Opioid Toxicity

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ABSTRACT

In recent years, there has been a substantial increase in opioid use and abuse, and in opioid-related fatal overdoses. The increase in opioid use has resulted at least in part from individuals transitioning from prescribed opioids to heroin and fentanyl, which can cause significant respiratory depression that can progress to apnea and death. Heroin and fentanyl may be used individually, together, or in combination with other substances such as ethanol, benzodiazepines, or other drugs that can have additional deleterious effects on respiration. Suspicion that a death is drug-related begins with the decedent's medical and social history, and scene investigation, where drugs and drug paraphernalia may be encountered, and examination of the decedent, which may reveal needle punctures and needle track marks. At autopsy, the most significant internal finding that is reflective of opioid toxicity is pulmonary edema and congestion, and frothy watery fluid is often present in the airways. Various medical ailments such as heart and lung disease and obesity may limit an individual's physiologic reserve, rendering them more susceptible to the toxic effects of opioids and other drugs. Although many opioids will be detected on routine toxicology testing, more specialized testing may be warranted for opioid analogs, or other uncommon, synthetic, or semisynthetic drugs. *Acad Forensic Pathol.* 2017 7(1): 19-35

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INTRODUCTION

In recent years, there has been a substantial increase in opioid use and abuse, and in opioid-related fatal overdoses, due at least in part from individuals transitioning from prescribed opioids to cheaper, more accessible illicit heroin and fentanyl (1-13). The term “opiate” technically refers to wholly natural substances found in the resin of the opium poppy, such as morphine and codeine, that have affinity for the body’s opioid receptors. “Opioid” is a broader term, and includes opiates, semisynthetic derivatives of opiates, and synthetic compounds that bind to the body’s opioid receptors, causing similar clinical effects as opiates. Opioids, by acting on the opioid receptors, have the beneficial therapeutic effect of blocking pain sensation, but also may cause various deleterious effects, including nausea, constipation, somnolence, sedation, and most significantly, respiratory depression (14-16).

Respiration is controlled primarily by medullary respiratory centers along with input from chemoreceptors and other sources. Opioid-induced respiratory depression can be caused by effects of opioids at multiple sites, including respiratory neurons located in the medulla, which can lead to suppression of respiratory rate and inhibition of respiratory drive, effects on peripheral chemoreceptors located in the carotid and aortic bodies and lungs, which can cause suppression of ventilatory responses to hypoxemia and hypercapnia, and suppression of brain arousal systems/wakefulness, which can cause sedation. The three main classes of opioid receptors are mu, kappa, and delta (17, 18). Opioids exert their effect by stimulating predominantly the mu-opioid receptor, but also have weak activity at the kappa- and delta-opioid receptors. Activation of mu-opioid receptors in the brainstem can cause respiratory depression. The blood-brain barrier protects the central nervous system from various pathogens and chemicals. However, some drugs such as heroin (3,6-diacetylmorphine) are fairly lipid-soluble, and hence, more readily cross the blood-brain barrier. Heroin crosses the blood-brain barrier more readily than its main metabolite, morphine. The high lipid solubility of fentanyl also allows it to cross the blood-brain barrier quickly and thus has a rapid onset

of action. Opioids also have an effect on cerebral cortical centers that regulate breathing (19).

Opioid activity in the central respiratory center in the medulla causes decreased tidal volume at lower concentration and decreased respiratory rate and tidal volume at higher concentration, resulting in decreased minute ventilation (16, 20). Opioid-induced respiratory depression is characterized by hypoventilation with slow, irregular breathing that leads to hypercarbia, then hypoxia, and may progress to shallow breathing, apnea, and if resuscitative efforts are not initiated in a timely fashion, ensuing cardiac arrest and death (21-27). Initially, tidal volume falls, but ventilation and oxygenation are maintained via tachypnea. As arousal progressively deteriorates, the respiratory rate falls, the tidal volumes fall, and in order, hypercarbia, acidosis, and hypoxemia develop, with possible progression to respiratory arrest. Acute opioid toxicity by fentanyl or its analogs may also cause the rapid onset of rigidity of muscles in the jaw, neck, chest wall, and abdomen, impairing an individual’s ability to breathe, and making it difficult for other individuals to provide ventilation for them (23, 28-37). The risk of such rigidity appears to increase along with the dose of fentanyl and the rapidity with which it is administered, however, the dose required to cause such rigidity need not be excessively high (34). Another possible risk is acute vocal cord closure, which has been reported to occur with the administration of sufentanil (38).

