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Variability of Response to Hypnotics: Sleep Studies in Man

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COCHRANE, L. A., A. N. NICHOLSON AND B. M. STONE. *Variability of response to hypnotics: Sleep studies in man.* PHARMACOL BIOCHEM BEHAV **18**(2) 307–310, 1983.—Effect of diazepam on sleep in man was investigated in a series of placebo controlled studies and the data on various measures from two groups (young adults and middle age) were retrospectively analysed. Variability of the measures between the two groups with placebo was not different, but the variability of their response to the drug was different, and that of the middle aged group was high. In the young adults there were drug effects, but in the middle aged group no drug effects could be established. The studies suggest that variability of data must be taken into consideration when it is used to indicate the most appropriate dose range. If the variability of response is low the data may indicate the likely effect of the drug on each individual. On the other hand if the variability is high then data obtained from analysis of the group may have limited relevance, and suggest doses which are too high for the majority of the individuals within that group.

Drug response Variability Sleep Young adults Middle age Diazepam

THE efficacy of hypnotics is usually investigated during their development by trials which involve a relatively small number of subjects. This is inevitable when one considers the logistic problems involved with sleep laboratory studies, but raises questions concerning the value of such information in the clinical use of the drug. In particular, variability of the data may be interpreted as a statistical phenomenon, though equally it may be due to different thresholds of response to a drug. In this way variability may influence the dose required to produce a significant effect, and preoccupation with statistical significance may lead to unnecessarily high doses in some, if not many, individuals. It is in this context that we have brought together information on the effects of diazepam on sleep in young adults and middle-aged individuals obtained from several of our studies over the period 1976–1980 [1–5]. The influence of variability on the apparent drug effect indicated by analysis of two different age groups has been examined.

METHOD

The effect of diazepam on sleep in man was investigated in a series of placebo controlled studies. The subjects were healthy males familiar with sleep recording techniques. They were aged between 18 and 30 years and between 42 and 55 years. They were required to refrain from napping and undue exercise, and to abstain from alcohol during the day preceding the experimental night. Subjects reported 1.5 hr before bedtime. Their individual rooms were light-proofed, sound-attenuated and temperature (18±1°C) and humidity (55±1%) controlled. In an adjoining room three channels of electroencephalographic activity were recorded (C4-A1, P1-T5 and OzPz-03) together with the electromyogram and the electro-oculogram. Each sleep record was scored independently into 30 sec epochs by two analysts according to accepted criteria [6]. Differences in the annotation of sleep stages between the scorers were resolved, but did not occur in more than 4% of the epochs.

Data were obtained on various measures of sleep, but in this paper only four measures have been examined. They are the total amount of awake activity and drowsy (Stage 1) sleep, the total amount of stages 2, 3 and 4 (non-rapid eye movement sleep) and the total amount of rapid eye movement sleep—each within the first 6 hr of sleep, together with the latency to the first period of rapid eye movement sleep. The last measure was included as it appeared that some delay to the first period of rapid eye movement sleep had occurred in most studies.

Each of the 12 subjects in the young adult group ingested 10 mg diazepam, and 4 of these took part in two trials and 1 in 3 trials [1, 3–5]. The group of middle-aged subjects comprised 9 individuals (some of whom were tested in trial 1 and some in trial 2) and each ingested 5 and 10 mg diazepam [2,4]. The data of the two age groups were analysed separately, and in each group that relating to each trial were combined. The variability of the four sleep measures was analysed, using least squares methods to estimate terms in the general linear model. Subjects were treated as a random effect while factors representing trial and drug level were fixed. Trial, drug and subject effects were examined, as well

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TABLE 1

ANALYSIS OF VARIANCE FOR EFFECT OF DIAZEPAM (10 mg) ON VARIOUS SLEEP MEASURES (YOUNG ADULTS)

