Distribution of Etomidate in a Fatal Intoxication

D.K. Molina, V.M. Hargrove, and R.G. Rodriguez
Bexar County Medical Examiner’s Office, 7337 Louis Pasteur Drive, San Antonio, Texas 78229

Abstract

Etomidate is a commonly used anesthetic agent often utilized to induce anesthesia as it has a short half-life and allows for central nervous system depression without causing major cardiovascular disturbances, making it one of the preferred medications for trauma and hemodynamically unstable patients. Thus, etomidate is commonly found during a postmortem drug screen conducted for medicolegal reasons. Concentrations of etomidate in various fluids/tissues have not been reported in the literature. We report of a case of suicide by etomidate with concentrations of 0.40 mg/L in the femoral blood, 0.46 mg/L in the bile, and 0.30 mg/L in the vitreous with a blood alcohol content of 0.119 g/dL. For comparison, we identified two cases in which etomidate was administered during resuscitation after trauma with levels of 0.05 mg/L and < 0.026 mg/L, respectively.

Introduction

Etomidate is a carboxylated imidazole derivative hypnotic agent that is commonly used to induce anesthesia. It is short-acting (half-life 1.25–5 h) and usually given intravenously at doses of 0.3 to 0.6 mg/kg for adults (20–40 mg). Etomidate causes depression of the central nervous system, including sleep and/or coma, without causing significant decreases in heart rate or blood pressure, making it an ideal anesthetic agent for hemodynamically unstable patients. It is rapidly distributed to the body tissues and brain (Vd 2.4–8.1 L/kg; mean 4.5 L/kg) (1) and is quickly hydrolyzed in the liver to 1-(1-phenylethyl)-1H-imidazole-5-carboxylic acid, an inactive metabolite (2). Etomidate is commonly found during a postmortem drug screen conducted for medicolegal reasons. Often, the results are simply reported as positive and not further quantified, much the same way as atropine and other drugs are reported as these drugs are often found because of resuscitation efforts and not believed to be involved or influential in the cause of death. Therefore, concentrations of etomidate with various autopsy specimens have not been previously reported in the literature.

Case History

A 44-year-old female nurse (Case 1) with a history of chronic ethanol use and previous suicide attempts expressed suicidal ideations after having recently broken up with her boyfriend. She checked into a local hotel and left instructions not to be disturbed. After several hours, the family became concerned and went to the hotel to check on her. Upon entering the room, the family found her unconscious within the bathtub and called emergency services. Upon arrival, emergency medical personnel attached cardiac monitors to the decedent’s thorax, and she was pronounced dead without undergoing life-saving interventions.

The death was reported to the Bexar County Medical Examiners Office (BCMEO) which took jurisdiction of the case. Upon arrival of the BCMEO to the scene, the body was found within a bathtub filled with warm, blood-tinged water that covered the body but not the head. Next to the bathtub, on the bathroom floor, were two empty vials of 20 mL (40 mg) Amidate® and their packaging, a 30-cc syringe containing a clear fluid, an empty 10-cc syringe, numerous needles, a bucket of ice, and a .38 Special revolver (Figure 1). Multiple bags of normal saline were suspended from the shower curtain rod above the bathtub. Two bottles of alcohol (wine and vodka) and additional medical equipment, including intravascular catheters, tubing, and bags of saline, were present throughout the room. The decedent was found to have intravascular catheters within her left wrist, right posterior hand, and right antecubital fossa.

At autopsy, the decedent was found to be normally developed and well-nourished, measuring 66 in. in length and weighing...
144 lbs. Acute needle puncture wounds were noted in the right antecubital fossa, left anterior wrist, and left antecubital fossa. An intravascular catheter was present in the right antecubital fossa, which was pierced by two needles connected to two separate 250-mL saline bags. Internal examination was unremarkable. There was no evidence of natural disease or trauma to account for the death.

Materials

An analytical standard of etomidate was purchased from Bedford Laboratories (Bedford, OH, manufactured by Reliable Bio-pharmaceutical) and was prepared as a 0.102 mg/mL stock solution in methanol. Prazepam was purchased from US Pharmacopeia Convention and prepared as a 0.454 mg/mL stock solution in methanol. Methapyrilene was purchased from Sigma and prepared as a 0.103 mg/mL stock solution in methanol. All other reagents used were purchased from various scientific vendors and of analytical grade.

Methods

Controls, calibrators, and case samples (blood, bile, and vitreous) were analyzed using the standard Alkaline Drug Screen procedure employed at the Bexar County Medical Examiners Office. Initially, 25 µL of a mixture of prazepam and methapyrilene (final concentration 2.8 mg/L and 0.64 mg/L, respectively) was added to 4 mL of specimen and mixed with 8 mL of n-butyl chloride and shaken for 15 min. Then 250 µL of concentrated (28–30%) NH₄OH was added, and the specimens were shaken for 15 min and centrifuged. The organic phase was removed and combined with 4 mL of 1 N HCl and shaken for 15 min. Following centrifugation, the aqueous layer was combined with 1 mL of concentrated NH₄OH and allowed to cool. The basic drugs were back-extracted into 150 µL of methylene chloride for analysis.

