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Original Article

Efficacy and tolerability of indiplon in older adults with primary insomnia

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Abstract

Objective: To evaluate the efficacy and safety of indiplon in elderly patients with primary insomnia.
Patients and methods: Elderly patients, 65–80 years ($N = 358$; 55% female; mean age, 71 years) who met the criteria for primary insomnia according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) for three months were randomized to two weeks of double-blind nightly treatment with 5 mg or 10 mg indiplon or placebo. Daily self-assessments by the patients included latency to sleep onset (LSO), total sleep time (TST), number of awakenings (NAW), wake time after sleep onset (WASO), and sleep quality. Data were collected between July, 2002, and October, 2003, at 52 clinical research sites in North America.
Results: Treatment with indiplon was associated with significant reduction in LSO at Week 1 for the 5 mg (34.6 ± 1.8 min) and 10 mg doses (30.4 ± 1.6 min) relative to placebo (47.4 ± 2.5 min; $p < 0.0001$ for both comparisons). During Week 2, LSO remained shorter on both indiplon doses compared to placebo (5 mg, $p = 0.016$; and 10 mg, $p = 0.0028$). During both study weeks, treatment with indiplon was also associated with significant improvement, relative to placebo, in TST, NAW, WASO, and sleep quality. The frequency of adverse events was similar in the indiplon 5 mg and placebo groups; somnolence, nausea, depression and decreased appetite were slightly more common in the indiplon 10 mg group.
Conclusion: In elderly patients with primary insomnia, indiplon 5 mg and 10 mg were efficacious in inducing and maintaining sleep and improving sleep quality during the two weeks of treatment. Indiplon 5 mg was well-tolerated, with no serious adverse events and no significant changes in electrocardiogram (ECG) or routine clinical laboratory evaluations; the 10 mg dose produced slightly greater efficacy as well as somewhat increased adverse events.

Keywords: Primary insomnia; Indiplon; Elderly; Sleep latency; Sleep maintenance; Hypnotic medication

1. Introduction

The recent National Institutes of Health statement on the Manifestations and Management of Chronic Insomnia in Adults [1], which summarizes the June 13–15, 2005 State-of-the-Science Conference, concludes that "chronic insomnia is a major public health problem affecting millions of individuals, along with their families and communities." The statement also emphasizes the need for systematic evaluation of insomnia therapies. The current paper reports the results of a study of the efficacy and safety of indiplon for the treatment of primary insomnia in older adults.

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Indiplon is a benzodiazepine receptor agonist (BzRA) with high affinity and selectivity for the α1 subtype of the GABA-A receptor complex. The selectivity ratio of indiplon ranges from approximately 10-fold for α1 subtype versus α2-subtype, and up to 350-fold for the α1 subtype relative to the α4 and α6-subtypes [2,3], suggesting lack of clinical effect at the latter receptors. Indiplon is rapidly absorbed, with a time to maximum blood concentration (T_{max}) of approximately 1 h, and is metabolized quickly, with an elimination half-life of ~1.5 h. Pharmacokinetics are linear and do not vary significantly with age; C_{max} and area under the curve are dose-proportional [4,5]. Two separate metabolic pathways are involved: via CYP3A4 to form desmethyl indiplon, and via carboxyesterase to form desacetyl indiplon. The alternative carboxyesterase pathway reduces the effect of inhibition of the CYP3A4 pathway. There are no active metabolites.

Given the binding selectivity at receptors which mediate sedation and a pharmacokinetic profile consistent with low concern for morning residual effects, we evaluated indiplon for the treatment of insomnia in older adults. Specifically, the efficacy, tolerability and safety of two doses (5 mg and 10 mg) of indiplon were compared to placebo in elderly patients with primary insomnia according to Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) criteria [6].

2. Methods

A double-blind, placebo-controlled, parallel-group design was conducted at 52 sites in the United States and Canada using a common protocol which was approved by the Institutional Review Board for each site. Research conduct was consistent with the guidelines for Good Clinical Practice, the US Code of Federal Regulations dealing with clinical studies, and the Declaration of Helsinki.

Study procedures included (1) an initial screening study visit; (2) a two-week, single-blind placebo phase ending with a second screening study visit; (3) weekly study visits during two weeks of double-blind treatment; and (4) a one-week, single-blind placebo discontinuation phase ending with a final study visit. Each patient's participation lasted 30–49 days.

2.1. Patient selection and screening

Men and women aged 65–80 years (inclusive) were recruited principally by media advertisements. On preliminary screening (conducted either by phone or at the initial visit) study requirements and procedures were explained, and key entry criteria were evaluated. Interested individuals who continued to qualify participated in an initial study visit during which the study was thoroughly explained, and written informed consent was obtained prior to initiation of any study procedure.

The initial visit was comprised of physical and neurological examination, vital signs, routine laboratory tests (hematology, serum chemistry and urinalysis), hepatitis B surface antigen and hepatitis C antibody test, 12-lead electrocardiogram (ECG), and urine drug screen. Vital signs (i.e., blood pressure, heart rate, respiratory rate and oral temperature) and weight were recorded. Medical, psychiatric and sleep histories were taken as well to determine if the patient met criteria for a DSM-IV primary insomnia diagnosis [6] and also the following criteria: (1) insomnia symptoms present for $\geqslant$3 months; and (2) self-reported latency to sleep onset (LSO) $\geqslant$45 min and total sleep time (TST) $<$6.5 h, both on $\geqslant$3 nights per week. Patients were excluded for any of the following: (1) a clinically significant or unstable medical disorder in the past 30 days; (2) a history of epilepsy or serious head injury; (3) a clinically significant abnormal finding on physical examination, laboratory testing, or ECG; (4) a past history of sensitivity to benzodiazepines or other drugs acting at the GABA-A complex; (5) a history in the past year of alcohol or substance dependence or abuse as defined by DSM-IV criteria, or presence of a positive urine drug screen; (6) regular consumption of $\geqslant$5 alcoholic beverages per day, or $\geqslant$14 alcoholic beverages per week; (7) use in the prior two weeks of any hypnotic, anxiolytic, antidepressant, anticonvulsant, histamine-1 receptor antagonist (except loratidine and fexofenadine), narcotic analgesic, or potent P450 3A4 inhibitor or inducer; (8) napping $>$5 times per week, or napping $>$1 h per day; (9) current or planned travel across $\geqslant$4 time zones, or night or rotating shift work; or (10) presence of symptoms of any sleep disorder other than primary insomnia (e.g., sleep apnea, narcolepsy, restless leg syndrome, etc.).

After the initial study visit (and a 7–14 day drug-free period, if needed), eligible patients entered a two-week, single-blind placebo run-in phase. Patients slept at home and were instructed to maintain their usual sleep-wake schedule and to take study medication each night at bedtime with 100 mL of water. Study drug was provided in blister cards, 10 capsules per card, with one card for each study week. Only one capsule was to be taken each night. Extra capsules were provided in case a study visit needed to be delayed, or medication was lost, and were returned in the study packaging at every visit. Alcohol intake was restricted to no more than two drinks per day, with none being consumed within 4 h of bedtime. All changes in concomitant medications were recorded.

Each patient completed a daily sleep diary each morning to record patient reports of bed time and rise time, LSO, TST, WASO (all in minutes and hours), NAW, and sleep quality (7 point scale; 1 = extremely good and 7 = extremely poor). In order to continue in the study, bedtime was required to have been between