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PROCEEDINGS

From Death to Death Certificate: What do the Dead say?

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Abstract This is an overview of medicolegal death investigation and death certification. Postmortem toxicological analysis, particularly for ethanol and drugs of abuse, plays a large role in the forensic investigation of natural and unnatural deaths. Postmortem drug concentrations must be interpreted in light of the autopsy findings and circumstances. Interpretations of drug and ethanol concentrations are important for death certification, but they also may be important for other stakeholders such as police, attorneys, public health practitioners, and the next-of-kin.

Keywords Forensic pathology · Toxicology · Opioids · Ethanol · Autopsy · Death certification

Introduction

The goals of these proceedings are to provide an overview of medicolegal death investigation and discuss death certification. It will focus on the forensic pathology aspects of drug and ethanol abuse. There is a Latin inscription in the New York City Office of Chief Medical Examiner that states: "Taceat colloquia. Effugiat risus. Hic locus est ubi mors gaudet succurrere vitae," which translates to: "Let conversation cease. Let laughter flee. This is the place where death delights to help the living." Although forensic pathologists in the USA are largely involved with death investigations, we hope and believe that our work helps the living.

Forensic Pathology

Forensic pathology is a subspecialty of pathology involved in the examination of the living and the dead in order to provide an opinion concerning the cause, mechanism, or manner of a disease, injury, or death. Of the greater than 1,000,000 physicians in the USA, there are approximately 500 practicing board-certified forensic pathologists. In order to become a forensic pathologist, following medical school, one must complete a residency in anatomic or anatomic/clinical pathology and then a fellowship in forensic pathology. Passing two national examinations is required to become a board-certified forensic pathologist.

Medical Examiners and Coroners

In the USA, there are two public death investigation systems: the medical examiner (ME) and the coroner (C) system which vary by jurisdiction such as by State or County [1]. For example, Connecticut has a state-wide medical examiner system while New York State has a mixed ME/C system by county. Coroners are typically elected officials who may not be required to have a medical degree. Medical Examiners are usually forensic pathologists and are typically appointed by some government agency. ME/C systems themselves vary in quality, but the key to assure accurate death certification is to have a forensic pathologist involved. There has been a general trend in the US toward medical examiner systems [1]. Interestingly, some coroners are funeral directors, which may create an appearance of a conflict of interest if their business could be affected by their certification of death.

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Death Investigation and Public Health

In general, death investigation systems need the authority to take charge of the body, perform an autopsy without permission, and subpoena records. The forensic pathologist will determine the cause and manner of death, testify at criminal and civil trials, teach, and monitor the public health.

There are certain deaths that by law are reportable to the ME/C. These vary slightly from jurisdiction to jurisdiction but generally include the following: accidents, suicides, and homicides. In addition, the following also may be reportable: deaths due to disease with potential public health threat, deaths resulting from employment, and sudden and unexpected deaths not caused by a readily recognized disease. These investigations typically involve an autopsy, which includes an external examination and an internal dissection of the body. The goal of the autopsy is to determine the cause of death and assist in determining the manner of death.

There are numerous ways that a forensic pathologists work benefits the living such as reporting certain deaths to the FDA MedWatch program, which tracks adverse medical events including deaths due to medications and medical devices. For example, a young woman was found dead in bed. At autopsy, she had coronary artery disease and sibutramine was detected in her blood. She had been using an over-the-counter weight loss herbal remedy. Testing of the remaining herbal supplement also detected sibutramine (an amphetamine derivative), linking the autopsy findings with the implicated product. Her death was determined to be due to a combination of her heart disease and this prescription medication that was surreptitiously added to this over-the-counter dietary supplement [2]. Her death was reported to the FDA MedWatch program [3]. Other examples of public health benefits include identification of faulty cribs that may result in fatal entrapments of infants (reported to the Consumer Product Safety Commission) and identification of infectious diseases such as meningitis (reported to the CDC or health department).

In addition, autopsies also help monitor the public health, identify new and changing disease (e.g., West Nile Virus), produce accurate death certificates for vital statistics, assess the quality of medical practice, compare and relate premortem and postmortem clinical and pathological findings and diagnoses, evaluate the safety and effectiveness of new therapies, reassure family members, and instruct medical students and physicians [4–6].

The Autopsy

The autopsy (including toxicological testing) is a battery of laboratory tests that must be interpreted in the light of the history. It begins with an investigation (medical record review, scene investigation, discussions with family or police). Similar to clinical medicine, forensic pathologists begin with the history and form hypotheses and then perform a physical examination (the autopsy) and other laboratory tests (microscopy, toxicology) to support or refute these hypotheses. During this process, the forensic pathologist is forming, testing, refining, and rejecting hypotheses.

