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CASE REPORT

PATHOLOGY/BIOLOGY; TOXICOLOGY

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Anaphylaxis After the Injection of Buprenorphine*

ABSTRACT: Cause of death rulings in cases when the concentration of a drug or drugs is higher than observed following therapeutic use are generally straightforward "drug deaths." However, when toxicology testing identifies drug concentrations consistent with therapeutic use or detects no drugs at all, then the cause of death determination is more complicated. Given the rapidity and protean manifestations of anaphylaxis, it should be considered in deaths where no other cause of death is apparent in a suspected drug death. This article reports two cases where an anaphylactic reaction was observed following either the actual or alleged use of therapeutic formulations of buprenorphine intravenously.

KEYWORDS: forensic science, toxicology, drug reaction, anaphylaxis, buprenorphine, injection, tryptase, postmortem

Case 1

A 29-year-old woman with a history of asthma and injection drug use who had been hospitalized due to anaphylactic reaction in the past was witnessed by her boyfriend to inject herself with a crushed tablet, immediately gasp for breath and collapse. Her boyfriend administered 2 puffs of her albuterol inhaler and called 911. Upon arrival, emergency medical services (EMS) found her in cardiac arrest, administered intramuscular and intravenous naloxone and intravenous epinephrine, and performed cardiopulmonary resuscitation (CPR). The patient was transported to the emergency department (ED) where naloxone and epinephrine were again administered; however, the patient's circulation was not restored, and she was pronounced dead. Upon further questioning of the patient's boyfriend, he stated that he and the decedent often purchased tablets online, crushed and dissolved the tablets, and injected themselves with the solution. On the day of death, the patient's boyfriend had prepared a solution with a new shipment of buprenorphine that had been purchased via the Internet from a foreign-based pharmacy. After purging the air from the syringes, he and the patient had injected themselves with half of the solution each. He reported that no other drugs or alcohol was consumed prior to injection.

Analysis of the contents of the syringes revealed no buprenorphine. Findings at autopsy were significant for hyperinflated lungs with mucous plugging of the airways, peribronchial smooth muscle hypertrophy, and eosinophilic infiltration. A comprehensive postmortem toxicology screen performed on heart blood was positive for only naloxone (22 ng/mL). Additionally, postmortem serum tryptase concentration was elevated (179 ng/mL). Due to the reported medical history, symptoms and chronology of the death, and the elevated serum tryptase concentration, the cause of death was anaphylactic reaction complicating asthma, and the manner was accident.

Case 2

A 30-year-old woman, 3 months postpartum with a history of heroin abuse, was witnessed by her boyfriend to complain of not feeling well after having injected herself with Suboxone® from a 8 mg/2 mg strip that she had purchased on the street. She then went to her bedroom, and 5 min later, she was found to be in bed and unresponsive by her mother. EMS was called, and upon arrival, they found the patient in asystole. CPR was initiated, and the patient was transported to the ED where she was pronounced dead. Findings at autopsy were significant for rare polarizable foreign material within pulmonary macrophages, scattered multinucleated giant cells in the lungs, and focal interstitial hemorrhage and edema of the larynx; however, no mast cells were noted. A comprehensive postmortem toxicology screen performed on heart blood was positive for buprenorphine (17 ng/mL), norbuprenorphine (7.6 ng/mL), and naloxone (96 ng/mL). Additionally, postmortem serum tryptase concentration was elevated (>200 ng/mL). The cause of death was anaphylactic reaction due to intravascular injection of Suboxone®, and the manner was accident.

Discussion

Buprenorphine, a thebaine-derived, partial opioid agonist, was developed for pain management in the 1970s; it was introduced

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to the United States in 1985 as an analgesic and formulated for injection only (Buprenex®). In late 2002, the FDA approved two new buprenorphine products for the treatment of opioid dependence. The formulations of buprenorphine are sublingual and available in 2 mg and 8 mg strengths. Subutex® is a sublingual tablet that contains buprenorphine-only, and Suboxone® is a formulation of buprenorphine/naloxone in a 4:1 ratio, which was designed to reduce diversion and misuse (1–7). As a partial μ-receptor agonist with relatively low intrinsic activity, buprenorphine reaches ceiling effects for respiratory depression at high doses. In the United States, reports of toxicity following intentional nonmedical use of buprenorphine alone (or buprenorphine/naloxone alone) confirm that respiratory depression is not common (8). As mentioned, reports of death associated with the use of buprenorphine alone (or buprenorphine/naloxone alone) are also not common in the United States, even in special populations such as pediatric unintentional exposures (8,9).

Despite the safety of buprenorphine, morbidity and mortality may occur when it is used along with other medications, particularly other sedatives. For example, the first buprenorphine-related death was described in 1996 in the French literature and implicated the combination of buprenorphine and benzodiazepines (7). In several subsequent published reports, buprenorphine use or misuse was implicated as the cause of death or illness despite questionable evidence. In many of these cases, the blood concentrations of buprenorphine were not supratherapeutic (most were in the reported therapeutic range of 14–110 ng/mL), yet buprenorphine intoxication was listed as the cause of death (10–15). In Case 1, as described above, the decedent did not have a detectable quantity of buprenorphine or its metabolites in her blood or in the syringe recovered from the scene, so a cause of death was not apparent until the elevated tryptase concentration was identified. In fact, there was no analytical evidence to indicate that buprenorphine had been injected. The decedent in Case 2 had a supratherapeutic concentration of buprenorphine identified in her blood, but the rapidity of her death in combination with the elevated tryptase concentration supports anaphylaxis as the cause of death.

