CASE REPORT

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Fatal Overdose of Zopiclone in an Elderly Woman with Bronchogenic Carcinoma

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ABSTRACT: The death of a 72-year-old woman with respiratory debilitation due to bronchogenic carcinoma is described. She overdosed herself with probably 200 to 350 mg of zopiclone. Zopiclone, quantitated by HPLC in femoral postmortem blood, was found to be 1.9 mg/L (4.8 μmol/L). This level is higher than many other zopiclone fatalities reported. We report a case where only zopiclone was detected.

KEYWORDS: forensic science, forensic toxicology, zopiclone, high performance liquid chromatography, overdose, fatality

Zopiclone is a short acting, nonbenzodiazepine hypnotic used for treating insomnia (1). This cyclopyrrolone is chemically different from benzodiazepine hypnotics, but its mode of action is similar, as an agonist to benzodiazepine receptors on CNS GABA-ergic chloride channels. In recent years there has been a sharp increase in the prescription of this drug in Norway, now holding a market share close to 50% for hypnotic drugs (2). We have earlier reported the similarities of zopiclone compared with benzodiazepine hypnotics with respect to tolerance, psychomotor impairment, subjective hangover (3), and possible abuse (4). Here, we report a case of fatal zopiclone intoxication in a patient with bronchogenic carcinoma.

Case History

A 72-year-old single woman had over the last six years, and especially during the last year, experienced increasing difficulties in breathing. She had smoked all her adult life and had worked as a waitress in a smoking environment. Over the years she had regularly been using nitrazepam 5 mg at bedtime for sleep until four years prior to her death when a switch to zopiclone 7.5 mg was made. Over the years the patient did not increase her dose of hypnotics. At one point she was prescribed aspirin 160 mg tablets after a possible transient ischemic attack, but she refused to take the tablets. A year before her death she was referred to the local outpatient clinic specializing in pulmonary disorders due to increasing breathing difficulties. Chest X-rays were negative and she was treated with corticosteroids and β_2-agonists for inhalation with moderate success. During a second visit six months later no X-ray was taken, but due to poor response the treatment with inhalations was intensified. Just before she died, due to increasing breathing difficulties, she was again referred to the outpatient clinic, but did not attend. Her physician was under the impression that the patient was suffering from an anxiety disorder with panic attacks partially due to cancrophobia. She was given prescriptions for chlorprothixene 25 mg tablets and oxazepam 15 mg tablets, using these infrequently. No signs of major depression were noted by her physician. The last prescription for 100 tablets of zopiclone 7.5 mg was given 14 days prior to death. She was found dead in her bed with the box of zopiclone tablets by her side containing the remainder of 55 tablets. All her other present medication, including chlorprothixene, aspirin, and inhalation corticosteroids (budesonide) were found in her refrigerator. A farewell note was also found.

At autopsy the woman was found to have small cell carcinoma 7.5 cm in diameter originating from the main bronchus of the right lung, with local metastases to mediastinal lymph nodes. The pleura of the right lung showed some adherences and the right lung cavity contained 2300 mL of flaxen liquid. The right lung weighed 470 g and the left 465 g. Her body weight was 61 kg, which gives a lung-body weight ratio of 0.015. For forensic toxicological analyses, blood was collected from the right femoral vein. Urine was also collected.

Zopiclone Analytical Method

The method used was modified from the method described by Le Liboux and co-workers (5).

Zopiclone was determined in the postmortem blood with liquid chromatography (HPLC) using an integrated system from Shimadzu Corp., Japan consisting of a fluorescence detector (RF-10AXL), a pump (LC-10AT), an autosampler (SIL-10AXL), and SCL-10A system controller. Peak-height ratios were measured with Multichrom Chromatography software (version 2.2-1, Lab Systems, England).

Chromatographic separation was performed at ambient temperature by a Symmetry C8 column (Waters, USA: 3.9 mm ID × 15

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cm, 5 μm particles). The mobile phase consisted of 0.05 M ammonium acetate-acetonitrile (70/30, v/v). The flow rate was 1.7 mL/min and the injection volume 20 μL. The fluorescence detector was operated at excitation 300 nm and emission 470 nm.