Source	Degrees of Freedom	Mean Squares	F	Significance Level
Awake Activity & Drowsy (Stage 1) Sleep				
Trial (T)	2	24.38		
Subject (S)	11	97.10		
T × S	4	36.82		
Drug (D)	1	55.5	29.02	$p<0.001$
D × T	2	5.565		
D × S	11	25.07	29.48 (pooled)	
D × T × S	4	41.59		
Non-REM Sleep				
Trial (T)	2	119.0		
Subject (S)	11	428.9		
T × S	4	95.05		
Drug (D)	1	1590	24.30	$p<0.001$
D × T	2	6.640		
D × S	11	31.78	65.42 (pooled)	
D × T × S	4	158.0		
REM Sleep				
Trial (T)	2	57.25		
Subject (S)	11	315.2		
T × S	4	85.20		
Drug (D)	1	137.5		
D × T	2	3.920		
D × S	11	45.88	97.61 (pooled)	
D × T × S	4	239.9		
Latency to REM Sleep				
Trial (T)	2	655.0		
Subject (S)	11	1393		
T × S	4	764.0		
Drug (D)	1	6340	7.34	$p<0.051$
D × T	2	649.5		
D × S	11	1009	863.5 (pooled)	
D × T × S	4	463.5		

as their interactions. The data for the young subjects were analysed by an incomplete blocks design analysis of variance, and that for the middle aged group by a nested design.

RESULTS

Young Adults

There were repeat data with placebo in all subjects. With each of the four measures there was consistency between the placebo nights, and there were no differences related to trial or to subject. There was a drug effect with awake activity and drowsy sleep ($p<0.001$), non-rapid eye movement sleep ($p<0.001$) and latency to the first period of rapid eye movement sleep ($p<0.05$). There was no effect of the drug on the duration of rapid eye movement sleep (Table 1).

In the analyses of non-rapid eye movement and rapid eye movement sleep the D × S interaction was small ($p<0.05$) when tested against the T × D × S term. There was no obvious explanation for this finding. However the test was made, there was no evidence to suggest an effect of diazepam on rapid eye movement sleep.

The effect on non-rapid eye movement sleep was tested against a pooled D × S, T × D × S term, and if the test was made against T × D × S alone an effect could still be established ($p<0.05$). This was supported by the sign test which made no assumptions about subject and drug effects ($p<0.001$).

Middle Age

There was a subject within trials effect ($p<0.05$) for the duration of rapid eye movement sleep, but no drug effect was established with this measure. With the other three measures there were also no drug effects (Table 2).

The variability of the measures obtained with placebo was not different between the young adults and the middle aged group, but the variability of their response to the drug with respect to awake and drowsy sleep and non-rapid eye movement sleep was different ($p<0.05$).

DISCUSSION

The studies in young adults revealed that subject varia-

TABLE 2

ANALYSIS OF VARIANCE FOR EFFECT OF DIAZEPAM (5 AND 10 mg) ON VARIOUS SLEEP MEASURES (MIDDLE AGE)

Source	*df*	Mean Squares	F	Significance Level
Awake Activity and Drowsy (Stage 1) Sleep				
Trial (T)	1	860.0		
Subject (S(T))	7	230.7		
Drug (D)	2	347.8		
D × T	2	285.9		
D × S (T)	14	165.7		
Non-REM Sleep				
Trial (T)	1	322.7		
Subject (S(T))	7	808.4		
Drug (D)	2	39.87		
D × T	2	209.7		
D × S (T)	14	507.8		
REM Sleep				
Trial (T)	1	1451		
Subject (S(T))	7	1188	3.93	$p<0.05$
Drug (D)	2	114.5		
D × T	2	245.5		
D × S (T)	14	303.3		
Latency to REM Sleep				
Trial (T)	1	422.2		
Subject (S(T))	7	2050		
Drug (D)	2	626.7		
D × T	2	543.4		
D × S (T)	14	1113		

