

New Hypnotic Agents: Clinical Studies in General Practice

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WHEATLEY, D. *New hypnotic agents: Clinical studies in general practice*. PHARMACOL BIOCHEM BEHAV 29(4) 811-813, 1988.—The type of sleep problem should be determined so that the most appropriate hypnotic can be used, and in this respect duration of action is an important property. The benzodiazepine hypnotics are adequate for this purpose, but problems may arise due to daytime after-effects and the possibility of dependence developing. Non-benzodiazepine hypnotics may be useful alternatives and our group has undertaken double-blind comparative trials with two such compounds, namely zopiclone and zolpidem. Zopiclone was compared to temazepam in a cross-over trial on 36 patients and similar hypnotic effects were recorded. In a parallel group study, zolpidem 10 mg was compared to zolpidem 20 mg and placebo in 88 patients. Both doses of zolpidem were significantly better than placebo on a number of the parameters recorded, side-effects were negligible and there was no evidence of any rebound insomnia during the final control week.

Zopiclone Zolpidem Somnography General practice Insomnia types Insomnia etiology

IN general practice, insomnia may appear to be a simple problem with a simple remedy, namely the prescription of a hypnotic drug. However, before reaching for the prescription pad, the etiology and nature of the sleep disturbance should be carefully evaluated, as in many cases it may be remediable without resort to pharmacotherapy. On the other hand, there will be many occasions when the adverse effects of lack of sleep far outweigh any adverse effects that might arise with modern hypnotic drugs. Although the present range of benzodiazepine hypnotics provides a most useful pharmacological spectrum to enable the general practitioner to match "the right drug to the right patient," their use may be in jeopardy because of problems of daytime side-effects, particularly drowsiness, dependence, interactions with alcohol and driving skills, and withdrawal effects. Just as the benzodiazepines were welcomed as "non-barbiturates" to replace that group of drugs, so new-benzodiazepine hypnotics are now being developed which will, presumably, replace the latter drugs in course of time.

SOMNOGRAPHY

The electroencephalogram (EEG) is the only reliable objective method of recording sleep but, in its present form, is not practicable for use in the patient's home. Therefore, we have devised a clinical method of recording sleep, which is termed "somnography" [2]. By this means, the patient makes a record every quarter-of-an-hour when awake and, of course, the records cease when sleep intervenes. It might be argued that because the patient is aware of the necessity to mark the card the onset of sleep may be delayed, but of course an effective hypnotic drug induces sleep whether the patient tries to resist its effect or not.

The method allows the various types of insomnia to be distinguished and cases can be classified into four categories as follows:

Group A—Prolonged latency or delayed onset of sleep. Defined as longer than one hour to fall asleep.

Group B—One or two long periods of wakefulness during the night, lasting for 1 hour or longer each.

Group C—Several short periods of wakefulness during the night. More than two periods of any length.

Group D—Early awakening. No further sleep for one hour before normal arousal time.

Classifying patients according to the type of insomnia enables the investigator to select patients suffering from specific types of insomnia that may respond specifically to the hypnotics under investigation. For example, an ultra short-acting hypnotic (3-4 hours) would be most suitable for prolonged latency; whilst a medium-acting drug (7-8 hours) would be more appropriate for early morning waking.

ETIOLOGY OF INSOMNIA

From the clinical point of view the causes of insomnia can be classified into six groups [2].

Physical Causes

The patient's inability to sleep may be due to symptoms occasioned by an underlying organic illness that interferes with the sleep process. Pertinent examples are the pain of toothache and cough due to underlying respiratory infections, etc.

Physiological Causes

This category embraces any alteration to the normal sleep pattern that may be brought about by the individual's life and work habits, such as changes in the normal sleep routine experienced by night workers, air-crews, etc.

