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CASE REPORT

Sleep self-intoxication and sleep driving as rare zolpidem-induced complex behaviour

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Abstract
Introduction The $GABA_A$ receptor agonist zolpidem has been used for treatment of insomnia since years, but special side effects have been reported. These side effects were called zolpidem-induced sleep-related complex behaviour. Such complex behaviour is associated with somnambulism and includes sleepwalking, sleep eating, sleep conversation and sleep driving.
Case presentation Two cases of zolpidem-induced sleep-related complex behaviour following self-intoxication, sleep driving and amnesia are presented. In both cases, the subjects reported the voluntary intake of only one zolpidem tablet of 10 mg and amnesia for the time afterwards. Shortly after the onset of the drug's action, both individuals drifted into a somnambulism-like state and toxicological blood analysis suggested the intake of the remaining zolpidem tablets which might be called "sleep intoxication". Later, the subjects were arrested by police after driving under drug influence and not realizing the situation. Retrospectively, both subjects suffered from psychiatric disorders and in case 2, the subject was treated for depression with doxepin. Consequently, these co-factors may have increased the risk for the occurrence of the sleep-related complex behaviour.
Discussion Involuntary self-intoxication should be taken into account in addition to the known pattern of zolpidem-induced complex behaviour. In legal cases, the forensic expert has to assess the blood concentration of zolpidem in evaluating this strange behaviour.
Conclusion Amnesia and incoherence of speech, disorganization of behaviour, inability to realize the situation and mood changes may indicate a zolpidem-induced somnambulism-like state with sleep-related complex behaviour.

Keywords Zolpidem · Somnambulism · Self-intoxication · Complex behaviour

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Introduction

Since more than two decades, the $GABA_A$ receptor agonist zolpidem has been used for the treatment of insomnia. Epidemiological data indicate a lower incidence of abuse and an improved side-effect profile (e.g. daytime sedation) when compared to classic benzodiazepines. Nevertheless, attention has been drawn recently to its potential to cause sleep-related complex behaviour like sleepwalking, sleep eating, sleep conversation and sleep driving [1–6]. In two studies, these side effects have been reported with incidences between 0.3 % [7] and 1 % [8] and may be considered as rare, but regulatory agencies issued warnings regarding the potential of zolpidem to produce complex behaviour [2, 9]. Although this curious side effect is written in the patient's information and the package leaflet, only few studies focused on the biological mechanism [2, 4]; however, the cause of the sleep-related complex behaviour remains unknown.

We present two cases with zolpidem-induced self-intoxication, sleep driving and amnesia, which were brought to court. Although case reports exist dealing with zolpidem-induced complex behaviour, to our knowledge, the present cases are the first with zolpidem-induced self-intoxication.

Case presentation

Case 1

A 31-year-old zolpidem-naïve man, who suffered from adult attention deficit/hyperactivity syndrome with non-treated anxiety and depressive episodes, complained about occupational stress and sleeping disorders since 2–3 days. Suicidal attempts had never occurred. In the early evening, he took 10 mg of zolpidem and went to bed. He could not remember the events before, when he woke up on the floor in the morning 1.5 days later. He felt thirsty and sick and vomited. After staggering to the bathroom, he went to bed again and fell asleep for another day. The next day, he was slowly able to realize the situation and found his flat in a total mess. During the cleanup, he found the zolpidem package and noted the lack of several zolpidem tablets, but could not remember to take more than a single 10-mg dose of zolpidem. Moreover, he found his car keys with a notice of the police. One to 2 weeks later, some memory on blood sampling by the police returned, but he was not able to remember the whole situation.

According to the toxicological analysis (c.f. "Analytical details") of the blood sample, he must have taken definitely more than 10 mg of zolpidem as the serum concentration was 1.6 mg/l. However, with the exception of zolpidem, the screening analyses did not reveal any other drugs or alcohol. After the zolpidem intake, he obviously started driving with his car. One witness reported that he seemed driving under the influence of alcohol such as leaving the lane, touching a parked car and after 20 m hitting a traffic sign. After the accident, the witness found the driver asleep at the wheel. Shortly afterwards, the driver left the car staggering and seemed to be half-asleep. The police had problems to interact with him. He was not responsive, declined any cooperation and fell asleep again and again. Two hours later, blood was taken and during the blood sampling procedure, the man seemed not to be impaired, he was able to move normally and gave appropriate answers, but it was not clear whether he was realizing the situation.

