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CASE REPORT

PATHOLOGY/BIOLOGY; TOXICOLOGY

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Suicide by Gabapentin Overdose

ABSTRACT: Gabapentin is an antiepileptic drug that is prescribed for both FDA-approved and multiple off-label conditions, and has a relatively safe side-effect profile. Rare cases of overdose-related adverse effects have been reported in the literature. Described herein are the circumstances and autopsy findings of a 62-year-old woman with a history of depression, whose death was caused by intentional ingestion of excess gabapentin. The postmortem peripheral blood gabapentin concentration as determined by high-performance liquid chromatography/tandem mass spectroscopy was 88 μg/mL. Previously reported cases of individuals surviving gabapentin overdoses are discussed and compared with this case. Based on a review of the available literature, this appears to be the first published report of a death due solely to gabapentin toxicity.

KEYWORDS: forensic science, gabapentin, overdose, death, suicide, toxicity

Gabapentin is an antiepileptic drug that is prescribed for the treatment of seizures, postherpetic neuralgia, and numerous off-label conditions (1–3). The minimal side-effect profile of the medication likely contributes to its popularity; however, like any medication it has the potential to be administered in excessive amounts. Relatively few cases of serious adverse effects have been reported in the literature (4–12). Reported herein is a death resulting from intentional gabapentin overdose.

Case Report

Case History

A 62-year-old woman was found unresponsive in a locked hotel room by an employee. She was discovered supine on the floor, with disheveled furniture and linens nearby. At the time of discovery, rigor that relented with moderate force and dependent lividity that blanched with moderate pressure were present. Hotel records indicated she had paid for 2 days of room usage. Security review of electronic records indicated that her room key had been used to unlock the door several times on the day of her arrival. A search of the room revealed numerous loose medication capsules and an empty prescription bottle for gabapentin within the bedding. Additional similar loose capsules were on the floor adjacent to the body, some of which appeared to have been crushed. Closer examination of the capsules revealed markings indicating gabapentin, simvastatin, and fluoxetine. Multiple empty prescription medication bottles were found elsewhere within the hotel room, including one empty bottle labeled for 150 capsules of 300 mg gabapentin, filled on the same day she purchased the room. Several pages of handwritten notes of suicidal intent, inclusive of statements indicating ingestion of excessive medication, were recovered from the death scene.

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Her medical history was significant for a long history of major depression with several previous episodes of suicidal ideation. She had been treated with hospital psychiatric admissions, electroconvulsive therapy, and medical management. Other natural diseases included diabetes, hyperlipidemia, and obesity, without mention of renal impairment. Additional investigation disclosed that the decedent had contacted her father several days prior to being found to inform him that she would be staying in a hotel for several days, without providing additional details. Given her history, he attempted to ascertain which hotel, but she refused to divulge the requested information, further alluding to her depressed mental status in the days prior to death.

Autopsy Findings

An autopsy was performed *c*. 22 h after her discovery, following overnight refrigeration, and revealed an obese woman (121 kg) with cardiomegaly (450 g) for her height (65 inches). Other incidental findings included lipomatous hypertrophy of the atrial septum, tunneling of the left anterior descending coronary artery within the myocardium, mild nephrosclerosis, goiterous change of the thyroid gland, and a metanephric adenoma of the left kidney. Chemistry studies performed on a postmortem vitreous specimen revealed a urea nitrogen concentration of 20 mg/dL. High-performance liquid chromatography/tandem mass spectrometry (LC-MS/MS) testing performed by a reference laboratory (NMS Labs, Willow Grove, PA) on postmortem peripheral blood specimens revealed gabapentin (88 μg/mL), clonazepam (7.7 ng/mL, normal therapeutic range 10–60 ng/mL), and the clonazepam metabolite 7-amino clonazepam (56 ng/mL, normal therapeutic range 20–140 ng/mL). The blood gabapentin quantitation was considered markedly elevated compared to published expected mean steady-state plasma concentrations for highest dose therapeutic administration, reported to be 2.6 μg/mL (1). The blood clonazepam concentration was lower than the reported normal therapeutic range, while the concentration of its metabolite was within the expected therapeutic range. Subsequent gabapentin quantitation of

the postmortem gastric contents (NMS Labs) yielded a concentration of 13,000 μg/mL. Given a total autopsy gastric contents volume of 170 mL, the residual gastric gabapentin dose was estimated to be 2210 mg (13,000 μg/mL × 170 mL), or *c*. the equivalent of seven to eight of the 300 mg capsules prescribed to her. The cause of death was certified as gabapentin toxicity with the manner of death certified as a suicide.

Discussion

Approved for use in 1993, gabapentin is an antiepileptic drug with a structure similar to that of the neurotransmitter gamma-aminobutyric acid (GABA) (2). Its mechanism of action is currently unknown. Although it is indicated for the treatment of seizures and postherpetic neuralgia, it is commonly prescribed for numerous off-label uses ranging from bipolar disorder to drug and alcohol withdrawal seizure control (2,3). The popularity of the medication is partially attributed to its minimal side-effect profile. The most common adverse effects that have been reported with therapeutic doses include drowsiness, dizziness, diarrhea, and movement disorders. An associated increased risk of suicidal acts or violent deaths has been reported in patients receiving therapeutic levels of the drug (13).

