CHAPTER 6

Pseudo-hallucinations after zolpidem intake: A case report


Sanne de Haas¹, Jasper Dingemanse², Petra Hoever², Adam Cohen¹, Joop van Gerven¹

¹ Centre for Human Drug Research, Leiden, The Netherlands
² Actelion Pharmaceuticals Ltd, Allschwil, Switzerland
TO THE EDITORS

Zolpidem is a widely used hypnotic [1] with a selective high affinity for the GABA_{\alpha1} subtype receptor, which is believed to mediate sedation. Previous case reports have shown that zolpidem use is sometimes associated with hypnagogic or visual hallucinations, both in patients [2-5] and during healthy volunteer studies. We describe a case of a healthy volunteer who experienced an episode of florid visual hallucinations after zolpidem intake during a clinical study, in which plasma concentrations of zolpidem and a range of central nervous system (CNS) effects were studied. This case provided an opportunity to study zolpidem-induced hallucinations, in relation to its plasma concentrations and other CNS-effects, and to get some more information about the reasons for this adverse event.

Case Report

In the context of a double blind parallel clinical trial with a new potential hypnotic (ACT-078573) in healthy volunteers, zolpidem 10 mg was given as a positive control drug [6]. Zolpidem was administered in the morning, in a fasted state with 150 mL of water. A 32-year-old male subject (BMI 18.5) with a mixed race had been medically screened one week before study participation after signing informed consent. He had a negative psychiatric personal or family history, did not use any concomitant medication or illicit drugs and showed negative results in a drug screen for different centrally active compounds. After receiving blinded zolpidem on the study day, the subject reported visual hallucinations that started 20 minutes after drug intake. He experienced these hallucinations when closing his eyes. He saw persons, e.g. his neighbour who talked to him, and he wanted to reply. He also saw dark figures with no precise form or at no precise location. On the computer screen that was used to perform some of the pharmacodynamic (PD) assessments, he noticed different colours and figures. He was aware of the fact that the things he saw were unreal, which signifies these as pseudo-hallucinations. He did not feel anxious, but did not like the experience. The hallucinations lasted two hours and subsided gradually. Other reported adverse events were sleepiness, nausea, dizziness, diplopia and dysphasia that all started at the same time as the hallucinations and were present for 3.5 hours. During this period, the subject was able to perform all scheduled study measurements.

Pharmacokinetic (PK) analysis for this subject showed that the maximum zolpidem concentration was 164 ng/mL, which was in the range of the values for the other subjects (mean: 137.9, range 59.2 to 227 ng/mL). PK-profiles and most PD-effects are presented in figure 1.
The effects on body sway (postural instability) and the Bond & Lader Visual Analogue Subscale (VAS) for alertness were more pronounced for this subject, compared to the mean responses of the other subjects after zolpidem intake. The Bowdle VAS evaluates psychedelic effects that cluster into two distinct total sum-scores: internal perception (inner feelings that do not correspond with reality, including mistrustful feelings) and external perception (misperception of an external stimulus or a change in the awareness of the subject’s surroundings, including hallucinations) [7]. For both components, much higher scores were achieved compared to the others. Similar results were obtained for the ‘feeling high’ Bowdle subscore. To compare the PD effects relative to each other and to the other subjects, Z-scores were calculated, representing the distance between the individual PD values and the mean of the others in units of standard deviation. All PD effects of this subject were considerably beyond the mean of the other subjects (Z-scores 2.1-6.2; see figure 1). For adaptive tracking and saccadic eye movements (graphs not shown) reverse Z-scores were 3.7 and 6.2 respectively. In contrast, the Z-score for the maximum plasma concentration \( C_{\text{MAX}} \) was 0.5.

DISCUSSION

The current subject developed (pseudo)hallucinations after a single zolpidem dose of 10 mg during a study with intensive PK and PD assessments, including psychomimetic visual analogue scales. This allowed a quantitative assessment of the relationships between the hallucinations, other CNS PD-effects and the PK-profile. The various publications describing visual hallucinations showed that these occurred in subjects who differed with regard to concomitant medication, age and gender [5]. However, our case report does not support the suggestion of a psychiatric disposition, an interaction with another (therapeutic or illicit) agent, or the need for abnormally high plasma levels, although these options may still explain other cases. In our case, plasma levels were in the mid-range of those in subjects without hallucinations, and comparable to levels measured in other clinical studies [8]. In contrast, all CNS-effects were more pronounced than the average responses of the other subjects, including psychomimetic VAS. These observations allow for some speculations on the cause of zolpidem-induced hallucinations.