The acute effects and potential lethality of opioids can be reversed by the timely administration of naloxone, which is a nonselective competitive opioid antagonist at the opioid receptors that inhibits all pharmacologic effects of opioids (39, 40). Naloxone may be quickly, safely, and effectively administered intranasal by first responders, with low overall risk (41, 42). However, in order for it to be effective, one must first have the clinical suspicion that an opioid overdose may have occurred and also have naloxone readily available for administration in a timely fashion (43). However, many opioid-related deaths occur in isolation, possibly in attempts of the user to maintain a covert nature to their drug use, limiting the opportunity for other individuals to administer naloxone in a timely fashion.

Opioids that have a longer plasma half-life than naloxone have the potential to “renarcotize” an individual with the passage of time post-administration, as the effects of naloxone may wear off more rapidly than the effects of the opioid. Regarding the addictive potential of opioids, activation of the mu-opioid receptor is believed to initiate a series of intracellular signaling events that cause the release of dopamine from the nucleus accumbens, an area of the brain that is involved in reward circuitry, and links the event to the euphoria or “high” feeling caused by the drug use (44).

DISCUSSION

Conditions That Make an Individual More Susceptible to Opioid Toxicity

An individual’s baseline respiratory function may be compromised by various medical conditions such as heart disease (e.g., pulmonary edema from congestive heart failure), lung disease (e.g., chronic obstructive lung disease), obstructive sleep apnea, obesity, and advanced age. Conditions such as these would limit one’s physiologic reserve, and hence, one’s ability to overcome any compromising conditions that stress the body, such as the effects of drug toxicity. The nature of opioid-related deaths is varied, but generally involves the consumption of an excessive amount of opioid drug with or without other drugs/substances that result in severe respiratory depression, overwhelming the body’s ability to compensate for the drug effect. Potentiating conditions may include the relaxant effects of sleep and positional asphyxia or suffocation, as may be indicated at scene investigation.

The Physiologic Effects of Sleep and Sedation

Opioid deaths generally occur during sleep – a time when an individual no longer has conscious awareness, and is dependent upon autonomic mechanisms to maintain proper respiratory effort. During wakeful periods, an individual is generally alert and aware of their need to breathe, as cerebral activity associated with wakefulness helps regulate breathing (45, 46). However, during sleep, there is no longer an active, conscious stimulus to breathe, and an individual is

more vulnerable to a compromise in respiratory function, such as that caused by drug toxicity. During even light sleep, the body is dependent upon chemoreceptor activity to maintain adequate respiratory rhythm (46). Conditions that compromise ventilation may occur during sleep, such as drug-altered chemoreception. Also, during sleep, the upper airway (in particular, the oropharynx) tends to stenose to some degree, due to decreased tone from relaxation of upper airway dilator muscles, the genioglossus muscle, and other soft tissues, and from other factors, the effects of which appear to increase with age, making an individual more susceptible to drug-induced upper airway collapse/obstruction (47-51). Opioids, ethanol, and other potentiating drugs likely exacerbate respiratory events such as episodes of hypopnea and oxygen desaturation that normally occur during sleep. All of these drug effects can be compounded by obesity, the effects of advanced age, sleep-disordered breathing problems, and by an individual’s physiologic cardiac, respiratory, hepatic, and other comorbid limitations imposed by various natural disease processes (52).

