CONSIDERATIONS OF DOSE-RESPONSE WITH CENTRALLY-ACTING DRUGS

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Dose-response studies on the effects of drugs in man are important to a clear understanding of their activity. Such studies not only provide accurate information on the most appropriate dose range of a drug, but may also suggest the dose relations of potentially adverse effects. Adequate dose-response data are essential in deciding therapeutic dose ranges but, unfortunately, such studies in man are usually limited. Information on the nature, or even presence, of a relationship is frequently not sought, and in much published work related to clinical assessment it is difficult to be certain whether activity is related to dose, and the limits of the response are often not defined.

This situation certainly applies to centrally-acting drugs, and it is in the context of the importance of such relations that we look at the issues encountered in deciding the appropriate dose range for hypnotics. Indeed, at least until recently, the introduction of hypnotics into clinical practice has been characterised by adverse effects and these have been, undoubtedly, related to the prescription of unnecessarily high doses. With several hypnotics the dose range recommended initially has had to be markedly reduced, and there are examples of hypnotics in which the dose recommended in one country has been decreased by a factor of four, or even more, when introduced later elsewhere.

In this paper we will examine approaches to studies on sleep carried out to determine the effective dose range of hypnotics. In each study considered the design was essentially the same. Subjects were familiar with the laboratory and recording techniques, and were required to avoid napping and undue exercise and to abstain from alcohol and caffeine on the day before each sleep recording. They reported to the laboratory at weekly intervals, and medication was taken at "lights out" prior to the electroencephalographic recording of sleep. Each experiment included two placebos, and treatments were arranged in a pseudo-random order. Medications were identical in appearance and studies were double-blind.

DOSE-RESPONSE CURVES

In the early evaluation of the sedative activity of a non-benzodiazepine hypnotic (1) six healthy adults aged between 21 and 33 years were studied. Each subject received four doses of hypnotic (2.5, 5.0, 7.5 and 10mg) and on two other occasions placebos. The electroencephalographic data were analysed

initially by analysis of variance (ANOVA). If the F ratio for the five treatments (four doses and mean placebo) was significant ($p < 0.05$), a test was made for a linear trend with dose. In addition, the individual dose means were compared with mean placebo using the multiple comparison method of Dunnett (2).

Various sleep measures were obtained from the electroencephalographic recordings but, for the purpose of the present paper in which dose-response is of particular concern, the duration of non-rapid eye movement (NREM) sleep, i.e. stages 2, 3 and 4, during the first 6h of sleep will be considered, although other measures may be equally relevant to the assessment of the efficacy of an hypnotic. NREM sleep increased with 7.5 and 10.0mg compared with placebo ($p < 0.01$), but no significant effect was detected with 2.5mg and 5.0mg (Table I).

TABLE I

Effect of zopiclone on the duration (min) of non-rapid eye movement sleep (stages 2, 3 and 4) in the first 6h of sleep.

	Placebo	Zopiclone (mg) 2.5	5.0	7.5	10.0
Young Adults (n = 6)	258.8	262.7	269.6	278.8 **	282.4 **
Middle Age (n = 6)	241.8	-	264.4 *	277.9 **	282.8 **
All Subjects (n = 12)	250.3	-	267.0 *	278.4 **	282.6 **

Significance levels: * $p < 0.05$; ** $p < 0.01$.

The effect was linear ($p < 0.05$) over the dose range, though a sigmoid relationship between NREM sleep and dose was suggested by a continuous line through the individual means (Fig. 1), and this was also a reasonable form for the dose-response. Although other types of curve would have been statistically compatible with the data, many of these did not represent a likely dose-response relationship.

However, although the implications of the form of the two most reasonable curves, sigmoid and linear, in the interpretation of the data scarcely mattered over the lower and middle of the dose range studied, to be certain of the response at a higher dose it would have been necessary to establish whether the effect was approaching a plateau around the two highest doses. To

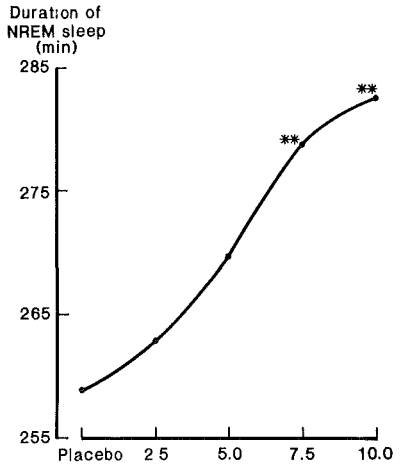

Fig. 1. Duration of non-rapid eye movement (NREM) sleep (min) related to dose (mg) of a hypnotic.

