APPROACHES IN THE EVALUATION OF HYPNOTICS: STUDIES WITH TRIAZOLAM

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- 1 The evaluation of an hypnotic may be approached from the view that insomnia is a primary disease or the symptom of an underlying emotional or physical problem.
- 2 The two approaches have been used in the investigation of triazolam.

Introduction

THE evaluation of a new hypnotic may be approached from two views of insomnia. Many clinicians consider insomnia to be a primary disease, whereas others look at insomnia as the symptom of an underlying emotional or physical problem. In the first approach the effectiveness of the medication in the treatment of insomnia as a primary disease is evaluated. In this situation the study populations are relatively heterogeneous, and the circumstances closely resemble those found in clinical practice. In the second approach the drug is evaluated in treating insomnia as a symptom caused by, or at least associated with, a variety of specific diseases. It also evaluates the effect of the drug on that underlying disease, and in this approach homogeneous study populations may be selected.

The Diagnostic Classification of Sleep and Arousal Disorders (see *Sleep*, 2, 1-137, 1979) proposed by the Association of Sleep Disorders Centers and the Association for the Psychophysiology of Sleep, divides sleep disorders into four groupings. A significant percentage of patients fall into the first group, "Disorders of Initiating and Maintaining Sleep". These are the so-called insomnias. Many patients with this disorder show no clear physical or polysomnographic evidence of a sleep abnormality, yet complain of insomnia. The second group, "Disorders of Excessive Daytime Somnolence", in many cases simply reflects the daytime consequences of sleep deprivation caused by insomnia. In other instances the disorder is symptomatic of narcolepsy, idiopathic CNS hypersomnolence or Kleine-Levin syndrome. Menstrual associated hypersomnia also falls into this group. The "Disorders of Sleep-Wake Schedules" are most often caused by rapid time zone changes, shift work and non-24-hour sleep-wake schedules. The fourth group, the "Parasomnias", are characterized by sleep-walking, nightmares and enuresis.

Using the Diagnostic Classification of Sleep and Arousal Disorders offers three advantages in design-

ing clinical studies for treating insomnia. (1) Hypnotics may be used more appropriately, because (2) the underlying etiologic problem may be more carefully defined, and (3) the use of a drug may be avoided in treating sleep disorders for which it is contraindicated. In the evaluation of triazolam, both the "primary disease" and the "symptom" approaches were used in Phase III studies. Phase I pharmacokinetic studies established that the compound was rapidly absorbed and eliminated, and so suitable as an hypnotic (Eberts, Philopoulos & Vliek, 1979; Adams, Rykert & Bombardt, 1980). Phase I and II safety and tolerance studies revealed no evidence of toxicity or tolerance development in single-dose, short-term and chronic treatment in daily doses up to 1 mg (Elliott, Navarro, Kokka & Nomof, 1975; Knapp, Remen, Linsenmeyer & Boyd, 1977). Later studies confirmed that there was little or no tolerance development or withdrawal effect (Kales, Kales, Bixler, Scharf & Rossek, 1976; Nakazawa, Vmajima, Hazama, Komuku, Vmezawa & Akamatsu, 1977; Roth, Kramer & Schwartz, 1974; Roth, Kramer & Lutz, 1976; Vogel, Barker, Gibbons & Thurmond, 1976; Vogel, Thurmond, Gibbons, Edwards, Sloan & Sexton, 1975), although possible tolerance development or a withdrawal effect was seen in one study (Kales, Scharf & Kales, 1978).

Insomnia as a primary disease

Initial Phase III studies assessed the overall effectiveness of triazolam compared with flurazepam and placebo in the treatment of insomnia as a primary disease. Multiple-day crossover studies and randomized group comparative studies against placebo or flurazepam, ranged from 14-91 d in length (Wang & Stockdale, 1973; Rickles, 1975; Weintraub, Sundaresan, Wardell & Lasagna, 1976; Chatwin & Johns, 1977; Deleuse, Mahieu & Raes, 1977; Fabre, Gross,

Pasigajen & Metzler, 1977; Liebowitz & Sunshine, 1978), and these studies established the safety and efficacy of triazolam in short, intermediate and long-term use. Although results varied somewhat over the 39 studies the conclusions reached were similar. Triazolam was superior to placebo on sleep parameters, including total sleep time, sleep onset, nocturnal awakenings, quality of sleep, and most importantly, on the patient's feeling of well-being the next day. The methodology used in these studies was sensitive not only to differentiating between an active hypnotic and placebo but also between two active hypnotics, and in these studies triazolam frequently seemed more effective than flurazepam, though flurazepam did not appear superior to triazolam.

