

Visual Tracking Following Lorazepam or Pentobarbital

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Lorazepam, a new benzodiazepine, has recently been under investigation as a parenterally administered premedicant. These studies, in man, have shown not only that subjects experienced sedation and hypnosis, but also that many experienced a marked lack of recall.¹⁻⁵

In a previous study, we were able to demonstrate significant impairment of human performance, specifically hand-eye coordination, produced by oral administration of Δ^9 tetrahydrocannabinol.² Others have shown the visual tracking task to be sensitive to the effects of drugs such as alcohol and smoked marijuana cigarettes.³⁻⁷ Therefore, this investigation was done to study the effects of lorazepam and pentobarbital on visual tracking and to determine whether they affected it. We believed this would be important because there is evidence that performance on critical tracking tasks correlates with skills used in driving, flying, boating, and industrial work.

METHOD

The subjects were six healthy normal men who were asked to refrain from using analgesics, tranquilizers, marijuana, or ethanol for 24 hours preceding each experimental period. They ranged in age from 20 to 25 years and gave informed consent to participate.

Lorazepam, 2 and 4 mg, pentobarbital, 75 and 150 mg, and placebo were administered intramuscularly, double-blind, according to a

Latin square design. At least three days, but usually a week, elapsed between test sessions.

The critical tracking* task uses an unstable controlled element, $Y_c = \lambda(S - \lambda)$,** in which the rate of divergence, measured by its inverse time constant, λ (radians/sec), steadily increases as the task progresses. As the level of instability, λ , increases, control becomes increasingly difficult, until the operator is unable to maintain control. The value of λ at which control is lost is referred to as the "critical instability level," λ_c , which roughly approximates the reciprocal of the operator's effective time delay.

The tracking task was generated by a special-purpose digital computer†† and a line displayed on an oscilloscope. The subject's task was to maintain stability and keep the line centered on the oscilloscope by means of a "joy stick" (force transducer).

Each subject was given approximately 150 trials of the tracking task on a practice day and then 12 trials on the experimental day before the drug was administered. Determinations (12 trials) began 30 minutes after administration of the drug and were repeated every 30 minutes for eight hours. Motivation was maintained through self-competition, verbal encouragement, and a monetary reward for good performance.

RESULTS

The 12 response scores for each determination were averaged for the control and each half-hourly period. The resulting data were examined by analysis of variance, with the control mean for each particular medication used as a covariant. The data corrected for the control variant are plotted in figure 1. Examination of these data indicates that the change in performance following the placebo was negligible, whereas lorazepam and pento-

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§ Heisterkamp DV, Cohen PJ: The effects of lorazepam (WY-4036), pentobarbital and diazepam on recall. Presented at American Society of Anesthesiologists' Annual Meeting, Washington, D.C., October 1974.

* Sharna S, Moskowitz H: Smoked marijuana effects on a critical tracking task (personal communication).

** Y_c is the transfer function of the unstable controlled element in which S is a complex variable given by the Laplace transform.

†† Systems Technology, Inc., Critical Task Tester Mark IV, Model 401B.

barbital degraded performance over time. Eleven determinations were significantly different from placebo responses at any one observation period (see fig. 1).

These data were examined by analysis of variance (table 1), and the drug effect was found to be significant ($P < 0.03$). The drug effect was further analyzed by four orthogonal contrasts. The common-slope effect was significant ($P < .05$), but neither deviation from parallelism nor mean drug difference was significant. The placebo results differed significantly from results obtained with the other four medications ($P < .05$).

Total difference from placebo over eight hours was computed. These totals are plotted in figure 2. Relative potency, calculated from these data according to Feiller's theorem, was determined to be 53.1 (rho) (2 mg lorazepam = 106 mg pentobarbital) with upper and lower 95 per cent confidence limits of 64 and 46, respectively.

DISCUSSION

Both lorazepam and pentobarbital impaired hand-eye coordination. Based on the difference between the medication and placebo scores totalled over eight hours, it was deter-

mined that lorazepam is 53 times as potent as pentobarbital. This indicates that 2 mg lorazepam interferes with hand-eye coordination to the same extent as 106 mg pentobarbital.

We are not able to predict relative potencies at higher dosages. Although the dose-effect curves were not significantly different from the common slope, the lorazepam dose-effect curve slope appears steeper and, as in any assay, it would be unwise to extrapolate data outside the dosages studied.