Hallucinations with zolpidem could be related to individual variations in PD sensitivity. In our subject, this would imply a general increase in the sensitivity of GABA receptors, since his CNS-responses were all in the upper range of the distribution for the study group (Z-scores 2.1-6.2) despite average plasma levels (Z-score 0.5).
However, if hallucinations in our subject would just be a manifestation of a general increase in zolpidem sensitivity, psychomimetic effects could also be expected at high plasma levels in less sensitive subjects. Since hallucinations are rare and most subjects fall asleep at high zolpidem-levels without reporting psychomimetic effects, other explanations should be considered.

Hallucinations have not only been reported for selective GABA<sub>A</sub> ligands such as zolpidem or zaleplon, but also for the non-selective benzodiazepines midazolam, diazepam and triazolam [9,10] and in about 1.3% of patients receiving intravenous diazepam [10]. All these drugs have a rapid absorption, which is in line with the suggestion by Ansseau et al. that psychotomimetic reactions with hypnotics depend more on the PK-profile of the drug than on its specific receptor selectivity [4]. Our subject showed average plasma concentrations, but he had by far the fastest rise in plasma concentrations in this study (14.8 ng·ml<sup>-1</sup>·min<sup>-1</sup> cf a group mean of 4.8). It could be hypothesized that rapid GABAergic activation leads to an inhomogeneity of different aspects of sleep onset, in which dream-like states occur before sleep has actually ensued. The reverse may be true following abrupt zolpidem withdrawal, which may also lead to visual hallucinations [11]. Drugs with a slower absorption or onset of action would cause a more gradual and more balanced development of different GABAergic effects, including the ones that cause sleep and hence obscure other (psychomimetic) effects. Although compatible with our observations, this remains speculative, since the different components of sleep induction and their concentration- or rate-dependence have not been studied systematically for α<sub>1</sub>-specific GABA<sub>A</sub> agonists. Carefully designed studies with the benzodiazepine temazepam showed that other so-called rate-dependent effects did actually not depend on the rate of infusion [12]. This suggests that other factors beside rate of onset could also be involved in the occurrence of GABAergic hallucinations.

It could be speculated that this is due to individual neuro-anatomical differences. The current subject might have a higher density of the α<sub>1</sub> receptor subtype in areas that are associated with psychomimetic effects. If so, specific stimulation of α<sub>1</sub> receptor subtypes would evoke hallucinations, although these would also be expected with non-specific GABA<sub>A</sub> agonists in sensitive individuals. It would therefore be interesting to examine which kind of effects (and to which extent) would occur in this subject after intake of a non-selective benzodiazepine, or after manipulation of the infusion rate. In our case, this has for ethical and practical reasons not been proposed, as this would entail re-exposure of the subject to potentially unpleasant events.
It was clear that all PD effects were more expressed in the current subject, compared to those of other subjects. Hallucinations could therefore be an effect of zolpidem that can also occur at supratherapeutic concentrations in other individuals. Highly sensitive subjects may possess an over-expression of GABA receptor α1-subtypes or show a more rapid activation of GABA_A receptors after intake of a compound with a quick absorption.
Figure 1  Graphs show average time profile of average zolpidem plasma concentrations (A) and pharmacodynamic measurements: body sway (B), VAS alertness (C) >

Zolpidem group (continuous line n=13), placebo (dotted line n=14) and hallucinating subject (broken line n=1). Shaded area shows range between minimal and maximal concentration-time profile for graph A and reflects 95% CI of zolpidem group for other graphs.
> VAS Bowdle internal perception (D), external perception (E) and VAS feeling high (F), with SD as error bars of zolpidem group.

Zolpidem group (continuous line \( n=13 \)), placebo (dotted line \( n=14 \)) and hallucinating subject (broken line \( n=1 \)).

Shaded area shows range between minimal and maximal concentration-time profile for graph A and reflects 95% CI of zolpidem group for other graphs. Placebo graphs are not presented for graph D, E and F as no effects were seen for this group.
9 Dundee JW. Fantasies during sedation with intravenous midazolam or diazepam. Med Leg J 1990; 58 (Pt 1): 29-34.