ZOLPIDEM
Melhora na qualidade do sono e menor efeito colateral

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DESCRIÇÃO
O Zolpidem é ansiolítico/sedativo da classe das imidazopiridinas, com início de ação dentro dos 30 minutos e meia vida curta, usado no tratamento da insônia sem produzir alterações relevantes na arquitetura do sono.

MECANISMO DE AÇÃO
O Zolpidem é um agente sedativo e rapidamente absorvido, onde diferentemente dos benzodiazepínicos, observou-se em estudos in vitro a ligação seletiva ao receptor (GABA-ω1) com uma elevada afinidade pelas subunidades α1α5, modulando a abertura do canal de cloro. Esta ligação seletiva pode explicar a manutenção de efeitos como a redução do tempo de indução ao sono, do número de despertares noturnos, aumento da duração total do sono, além da ausência dos efeitos indesejados presentes nos benzodiazepínicos.

INDICAÇÕES
✓ Insônia, inclusive a causada por fogachos (menopausa e tratamento do câncer de mama);
✓ Qualidade do sono;

DOSE USUAL
Recomendação oral de 5 a 10mg de Zolpidem ao dia.

SUGESTÕES DE FÓRMULAS

<table>
<thead>
<tr>
<th>Zolpidem</th>
<th>Venlafaxina</th>
</tr>
</thead>
<tbody>
<tr>
<td>10mg</td>
<td>75mg</td>
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</tbody>
</table>

**Modo de uso:** 1 dose antes de deitar.
**Indicação:** melhora da qualidade do sono durante o tratamento da HPB.

**Obs:**
Adultos > 65 anos, recomenda-se 5mg.
Pacientes com insuficiência hepática - recomenda-se 5mg e monitoramento.

<table>
<thead>
<tr>
<th>Zolpidem</th>
<th>Tansulosina</th>
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<tbody>
<tr>
<td>5mg</td>
<td>0,4mg</td>
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</table>

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PRINCIPAIS REFERÊNCIAS

Zolpidem is a potent stoichiometry-selective modulator of α1β3 GABAA receptors: evidence of a novel benzodiazepine site in the α1-α1 interface.

Zolpidem is not a typical GABAA receptor hypnotic. Unlike benzodiazepines, zolpidem modulates tonic GABA currents in the rat dorsal motor nucleus of the vagus, exhibits residual effects in mice lacking the benzodiazepine binding site, and improves speech, cognitive and motor function in human patients with severe brain injury. The receptor by which zolpidem mediates these effects is not known. In this study we evaluated binary α1β3 GABAA receptors in either the 3α1:2β3 or 2α1:3β3 subunit stoichiometry, which differ by the existence of either an α1-α1 interface, or a β3-β3 interface, respectively. Both receptor stoichiometries are readily expressed in Xenopus oocytes, distinguished from each other by using GABA, zolpidem, diazepam and Zn(2+). At the 3α1:2β3 receptor, clinically relevant concentrations of zolpidem enhanced GABA in a flumazenil-sensitive manner. The efficacy of diazepam was significantly lower compared to zolpidem. No modulation by either zolpidem or diazepam was detected at the 2α1:3β3 receptor, indicating that the binding site for zolpidem is at the α1-α1 interface, a site mimicking the classical α1-γ2 benzodiazepine site. Activating α1β3 (3α1:2β3) receptors may, in part, mediate the physiological effects of zolpidem observed under distinct physiological and clinical conditions, constituting a potentially attractive drug target.

Pharmacokinetics of a Novel Zolpidem Nasal Spray for Rapid Management of Insomnia: First Trial in Humans.

STUDY OBJECTIVES: The present single-dose, parallel-group, randomized, double-blind, placebo-controlled study is to evaluate the pharmacokinetics, tolerability and safety of zolpidem tartrate nasal spray (ZNS) as compared to placebo in healthy subjects. METHODS: Thirty-six healthy subjects participated in this study, with 19 male and 17 female subjects in 3 cohorts (12 subjects per cohort), who were randomly assigned to receive either an intranasal dose of ZNS 1.75 mg, 3.5 mg, 5.0 mg (n = 10 per dose), or an intranasal placebo (n = 2). Multiple venous blood samples were collected for pharmacokinetic analyses. RESULTS: Plasma zolpidem concentrations rapidly increased after intranasal ZNS 1.75, 3.5, and 5.0 mg with mean Tmax of 0.42, 0.76 and 0.50 h, respectively, followed by rapid decreases at all three doses. Cmax, AUC0-t, and AUC0-∞ were found to increase in a dose-proportional manner. Female subjects had generally higher AUC0-t, AUC0-∞, and lower weight-normalized clearance rate (CL/F) than male subjects. In this study, ZNS was safe and well tolerated over the evaluated dose range. There were no serious adverse events. CONCLUSIONS: Zolpidem was rapidly absorbed and eliminated after intranasal administration of ZNS. Dose proportionality was found at the doses ranged from 1.75 mg to 5.0 mg. Intranasal exposure of zolpidem was generally higher in female subjects than that in male subjects. It could be concluded that ZNS is safe and well tolerated over the evaluated range of intranasal doses.