Values marked by asterisks in figure 1 showed statistically significant differences from placebo values. This means that at these observation periods there was no overlap between drug response ± 2 SD and placebo response. We would predict that if the same trend continued with more subjects the magnitudes of standard deviations about individual points would decrease; hence, other determinations might show statistically significant differences as well.

Inspection of figure 1 suggests durations of effect of 4 hours for 75 mg pentobarbital; 4 hours for pentobarbital, 150 mg; 4 hours for lorazepam, 2 mg; 8 hours for lorazepam, 4 mg. There are, however, several reasons

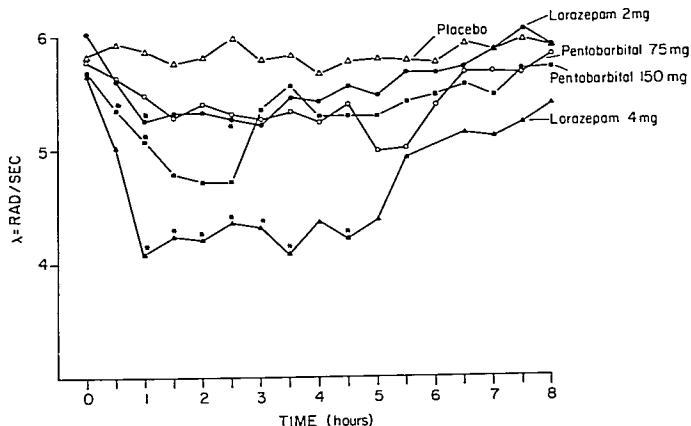
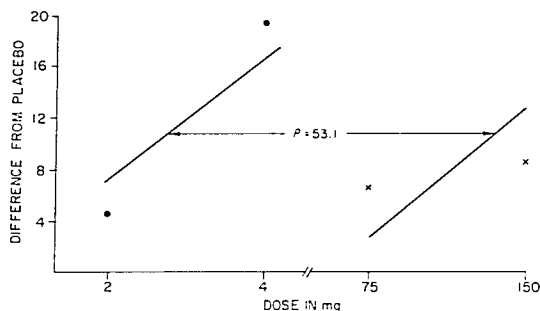


FIG. 1. Mean tracking score plotted versus time. These scores in radians per second are corrected for the mean baseline determination at that test session. Significant ($P < 0.05$) differences from placebo are indicated by asterisks.

FIG. 2. Mean difference from placebo plotted against dosage of medication in mg $\rho(\rho)$; the relative potency is indicated.



these data cannot be used to predict precisely when it would be safe to operate a motor vehicle, or engage in a hazardous occupation or sport. In this study, the selected subjects were healthy Caucasian men 20 to 25 years old, with normal scores on the MMPI. The performance of these selected subjects cannot be used to answer the duration question where Negroes (who show greater sedation with lorazepam)⁹ or the elderly are involved. Also, to illustrate the wide variation in performances among individuals, the mean score of one subject for the two-hour determination with lorazepam, 4 mg, was 6.03, and that of another, 3.50. More importantly, this study does not take into account possible drug interactions with other medications and the effects of repeated doses of lorazepam.

It is of interest that our relative potency, 53, agrees with what one would get based on the data of Comer *et al.*¹⁰ Using their pre-medication study data, the change in anxiety (15 minutes) relative potency was 57, and at 30 minutes the relative potency was 80. Based on

patient acceptance, the relative potency was 45. Thus, it appears that the pharmacologic effects causing interference with hand-eye coordination are comparable to the anti-anxiety response, since the relative potencies are similar. However, this is not the case for respiratory depression, since lorazepam, 2 or 4 mg, does not appear to cause respiratory depression.¹¹

One of the most satisfactory methods for analyzing side effects in operation would be to measure their intensities and, based on mean intensities following various doses of the drugs being studied, to carry out a parallel-line assay. This implies that the scoring method is sensitive enough to produce a dose-effect curve following a standard as well as a test medication.

