Zolpidem Relieves Middle-of-Night Insomnia

BY CAROLINE HELWICK

FROM THE ANNUAL CONGRESS OF THE EUROPEAN COLLEGE OF NEUROPSYCHOPHARMACOLOGY

AMSTERDAM – A sublingual 3.5-mg formulation of zolpidem tartrate is effective for middle-of-the-night insomnia, producing no tolerance, rebound, or increase in use over 4 weeks, investigators reported at the congress.

"Awakening during the night with difficulty falling back to sleep is a prevalent condition, and a p.r.n. treatment for this is needed as it may decrease overall drug exposure," said the study's coinvestigator, Thomas Roth, Ph.D., of Henry Ford Hospital, Detroit.

Zolpidem sublingual tablets 3.5 mg and 1.75 mg were developed for the treatment of insomnia that is characterized by difficulty returning to sleep after middle-of-the-night (MOTN) awakening. The compound is formulated with binary buffers to promote buccal absorption of a portion of the drug. This facilitates bioavailability, resulting in a rapid return to sleep. Previous studies have found that sublingual zolpidem significantly reduces sleep latency after MOTN dosing. In a sleep laboratory study, sleep latency time was approximately 28 minutes with placebo but just 10 minutes with zolpidem 3.5 mg (Sleep 2008;31:1277-84).

"This is a reduced dose of zolpidem, and importantly it is a sublingual formulation so you achieve much faster blood levels to help you fall back asleep but you reduce the total blood level as compared to taking it prophylactically. The concern is that over time, people take more and more of the medication," Dr. Roth said.

The drug is currently under review by the Food and Drug Administration for MOTN awakening.

In a study designed to address possible abuse liability associated with p.r.n. use of the drug, 75 outpatients received zolpidem and 71 patients received placebo; all were assessed for latency to sleep onset after MOTN dosing across a 4-week treatment period. For a check of rebound potential, outcomes also were observed on the first night of nondosing after 1 or more nights of medication use.

The study found no evidence of residual sleepiness after MOTN dosing with zolpidem. Patients who received the drug actually reported greater alertness compared with baseline. On a scale of 1-9 (with 9 being most alert), the mean score was 4.9 at baseline, increasing to 5.7 after zolpidem dosing. Scores in the placebo arm were 4.7 and 5.2, respectively.

Sleep quality also improved significantly. Mean scores were 4.7 at baseline and 5.8 with zolpidem, vs. 4.5 and 5.2, respectively, with placebo.

The study found no evidence for the development of tolerance to zolpidem's efficacy. Latency to sleep onset improved over the first 2 weeks, and apparently stabilized by week 3, for both the active-treatment and placebo groups, suggesting a nonspecific trend toward improvement in outcome over time.

The response to the medication did not change across the entire treatment period, and drug use was not different between treatment and placebo groups. In fact, drug use during week 4 was significantly lower than during week 1 in both the active and placebo arms.

There was no evidence of rebound effects on sleep initiation or total sleep time on nondosing nights, regardless of the number of nights of continuous use. On average, for nights during which zolpidem was not dosed, total sleep time was similar for the active and placebo groups.

Dr. Roth noted that the improvement over placebo of about 20 minutes is clinically meaningful. "It doesn't sound impressive, but try sleeping 20 minutes less every night for 3 months – you'll be in a coma. The effect is cumulative. It's about 2 hours a week." ■

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Sublingual zolpidem helped patients get back to sleep, with no evidence of residual sleepiness.

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Major Finding: Persons who received a new formulation of low-dose sublingual zolpidem for middle-of-the-night insomnia showed no potential for abuse of the drug in the form of dependency, tolerance, or rebound potential, compared with placebo recipients.

Data Source: A 4-week outpatient study of 146 subjects.

Disclosures: Dr. Roth has served as a consultant to Transept Pharmaceuticals Inc., the manufacturer of the sublingual formulation of zolpidem tartrate. He has also received research support from and had other relationships with numerous pharmaceutical companies.

