Br. J. clin. Pharmac. (1984), 83S–86S

Ambulatory motor activity monitoring to study the timecourse of hypnotic action

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1 A solid state activity monitor worn on the wrist was used to study the effect of flunitrazepam, flurazepam, temazepam, triazolam and midazolam.
2 All compounds reduced motor activity in the first half, but only flunitrazepam and flurazepam had an effect during the second half of the bed rest period.
3 Ambulatory activity monitoring is an unobtrusive and simple method for investigating timecourse of action.

Keywords hypnotics ambulatory motor activity

Introduction

Night-time motor activity has been previously used to assess the effects of hypnotics on sleep (e.g. Hinton, 1961; Oswald *et al.*, 1963). Recent progress in electronics has made it possible to develop a solid-state activity monitoring device which is sufficiently small and unobtrusive to be worn on the wrist. This allows us to obtain a quantitative measure of motor activity during sleep under home conditions as well as in the sleep laboratory. Here we present results to show that the method is useful for estimating the timecourse of the hypnotic effect of various compounds.

Methods

The data shown in Figure 3 were obtained in three separate studies from which other results have been already published (flunitrazepam (Rohypnol) and flurazepam (Dalmadorm) (Borbély *et al.*, 1983a); triazolam (Halcion) and midazolam (Dormicum) (Borbély *et al.*, 1983a); temazepam (Planum) (Borbély *et al.*, 1984). The reader is referred to these papers for details. In short, the subjects of each study were paid young adults who did not report any sleep disturbance and who gave informed consent to the project. The drug or placebo was administered 30 min before bedtime in a double-blind crossover design. At least 1 week elapsed between drug nights. One of the studies (Borbély *et al.*, 1983b) was performed in the sleep laboratory, the other two with the subjects sleeping at home.

Motor activity was recorded by an unobtusive, wrist-worn, solid state activity monitor (Borbély *et al.*, 1981). Its dimensions are 30 × 51 × 17 mm, its weight 87 g, and power is supplied by four 1.4 V batteries. The block diagram is shown in Figure 1. Accelerations are recorded by a piezoelectric transducer whose amplified output signal triggers a pulse whenever it exceeds a preset threshold (corresponding to an acceleration of 0.1 g in the sensitive direction). The pulses are computed over a time interval of 7.5 min and the total count is stored as an 8-bit word in a 1-K memory. After the experiment the data are read out into a computer.

The time of sleep onset in the evening, and of awakening in the morning was estimated from the subjects' protocol as well as from the activity record. The number of 7.5-min periods

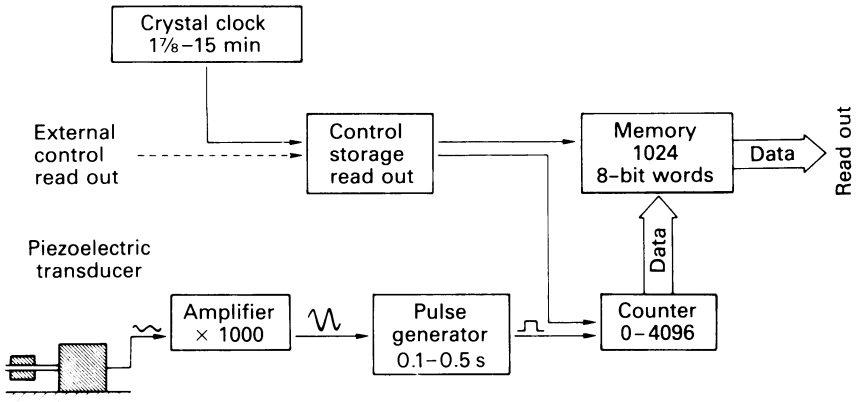

Figure 1 Block diagram of the activity monitor.

with any movement (activity count > 0) was determined separately for the first and second half of the sleep period and served as a measure of night-time motor activity. For each subject the value for the drug night was expressed relative to the value of the placebo night. The Wilcoxon matched pairs, signed rank test (2-sided) or the Duncan test (2-sided) served to determine whether the differences were statistically significant.

Results and Discussion

Figure 2 illustrates the effect of placbeo and temazepam (30 mg) on night-time motor activity. The waking period before and after bedtime is indicated by horizontal bars above the records. Waking activity usually exceeded 30 counts which was selected as the upper limit of the activity plots. The vertical bars at night indicate the activity level during sleep (i.e. arm

