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CASE REPORT

A case of fatal poisoning caused by etomidate: evidence from pathological and toxicological analyses

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Abstract

Etomidate is a nonbarbiturate sedative derived from imidazole. Prolonged and excessive use of etomidate can lead to the suppression of adrenocortical function, myoclonus, and even death. This report describes a rare case of a 47-year-old man who died from acute intoxication after oral ingestion of liquid containing etomidate. The cause of death was conclusively attributed to etomidate based on a comprehensive investigation, including autopsy, histopathological examination, toxicological analysis, and biochemical analysis. This is the first reported case of a fatality solely resulting from the oral ingestion of etomidate, which can provide valuable insights for future forensic investigations involving etomidate poisoning. Therefore, it is imperative to share this case with the scientific community.

Keywords Forensic toxicology · Etomidate · Drug abuse · Autopsy

Introduction

Etomidate is a nonbarbiturate sedative derived from imidazole that is known for its ability to induce reversible loss of consciousness and sensory depression by affecting the central nervous system [1]. Due to its rapid onset, short duration of action, quick recovery after a single dose, and minimal cardiovascular side effects, etomidate is widely utilized in clinical settings [2]. Recent studies have shown an increase in the illegal misuse and smuggling of etomidate, which is used as a substitute for other drugs [3, 4]. However, prolonged and excessive use of etomidate can lead to the suppression of adrenocortical function, myoclonus, and even death [5].

Given these circumstances, forensic scientists must focus on the detection of etomidate and its associated fatal blood levels and histopathological changes. Several articles have been published on the abuse and detection of etomidate [4, 6, 7]. However, there is limited research on the toxicity and fatalities related to etomidate. A search of the PubMed, Web of Science, and Google Scholar databases for "etomidate, deaths, and case reports" identified only two deaths directly related to etomidate [8, 9]. Furthermore, very few autopsy cases involving etomidate have been reported in the literature, and these fatalities often involve poisoning by etomidate mixed with other substances [6, 10, 11]. The fatal blood levels and characteristic histopathological

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changes associated with etomidate poisoning remain largely unknown. In this study, we present a case of acute intoxication resulting from the oral ingestion of etomidate, with no involvement of other factors. This conclusion was based on a thorough investigation, including autopsy, histopathological analysis, and toxicological analysis.

Case Presentation

A 47-year-old man (height 168 cm, weight 65 kg) experienced a sudden loss of consciousness while drinking coffee on a boat. The witnesses called the emergency services, and resuscitation efforts, including cardiopulmonary resuscitation and intravenous epinephrine hydrochloride (3 times, 1 mg/ml per time) were performed by the doctors immediately. However, doctors were unable to detect a heart rate or blood pressure, and the electrocardiogram showed a straight line. The man was confirmed to be dead by a physician after one hour of rescue attempts. During the scene investigation, a bottle labeled "Guava" containing a clear liquid (750 ml) was discovered. A video retrieved from the scene showed that the man took a sip of liquid from the bottle to demonstrate its safety upon boarding the ship. He lost consciousness 20 min later. According to the police report, the man had previously sold etomidate illegally and showed no signs of suicidal tendencies prior to his death. The clinical cause of death remained uncertain, prompting the initiation of a medicolegal examination.

Upon external examination of the deceased's body, notable findings included facial and conjunctival hyperemia, as well as cyanosis of the lips and nail beds. No signs of injection were observed on the body. Postmortem internal examination revealed pulmonary congestion and edema, dark red frothy fluid in the trachea and bronchi, and 50 ml of coffee-colored fluid in the stomach (Fig. 1A and C). Histopathological examination revealed tissue hyperemia and edema, consistent with previous studies (Fig. 2A and B) [10]. Additionally, the examination revealed no secretion of glucocorticoids from the zona fasciculata gland cells, degeneration and necrosis of adrenal gland cells, hepatocyte cord dissociation, and degeneration and necrosis of hepatocytes (Fig. 2C and D).