Anaphylaxis is a well-known and not uncommon systemic reaction to insect stings, medications, foods, and other agents via IgE receptor activation on mast cells and basophils. However, other nonimmunologic and poorly understood immunologic mechanisms have also been implicated in anaphylactic reactions. Nonimmunologic factors that have been shown to cause mast cell degranulation include "exercise, cold air or water exposure, radiation, ethanol, insect venom constituents, radiocontrast media, and medications such as opioids and vancomycin" (16, p. S402). The downstream effects of all of these triggers are the same: release of inflammatory mediators including histamine, tryptase, prostaglandins, and leukotrienes (16,17).

The rate of anaphylaxis is increasing especially among persons in higher socioeconomic classes, and current estimates of lifetime prevalence range from 0.05 to 2% (16). Diagnosing anaphylaxis depends upon a complete clinical history with focus on the details of the reaction and the investigation of the events surrounding it. Anaphylaxis is a multisystem event that most commonly affects the skin and respiratory tract, but can also affect the gastrointestinal, cardiovascular, and central nervous systems, so symptoms can vary greatly from patient to patient. Despite the protean manifestations of anaphylaxis, the primary method of diagnosis in individuals who survive continues to be based on history; however, many laboratory tests have been developed to aid in diagnosis, which range from serum concentrations of tryptase, as used in these cases, to plasma concentrations of histamine, to identification of antibodies for specific known antigenic triggers (16).

Tryptase serum concentrations can be helpful in clinical settings when a patient presents with anaphylactic symptoms because, unlike specific antibody testing, the offending agent does not need to be known. Also, unlike histamine, which has a peak concentration at 5 min after exposure and half-life of 12–30 min in serum, tryptase peaks later in the clinical course at 15–120 min and has a half-life of 1.5–2.5 h. Additionally, tryptase is more specific for mast cell degranulation, because, unlike histamine, it is only produced in mast cells and, to a much lower quantity, in basophils. Hence, tryptase is a more specific marker for mast cell activation, which is helpful in the diagnosis of an anaphylactic reaction. Tryptase is a protein product of mast cells that is encoded by two genes on chromosome 16: α-tryptase and β-tryptase. However, of the two genes, only the protein product of the β-tryptase gene appears to be enzymatically active. Given the homogeneity of the two gene products, currently used monoclonal antibodies detect both the α- and β-tryptase proteins in serum (17).

Serum tryptase testing is performed for us by a reference laboratory that uses a monoclonal antibody that detects both the α- and β-tryptase proteins. The blood samples for testing must be centrifuged after collection to minimize the effects of hemolysis on the detected tryptase concentration. Published serum concentrations in normal subjects from the original work by Schwartz et al. (18,19) describing the monoclonal antibody's sensitivity were 0.4–13.9 ng/mL. However, 10 ng/mL was 2 standard deviations above the mean, so some nonsymptomatic individuals do have elevated baseline serum concentrations of tryptase. For this reason, clinical presentation and medical history are needed when interpreting serum tryptase concentrations, especially when the values are within the reported ranges within normal test subjects (18,19). An elevated tryptase concentration is not specific for anaphylactic reactions. In addition to disorders that result in an increased mast cell population, acute myeloblastic leukemia, certain myelodysplastic disorders, hypereosinophilic syndrome associated with the FIP1L1/PDFGRA mutation, end-stage kidney disease, onchocerciasis, atopic dermatitis, allergic rhinitis, fat embolism, systemic mastocytosis, significant atherosclerosis, myocardial infarction, heroin-related death, chest trauma, and asphyxia can also result in increased tryptase concentrations (20,21). An additional confounder of tryptase concentrations in postmortem specimens when compared to antemortem specimens is leakage of tryptase from mast cells due to autolysis or tissue damage from injuries (20). The higher postmortem concentrations of tryptase in heart blood compared to femoral blood have been attributed to the higher concentration of mast cells in the lungs and postmortem redistribution of tryptase from the lungs (21).

In the presented cases, it is unclear as to whether buprenorphine itself or another component in the formulations led to the anaphylactic reaction. In both cases, a drug intended for oral consumption was crushed and administered intravenously. Given the increasing number of people using buprenorphine in opioid substitution therapy and abusing diverted supplies, the number of deaths associated with buprenorphine will likely increase. Furthermore, in light of the cases presented here, it would be prudent to check the serum tryptase concentration in all patients who are suspected to have died of overdose where the toxicology screen is negative or the drug concentration is within the therapeutic range and where the individuals have not had a witnessed collapse. Given the stability of tryptase as an analyte

in frozen postmortem specimens, delaying the testing until after the toxicology results are received would be possible as long as the specimens are stored correctly. Although tryptase is not specific for anaphylaxis, high concentrations in combination with appropriate circumstances surrounding death are sufficient for diagnosis as a cause of death, and when all other causes of death have been ruled out, an elevated tryptase concentration can be helpful in determining the cause and manner of death (22).

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