Zopiclone
A Review of its Pharmacological Properties and Therapeutic Efficacy as an Hypnotic

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Summary

Zopiclone is a cyclopyrrolone which is chemically unrelated to the benzodiazepines and is thought to act on the GABA_A receptor complex at a site distinct from, but closely related to, the benzodiazepine binding site. The hypnotic efficacy of zopiclone administered as single oral doses has been demonstrated in patients undergoing next-day surgery and in patients with insomnia, and these studies have established an optimal dose of 7.5mg for elderly patients. Using this dose, clinical studies have shown that zopiclone improved sleep in elderly patients to a similar extent as triazolam 0.125 to 0.5mg, flurazepam 15mg, and nitrazepam 5mg. Studies that also included younger patients have shown that zopiclone 7.5mg is at least as effective as triazolam 0.25 or 0.5mg, and on most sleep parameters is comparable to temazepam 20mg, nitrazepam 5mg, flurazepam 2mg, and flurazepam 20mg.

Zopiclone causes minimal impairment to psychomotor performance and mental alertness the morning after night-time administration. The drug is generally well tolerated by patients of all ages; the most frequently reported adverse effects being bitter taste and dry mouth. Treatment withdrawal due to adverse effects is seldom required and reports of rebound insomnia after zopiclone withdrawal are rare. While symptoms of physical dependence have not been observed in clinical studies, there have been isolated reports of physical dependence in patients with a history of substance abuse. Although the latter finding should be kept in mind, it appears that zopiclone has a low dependence liability.

Thus, with its short duration of action and good tolerability profile, zopiclone is a well established alternative to the benzodiazepine hypnotics and may be particularly beneficial in those patients unable or unwilling to tolerate the residual effects associated with many other hypnotic agents.

Pharmacological Properties

Although structurally unrelated to the benzodiazepines, zopiclone also binds to regulatory sites on the GABA_A receptor complex in the central nervous system. Zopiclone has marked sedating effects and improves sleep parameters in patients undergoing next-day surgery. Optimum hypnotic activity is achieved with an oral 7.5mg dose. Rebound insomnia after zopiclone withdrawal is rare and is generally less severe than after withdrawal of flurazepam or temazepam, and less frequent than after flurazepam, nitrazepam or triazolam withdrawal. Zopiclone has limited anxiolytic effects but these have not been evaluated in a clinical setting.

Some deterioration of psychomotor function and memory is evident 1 to 2 hours after zopiclone administration; however, only minimal residual impairment is evident after 8 to 10 hours. Combined administration of alcohol (ethanol) 0.2 to 0.8 g/kg and zopiclone 7.5mg has an additive effect on impairment of psychomotor function after 1.5 hours which is negligible after 8 hours. Zopiclone does not appear to have any significant effect on respiration. Symptoms of physical dependence have not been observed in studies of psychiatric patients or former alcoholics given zopiclone in dosages up to 30 mg/day; however, there have been isolated reports of physical dependence in patients with a history of substance abuse.

Peak plasma concentrations following a single oral dose of zopiclone 7.5mg range from 64 to 86 μg/L and are achieved within 2 hours. Bioavailability is approximately 80% but is increased to 163% in the elderly. Zopiclone undergoes extensive hepatic metabolism; only 4 to 5% is excreted unchanged in the urine and approximately 11% is excreted as a partially active N-oxide metabolite. Plasma zopiclone clearance is about 14 L/h and is not altered by haemodialysis. In elderly patients (aged >65 years), the elimination half-life of zopiclone is approximately 8 hours (the elimination half-life of the partially active metabolite is about 6 hours) compared with 3.5 to 6.5 hours in young healthy volunteers. Despite this small increase in half-life, there is no apparent accumulation during repeated administration.

Clinical Efficacy

The efficacy of zopiclone in young and elderly patients with insomnia has been well established in noncomparative and placebo-controlled investigations. Results of the largest reported study, a postmarketing surveillance study in 20 513 patients with insomnia (mean age 52.3 years) have