HYPNOTIC ACTIVITY OF LORMETAZEPAM AND CAMAZEPAM

In their paper about the effects of two hypnotic drugs on sleep and daytime skills, Nicholson & Stone (1982) referred to work by my colleagues and myself, so perhaps comments may be acceptable.

Sleep is subject to biological variability between subjects and from night to night for the same subject. In Table 1 by Nicholson & Stone (1982) it is recorded that the mean ratio of REM/NREM sleep was 0.36 on placebo and 0.35 in one drug condition, and this difference is said to be statistically significant at the 0.05 criterion. Wakefulness intervening in the first 6 h of sleep is usually subject to wide scatter, yet in Table 4 the mean is given as 2.9 min on placebo and 1.8 min in one drug condition, and this difference is again described as significant. The authors make comments about what they see as the clinical value of the drugs, but I would have difficulty in attaching clinical significance to a 1.1 min difference in nocturnal wakefulness, especially when the original measurements had been accurate only to 0.5 min, as a consequence of the paper speed used, and when the data had been derived from only six healthy young men. I myself find statistical significance to be elusive when there are very small differences between means.

When one looks at total sleep times, as given by Nicholson & Stone, again a statistically significant difference is stated to have been present when mean sleep increased by 6 min from 489.3 min to 495.4 min. The duration of sleep of healthy young men depends on how much time they are given in bed, and one sees that the ratio of total sleep time to total time in bed was always 0.96 or 0.97 and that no significant differences were claimed among any of these 'sleep efficiencies'. Calculating also from sleep latency and time awake, it appears that where there had been 'significant' increases of total sleep, the small reported increases might parsimoniously be attributed to greater time allowed in bed. In that none of the drug conditions affected the proportion of time spent asleep one might conclude either that the drugs are inactive (implausible) or that the particular choice of subjects provided an ineffective research instrument.

Reference

NICHOLSON, A.N. & STONE, B.M. (1982). Hypnotic activity and effects on performance of lormetazepam and camazepam—analogs of temazepam. *Br. J. clin. Pharmac.*, **13**, 433–439.

Dr A.N. NICHOLSON REPLIES AS FOLLOWS:

It is possible to establish week-on-week effects with an unbalanced design, and we would refer to the text by John & Quenouille (1977). With such a design

One may further wonder how time allowed in bed could have varied systematically, and it would seem possible that it was because the subjects had slept in trios and because the authors had had nine conditions, yet only six subjects; balance of order thereby being impossible. Order of conditions was described as 'random' week to week, but in such circumstances this can often mean heavily biased order among conditions. Unbalanced order of presentation of conditions would also be expected to affect the daytime skill results. Nicholson & Stone (1982) affirm that subjects performing, for example, the DSS had 'reached steady performance', but it would seem unjustified to assume that practice effects or even seasonal effects would not appear during 10 weeks. The authors give no data to show that there were not effects by week, and would not be in a position to provide such a check on their assumptions because they had used an unbalanced design.

The upper half of their Table 6 presents an analysis of variance based on the performance data and reveals most of the variance as deriving from the subjects. It fails to show any drug effect and as the *P*-value for the drug $\times$ time interaction is given as 0.58, more than 10 times greater than the usual criterion for significance, the null hypothesis cannot be rejected. In these circumstances the more detailed analysis next given, using least significant differences, must be held to be spurious. The conclusions in Nicholson & Stone's (1982) discussion therefore appear untenable.

IAN OSWALD

University Department of Psychiatry, Royal Edinburgh Hospital, Morningside Park, Edinburgh EH10 5HF

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week-on-week effects can be tested for and, if necessary, removed through an analysis of co-variance. Our subjects ingested the drugs in a random order,