Extraction of cardiac blood and stomach contents was performed for toxicological analysis. Etomidate was detected in the cardiac blood at a concentration of 3.63 μg/mL and in the stomach contents at a concentration of 1.5×10^4 μg/mL. The liquid from the beverage bottle was subjected to toxicological analysis and tested positive for etomidate at a concentration of 1.7×10^5 μg/mL. However, etomidate was not found in the remaining coffee. Next, a biochemical analysis of cardiac blood was conducted to assess adrenal function indicators. The results revealed a significant decrease in both adrenocorticotropic hormone (ACTH; < 0.22 pmol/L; normal reference value: 1.6–13.9 pmol/L) and cortisol (24.77 nmol/L; normal reference value: 100–400 nmol/L) levels in the deceased's blood.

Based on the findings from the autopsy, histopathological examination, toxicological analysis, and biochemical assessment, the official cause of death was determined to be lethal etomidate poisoning.

Discussion

Etomidate is a nonbarbiturate hypnotic agent that induces anesthesia by acting on the reticular activating system [12]. Its hypnotic effects are achieved by binding to two sites on the gamma-aminobutyric acid (GABA) type A receptor, enhancing the potency of GABA [13]. Due to its rapid onset, high potency, and stable hemodynamic profile, etomidate is widely used for induction and maintenance of anesthesia [14]. However, previous studies have demonstrated that etomidate can cause adrenocortical insufficiency by inhibiting the cytochrome P450 11-beta (CYP11b) hydroxylase enzyme, which is responsible for adrenal cortisol production [13]. Currently, etomidate is not regulated as a narcotic or psychotropic substance due to its pharmacological

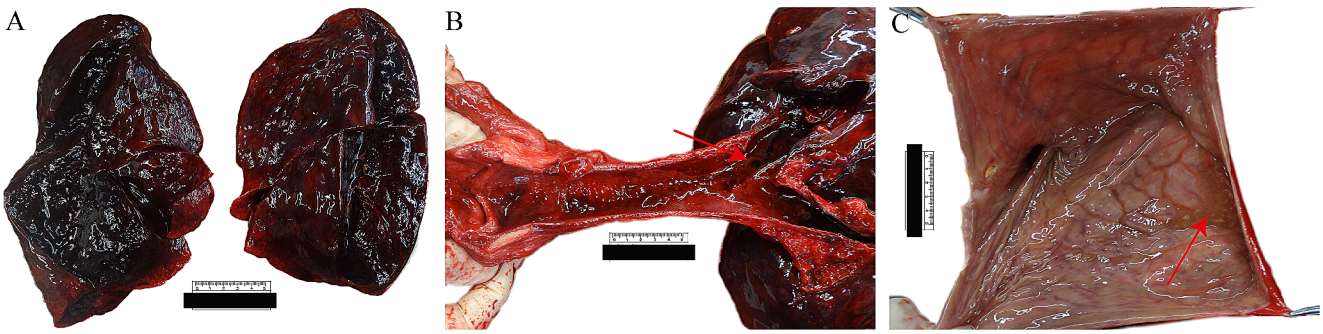

Fig. 1 Photographs of autopsy organ findings. (**A**) Lung section; (**B**) presence of dark red frothy fluid in the trachea and bronchi (indicated by arrow); (**C**) presence of coffee-colored fluid in the stomach (indicated by arrow)

