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*Case Report*

# IS AN ACUTE OVERDOSE OF ZOLPIDEM FATAL? CASE REPORT OF A SUICIDE ATTEMPT WITH ZOLPIDEM AND PARACETAMOL

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**ABSTRACT**

Zolpidem, widely prescribed for short-term management of insomnia, is a non-benzodiazepine hypnotic agent. It carries a high potential for abuse and an elevated risk of suicide. Overdose generally results in mild central nervous system depression, though severe outcomes are possible when co-ingested with other CNS depressants. Standard treatments include gastric lavage, flumazenil administration, and intravenous fluids.

This case report describes a 66-year-old female admitted after an apparent suicidal ingestion of approximately 200 mg of zolpidem. Upon admission, she was unconscious, with bradypnea and hypotension, scoring 5 on the Glasgow Coma Scale. Gastric lavage and N-acetylcysteine were administered due to elevated liver enzymes suggesting concomitant paracetamol poisoning, which was confirmed by urine tests. Flumazenil temporarily improved her condition, and she was subsequently transferred to the Intensive Care Unit for mechanical ventilation. Her clinical status stabilized, leading to extubation on the second day and transfer to the Psychiatry Unit.

This case highlights the critical need for timely intervention and continuous monitoring in zolpidem overdose scenarios, particularly when polypharmacy is involved. In instances of respiratory failure following zolpidem overdose, it is imperative to investigate the potential co-ingestion of additional substances.

**KEYWORDS:** zolpidem overdose, suicide, Z-drugs, nonbenzodiazepine.



## 1. Introduction

### 1.1. Background

The demand for sleeping aids is steadily increasing. In the United States, it is estimated that the consumption of sleep medications exceeds 10% of the population [1]. Zolpidem is an imidazopyridine derivative with sleep-inducing effects, for which the indication for use is the treatment of short-term insomnia. Zolpidem is a nonbenzodiazepine modulator of the GABA receptor, and although its structure is different, some side effects are analogous to benzodiazepines. However, it is pointed out that zolpidem lacks muscle relaxant and anticonvulsant effects [2]. The risk of zolpidem abuse is high, and the risk of suicide is higher in patients taking zolpidem compared to those not taking the drug [3, 4].

### 1.2. Sedative-hypnotic toxidrome

The overdose syndrome of sedative drugs, including those in the benzodiazepine (BZD) group, is referred to as sedative-hypnotic toxidrome. It includes symptoms such as ataxia, disorientation, visual and speech disturbances, hallucinations, delirium, sedation and even coma and apnea [5]. Nonbenzodiazepine receptor agonists (including zolpidem), however, have a different chemical structure than BZDs and selectively act on one type of GABA-A receptor, making the effect dominated by a sleep-inducing effect without presenting a complete picture of

the toxidrome. Side effects are therefore often sleep-related (sleepwalking, sleep-driving and other behaviors resulting from incomplete awakening) [6].

### 1.3. Zolpidem overdose

Zolpidem overdose leads to central nervous system depression, cognitive impairment, drowsiness, coma and respiratory depression, but these effects are not as severe as those of short-acting benzodiazepines [2]. Studies to date report that poisoning with zolpidem as a single drug usually has mild effects, but ingesting it together with other central nervous system depressants can be dangerous even at low doses. Based on Material from the Forensic Medicine Institute in Krakow, it is estimated that zolpidem accounted for 5.61% of deaths related to suicide drug poisoning in Poland in 2010-2019. Of the single drug poisonings, as many as 11% were related to zolpidem [7]. The recommended treatments for acute zolpidem poisoning are gastric lavage within the first hour of ingestion, administration of flumazenil and IV fluids [2].

### 1.4. Case report

This paper describes the case of a 66-year-old female patient who was suspected of being poisoned with zolpidem with the goal of committing suicide. Additional investigations revealed co-poisoning with paracetamol.

## 2. Case report

In May 2024, a 66-year-old woman was brought to the Emergency Unit by the Medical Response Team, presumably for suicidal purposes, having taken the drug Nasen (zolpidem). She was found at home in the bathroom, having left a suicide note. About 20 tablets (200 mg) were missing from the packages found.

On admission, the patient was in a serious general condition, unconscious, unresponsive to stimuli, with bradypnoe and hypotension. She was rated at 5 points on the Glasgow Coma Scale (GCS). Detailed scores are shown in Table 1. Table 2 summarizes the patient's vital signs on admission.