Rhône-Poulenc Rorer, France supplied zopiclone chloride and the internal standard (RP 29481). The acetonitrile was of HPLC grade, and all the other chemicals were of analytical grade. Borate buffer was made of saturated sodium tetraborate in water adjusted to pH 11.1 with 6 M sodium hydroxide.

Blood zopiclone standards 0.02 to 0.78 mg/L (0.05 to 2.0 μmol/L) were prepared in human blood. Borate buffer 0.5 mL, 50 μL of the internal standard (0.01 mg/mL (0.02 μmol/mL)) in acetonitrile) and 1.5 mL hexane–dichloromethane mixture (3/4, v/v) was added to 1.0 mL blood in a silanized tube. The tube was stoppered and mechanically shaken for 10 min, then centrifuged for 10 min at 740 X g. The organic phase was transferred to 1.1 mL autosampler vials, evaporated at 40°C under vacuum, and the residue was reconstituted with 100 μL of acetonitrile.

The calibration curve for zopiclone was linear in the concentration range from 0.02 to 0.78 mg/L (0.05 to 2.0 μmol/L). The minimum detectable concentration was 0.004 mg/L (0.01 μmol/L). The between run precision ($n = 10$) was found to be 14.5% (conc. 0.02 mg/L (0.05 μmol/L)), 4.0% (conc. 0.08 mg/L (0.2 μmol/L)), and 6.5% (conc. 0.39 mg/L (1.0 μmol/L)). Extraction recovery was more than 80%.

Results

On screening for drugs of abuse (amphetamine, opiates, diazepam, cannabis, and cocaine) using immunological methods (6), no drugs were found neither in urine nor blood specimens. The further screening analysis for benzodiazepines and acid and alkaline drugs (GC-HPLC) revealed presence of zopiclone, but no other drugs. The quantification of zopiclone was performed by HPLC and found to be 1.9 mg/L (4.8 μmol/L).

Discussion

It is reasonable to assume that our case represents a suicide. There had been an increased anxiety, increasing insomnia, and the patient was cancrophobic. She wrote a suicide note and the half-empty container for zopiclone was found by her bed, while the other medication was stored in her refrigerator. Suicide is often attempted with the drugs at hand, and hypnotics are often used. The knowledge that benzodiazepines or newer hypnotics taken alone by otherwise physically well individuals seldom lead to lethal intoxication is knowledge with limited distribution.

After ingestion of a therapeutic dose of 7.5 mg of zopiclone, a maximum serum concentration (C_{max}) of 0.07 mg/L (0.18 μmol/L), range (0.06 to 0.09 mg/L (0.15 to 0.22 μmol/L), will be reached after about 1.5 h (1). The blood/plasma ratio for zopiclone is 1. The elimination half-life of the drug is 4 to 6 h and after a night's sleep, the concentration will be less than 0.04 mg/L (0.1 μmol/L). Zopiclone is not subject to the phenomenon of postmortem redistribution (7). The postmortem concentration of zopiclone will hence roughly match the antemortem concentration. In our case the half-empty glass of originally 100 tablets of 7.5 mg zopiclone contained a remainder of 55 tablets. This could indicate an intake of up to 45 tablets or 335 mg of zopiclone. Death due to respiratory depression does not necessarily occur immediately and the patient could have ingested these tablets some time before circulatory arrest. An intake in the area of 200–250 mg or 25–35 (7.5) mg tablets could give rise to the present blood level of zopiclone. The patient was prescribed the drug 14 days prior to her death and the postmortem concentration could imply an intake of this order of magnitude and death occurring around C_{max}.

A total of 85 autopsy cases with detection of zopiclone have been identified at the National Institute of Forensic Toxicology in Norway. Seventeen of these cases showed a concentration above 0.4 mg/L (1.0 μmol/L) of zopiclone. In six of these cases, zopiclone represented the most significant postmortem toxicological finding. In four of these cases there were other causes of death (drowning, hanging, etc.). The remaining two cases represented a case with considerable postmortem decomposition and this case.