In the court hearing, the man claimed that he neither took zolpidem for abuse nor for suicide. He said that he cannot remember driving a car and having an accident; he did not provide a reason why he started driving. The court believed his testimonies and ruled that he was held not accountable for his actions because of drug intoxication.

Case 2

A 43-year-old zolpidem-naïve woman, who suffered from depressive episodes and was treated with doxepin, complained about sleeping disorders. She took 10 mg of zolpidem at 21:00 and went to bed. She could not remember the following events, and her memory returned only in the morning, when she awoke and her daughter told her what happened during the night.

According to the toxicological analysis (c.f. "Analytical details"), she must have taken more than 10 mg of zolpidem as the serum concentration was 1.4 mg/l together with 0.045 mg/l doxepin (therapeutic level) and 0.083 mg/l nordoxepin. Other drugs or alcohol could not be detected. According to the police report, she was observed at about 21:30 by other road users driving her car without lights. The police was called and found her sitting in the car, stopped in a roundabout with one wheel in a flowerbed. She wore only a bathrobe, slippers and pyjama bottoms, which were turned inside out. She told the police officers that she was on the way to her work, but this seemed to be implausible because of her dress and because she negated to be a night worker. Despite several attempts, she was not able to complete an alcohol breath test and seemed to be confused as she could not explain how she drove in the roundabout and why her car stood transversely to the travel direction. Moreover, she could have experienced a minor car accident as the right mudguard and the exterior mirrors were slightly damaged. She moved slowly out of the car and exhibited gait disturbances, a slurred speech and limited power of comprehension. During the police measures, she asserted that the police officers took her mobile phone, but neither in the car nor in her clothes a mobile phone was found. After she was brought to the police station, a urine sample was taken, but she was not able to flush the lavatory and was throwing all toilette tissues aside the toilet bowl. Moreover, she thought to be in a hospital and believed the urine drug test would be done for a pregnancy test. During blood sampling, she still was confused, her answers to questions were senseless and she was not able to realize the situation. In the court hearing, the police officers stated that she acted like in a dream with several consecutive sequences of changing mood. When her daughter came to pick her up, she told her that she actually had been in a quiz show and won a Ferrari.

In the court trial, the woman denied any abuse of zolpidem or suicidal attempt. The court believed her testimonies and she was held not accountable for her actions because of drug intoxication.

Analytical details

The blood samples were analysed for alcohol using headspace-gas chromatography coupled with flame ionization detection. Before toxicological analysis, the blood samples were centrifuged and the serum was taken. The blood samples were screened for medical drugs and drugs of abuse. For drug screening, immunochemical assays for cannabinoids, amphetamines, opiates, methadone, benzodiazepines and cocaine were performed. In addition for screening and quantification,

high-performance-liquid chromatography (Agilent 1200 HPLC) coupled with electrospray-ionization time-of-flight mass spectrometry (ESI-TOF-MS from Agilent, Waldbronn, Germany) was employed as described previously [10]. The separation was achieved on a Polaris C18-Ether 3-μm, 125× 2 mm column (Agilent, Waldbronn, Germany) protected by a Polaris C18-Ether guard column at 40 °C. The mobile phase consisted of acetonitrile (A) and formic acid 0.1 % (B) at a flow rate of 0.4 ml/min. After a 0.5-min isocratic period with 5 % A, a linear gradient to 75 % A was applied up to 6 min. After a 2.3-min period of 100 % A, the column was re-equilibrated with 5 % A for 3.7 min. The total run time was 12.5 min including re-equilibration. For quantification, 1 ml serum was diluted with 1 ml di-ammonium hydrogenphosphate buffer (1 M, pH 9.5) and 5 ml of a chlorbuthane/diethylether (50:50, *v*/*v*) mixture was added together with 50 μl of a mixture of deuterated substances as internal standards. Doxepin-d_3 served as internal standard for doxepin and nordoxepin and methadone-d_9 served as internal standard for zolpidem. After extraction for 1 min and subsequent centrifugation, the organic phase was evaporated at 24 °C and the residue was redissolved in formic acid/acetonitrile 80:20 (*v*/*v*) of which 3 μL were analysed. Calibrators and quality controls were prepared in blank serum and were analysed as described. The method has proved itself in praxis and in various proficiency tests.

