Poisoning, overdose: Better technology, workflow improve patient odds

Anne Paxton

July 2016—As pronouncements by fictional detectives go, one of the most famous is Sherlock Holmes' declaration to Dr. Watson: "When you have excluded the impossible, whatever remains, however improbable, must be the truth."

Unfortunately, Holmes' advice is no practical rule of thumb for solving the real-world mysteries of patient poisoning or overdose, because the possibilities are often so vast. Some 2.3 million toxic exposures are reported annually and they may involve thousands of different agents—frequently more than one for an individual patient, says Kara Lynch, PhD, associate chief of the clinical chemistry and toxicology laboratory at Zuckerberg San Francisco General Hospital and associate professor at the University of California, San Francisco.

Dr. Lynch

"Half of these agents are pharmaceutical drugs, and as laboratories we can actually look for these with published methods, using mass spectrometry," Dr. Lynch said last year in a presentation at the American Association for Clinical Chemistry annual meeting. "The question is, should we be doing this?"

As she notes, the top reasons patients seek emergency care, including trauma and seizures, could stem from drug exposure. "Drug use or drug overdose is almost always on the differential when someone comes into the ER with any of these types of conditions."

Mass spectrometers in general are ideal platforms for evaluating drug poisoning and overdoses, Dr. Lynch says. But for toxicologists deciding on laboratory testing strategies where overdosing or poisoning is suspected, there are advantages and disadvantages to different technologies and workflows, as Dr. Lynch outlined at AACC and in a recent interview with CAP TODAY.

San Francisco General's laboratory, affiliated with the academic center at UCSF, is not typical in poisoning evaluation. The majority of laboratories are still using urine testing and ordering a comprehensive drug screen (CDS), often referred to as a broad-spectrum drug screen or systematic toxicological analysis, Dr. Lynch said.

Under the typical workflow, a Utox or CDS is ordered. "Then usually, the first line of defense is screening for classes of abuse drugs or some prescribed medications by immunoassay. But the panels vary substantially depending on the laboratory doing the testing."

The disadvantage of a urine screen is that it's not indicative of the current clinical state of a patient. "So you could find a compound in the urine, but the patient may not be under the influence of that drug at that moment in time."

Immunoassays are also prone to false-positives and false-negatives.

A simplified approach might be better, she says. "If a Utox or CDS is ordered, we've done some work in our lab to look at this and there are advantages to going directly to mass spectrometry in certain situations."

Many labs conduct a confirmatory test by sending the test out. In her laboratory, tests for amphetamines automatically reflex because false-positives are common. “For opiates, we reflex to confirmation because the clinicians usually need to know exactly which opiate patients have taken for compliance monitoring.” Some laboratories use mass spec for confirmation. “Those tests are targeted, so you’re only going to see the drug you’re looking for.” However, broad-spectrum drug screens that are untargeted are also available.

A few serum drug tests are FDA approved and can be performed on automated analyzers, Dr. Lynch said, noting that the tests can be used for acetaminophen, salicylate, digoxin, iron, and others. “In many of these situations, if you can identify the compound, there is an antidote available and it can help the patient immediately. Sometimes doctors don’t think they need toxicology testing because they’re just going to do supportive care and it won’t change the treatment, but many people still want to know toxicology results because that can help facilitate treatment and prevent further medical workup down the road.”

Volatile analyses can be done in very particular cases, Dr. Lynch said. “It can be apparent that a patient may have been exposed to something like ethanol, methanol, isopropanol, or acetone. We have had a few cases in our hospital and the usual methodology is using headspace gas chromatography and sometimes GC-MS.” Ethylene glycol or antifreeze is sometimes ingested and there are few methods available for this, she added. Her laboratory uses an enzymatic method to test for ethylene glycol, but most hospitals do not offer such testing routinely.

In 2007, when Dr. Lynch began a postdoctoral fellowship in San Francisco, the laboratory at the hospital had just purchased its first two liquid chromatography tandem mass spectrometers. Developing a comprehensive drug screen on the LC-MS was one of her early missions, giving her an opportunity to compare different mass spec technologies such as LC-MS with GC-MS (gas chromatography mass spec) and HPLC (high-performance liquid chromatography). Around 2009, her laboratory started looking toward high-resolution mass spectrometry (HRMS) and ended up purchasing a QTOF (quadrupole time-of-flight MS).

