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REVIEW ARTICLE

Etomidate-related fatalities: A systematic review of case reports

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Abstract

Introduction: Etomidate is a widely used anesthetic agent. Although its abuse had been reported in scant reports, there has been a recent surge in cases, raising concerns for public safety.

Objective: This review aims to retrospectively analyze case reports of fatal etomidate abuse.

Methods: A literature search on MEDLINE/PubMed, Web of Science, Scopus, the Chinese Biomedical Database, and Google Scholar was conducted. Search terms were developed in relation to the review's aim, and reports were restricted to the English language.

Results: This review did not identify any published reports of overdose leading to hospital admission and/or treatment. Seven reports of overdose and incidental use were identified and included for evaluation. All cases, except one, occurred in young-to-middle-aged adults, with a dominant male pattern (71%). Three cases occurred in healthcare professionals, and four cases had prior mental illness. Blood concentrations at postmortem and attributed to death ranged from 0.4 to 3.6 μg/mL.

Conclusion: This review identified that ease of access to etomidate among registered healthcare professionals, male gender, young adult age, and history of mental illness were associated with etomidate abuse. However, more research is needed to explore these factors in larger samples. Improved methods to detect and diagnose etomidate misuse are needed to guide clinical and toxicology practices. Active surveillance of misuse is also needed to inform primary and secondary prevention efforts.

Keywords: Etomidate; Fatalities; Abuse; Overdose; Toxicology; Case reports; Healthcare professionals; Substance misuse

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1. Introduction

Etomidate is a widely used non-barbiturate anesthetic agent and has remained in widespread use for a range of indications due to its cardiovascular stability and rapid onset and offset of action.[1] It can provide optimal anesthetic conditions requiring cerebral protection, as well as avoiding histamine release and respiratory depression, providing a desirable option for several clinical situations.[2] However, etomidate has several side effects, and these can arise following bolus induction doses, with one of the most notable effects being adrenocortical suppression. This adverse effect was identified following

excess cases documented in research demonstrating a relationship between adrenal suppression and increased mortality in patients who received etomidate, leading to more recent drives in the development of etomidate analogs, designed to counter adrenal suppression.[1,3] Outside of clinical settings, there has been a recent surge of etomidate abuse cases, with rises in hospital admissions due to abuse and overdoses, leading to several fatalities.[4-6]

In Hong Kong, the Poison Control Centre reported 300 cases of etomidate abuse (183 in males and 117 in females), but the number requiring hospital admission and/or inpatient treatment, inclusive of critical care, is not clear.[7] A letter to the editor reported 45 cases of etomidate-containing "space oil" abuse requiring hospital admission over a period of 8 months in 2024, and thus, a crude estimate is that emergency department treatment is required for around 20% of those who misuse etomidate via the vaping route alone.[7] These cases were recorded only since 2024, with no historical insight into previous abuse. This is because etomidate abuse outside of clinical settings is a newly recognized problem with significant public health concerns.[7] Most cases of etomidate abuse have presented with signs or complications, such as confusion, ataxia, and myoclonus, that are mostly self-limiting; however, hypokalemia occurs in over two-thirds of cases, which confers a risk of cardiac arrhythmias and sudden death.[7,8] Wong *et al*.[7] also noted that there were four intensive care admissions, of which three deaths occurred; however, the mode of death was not reported.

Due to the rising number of abuse cases, the Hong Kong Security Bureau has intensified the surveillance of etomidate misuse, potentially providing valuable insight into temporal trends in abuse and related risk factors in the near future.[9] The present characteristics and potential risk factors among etomidate abusers remain unclear, highlighting an important evidence gap. Moreover, the Hong Kong Government has revised its legislation within the Dangerous Drugs Ordinance with increases in penalties for offenders who engage in etomidate distribution and/or abuse.[10] Such revisions were only incurred as of February 2025, and thus, there remains uncertainty over whether such laws will lead to a meaningful decrease in etomidate abuse and the rate of toxicity and fatalities.[11]

In other nations, including the United States and South Korea, there have also been several historic and recent etomidate abuse cases, leading to revisions to legislation similar to that of Hong Kong.[6,12,13] However, the extent of etomidate misuse on a global level is largely unclear due to difficulties in detecting and reporting cases. In addition, there are challenges in identifying potential solutions to the problem, as information, such as modes of access to etomidate and mechanisms of distribution and abuse, remains unclear.[6] In response to a rise in etomidate overdose cases and multiple fatalities, research is urgently needed to understand the true scale and nature of this growing public health issue. To contribute, in part, to this vision, this review aims to retrospectively analyze and evaluate prior etomidate abuse cases to elicit the common characteristics associated with its abuse. The objectives were to explore the clinical presentations of etomidate abuse (including signs/symptoms and toxicological findings), demographic trends (such as influences by age, sex, and other factors), and outcomes due to abuse (inclusive of treatment instigated by care services).

