormal osmol gap in these cases was speculated to be due to either metabolism of the parent alcohol or a low baseline osmol gap that masked the toxin's presence.

The osmol gap should be used with caution as an adjunct to clinical decision making and not as a primary determinant to rule out toxic alcohol ingestion. If the osmol gap obtained is particularly large, it suggests an agent

or condition from **Box 2** may be present. A “normal” osmol should be interpreted with caution; a negative study may not rule out the presence of such an ingestion—the test result must be interpreted within the context of the clinical presentation. If such a poisoning is suspected, appropriate therapy should be initiated presumptively (ie, ethanol infusion, 4-methyl-1H-pyrazole, hemodialysis) while confirmation from serum levels of the suspected toxin is pending.

Anion gap

Obtaining a basic metabolic panel in all poisoned patients is generally recommended. When a low serum bicarbonate is discovered on a metabolic panel, the clinician should determine if an elevated anion gap exists. The formula most commonly used for the anion gap calculation is the following [45]:

$$[\text{Na}^+] - [\text{Cl}^- + \text{HCO}_3^-]$$

This equation allows one to determine if serum electroneutrality is being maintained. The primary cation (sodium) and anions (chloride and bicarbonate) are represented in the equation [46]. There are other contributors to this equation that are “unmeasured” [47]. Other serum cations are not commonly included in this calculation because either their concentrations are relatively low (ie, potassium) or assigning a number to represent their respective contribution is difficult (ie, magnesium, calcium) [47]. Similarly, there are a multitude of other serum anions (ie, sulfate, phosphate, organic anions) that also are difficult to measure and quantify in an equation [46,47]. These “unmeasured” ions represent the anion gap calculated using the previous equation. The normal range for this anion gap is accepted to be 8 to 16 mEq/L [47], but some authors have suggested that owing to changes in the technique for measuring chloride, the range should be lowered to 6 to 14 mEq/L [46]. Practically speaking, an increase in the anion gap beyond an accepted normal range, accompanied by a metabolic acidosis, represents an increase in unmeasured endogenous (eg, lactate) or exogenous (eg, salicylates) anions [45]. A list of causes of this phenomenon is organized in the classic *MUDILES* mnemonic (**Box 3**). The “P” has been removed from the older acronym of *MUDPILES* because paraldehyde is no longer available.

It is imperative that clinicians who admit poisoned patients initially presenting with an increased anion gap metabolic acidosis investigate the etiology of that acidosis. Many symptomatic poisoned patients may have an initial mild metabolic acidosis on presentation as a result of the processes resulting in the elevation of serum lactate. With adequate supportive care, including hydration and oxygenation, the anion gap acidosis should

Box 3. Potential toxic causes of increased anion gap metabolic acidosis**Methanol****Uremia****Diabetic ketoacidosis****Iron, Inhalants (carbon monoxide, cyanide, hydrogen sulfide, toluene), Isoniazid, Ibuprofen****Lactic acidosis****Ethylene glycol, Ethanol ketoacidosis****Salicylates, Solvents (benzene, toluene), Starvation ketoacidosis, Sympathomimetics (eg, amphetamines)**

Data from Refs. [45,47,67].

improve. If, despite adequate supportive care, an anion gap metabolic acidosis worsens in a poisoned patient, the clinician should consider continued absorption of exogenous acids (ie, salicylate), formation of acidic metabolites (ie, ethylene glycol, methanol, toluene metabolites), or cellular ischemia with worsening lactic acidosis (ie, cyanide) as potential causes.

Bedside testing

A few simple, rapid bedside diagnostic tests have been suggested to aid in the confirmation of toxic ingestion. Favorable characteristics of the “perfect” test include the following points: inexpensive, readily available, and highly sensitive. The first two qualifications are easily obtained, but the last is not consistently present with some of these proposed tests.

Ferric chloride and Trinder spot test

Two bedside tests have been proposed for the rapid identification of a patient with salicylate toxicity. Both tests involve applying a few drops of a prepared reagent to a small sample of a patient’s urine and watching for a characteristic color change. The first reagent is ferric chloride. Applying a few drops of a 10% solution of ferric chloride to 1 mL of urine containing even very small amounts of salicylate produces a characteristic purple color caused by the formation of an iron-salicylate complex [48]. This color change also occurs if the urine in question contains acetoacetic acid and phenylpyruvic acid [3]. The urine Trinder spot test uses a reagent composed of mercuric chloride, ferric nitrate, concentrated hydrochloric acid, and deionized water [49]. Applying 1 mL of this solution to 1 mL of urine with salicylates present also leads to a purple color change [3].

