Part IV. Recommendations on Laboratory Assays for Other Toxicants as Causes of Poisonings

A. Cyanide and Hydrogen Sulfide

Cyanide and hydrogen sulfide are chemical asphyxiants that disrupt cellular oxidative phosphorylation. These toxic gases are often produced as byproducts of industry and combustion. Patients exposed to low concentrations of cyanide have non-specific symptoms of nausea, vomiting, abdominal pain, and upper gastrointestinal irritation with higher concentrations or prolonged exposure causing cardiac and CNS dysfunction and death (78).

Recommendation: There are no laboratory tests that can be performed in a timely fashion to be effective in diagnosis or management of patients who have been exposed to cyanide or hydrogen sulfide. The ED must rely on history and physical examination to determine if treatment with cyanide antidote is appropriate. Collection of a blood sample for later cyanide and sulfide testing may be useful to document exposure. *Degree of consensus: A*

Discussion

Although rapid experimental assays have been developed (79), they have not been tested or implemented in an ED setting. In the case of cyanide and sulfide exposure, immediate application of the antidote is indicated if the patient has a history of possible exposure and rapid onset of symptoms of hypoxemia (gasping), oxygenated venous blood (non-cyanotic), wide anion gap, and tachycardia; occasionally, the smell of bitter almonds on the patient's breath or clothing will indicate the presence of cyanide while a rotten egg odor identifies hydrogen sulfide. Treatment must be started immediately if therapy is to be successful (80). The ED cannot wait

for the results of laboratory test to confirm cyanide or sulfide exposure. However, it is useful to collect a blood sample for later testing to validate (or refute) exposure.

A potential stat surrogate is the measurement and comparison of arterial and (mixed) venous blood gases. A narrow pO_2 difference suggest poor extraction of oxygen by the tissues and is consistent with the presence of a cellular asphyxiant (81,82).

B. Anticoagulants

Anticoagulants are used as rodenticides and act by inhibiting critical vitamin K-dependent coagulation factors, especially II, VII, IX, X, and proteins C and S, causing severe bleeding and eventual death. Most cases of rodenticide exposures do not require an ED visit, as toxicity is uncommon with accidental ingestions. In patients with intentional ingestion with rodenticides, the appropriate therapy is to provide an infusion of fresh frozen plasma and administer parenteral vitamin K_1 after the patient has stabilized (83). Patients having prolonged coagulation studies which are responsive for 2-3 days on vitamin K therapy, and then become abnormal again, should be evaluated for exposure of long-acting anticoagulants such as brodifacoum. This follow-up is not usually performed in the ED. Testing for Factor V and VII may be useful in the workup to differentiate between hepatic factor insufficiencies vs. anticoagulant exposures, but stat testing is unlikely to be available.

Recommendation: Patients with intentional ingestion of anticoagulants, particularly the long-acting formulations, should be monitored for coagulation status using the prothrombin time (PT). Samples should be collected at 24-36 hours after exposure to monitor anticoagulation effects

without prophylactic vitamin K administration. There is no stat clinical need for determining the identity or concentration of the specific anticoagulant taken. *Degree of consensus: A*

C. Lead Poisoning

Lead is a toxin with major sequelea if left untreated and significant exposure opportunity; it is estimated that 3% of the population of the United States will experience some significant exposure at some time during life. Acute exposure to lead produces gastrointestinal distress and encephalopathy at very high concentrations, while chronic exposure interferes with mental development, bone growth, nerve function, and causes anemia and nephropathy. Young children are particularly sensitive to the effects of lead. Guidelines (84) published by the U.S. Centers for Disease Control and Prevention (CDC) in 1991 recommend screening of all children at the age of 2 years for low-level exposure. These have subsequently been amended to focus screening in areas of high environmental lead contamination (85).