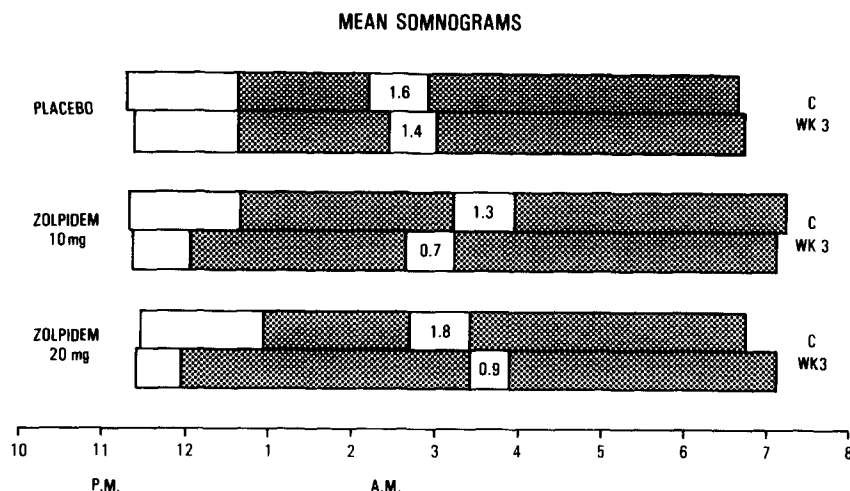


FIG. 1. Mean somnograms from the three treatment groups comparing the initial control period to the final treatment week. Shaded portions represent sleep and clear portions wakefulness. Periods of wakefulness during the night have been amalgamated and are shown as a total in the middle of each somnogram, the figure referring to the mean number of hours awake during the night.

Psychological Causes

These embrace events occurring in the patient's life, mainly of an emotional nature, that may cause excitement or worry which will keep the patient awake.

Psychiatric Causes

Inability to sleep is a prominent feature of the affective disorders, particularly depressive illness, and it may also occur in anxiety states and in psychotic illnesses.

Iatrogenic Causes

A number of drugs have stimulant properties as for example bronchodilator compounds which may still exert this effect even when used in the form of a nasal spray. Other examples are thiazide diuretics taken too late in the day and beta-adrenergic blockers which may interfere with sleep.

Idiopathic Insomnia

Having ruled out the foregoing etiological factors that might contribute to the patient's insomnia, in many cases it may not be possible to determine any factors that can be held responsible for the patient's disturbed sleep.

NON-BZD DRUG TRIALS

Our research group of general practitioners has undertaken double-blind clinical studies on the effectiveness of two such drugs, namely zopiclone and zolpidem.

Zopiclone

This is a new cyclopyrrolone hypnotic, and was compared to temazepam in a double-blind cross-over trial, using the methodology already outlined [3]. Similar hypnotic effects were recorded with both drugs, sleep latency being more than halved in comparison to the control period with significant reductions in the number of times waking, and improvement in quality and duration of sleep. Daytime

side-effects were minimal with both drugs with no significant differences from the control period.

Zolpidem

This is an imadazopyridine compound, which binds to benzodiazepine receptors in the brain [1]. Following a 3-night control period, patients were randomly allocated to 3 weeks treatment with: (1) placebo, (2) zolpidem 10 mg or (3) zolpidem 20 mg, after which there was a further 7-day post-treatment control period. The patients completed questionnaires on awakening and at the end of the day after taking drug doses. On these questionnaires, sleep latency was significantly less in both zolpidem groups at all periods of the trial compared to placebo ($p > 0.05$) and the quality of sleep was significantly better at weeks 1 and 3 for the 20 mg dose of zolpidem and at week 3 for the 10 mg dose ($p < 0.05$). There were no significant between group differences in relation to any of the daytime measures assessed and there were no significant differences between pre- and post-control periods.

Somnographic Records

The mean somnograms, comparing the initial control period to the final 3-week treatment period, are shown in Fig. 1. The somnographic records confirmed the questionnaire results showing no significant effects from placebo, but significant reductions in latency and in number of times waking with both zolpidem doses, and significant increases in total hours of sleep and prolongation of time of final awakening with zolpidem 20 mg. The incidence of side-effects did not differ significantly with either zolpidem dose from placebo.

CONCLUSIONS

When treating insomnia in general practice, it is important to accurately define the nature and etiology of the sleep disorder. Although the present range of benzodiazepine hypnotics provides effective treatment for the different types of

insomnia, daytime after-effects and dependence problems warrant the search for new non-benzodiazepine drugs. However, it is of the utmost importance to assess such new com-

pounds in comparison to standard benzodiazepines in the setting in which they will be mainly used, namely general practice.

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