The examination of the body includes the gross (external and internal) exam, removal of tissue specimens for toxicological testing, microscopy, and DNA analysis as indicated. Consultants (anthropology, entomology, odontology, anesthesiology, medical toxicology) are retained as needed. The technical components of performing an autopsy dissection are fairly standard for hospital and forensic autopsies. Aside from the occasional limited hospital autopsy to answer a specific diagnostic question (e.g., what was the nodule in the liver?), both autopsies are concerned with determining the cause of death. One major difference between hospital and forensic autopsies is toxicological analysis, which usually is not done with hospital autopsies. Typical forensic autopsy toxicology specimens include the following: blood (peripheral preferred, collected with sodium fluoride, NaF), vitreous humor, urine, liver, brain, and gastric contents. Peripheral blood samples are preferred to minimize the effects of postmortem redistribution that occurs with some compounds in central/cardiac samples (see below). Sodium fluoride has anticoagulation and antimicrobial properties that prevent in vitro production of ethanol. It also slows/prevents the spontaneous hydrolysis of cocaine to benzoylecgonine (BE). In order to certify an acute cocaine intoxication death, the detection of cocaine (not just BE) is usually needed.

Vitreous Humor

The vitreous humor, as opposed to blood, is the preferred postmortem sample for glucose and electrolyte analysis. The vitreous glucose concentration decreases after death; therefore, a vitreous glucose concentration of greater than 200 mg/dL supports a diagnosis of diabetes. Sodium, potassium, chloride, urea, and creatinine also can be assessed in vitreous. Although these may vary with postmortem interval, they change in a predictable pattern. Creatinine and urea are relatively stable and elevations may indicate dehydration or kidney failure. Postmortem vitreous testing has been proposed to estimate postmortem interval (by the rate of the rise of potassium) although it is not widely used. Vitreous ethanol testing may help determine if the decedent is in the pre-or post-absorptive phase by comparing the vitreous alcohol concentration (VAC) to the blood alcohol concentration (BAC). As vitreous has relatively more water than blood (1.3:1) and ethanol distributes in total body water, the ratio of VAC to BAC is 1.3:1 following absorption and equilibrium. If the $BAC \geq VAC$, the decedent would still be in the absorptive phase unless other processes such as postmortem ethanol production has occurred (see below).

Hair

Testing of hair is not part of routine forensic toxicology analysis. Generally, forensic pathologists are interested in acute intoxicants. Hair provides information about chronic drug or toxin use/exposure. Analysis of hair is useful to document abstinence, for delayed testing in suspected drug-facilitated sexual assault cases, and to examine long-term drug use/exposure history particularly when done as segmental analysis.

Urine

Urine is a common screening specimen in forensic toxicology and is the usual specimen tested in hospital/clinical laboratories. Some drugs or metabolites may be detected in the urine for a longer period of time than in the blood. This is a useful feature for a screening specimen which can then guide further confirmatory testing in blood or tissue. Because urine is stored in a reservoir (the bladder), care must be taken with interpretation of drug concentrations as blood-urine ratios may vary and one may not know how much urine was in the bladder before one ingested the drug. As urine has relatively more water than blood, for ethanol, the ureteral urine ethanol concentration would be higher than for blood. This ureteral urine to blood conversion factor (~1.3:1, urine to blood) is for urine just produced by the kidney which cannot be collected after death. Therefore, an ethanol concentration from postmortem bladder urine should not be used to estimate the BAC. In decomposed remains, toxicology samples include skeletal muscle or maggots as blood may not be available.

Intoxication Deaths

Intoxication deaths are largely functional deaths and there are few definitive gross or microscopic findings at autopsy to confirm the diagnosis. The methods described in *Final Exit*, a book that provides methods to commit suicide, are an example of this phenomenon [7]. In these deaths, a person may ingest a sedative and then place a plastic bag over the head secured around the neck with rubber bands. Although these are pure asphyxial deaths, if the bag was removed prior to discovery by the police, the ME/C may not be able to determine the asphyxial versus toxicological nature of the death. Helium also has been used with this method to inflate the bag and displace the oxygen [8, 9].

Other autopsy findings that suggest drug use or abuse include the following: powder residue in the nostrils, histopathological changes (e.g., foreign body giant cell granulomas in the pulmonary vasculature), gingival hyperplasia (side effect of phenytoin), linear scars over subcutaneous veins (track marks), and round depressed scars with a non-vascular distribution of the extremities consistent with skin popping [10–13]. All of these signs, except the first one, are indicators of chronic drug use; they do not, however, prove that the use continued at the time of death.