**Table 1.** Glasgow Coma Scale score on admission.

| | Description | Score |
|---|---|---|
| **Eye response** | No eye opening | 1 |
| **Verbal response** | No verbal response | 1 |
| **Motor response** | Abnormal flexion | 3 |
| **Overall** | Coma | 5 |

**Table 2.** Vital parameters of the patient on admission to the Emergency Department.

| | |
|---|---|
| **Blood pressure [mmHg]** | 90/50 |
| **Heart rate [per minute]** | 85 |
| **Respiratory rate [per minute]** | 10 |
| **Temperature [°C]** | 36.5 |

On physical examination, auscultation showed numerous furcations and crackles over the lung fields. The pupils were equal, narrow (pinpoint), non-reactive. No other significant abnormalities were noted.

In the Emergency Department, gastric lavage was performed. No residual medication was visualized. Activated charcoal, a total of 1500 ml intravenous fluids and 0.5 mg of intravenous flumazenil were administered. After the administration of flumazenil, a brief improvement in consciousness was observed. Drug panel made from urine sample showed the presence of paracetamol. Therefore, concomitant paracetamol intoxication was suspected. It was decided to administer intravenous acetylcysteine (150 mg per kg of body weight) and a blood sample was sent for testing of serum paracetamol levels. Gasometry showed no signs of respiratory distress (Table 3). Other laboratory results and their changes during the following days of hospitalization are shown in Table 4. Not including the results in the table means that their values were within the normal range.

**Table 3.** Gasometry findings on admission to the Emergency Department.

| | |
|---|---|
| **pH** | 7.40 |
| **$paCO_2$ [mmHg]** | 34 |
| **$paO_2$ [mmHg]** | 99.5 |
| **$saO_2$ [%]** | 98.6 |
| **$HCO_3$ [mmol/L]** | 22.1 |
| **BE [mmol/L]** | -3.6 |

**Table 4.** Laboratory results and their changes during the following days of the patient's hospitalization.

| Day of hospitalisation | 1 | 2 (7:00) | 2 (17:00) | 4 |
|---|---|---|---|---|
| **alanine transaminase (ALT) [U/L]** | 8 | 227 | 154 | 110 |
| **asparagine transaminase (AST) [U/L]** | 17 | 663 | 241 | 189 |
| **D-dimer [ng/ml]** | 5187 | - | - | - |
| **glucose [mmol/L]** | 10.6 | - | - | - |
| **serum creatinine [umol/l]** | 89.8 | 68.4 | - | 55.9 |
| **blood urea nitrogen (BUN) [mmol/L]** | 7.8 | 5.3 | - | 5.0 |
| **estimated glomerular filtration rate (eGFR) [ml/min/1.73 $m^2$]** | 60 | 82 | - | >90 |

Due to the risk of respiratory depression, the patient was transferred to the Intensive Care Unit. On admission, she was intubated, a central venous catheter (CVC) was placed, an arterial cannula was inserted, IV fluids were given, and hemodynamic monitoring was performed. Circulation was stable with a tendency toward hypotension. The patient was ventilated in SIMV mode (Synchronized Intermittent Mandatory Ventilation) with morphine sedation. Bronchoscopy did not reveal features of regurgitation.

On the second day of hospitalization, sedative drugs were discontinued. The patient was circulatory stable, own breathing was efficient, gas exchange was good. Extubation was performed. Periodically, the woman was tearful and tangled. Due to the risk of withdrawal reaction, zolpidem was administered.

On the third day, the patient's condition was described as moderate, stable. She was respiratory efficient. There was still a tendency to hypotension. Therefore, a norepinephrine infusion was administered, which was discontinued in the afternoon after stable blood pressure values of about 100/60 mmHg were achieved. An easy-to-digest diet was started. The next day, the patient was transferred to the Psychiatry Department.

**3. Discussion**

An intensive study of the safety profile of zolpidem at the end of the 20th century led to the conclusion that the serious consequences of zolpidem poisoning as a sole drug are rare. In almost all cases, respiratory failure can be explained by simultaneous ingestion of another drug [8-11]. Previous retrospective reports suggest that in poisoning with zolpidem as the only drug up to a dose of 600 mg, only mild symptoms are observed, the most common of which is drowsiness [9]. In contrast, multidrug poisoning (in combination with ethanol and other central nervous system depressants) has led to coma in some patients in doses as low as 100-150 mg [2]. A fatal case was also reported after the use of more than 300 mg of zolpidem (estimates based on blood concentrations of the drug), while concentrations of other central nervous system depressants (carisoprodol) were therapeutic [10]. In a retrospective analysis of 105 cases in which symptoms of intoxication were associated with the ingestion of zalpidem, dizziness was observed in 89 patients, coma in four, and one person developed respiratory failure [2]. Few cases of respiratory failure after pure zolpidem overdose have been described in the literature. One was a 44-year-old, generally healthy man who developed coma with a Glasgow Coma Scale score of 7 and complete respiratory failure after ingesting about 200 mg of zolpidem. The patient required intubation, but was discharged after 26 hours without any complaints, which is consistent with the short-acting nature of zolpidem. Toxicological studies of urine and plasma ruled out poisoning by other substances [11]. There was also a case of zolpidem poisoning in a 40-year-old woman with a GCS score of 3 and absent brainstem reflexes, which has not been reported in other overdose cases [13].

