Residual Effects of Short Half-life Non-benzodiazepine Hypnotics

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Background
Since their introduction at the beginning of the 1990s the short half-life non-benzodiazepine hypnotics, zolpidem and zopiclone, rapidly were among the most frequently prescribed hypnotics. Surveys showed that around 1996 the most frequently prescribed hypnotic in the US was zolpidem, while zolpidem and zopiclone were among the five most frequently used hypnotics in Europe [1, 2]. Their popularity is probably due to a growing awareness among patients and prescribing physicians of the disadvantages of benzodiazepine hypnotics, in particular the development of tolerance and the potential for addiction. In addition, benzodiazepines changed normal sleep architecture by reducing the relative amounts of REM sleep and slow wave sleep (deep sleep), both considered essential sleep stages for mental and physical well being. Another disadvantage, in particular of the older benzodiazepine hypnotics, was their generally long half-life which resulted in significant residual effects. Although there were a number of short acting benzodiazepines, such as triazolam and midazolam, these drugs also had drawbacks such as rebound insomnia and problems with abrupt withdrawal. However, all these problems seemed to be less for short half-life hypnotics from other chemical classes, i.e., zolpidem and zopiclone. This probably explains their popularity.

At the end of the 1990s a third non-benzodiazepine hypnotic, zaleplon, entered the market. Zaleplon is a pyrazolopyrimidine, which, like zolpidem, selectively binds as an agonist to a subset of benzodiazepine receptors containing an alpha-1 subunit. Furthermore, it has an unusually short elimination half-life of only 1 hour.

With respect to traffic safety, the short half-lives of these non-benzodiazepine hypnotics (table 1) are their most important advantage. After all, epidemiological studies have shown that risks for injurious accidents, such as hip fractures and car crashes, generally increase with increasing half-life of benzodiazepines. For example, Neutel [3] found that risks for injurious traffic accidents associated with the use of the long half-life hypnotic flurazepam (t1/2= 74 hrs) were higher than those associated with the use of the short half-life hypnotic triazolam (t1/2= 3 hrs).

Nevertheless, half-life is not the only determinant of a drug’s duration of action and residual effects. Dose, tolerance and the use of other drugs are important factors as well (for a review see [4]). Experimental studies clearly show that short half-life hypnotics, such as triazolam, can produce residual effects depending on the dose. In addition, epidemiological studies found that triazolam was associated with significantly increased risks of traffic accidents (OR 3.2), despite its short half-life [3]. Thus, a short half-life does not imply that a hypnotic is free of residual effects and safe for driving.

So, when the manufacturer of zaleplon applied for registration of this new hypnotic, the residual effects of zaleplon had to be evaluated in empirical studies, even though it might be expected that this drug in its recommend dose would have minimal or no residual effects, based on its extremely short half-life. For this purpose we carried out two experimental studies assessing the residual effects of two doses of zaleplon on actual
driving performance and cognitive functions in healthy volunteers [5, 6]. The residual effects of zaleplon were compared to those of zopiclone 7.5 mg and to the acute effects of a low dose of alcohol in the same volunteers. To assess driving performance we used a standardized highway driving test and a battery of laboratory tests measuring attention and psychomotor performance.

Zopiclone 7.5mg was chosen as an active control in these studies, because this drug and dose were previously found to have residual effects on driving performance in a study using the same standardized driving test [7]. The purpose was to replicate these findings, because several studies using laboratory tests failed to find significant residual effects of zopiclone 7.5 mg. As a consequence of these inconsistent results the two most recent reviews of zopiclone’s residual effects came to very different conclusions. Noble et al. [8] conclude that zopiclone has a relatively low propensity to cause residual clinical effects (such as difficulty in waking or reduced morning concentration). In contrast, Nicholson [9] concludes that ‘the 7.5mg dose should be avoided by those whose activity the next day involves skilled work and where impairment of performance could be a danger to others. The inconsistencies between results of different studies are most likely due to differences in study designs and sensitivity of test and procedures used [9, 10].