Discussion

The question whether a reduced or negated criminal liability has to be assumed is often discussed in legal cases especially when the crime was committed under the influence of drugs like zolpidem. For a reduced or negated criminal liability, it has to be shown that the accused person was in an altered state of mind, such that he was unaware of his actions. For this purpose, the forensic expert has to assess the nature and quantity of the ingested drugs together with the conduct of the defendant during the events. A serum concentration in a toxic range together with an inappropriate, unreasonable behaviour and amnesia can be a very clear indication for an altered state of mind. To demonstrate his innocence, the defendant must additionally show that he did not willingly overdose the drug and that he was not aware of the risks of an unwilling intoxication. More detailed information of zolpidem in legal cases is given by the review of Daley et al. [1]. It should be noted at this point that the possibility of a drug ingestion in the period of amnesia does not necessarily mean that the ingestion was unintentional or out of the responsibility of the subject. However, it is up to the court to finally decide whether the conditions of a reduced or negated criminal liability are fulfilled. An overview over similar cases is given by Poceta (zolpidem blood concentration reported 0.025–0.428 mg/l) [11] and Pressman (no blood concentrations but information on the dosages) [12].

We reported two cases of zolpidem-induced involuntary self-intoxication resulting in similar high serum concentrations of zolpidem, which are considered toxic (>0.5 mg/l [13]) and could be explained with the intake of at least 8–10 zolpidem tablets of 10 mg each. For example, a single oral dose of 10 mg zolpidem leads to a serum concentration of approximately 0.121 mg/l after 1.6 h [14]. In both cases, the individuals reported the voluntary intake of only one zolpidem tablet and an anterograde amnesia shortly after they went to bed. During their amnesia, both subjects exhibited a behaviour pattern, which reminds of automatic or compulsory behaviour accompanied with somnambulism. It is likely that shortly after the first 10 mg dose, the subjects drifted in a somnambular state and were not aware of the further drug intake. As their original intention was to take only 10 mg of zolpidem, they took compulsory more tablets which might add *sleep intoxication* to the list of reported zolpidem-related complex behaviour. Subsequently, the woman in case 2 began to perform habitual actions like leaving the bed, getting dressed and driving to work, which, however, was irrational and due to her disturbed spatial and temporal orientation. Consequently, confused behaviour continued till both subjects awoke. Taking into account other case reports [3–5, 15–17, 11], the behaviour in the present cases can be explained as a complex form of somnambulism. The subjects became amnestic shortly after the intake of a regular dose of zolpidem and exhibited automatic and compulsory behaviour (e.g. sleepwalking [3, 4], sleep cleaning [15], sleep eating [4, 5, 16], sleep conversation [15, 17] and sleep driving [4, 11]). Moreover, in case 2, the subject went through different dream sequences, at last when she thought to be in a quiz show and winning a Ferrari. An examination of already published case reports/studies provides no explanation for the emergence of medication-induced sleepwalking or for the emergence of the zolpidem-induced complex behaviour [12]. Moreover, a profound assessment seems difficult as there are no controlled studies with known sleepwalkers to examine the effects of zolpidem or other drugs under controlled conditions [12]. A detailed review about factors that predispose sleepwalking and non-rapid-eye-movement (NREM) parasomnias is given by Pressman [12]. However, we agree with Daley et al. [1], who considered a personal or family history of parasomnia, the use of alcohol or drugs, sleep deprivation, fever or personal stress as special risk factors. Moreover, the risk for zolpidem-induced complex behaviour seems to increase in a dose-dependent manner; co-medication with other psychotropic drugs may produce additional risks [1]. It should also be considered that the individuals suffered from insomnia and psychiatric disorders (case 1) or were treated for depression with doxepin (case 2), which may have increased the risk for occurrence of this complex behaviour.

Conclusion

Zolpidem is a well-known sleep-inducing drug, but the incidence of sleep-related complex behaviour is relatively rare. The occurrence of such side effects should be taken into account especially in patients with a personal or family history of somnambulism, the presence of psychiatric diseases or when psychotropic drugs are involved and the possibility of involuntary self-intoxication should be added to the patient's information and the package leaflet. Moreover, for the first treatments, the patient should be advised to take zolpidem under the supervision of a confidant (e.g. friend, partner etc.) if possible and the prescribing physician should document the medical advise in order to avoid liability claims. However, in order to determine whether sleep-related complex behaviour have occurred in legal cases, the forensic expert has to take into account the blood concentration of zolpidem in addition to symptoms of amnesia, a probable incoherence of speech, the disorganization of behaviour and the inability to realize the situation suggesting a somnambulism-like state.

Conflict of interest None of the contributing authors have any conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript.

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