2. Methods

To support the noted aim and objectives, a rapid systematic review was performed to identify all published reports of etomidate overdoses. The review protocol was not registered; however, the Prospective Register of Systematic Reviews: PROSPERO[14] was searched to ensure that no similar reviews had already been registered, thereby justifying the need for this study. This search confirmed the absence of any recent systematic reviews on this topic. Rigor in the evidence searching and filtering/selection steps was supported by compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[15] The literature search was conducted on MEDLINE/PubMed, Web of Science, Scopus, the Chinese Biomedical Database, and Google Scholar. Searching multiple databases was necessary to reduce the risk of evidence searching bias and the risk of incidentally excluding one or more relevant studies from review syntheses.[16] However, as a residual risk of searching bias can exist in reviews, citation screening was also performed to capture any studies that may have been missed or that were contained in journals not indexed to any of the searched databases.[17]

The search string was constructed in accordance with the population, exposure, and outcome/interest elements of the review aim and objectives.[18] Truncation syntax and mapping to topic headings (Medical Subject Headings) were applied to certain search phrases to optimize the breadth of the search. In addition, Boolean connectors, including OR/AND, were used to maximize search precision by providing optional and mandatory linking of terms and groups of terms.[18] The search strategy applied to the core databases comprised: ("etomidate" OR "space oil") AND ("toxic*" OR "overdose" OR "misuse*" OR "abuse" OR "adverse effect*" OR "fatal*" OR "mortal*").

Following the search using the given strategy, the records were systematically filtered to identify case reports of relevance to this review. Inclusion and exclusion criteria,

as detailed in Table A1, were used to inform inclusion/retention and discard decisions via title/abstract and full-text screening.[19] Studies for inclusion were limited to the English language to ensure the original information could be comprehended in the absence of translational errors and to negate the need for professional translation of non-English texts. Only case reports or case series describing etomidate overdose in humans were included, as this review specifically focused on clinical manifestations and outcomes in human subjects. Animal reports and experimental models of etomidate overdose were excluded due to limited generalizability to clinical practice.[20] The filtering and selection process is shown in Figure 1.

Included case reports were appraised to ascertain the risk of bias. Due to the lack of standardized risk of bias assessment tools for case studies/series, the judgments of quality were based on the recommendations of Murad *et al.*[21] Appraising quality of case reports centers on four domains: Case selection, exposure/outcome ascertainment, causality, and reporting. The core issues in question relate to whether the cases reflect the wider patient groups and center-related experiences, whether the exposures and outcomes were accurately measured, whether outcomes could be influenced by mediators or confounders, whether the follow-up was long enough, and whether sufficient description of the case was reported to inform appropriate inferences.[21] Regarding the synthesis, the key findings were analyzed in keeping with the principles of narrative analysis, as recommended by Campbell *et al.*[22]

3. Results

3.1. Overview

This review did not identify any case reports or series describing cases of etomidate abuse resulting in hospital admission, although such cases are likely to have occurred. In such instances, an overdose of etomidate may have gone unrecognized due to the abuse of multiple illicit substances, predominantly sedatives—a pattern identified in several fatal case reports described in this section.[4,23-25] The lack of evidence highlights challenges in detecting etomidate as the causative or likely sedative in abuse cases, as well as limited awareness among clinicians regarding the emerging issue of etomidate abuse.