One study [50] examined the use of the ferric chloride test in 187 patients presenting to the emergency department. The urine of each of these patients was tested with ferric chloride, and a color change of purple or dark brown was considered positive. These ferric chloride tests subsequently were followed with serum salicylate levels. The sensitivity of the ferric chloride test was 93.2% for salicylate levels 3 mg/dL or greater and 93.8% for levels 30 mg/dL or greater. Specificity was 88.8% and 75.4%, respectively. There were three false-negative results, one of which did have a toxic salicylate level of 34 mg/dL. Another study used ferric chloride in an attempt to test unknown substances (tablets, liquids, and creams) for salicylate content [48]. The expected color change was seen consistently when the product in question contained salicylate and was missing when salicylate was not present. King and colleagues [49] evaluated the clinical utility of the Trinder reagent. The investigators enlisted 12 volunteers who ingested 975 mg of aspirin. Urine samples collected from these individuals at 2 and 4 hours after ingestion produced the characteristic purple color when added to Trinder reagent. The sensitivity of the test in this study was 100% with two false-positive results from controls.

Weiner and colleagues [51] examined the application of these two bedside tests in patients presenting to the emergency department with suspected drug overdose with or without unexplained metabolic acidosis. Both reagents were added to urine samples from all 180 patients enrolled, and confirmatory serum salicylate levels were drawn. Different from the previous studies, however, any darkening of color was regarded as a positive test. Twenty of these patients (11%) had salicylate levels 5 mg/dL or greater. Both tests were 100% sensitive for recognizing these patients. There were several false-positive results (44 with Trinder and 47 with ferric chloride), and the specificities for both tests were relatively low (Trinder 73% and ferric chloride 71%).

Overall, both of these tests could be used for rapid bedside testing. Each is relatively inexpensive, and, when interpretation of color change is performed as suggested by Weiner and colleagues [51], very sensitive. Positive tests indicate the possible presence of salicylate and not toxicity. Both tests should be followed with serum salicylate levels to confirm toxicity and quantitate the salicylate level.

Urine fluorescence

Serum ethylene glycol levels are not readily obtained at many hospitals. A good bedside screening test would be extremely useful in these cases to help prevent morbidity and mortality and avoid expensive (4-methylpyrazole) and labor-intensive (ethanol drip) interventions that are often performed presumptively until definitive diagnosis is possible. Automotive antifreeze is a major source of ethylene glycol exposure. Sodium fluorescein is added to the antifreeze to aid in identifying cooling system leaks. Some

sources have suggested that fluorescein excreted in the urine of a patient who has ingested antifreeze would fluoresce with the aid of a Wood's lamp [52].

One of the first studies to look at the possibilities of this test was done by Winter and colleagues [53]. This study had six volunteers ingest the amount of sodium fluorescein found in 1 oz of antifreeze (an approximate ethylene glycol toxic dose). Urine samples were collected at 2-hour intervals for 10 hours. Controls also were obtained from the same volunteers. Samples obtained after fluorescein ingestion and controls were placed in glass nonfluorescent test tubes and examined, seven test tubes at a time, by three evaluators. Fluorescence was reliably identified 100% of the time in the samples collected in the first 2 hours after ingestion. This reliability decreased with time to 60% by 2 to 4 hours and 20% by 4 to 6 hours. Fluorescence was not detected after 6 hours. Controls were identified consistently as negative. As a second part of the study, another group of volunteers ingested fluorescein and had their urine collected during a 6-hour period. These samples were analyzed with a fluorometer. Fluorescence was detected by the fluorometer in all of these samples except the zero time point controls. By Wood's lamp, urine fluorescence could be identified reliably only within 2 hours after ingestion, however. The authors concluded that use of a Wood's lamp in this fashion could be a useful adjunctive test for ethylene glycol poisoning while waiting for serum levels.