“When fragmentation happens during testing, each compound has a distinct fragmentation pattern, and with the QTOF you get both the pattern and the accurate mass of the fragments,” she explains. “This is an advantageous technique for identifying small molecules,” and it helps in identifying the compound.

Many laboratories still use immunoassays for toxicology. “We still use immunoassays as well for detecting drugs, but they don’t provide as much information.” They determine the class of drug, not the exact drug. Mass spec can help differentiate between drugs.

However, the data analysis is complex. “You get a ton of data from mass spec, and you need basically a software package to ‘deconvolute’ all that information and help you understand what you are seeing.”

By using a targeted analysis, Dr. Lynch says, the laboratory can validate the compounds detected against spectra in a library that the laboratory has created. A suspect analysis is different, though also targeted in a sense. “A suspect analysis involves a large list of drugs and metabolites that could potentially be in a patient’s sample, and we query the data to see if any of those molecular formulas are present. It significantly expands the number of compounds you can presumptively identify compared to just basic targeted data analysis.” She estimates her hospital has 15 or 20 cases a year in which suspect analysis is the only way the laboratory can identify the agent.

One of these, like a Conan Doyle story, could be titled The Case of the Poisoned Toddler. The case illustrates some of the laboratory’s processes and challenges in finding answers, especially where improbable agents might be implicated.

The patient was an 18-month-old child who presented with diarrhea, vomiting, somnolence, lethargy, and pinpoint pupils. He was bradycardic with first-degree heart block, a temperature of 36.5°C, respiratory rate of 25, and glucose of 101. “This fit very closely with what you see when someone presents with an opioid intoxication. However, his urine drug screen was negative,” Dr. Lynch said.
That didn’t necessarily mean the child had not taken an opioid because some types of opioids are not detected by

the opioid immunoassay. “So the sample was sent to our lab to do high-resolution testing. We did targeted and suspect data analysis. And the suspect analysis was positive for tetrahydrozoline. That’s the active ingredient in Visine eye drops.”

As it turned out, the child had ingested milk that had been adulterated with Visine, which people sometimes think—thanks to a scene in the movie Wedding Crashers—is a harmless prank but is quite dangerous. “There had been a fight in the household and the parent had put Visine in the milk for the grandfather who lived there to drink. However, the child drank the milk.” The child recovered with supportive care and close observation (and child protective services was called in).

Everything the toxicology lab does is dictated by a doctor’s order, Dr. Lynch notes, but her laboratory has worked hard to streamline the process so there’s only one workflow. “A doctor can order a urine drug screen, basically just immunoassay screening, and then it will be automatically reflexed to confirmation by mass spec; the reflex testing is built in. For poisoning and overdose, the doctor can order a comprehensive drug screen with either urine or serum or both. That’s where we would utilize a high-resolution mass spec instrument to determine what the patient may have been exposed to,” although additional testing is needed for such tests as toxic alcohol.

However, high-res mass spec is not yet widely used. “The problem is that the demand is fairly low in certain geographical regions,” and purchasing and maintaining an instrument, and having the expertise to analyze the data, can be costly. Under the traditional model of poison evaluation, hospitals offer only a basic urine screen and some immunoassays, she notes. “If they want to do a larger comprehensive drug screen or a mass-spec-based test, it goes to the reference lab, the turnaround time is days, and the result isn’t available in time to affect patient management.”

The model her institution is trying to promote is based on a practice guideline developed and advocated by the National Academy of Clinical Biochemistry since 2003, which recommends use of regional toxicology labs. Typically, “these labs would interface with poison control centers, and ERs and ICUs in a particular geographical region would be consulting with the poison control center in that region.”

San Francisco General is the site of one such regional toxicology lab. Other major hospitals in the Bay Area use the regional lab when cases of poisoning and overdose are transferred through the Northern California Poison Control Center. About three to five cases per week come in, she says. “Unfortunately, I would say San Francisco has a high percentage of drug use, and new novel psychoactive substances often surface here first.”