The samples were analyzed using a Hewlett-Packard 6890 gas chromatograph (GC) with a flame-ionization detector (FID). The GC was equipped with a J&W Scientific HP-1 capillary column (12.5 m x 0.2-mm i.d., 0.33-µm film thickness). The carrier gas was helium at a flow rate of approximately 1.2 mL/min. Head pressure was adjusted as needed until the retention time of prazepam (internal standard) was between 7.898 and 7.910 min. The injector and detector temperatures were 225°C and 300°C, respectively, and the initial oven temperature was 125°C, ramped to 290°C at 20°C/min, and held at that temperature for a total run time of 12.5 min. Two microliters of the extracted sample was injected into the system with a 20:1 split ratio. Confirmation was performed using an Agilent Technologies 6890 GC coupled with a 5975 mass selective detector (MSD). The operating conditions and column were the same as those used in the GC–FID. The resulting chromatogram and mass spectral identification for etomidate obtained for this case are shown in Figures 2 and 3.

The quantitation was based on a five-point calibration curve (0.026, 0.051, 0.128, 0.255, and 0.510 mg/L) with two levels of control (0.083 and 0.330 mg/L). The limit of detection was 0.005 mg/L with a linear range between 0.026 and 0.510 mg/L. Calibration curves were generated by linear regression each time the cases were analyzed and all had correlation coefficients (R²) of approximately 0.999. The extraction efficiency or recovery for etomidate was determined by the comparison of the mean peak areas of an extracted 0.330 mg/L sample (n = 5) to the mean peak areas of an unextracted 0.330 mg/L sample (n = 5). The recovery of etomidate was approximately 75.0%. Two etomidate standards (0.083 and 0.330 mg/L) were extracted in multiple (n = 10), yielding an intraday precision with coefficients
of variation of 1.19% (0.083 mg/L) and 1.06% (0.330 mg/L) and interday precision with coefficients of variation of 1.36% and 1.32% for the 0.083 and 0.330 mg/L standards, respectively.

Results

The toxicology results for the presented case are summarized in Table I. The concentration of etomidate in the femoral blood was 0.40 mg/L. No other medications were present within the blood sample; however, the blood alcohol content was found to be 0.119 g/dL.

For comparison, two cases (Cases 2 and 3) where etomidate was administered for anesthesia/medical intervention 2 h prior to death, but in which the etomidate neither contributed to nor caused death were identified. The case specifics are summarized in Table II. In neither case was etomidate felt to be contributory to death as the patients were intubated and were being actively resuscitated when it was administered. The toxicology results for these cases are presented in Table III. In these cases, the femoral blood concentrations ranged from less than 0.026 to 0.05 mg/L.

Discussion

According to Van Hamme et al. (1), when etomidate was used to induce anesthesia, the plasma concentration ranged from 0.134 to 0.322 mg/L during the first 15 min and declined to an average concentration of 0.054 mg/L at 1 h. Hebron et al. (3), looked at the plasma concentrations obtained when etomidate is given in a constant infusion and obtained steady state concentrations ranging from 0.082 to 0.32 mg/L with a mean of 0.158 mg/L. The femoral blood concentration of 0.40 mg/L in this case was just above the therapeutic range for the medication; however, the drug was not administered in a hospital setting, and the patient was not intubated at the time of administration. The concentration was significantly higher than the concentrations of etomidate found in two trauma cases where the etomidate was administered during resuscitation.

The present case is the first reported case of death caused by etomidate, although there are three other reports in the literature of deaths associated with etomidate. Chalmers (4) reported a case of a 67-year-old ventilated female who was accidentally administered 250 mg of etomidate within 43 min in a hospital setting. The patient remained ventilated, unconscious, and unresponsive, but hemodynamically stable. The patient recovered from this incident, but eventually died six days later from unrelated causes. Blood levels were not performed. Howell and Driver (5) published a case of a 61-year-old male who was hospitalized for a ruptured cerebral aneurysm and inadvertently received 20 mg of etomidate and rocuronium through a ventriculostomy catheter. The patient immediately lost consciousness and became apneic. Though the patient’s neurological status declined after the incident, it cannot be known for certain the role etomidate played in the diminished function. Blood and CSF levels were not performed. Lastly, Bloomfield et al. (6) hypothesized that etomidate could be potentially lethal even at therapeutic doses in people with adrenal insufficiency because of the etomidate causing inhibition of steroidogenesis by its effects on the enzyme 11-β-hydroxylase.

An insignificant level of ethanol was also present in this case, along with the etomidate (BAC 0.119 g/dL). Ethanol and etomidate can both cause central nervous system and respiratory depression and may have acted synergistically to result in death. However, the medical examiner felt that the etomidate was the more significant drug, especially given the decedent’s long history of chronic ethanol use.

The authors also report the concentration of etomidate found in the bile and vitreous fluids for both the overdose and trauma cases presented. Concentrations of etomidate in samples other than blood have not been previously reported, possibly because most toxicology laboratories, like the BCMEO toxicology laboratory, may report etomidate as present, but do not quantitate it, as it is usually seen as a medication associated with cardiopulmonary resuscitation.

Conclusions

In summary, the medical examiner determined the manner and cause of death to be suicide by etomidate intoxication with alcohol intoxication contributing. Although the Alkaline Drug Screen procedure at the BCMEO identified
the intoxicant, the concentrations would normally have not been quantitated had the scene not indicated its potential use in causing death. Though uncommon, death by anesthetic/resuscitative medications can occur, especially in personnel who have access to them such as nurses, emergency medical personnel, and doctors. The toxicology results should always be compared to the circumstances and autopsy findings to ensure drugs present are not merely dismissed as inconsequential.

Acknowledgments

The authors would like to thank Mr. Dan Anderson for all of his work in assisting in the preparation of this manuscript.

References