Another research group later performed a similar, larger study that resulted in a different conclusion [52]. The volunteers ($n = 28$) provided control urine samples, ingested sodium fluorescein, and provided urine specimens at 1 to 2 and 4 to 6 hours after ingestion. Investigators evaluating the urine samples for fluorescence examined all the samples with a Wood's lamp in two different formats. First each sample was viewed singly in a random temporal sequence. After a break, the samples were presented again in groups of 27 to 30 at a time. With sequential presentation of urine for analysis, the mean sensitivity (35%), specificity (75%), and accuracy (48%) were poor. Grouped presentation of samples for comparison made little difference, and the sensitivity (42%), specificity (66%), and accuracy (50%) also were poor. These values were not significantly better if only the samples within the initial 2-hour period after ingestion (the ideal period reported by Winter and colleagues [53]) were considered. The authors of this study concluded that using this technique had limited diagnostic utility.

In another study, investigators collected convenience urine samples from an inpatient pediatric population (30 samples total) and from a group of healthy children (16 samples total) [54]. None of these children had a history of a suspected poisoning. All samples were examined by Wood's lamp. These samples were placed in containers and compared with a negative control (tap water in a similar container) and a positive control (fluorescein in tap water). Twenty-one of the 30 inpatient samples and 11 of the 16 healthy children's samples were reported as fluorescent by two of the three investigators. Considering this apparent baseline fluorescence, the authors

gave serious challenge to using this technique to screen for ethylene glycol toxicity because their data suggested the false-positive rate would likely be high.

There seems to be little advantage to checking for urinary fluorescence by Wood's lamp in individuals suspected of ethylene glycol poisoning. Follow-up studies since the work done by Winter and colleagues [53] so far suggest that such a diagnostic approach lacks the clinical reliability necessary to guide management. The authors see no advantage to performing this proposed bedside test.

Urine drug screening

Many clinicians regularly obtain urine drug screening on altered patients or on patients suspected of ingestion. Such routine urine drug testing is of questionable benefit, however. Kellermann and colleagues [55] found little impact of urine drug screening on patient management in an urban emergency setting, and Mahoney and colleagues [56] similarly concluded that toxic screening added little to treatment or disposition of overdose patients in their emergency department. In a study of more than 200 overdose patients, Brett [57] showed that although unsuspected drugs were detected routinely, the results rarely led to changes in management and likely never affected outcome. In a similar large study of trauma patients, Bast and colleagues [58] noted that a positive drug screen had minimal impact on patient treatment.

Some authors argue in favor of routine testing. Fabbri and colleagues [59] argued that comprehensive screening may aid decisions on patient disposition, resulting in fewer admissions to the hospital and less demand on critical care units. The screen used in their retrospective study tested for more than 900 drugs, however, and is not available to most clinicians. Milzman and colleagues [60] argued in favor of screening trauma victims, stating that the prognosis of intoxicated patients is unduly poor secondary to low Glasgow Coma Scale scores, although patient treatment and disposition did not seem to be affected [60].

The effect of such routine screening in management changes is low because most of the therapy is supportive and directed at the clinical scenario (ie, mental status, cardiovascular function, respiratory condition). Interpretation of the results can be difficult even when the objective for ordering a comprehensive urine screen is adequately defined. Most assays rely on the antibody identification of drug metabolites; some drugs remain positive days after use and may not be related to the patient's current clinical picture. The positive identification of drug metabolites likewise is influenced by chronicity of ingestion, fat solubility, and coingestions. In one example, Perrone and colleagues [61] showed a cocaine retention time of 72 hours after its use. Conversely, many drugs of abuse are not detected on most urine drug screens, including gamma hydroxybutyrate, fentanyl, and ketamine.

Interpretation is confounded further by false-positive and false-negative results. George and Braithwaite [62] evaluated five popular rapid urine screening kits and found all lacked significant sensitivity and specificity. Additionally, cross-reactivity of prescription and over-the-counter medications used in therapeutic amounts for true illness may elicit positive screens. Codeine would give a positive opioid screen, which may be attributed incorrectly to morphine or heroin use.

The utility of ordering urine drug screens is fraught with significant testing limitations, including false-positive and false-negative results. Many authors have shown that the test results rarely affect management decisions. Routine drug screening of patients with altered mental status, abnormal vital signs, or suspected ingestion is not warranted and rarely guides patient treatment or disposition.

Summary

Numerous diagnostic tests may be useful to clinicians caring for poisoned patients. Clinicians should not order a broad range of tests indiscriminately, but rather thoughtfully consider appropriate tests. The results of the tests should be reviewed in the context of the clinical scenario.

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