A total of seven case reports of etomidate abuse (Table 1) resulting in out-of-hospital death or death during admission were identified, with publications published

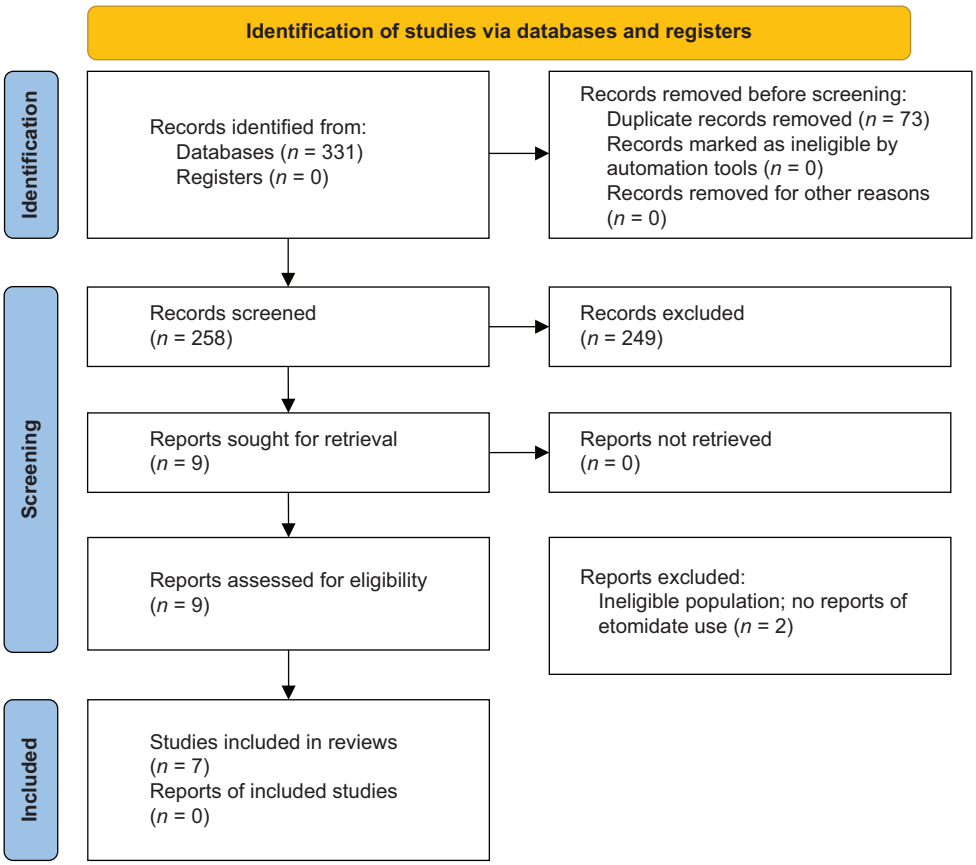

Figure 1. Record filtering and study selection process using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses method

Table 1. Summary of case report characteristics

Study	Setting	Design	Demographics	Description	Toxicology of Etomidate
Chen *et al.*[5]	Hainan, China	Case report	Male; 47 years	Abuse of etomidate through oral ingestion of a clear liquid, and he was found dead on his boat from a suspected overdose	Cardiac blood concentration 3.63 μg/mL
Detweiler and Mambo[25]	United States	Case report	Male; age unclear (no reporting)	Found dead at home with injection equipment *in situ* and empty vials of vecuronium and etomidate	Blood concentration 0.04 μg/mL
Howell and Driver[27]	United States	Case report	Male; 21 years	Presented to the hospital and accidentally received etomidate and rocuronium via a ventriculostomy catheter, leading to death	None reported
Molina *et al.*[23]	United States	Case report	Female; 61 years; registered nurse	A patient with a history of alcohol abuse and suicidal ideation was found dead	Femoral blood concentration 0.40 μg/mL, bile 0.46 μg/mL, and vitreous humor 0.30 μg/mL
Shuquan *et al.*[26]	Guangdong, China	Case report	Male; 42 years; registered nurse	History of etomidate smoking resulting in death	Etomidate detected in cardiac blood by high-performance liquid chromatography–tandem mass spectrometry (HPLC-MS/MS); concentration 0.56 μg/mL; no other common toxins or drugs detected
Smedra *et al.*[4]	Poland	Case report	Male; age unclear (no reporting); registered paramedic	Found dead alongside empty vials of etomidate, rocuronium, diazepam, and morphine	None reported
Yum *et al.*[24]	South Korea	Case report	Female; 20 years	Found unconscious in the hotel room bath and had died	Femoral blood concentration 0.11 μg/mL and cardiac blood concentration 0.21 μg/mL