The etiology of sudden deaths due to zolpidem overdose is unclear, especially the described case of a young, disease-free male [14]. However, it should be emphasized that the effects of zolpidem are individually variable. Recent studies have reported that zolpidem can prolong the QT interval [15, 16]. Surprisingly, a Swiss analysis of single-substance poisoning cases from 2000-2010 shows a higher mortality rate in suicide attempts with zolpidem compared to benzodiazepines [17].

The highest dose described so far for zolpidem poisoning is 9000 mg and unknown amounts of alprazolam. The female patient was admitted with GCS-3 and pinpoint pupils. No reaction to naloxone and flumazenil. She was intubated and received symptomatic and supportive therapy, and blood tests confirmed remarkably high concentrations of zolpidem. She regained consciousness on the sixth day. The case shows that with proper care, the consumption of even extremely high doses of zolpidem can bring a positive outcome [18].

Despite the growing popularity of the use of zolpidem as a sleep medication in Poland, the cases of acute poisoning described so far are few. In the case of a 15-year-old girl who ingested 60 mg (1.2 mg per kg of body weight) of zaleplon – which also belongs to the group of nonbenzodiazepine sleep medications – the intoxication manifested as drowsiness, speech disorders, motor awkwardness and slowed contact. The patient was treated conservatively and did not require specialist therapies [19]. However, it is indicated that zaleplon poisoning manifests itself more mildly compared to zolpidem [20].

A retrospective analysis of 91 cases of zolpidem poisoning, about 60% of which were suicides, showed co-poisoning with other substances in 76 (83.5%) cases, among which were primarily benzodiazepines, alcohol, opioids and antidepressants. The authors did not provide details of the remaining cases of mono-poisoning. The median blood concentration of zolpidem was quite low, which supports the lack of a direct effect of zolpidem on death. No case of concomitant paracetamol ingestion was described in this study [21].

It should be noted that zolpidem can also be an indirect cause of death. It has been proven that zolpidem users have a higher risk of committing suicide [3, 4]. In addition, cases of suicidal thoughts after using small (20 mg) doses of zolpidem have been reported, even in people without known mental illnesses [22].

A similar case of a suicide attempt with zolpidem was reported in a 64-year-old patient who took about 200 mg of the drug. On admission, he had a GCS 6, with no abnormalities in laboratory tests, and a gastric lavage showed no residual drug. Similarly, as in the present study, the patient showed brief improvements in consciousness after flumazenil. Urinalysis revealed no substances, including benzodiazepines. Approximately 20 hours after admission, the patient regained consciousness and admitted to consuming large doses of zolpidem [23].

Drug interactions between zolpidem and paracetamol have not yet been described. The literature only presents the case of a woman who experienced a 30-minute visual disturbance in the form of curved vision after consuming 500 mg of paracetamol and 10 mg of zolpidem. Since such side effects involve zolpidem per se, it has not been proven that concomitant consumption of paracetamol contributes to them [24]. This interaction requires further study, especially given the widespread use of both drugs.

Flumazenil used as an antidote has positive effects both in isolated zolpidem poisoning and in multidrug poisoning [2].

**4. Conclusion**

The present patient's case is an example of zolpidem (about 200 mg) intoxication in combination with paracetamol. A disturbed state of consciousness in a person who has ever been prescribed zolpidem should raise suspicion of its overdose. A good, but short-term response to flumazenil is a particular clue. Multidrug overdose of zolpidem, even in combination with drugs that would not cause coma alone, often leads to it. The occurrence of coma with a history of zolpidem poisoning alone (finding empty packages) should raise suspicion of

the use of other drugs. On the other hand, confirmed excessive ingestion of zolpidem together with other preparations should be monitored for at least 24 hours to exclude the possibility of coma. Isolated ingestion of even large doses of zolpidem (up to 600 mg) should not result in a life-threatening condition. Gastric lavage and administration of flumazenil have good clinical effects.

The present study confirms previous reports showing that multi-drug poisoning with zolpidem is particularly dangerous and life-threatening.

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