Pain stimulates wakefulness and respiration, and can attenuate the respiratory depressant effects of opioids (53-55). Opioids are often administered therapeutically to help alleviate the acute effects of pain. Discomfort from pain generally aids in keeping an individual awake and aware. After opioids are consumed, often with the intent of minimizing pain to allow for restful sleep, an individual is more likely to be able to fall asleep and hence, lose the pain-induced stimulation of breathing (56). Patients are at highest risk of respiratory depression during the first 24 hours of opioid therapy (57), particularly if the individual has preexisting obstructive sleep apnea, heart failure, lung disease, obesity, or achieves a deep level of sedation. Sedation precedes opioid-induced respiratory depression. In monitored situations, assessment of respiratory status during opioid therapy involves visualization of the rise and fall of the patient’s chest to best assess the rate, depth, and regularity of respirations (57). Snoring should be given considerable attention, as it may indicate impending upper airway obstruction in a sedate patient, and may be alleviated by repositioning the patient to a lateral position, which helps maintain the patency of

the collapsible oropharyngeal tissues (58-60). Patients who usually snore are typically awakened by their own snoring and inadequate respirations; however, obtundation caused by the sedative effects of opioid therapy, additional sedative effects of other medications, and perhaps fatigue/sleep may prevent the patient's usual "self-arousal" during snoring, allowing progression of respiratory insufficiency to apnea.

In gauging the effectiveness of ventilation in monitored situations, continuous capnography (end-tidal carbon dioxide monitoring) is better than periodic pulse oximetry monitoring, which measures oxygen saturation (24, 61-63). Periodic assessment of oxygen saturation typically is performed at the time that patients are aroused to assess their vital signs, and arousing the patient will usually cause them to breathe deeper, providing a higher oxygen saturation at that particular time and a false sense of security regard-

ing their respiratory status. Because arousal stimulates respiration, respiratory status is best evaluated in the sleeping or calm, resting patient (57). Supplemental oxygen may also result in deceiving effects, as it may bolster the oxygen saturation of a patient who is, in fact, in respiratory failure, as would be demonstrated on capnography by an increased carbon dioxide level. Low oxygen saturation (hypoxemia) is considered a later indicator of inadequate ventilation than increased carbon dioxide concentration (hypercarbia) (24, 62, 64). Thus, in patients who are receiving supplemental oxygen, pulse oximetry may show high or at least adequate oxygen saturation despite current or impending respiratory depression (57, 62).

The Physical and Physiologic Effects of Obesity

Many physical effects of obesity can work individually or in combination to impair ventilation (**Figure**

Figure 1: Physiological effects of obesity that can impair ventilation. Created under contract by professional medical illustrator Diana Kryski.

1). One of the effects is reduced chest wall compliance due to an increased amount of adipose tissue that adds weight on to the rib cage, which can make expansion of the rib cage with inhalation more difficult. Another factor is an increase in abdominal mass caused by increased liver size and a large amount of mesenteric and omental adipose tissue that can displace the diaphragm cephalad, decreasing the volume of the pleural cavities at baseline and hindering diaphragmatic excursion with inhalation. This can lead to atelectasis at the lung bases with ensuing ventilation/perfusion mismatch, hypoxemia, and overall impaired lung function. These effects are most significant when the body is in the prone or supine position, and are somewhat attenuated when the body is in the lateral (“recovery”) position. Increased heart size is often associated with obesity, and, along with an increased amount of mediastinal adipose tissue, also limit the amount of space available for the lungs to expand.

Obese individuals are more prone to upper airway obstruction (**Figure 2**). The retropalatal oropharynx is generally recognized as the narrowest segment of the upper airway in most people (65-67). An increase in the thickness of the muscle mass of the lateral or posterior pharyngeal walls or an increase in the amount of adipose tissue and/or muscle mass in the soft palate and tongue that often accompanies obesity can result in chronic stenosis of the airway. This can predispose to further stenosis or even collapse and obstruction of the collapsible upper airway secondary to the negative pressure generated in the airway with inspiratory effort, resulting in hypoventilation and possibly apnea (65, 68). Because the upper airway lacks rigidity and structural support, soft tissues such as the tongue and soft palate can shift posteriorly according to the effects of gravity, predisposing to oropharyngeal collapse, particularly when an individual is in the supine position (69, 70). Opioids and other drugs can cause relaxation of the pharyngeal muscles, which can potentiate upper airway obstruction (71, 72). Such conditions would also likely potentiate airway obstruction in individuals with obstructive sleep apnea (73, 74).