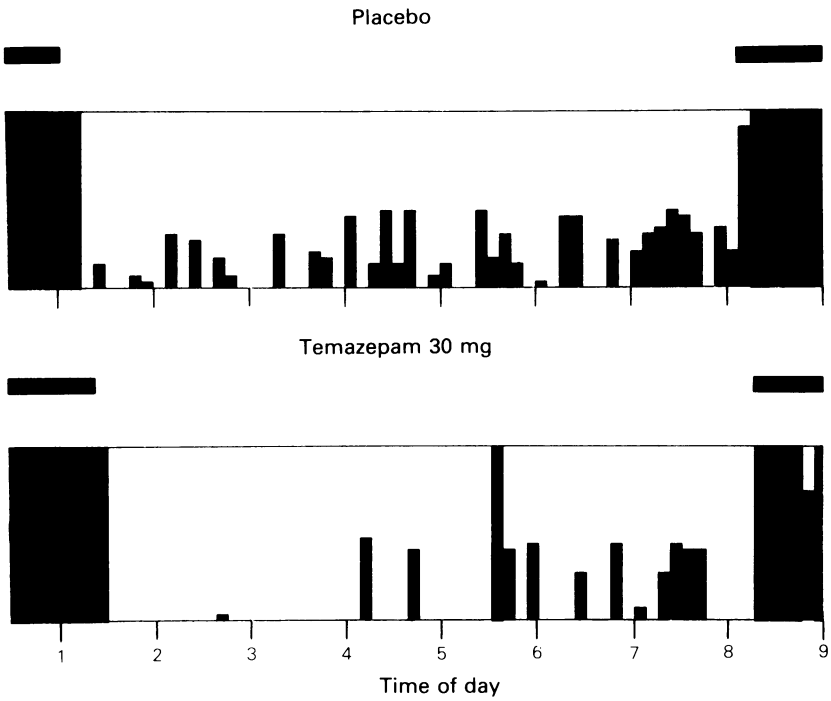

Figure 2 Night-time motor activity of a subject after placebo and temazepam 30 mg. Activity is plotted as counts per 7.5-min period, the top line corresponding to 30 counts. Waking activity before and after bedtime periods is indicated by horizontal bars above the records (modified from Borbély *et al.*, 1984).

or body movements) for consecutive 7.5-min periods. It is evident that night-time motor activity is markedly reduced after temazepam. Particularly in the first hours after drug intake, long periods of immobility were present.

Figure 3 shows the effects of various hypnotics on motor activity in the first and second half of the sleep period. The values have been expressed as differences from the respective placebo values. It should be noted that in the placebo night the mean number of activity periods was higher in the second half of the sleep period than in the first half (e.g. for triazolam and midazolam: 55.0% *vs* 46.7% of all 7.5-min periods during sleep). It is evident from Figure 3 that flunitrazepam and flurazepam caused a marked reduction of night-time activity periods throughout the night, whereas the effect of the other hypnotics was restricted to the first half of the sleep period. Thus in the second half of the night, activity was only little below the placebo level for triazolam, and even somewhat above the placebo level for midazolam.

There appears to be a good correlation between the pharmacokinetics of the various benzodiazepines and the duration of their activity reducing action. Hypnotics with a long elimination half-life (i.e. flunitrazepam and flurazepam) induced a long-lasting reduction of motor activity, whereas compounds with a short half-life (triazolam and midazolam; see Breimer & Jochemsen, 1981; Greenblatt *et al.*, 1981) had only a short-lasting effect. Dettli (1983) has recently pointed out that the elimination half-life cannot be regarded as a valid classification criterion for separating long-acting and short-acting hypnotics, since the duration of action may be influenced also by several other parameters (e.g. the absorption and distribution rate). In view of the complexities of pharmacokinetics, it would be desirable to have a reliable and easily measurable indicator for the duration of action of hypnotics. The present study indicates that night-time activity might be a good candidate.

This study was supported by the Swiss National Science Foundation, grant number 3.171-0.81.

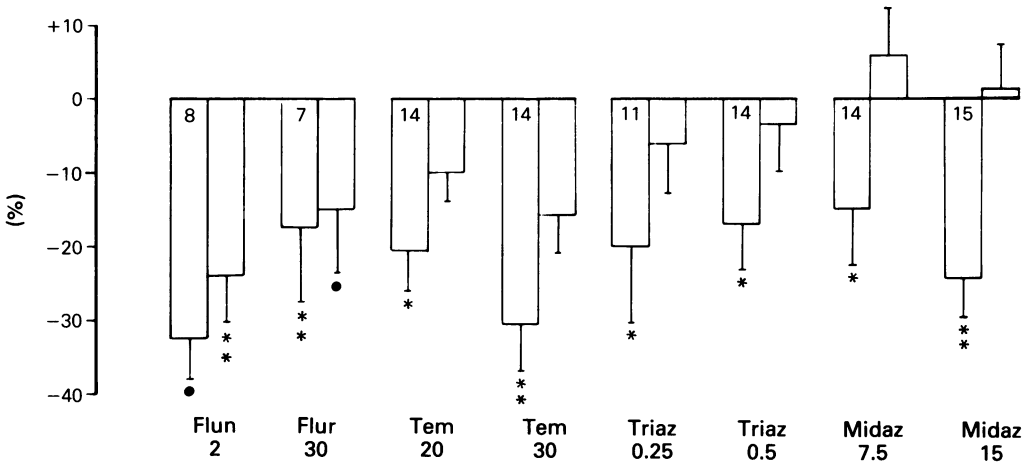

Figure 3 Motor activity in the first (left bar) and second half of sleep (right bar of each pair) after flunitrazepam (2 mg), flurazepam (30 mg), temazepam (20 and 30 mg), triazolam (0.25 and 0.5 mg) and midazolam (7.5 and 15 mg). The bars represent mean values (s.e. mean and the number of subjects are indicated) which are expressed as the percentage of the placebo value (= 100%). • $P < 0.1$; * $P < 0.05$; ** $P < 0.01$.

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