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Zopiclone, a Cyclopyrrolone Hypnotic: Review of Properties

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BRUN, J. P. *Zopiclone, a cyclopyrrolone hypnotic: Review of properties.* PHARMACOL BIOCHEM BEHAV **29**(4) 831–832, 1988.—Zopiclone is a non-benzodiazepine hypnotic with a pharmacological spectrum of activity which resembles that of the benzodiazepines (BZD), but it binds to the GABA complex at a site different from the BZD receptor. Pharmacokinetic properties class ZPC in the category of hypnotics with intermediate–short half-life (5–7 hours) and explain the low incidence of unwanted effects reported. The influence of zopiclone 7.5 mg on sleep architecture is minimal. In healthy volunteers, the amount of deep sleep is increased. No depressant effect on respiratory function and no rebound effect has been demonstrated.

Zopiclone Hypnotic Cyclopyrrolones

PRECLINICAL DATA

ZOPICLONE (27267 RP, Imovane®) possesses a chemical structure unrelated to the benzodiazepines (BZD) or the barbiturates. However, in conventional psychopharmacological tests, zopiclone (ZPC) was shown to possess the five key activities considered as the pharmacological profile of a tranquilizer [1]: anticonvulsant, antiagressive, anticonflict, sedative-hypnotic and myorelaxant (106 times weaker than nitrazepam). Electrophysiological studies performed in cats have shown ZPC to have an activity which resemble that of nitrazepam, but with a shorter duration. From a biochemical point of view ZPC possesses a high affinity for BZD receptors in three rat brain regions (cortex, cerebellum and hippocampus). No other brain or peripheral BZD binding sites are affected [1]. The study of the modulating effects of GABA on ZPC binding revealed some differences with BZD and recently [4] a separate site for cyclopyrrolones in the GABA receptor has been identified.

CLINICAL PROFILE

ZPC is undoubtedly an hypnotic [3]. The usual dosage of 7.5 mg has been shown to be optimum in dose ranging studies in adult and in geriatric patients. Nevertheless, 3.75 mg may be recommended in certain cases such as geriatrics or patients with somatic deficiences which may interfere with the pharmacokinetic parameters, although the efficacy of the drug has not been consistently established versus placebo in this context. Higher dosages (11.25 and 15 mg) do not appear to present any advantage in common insomnia (transient or situational) but could be applicable to patients with psychiatric diseases.

More than 30 Phase III controlled studies involving about 1200 patients who received ZPC have been performed. They demonstrate the hypnotic activity of 7.5 mg of ZPC:

(a) in comparison with flunitrazepam (1 or 2 mg), flurazepam (15 or 30 mg), nitrazepam (5 or 10 mg), triazolam (0.25 or 0.50 mg), temazepam (20 mg);

(b) in short and long treatment (up to 8 weeks in controlled trials);

(c) in adult and in geriatrics;

(d) in different kinds of insomnia: situational, transient and secondary insomnia (psychiatric and neurologic patients).

In these studies, the activity of the drug appears from the first day of treatment and is maintained throughout the whole duration of the study without any diminution or potentiation of activity in adults and in geriatric patients.

Since ZPC has a good absorption profile (bioavailability around 90%—T max 60–90′), and an intermediate-short elimination half life (5–7 hr), predicting coverage of the duration of the night [2], it is not surprising that minimal unwanted effects were observed.

Residual effects on alterness and performance have not been detected 10 hours after the intake of drug in any of the 16 studies designed specifically to assess these effects.

The only side effect which occurs significantly when compared with the level of side effects recorded in placebo controlled studies, consists of a bitter taste due to the salivary excretion of the drug, reported in 15–20% of the cases. Drowsiness, tiredness, and headache reported in this panel of studies have a frequency between 10–20%, similar to that observed in placebo groups.

Standard laboratory tests to monitor the possible incidence of ZPC haematologic, hepatic and renal dysfunctions were performed on more than 1000 patients who received the drug for at least 7 days at a dosage of 7.5 mg. No significant changes related to the treatment were reported.

No significant rebound phenomena was detected in the relevant studies. Cross dependence with alcohol appeared weaker than that observed with a short half-life benzodiazepine in two studies specifically designed for this purpose. No depressant effect of the respiratory function was detected in studies involving healthy volunteers as well as patients with respiratory insufficiency. This may be put in

relation with the lack of pronounced myorelaxant properties shown in animal models.

The incidence of ZPC on sleep architecture is somewhat different than that observed with the BZD. Although 7.5 mg delays the first period of REM latency, it does not consistently affect the overall duration of the REM period. Sleep lab studies performed on healthy volunteers give coherent results showing that the drug enhances the percentage of deep sleep power. However, the modification induced by 15 mg resembles those usually with described with BZD.

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