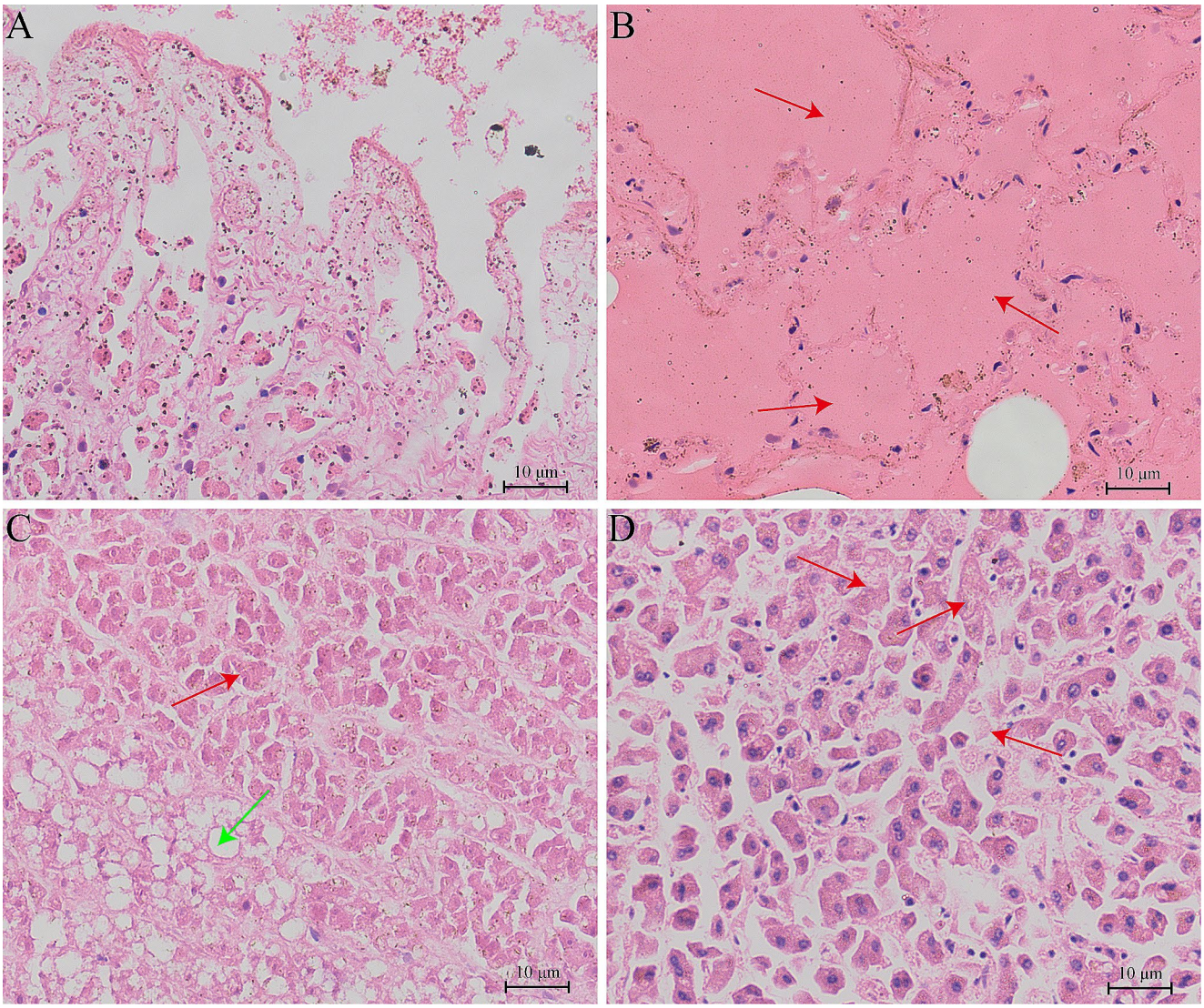

Fig. 2 Histopathological examination of multiple organs (hematoxylin and eosin staining; magnification ×100). (**A**) Congestion and edema in gastric tissue; (**B**) substantial eosin edema in the alveolar cavity (indicated by red arrow); (**C**) absence of glucocorticoid secretion from zona fasciculata gland cells (highlighted by green arrow) and degeneration and necrosis of adrenal gland cells (highlighted by red arrow); (**D**) hepatocyte cord dissociation, degeneration, and necrosis of hepatocytes (indicated by red arrow)

properties, making it a common choice for illicit use, and the illicit distribution and misuse of etomidate are increasing internationally [3]. Reports in the literature have indicated that prolonged excessive use of etomidate can result in symptoms such as reduced consciousness, apnea, and even death [6]. The uncontrolled distribution and illegal consumption of this substance may contribute to an increase in poisoning deaths caused by etomidate overdose. Our analysis of reported cases of etomidate poisoning in the PubMed, Web of Science, and Google Scholar databases suggests that this is the first documented case of an individual dying from oral etomidate poisoning alone. Therefore, this report describes a rare case of etomidate poisoning in which a comprehensive investigation, including autopsy, histopathological examination, toxicological analysis, and biochemical assessment, was conducted to ascertain the cause of death.

