Residual Effects of Hypnotics on Actual Driving of Healthy Young Volunteers

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OBJECTIVE: Residual sedation the morning after bedtime use of hypnotics is a major problem with respect to traffic safety. Gaboxadol is a selective extrasynaptic GABA_A agonist (SEGA) intended for the treatment of insomnia. It acts primarily by activating benzodiazepine-insensitive extrasynaptic α4β3δ- and α6β3δ-containing GABA_A receptors involved in tonic inhibition. After oral doses the drug is rapidly absorbed (t_max approximately 30 min) and eliminated (t_1/2 1.5 - 2.0 hours). Clinical trials did not reveal any residual effects on cognitive functioning of bedtime doses up to 20 mg. The hypothesis of the study was that gaboxadol 15 mg is free of residual effects on driving the morning after bedtime administration, and that it may be safe for use later in the night.

METHODS: Twenty-five healthy volunteers (13 men and 12 women, mean ±SD age 31.4 ± 1.5 years) participated in a double-blind, placebo controlled, 5-way crossover study. They ingested capsules twice on each treatment night; once at 23:00 hours before initiating sleep and again after being briefly awakened 5 hours later. Treatments were: one session with placebo at both times, two sessions with active treatment (gaboxadol 15 mg and zopiclone 7.5 mg) in the evening followed by placebo in the middle of the night, two sessions with placebo in the evening and active treatment in the middle-of-the-night (gaboxadol 15 mg and zolpidem 10 mg). Subjects arose at 07:00 hours. Residual drug effects on laboratory tests (tracking, divided attention, digit symbol substitution, word learning, postural stability, subjective alertness) were assessed between 7:30 and 8:15 hours and on actual driving ability between 9:00 and 10:00 hours. The primary dependent variable was Standard Deviation of Lateral Position (SDLP in cm, an index of weaving) in the standardized highway driving test.

RESULTS: Gaboxadol 15 mg was without significant effects on driving as measured by SDLP between 10-11 hours after evening administration. Nonetheless, it had minor effects on speed variability and performance in the divided attention test. In contrast, zopiclone 7.5 mg significantly impaired driving. The effects on SDLP were comparable to those found previously for alcohol while BAC was 0.05 g/dL. In addition zopiclone significantly impaired performance in all laboratory tests, except tracking. Remarkably, subjects did not feel significantly less alert in the morning, as compared to placebo. The middle of the night doses of zolpidem 10 mg and gaboxadol 15 mg both impaired driving between 5 to 6 hours after administration. The effects of zolpidem 10 mg were most pronounced. In addition it impaired all laboratory performance parameters. Gaboxadol, on the other hand, had significant effects on psychomotor performance, but not on memory. Subjects felt significantly less alert and contented following both middle of the night doses of hypnotics.

CONCLUSIONS: Gaboxadol 15 mg is unlikely to produce residual effects on driving between 10 and 11 hrs after evening administration. However, patients should be warned not to drive within 6 hours after use of gaboxadol 15 mg later in the night, as is the case for zolpidem 10 mg. Interestingly, gaboxadol seems to be the first GABAergic hypnotic that does not impair memory. Finally, patients should be warned not to drive within 11 hours after bedtime use of zopiclone 7.5 mg, in particular because they seem unaware of residual sedation of this drug themselves.

Keywords: Hypnotics, Residual effects, Over-the-road driving