Drug overdose deaths and toxicology tests: Let's talk

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December 2018—Drug overdose deaths in the United States continue to rise, and recently many of these deaths have been attributed to opioids, including fentanyl, fentanyl analogs, and other opioid receptor agonists. The rise in drug overdoses and drug-related deaths, and the devastating effects of the opioid crisis, highlight the need for communication and coordination among forensic pathologists, hospital clinicians, and laboratorians.

Typically, coordinated efforts between these groups in death investigations are few or nonexistent. In fact, non-forensic health care providers are often unaware of the challenges their forensic pathology colleagues face and may not fully understand how their collaboration with forensic pathologists might have an impact on public health. The lack of a coordinated effort to foster communication among these groups results in a lost opportunity to collectively raise the level of awareness of the emergent public health crisis, obscures the extent and prevalence of the various types of drugs being used, and diminishes efforts to reduce the overall rate of drug overdose deaths.

Hospital-based pathologists, laboratory professionals, emergency department physicians, and hospital administrative personnel should work with local medicolegal death investigation offices to establish protocols for collecting and retaining appropriate blood samples for eventual toxicologic analysis in cases in which patients are admitted for a suspected drug overdose and eventually die. We will present five cases that illustrate the importance of quantitative toxicologic testing and collaboration between medical examiner/coroner (ME/C) and hospital staff.

Drug overdose deaths fall under ME/C jurisdiction and require unbiased and scientifically sound cause of death determinations. Fundamental and often pivotal components of those determinations are the decedent's medical history, circumstances involving the death, collection of appropriate specimens, postmortem examination, integration of comprehensive laboratory tests, and a recognition of the unique requirements for the interpretation of postmortem results. Despite a thorough investigation and the attention given to these components, questions about the cause of death may persist in some cases. A collaborative effort among the ME/C community, clinicians, hospital pathologists, and laboratories—especially when there is suspicion of drug-related involvement—is critical in ensuring that these deaths are categorized accurately and the certification of death is appropriate.

Postmortem and antemortem specimens. Biological specimens collected during an autopsy and submitted for toxicological analysis are typically considered the gold standard for providing information to assist in determining the cause of death in cases of suspected drug overdose. Without question, the reliability of toxicology results relies heavily on the fidelity of the specimen collection process. Forensic pathologists are trained in multiple aspects of specimen collection protocol, including the selection of a suitable specimen container, collection of an appropriate volume of specimen, proper specimen labelling, and storage in a manner that best preserves endogenous and xenobiotic constituents until the specimen can be delivered to the testing location. In certain cases, however, it may not be possible to establish the cause of death by analyzing postmortem specimens, and the availability of blood collected prior to death becomes critical.

Patients who have overdosed may be hospitalized for hours, days, or even weeks prior to death. This interval provides time for the body to significantly metabolize drugs and alcohol, leading to lower or undetectable drug levels in postmortem specimens. Additionally, resuscitative efforts such as high-volume fluid restoration may have a diluting effect on drug or alcohol concentrations in postmortem specimens. In such cases, blood samples procured soon after hospital admission can be essential in ascertaining which drugs were present and to what degree they likely contributed to death. These antemortem blood samples generally reflect the substances circulating throughout the body prior to death, have the potential to provide information about the likelihood that a

toxic effect was produced, and have the advantage of eliminating potential interpretive issues associated with changes in the concentration of drugs or other substances in the blood due to their movement from one area of the body to another after death (postmortem redistribution).

Antemortem specimens also make it possible to perform a quantitative and comprehensive array of toxicologic testing. Unfortunately, in many hospitals, unused antemortem specimens such as blood, plasma, or serum are discarded relatively rapidly, often triggered by the results of urine drug screen results. Urine drug screens are used extensively in the clinical setting to corroborate a clinical suspicion of drug overdose; however, while urine drug screens may be adequate in the hospital setting, they do not provide the quantitative blood levels necessary to determine whether a drug contributed to death. Also, many designer drugs such as fentanyl analogs are not currently detected by standard urine drug screen panels, and urine drug screening immunoassays are subject to many false-positive and -negative results. As such, for the purposes of identifying potentially lethal substances in the setting of clinically suspected overdose, urine testing is inadequate.