differentiate between the sigmoid curve and a purely linear relationship using these five treatments, the number of subjects in the study would need to have been increased from 6 to over 130. Alternatively, a study could have been carried out using higher doses where there is a greater difference between the two curves. Such studies may also have provided information on possible adverse effects with the use of high doses. However, whatever the approach, the experimental work would have been considerable, involving repeated observations, a revised dose range, or a considerable number of subjects.

COMPARISONS WITH PLACEBO

It is the practical implications of carrying out adequate dose-response studies, particularly at the clinical stage, that has probably led to the widespread use of comparisons with placebo of a few doses - usually two or, rarely, three - to analyse and interpret data from human studies. However, in the above study, doses of 7.5 and 10.0mg increased NREM sleep compared with placebo, but no effect was established with 2.5 and 5.0mg. Even though the mean response to the lower doses was not significant, there could have been an acceptable response in some individuals, and inspection of the data suggested that some subjects responded adequately to 5.0mg or less. Of course, the experiment was not designed to assess individual response, and the observations in some

subjects at low doses may have been part of the inherent variability of the data, and would have required confirmation by another study.

However, if it can be assumed that the relationship has a simple form, it is possible to examine dose-responses using regression techniques. In the above study, a linear function provided a reasonable fit for individual subjects as well as for the mean relationship, and so individual dose-response could be estimated by linear regression analysis. Using a group of 12 subjects, which included those above, this analysis emphasised the wide range of response to the drug (Fig. 2). One subject apparently failed to respond to the 10mg dose, whereas in the most sensitive subject the increase in NREM sleep given by the regression line was over 70 minutes at this dose. Further, the analysis with an increased number of subjects showed that the effect of 5mg was now significant at the 5% level.

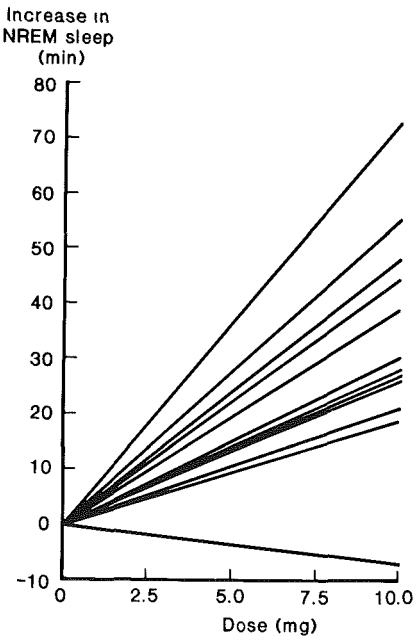

Fig. 2. Individual regressions relating increase in non-rapid eye movement (NREM) sleep (min) to dose (mg) of a hypnotic.

It is, therefore, possible that the procedure of selecting a dose that is shown to be effective in the population as a whole (usually at the 5% level of

significance) can lead to a sizeable proportion of individuals receiving either a less than or more than appropriate dose. Such an approach takes no account of the response required, and at any particular dose does not provide an estimate of the proportion of the population who received either a suitable or an excessive dose. Nevertheless, levels of significance have been used for many years to establish dose ranges for hypnotics. Individual response and, especially, careful examination of the effect of doses which do not reach accepted levels of significance compared with placebo are important considerations in the choice of the therapeutic dose range of centrally-acting drugs.

HOMOGENEITY OF SUBJECTS

The question, therefore, arises concerning the nature of individual response to drugs. It has already been shown that response may vary considerably within the population under investigation, but this variability may be reduced by considering subgroups of the population defined with respect to attributes that influence the selected response. There are many factors that could influence response, but for the purpose of this paper it is useful to consider the influence of age over a restricted range using data obtained from a study on another hypnotic (3,4).