The effects of obesity often compromise an individual’s baseline respiratory status, making the obese

individual more vulnerable to the respiratory depressant effects of opioid toxicity. Some of the deleterious long-term respiratory effects of obesity include chronic hypoxia, obstructive sleep apnea, an ataxic breathing pattern, and central sleep apnea (75). Obese individuals often have a more rapid, shallow ventilatory pattern, and have decreased ventilatory reserve. Obese individuals (particularly those with prominent upper body fat distribution) have impairment among multiple pulmonary function test parameters and are more prone to develop atelectasis (76-84). These impairments in ventilatory function have been shown to improve upon weight loss (82, 83).

Cointoxicants

Any substance that can increase somnolence/sedation or cause respiratory insufficiency has the potential to augment and/or prolong the deleterious respiratory effects of opioids. Such substances include ethanol, benzodiazepines, benzodiazepine-like hypnotosedatives, barbiturates, and various types of relaxants that can cause sedation and depress the body’s hypoxemic and hypercapnic ventilatory drives (16, 52, 85-101). Although these substances may have little respiratory depressant effect on their own, particularly when not consumed in excessive amounts, the use of these substances in combination with opioids has the potential to augment and/or prolong the deleterious respiratory depressant effects of opioids, and to also augment a stuporous or comatose condition. In many opioid-related deaths in which such cointoxicants are detected, oftentimes the opioid concentrations are lower than if the opioid was consumed in isolation (99). This finding is indicative of the cumulative respiratory depressant effects that multiple drugs can have on the body.

In excessive amounts, ethanol has the ability to increase the resistance of airflow through the upper airway, and may cause collapse of the tissues of the upper airway, resulting in disordered breathing and even obstructive apnea during sleep in unsuspected individuals (102, 103). Ethanol is a solvent and may also increase the rate of absorption of drugs when ingested around the same time as the drugs, leading to a more heightened drug effect. Ethanol has also been

Figure 2: A) Normal oropharyngeal anatomy. B) Effects of obesity and opioids on oropharyngeal anatomy. Created under contract by professional medical illustrator Diana Kryski.

shown to decrease the ventilatory response to hypercapnia when combined with an opioid (104). Benzodiazepines can cause upper airway obstruction via relaxation of the muscles of the tongue and neck, which increases the work of breathing (72, 105, 106). Sleep medications and any medications that can cause sedation and drowsiness such as carisoprodol, diphenhydramine, and some antidepressants can potentiate the sedative effects of opioids. When detected, such cointoxicants and their associated pharmacodynamic effects should be considered as additional significant factors in opioid-related deaths. As many cases of opioid-related death exhibit polypharmacy, toxicology testing should be comprehensive enough to include such drugs, and also various stimulants and other drugs that may have a deleterious effect on an individual's health (98).

The History and Scene Investigation

The identification of drugs or drug paraphernalia at the scene, needle punctures or needle track marks on the decedent, and/or pertinent medical/social information gleaned from interviews from friends, family, or acquaintances often suggest that a death may be drug-related. The presence of a syringe, needle, drugs, drug packaging material, tourniquets, or other drug paraphernalia at the death scene is important information that initiates investigating the death as possibly being drug-related. However, one should not rely on the presence of these typical findings, as many times they are absent, as the drug(s) may have been consumed previously at another location, the scene may have been altered or cleaned up by another individual prior to summoning help, or the drugs may have been in pill form, and no drug-related paraphernalia required for consumption of the drug. A significant number of opioid-related deaths will likely be missed if one performs toxicology testing only if illicit drugs or drug paraphernalia are documented at the scene (12, 100, 107).