If the overdose results in death, only quantitative blood testing provides sufficient information to confidently certify overdose deaths. Testing of antemortem blood samples collected in the hospital setting is of paramount importance in these cases. Unfortunately, even in instances where unused antemortem specimens are successfully requisitioned by the ME/C prior to disposal, sample quantity or a compromise in specimen quality due to handling or storage conditions may result in a specimen that is suboptimal for toxicological analysis. Thus, collaboration among forensic and hospital pathologists, other hospital clinicians, and laboratorians is key to ensuring that necessary samples are collected, procured, and retained prior to death in suspected drug overdose cases.

Specimen collection and death certification. Given the importance of the type of specimen needed for analysis, the required specimen type should be defined clearly in preanalytical protocols. Numerous collection tube additives exist (typically identified by the tube closure/stopper) and must be considered because not all additives are interchangeable and suitable for all testing. The antemortem collection of blood in a collection tube that contains an anticoagulant and preservative additive should be a requisite component of any care set designated for suspected drug overdose cases. The conventional gray stopper tube, which contains the anticoagulant potassium oxalate and the preservative sodium fluoride, is ideal for this purpose. Immediately after specimen collection, the gray stoppered tube should be gently inverted several times to ensure proper mixing of the anticoagulant and preservative with the blood. This mixing results in a specimen that is not clotted and affords a degree of protection from degradation. Upon centrifugation the mixed specimen yields plasma; without centrifugation the specimen is considered sodium fluoride-enriched whole blood. For some testing scenarios, the distinction between the use of plasma versus whole blood or the use of serum is important and may have a bearing on test results. The specific additive required depends on the laboratory's testing method. For example, if an analytical method employs the use of plasma in the analysis of ethanol (alcohol) rather than whole blood, the plasma alcohol result is expected to be approximately 15 percent higher than in a concomitantly collected whole blood specimen. Despite some testing limitations, the ubiquitous gray stoppered tube is the preferred specimen collection tube for toxicology analysis. Arrangements for proper storage of specimens is required before, during, and upon completion of testing.

Specimens not meeting these criteria are generally deemed unacceptable but should not be discarded without consultation with the toxicologist, forensic pathologist, or both. Occasionally, a specimen deemed unacceptable for one test might be acceptable for another test or be acceptable for the requested test provided the laboratory has an ancillary method in its armamentarium. When decisions are being made about analytical testing, heed should be given to the adage coined during the early years of computer science: "Garbage in, garbage out." The integrity of analytical testing results relies not only on the quality of the specimen collected but also on adherence to documented and well-purposed preanalytical, analytical, and postanalytical practices.

Particularly when deaths are related to drugs/toxins, the ME/C community is strongly advised to be as specific as possible on death certificates about the drugs involved in a given death. As such, the use of nondescript, general terms or phrases, such as "mixed drug intoxication" or "opiate overdose," is discouraged. The use of such terms does not allow for adequate tracking of individual drugs related to death. Without knowledge of the specific drug

types involved in death, devising appropriate preventive strategies is more difficult. To determine which drugs are involved in a particular death, forensic pathologists rely on the performance of toxicology testing on blood samples collected at or shortly after the drug-related event/death.

Here are the five cases that illustrate the importance of quantitative toxicologic testing and collaboration between ME/C and hospital staff.

Case No. 1: Opioid-related death occurring outside hospital setting. A 57-year-old male with a known history of substance abuse was found dead in his bed. A medical examiner autopsy was performed. Internal examination revealed pulmonary emphysema and mild atherosclerosis. The combined lung weight was 2,040 grams. A postmortem urine drug screen was positive for methamphetamine, alprazolam, fentanyl, norfentanyl, morphine, 6-monoacetylmorphine (6-MAM), codeine, and hydromorphone. Toxicology tests performed on postmortem femoral blood revealed the following: alprazolam: 13.7 ng/mL; fentanyl: 22.4 ng/mL; morphine: 15.1 ng/mL; acetylfentanyl: 136 pg/mL. The cause of death was ruled "combined toxic effects of fentanyl, acetylfentanyl, heroin, and alprazolam."