ranging from 2008 to 2024.[4,5,23-27] The limited number of case reports may simply highlight a paucity of etomidate abuse over the past few decades or insufficient reporting of overdose cases and related publications in journals and other information sources. There may also be a problem of publication bias in this area, as clinicians may be increasingly inclined to describe and publish cases of etomidate-related fatalities, as opposed to survivors of toxicity. Recent reports from poison centers in the United States and the United Kingdom have failed to identify and report on cases of etomidate overdose, highlighting important implications for current reporting mechanisms.[28,29] Those in Asia appear less developed, contributing to further suspicions regarding under-reporting of etomidate abuse and publication bias across the literature.[30,31] The paucity of research in this area warrants ongoing researchers to engage in means of monitoring and reporting cases in a way that can lead to a deeper understanding of the factors influencing or associated with abuse, as we have attempted to delineate in the preceding subsections.

3.2. Risk of bias

Based on the approach to appraising the quality of the included case reports, as previously described, the risk of bias judgments was based on domains of case selection, ascertainment, causality, and reporting.

In view of rising etomidate abuse in Asia, as noted in the background chapter, the selection of three case reports of etomidate fatalities may be deemed to lack representativeness to the wider experiences of centers in these regions.[5,24,26] This essentially implies that issues of selection and reporting bias exist in these reports, as other cases of etomidate abuse have not been reported and published. The method of case selection was undefined in all case reports,[4,5,23-27] presenting further uncertainty over the representativeness of the findings to wider and larger groups of persons who abuse etomidate. While the remaining four case reports outside of Asia could be deemed more representative on the assumption that etomidate abuse is less prevalent than in Asia, the single sample sizes precluded certainty in judging representativeness.[4,23,27] In addition, the inclusion of only seven case reports in this review warrants caution when interpreting the findings in light of a markedly small overall sample size.

Regarding ascertainment, the exposure of etomidate abuse was deemed sufficient in most case reports[5,23-26] as the blood concentrations were determined at postmortem using highly accurate and validated methods of quantification. Methods of quantification of etomidate in blood included liquid chromatography–tandem mass spectrometry,[5,24] gas chromatography,[23] and high-performance liquid chromatography.[25] The method of quantification was not reported in one case report.[26] Variances in the use of these methods may preclude inter-report comparisons. In addition, the concentrations of etomidate were determined from differing sampling sites,

and this may also preclude insight into the mean blood concentrations associated with toxicity, as well as further impeding inter-study comparisons of toxicology.

Ascertainment of the outcome is not applicable for assessing the risk of bias in this review, as the outcome was simply fatalities. However, inferences of causation between etomidate abuse and said facilities are important, but due to a lack of guidelines concerning toxic and fatal limits of etomidate in blood, such inferences cannot be ascertained. In some cases, etomidate was abused in combination with other drugs and therefore provided little insight into the association or causation with fatalities.[4,25,27] Furthermore, failure to quantify etomidate levels at postmortem also precludes insight into the relationship between abuse and fatality.[4,27] However, the sole overdose of etomidate, based on reports describing first responders discovering empty vials of etomidate, implies that such abuse led to fatality, independent of blood concentration measurement.[5,23-25] Finally, cases were largely described in sufficient detail to permit inferences about the cause of death.

3.3. Demographic trends

The majority of abuse cases (5/7) were in males,[4,5,25-27] with only two occurring in females.[23,24] All cases led to death. Intentional overdose was evident in some cases where individuals had left suicide notes,[23,25] whereas others were unintentional[5,26] or assumed overdoses based on the observations and reports.[4,24] One case was a suspected accidental overdose incurred by healthcare providers during an inpatient admission, where a potentially fatal dose of etomidate was administered via a ventriculostomy catheter.[27] The ages of persons who died due to etomidate overdosing were 21 years,[24] 42 years,[25] 44 years,[23] 47 years,[5] and 61 years.[27] However, in two cases, the age of the individuals was unclear due to a lack of reporting, although based on the information, the persons in question were young or middle-aged adults.[26,27] Three of seven cases occurred in healthcare professionals—individuals with ease of access to etomidate—with the professions including a registered paramedic[4] and two registered nurses.[23,25] These cases involved the self-administration of etomidate via intravenous catheters and/or injections. The incidental overdose also resulted from etomidate administration via an indwelling catheter.[27] In the three cases of etomidate abuse, the routes of administration were inhalation via vaping,[26] injection,[24] and oral ingestion.[5] A previous history of depression, substance misuse, and/or suicidal ideation was noted in four cases.[4,23,26,27] Due to insufficient reporting, information about the mental and/or physical medical history was not available in some cases.[5,24] One case reported no known medical history in a nurse who committed suicide with etomidate and vecuronium.[25]