Non-toxicological testing can identify some poisoning deaths. Ethylene glycol is one of the rare intoxications in which there may be microscopic findings to make or at least suggest the diagnosis. Calcium oxalate crystals will be found in the kidneys under polarized light. Other findings that might suggest an intoxicant include odors (e.g., almond smell of cyanide [14]), corrosive mucosal changes of the gastrointestinal tract [15, 16], or discoloration (e.g., hydrogen sulfide's green discoloration of the brain [17, 18]). For suspected insulin intoxications, testing for insulin and c-peptide concentrations may provide support for the administration of endogenous insulin [19].

Postmortem Interval

Estimating the postmortem interval, unfortunately, is not as accurate as it appears in various media representations. The circumstances and the changes in rigor (stiffening), livor (color), and algor mortis (temperature) are the classic postmortem observations for determining the time of death. Such autopsy findings may narrow the time range, but only imprecisely as there are a number of environmental (e.g., temperature) and body factors (size, cause of death) that may affect them.

Death Certification

The death certificate lists the cause and manner of death. The cause of death is the disease or injury responsible for the fatality. The manner of death is an explanation of how the cause arose. Typically, only ME/C can certify an unnatural death certificate. Proper death certification has multiple benefits. In addition to cataloging national vital statistics for the cause of death, it can individually assist with proper life insurance claims (accident vs. natural may have different benefits), social security benefits, and resolutions of estates. Police and prosecutors may use it for internal administrative purposes (e.g., close a case).

The manners of death include the following: natural, homicide, suicide, accident, therapeutic complication, and undetermined. The proximate (underlying) cause of death is that which in a natural and continuous sequence, unbroken by any efficient intervening cause, produces the fatality and without which the end result would not have occurred (must be an etiologically specific disease or injury). Most intoxication deaths due to substance abuse are certified as accidents and are based on the autopsy, circumstances, and toxicology findings.

Natural deaths are those caused exclusively by disease (or old age). Homicides are violent deaths at the hand of another person or deaths due to the hostile or illegal acts of another person. Suicides are violent deaths caused by an act of the decedent with the intent to kill him/herself. For suicides, there must be a preponderance of evidence showing an intent to die. Accidents are deaths caused by violent means that are not an intentional or criminal act by another. Most substance abuse drug intoxication deaths and motor vehicle collisions are certified as accidents.

There are three main factors that a forensic pathologist considers to certify a death as due to an intoxication. First, the autopsy (or medical investigation in delayed deaths) fails to disclose a disease or physical injury whose extent or severity is inconsistent with continued life. Second, the toxicology results are in the range typically encountered in such deaths. And third, the history and circumstances are consistent with a fatal intoxication. Drug concentrations, per se, usually are not determinative of cause of death. Toxicological data are no substitute for an entire case study and the exercise of medical judgment in the evaluation of these deaths. Particularly with instances of chronically used (methadone) and abused (heroin) substances, tolerance and other variables produce a wide range of drug concentrations that often overlap in the living and the dead [20]. Postmortem redistribution and the postmortem interval also may affect these concentrations [21–25]. Postmortem redistribution is the change that occurs in drug concentrations after death with the redistribution of drugs, for example, into the blood from the lungs, liver, or myocardium. Drug properties such as volume of distribution, lipophilicity, and pKa are important factors as to how much a specific drug will redistribute [26]. Blood from peripheral sources (e.g., femoral vein) are preferred postmortem toxicological samples to lessen the impact of postmortem redistribution effects. Central samples (e.g., cardiac) are more prone to the effects of postmortem redistribution with certain drugs (e.g., digoxin).

Opioid Deaths

Most opioid deaths occur acutely although some may be delayed by hours, days, or years. A 35-year-old man with a history of substance abuse was found dead on the bedroom floor of a friend's apartment. According to the friend, the night before, they were drinking beer and using cocaine and heroin. The decedent had gone to sleep on the floor and was "snoring very loudly during the night." He was found dead the next morning along with a nearby syringe and an empty prescription bottle. There was foam from his mouth and pulmonary edema at autopsy. There was no disease or physical injury at autopsy to explain his death. The toxicology analysis detected ethanol 0.07 g%, morphine <0.05 mg/L, cocaine < 0.05 mg/L, and benzoylecgonine (BE) <0.05 mg/L. Morphine, codeine, 6-acetylmorphine, cocaine, and BE were detected in the urine. The death was certified as an accidental acute intoxication. The drug concentrations and circumstances are consistent with a survival interval of hours.

The mechanisms of death with opioids may include a slow respiratory depression often accompanied by coma with pulmonary edema and foam from the mouth. But there also are instances that appear more sudden with the tourniquet still found on the arm and the syringe in the hand. These may be more related to concomitant use of other drugs with direct cardiovascular effects (e.g., torsade de pointes), rapid respiratory depression (ultra-potent opioids), neurologic effects (e.g., fentanyl chest wall induced rigidity), or impurities [27]. Pulmonary edema is common with opioid fatalities; however, edema/foam is not limited to intoxication deaths. It may occur with drownings, seizures, heart disease with congestive heart failure, and neurogenic mechanisms. Other "soft" autopsies findings in opioid deaths include a distended urinary bladder, enlarged porta-hepatis lymph nodes, splenomegaly, and patterned skin scars.