Recommendation: Emergency testing for lead is not required to support ED practice. Since the serious sequelae associated with lead occur with chronic exposure, the work-up usually takes place in the outpatient setting. The ED should be prepared to collect heparinized blood samples for lead testing when lead exposure is suspected, however specific treatment is usually not initiated in the ED. Since lead is ubiquitous in the environment, needles, collection and transfer tubes need to be free of lead contamination. Next-day availability of the blood lead result is adequate to ensure appropriate follow-up. Collection of serum for lead evaluation is not appropriate. The erythrocyte protoporphyrin (EPP) test is not useful for detecting low-level exposure. *Degree of consensus: A*

Discussion

Whole blood lead measurement has been identified by the CDC (84) as the best test to detect lead exposure. Whole blood lead concentrations lower than 10 µg/dL are considered normal in children. Higher measurements initiate a cascade of evaluation and potential treatment recommendations. Whole blood lead concentrations greater than 30 µg/dL in adults are indicative of significant exposure. Blood lead concentrations greater than 60 µg/dL represent serious exposure requiring removal from the workplace and often chelation therapy.

The EPP test does not have the sensitivity for detecting low–level lead exposure, but is a marker for overdose. An EPP concentration greater than 60 µg/dL is a significant indicator of acute lead exposure. Serum lead analysis has no clinical utility in cases of acute lead exposure because serum lead concentrations are abnormal only for a short period of time after exposure. Measurement of urine excretion rates either before or after chelation therapy has been used as an indicator of lead exposure, but this approach is not indicated in ED practice. Since blood lead concentration has the strongest correlation with toxicity, this test is recommended for evaluation of lead exposure by the ED.

D. Testing for Iron Toxicity

Excessive ingestion of iron-containing vitamins will cause toxicity; it is estimated there are 500 cases of iron poisonings per year in the U.S. Inappropriate handling of these commonly available products can cause overuse and rarely toxicity. The patient presents with nonspecific symptoms of gastrointestinal distress, GI bleeding, and cardiac rhythm disturbance. The history

and clinical examination in the ED are the keys to identifying these toxic agents. Serum iron analysis, readily available from most clinical laboratories, is useful to identify iron overdose.

Recommendation: The clinical laboratory should be prepared to provide serum iron on a stat basis to aid in the diagnosis of iron overdose. Due to analytical limitations, heterogenous assays for the total iron binding capacity (TIBC) cannot be used to determine the absence of free iron and toxicity. Serum transferrin is a more reliable marker for estimating free and potentially toxic iron. If this assay is not available on a stat basis, the homogenous unsaturated iron-binding assay (UIBC) is more useful than TIBC assays requiring a pretreatment step. *Degree of consensus: A*

Discussion

Serum iron analysis, readily available from most clinical laboratories, is useful to identify iron overdose; serum iron >350 μg/dL indicates significant exposure (86). If the serum iron concentration exceeds the total iron binding capacity, it has been presumed that there is free and potentially toxic iron. However, TIBC tests that require separation between transferrin-bound iron from the added adsorbent can over-estimate TIBC, producing a falsely low free iron estimation (87) and an incorrect assumption that there is no risk for iron toxicity (88). Measurement of transferrin is the preferred test (1 μmole/L of transferrin binds 2 μmole/L of iron). If this test is not available, direct UIBC assays are more immune towards falsely high results due to iron overdoses (89). Some patients with iron overdoses are treated with deferoxamine. It should be noted that this chelator will interfere with some dye-binding colorimetric iron methods of analysis producing falsely low iron results (90). The Committee recommends that blood specimens should be taken for iron determination prior to deferoxamine

administration. Alternatively, an assay based on atomic absorption spectormetry can be used without interference with deferoxamine.

E. Arsenic and Mercury

Arsenic exposure results from either occupational or nonoccupational sources. At one time, arsenic was widely used as a rodenticide, pesticide, herbicide, and for treated wood for outdoor use. Industrial arsenic results from dusts and fumes generated in connection with the smelting of copper, lead, and other iron ores. Acute cyanide poisoning can be fatal usually to heart failure. Arsenic exposure can also produce renal, neurologic, and hematologic disorders.