3.4. Clinical presentation

As six of seven cases resulted in suicide and death, no prior information about the signs and symptoms of etomidate abuse was reported.[4,5,23-26] In the incidental case occurring within a hospital, Howell and Driver[27] described a need to re-intubate a patient who had a ruptured cerebral aneurysm, and 20 mg etomidate, as well as 100 mg rocuronium, was administered accidentally via a ventriculostomy catheter under a rapid sequence induction protocol. After one minute, the patient lost consciousness and became apneic. The error was then recognized, the patient was intubated under good conditions, and no changes in hemodynamic parameters were noted. After several hours, the patient was assessed to have a Glasgow Coma Scale (GCS) score of 8, indicating a state of severely impaired consciousness. A GCS of 8 is generally considered the clinical threshold for coma and is associated with the need for airway protection and intensive neurological monitoring.[32] Cerebral angiography revealed persistent vasospasm at the site of the initial rupture. Despite ongoing supportive care, the patient's neurological status did not improve, and over the subsequent 30 days, complications accumulated, ultimately leading to the withdrawal of life-sustaining treatment.[27] In all cases were reported, the toxicological analyses showed that the etomidate concentration in blood comprised 0.04 μg/mL,[25] 0.4 μg/mL,[23] 0.56 μg/mL[26] 0.11–0.21 μg/mL,[24] and 3.6 μg/mL.[5] Blood levels were either not examined or not reported in the other two cases.[4,27]

The clinical significance of the blood concentrations of etomidate identified in the noted cases (Figure 2) is evaluated in the discussion chapter and briefly noted here. Pharmacokinetic studies have shown that a usual induction dose of etomidate of 0.2–0.6 mg/kg is generally associated with blood concentrations of 0.2–0.5 μg/mL.[33-35] Therefore, in two case reports, the blood levels were < 0.4 μg/mL, indicating that etomidate toxicity may not have been present and resulted in death.[23,25] However, caution is needed here as the blood concentrations in the reports were obtained postmortem and therefore reflect measurements taken some time following death. As such, there was likely a period of etomidate metabolism and clearance before blood sampling, which could have resulted in marked underestimation of the blood concentration and, thereby, obscured inferences about toxicity. This uncertainty appears to be reflected in the case report of Yum *et al.*,[24] where femoral and cardiac blood concentrations of etomidate differed markedly: 0.11–0.21 μg/mL, respectively. This difference in concentration supports the likelihood of variable distribution, redistribution, metabolism, and clearance of etomidate, which could further depend on the timing of blood sampling, whether

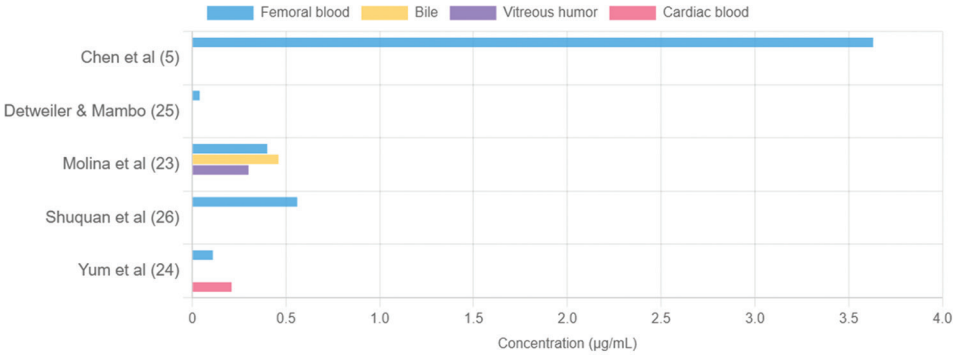

Figure 2. Variability in etomidate blood concentration across case reports

at or before postmortem. In the remaining case assessing etomidate concentration,[5] the level markedly exceeded the post-induction levels reported in pharmacokinetic studies (3.6 µg/mL)—7.3-fold higher than the usual 0.5 µg/mL—providing greater certainty that etomidate was abused to toxic levels and resulted in death.