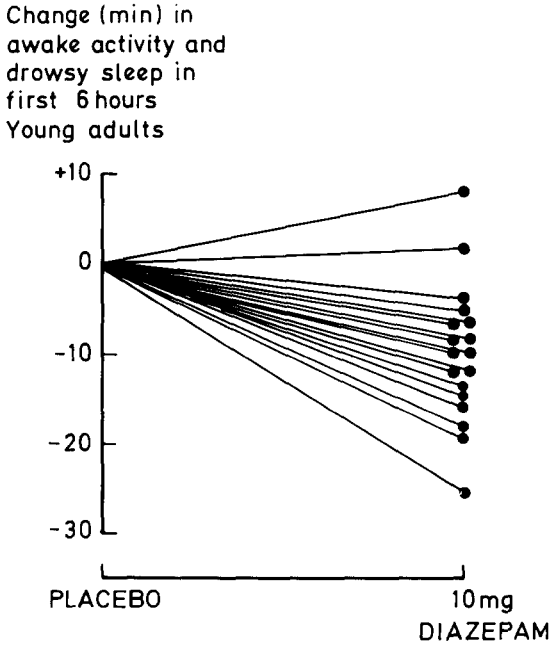

FIG. 1. Effect of 10 mg diazepam on change in duration (min) of awake activity and drowsy sleep during the first 6 hours of sleep in young adults.

bility with regard to the four measures of sleep was not an important factor. A drug effect was established across the subjects as a group in three out of the four measures, and the individuals tended to respond in the same way (Fig. 1). The three measures in which an effect was established were important indicants of the efficacy of the drug as an hypnotic. Diazepam reduced wakefulness and drowsiness, and increased non-rapid eye movement sleep, and though it delayed the onset of the first period of rapid eye movement sleep this was without reduction in the amount over the first 6 hr. As the same trend of response was seen between subjects, it would suggest that experiments with groups with low variability of response to the drugs are likely to predict the effect of the drug on the individuals of that group.

However the consistency seen in the young adults was not present in the data from the middle-aged. A dose related effect could not be established over the subjects as a group, and the response of individuals was variable (Fig. 2). This would suggest that trials on groups with high variability, such as the present study with middle-aged subjects, are unlikely to predict the effect of a drug on the individuals or the way in which they are likely to respond over a dose range. A statistically significant response is likely to require a dose level far too high for many individuals, if not the majority, of the group.

These studies suggest that variability of the data must be taken into consideration when the data are used to indicate the most appropriate dose range. If the variability of the

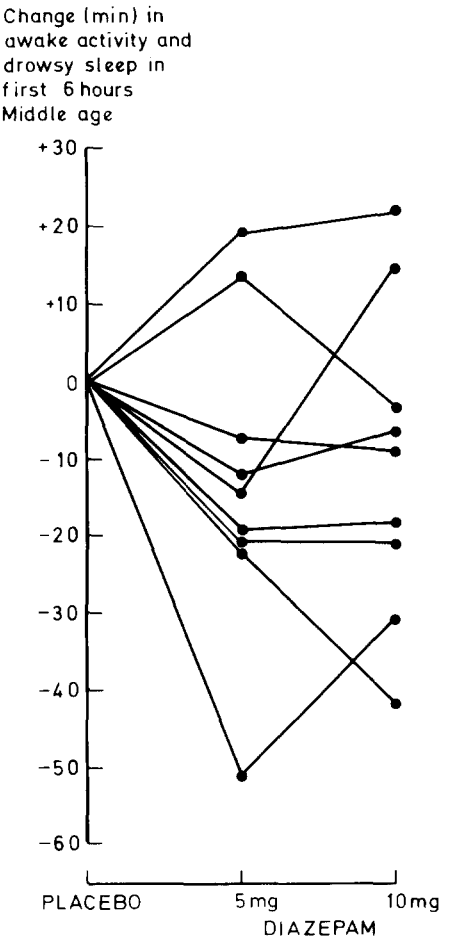

FIG. 2. Effect of 5 and 10 mg diazepam on change in duration (min) of awake activity and drowsy sleep during the first 6 hours of sleep in middle aged subjects.

response to the drug of the group is low, then the data may be taken to indicate the likely effect of the drug on each individual. On the other hand if the variability of response is high then data obtained from analysis of the group may have limited relevance. This conclusion has been drawn from studies in healthy individuals under carefully controlled experimental conditions, and so it is likely to be even more relevant in studies where there is less ability to control the circumstances. In this way, studies with patients may suggest doses of drugs which are too high for the majority, and it is essential that such studies should take into consideration results obtained from investigations which can be more carefully controlled.

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