The markedly heavy lung weights in this case represent a classic finding in opiate-related deaths. The urine toxicology results provide insight into why it is important to use blood levels (rather than urine levels) when attempting to determine which drugs are involved in a death. For instance, had urine results alone been used, methamphetamine would likely have been considered a contributing factor in the death.

Case No. 2: Opioid-related death occurring acutely within hospital setting. A 26-year-old female with a history of polysubstance abuse was found unresponsive and emergently transported to the emergency department. She had a history of multiple intentional and unintentional drug overdoses, suicidal ideation, depression, and anxiety. A urine drug screen in the ED was positive for opiates, cocaine, and amphetamines. She was admitted to the intensive care unit, diagnosed with anoxic brain injury, and pronounced brain dead two days later. Following organ and tissue donation, her body was transported to the medical examiner for autopsy. Autopsy disclosed no significant findings other than changes consistent with anoxic encephalopathy. Autopsy samples were not tested. Admission hospital blood samples were positive for acetylfentanyl, at a level of 1,121 pg/mL. The cause of death was ruled as "complications of acetylfentanyl toxicity."

This case highlights the fact that admission hospital blood samples can be essential in identifying the drug(s) responsible for death. In addition, the case is a good example of situations in which designer opioids can be considered the sole cause of death.

Case No. 3: Opioid-related death following prolonged hospital admission (blood sample available but quantity insufficient for complete testing). A 29-year-old male with a history of heroin abuse was found unresponsive and transported to the ED via ambulance. A urine drug screen performed on admission was positive for opioids and marijuana. He was admitted to the ICU but subsequently diagnosed with anoxic encephalopathy and died three days later. His body was sent for medical examiner autopsy, which revealed slight cardiomegaly and mild coronary artery atherosclerosis. Admission and subsequent hospital blood samples were retained and tested, but the quantity of samples was insufficient to perform complete toxicologic testing. Autopsy blood samples were not tested due to the several day hospital stay. The cause of death was ruled "toxic effects of opioids" with a contributing cause of "cardiomegaly."

This case represents an example of a situation in which hospital blood samples were still available for testing, but insufficient sample quantities resulted in the inability to determine a definitive cause of death. Had a higher volume of blood been available, testing could have provided definitive results. Additionally, if blood had been collected in a gray-top tube, the testing would have been even more suitable for toxicology testing.

Case No. 4: Opioid-related death following prolonged hospital admission (no blood sample available). A 30-year-old woman with a known history of drug abuse and depression was found with altered mental status and an empty Norco pill bottle on her lap. Emergency medical services administered Narcan, after which there was noted respiratory improvement but the patient remained obtunded. She was transported to the emergency

department, where a urine drug screen was positive for opiates, amphetamines, cocaine, and THC. She was admitted to the ICU with a diagnosis of suspected drug overdose. After a 20-day stay in the ICU, which was complicated by aspiration pneumonia and acute respiratory distress syndrome (ARDS), the patient died. The case was referred to the medical examiner. No hospital admission blood was available for testing. Autopsy disclosed diffuse alveolar damage, consistent with the clinical impression of ARDS. The cause of death was certified as "complications related to a drug overdose."

This is an example of a classic case where a final, definitive answer regarding which drug(s) was/were responsible for death could not be determined. Without knowledge of the specific drugs present within the patient's blood on admission, there is no possible way to provide such valuable information on the death certificate. Although several drugs were evident in the urine on admission, relying on urine test results is not acceptable and allowed the certifier only to provide very general terms about the cause of death.