TNF Blockade May Lower Risk of Depression in Arthritis

BY DIANA MAHONEY

FROM THE CONGRESS OF CLINICAL RHEUMATOLOGY

DESTIN, FLA. – The benefits of tumor necrosis factor blockade extend beyond the joints to the hearts and minds of rheumatoid arthritis patients, Dr. Iain McInnes reported at the congress.

Findings from two studies suggest anti-TNF treatment can inhibit the cytokine-induced chain of events that leads to the increased risk of cardiovascular disease and clinical depression in RA.

Along with lead investigator Dr. Mike J.L. Peters of VU University Medical Center in Amsterdam, Dr. McInnes and colleagues at the University of Glasgow (Scotland) have shown, for the first time, that anti-TNF-alpha therapy lowers circulating levels of the cardiac neurohormone N-terminal prohormone brain natriuretic peptide (NT-proBNP) in patients with rheumatoid arthritis (RA) who do not have evident heart failure.

Previously identified as a clinically relevant biomarker for heart failure, NT-proBNP is independently associated with cardiovascular risk in individuals with and without preexisting cardiovascular disease. Thus, the observed reduction in NT-proBNP suggests a "potential beneficial effect of [TNF-alpha] blockers with respect to vascular risk and ventricular function in rheumatoid arthritis," Dr. McInnes said.

The study measured serum NT-proBNP at baseline and after 16 weeks of biweekly adalimumab treatment in 171 consecutive RA patients without heart failure (Ann. Rheum. Dis. 2010 April 7 [doi:10.1136/ard.2009.119412]).

After week 16, the investigators observed an approximately 18% reduction in NT-proBNP levels, providing biological evidence that TNF-alpha blockade does not worsen ventricular function in patients with RA who do not have prevalent heart failure, and supporting epidemiologic findings that indicate it may reduce overall cardiovascular risks in these patients, said Dr. McInnes.

The results also add weight to the accumulating evidence that implicates TNF-alpha in the cardiovascular events associated with RA, and support the beneficial effect that blocking TNF-alpha has on surrogate vascular markers, he said.

In a separate study, Dr. McInnes and colleagues sought to assess the functional effects of anti-TNF-alpha therapy on the brains of depressed patients with RA, and determined that TNF-alpha blockade mediates altered serotonin transporter availability and induces an improvement in depression measures.

'I think we as rheumatologists underappreciate the prevalence and impact of depression on our patients.'

DR. MCINNES

"This is critically important," Dr. McInnes stressed. "I think we as rheumatologists underappreciate the prevalence and impact of depression on our patients," he said, referring to a 2006 report suggesting that the prevalence of major depressive disorder exceeds 40% and that of suicidal ideation is up to 11% in RA patients (Rheumatology [Oxford] 2006;45:1325-7).

Findings from earlier research have shown that proinflammatory cytokines can increase the density and activity of the serotonin transporter (SERT), a primary target for antidepressant therapy. On that basis, Dr. McInnes and his associates hypothesized that TNF blockade might be associated with altered SERT activity in RA patients, he said. They tested this hypothesis in a clinical, proof-of-concept study by measuring SERT density using SPECT (single-photon emission CT) in six patients with seropositive RA 2 weeks before the initiation of adalimumab therapy and 4 days after the last treatment, he said.

After anti-TNF-alpha therapy, "there was a significant decrease in the [SERT] density in all of the patients." Along with that came overall improvements in physical and mental functioning, as measured by the Hamilton Rating Scale for Depression, the Social Functioning 36-item scale, the Hospital Anxiety and Depression Scale, and the composite 28 joint count Disease Activity Score, Dr. McInnes reported.

Although it is yet unclear whether the observed SERT alterations are specific to RA or are related to cytokine action in general, "the findings provide important insight into the biology linking clinical depression and rheumatoid arthritis." If confirmed in larger studies, the findings may offer guidance for developing treatment strategies, according to Dr. McInnes. ■

Disclosures: Dr. McInnes has received research support or honoraria from Schering-Plough, Roche, Bristol-Myers Squibb Co., and Wyeth and has served as a consultant for Schering-Plough and Roche.