For the regional toxicology lab model, which is increasingly being adopted around the country, “the biggest issue is getting the sample to the lab. Once it is there, in a rush we could get a result out in an hour. The data analysis can be quick or may take a little longer, depending on how complex the sample is or how many agents are in the sample.”

In poisoning and overdose, the timing of the test order and results are important variables. “The lab may do no testing at all just because they don’t have the capability or the result would not come in time to affect the patient,” Dr. Lynch says. “But if you think about a patient who might have a seizure, one of the things on a differential for a seizure would be drug use, and if the person doesn’t admit to taking a drug, they could be put on an antiepileptic they don’t need, or have to have follow-up work by a neurologist. If we can provide a result that says you took this drug and this drug is known to cause seizures, then they can stop taking the drug, in which case there would be no need for further medical workup.”

Antidotes, where available for certain drugs, also affect the need for a test order. “If we can determine that the patient has ingested ethylene glycol, ethanol, methanol, or acetaminophen, for example, there are antidotes for those that can help the patient recover quickly. If a person overdoses on an opioid, in those cases they’re going to treat based on the symptoms, but it helps to have the confirmation eventually. Usually, if they get the answer sooner, there’s an antidote such as naloxone for opioid overdose.” In quite a few cases, a test can help in real time. “But there are also a lot of cases where it just helps to provide the answer after the fact to prevent additional

testing and medical workup."

The limitations of urine drug screening assays can be fairly complex, Dr. Lynch says. "A lot of things can cause false-positives and false-negatives. There are interferences, and when you get confirmatory results back for opiates, you need to know the metabolic pathway for the opiates to understand what the patient has taken. Because what you found may not be what the patient took; it may be a metabolite of what they took." Some drugs (like cocaine and heroin) are rapidly converted in the body into the metabolite, while other drugs have a long half-life and can be detected for weeks.

For instance, in another case, a mother gave birth to a baby girl who showed symptoms of neonatal drug withdrawal. "The mother had a previous history of abusing Soma, which is a centrally acting skeletal muscle relaxant. The potential abuse of Soma wasn't recognized until the 1990s but the drug was responsible for more than 300,000 ED visits in 2009," Dr. Lynch said.

The mother denied drug use and pointed to her urine screening throughout her pregnancy, which was negative. "A urine drug screen is not helpful in that type of situation. So we did the comprehensive screen with the baby, and we identified carasoperol and meprobamate, which is Soma and its primary metabolite." The mother, on the same screen, was indeed negative. But child protective services intervened and placed the child in the care of other family members. As it turned out, the next day the mother was found semi-unresponsive in the hospital lobby and said she had taken Soma and Benadryl together.

Urine drug screening is not ideal for assessing poisoning and overdose, Dr. Lynch says, "because people know they can get away with using drugs that aren't detected on your typical urine drug screen. Mass spec instruments in general are ideal platforms for evaluation of these drug poisonings and overdoses." This case illustrates the benefit of a regional toxicology laboratory. But there are many ways of doing this test, she adds. "If your lab doesn't have these capabilities, you can do all of this or most of it using a tandem mass spec instrument as well. You can operate them in full scan mode and use libraries."

Side by side, the different mass spec technologies each have distinctive merits and drawbacks. GC-MS, the long-standing gold standard for drug testing, has high reproducibility in generated mass spectra, and headspace GC is ideal for volatile analysis. "You can purchase large libraries for GC-MS for somewhere in the $2,000 to $5,000 range," Dr. Lynch notes, although her own laboratory has developed most of its own spectra. However, GC-MS requires lengthy sample preparation and cannot detect nonvolatile, polar, and thermally labile compounds.

LC-MS/MS, often considered the new gold standard for toxicology testing, boasts even better sensitivity and specificity, as well as minimal sample preparation. "You can differentiate co-eluting compounds, which is really helpful, and LC-MS/MS has the ability to detect nonvolatile, polar, and thermally labile compounds," Dr. Lynch said. But, on the minus side, LC-MS/MS lacks the large transferable mass spectra libraries, and matrix effects can be an issue.