The lack of serious toxicity of gabapentin is underscored by the few number of nonfatal case reports of overdose found within the literature. Of the reported cases with discussion of gabapentin toxicity, five were unintentional overdoses and four were intentional. The five unintentional nonfatal overdose cases involved patients with renal impairment, which is not surprising given that the drug is almost entirely excreted unmetabolized via this route (4–8). One of these patients became comatose and another required intubation, but all recovered without adverse effect, with most receiving only supportive therapy or hemodialysis. Gabapentin concentrations were recorded as 22.6 and 85 μg/mL in two of the patients with renal impairment, respectively (4,5). Drug levels were not available for the remainder of the unintentional overdose cases. Renal impairment was not considered to be a factor in the present case as the postmortem vitreous urea nitrogen was not significantly elevated. Additional renal function tests were not performed.

Of the four cases of intentional nonfatal gabapentin overdose that have been reported with discussion, all have been associated with other substances (9–12). All of the intentional overdose patients survived the ingestion event with the aid of supportive therapy, with at least one case requiring intubation (9–12). Gabapentin concentrations ranged from 44.5 to 104.5 μg/mL in three of the patients with intentional overdose, with the estimated ingested doses ranging from 12 to 91 g (9–12). Interpretation of the intentional overdose cases was confounded by the presence of one or more other substances, including the cocaine metabolite benzoylecgonine, lamotrigine, quetiapine, valproic acid, and ethanol. Quantification results of the additional substances were provided for only one of the cases, and revealed elevated valproic acid and ethanol concentrations (10).

One published case series of reports to the American Association of Poison Control Centers (AAPCC) Toxic Exposure Surveillance System over a 2-year period characterizes overdoses in 20 individuals with a wide age range, with gabapentin-only exposures (14). None of the individuals died in this case series; however, three reported fatalities that fell outside of the study period are alluded to in the introductory discussion. Review of the Annual Reports of the AAPCC Toxic Exposure Surveillance System from 1999 to 2008 (the latest year available at the time of review) revealed four gabapentin-only deaths during that time period, in addition to numerous gabapentin-related deaths associated with other substances (15–24). Three of the gabapentin-only deaths from the Annual Reports were documented as intentional excessive ingestions; the reason for ingestion in the fourth case was unknown. Unfortunately, no additional case history, brief summary, autopsy results, or drug levels were available for evaluation in these publications. Thus, while other deaths have been attributed to gabapentin toxicity, information regarding those deaths is not readily available for comparison with the current case of suspected fatal gabapentin ingestion.

Postmortem drug redistribution is a factor to consider in any fatality where toxicology results potentially contribute to the cause of death. Previous studies have suggested that peripheral blood samples are generally a more accurate reflection of antemortem drug concentrations than central blood (25,26). Given the physical properties of an acidic molecule with a relatively low volume of distribution, postmortem redistribution of gabapentin is likely negligible, although this remains to be reported in the literature (1). To further minimize the possibility of postmortem redistribution in this investigation, confirmatory drug concentration testing was performed on blood samples acquired from the femoral veins at the time of autopsy. However, the peripheral blood samples were collected after organ removal without prior clamping of the proximal iliac veins.

Conclusion

While comprehensive studies in the literature have described toxicological findings in suicide, the present case represents the first published report of death because of gabapentin toxicity classified as a suicide (27). The present report highlights the postmortem peripheral blood gabapentin concentration in an intentional overdose, with gabapentin as the sole contributory substance. The toxicology results in this case, considered together with the scene and autopsy findings, support the certification as a suicide. The gabapentin concentration in this case (88 μg/mL) was similar to the higher levels determined in those who suffered nonfatal accidental overdoses as a result of renal impairment, and was in the middle of the range for those surviving patients who intentionally overdosed and had gabapentin levels available. The overlap of gabapentin concentrations in accidental versus intentional overdose situations illustrates the need for circumstantial information to interpret the laboratory results, as is well known with other substances. Although the presence of clonazepam and its metabolite could arguably have contributed in some way to the death, the concentrations of the parent drug and its metabolite were at or below the lower end of the expected reported therapeutic concentration ranges; therefore, the presence of these substances was determined to be of minimal consequence. Previous reported gabapentin overdoses have survived, but frequently this outcome was dependent on the availability of medical support. In the current reported death, the individual had findings at autopsy that could account for her death in the absence of the toxicology results. However, given the lack of a finite immediate natural cause and the totality of the circumstantial evidence, the role of the decedent's natural disease is that it likely hastened the cardiorespiratory compromise from the overdose. Thus, this report is the first gabapentin-only death with available autopsy and toxicology findings known to the author.

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