3.5. Treatment and Outcomes

In most case reports, persons with etomidate abuse were found after a prolonged period of the event, and thus, no means to initiate advanced life support were utilized.[4,5,23-26] In the hospitalized case, Howell and Driver[27] reported a treatment protocol comprising a usual approach to rapid sequence induction. However, no specific measures were instigated as the dose of etomidate administered was a common dose for induction, but delivered via a ventriculostomy catheter. Thus, although the drug complication occurred, the administration of etomidate did not appear to result in toxicity. As previously noted, all patients described in the case reports included in this review died; six were due to etomidate and/or other coadministered sedatives,[4,5,23-26] and one was due to seemingly unrelated causes.[27] Death was attributed to vecuronium, rather than etomidate, in one case, as the blood level of etomidate was low (0.04 µg/mL).[25]

4. Discussion

In summary, this review aimed to conduct a retrospective analysis of etomidate abuse cases resulting in fatalities. In addition, the intention was to explore hospital admissions following etomidate abuse; however, the literature search was unable to capture any pertinent case reports or case series. A lack of case reports may simply indicate insufficient desire or action in describing and publishing cases of etomidate overdose. Alternatively, there may be poor awareness among clinicians regarding the emerging and prior misuse of etomidate, with abuse cases presenting to the hospital likely having abused additional sedatives. This was noted in several suicide cases reported in this review with self-administered agents, in addition to etomidate, including rocuronium, vecuronium, metomidate, diazepam, morphine, and alcohol.[4,23-25] Some of these cases occurred under the care of healthcare professionals, suggesting difficulty for individuals outside of healthcare professions to access multiple controlled drugs. However, literature has shown that drug accessibility is not a significant barrier for individuals engaged in illicit and criminal activity.[36] The ease of access to controlled drugs, such as etomidate, therefore represents a pertinent risk factor for abuse, particularly among healthcare professionals. Previous research has shown that 10–15% of clinicians experience a lifetime risk of becoming dependent upon a substance, with the highest risk observed among those working in anesthesia—likely due to their easier access to commonly misused drugs, including opioids, benzodiazepines, and other hypnotic agents.[37]

Recognizing signs of substance abuse among clinicians can be challenging; however, diligence and observation by colleagues within healthcare settings remain among the few means of identifying and intervening in such situations. Indicative signs may include physical or behavioral changes, as well as suspicious actions that prompt others to raise concerns through proper reporting channels or protocols.[37] Formal interventions with robust evidence-based approaches, such as the substance version of the 12-step method founded within the "Alcoholics Anonymous" program, have demonstrated effectiveness in supporting recovery from substance dependence.[38] Nonetheless, various factors can influence the extent of engagement and effectiveness of "Narcotics Anonymous" interventions, and certain limitations persist, as such programs primarily target persons misusing opioids rather than hypnotic agents such as etomidate.[39,40]

In this review, other cases included an incidental administration of etomidate, as well as rocuronium, via a ventriculostomy catheter, as part of a rapid sequence

induction protocol due to increasing oxygen requirements in a patient with a ruptured cerebral aneurysm. The dose administered did not lead to any clear signs of toxicity, and in effect, the rapid sequence induction was successful in enabling mechanical ventilation for a period up to 30 days. Death in this case occurred due to complications that cannot be considered related to the drug administration error—a secondary brain injury with infarctions of the right temporooccipital lobe and bilateral periventricular white matter.[27] In the cases of illicit etomidate abuse and suicide, the bodies were found at prolonged periods following the abuse, and thus, no signs of toxicity could be described.[4,5,23-25] Rather, the blood concentrations at postmortem ranged from 0.4–3.6 μg/mL—levels that are 8–13-fold higher compared to concentrations drawn from trauma cases who died but were initially administered a rapid sequence induction dose of etomidate.[5,23,26]