The study involved twelve healthy male volunteers aged between 18 and 52, which could be divided easily into two age ranges of 18 and 23 and of 45 and 52 years. Each subject received 10, 20 and 30mg of the hypnotic and two placebos. The sleep data were analysed separately for each age group using ANOVA and, in addition, the data for both groups were combined in the same ANOVA, in which group was included as a second fixed factor with subjects nested within group. To ensure that the assumptions of ANOVA - homogeneity of variance, normality and additivity - were justified, the data were transformed prior to analysis using the maximum likelihood method of Box and Cox (5) together with the examination of the residuals (6). For the purpose of this paper, slow wave sleep (stages 3 and 4) and wakefulness with drowsy sleep (awake and stage 1) will be considered. Each of these measures required a logarithmic transformation, and so random variation and treatment effects were proportional rather than additive. The same procedure was used to test the significance of individual means compared with placebo as in the previous study.

A clear effect of each dose on sleep continuity (reduction in wakefulness and drowsy sleep) was established for the 12 subjects as a group, but there was no significant effect on slow wave sleep (Table II). However, the analysis revealed a significant dose by group interaction on both variables which indicated that the effect of the drug differed across the age range. Indeed, improved sleep continuity was established in the middle-aged subjects whose

TABLE II

Effect of zolpidem on duration (min) of sleep stages in the first 6h of sleep.

	Placebo	Zolpidem (mg) 10	20	30
All Subjects (n = 12)				
A & DS	66.0	48.3 **	51.6 *	49.5 **
SWS	26.0	32.5	41.9	42.5
Young Adults (n = 6)				
A & DS	46.2	35.6	43.8	46.0
SWS	45.7	62.3	81.4 *	78.8 *
Middle Age (n = 6)				
A & DS	85.7	60.9 *	59.4 *	52.9 **
SWS	6.3	2.7	2.3	6.1

A & DS = Awake and drowsy sleep (awake + stage 1)
SWS = Slow wave sleep (stages 3 + 4)
Significance levels: * $p < 0.05$; ** $p < 0.01$

sleep with placebo was less restful, whereas nocturnal wakefulness was little affected in the young adults (Fig. 3). Moreover, no change in slow wave sleep occurred in the middle-aged group, but there was a significant increase among the young adults (Fig. 4). The effect on slow wave sleep was again related to the "substrate" as increased slow wave sleep with drugs would appear to occur only when a significant part of sleep is occupied by such activity.

Clearly, homogeneous groups are more likely to provide accurate information on the activity of a drug than studies in which data from disparate groups are pooled. In the context of age, it is well recognised that the elderly may respond differently from others to drugs, but it is not well appreciated that considerable differences in response may occur across shorter and younger age ranges. In the case of hypnotics, this shorter age range, i.e. from the early twenties to around fifty years, has much practical significance. Indeed, in the clinical investigation of centrally-acting drugs such age spans are often used, and often no attempt is made to evaluate the influence of this variable. Many other factors, equally little understood, could well have

important influences on dose-response, yet remain undetected while contributing significantly to the variability of the data.

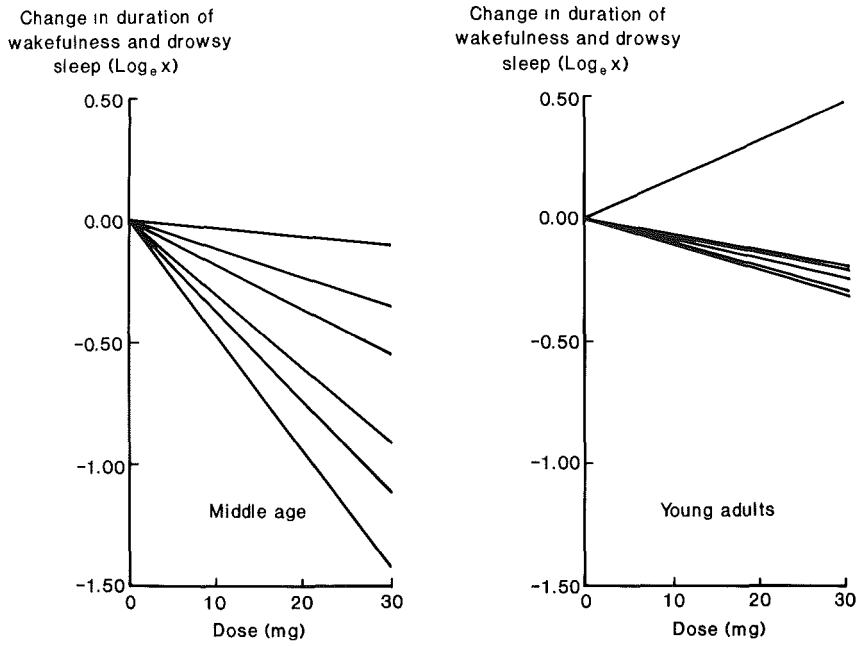

Fig. 3. Change in duration of wakefulness and drowsy sleep (transformed data) with dose (mg) of a hypnotic in middle age and young adults.