Recent forced abstinence from drugs such as incarceration in prison or enrollment in a drug treatment program can lead to a desire for drug use upon release from the facility with fatal results, which tend to occur with-

in two weeks after release, but the risk persists even longer (12, 108, 109). In such instances, the individual may have lost a degree of tolerance to opioids and other drugs, may exhibit bad judgment, or may return to a familiar environment of drug use and as a result, be more susceptible to overdose (110). In addition, an individual's tolerance to the respiratory depressant effects of opioids may lag their tolerance to the euphoric effects of opioids, putting the chronic drug abuser more at risk of a fatal overdose when attempting to achieve a previously experienced desired state of euphoria (16). An individual's drug tolerance is difficult to gauge even if their drug prescription history is known. Clues that may suggest an opioid death include a history of preterminal snoring, which can be indicative of upper airway obstruction caused by opioids, benzodiazepines, other drugs, or a combination thereof (111). Query should include whether the decedent was known to normally snore, and if so, whether or not their preterminal snoring was any different than usual.

All of the decedent's prescription pills and any free/unlabeled pills should be collected to be inventoried and possibly analyzed. The chemical composition of pills may not always match what may be indicated by the appearance of the pill. An individual may abuse their prescribed opioids, or he/she may obtain opioid medications from another source ("diverted medications") for nonmedical use (112, 113). The use of diverted medications has increased risk. The drug user does not know for certain what drugs they are purchasing and using, as nonregulated pills may be intentionally mislabeled as a different drug, drug powders will likely be of varying concentration and intensity, and may in fact consist wholly or in part of unintended substances that may be used to dilute a drug or to augment the effects of a drug (114).

The chemical composition of powdered drug encountered at a scene or on a decedent can vary and may represent a mixture of different drugs of varying concentration. A powder's composition cannot be predicted by visualization alone. Heroin is a potent opioid that can cause death quickly or in a more prolonged manner following a comatose period. More powerful drugs such as fentanyl, acetylfentanyl, carfentanil, or

other fentanyl analogs may be consumed individually or may be added to powdered heroin or other drugs to augment the drug's euphoric effects, but would also increase the drug's respiratory depressant effects, which would increase the drug's lethality (98, 111, 115-122). If drugs, particularly powdered forms of drugs are encountered, either at a death scene or on the decedent, they must be handled with caution, using appropriate personal protective equipment because some drugs such as carfentanil are very potent and can be toxic or even fatal if inhaled or absorbed in sufficient amount either transcutaneously or through mucus membranes. For this reason, it is also advantageous for investigators of such cases to have naloxone readily available if needed. Powders or syringes recovered from the death scene can be chemically analyzed to determine the purity of the drug or if the powder is a mixture of drugs, which drugs are present. Care must be taken when examining the decedent, their clothing, and other items at the scene to avoid needle stick injuries, which have the potential to transmit infectious disease such as hepatitis viruses and human immunodeficiency virus.

On occasion, a syringe will be present in the decedent's hand or remain embedded in his/her arm or other injection site. Intravenous injection of a drug may deliver a particularly large amount of drug in a short amount of time that may overwhelm the body's compensatory abilities. Intravenous drug use and poly-drug abuse each predispose to increased lethality (12). Injected opioids are more likely to cause significant respiratory depression than oral opioids (24). This is because the ingestion of opioids results in a more gradual increase in opioid concentration in the blood and the resultant progressive respiratory depression will cause hypercarbia and hypoxemia more slowly, which will, if not overwhelming, elicit an increased reactive respiratory response via chemoreceptor activity (21). In contrast, an intravenous bolus of an opioid or the injection of a particularly potent opioid may lead to a rapid and overwhelming increase in central opioid receptor occupancy, causing a rapid development of apnea that may be refractory to the body's response to the ensuing hypercarbia and hypoxemia. Hence, opioids that cross the blood-brain barrier more slowly, and those that exhibit slower receptor binding, may be

less lethal than those that bind more quickly despite having equivalent analgesic effects because the slower acting drugs allow the body more time to mount a counteracting physiologic response. The body's response, however, may be limited anyway, as opioids variably depress the body's central and peripheral chemoreceptors, impairing the body's ability to respond to hypoxemia and hypercarbia (27, 91, 123).