In this case, both the autopsy and histopathological examination revealed tissue congestion and edema, with the lungs exhibiting particularly severe manifestations. Additionally, hepatocyte cord dissociation and degeneration, as well as hepatocyte necrosis, were observed, possibly attributed to etomidate metabolism in the liver [15]. Unfortunately, indicators related to liver function were not assessed via our blood biochemical examination. Furthermore, we identified degenerated and necrotic adrenal cells and the absence of glucocorticoid secretion by zona fasciculata gland cells, possibly due to the suppression of adrenocortical function

resulting from an overdose of etomidate. These findings may be specific histopathological changes associated with etomidate intoxication, and further research is needed to confirm our preliminary data. Biochemical analysis revealed significant reductions in adrenocorticotropic hormone and cortisol levels, which was consistent with the histopathological observations. In the two previously reported cases of deaths associated with etomidate, acute needle stick injuries were observed, and other toxins were detected in the bodies. Moreover, postmortem examination did not reveal any abnormal histopathological changes, except for typical acute death-related alterations such as tissue edema and congestion [10, 11].

The recommended dose of etomidate falls within the range of 0.1–0.3 mg/kg, resulting in steady-state levels ranging from 0.082 to 0.32 μg/mL, with a biological half-life of 75 min [7, 10, 14]. In this case study, the liquid found in the bottle carried by the deceased contained etomidate at a concentration of 1.7×10^5 μg/mL. Through toxicological analysis utilizing liquid chromatography-tandem mass spectrometry (LC–MS/MS), etomidate was detected in cardiac blood at a concentration of 3.63 μg/mL, a level sufficient to cause death. Etomidate was also found in the stomach contents, indicating the route of entry into the body. The concentration of etomidate detected in the cardiac blood was notably greater than that in previous cases, possibly due to synergistic effects with other drugs reported in those cases [6, 10]. However, the exact toxic concentration range and minimum lethal concentration (MLC) of etomidate remain unclear. Therefore, the etomidate concentration detected in this case may serve as a potential reference for future cases.

To our knowledge, this is the first documented case of death resulting from oral etomidate poisoning without coingestion of other substances. Consequently, this case may offer valuable insights and experience for forensic experts tasked with identifying similar cases in the future. Additionally, it serves as a reminder for health care providers to consider the potential for etomidate toxicity in cases of poisoning and promptly administer appropriate symptom management.

Conclusion

Through this case, the authors wish to emphasize the following points: (a) Although there have been few cases of death attributed to oral etomidate poisoning alone, this possibility should not be overlooked in future cases. (b) The capacity of etomidate to suppress adrenocortical function can be fatal when etomidate is taken in excessive doses. Therefore, careful attention should be given to the pathological and biochemical changes associated with adrenocortical suppression. (c) Thorough autopsy examinations, histopathological analysis, toxicological assessments, and biochemical analyses are crucial for accurately determining the cause of death resulting from toxic substances. (d) Enhanced regulation of the illicit sale of etomidate is necessary to reduce the incidence of poisoning deaths resulting from its ingestion or overdose.

Key points

1. Cases of illicit circulation and abuse of etomidate are rapidly increasing both domestically and internationally. The illegal sale of etomidate necessitates enhanced control measures.
2. Cases of death solely caused by etomidate are rarely reported.
3. Detection methods, lethal blood concentrations, and characteristic histopathological changes of etomidate need to be brought to the attention of forensic practitioners.
4. Detailed autopsy examinations, along with histopathological, toxicological, and biochemical analyses are imperative in accurately determining the cause of death.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s12024-024-00813-8.

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Declarations

Ethics approval Ethical permission was granted through the Science and Ethics Committee of Hainan Medical University.

Consent to participate Informed consent was obtained from the fam-

ily of the deceased in this study.

Competing interest The authors declare that they have no conflict of interest.

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