Mercury is found in three principal forms: elemental or inorganic mercury and mercury salts, alkyl mercury, and aryl organic mercurial compounds. Mercury exposure can result in neurologic impariment, renal tubular acidosis, and gastrointestinal symptoms. Mercury is found in thermometers, barometers, dental amalgam, and seafood. Neither arsenic or mercury contribute to significant acute toxicities and testing is not useful to support ED practice.

Recommendation: A 12 or 24 hour timed urine collection in a metal-free container (use opaque plastics with no metal caps) is the best sample for arsenic and mercury analysis. Results of urine testing should be available within 48 hours of specimen collection. *Degree of consensus: A*

Discussion

Timed urine is the specimen of choice to identify the exposure and body burden of arsenic and mercury and the need for chelation therapy (91). These tests are not generally available from the clinical laboratory; these tests are provided by reference laboratories. At this

time, obtaining a general trace metals screen in asymptomatic subjects or those without a history of recent exposure is inappropriate. Therapeutic protocols to manage these patients are also recommended without adequate evidence. Testing of workers who have occupational exposures to heavy metals, however, may be appropriate (92). There is no current role for blood testing for these metals.

G Broad spectrum trace element screening

Broad-spectrum trace element screening was defined by the Committee as uncommonly performed laboratory analyses for trace elements, environmental contaminants, or endogenous enzymes obtained from samples of blood, urine, hair or other body tissue. These tests or matrices generally lack a published reporting of validated reference ranges or suffer from significant procedural difficulties. At this time, many of these are best utilized as research tools, such as the current population evaluations by the National Center for Environmental Health of the Centers for Disease Control and Prevention (93). Application of these test results to individual patients is fraught with problems. In addition to problems with patient preparation, specimen collection, analysis, reliability, and reporting issues, there are practitioners and laboratories that provide diagnoses of heavy metal poisoning or trace element excesses or deficiencies to normal individuals, and then prescribe expensive tailored treatment from their offices.

Recommendation: In the absence of probable cause, occupational and/or accidental environmental exposure, broad-spectrum screening for trace elements or other analytes (including uncommonly assayed elements such as boron or selenium, environmental

contaminants such as phthalates and aliphatic hydrocarbons, and analytes such as D-glutaric acid and mercapturic acid) is inappropriate. These tests have not been sufficiently validated in a general patient population nor have the implications of clinical decisions based on one-time measurements been discussed to warrant any use other than research and biomonitoring for occupational exposure. *Degree of consensus: B*

Discussion

The Committee's concern is that the laboratory standards are not available for these studies outside the research setting or possibly monitoring with known (usually occupational) exposures. Some of the information that are lacking include limit of detection and quantitation, true population range, applicability of one medium to another (e.g.. hair, urine, saliva, serum, RBC mass), method of collection, stability during transport, and sensitivity or specifity for disease (94). Of significant concern to the Committee, some of these treating practitioners have financial connections with the testing laboratory.

The status of this recommendation will change as laboratories provide more information regarding standardization (95). In addition, the NHANES studies should provide better population estimates for many of these measurements (93). The Agency for Toxic Substances and Disease Registry (ATSDR) has indicated there is sufficient evidence for the value of hair analysis for individuals potentially exposed to methylmercury, particularly children (96). Even so, this analysis should be based on an appropriate clinical evaluation (97). Until these concerns can be resolved with research and clinical studies, biomonitoring other than for occupational exposure, is not recommended.