Visualization of the decedent undisturbed at the scene of death is essential to adequately appreciate and document various physical conditions that can potentially compromise an individual's ability to adequately ventilate. Conditions suggestive of positional asphyxia and suffocating/smothering include the decedent positioned prone with their face pressed into a soft object such as a pillow, cushion, or mattress, or the body positioned with their head/neck at an awkward angle, potentially compromising airflow through the upper airway. In obese individuals, the supine position can predispose to upper airway obstruction. Compared to the neutral position, head flexion increases the likelihood of upper airway collapse, while head extension decreases the likelihood of upper airway collapse (124). Once the decedent is moved at the scene, these factors may go unnoticed by subsequent observers, aside from the distribution of lividity, which may shift with time. Blanched lividity about the nose, mouth, and central face in individuals who are found prone would add support to a theory of smothering or suffocation. In opioid fatalities, there is often a variable amount of foamy fluid about the mouth and/or nose ("foam cone"), resulting from the marked pulmonary edema that often develops in such cases (125). The edema fluid extends from the lungs through the bronchi, trachea, larynx, and oropharynx, eventually exiting the nose and/or mouth. It is, however, not specific for overdose, as pulmonary edema and the associated foamy fluid on the face may also be seen with other causes of death such as drowning, congestive heart failure, epileptic seizure, and traumatic head injury.

The Autopsy Findings

It is best to perform a complete autopsy when a death is suspected to be drug-related to rule out any more

convincing cause of death, to allow for optimal collection of toxicology specimens, and to allow for optimal interpretation of toxicology results (100, 107). Individual case circumstances and office protocol may dictate making the diagnosis of acute drug toxicity without an autopsy having been performed in cases in which the decedent had experienced a delayed death with preterminal hospitalization, in cases in which the decedent's family has an objection to autopsy, or other reasons. Needle track marks, recent needle punctures, and skin popping scars from remote subcutaneous drug injections may indicate drug use, although they are not necessary, as heroin and other opioids may be smoked, insufflated, ingested, or consumed by other means. Although these cutaneous findings are often located on the upper extremities, they may be located on more discrete areas of the body such as the lower legs or feet, possibly in an attempt by the user to hide the visual stigmata of intravenous drug use, because of difficult venous access in the upper extremities, or as a matter of convenience or personal preference.

In the vast majority of respiratory-related fatal opioid overdoses, the most significant internal finding revealed at autopsy is pulmonary edema, which is characterized by heavy, congested, edematous, boggy lungs (114, 126). Lung weights in such cases often exceed 500 g each, and may on occasion exceed 1000 g each (126). The observation of such marked pulmonary edema from opioid overdose was first reported by William Osler in 1880 (127), and since then, it has been widely reported in the literature (125, 128-132). Although the phenomenon of pulmonary edema in these cases is well-described, it is poorly understood. The mechanism is probably multifactorial, and most likely involves an imbalance between hydrostatic forces in the pulmonary blood vessels and increased pulmonary capillary permeability. Hypoxemia is likely a factor, as it is known to cause an inhomogeneous constriction of pulmonary arteries in order to attenuate ventilation/perfusion mismatches in the lungs, which leads to an increase in pulmonary artery pressure throughout the lungs (133, 134). Pulmonary arteries that are not constricted by the effects of hypoxemia become relatively overperfused as compared to the other, constricted arteries, and are hence subject-

ed to high-pressure flow. The pulmonary response to hypoxemia differs among people, and the magnitude of the resultant pulmonary vasoconstriction can vary greatly among individuals (135, 136).