The critical tracking task has been designed so that the difficulty of operation is neither too little, causing loss of alertness due to boredom, nor too great, causing a decrement in performance due to fatigue. With regard to low-task-load failures, it has been hypothesized (Bixler *et al.*)¹² that a "reserve

TABLE 1. Analysis of Variance, Tracking Data

Source of Variance	Degrees of Freedom	Sum of Squares	Mean Square	F Ratio	Probability F Exceeded
Medication (M)	4	56.48	14.12	3.30	0.033
Covariant	1	32.83	32.83	7.76	0.012
Error	19	81.36	4.28		
Time (T)	15	23.26	1.55	7.76	0.001
Error	75	14.98	0.20		
M \times T	60	16.52	0.28	1.61	0.005
Error	300	51.26	0.17		

capacity" masks changes in ability to perform because the subject modifies his efforts in relation to how he feels at the time to maintain this accepted level of performance. In other words, there is usually a difference from the level at which he could maximally be performing.

A solution to the problem of subjects performing below their maximum capabilities is to employ a secondary task superimposed upon the primary one, thus causing the subject to time-share the performance of tasks. However, unless the performance on one task can be treated independently of performance on another, drawing conclusions from sequential task performance requires modalities to account for task combining and difficulty.¹²

Possibly one of the most unique features of our visual tracking study was that it allowed the subject to have instantaneous feedback on his performance. When control was lost the special-purpose digital computer produced the subject's final score, "critical instability level," on a digital voltmeter. This was a major motivator of performance and contributed, along with a monetary reward, to the subject's consistently trying for a high score.

Even the most carefully designed study cannot exclude all effects caused by learning. Having the subjects practice on the tracking task before the study begins still cannot eliminate learning effects that take place in a study running several weeks. Therefore, a control determination was used as a covariant in the analysis of variance.

Between-subject variability was removed by using a cross-over Latin square design. This also allowed us to use a relatively small number of subjects. It is important to note that a minimum of three days was required before a subject was allowed to start another test, thus eliminating any prolonged gross behavioral effect of one drug from confounding the effects of another drug.

Lorazepam, which has been shown to produce lack of recall in some patients and to have anti-anxiety properties, interferes with hand-eye coordination. This suggests that the operation of a motor vehicle or engaging in a hazardous sport or occupation should be ap-

proached with caution after using this medication.

REFERENCES

- Knapp RB, Fierro L: Evaluation of cardiopulmonary safety and effects of lorazepam as a premedicant. *Anesth Analg* (Cleve) 53: 122-124, 1974
- Stoller KP, Swanson GD, Bellville JW: Effects on visual tracking of Δ^9 -tetrahydrocannabinol and pentobarbital. *J Clin Pharmacol* 16:102-106, 1976
- Chiles WD, Jennings AE: Effects of alcohol on complex performance. *Hum Factors* 12:605-612, 1970
- Hughes FW, Forney RB: Comparative effects of three antihistamines and ethanol on mental and motor performance. *Clin Pharmacol Ther* 5:414-421, 1964
- Manno JE, Kiplinger GF, Scholz N, et al: The influence of alcohol and marijuana on motor and mental performance. *Clin Pharmacol Ther* 12:202-211, 1971
- Mortimer RG: Effect of low blood-alcohol concentrations in simulated day and night driving. *Percept Mot Skills* 17:399-408, 1963
- Roth WT, Tinklenberg JR, Whitaker CA, et al: The effect of marijuana on tracking task performance. *Psychopharmacologia* 33:259-265, 1973
- Jex HR, McRuer DT, Allen RW, et al: Control characteristics of alcohol-impaired operators. *American Institute of Aeronautics and Astronautics (AIAA) Paper No. 74, 1300*, 1974
- Elliott HW, Navarro G, Kokka N, et al: Early phase I evaluation of sedatives, hypnotics or minor tranquilizers. *Hypnotics, Methods of Development and Evaluation*. Edited by Kagan F, Harwood T, Rickels K, et al. New York, Spectrum Publications, 1975, pp 87-108
- Conner JT, Parson N, Katz RL, et al: Evaluation of lorazepam and pentobarbital as surgical premedicants. *Clin Pharmacol Ther* 19:24-29, 1976
- Gasser JC, Kaufman RD, Bellville JW: Respiratory effects of lorazepam, pentobarbital and pentazocine. *Clin Pharmacol Ther* 18:170-174, 1975
- Bixler EO, Scharf MB, Leo LA, et al: Hypnotic drugs and performance. A review of theoretical and methodological considerations. *Hypnotics, Methods of Development and Evaluation*. Edited by Kagan F, Harwood T, Rickels K, et al. New York, Spectrum Publications, 1975, pp 175-196
- Mills RG, Hatfield SA: Sequential task performance: Task module relationships, reliabilities and times. *Hum Factors* 16:117-128, 1974