H. Pesticides

Carbamates and organophosphates such as diazinon, chlorpyrifos, parathion and malathion are popular pesticides used in the agricultural industry (98). The carbamates and organophosphates inhibit cholinesterase at cholinergic synapses, thereby preventing the degradation of the neurotransmitter acetylcholine. Excess acetylcholine at neuroeffector (muscarinic), myoneural junctions, and autonomic ganglia (nicotinic) results in symptoms of bradycardia, bronchorrhea, lacrimination, salivation, emesis, diarrhea, fasciculations and muscle paralysis, and diaphoresis. Atropine is used to compete with acetylcholine for muscarinic receptors, thereby protecting the end organs from excess acetycholine, while pralidoxime is effective in treating both muscarinic and nicotinic symptoms. Patients exposed to substances that produce cholinergic response can be screened for the presence of low activity for pseudocholinesterase (99). However, this test is not specific for cholinergics, as depressed activity can be due to genetic variability. The dibucaine inhibition test can identify such variants. Red blood cell (RBC) cholinesterase activity is the definitive test to document cholinergic agent exposure.

Recommendation: Clinical laboratories should provide access to stat pseudocholinesterase testing to screen for cholinergic agent exposure, and not for monitoring therapy. *Degree of consensus: B*

Discussion

The Committee recognizes that most laboratories will not have the red blood cell cholinesterase test because it is a very difficult test to perform, and because of the infrequency of its need. In a survey of participants to the AACC meeting, only about 20% of attendees stated

they had the ability to perform the RBC cholinesterase test. Thus reference laboratories are the usual provider of red cell cholinesterase tests and results should be made available within 24 hours. Reagents for serum pseudocholinesterase tests are more available. Roughly half of the participants of the AACC meeting indicated capability of testing. Results should be made available with a target TAT of 4 hours. However, due to low testing volumes, many small laboratories cannot justify the expense for providing this testing. Therefore results of serum testing from a reference laboratory should be made available within 24 hours. While it is recognized that the pseudocholinesterase activity is an imperfect marker of cholinergic agent exposure, the test is useful to address whether the patient has been exposed to an cholinergic agent (100). Furthermore, given recent increased concern regarding chemical and biologic terrorism, such screening tests may become part of a clinical laboratory's support to state agencies, given that the nerve agents are potent organophosphates (101).

I. Inhalants

Inhalants are popular substances that are abused by children and adolescents. Aromatic hydrocarbons such as toluene are found in solvents, paint thinners, and plastic cements. These volatile compounds produce euphoria and hallucinations similar to other stimulants. There are a number of central nervous system manifestations to inhalant abuse including dizziness, blurred vision, violent behavior, tremors and convulsions (102). Long-term abuse can lead to learning deficits (103). Other organic solvents such as benzene, carbon tetrachloride, chloroform, xylene, acetonitrile, formaldehyde etc., can also produce toxicity, and are hazards within particular occupations.

Recommendation: Due to the lack of stat availability, there are no clinical laboratory tests that are currently appropriate for monitoring acute inhalant abuse or solvent exposure. *Degree of consensus: A*

Discussion

ED personnel should be cognizant of signs of inhalant abuse. Clues to inhalant abuse include chronic sore throat, cough, and runny nose; unexplained listlessness, moodiness, weight loss, bloodshot eyes and/or blurred vision; chemical odors on breath, hair, bed linen, and clothes. Oral and nasal ulceration or a rash around the mouth ("glue sniffer's rash") may be observed. Sometimes the products themselves may be discovered in the room of the abuser or as residua about the nose, mouth and hands (104). Toluene and benzene metabolize principally to hippuric acid and phenol (105), respectively. The presence of increased concentrations of hippuric acid is not specific to inhalant abuse (e.g., certain food and beverages containing benzoate (106,107)). Urinary phenol concentrations can increase with the consumption of some over-the-counter drugs such as Pepto Bismol and Chloraseptic (108). More specific urinary metabolites have been studied for toluene, such as *o*-cresol (109), S-p-toluylmercapturic acid (110) and trace concentrations of toluene itself (111), and benzene, such as trans, trans-muconic acid, and S-phenylmercapturic acid (112). Unfortunately, assays for these metabolites are not in routine use at clinical laboratories. Thus samples must be sent to specialty laboratories where the turnaround time makes them impractical for critical care management. In addition, there are currently no guidelines for the interpretation of results.