The preference technique (Jick, Sloane, Dinan & Mvinch, 1966; Jick, 1975) is one of the most sensitive and effective methods for evaluating the short-term efficacy of hypnotics. Using this technique dose-response can be established, hypnotics can be compared at specific doses, or an hypnotic can be compared with placebo. All compounds are identically packaged, and patients are assigned, in randomized fashion, to a treatment sequence. One compound is administered the first night and the other is administered the second night. On the morning after the second night, patients are asked which medication gave them the best night's sleep. They are also asked questions pertaining to sleep onset, sleep duration, number of nocturnal awakenings, feeling in the morning, and side-effects.

Although the preference technique is both sensitive and effective, its validity has been criticized for two reasons. The lack of a washout period between the two nights ignores possible carry-over effects of certain medications; and secondly, a single night of drug administration is not adequate to evaluate efficacy, tolerance development or side-effects. Although these points are important in the overall evaluation of an hypnotic, they do not invalidate the results obtained using the preference technique because, although carry-over effects might show up in a consistent preference for the drug administered the second night, a preference for night 2 occurred rarely in the triazolam studies, and the use of hypnotics is generally short term with only a small percentage of patients using these drugs chronically. Thus the single-dose preference technique is important in that it evaluates efficacy after the first dose, establishes relative efficacy of a new drug compared with a standard, and highlights overt side-effects such as hang-over and impaired performance. Subtle side-effects can only be identified in more chronic regimens.

Double-blind studies with the preference technique showed that triazolam was preferred over flurazepam (Kripke & Grant, 1974), secobarbital (Okawa & Allen, 1978), chloral hydrate, methypylon (Linnet & Anglin, 1975) and placebo. The preference technique

was sensitive enough to show that triazolam was significantly better than these compounds in shortening the onset of sleep, reducing the number of nocturnal awakenings, and increasing total sleep time. Triazolam was administered in doses ranging from 0.1–0.6 mg with the majority of patients receiving 0.5 mg. Forty-two studies compared triazolam with placebo. Of the 541 patients in these studies, 480 preferred triazolam and 61 preferred placebo. In terms of sleep latency, total sleep time, number of nocturnal awakenings, and feeling of alertness in the morning, triazolam was more effective than placebo, and the occurrence of side-effects was similar in both groups.

Another example of a study using the preference technique in which triazolam 0.5 mg was compared with chlordiazepoxide 25 mg is given. Before taking the drugs, patients had significant impairment of sleep as noted by a mean sleep latency of 92 min, mean total sleep time of 5.3 h, and a mean of 2.5 awakenings during the night. During the night of chlordiazepoxide therapy, whether the first or second night, little improvement was seen. Mean sleep latency was 89 min, mean total sleep time was 6.1 h, and mean number of awakenings during the night was 2.2. However, during the one night of triazolam therapy, again whether the first or second night, mean sleep latency decreased to 28 min, mean total sleep time increased to 8.1 h, and mean number of awakenings decreased to less than 1. Of the 42 patients in this study, 34 patients preferred triazolam, two preferred chlordiazepoxide, and six had no preference. Sleep quality was also evaluated subjectively using a seven-point scale ranging from worst sleep to best sleep the patient ever had. Thirty-two patients rated their sleep as either much better, very much better, or best with triazolam. Only two patients made such ratings with chlordiazepoxide.

Similar results were seen when triazolam 0.25 mg was compared with flurazepam 15 mg. However, when triazolam 0.25 mg was compared with flurazepam 30 mg, no differences were detected. Triazolam 0.5 mg was more effective than flurazepam 30 mg, secobarbital sodium 100 mg, chloral hydrate 500 mg, diazepam 10 mg, and methypylon 300 mg.

Insomnia as a symptom

In using the second approach, disorders of initiating and maintaining sleep were considered. Among the patients were presurgical and other hospitalized patients, psychiatric patients with anxiety, depression and other disorders, and alcoholic patients.

Presurgical patients

In hospitals, hypnotics are used widely the night be-

fore surgery to allay anxiety and apprehension, although most of these patients do not have insomnia in their normal settings. Studies involving 352 patients compared triazolam with flurazepam, pentobarbital and placebo. Triazolam proved to be effective in reducing and maintaining sleep. Few side-effects occurred (Matta, Franco & LeZotte, 1974; Knapp, Bond, Linsenmeyer & Linet, 1978).