Hypoxia may also cause decreased myocardial contractility which, along with pulmonary vasoconstriction, exposes pulmonary capillaries to high pressures that can damage their walls, leading to a high-permeability form of pulmonary edema. Increased pressure on the capillary wall imparts excessive strain on the collagen and the extracellular matrix of the alveolar capillary barrier, which could lead to mechanically induced breaks in the blood-gas barrier, resulting in increased pulmonary capillary permeability (137). In experiments, morphine has been implicated in increased vascular permeability and endothelial dysfunction, with greater effects more likely at higher concentrations (138, 139). However, in one study, no increase in defects of alveolar capillary membranes was detected by immunohistochemical microscopic study with antibodies directed against collagen IV and laminin in acute heroin toxicity deaths compared to sudden cardiac death controls (140). Because the protein content of pulmonary edema fluid in opioid overdose cases has been reported as being significantly higher than that of cardiac-related pulmonary edema (141), the pathogenesis of the edema likely involves, at least to some extent, increased pulmonary capillary permeability. The edema may be augmented by hydrostatic forces mentioned previously, possibly in combination with those generated by efforts made to respire despite a partially obstructed glottis/upper airway (negative pressure pulmonary edema) (142). Negative pressure pulmonary edema refers to instances in which high negative intrathoracic pressure is generated in order to overcome upper airway obstruction, causing an increase in transmural pulmonary capillary pressure and the rapid transudation of fluid from the pulmonary capillaries into the interstitium and alveolar spaces (142, 143).

Opioids may cause a hypersensitivity reaction, as has been demonstrated by the detection of elevated tryptase concentrations in heroin fatalities (144, 145). In many people, morphine injection causes the activation

of mast cells and the subsequent release of histamine and tryptase (146-152). Histamine can cause hypersensitivity reactions that include peripheral vasodilation that can lead to systemic hypotension and shock (151). Histamine can also cause bronchospasm and an increase in the permeability of capillaries, as has been demonstrated in animal experiments (153-157). Many opioids are potent histamine releasers and are capable of causing a vast array of hemodynamic/anaphylactoid reactions (151, 152). In cases in which it appears that the pulmonary edema and death are evident soon after the opioid use (such as the presence of an inserted needle), its pathogenesis may be due to a hypersensitivity reaction.

In all, respiratory depression that occurs in opioid toxicity causes hypoxemia, which can cause pulmonary vasoconstriction and decreased myocardial contractility, which can cause increased pulmonary capillary pressure that can augment the transudation of fluid through the capillary walls, particularly if their permeability is increased from the effects of hydrostatic forces, hypoxia, hypersensitivity reaction, primary drug toxicity, or other factors. The transudation of fluid leads to pulmonary edema, which in turn exacerbates the hypoxemia, forming a vicious cycle that is not broken until adequate oxygenation can be restored. Systemic shock from hypersensitivity to opioid or a different substance that was used to dilute or enhance the drug may help explain rapid deaths.

Other findings often observed at autopsy in cases of opioid overdose include frothy tan, sometimes bloody fluid in the airways and about the nose and/or mouth (a “foam cone”), and sometimes mucus in the airways or about the nostrils and face. The mucus may arise from several factors, including stimulation of the parasympathetic nervous system in an attempt by the body to protect the tracheal and bronchial mucosa from the irritant and caustic effects of aspirated material. Histologically, one may also see early acute inflammation in the lungs (e.g., pneumonia, bronchitis), as a reaction to aspirated material if the comatose period is of sufficient duration (126). Some opioids such as codeine decrease the tone of the lower esophageal sphincter and suppress the cough reflex, predis-

posing to aspiration. One may also encounter a large amount of urine in the urinary bladder, or saturation of the decedent’s clothing with urine, particularly if the comatose state was unusually prolonged, or if a large volume of liquid such as ethanol was also ingested. Toxicology specimens collected should at a minimum include blood (femoral vein blood preferred), urine, and vitreous fluid as they are available, and additional specimens as needed (100). Toxicology specimens should be appropriately preserved and stored.

The Toxicology Report

Interpretation of the data generated on the toxicology report must proceed with careful and critical evaluation with consideration of other information, such as the body’s physiologic response to drug toxicity, the possibility of drug metabolism down to lower concentrations, and the effect that postmortem processes can have on drug concentrations. One need not expect a drug-related death to have drug concentrations that have achieved fatal levels as have been reported in various publications. During the dying process, which may be prolonged, drugs may be metabolized down to lower concentrations, and parent/metabolite drug ratios altered. The drug concentrations measured from postmortem samples do not necessarily reflect the concentrations that the individual had at the time that he/she died, or at the time that he/she had reached peak intoxication. Many drug analogs will not be detected by “routine” toxicology testing, and must be specifically tested for. Suspicion for such analogs should be heightened in a case in which the circumstances are suspicious for an opioid-related death, yet toxicology tests are negative or reveal only trace/low concentrations of a drug(s) that is/are deemed to be insufficient to have caused the death. In such instances, additional, more focused testing is warranted.