Objectives

1. to assess the residual effects of zaleplon 10 and 20 mg on actual driving and cognitive functions the between 10 and 11 hours after bedtime administration and 5 to 6 hours after middle of the night administration 
2. to assess the residual effects of zopiclone 7.5 mg on actual driving and cognitive functions the between 10 and 11 hours after bedtime administration and 5 to 6 hours after middle of the night administration 
3. to compare the residual effects of zaleplon 10 mg and zopiclone 7.5 mg with the acute effects of a low dose of alcohol in the same subjects

Methods

Study 1
This was a 7-period, double-blind, crossover study with 28 healthy volunteers (14 men, 14 women, mean age 31 ±6 years) [5]. Subjects ingested medication twice on each treatment night; once in the evening before initiating sleep, and again after being briefly awakened 5 hours later in the middle of the night. Treatments were: placebo at both times, zaleplon 10 or 20mg, or zopiclone 7.5mg followed by placebo, or the same in reverse order. Subjects arose 3 hours after the middle-of-the-night dose. A standardized highway driving test was undertaken in the morning 5-6 hours after the middle-of-the-night dose (i.e. 10-11 hours after the evening dose). A laboratory test battery including tests for word learning, semantic memory, spatial memory, reasoning and body sway, was conducted 3.75-4.5 hours after the middle-of-the-night drug dose (i.e. 8.75-9.5 hours after the evening dose).

Study 2
This was a two-part (5-period), crossover study with 30 healthy volunteers (15 men and 15 women, mean age 32 ±7 years) [6]. In part 1 the effects of alcohol and alcohol-placebo drinks on driving and cognitive functions were evaluated in a 2-period, single-blind crossover design. In Part 2 the residual effects of zaleplon 10mg, zopiclone 7.5mg and placebo were evaluated in the same subjects, using a 3-period double-blind crossover design. In part 1 a standardized highway driving test was undertaken in the afternoon (40-100 minutes after alcohol consumption), and in part 2 the driving test was undertaken in the morning (10-11 hours after drug intake). A laboratory test battery including tests for
word learning, critical tracking and divided attention, was conducted 8.75-9.5 hours after the bedtime drug dose.

**Driving Test**
Both studies used an over-the-road highway driving test. This test evolved from studies on driver fatigue conducted in the USA during the early 1970s and was standardized in 1984 for assessing drug effects on actual driving performance [11]. It involves subjects driving a specially instrumented car over a 100-km (61 mile) primary highway circuit while maintaining a constant speed of 95 km/h (58 miles per hour) and a steady lateral position between the delineated boundaries of the right (slower) traffic lane. Subjects are accompanied by a licensed driving instructor, having access to dual controls. During the test the vehicle's speed and lateral position relative to the left lane delineation are continuously recorded. The primary performance parameter, Standard Deviation of Lateral Position (SDLP, in cm) can be interpreted as an index of allowed weaving and swerving, i.e. course-keeping error. It is a reliable characteristic of individual driving performance that has proven sensitive to many sedating drugs [12-15]. The test was calibrated for the effects of alcohol so that mean changes in performance under the influence of medicinal drugs can be compared to those associated with BACs at various legal limits [16].

**Results**
Figure 1 shows the mean changes in driving performance as measured by Standard Deviation of Lateral Position the highway driving test (an index of road tracking error or ‘weaving’) the morning after use of zaleplon 10 and 20mg and zopiclone 7.5mg in both studies.

**Zaleplon**
Results of both studies showed that zaleplon had no significant residual effects on driving. The only significant effect of zaleplon found was slight memory impairment after the middle-of-the-night dose in study 1 [5]. Delayed recall of lists of words learned nearly 4 hours after middle-of-the-night administration of zaleplon 10 and 20mg was slightly but significantly decreased as compared to placebo (p<0.014 and p<0.007, respectively) [5].