At the more advanced end, liquid chromatography high-resolution mass spectrometry features less labor-intensive method development, with untargeted data collection ability and targeted, suspect, and untargeted data analysis. LC-HRMS produces positive compound identification dependent upon accurate mass, isotope pattern, fragmentation pattern, and retention time. The technology's downside is the instrument price—and sometimes the scarcity of experienced users.

The advantages of LC-HRMS were evident in another case Dr. Lynch described, in which a poison control medical toxicologist suspected a patient had ingested psychoactive substances.

The patient, an 18-year-old male presenting with vomiting, shortness of breath, chest tightness, and altered mental state, thought he had purchased the designer drug MDMA. "His admissions urine sample was sent for drug screening and was positive for amphetamines, opiates, and THC. So the poison control medical toxicologist requested that we do an extended toxicological screen using high-resolution mass spec." In the meantime, the patient developed cardiogenic shock, requiring an intra-aortic balloon pump and ventilatory support.

The laboratory again began with a targeted approach, Dr. Lynch said. “Our targeted drug screen has about the 200 most common compounds, and the majority of the time it’s going to be on that list. So with the targeted data analysis we found naltrexone, naproxen, fluoxetine, and trazodone. That’s a lot more information than you would get with the urine drug screen, but the medical toxicologist didn’t think those four would be responsible for the presentation.”

Using a suspect analysis, the lab found 4-fluoroamphetamine, or a peak that corresponded to the formula for 4-fluoroamphetamine. But no cases had been reported in the literature when the laboratory did this case. “It’s a substituted amphetamine, a phenethylamine, and a stimulant that causes euphoria and mood elevation.” So although the patient eventually recovered, he had experienced what occurs frequently with designer drugs: The person doesn’t know what he or she is ingesting.

Recently, an ER patient said he thought he had taken a drug with the street name “U-boat.” “We didn’t have that on our targeted list, but we can still run the sample on a mass spec, and then use suspect analysis and look for the formula of a U-boat compound. Then, to confirm or to quantitate it in a sample, we just order the standard test for it. So even if it’s not in your targeted method, you can still look for it.”

Dr. Lynch outlined how some fairly standard but not necessarily helpful test-ordering practices in toxicology can be improved by use of an algorithm. A patient in one emergency presented with anion gap metabolic acidosis, a fairly common situation, in which some type of volatile ingestion is suspected. Here, the patient was a 50-year-old man found unconscious in his home with a Glasgow Coma Scale of three.

“Most of the things you think about doing for toxicology testing”—creatinine, LFTs, urine drug screen, APAP, salicylates—“were negative,” Dr. Lynch said. But the patient’s lab findings, remarkably, were a bicarbonate of 5, very high osmolal and anion gap, pH low at 6.7, and lactate above the upper limit of quantitation. “You don’t see that very often, and that’s kind of a clue to what was going on in this case.”

Dialysis was ordered, since the clinicians knew the patient had been exposed to something, but the patient died before dialysis could start. Dr. Lynch believes that ordering a lactate in such cases should be the first order of business. If the lactate is not positive, she said, then a blood glucose or urine ketone bodies may be helpful in determining if a patient may be in diabetic ketoacidosis or lactic acidosis.

“We get cases where a doctor will call and say, ‘I have a patient in anion gap metabolic acidosis. I think they have ingested methanol or antifreeze.’ If they haven’t ordered a lactate or a beta hydroxybutyrate yet, I say, ‘Okay, let’s do those tests first’—because we don’t see volatiles that often.” In fact, this patient, who turned out to have positive ethylene glycol of 162 mg/dL, was the only case she has encountered that was positive for ethylene glycol following such a presentation.

Sometimes toxicology results may not be helpful even though the patient’s symptoms are probably toxicology related. Dr. Lynch described the case of a patient who had been using LSD and marijuana with friends, began seizing, and was found unresponsive by an emergency medical support team. “He was taken to the ED still having seizure activity and was sedated, paralyzed, and intubated. And a lot of labs were sent.”

The lab tests revealed the patient had anion gap metabolic lactic acidosis, profound leukocytosis, early rhabdomyolysis, and hyperglycemia. “His electrolytes were normal and his troponin was negative, which is good, but the urine drug screen was positive for opioids and cannabinoids, which didn’t necessarily fit with the clinical presentation.” The treating physician suspected a novel psychoactive substance and requested an extended screen.