Hospitalized patients with a variety of medical illnesses

The hospital setting is ideal for the multiple-night crossover design. This model allows for the determination of dose-response curves and potency ratios, as two or three different doses of the same compound can be tested in the same patient. In addition, the hospital setting allows sleep evaluations by an observer as well as subjective assessments by the patient. Observations on drug safety and tolerance are also possible.

Three hundred and sixteen patients were evaluated in ten multiple-night crossover studies in which triazolam was compared with flurazepam, diazepam, chloral hydrate, methaqualone, pentobarbital and placebo in patients who were hospitalized for a variety of medical illnesses (Sunshine, 1975; Boyd, Knapp, Remen & Linet, 1976). In all the studies triazolam was found to be better than placebo in helping the patients sleep, decreasing sleep onset, increasing sleep duration, decreasing the number of nocturnal awakenings, and improving the quality of sleep. In addition, triazolam did not produce more hangover effect than did placebo. Compared with the standard agents, triazolam was more effective on most parameters.

Geriatric patients

Geriatric patients consume 25% of all hypnotics prescribed, and so evaluation of any new hypnotic should include studies of safety and efficacy in this population. Twelve studies of various designs showed triazolam (0.25 and 0.5 mg) to be an effective, safe, well-tolerated hypnotic for the geriatric patient. No signs of adverse effects were seen in laboratory test results, electrocardiograms or physical examinations, and there was no evidence of tolerance (Roth *et al.*, 1976; Reeves, 1977; Okawa, 1978).

Patients with anxiety, depression, or other psychiatric disorders

Insomnia is one of the prominent symptoms of patients suffering from emotional or psychiatric disorders. Generally, these patients are treated with a daily regimen of psycho-active drugs, the largest dose given at bedtime to relieve insomnia. In many cases, however, the patient's insomnia seems to be refrac-

tory to the medication, and triazolam was evaluated in such patients.

In anxious patients with insomnia, triazolam's effect was compared with that of placebo and diazepam. In doses of 0.25 and 0.5 mg daily, triazolam was significantly more effective than placebo in relieving the patient's insomnia as well as their anxiety symptoms (Fabre & Smith, 1977; Fabre, McLendon & Purpura, 1978). Insomnia in depressed patients was successfully treated by triazolam in a comparison with secobarbital (Rickles, Gingrich, Morris, Rosenfeld, Perloff, Clark & Schilling, 1975). The latter was a 1-week crossover study of triazolam 0.5 mg, secobarbital 100 mg and placebo. The 100 family-practice outpatients had insomnia and scores on the Hopkins Symptom Checklist indicating more emotional distress than "normal" gynaecological or obese patients but less distress than anxious outpatients. Mean total Hopkins Symptom Checklist scores were 1.78 before medication, 1.50 after triazolam, 1.68 after secobarbital and 1.57 after placebo. Triazolam was particularly effective in alleviating emotional distress in patients who were initially more symptomatic. Further analysis of pre- and post-study data from the Hopkins Symptom Checklist showed that triazolam exerted the greatest hypnotic effect on high-depressed patients and secobarbital was most effective in low-depressed patients.

Sleep laboratory and performance studies

Whether a clinical study follows the "primary disease" approach or the "symptom" approach to insomnia, objective evaluation of the medication is an essential part of the research program. The all-night polysomnograph allows measurement of the effect of the hypnotic on sleep parameters which can be correlated with subjective assessments of the patient's sleep.

Twelve studies involving all-night electroencephalographic recordings were carried out with triazolam. In these studies 0.1–1 mg was administered for periods ranging from 1–21 nights. Measurements indicated that triazolam (0.25–1 mg) induced sleep more rapidly than did placebo, and decreased the number of nocturnal awakenings. Triazolam 0.5 mg had minimal effects on REM sleep, whereas 1 mg reduced REM sleep in one study. There was no REM rebound or increase in stage REM on withdrawal or recovery nights. No side-effects or toxic effects were noted.