In multidrug intoxications, it usually is not possible to tease out an individual drug's role. Therefore, it is customary to include all the drugs (with concentrations greater than trace amounts) in the cause of death statement. In rare instances, if one drug concentration is markedly elevated and consistent with the cause of death, or if one of the identified toxins is substantially more likely to be implicated, it may be listed alone. Generally, any drug is included when it may have a synergistic effect or explain death by itself. Therefore, in a suspected opioid death in which oxycodone and acetaminophen are detected, only the oxycodone would be included in the cause of death. To distinguish an accidental from a suicidal intoxication death, the circumstances, toxicology concentrations, gastric contents, and pill counts all may be useful. Due to postmortem redistribution and survival intervals, judgment must be exercised when interpreting postmortem drug concentrations.

The death of Karen Ann Quinlan is an example of a death due to delayed accidental drug intoxication. The underlying cause of death was the acute intoxication even though it occurred 20 years before she died. The manner of death is accident and the death is reportable to the ME/C despite the prolonged interval. She would not have died at this time from complications of the anoxic-ischemic encephalopathy "but for" the intoxication.

Suicide and gastric contents

It is rare to detect multiple intact pills in the gastric contents of a decedent with a suicidal ingestion. Usually a clump of congealed colored material or non-specific material is found. Testing of a sample of gastric contents provides a drug concentration which is then multiplied by the total volume of the stomach contents. This calculation will provide the total dose of drug in the stomach, which may provide an indication of an intentionally harmful act.

Ethanol

Forensic pathologists encounter the acute and chronic effects of alcohol on a daily basis. External signs of potential chronic alcoholism include jaundice, gynecomastia, pectoral wasting, ascites, testicular atrophy, and trauma (scattered contusions of varying ages of the legs, so-called "whisky bumps"). On internal examination, one may find injury such as subdural hematomas or splenic laceration, steatosis and/or cirrhosis of the liver, varices, acute and chronic pancreatitis, atrophy of the superior cerebellar vermis, necrosis of the mammillary bodies (Wernicke encephalopathy), and various other intoxicants including drugs of abuse and various alcohols (ethanol, isopropanol). Fatal internal injuries may occur with little if any external evidence of trauma. Since chronic alcoholics are at increased risk for a variety of injuries [28], a low-threshold is needed to perform an autopsy as it is required to exclude occult trauma that may be accidental or homicidal in manner.

As most alcohol is absorbed in the small intestine, the amount of gastric contents will affect the rate of absorption and the subsequent BAC. Ingestion of ethanol on an empty stomach will result in a higher and more rapid initial peak of blood-alcohol [29]. If there is survival interval following an injury (e.g., after a motor vehicle collision), one may obtain hospital admission blood for testing and/or test the vitreous fluid from the eye to help elucidate the BAC at the time of the incident. Ethanol analysis of blood in a subdural hematoma in delayed deaths also may provide an indication of the intoxication state at the time of the injury as this is sequestered blood that does not undergo hepatic metabolism [30].

Putrefaction is a type of decomposition due to the proliferation of endogenous bacterial microorganisms in the body. Putrefaction is manifested by green discoloration of the body, bloating, skin slippage, and foul odor. Certain bacteria may produce ethanol, isopropanol, acetaldehyde, and *n*-propanol. Ethanol detected in a putrefied body may be due to postmortem production and/or premortem ingestion. In one study, a 0.22-g% blood alcohol concentration was determined to be caused by postmortem bacterial production due to advanced putrefaction [31]. Typically, the blood-alcohol produced by bacteria after death, has a concentration that is below 0.1 g%; however, outliers of over 0.20 g% have been reported [31]. The vitreous fluid may help distinguish postmortem production from premortem ingestion. As the vitreous fluid is a relatively sequestered site that is difficult for bacteria to penetrate, detecting ethanol in the blood but not the vitreous is consistent with postmortem production of ethanol. If the blood and vitreous both have elevated concentrations of ethanol, this is most consistent with premortem ingestion.

Conclusion

In conclusion, postmortem toxicological analysis, particularly for drugs of abuse and ethanol, play a large role in the forensic investigation of natural and unnatural deaths. Care must be taken with the interpretation of postmortem concentrations as they must be interpreted in light of the autopsy findings and circumstances. There is a difference between whether a certain drug concentration is capable of causing a death and whether it is the cause of death.

Compliance with Ethical Standards

Conflicts of Interest None

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