DOSE-RESPONSE AND THERAPEUTIC RANGE

Though the use of homogeneous groups of subjects is an obvious and attractive approach, nevertheless, in clinical studies, with a wide variety of unknown influences, there would rarely be any certainty that a homogeneous group had been obtained. It is highly unlikely in the investigation of centrally-acting drugs that many of the factors that might be used to define separate subject groups could be identified. It may well be that some other strategy should be used to ensure that the use of unnecessarily high doses of drugs is avoided.

So, would dose-response data rather than comparison of the mean response to drug with placebo be a more useful approach? In the first place, of course, a range of doses which would adequately describe the relationship which may exist must be used. It would then be necessary to set a response criterion

and establish the distribution of the dose level required to satisfy this criterion in terms of therapeutic and, possibly, adverse effects. This approach does, of course, presume that we are able to decide the appropriate therapeutic response - a concept which has received less attention than it deserves in the development of centrally-acting drugs.

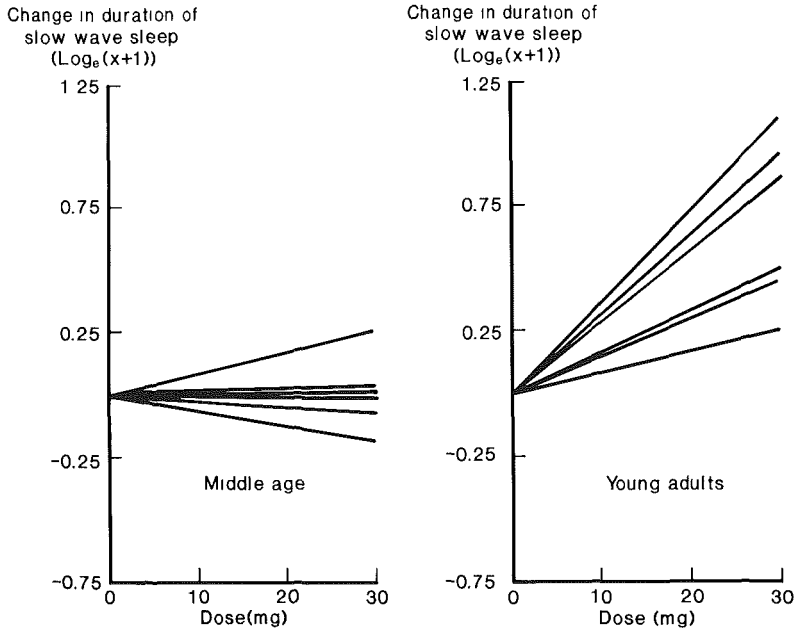

Fig. 4. Change in duration of slow wave sleep (transformed data) with dose (mg) of a hypnotic in middle age and young adults.

This approach is illustrated in Fig. 5. Using the data from the 12 subjects of the first study it can be seen that, if it was considered that an appropriate therapeutic effect would be an increase in NREM sleep of 10 minutes, then a dose of 3.2mg would be sufficient to provide an adequate response in 50% of subjects, and a dose of only 3.7mg would be required to provide an adequate response in 75% of subjects. Raising the appropriate therapeutic response to a 15 minute increase in NREM sleep would result in 50% of the subjects being adequately treated by a dose of 4:8mg and 75% of the subjects responding to a dose of only 5.6mg.