Improvement in sleep is an important consideration in the evaluation of any hypnotic, and it is generally agreed that over the short term most hypnotics will improve sleep. However, of primary importance is how the patients feel during the day. This is particularly true of the patient who complains of

insomnia when there is no evidence of a sleep disorder. Important questions include: "Is the patient able to perform effectively?" "Is the patient more alert?" and "Is the patient less sleepy during the day?" To address these questions, triazolam 0.25 and 0.5 mg was compared with flurazepam 15 and 30 mg, secobarbital 100 mg and flunitrazepam 0.25 and 0.5 mg in their effects on performance and cognitive ability. The overall results of performance studies (Roth, Kramer & Lutz, 1977; Nicholson & Stone, 1980) showed that all the compounds improved sleep efficiency, although placebo produced the worst sleep efficiency. A dose-response relationship for triazolam, flurazepam and flunitrazepam was observed with the higher dose of both hypnotics showing better sleep efficiency on all measures than the corresponding lower dose of the three compounds. The performance results indicated that hypnotics, in general, produced decrements in performance 3.5 h after drug ingestion. At 10–11.5 h after ingestion triazolam and flunitrazepam produced performance equal to or better than baseline performance, whereas the effect of flurazepam persisted. Subjective ratings of performance paralleled these results. A study of the effect of triazolam 0.25, 0.5 and 1.0 mg upon mood revealed no pre-sleep or post-sleep effect on mood (Schwartz, Kramer & Roth, 1974).

Adverse effects

In the evaluation of any compound, benefit-to-risk ratio must be taken into consideration. Adverse

effects from all clinical trials were tabulated for triazolam, flurazepam, other standard hypnotics, and placebo (Internal Report, The Upjohn Company). As the numbers are not sufficiently large to be of value for each standard hypnotic, tabulations are presented only for triazolam, flurazepam and placebo, and involved 5,397 triazolam patients, 1,471 flurazepam patients, and over 2,362 placebo patients. The most prominent adverse effects observed with triazolam were drowsiness, dizziness, ataxia and headaches, all of which seemed to be extensions of the pharmacological activity of the drug. The incidence of these particular effects was higher with triazolam than with placebo but lower, with the exception of dizziness, than with flurazepam. With regard to other adverse effects, few differences were seen between triazolam and placebo (Table 1). The incidence of adverse effects was extremely low (0.001–0.01%).

Conclusions

Clinical evaluation of a new hypnotic may be based on the assumption that insomnia is a primary disease, or that a sleep disorder is a symptom of an underlying disease or other circumstances. In a substantial number of clinical situations, insomnia is treated as a primary disease, so it is essential to know whether or not a new sleep medication is suitable for patients loosely defined as insomniacs. The triazolam studies in heterogeneous groups of patients with sleep problems indicate that the compound is safe and effective.

Table 1 Statistical evaluation of side-effect incidence

<i>Side-effect</i>	<i>Triazolam compared with flurazepam</i>	<i>Triazolam compared with placebo</i>	<i>Flurazepam compared with placebo</i>
Drowsiness	<(0.001) (T)	<(0.001) (P)	<(0.001) (P)
Dizziness	0.561	<(0.001) (P)	(0.001) (P)
Ataxia	(0.054) (T)	(0.003) (P)	<(0.001) (P)
Headache	0.242	(0.045) (P)	(0.009) (P)
Cramps pain	(0.038) (T)	≥ 0.999	0.119
Dry mouth	0.098	0.409	0.478
Nightmares	(0.016) (T)	(0.061) (T)	0.646
Speaking disturbance	0.264	0.234	≥ 0.999
Depression	<(0.001) (T)	0.413	(0.007) (P)
Hallucination	0.647	0.195	0.147
Confusion	(0.014) (T)	(0.034) (T)	0.669
Anoerxia	0.294	0.506	0.798
Disorientation	≥ 0.999	0.195	0.384
Nervousness	0.084	0.188	0.665
Memory defect	≥ 0.999	0.524	0.758
Concentration difficulty	(0.009) (T)	0.189	0.277
Paresthesia	0.481	0.772	0.417

Significant values are in parentheses ($P < 0.05$). The initial of the drug having significantly less side-effects is in parentheses.

Where insomnia is recognized as a symptomatic of underlying medical illness or mental state, hypnotics can be tested in special populations. With this approach triazolam was tested in presurgical and other hospitalized patients, geriatric patients, psychiatric patients with anxiety, depression and other psychiatric disorders, and alcoholic patients. It proved efficacious in all of these groups. Focussing on a homogeneous study population can yield additional information, as in the triazolam study of depressed patients. The new medication improved depression in addition to relieving insomnia.

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