Not all cases included in this review underwent postmortem toxicology, and in some cases, results were concealed for unclear reasons, indicating a need for more transparent investigations in the future to assist in corroborating or disputing the findings herein.[4,27] Aside from this issue, this review identified that all cases of illicit etomidate abuse occurred in young-to-middle-aged adults,[4,5,23-26] aligning with prior epidemiological observations that substance abuse generally occurs in these age groups.[41,42] In addition, we found that all but two of the cases occurred in males, consistent with previous literature showing that males are more likely than females to engage in substance abuse, with a prevalence averaging 80% in favor of males.[37,43] However, previous research has found that substance abuse is rapidly increasing in females and adolescents, balancing the skewed gender distribution and raising concerns regarding access to drugs such as etomidate, which can rapidly lead to death.[44,45]

This review also aimed to uncover patterns in the treatment and outcomes following etomidate overdose; however, due to a paucity of overdose and hospital admission case reports, this aim could not be addressed. Nonetheless, prior studies conducted in healthy persons to determine the pharmacological profile of etomidate, as well as research exploring its side effects in persons receiving the drug as part of anesthesia protocols, provide useful insights into its side effects and toxicity. These studies did not involve cases of etomidate abuse and were therefore excluded from the review findings. In one study involving healthy adult volunteers, Ding *et al.*[46] showed that the incidence of adverse events due to etomidate was 12.6%, with 13 of 52 participants noting 20 mild adverse effects, including alterations in various biomarkers; one moderate event, leukopenia, was also observed. All adverse effects were self-limiting and resolved without treatment. In another study of 18 healthy adult volunteers, Kaneda *et al.*[47] reported two adverse events, both of which comprised myoclonus—a widely recognized and self-limiting side effect of etomidate.[48]

A review of existing pharmacological and clinical studies also summarized the adverse effects of etomidate, including post-operative nausea and vomiting, pain on injection, and adrenal suppression.[1] Pain on injection is particularly common and appears to occur in almost all cases, although this can be mitigated with a prior injection of lidocaine.[33] The rate of post-operative nausea and vomiting in anesthetic contexts is around 40% but can be effectively prevented or resolved using anti-emetics, such as ondansetron.[49-51] Finally, adrenal suppression remains the most clinically concerning, as adrenal toxicity can occur for prolonged periods (6–8 h) following an induction dose and for over 24 h in those receiving infusions of etomidate.[52-54] The adrenocortical suppressive effects of etomidate and their potential association with mortality have prompted efforts to develop analogs that avert this problem—an ongoing area of research.[1]

Importantly, there are currently no established forensic thresholds to discriminate therapeutic from fatal etomidate concentrations; only the case reports in this review allude to such concentration variances. While no clear consensus exists regarding blood levels indicative of overdose, toxicity may be considered when concentrations are at least two-fold higher than the plasma concentrations observed after a typical induction dose of 0.2–0.6 mg/kg, corresponding to blood levels of 0.2–0.5 μg/mL.[33] The case report by Shuquan *et al.*[26] also advocated that peripheral blood concentrations of etomidate could be used as an initial reference for ascertaining lethal limits. Moreover, the levels of etomidate in the peripheral and central vasculature, as noted in other reports, could also be used for reference purposes.[5,23-25]

In a pharmacokinetic study of etomidate involving eight adult patients who received an intravenous induction dose of 0.3 mg/kg etomidate, Van Hamme *et al.*,[35] showed that the plasma concentration varied from 0.13 to 0.32 μg/mL, supporting the concentration reported by Williams *et al.*[33] Similarly, de Ruiter *et al.*[34] showed that a mean induction dose of 0.2 mg/kg produced a mean plasma concentration of 0.5 μg/mL in adult surgical patients. Following administration of a maintenance dose of 10 μg/kg/min, anesthesia was maintained with plasma concentrations <0.8 μg/mL. No clinical signs of toxicity were noted, suggesting that toxic plasma concentrations would likely exceed 0.8 μg/mL. In animal studies, daily dosing of etomidate as high as 5.0 mg/kg

has been tolerated, although such dosing has not been replicated in humans.[55] Other studies have shown that doses of 2.5 mg/kg etomidate in dogs tend not to incur marked changes in cardiovascular dynamics, and similar effects have been observed in children with a 0.3 mg/kg induction dose attaining plasma concentrations around 2.4 μg/mL within the first few minutes of administration, followed by a decline.[55-57]