Druid and Holmgren (8) reported four cases where zopiclone seemed to be the main cause of death. In these cases the median postmortem femoral blood zopiclone concentration was 0.7 mg/L (1.8 μmol/L) with a lower quartile of 0.6 mg/L (1.5 μmol/L) and an upper quartile of 1.8 mg/L (4.6 μmol/L). However, in their article, case histories and other significant findings were not presented. It is therefore difficult to test their conclusion that these cases represent true zopiclone fatalities.

Meatherall (9) reviewed eight case reports of possible zopiclone poisoning and added a case report. In all nine cases other drugs were also detected. Reviewing these nine cases zopiclone was thought to be a major finding in four of them (Table 1). Patient 1 (Table 1) had lung cancer, and accordingly, it is probable that a morphine concentration of 0.052 mg/L (0.17 μmol/L), although therapeutic in some cases, also could contribute to the respiratory depression of zopiclone. This could account for the low level of zopiclone detected. Patient 2 had an ethanol concentration of 1.5 g/L, which could contribute to respiratory depression. Patient 3 is poorly described, but had a therapeutic level of temazepam. Patient 4 had a therapeutic level of quinine in addition to a very high zopiclone concentration.

Other cases have been reported. A 26-year-old female was found to have a high blood concentration of zopiclone, but also a high and probably fatal concentration of pentazocine (10). Mannaert and coworkers describe a case of drowning where zopiclone together with diazepam (11) were detected.

In conclusion, no pure lethal zopiclone intoxications have earlier been decisively reported. In this study, the level of zopiclone in blood was relatively high (1.9 mg/L or 4.8 μmol/L), probably only surpassed by three cases described above (8,9,11). No other drugs were found despite thorough investigations by broad screening.

TABLE 1—*Major findings in four reported cases of zopiclone poisoning.*

Ref	Patient	Blood	[Zopiclone] mg/L (μmol/L)	Other Significant Findings
(9)	A 72-year-old man with lung cancer	femoral	0.25 (0.65)	Metoclopramide = 0.06 mg/L (0.2 μmol/L), Morfin = 0.052 mg/L (0.17 μmol/L)
(7)	A 29-year-old women with depression	femoral	1.3 (3.5)	Ethanol = 1.5 g/L
(13)	Unknown	unspecified	0.40 (1.1)	Temazepam
(14)	An 81-year old suicidal man	femoral	3.9 (10.1)	Quinine = 3.2 mg/L (8.9 μmol/L)

Benzodiazepines and other central benzodiazepine receptor agonists have a broad therapeutic window and taken as monotherapy will seldom induce potentially lethal respiratory depression in otherwise healthy individuals. Taken together with other respiratory depressants, it can cause serious central respiratory depression. Depending on the degree of debilitation, respiratory failure can be induced by smaller or larger doses of benzodiazepines in already respiratory incapacitated patients causing an acute-on-chronic respiratory failure. Elderly or seriously ill patients may have a lower general drug tolerance and thus require reduced dosage of any drug.

Patients with chronic respiratory failure can develop insensitivity towards a high carbondioxide tension. They will depend on the much coarser respiratory regulation provided by oxygen tension and may be on the verge of CO_2-narcosis. Several elements combined may create a vicious circle. Benzodiazepine receptor agonists can further reduce the response towards CO_2. The muscle relaxant effect of GABA-ergic drugs may induce hypoventilation. GABA-ergic agents can also produce a lowering of the blood pressure due to a depression of the central sympathetic regulatory mechanisms, thus lowering cerebral perfusion and worsening of the respiratory failure. Deep sedation and muscle relaxation brought on by GABA-ergic drugs can cause occlusion of the airways when in supine position.

Patients who die of respiratory failure due to drug overdose will generally have a higher lung-body weight ratio than controls (12), so is the case here. This is due to a noncardiogenic pulmonary edema, probably secondary to hypoxia.

This case report describes a case of lethal intoxication due to intake of only zopiclone. A 72-years-old respiratory debilitated woman with bronchogenic carcinoma died after intake of about 200 to 350 mg of zopiclone. Based on the review of the literature this may be the first zopiclone poisoning where no other drugs are found.

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