Case No. 5: Opioid-related death following prolonged hospital admission (blood sample collected in gray-top tube available for testing). A 52-year-old woman was at home with her family when she began to have difficulty breathing and became unresponsive. Paramedics intubated her and transported her to the local hospital where resuscitative efforts continued. An admission urine drug screen was negative. An admission tube of blood was collected in a gray-top tube and stored in the blood bank, as per established hospital protocol. Ultimately the patient remained on a ventilator for seven days before being pronounced dead. Further questioning revealed that she had purchased "Percocet" from an unknown individual the same day she was admitted to the hospital. Due to this history, and a known cluster of overdoses within a similar geographic area and time frame, the body was transported to the medical examiner for autopsy. The hospital admission blood sample was requisitioned and submitted by the ME for toxicologic analysis. Autopsy revealed acute (presumed ventilator-associated) bronchopneumonia. Testing performed on postmortem blood revealed only hospital-administered therapeutic drugs. The admission blood, however, was positive for cyclopropyl fentanyl and U-47700. The cause of death was certified as "acute intoxication of cyclopropyl fentanyl and U-47700."

This last case is an example of a situation in which the hospital, laboratory, and ME/C had previously established a mutually agreed upon protocol, such that all hospital admissions for suspected overdose included collection of an admission blood sample, retained in a sodium-fluoride (gray-top) tube, with the specimen stored for the patient's entire hospital stay. The benefits of such a protocol are twofold: Admission blood remains available for ME/C use should the patient die, even if the survival time exceeds the usual length of time that lab blood samples are retained, and the blood sample for subsequent ME/C testing is collected in a gray-top tube, which is the preferred sample for toxicology testing.

Conclusions. Although practices and protocols are likely to vary from hospital to hospital and from jurisdiction to jurisdiction, the following general recommendations may be applied to any hospital laboratory regarding the collection of blood samples for potential forensic testing in suspected drug overdose cases. It is unlikely that every jurisdiction and hospital will be able to employ the same protocols to assist ME/C offices in providing the most useful and correct information for death certification purposes in opiate and other drug-related deaths. However, several options exist. When considering how hospital laboratories can assist in these cases, the following options should be considered, either separately or in combination:

- Lengthen the amount of time all blood samples are retained in the laboratory prior to disposal.
- Selectively save blood samples from patients admitted for suspected drug overdoses, and do not dispose until patients are discharged (or die, at which time samples are to be sent to the ME/C).
- Implement a policy wherein a gray-top tube of blood is collected in all suspected drug overdose admissions, with samples retained as indicated

in the preceding second option.

- Notify law enforcement of admissions for drug overdose, with subsequent court-ordered blood draws for drug quantification (similar to cases of alleged drunk driving, where law enforcement obtains court order to obtain blood samples).

Identification of the appropriate tests to be ordered, proper specimen collection, accurate laboratory testing, timely reporting of test results, and the interpretation of test results are each essential parameters in diagnosis, prognosis, and providing guidance in health care decisions. However, communication regarding these parameters within the various health care groups and across multiple disciplines is lacking, thus stifling access to a collection of the best available information that might be resourced to develop effective health care strategies. In our quest to provide comprehensive patient-centric health care services, a collaboration among forensic and hospital pathologists, hospital clinicians, and laboratorians can improve death certification accuracy, ensure more focused monitoring and publication of drug overdose death trends, and ultimately better prevent future overdose deaths.

This article was written on behalf of the CAP Forensic Pathology Committee, of which Dr. Prahlow is vice chair and Dr. Brooks is a member. Dr. Brooks, a forensic pathologist, is associate professor of pathology and residency program director, Department of Pathology and Laboratory Medicine, University of Wisconsin Hospital and Clinics, Madison. Dr. Prahlow, a forensic pathologist, is deputy medical examiner, professor of pathology, and vice chair of the Department of Pathology, and Dr. Jones, a forensic toxicologist, is associate professor, Department of Biomedical Sciences—both at Western Michigan University Homer Stryker MD School of Medicine, Kalamazoo.