J. Methemoglobinemia

There are a number of drugs and toxic agents that can convert hemoglobin to methemoglobin, such as nitrates, chlorates, quinones, phenacetin, sulfonamides, aniline dyes, and local anesthetics such as procaine, benzocaine, and lidocaine (113). Methemoglobin is unable to bind to oxygen because the heme group is oxidized to the ferric state. Monitoring of oxygen saturation by pulse oximetry (where two spectrophometric wavelengths are used to measure the fraction of oxyhemoglobin from oxy- and deoxyhemoglobin) is insensitive to methemoglobin. Co-oximetry typically uses four wavelengths to discriminate oxyhemoglobin from oxy-, deoxy-, carboxy-, and methemoglobin.

Recommendation: For patients suspected of methemoglobinemia, measurement of the fraction of oxyhemoglobin (oxygen saturation) should be performed using a co-oximeter and not a pulse oximeter, as the latter overestimates the actual O_2 saturation. If a request for oxygen saturation is received, all results of a 4-part co-oximetry panel should be reported even if the specific tests for COHb and metHb are not received. Laboratories should not charge separately for the inclusion of these additional results. *Degree of consensus: A*

Discussion

Numerous studies have shown that pulse oximetry is not an accurate measure of methemoglobinemia (114,115). At low methemoglobin concentration, oxygen saturation as measured by pulse oximetry are slightly higher that the actual (e.g., 10% methemoglobin produces 95% O_2 saturation instead of 90%). When the methemoglobin concentration exceeds 35%, the O_2 saturation by pulse oximetry will be significantly overestimated, as the O_2 saturation

reaches a plateau of 85% and becomes independent of methemoglobin concentrations. In this situation, the patient will generally appear cyanotic with a falsely elevated pulse oximeter reading, unless the methemoglobinemia is also accompanied by hemolysis. Due to the extra wavelengths that are monitored, O_2 saturation as measured by co-oximetry is accurately measured in the presence of varying methemoglobin concentrations. In the presence of methylene blue, used to treat patients with methemoglobin, falsely low readings can occur by both pulse and co-oximetry (116) as methylene blue has significant absorptivity at methemoglobin's absorption maxima.

K. Regional Toxicology Centers

As evidenced by the discussion in this document, most laboratories will not be able to meet all of the needs of an emergency department in their workup of all intoxicated and overdosed patients. Some analytes require sophisticated methodologies that are expensive to acquire, or difficult to maintain and operate on a 24 hour-a-day basis. Many instruments (e.g., graphite furnace atomic absorption, gas chromatography/mass spectrometry), require very highly trained laboratory personnel. The low volume of testing does not justify the expense of providing the service. The lack of a commercial immunoassay for particular analytes (e.g., fentanyl, ketamine, gamma hydroxybutyrate, etc) also limits the availability of testing. Even the largest hospital laboratories will have difficulty in providing testing needed for all clinical circumstances.

Recommendation: A cooperative effort should be made to establish regional centers of toxicology where specialized techniques can be made available, in order to service the toxicological needs of a larger community of medical centers. *Degree of consensus: A*

Discussion

The success of a regional center will depend on good cooperation between facilities, and the proximity of the center to the clinical sites. To be useful in real time, it is important that samples be delivered, tested, and reported within a few hours after collection. Many reference laboratories have full-service toxicology capability and can serve as a regional center for the hospitals that are nearby. For areas where there are no reference laboratories in close proximity, a regional hospital toxicology laboratory would be desirable. To be economically viable, a commitment would be needed that all the regional toxicology testing is sent to this central facility, and that a reasonable reporting turnaround time (e.g., 4 hours) is met. It would be the responsibility of laboratory and hospital administrators to establish the facility and maintain its viability. Where appropriate, area poison control centers may be helpful in publicizing and referring laboratory testing to the regional laboratories. These public health information and poison treatment resources can also assist in the development of protocols and cooperation between institutions. A nationwide toll-free telephone number has been established (1-800-222-1222 and www.aappc.org) to facilitate contact to the nearest regional poison control center.