In an adult case report involving a patient receiving a high-maintenance dose of etomidate during extracorporeal membrane oxygenation (20 μg/kg/min), no adverse effects were noted over 6 days.[58] The authors predicted that metabolic acidosis could occur due to the presence of propylene glycol within the formulation, as suggested by a high osmolar gap; however, the blood pH remained stable on blood gas analysis. Other research has noted that propylene glycol, which is also used as a solvent in some benzodiazepine preparations, can incur toxicity when serum levels exceed 180–200 μg/mL, leading to hyperosmolarity, high anion gap metabolic acidosis, hemolysis, cardiac arrhythmias, hypotension, seizures, and coma.[59-61] A trial exploring the effects of etomidate (0.3 mg/kg, followed by 0.02 mg/kg/min) in patients with brain injuries was prematurely terminated due to rising osmolarity and renal impairment within 24 h, suggesting propylene glycol toxicity.[62] Therefore, it is plausible that excess administration of etomidate and constituent propylene glycol was responsible for toxic effects and the mode of death in overdose cases discussed in this review. Nonetheless, the injection of large doses of etomidate may not be directly comparable to continuous infusions associated with propylene glycol toxicity, highlighting knowledge gaps in this field.

Finally, the duration of etomidate's action has been estimated as 100 s of unconsciousness for every 0.1 mg/kg administered, though other reports suggest that the same dose can yield 7.5 min of hypnosis.[55] Recovery time can vary based on redistribution of the agent within inactive tissues, while the coadministration of narcotics can reduce the etomidate doses needed to induce anesthesia.[33] Notably, one case report included in this review involved the concurrent abuse of multiple substances,[4] including narcotics, suggesting that a lower-than-expected dose of etomidate may have been sufficient to cause death. However, the blood concentration of the abused substances was not determined or reported.

5. Conclusion

Given the increasing cases of etomidate abuse and suicide, several recommendations for ongoing research and for clinical and toxicology practices have been formulated. First, there is a need for point-of-care methods that can enable the rapid detection and quantification of etomidate in overdose cases to support diagnosis and treatment both within and outside hospital settings. This may be facilitated by the measurement of etomidate metabolites or related biomarkers, which is an ongoing area of investigation.[63,64] In addition, a recent study assessing etomidate and etomidate acid levels within hair samples using liquid chromatography yielded a markedly high coefficient of accuracy of 0.997, suggesting that this approach could prove valuable for postmortem toxicological assessment in suspected etomidate overdose.[65] However, the use of liquid chromatography within the cited literature is not a plausible method for assessing etomidate concentrations in patients presenting with suspected toxicity.[63-65] Therefore, there is a need for research to identify, develop, and evaluate novel point-of-care testing methods to ascertain etomidate levels and to improve the general efficiency and turnaround of conventional toxicological analyses. Second, there is a need for enhanced surveillance and reporting of etomidate abuse cases to assist in better understanding the risk factors for abuse. This may lead to better risk stratification and prevention efforts in substance abuse management. Finally, more stringent controls are needed to regulate access to controlled agents in hospital settings, in view of this review identifying several cases of abuse by healthcare professionals. However, introducing stricter measures within healthcare settings may prove challenging, as etomidate is often used as an emergency sedative and induction agent, requiring ready accessibility among a range of healthcare workers.[66] Nevertheless, more stringent legislation may help to deter healthcare workers who may harbor intentions to access and utilize or distribute etomidate. Despite this, some case reports included in this review demonstrated the abuse of etomidate in response to suicidal intentions.[4,23-25] Therefore, enacting stringent laws regarding access may fail to alter the distorted and acute mental states in persons experiencing suicidal ideation.[67] Moreover, inciting more stringent legislation could lead to increases in the abuse of other drugs, masking and overlooking the underlying factors leading individuals to abuse substances—factors that are critical to understand for effective primary prevention.[68]

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Not applicable.

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Availability of data

Data will be made available upon reasonable request to the corresponding author.

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Appendix

Table A1. Summary of inclusion and exclusion criteria

Study characteristics	Inclusion criteria	Exclusion criteria
Research design	Case reports or case series of etomidate overdoses	Editorials, animal studies
Language	English	Other languages
Population	Cases of etomidate overdose resulting in toxicity and/or fatalities within humans	Animals or experimental models
Exposures/outcomes/interests	Characteristics of overdose cases, including demographics, clinical presentation, treatment, and outcomes	-