Alcohol and Aldehyde Dehydrogenases Contribute to Sex-Related Differences in Clearance of Zolpidem in Rats.

OBJECTIVES: The recommended zolpidem starting dose was lowered in females (5 mg vs. 10 mg) since side effects were more frequent and severe than those of males; the mechanism underlying sex differences in pharmacokinetics (PK) is unknown. We hypothesized that such differences were caused by known sex-related variability in alcohol dehydrogenase (ADH) expression. METHODS: Male, female, and castrated male rats were administered 2.6 mg/kg zolpidem, ± disulfiram (ADH/ALDH pathway inhibitor) to compare PK changes induced by sex and gonadal hormones. PK analyses were conducted in rat plasma and rat brain. KEY FINDINGS: Sex differences in PK were evident: females had a higher C MAX (112.4 vs. 68.1 ug/L) and AUC (537.8 vs. 231.8 h(∗)ug/L) than uncastrated males. Castration induced an earlier T MAX (0.25 vs. 1 h), greater C MAX (109.1 vs. 68.1 ug/L), and a corresponding AUC increase (339.7 vs. 231.8 h(∗)ug/L). Administration of disulfiram caused more drastic C MAX and T MAX changes in male vs. female rats that mirrored the effects of castration on first-pass metabolism, suggesting that the observed PK differences may be caused by ADH/ALDH expression. Brain concentrations paralleled plasma concentrations. CONCLUSION: These findings indicate that sex differences in zolpidem PK are influenced by variation in the expression of ADH/ALDH due to gonadal androgens.
Comparison of pharmacokinetic profiles of zolpidem buffered sublingual tablet and zolpidem oral immediate-release tablet: results from a single-center, single-dose, randomized, open-label crossover study in healthy adults.

BACKGROUND: A zolpidem sublingual tablet (ZST) formulation was recently approved by the US Food and Drug Administration to treat middle-of-the-night (MOTN) awakening with difficulty returning to sleep. OBJECTIVE: The aim of this study was to compare the zolpidem pharmacokinetic profiles of 3.5-mg ZST and 10-mg immediate-release (IR) oral zolpidem in healthy female and male adults. METHODS: This randomized, open-label crossover study compared the pharmacokinetic profile of ZST with that of IR oral zolpidem in healthy adults. RESULTS: The study enrolled 19 males and 14 females. After 3.5-mg ZST and 10-mg IR, respectively, mean zolpidem plasma concentrations at 15 minutes (22 vs 17 ng/mL, respectively, in females and 18 vs 10 ng/mL in males) and AUCs from zero to 15 minutes (2.3 vs 0.8 ng · h/mL in females and 1.6 vs 0.5 ng · h/mL in males) were substantially greater for ZST, despite the larger absolute IR dose. After 3.5-mg ZST and 10-mg IR, respectively, clearance was lower in females, even after correcting for body weight (2.63 vs 2.88 mL/min/kg in females and 3.63 vs 3.91 mL/min/kg in males). The lag time prior to the start of first-order absorption was notably shorter for ZST than IR in both males (8 vs 21 minutes) and females (5 vs 22 minutes). Both zolpidem formulations were generally well tolerated by both genders. CONCLUSIONS: Systemic exposure of zolpidem was higher in females for both formulations. Plasma levels and AUC were higher, and clearance was lower, in females with both zolpidem formulations. The initial rate of absorption was faster, and initial systemic exposure was greater, with ZST compared with oral IR.

Lower doses of sublingual Zolpidem are more effective than oral Zolpidem to anticipate sleep onset in healthy volunteers.