In a toxicology report, heroin use is inferred by the documentation of morphine and 6-acetylmorphine in the decedent’s body fluids, as heroin itself is usually not detected. This is because heroin (3,6-diacetylmorphine) is rapidly deacetylated by blood esterases to the intermediate 6-acetylmorphine, which is then fairly rapidly broken down to morphine, which has a longer

half-life. Because heroin is broken down very quickly, it is usually no longer detectable. While the detection of morphine may represent the use of either morphine or heroin, 6-acetylmorphine is widely regarded as being a specific marker for heroin. Another clue that the morphine detected was likely derived from heroin is the detection of a very low concentration of codeine in comparison to the decedent's morphine concentration. Codeine is naturally present in the opium poppy from which heroin is synthesized, is not purified during the preparation of heroin, and therefore is often present in low concentrations when heroin is consumed. A femoral blood morphine:codeine ratio of greater than one is typical when heroin is consumed (158-160). The ratio is often much greater than one in most cases, as the codeine is often present in only trace concentrations. If, however, the codeine concentration is great, or at least larger than the decedent's morphine concentration, one should consider that the decedent had consumed codeine, with some of the codeine metabolized to morphine, or that the decedent had consumed a combination of codeine and heroin. In cases of heroin use, the morphine:codeine ratio is also greater than one in the urine (158, 161).

An additional factor that one must consider is the presence of cointoxicants, which may have cumulative effects on one's ability to adequately ventilate (93), or otherwise stress the body. In these situations, the presence of two, three, or more substances with similar deleterious physiologic side effects can prove just as fatal in so-called "average" or "below average" concentrations as a single drug at a "high" concentration, due to the cumulative effects of the drugs (96). Because of the effects of ongoing drug metabolism, in circumstances in which an individual has died during hospitalization following drug overdose, it is imperative to obtain blood, serum, and urine specimens that were collected during hospitalization in order to help obtain the best toxicology specimens and test results possible. The earlier the specimens were collected, the better their yield. One should also be careful to review the medical records to identify any therapeutically-administered drugs that may show up on the toxicology report.

In interpreting drug concentrations, and their likelihood of causing the death of an individual, one must interpret the values in the context of all available relevant information, including the autopsy findings, the decedent's medical history and social history, including possible drug tolerance, the scene findings, the location in the body from which the blood was obtained, the potential effects of drug metabolism, drug distribution and redistribution, the effects of drug metabolites, and the cumulative toxic effects of multiple drugs (100, 101, 162-166). One may also consider variability in an individual's response to drugs that may include many factors, including their genetic make-up (pharmacogenomics) and the extent of baseline natural disease that they may have. In the right situation, sometimes the mere presence of a powerful drug, at the exclusion of any more significant cause of death, can be enough to be the cause of death. In other situations, the cumulative toxic effect of more than one drug may have caused an individual's demise. In such cases, listing all of the contributing drugs on the death certificate would be appropriate. Every case is unique, and the autopsy and toxicology findings must be interpreted within the context of each particular case. Also, consider that in some cases, a drug may not be the cause of death, even though it is within what is reported to be a lethal concentration.

CONCLUSION

Opioids are becoming increasingly more common in drug-related fatalities. Suspicion that a death is drug-related begins with the decedent's history and scene investigation. At autopsy, the main findings are observed in the lungs, which often have marked edema and congestion. Frothy watery fluid is often in the airways. Various natural disease processes may limit one's physiological reserve, rendering them more susceptible to an overdose. Although many opioids will be detected on routine toxicological testing, more specialized testing may be warranted for opioid analogs, or other uncommon, synthetic, or semisynthetic drugs.

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