EDUCATIONAL COMMENTARY – TESTING FOR OVERDOSE OF ACETAMINOPHEN AND OTHER DRUGS

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Learning Outcomes

Upon completion of this exercise, the participant will be able to:

- List the qualitative urine and quantitative blood tests that laboratories should offer based on the recommendations of the National Academy of Clinical Biochemistry (NACB) guidelines for treatment of the poisoned patient.
- Discuss the sequence that occurs following acute ingestion of large amounts of acetaminophen and the role of the laboratory in administering the appropriate antidote.
- Interpret plasma acetaminophen levels to assess potential liver toxicity

Although the detection and identification of drugs is often secondary in the initial treatment of patients presenting with signs and symptoms of ingestion, drug screening can provide vital information in many situations. Identifying the drug ingested and determining blood levels helps determine appropriate treatment, including antidote administration and subsequent monitoring of the patient.

Urine is the single best specimen for a toxicology screen. Most drugs and metabolites are concentrated and excreted via the kidneys and can be detected in urine for several days after an exposure. While there is a lack of correlation between urine drug concentration and impairment, urine drug screening offers the advantages of noninvasive collection and relatively easy, cost-effective, proven detection technologies. Immunoassays on automated analyzers or point-of-care kits are the primary methods used for urine drug screening. These tests were originally developed for workplace drug testing but are frequently used for clinical testing because of their availability and ease of use.

A set of practice guidelines for the use of laboratory tests of poisoned patients was developed by several professional organizations and published by the National Academy of Clinical Biochemistry (NACB). These guidelines recommend that the clinical laboratory provide 2 tiers of drug testing: a first tier of qualitative and quantitative tests available on a stat basis to support evaluation of acute toxicity for specific toxins for which an antidote or specific therapy is available, and a second tier (turnaround time of 24 hours or less) of more comprehensive testing for patients with continuing medical problems from exposure to drugs and other chemicals.
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The recommended qualitative urine screening tests that should be available on a stat basis are: cocaine, opiates, barbiturates, tricyclic antidepressants (used in conjunction with electrocardiograph), and (based on regional usage) amphetamines, propoxyphene, and phencyclidine hydrochloride (PCP). A detailed discussion of immunoassay screening for specific drugs and classes of drugs can be found in a previous API Chemistry Educational Commentary (see “Urine Drug Testing”, 2003, 3rd Test Event). Quantitative testing of serum should be limited to those drugs for which levels can predict subsequent toxicity or guide specific therapy. The NACB guidelines recommend that laboratories have the capability of performing the following quantitative assays on a stat basis: acetaminophen, lithium, salicylate, cooximetry (for oxygen saturation, carboxyhemoglobin, and methemoglobin), theophylline, valproic acid, carbamazepine, digoxin, phenobarbital (if urine barbiturates are positive), iron, transferrin (or UIBC), ethanol, methanol, and ethylene glycol.

Laboratory testing plays an essential role in the determination of treatment for the patient ingesting acetaminophen (paracetamol), the common analgesic and antipyretic ingredient in hundreds of over-the-counter products. An acute acetaminophen overdose presents a unique danger because of the pattern of signs and symptoms. Within a few hours of ingestion nonspecific findings such as anorexia, nausea, vomiting, malaise, pallor, and diaphoresis occur and then usually lessen. Depending on the time lapse between ingestion and arrival at the emergency department, the patient who ingested dangerous amounts of acetaminophen may present with very few symptoms and with normal results for commonly ordered laboratory tests.

About 24 to 48 hours after ingestion, a second phase occurs if acetaminophen levels exceed certain plasma concentrations. The patient may appear to improve but elevation of liver function tests including enzymes and bilirubin indicates progressing hepatic necrosis. Three to 5 days postingestion, hepatic failure usually progressing to death occurs. Hepatotoxicity is caused by increased production of a metabolite usually detoxified by hepatic glutathione stores, but depleted when large amounts of acetaminophen are ingested.

Administration of the antidote N-acetylcysteine (Mucomyst, Sandoz, Princeton NJ) within 8 to 24 hours of ingestion prevents or minimizes hepatotoxicity, apparently by serving as a glutathione substitute to detoxify the acetaminophen metabolite. The decision to administer the antidote is based on determination of plasma/serum acetaminophen levels. In 1975 Rumack and Matthew developed a nomogram predicting hepatotoxicity risk based on a plot of hours after ingestion versus plasma acetaminophen concentrations (µg/mL) on a semilogarithmic scale.  They drew a straight line starting at the hepatotoxic concentration of 200 µg/mL at 4 hours postingestion (based on published half-life data and their investigation of cases at their institution), intersecting 50 µg/mL at 12 hours postingestion, and
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extending to 24 hours postingestion. Acetaminophen concentrations above the line were considered probable hepatotoxic, and values below the line were considered to indicate no hepatotoxicity. The nomogram was subsequently modified to include a parallel line at concentrations 25% below the line to introduce a zone of possible hepatotoxic risk.3

This modified Rumack-Matthew nomogram is considered the reference to be used in predicting the risk of hepatotoxicity and has been extensively reproduced in textbooks and other publications, including product information inserts for acetaminophen assays and acetylcysteine solution (the antidote). Users of this nomogram should be aware of its limitations. The nomogram should be used only for single acute overdoses and not for multiple doses, sustained-release formulations, or chronic ingestions.

Acetaminophen levels measured before 4 hours postingestion may be unreliable and may underestimate the risk of toxicity because of incomplete drug absorption. If the approximate time of ingestion is unknown, different courses of action have been proposed. Some protocols (including the product information insert for acetylcysteine) indicate automatic administration of the antidote, and others recommend calculation of acetaminophen half-life using plasma concentrations from 2 specimens collected over an 8-hour period. The Rumack-Matthew nomogram line of hepatotoxicity risk gives a half-life of approximately 4 hours, and half-life protocols indicate that the antidote should be administered when the calculated half-life is >4 hours.

Methods for measuring acetaminophen concentrations include colorimetric, chromatographic (gas and liquid), and immunoassay. Colorimetric and immunoassay methods are typically performed on automated analyzers. Chromatographic methods allow separation and detection of acetaminophen and its metabolites. Interference from some compounds, including bilirubin and acetylcysteine, has been reported for some of the initial colorimetric assays. Laboratory professionals should be aware of the parameters of their acetaminophen assays, including reporting units, potential interfering compounds, and linearity. The most commonly used unit for reporting acetaminophen concentrations is micrograms per milliliter (µg/mL), but concentrations are sometimes reported in milligrams per decaliter (mg/dL). Acetaminophen concentrations reported in units of mg/dL must be converted to µg/mL when using the Rumack-Matthew nomogram.

The combination of screening urine samples for identification of ingested drugs and quantifying blood levels of certain drugs provides a valuable tool in the treatment of poisoned patients. In particular, determination of plasma acetaminophen levels guides administration of the antidote, acetylcysteine, to prevent possible hepatotoxicity and subsequent death.
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References


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