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Original Investigations

Smooth-Pursuit Eye Movements, and Diazepam, CPZ, and Secobarbital*

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Abstract. This study examined the effects on smooth-pursuit eye tracking of single doses of CPZ (0.667 and 1.334 mg/kg), diazepam (0.071, 0.142, and 0.284 mg/kg), and secobarbital (100 mg). Only the barbiturate significantly affected the ability to follow a moving target with smooth-pursuit eye movements. In repeated testing of a single subject, 130 mg of secobarbital disrupted smooth-pursuit movements at least until 24 hrs after ingestion.

Key words: Eye Tracking – Smooth Pursuit – Schizophrenia – Diazepam – Chlorpromazine – Secobarbital.

Two previous reports have described impairments of smooth-pursuit eye movements in clinically diagnosed schizophrenic patients and their first-degree relatives (Holzman *et al.*, 1973, 1974). Since most of the subject-patients were receiving neuroleptic medication at the time of testing, the possibility existed that the medication could have produced the reported effect in patients, although there was presumptive evidence in the data that the phenomenon was not drug or state related. To resolve the question of the relationship of eye tracking to the subject's state, controlled observations of the effects on smooth-pursuit eye tracking of single and chronic drug dosages of chlorpromazine and other compounds in normals were undertaken, and in the process some interesting features of the time course and action of the drugs tested emerged. This paper reports a study of the effects of single dosages of chlorpromazine, diazepam, and secobarbital. A later paper will report data concerning effects of chronic drug dosages upon smooth eye pursuit movements.

Method

Eye Movements. Two independently generated mechanisms are employed by the visual system to perform the task of fixating on a moving object. The saccadic system brings the visual target onto the fovea by means of high velocity conjugate eye movements. The pursuit system maintains a stable image on the fovea by adjusting eyeball velocity to target velocity.

A common clinical test uses a pendulum to study pursuit eye movements. In normal eye tracking, the movement of the eye mirrors the sinusoidal motion of the pendulum within a critical oscillation frequency range.

Procedure. The procedure and method are described in Holzman *et al.* (1974). Briefly, the task required the seated subject to watch a moving pendulum suspended to eye level at a distance of 1 m. The pendulum had a frequency of 0.4 Hz, an amplitude of 20° visual angle.

The subject was instructed to follow the moving pendulum with only his eyes for 30 sec. A headrest held the head stationary.

Recording Apparatus. Silver-silver chloride skin electrodes were applied near the outer canthus of each eye, and a ground electrode was applied to the middle of the forehead. Eye movements in the horizontal plane were recorded on a chart dynograph by amplifying the changing corneoretinal field potential. Channel 1 of the dynograph displayed recordings of eye position with a time constant of 3 sec, and channel 2 displayed the derivative of the eye position signal. The 50% bandwidth was 10 Hz and 6 Hz for the direct and differentiator channels, respectively.

Subjects. The subjects in the following experiments were 5 males, ranging in age from 21–28 years old. They were recruited via newspaper advertisement, and underwent both physical and psychological screening before acceptance as test subjects. None of the subjects reported either a personal or family history of psychiatric illness or of oculomotor or vestibular disease, nor were any of the subjects taking prescribed medications. In addition to the pendulum tracking task, all subjects were tested for spontaneous and gaze nystagmus before and after drug ingestion. All subjects were paid for their services. During the experiment the subjects had no knowledge of which drugs they were receiving or of the empirical question being investigated. Subjects were restricted from eating for 8 hrs before testing (orange juice for breakfast was

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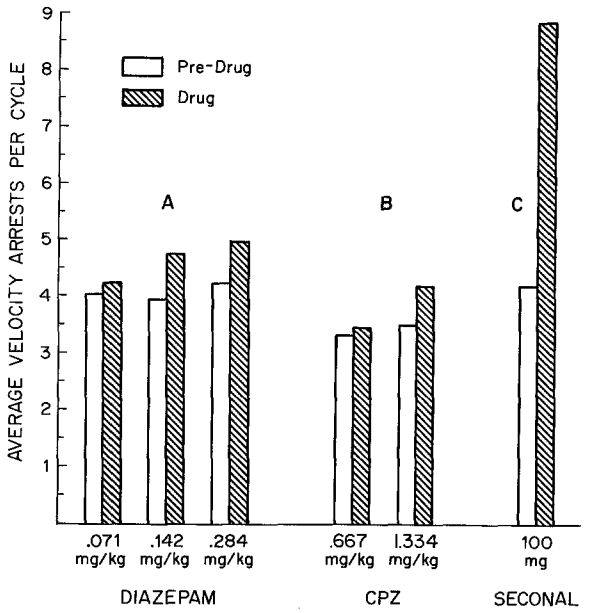

Fig. 1. Velocity arrests before and after aministration of diazepam (1 *A*), CPZ (1 *B*), and secobarbital (1 *C*)

the only exception), and from ingestion of alcohol, and street drugs for 48 hrs before and after the test time. We had no reason to doubt that these instructions were followed.