**Zopiclone**
In contrast, bedtime and middle-of-the-night administration of zopiclone 7.5mg significantly impaired performance in the driving test the next morning (all p<0.001). In both studies [5,6] the residual effects of evening doses of zopiclone 7.5mg were more severe than those of alcohol while BAC is 0.5mg/ml as determined in an earlier study [16]. The effects of alcohol in the study 2 corresponded to that predicted from a dose-response curve established by Louwerens et al. [16], indicating that the group of subjects in study 2 demonstrated normal sensitivity to the effects of a low dose of alcohol on driving. The effects of the middle-of-the-night dose on driving in study 1 were far worse: they were far more severe than 1.0mg/ml alcohol. Eighteen percent of the subjects in this study had to stop the test, because the driving instructor or the subject considered the subjects too drowsy to continue safely. In addition, zopiclone had significant residual effects on divided attention and memory as indicated by impaired immediate and delayed recall and recognition of a list of words learned nearly 9 hours after administration. In study 1, the middle-of-the-night dose of zopiclone 7.5 mg had highly significant impairing effects on performance in all cognitive tests (verbal learning, spatial memory, reasoning and semantic verification). Moreover, it dramatically increased body sway. Except for the effects on verbal learning, these effects were not seen when the drug was taken at bedtime.
**Figure 1** Mean changes from placebo in driving performance as measured by Standard Deviation of Lateral Position (SDLP) in the highway driving test. Tests were performed 5-6 hours after middle-of-the-night doses, or 10-11 and 16-17 hours after a bedtime doses of zaleplon 10 and 20mg and zopiclone 7.5mg (zal 10, zal 20 and zop 7.5). Dotted lines indicate effects of alcohol on driving while blood alcohol concentrations were 0.5, 0.8 and 1.0 mg/ml on performance in the same test in a previous study [11]. Numbers between brackets indicate the original studies data are derived from [5, 6, 7].

**Discussion**

Zaleplon had no significant residual effects on psychomotor performance, attention, and actual driving regardless of its dose and time of administration in the driving studies. With respect to the drugs' safety, the results of the driving test after the late-night administration of 20 mg (i.e., twice the recommended dose) are the most relevant. Since even this dose did not affect performance, it is clear that zaleplon in its recommended therapeutic dose of 10mg is highly unlikely to produce residual effects on driving in patients even as short as 5 hours after intake.

Zopiclone 7.5mg clearly has residual effects on driving in the morning, between 10 and 11 hours after bedtime administration. The effects were not only highly significant, but also clinically relevant; the magnitude of the effects was equivalent to those of alcohol while BAC ranges between 0.5 and 1.0 mg/ml. The relevance of these effects is supported by findings from recent epidemiological study in the UK [17] in which use of zopiclone was found to be associated with a significantly increased risk for traffic accidents (OR 4.0).

The effect of bedtime doses of zopiclone 7.5mg on driving in the present studies was greater in magnitude than that produced by the same drug and dose in an earlier study employing the same standardized test [7]. However, subjects in that study were tested
after the second consecutive nightly dose and may have begun to develop tolerance for the drug’s residual sedating effects. The latter study [7] did show that the residual effects of zopiclone 7.5mg rapidly wear off during the day, so that this drug-dose is unlikely to affect driving performance in the afternoon, i.e. 16-17 hours after bedtime administration.

Performance in laboratory tests of memory and divided attention was also significantly impaired after bedtime dosing, but the effects were less pronounced. Since the present studies used relatively large sample sizes (n= 28 and 30) as compared to previous studies using laboratory tests to assess residual effects of zopiclone, the power of the present studies to detect small effects was increased. This supports the conclusion by Nicholson and O’Hanlon that the failure to find effects in previous studies was probably due to insensitive tests and a lack of power.

The residual effects of zopiclone 7.5mg emphasize that short half-life is no guarantee that a hypnotic will be free of residual effects. Residual effects also depend on the dose. Nicholson [7] already concluded in his review of experimental studies with zopiclone that a slightly lower dose of 5mg seems free of residual effects, whereas a higher dose (10mg) is associated with marked impairment. Lowering the recommended dose of zopiclone to 5mg might therefore be a solution for the residual effects in the morning. Otherwise patients should be advised not to operate a motor vehicle the morning after intake of zopiclone 7.5mg.

In conclusion, the results of these studies show that zaleplon 10mg, certainly, and 20mg, probably, can be taken up to 5 hours before driving with little risk of serious impairment. It seems like zaleplon is the first hypnotic that can safely be used in middle of the night by young adults, if needed, when their activities over the next day include driving. In contrast, zopiclone 7.5mg should be avoided by those patients whose activity the next day involves skilled work and where impairment of performance could be a danger to themselves or others.

References