OBJECTIVE: To compare the efficacy of sublingual Zolpidem (5 and 10mg) to conventional oral Zolpidem (10mg). METHODS: This was an open, randomized, double-blind, double-dummy, controlled, and single center study. The study took place at the Laboratory of Clinical Neurophysiology and total number of participants was 58 volunteers completed the study whose demographics of age, gender, body mass index (BMI) were similar among everyone. Scores in Epworth, Pittsburgh, Beck and Hamilton Scales did not differ among groups. A model of transient insomnia was determined by the sleep anticipation in 120minute. Subjects were randomly divided in three groups for drug administration (5mSL; 10mgSL and 10mg oral), given in a single dose prior to polysomnography (PSG). Sleep parameters were assessed by PSG and post-sleep questionnaires. RESULTS: A significant main treatment effect was evident considering the sleep onset latency (SOL) and persistent sleep latency (PSL). An earlier sleep onset was induced by SL Zolpidem 10mg (SOL=p<0.004; PSL=p<0.006) and SL Zolpidem 5mg (SOL=p<0.025; PSL=p<0.046) compared to oral Zolpidem 10mg. Subjects that received SL Zolpidem 10mg reported an earlier sleep onset (latency to sleep and latency until persistent sleep) when compared to subjects from other groups (p<0.005). CONCLUSIONS: Sublingual Zolpidem, both 5 and 10mg, induced faster sleep initiation than 10mg oral Zolpidem. A subjective perception of earlier sleep onset was reported by subjects using SL 10mg.

Efficacy of combination therapy with tamsulosin and zolpidem on nocturia in patients with benign prostatic hyperplasia.

INTRODUCTION: We examined the efficacy of combination therapy with α1-blocker tamsulosin and hypnotic zolpidem in patients who had suffered from sleep disturbance associated with nocturia. MATERIAL AND METHODS: A total of 35 patients diagnosed with nocturia with lower urinary tract symptoms (LUTS) suggestive of benign prostatic hyperplasia (BPH) were studied. After treatment with tamsulosin for 4 weeks, 16 patients dissatisfied with nocturia (nocturiaquality of life index ≥4) and suspected to have sleep disturbance (Athens Insomnia Scale ≥6) received additional treatment with tamsulosin and zolpidem for 2 weeks. Outcomes were evaluated by the International Prostate Symptom Score (IPSS) and quality of life index (QOL), Athens Insomnia Scale (AIS) and nocturia-quality of life index (nocturia-QOL).
Augmentation of venlafaxine and selective serotonin reuptake inhibitors with zolpidem improves sleep and quality of life in breast cancer patients with hot flashes: a randomized, double-blind, placebo-controlled trial.

OBJECTIVE: Hot flashes are a major quality-of-life issue for breast cancer survivors, interrupting sleep, reducing quality of life, and diminishing treatment adherence to adjuvant endocrine therapies. Serotonin-norepinephrine reuptake inhibitors (SNRIs) and selective serotonin reuptake inhibitors (SSRIs) are used widely but are only partially effective for hot flashes. Alternative strategies are needed. We hypothesized that augmentation of SSRI/SNRI therapy with hypnotic agents would optimize hot flash therapy by improving sleep and quality of life. METHODS: Women with breast cancer or at high risk for developing the disease who had hot flashes in association with nocturnal awakenings were randomized to double-blinded treatment with zolpidem 10 mg or placebo for 5 weeks. SSRI/SNRI nonusers (81%) started venlafaxine XR 75 mg/day concurrently, whereas SSRI/SNRI users continued that therapy. We compared the proportion of responders, defined as study completers with improved subjective sleep quality (Pittsburgh Sleep Quality Index) and/or objectively assessed wake time after sleep onset on actigraphy, between groups. RESULTS: Of 53 women (aged 51 ± 8 y) randomized to zolpidem augmentation (n = 25) or placebo augmentation (n = 28), 38 completed the protocol (57% on placebo, 88% on zolpidem). More women augmented with zolpidem than placebo were responders on the sleep outcome (40% vs 14%; P = 0.035). Quality of life improved more with zolpidem than with placebo (P = 0.01). Treatment effects on hot flashes and mood did not differ between groups. CONCLUSIONS: Augmentation of SSRI/SNRI with zolpidem improves sleep and quality of life in breast cancer survivors with hot flashes and associated sleep disturbance. Adding a hypnotic agent to an SSRI/SNRI helps women to sleep through nighttime hot flashes. Treatments targeting sleep may be an important supplemental strategy to optimize well-being.

REFERÊNCIAS