Using a suspect analysis, “we found a nice peak for 2,5-Dimethoxy-4-chloroamphetamine, known as DOC. The acquired spectra of the patient sample and the product ion spectra of the standard were almost a perfect match. So we felt fairly confident that was what was present.”

A potent hallucinogen, DOC had been reported by the U.S. Drug Enforcement Administration as showing up near San Francisco in 2007. “It’s sold as blotter acid or as tabs, so you could see how someone may get confused thinking it’s LSD. But in reality it’s a designer drug.”

In this case, the patient recovered with supportive care but was discharged with a diagnosis of seizure due to ingestion of DOC. “This is helpful knowing that he had ingested something that caused the seizure, rather than having maybe an underlying seizure disorder triggered by the marijuana or LSD.”

A more typical case was a patient found wandering on the highway ramp, appearing dazed, and admitted to San Francisco General for altered mental status. The patient had normal lab results but showed normocytic anemia and transaminitis, plus elevated liver enzymes, AST and ALT, and a prolonged QT interval, which can be caused by a number of different compounds and is a biomarker for ventricular tachyarrhythmias, which can lead to sudden death.

“His urine drug screen was positive for EDDP, or methadone, and benzodiazepines, which was interesting though not necessarily helpful. However, methadone can cause QT prolongation, so doctors were curious if it was just the methadone that was causing it or if something else was going on.”

The targeted data analysis found clonazepam, venlafaxine, and methadone. “All of these were prescribed, but we also identified promethazine, which can cause a QT prolongation as well and is an additive risk when taken with methadone.”

In talking with the director of the methadone clinic, Dr. Lynch learned that promethazine was being sold outside the clinic. “Prior to discharge, the patient admitted to having taken half a bottle of Phenergan, which is promethazine, with his methadone to get high.” While many doctors don’t know that people try to get this medication to take with their prescribed opioids, “we actually have identified it in 26 percent of our methadone maintenance urines and in nine percent of chronic pain patients’ urines.”

The lesson for the laboratory from this case is the value of high-resolution mass spectrometry, Dr. Lynch says. “You’re collecting data in an untargeted manner so you can query the data for any compound, basically. So even retrospectively, if we identify a new drug that’s being used, we can look back at our cases from two years ago and query the data to see what’s there. It’s a powerful tool to help you identify new, emerging compounds, especially when people are selling drugs as one thing when they’re something else.”

Two recent outbreaks in the Bay Area involved patients who purchased Xanax on the street and then presented at the ER with symptoms more like those of an opioid overdose. “We quickly identified that the drugs contained fentanyl as well as a compound that was not on our targeted list, a non-FDA-approved benzodiazepine called etizolam.”

The second outbreak caused quite a few deaths after people thought they were purchasing the drug Norco on the street but were actually buying a drug that contained high levels of fentanyl. “We were able to quickly analyze the pills and then send out statements to warn people that if they get people who were purchasing Xanax on the street, it was most likely an opioid overdose.” The HRMS analysis became important from a public health standpoint.

Oral antidiabetic agents can sometimes be to blame when patients present with hypoglycemia and no one knows why. “We’ve had a couple of cases where illicit drug users have purchased a drug on the street that they thought was one thing but in reality it was an oral antidiabetic agent. Some of the early effects of a hypoglycemic agent can be somewhat similar to a benzodiazepine and a person may think it’s actually having an effect. But the only way you can determine if the symptoms are drug related is to do an MS-based test.”

The adoption of the regional toxicology laboratory model and the increased use of HRMS as well as other mass spectrometry in toxicology are proving helpful in quicker identifications and better patient management options in cases of poisoning or overdose, Dr. Lynch says.

“We in the clinical laboratory shouldn’t be afraid of new technologies that are utilized in other industries like the research lab and drug development,” she says, noting that her research is often geared to seeing how other technologies might benefit diagnostics, especially in smaller areas like poisoning and overdose. “We should really try to explore these technologies because they can have a major advantage in clinic settings or patient care.”
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