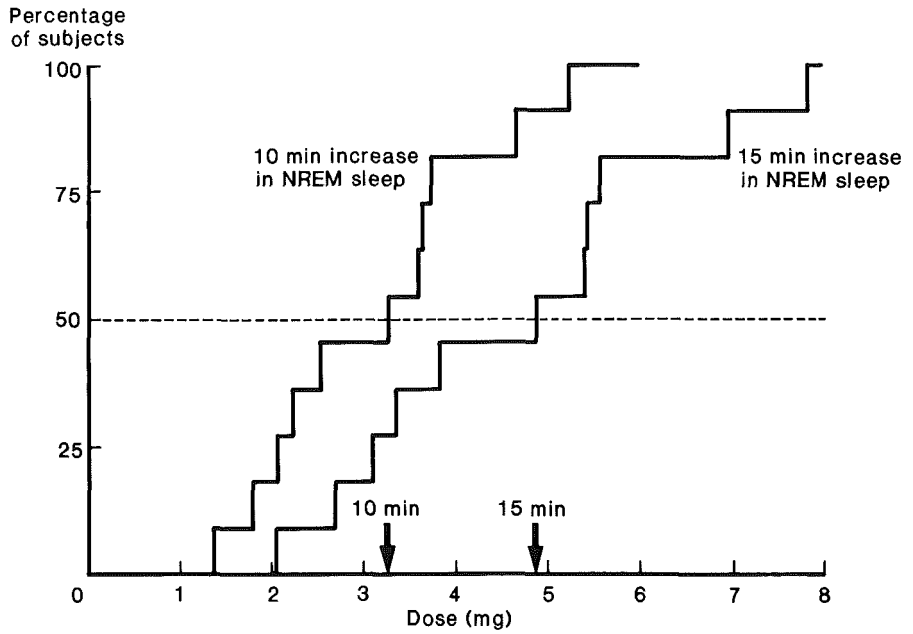

Fig. 5. Percentage of subjects responding to dose (mg) of a hypnotic with specified increase (min) in non-rapid eye movement (NREM) sleep.

CONCLUSION

These considerations demonstrate the possible advantage of an approach based on dose-response relationships, compared with one based on a statistically significant dose level. The achievement of a certain level of statistical significance depends on the power of the statistical test used, and this depends in part on the experimental design and the number of subjects. Indeed, statistical significance may be achieved at a dose level which has insufficient therapeutic effect as well as at a dose level that is too high for the majority of the population. If a suitable dose-response relationship can be derived, then by setting an appropriate threshold, it is possible to estimate the number of individuals who benefit from any particular dose level, and also to assess the range of the response in the population to a selected dose. Such an approach may suggest dose ranges more related to the desired therapeutic effect.

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Discussion - Centrally acting drugs: considerations of dose-response relationships

L. Lasagna

I would like to congratulate you on showing with real data the sort of theoretical stuff that I was hitting at in my own paper. It seems to me that by ungrouping data, you have provided a much richer description of what actually happens than with the usual grouping. I have a suggestion to make which I would like you opinion about. You talked about how to make value judgements about what is desired therapeutically. It seems to me that if one is studying a drug, let's say the way you are doing it with multiple doses in insomniacs, one could ask the subjects at the end to make a judgment about which dose was best for them, which would probably be a judgment that combined efficacy and safety.

A.N. Nicholson

I quite agree. If we could get a proper combination of objective assessment of sleep plus subjective assessment and be able to put the two together, this could be a very valuable approach. However, our experience of subjective assessments, often using analog scales, is that though they tend to be accurate, in some situations they break down completely and give completely wrong information. So, my reply would be that the subjective approach is very valuable, as long as you have supporting information.

L. Lasagna

Lest the sleep lab gods strike me dead, I submit humbly that what patients perceptions are about the effect of an hypnotic really would count with them, not the sleep lab data.

A.N. Nicholson

If we relied entirely on that information, I think we would be back to the days when people were using a drug not to improve their sleep, but to produce a euphoric effect the next morning. I think that when one is dealing with psychotropic drugs, one has to be very careful about subjective assessments, because the patient may be seeking an effect which is not related to the one we want.

P. Simon

I think that in terms of development of new hypnotic drugs the experimental studies can give a good indication of efficacy but practically none at all about side effects. These will appear when the drug is given to a large number of patients, in quite different conditions.

A.N. Nicholson

Perhaps experimental work is not being done carefully enough in healthy volunteers, and we do not get really sufficient data from the healthy volunteer. This is particularly relevant if one takes into account that many drugs are taken by healthy or near healthy people. I would agree with you that one has to balance the more careful experiments with homogeneous groups with the ones which show higher variability. It is this balance which I feel is not being done adequately at the moment.

A. Reinberg

When you ask people to self-rate the quality of sleep you do it during one or several nights?

A.N. Nicholson

We do it the morning after. We use a questionnaire, trying to cover sleep onset, continuity of sleep, residual effects and overall feelings. Variability of subjective assessment from day to day is a problem, which is compounded by possible direct effects of the drugs being studied on the subjects' ability to assess the quality of their sleep. Even using psychotropic drugs overnight the subjects' judgement may be changed the next day.