Scoring Procedures. Each eye-tracking record was studied by two scorers who independently classified the tracking as qualitatively *Normal* or *Deviant*. The criterion for a normal tracking is described in Holzman *et al.* (1974). Interjudge reliability of two raters in this present study was 100%.

One quantification of eye tracking is to count the number of times the eyes stop their pursuit of the target when they should be moving if accurately and smoothly tracking. These events are called *velocity arrests*, and are determined from the derivative of the eye position signal. The velocity arrest score is an arbitrary but convenient representation of deviation of eye movement from smooth pursuit.

Experiment I: Diazepam (Valium)

Diazepam was administered orally in doses of 0.071, 0.142, and 0.284 mg/kg body weight. The doses were mixed in a quinine base in liquid form at a concentration of 5 mg/ml (Roche). Average doses for the 3 dose strengths among our subjects were 5.12, 10.17, and 20.42 mg. Each dose consisted of drug and base totaling 2 liquid tablespoons. Single doses were administered on three consecutive weeks.

Each subject was tested under pre- and post-drug conditions. The post-drug test occurred 1 h and 45 min after drug administration as the best estimate of maximal effect (de Silva *et al.*, 1964, 1966; Schwartz *et al.*, 1965; Foster and Frings, 1970).

Results. Fig. 1 a shows the mean number of velocity arrests for the group under the three dosage conditions. A repeated measures analysis of variance of the two conditions (pre- and post-drug administration) at three dosage levels revealed no statistically significant effects of the drug on the velocity arrest score ($F = 0.177$, $P =$ n.s.). Nor is there a statistically significant effect of specific dosage levels on the velocity arrest score. Both pre- and post-drug velocity arrest scores fall below the mean of normal performance, which our experience indicates as approximately 7 (Holzman *et al.*, 1974), and below the pre-drug mean for this group of subjects.

The qualitative assessment of tracking performance based on resemblance of the examples in Fig. 1 remained normal for all subjects under all conditions 1 hr and 45 min after drug ingestion. There was, however, one subject whose tracking changed from its pre-drug state in the 0.071 mg/kg condition. This subject, however, showed no deviant eye tracking on 0.142 and 0.284 mg/kg of diazepam.

Experiment II: Chlorpromazine (CPZ, Thorazine)

Chlorpromazine hydrochloride concentrate was administered orally in doses of 0.667 and 1.334 mg/kg in liquid form (30 mg/ml, Smith, Kline, and French), mixed with an aromatic elixir agent (Lilly, No. 233). The average doses of CPZ were 47.85 and 95.84 mg. Testing occurred on two consecutive weeks. Each dose consisted of drug and elixir totaling 2 liquid tablespoons.

All subjects were tested under pre- and post-drug conditions as described above. Pre- and post-drug test sessions were separated by 1 hr and 45 min, to provide maximal drug effect (Curry, 1968; Curry *et al.*, 1968, 1970).

Results. Fig. 1 b shows the mean number of velocity arrests for the group under the two dosage conditions. A repeated measures analysis of variance showed no significant drug effect ($F = 0.675$, $P =$ n.s.), and no significant interaction effect ($F = 5.66$, $P =$ n.s.). There was, however, a significant difference between the two dosages of CPZ ($F = 11.801$, $P < 0.05$), although neither of these scores was itself significantly different from pre-drug performance, and both scores were well within the normal range of velocity arrests. The dosage effect is thus clinically insignificant. This analysis was performed on only four of the subjects because one subject reported having double vision following the 1.334 mg/kg dosage, a side effect which clearly pertained to task ability. Although the liquid base was an elixir, the alcohol was presumed insufficient to affect smooth eye tracking, although 100 g of alcohol has been shown to alter normal oculomotor response (*e.g.*, Bochenek and Ormerod, 1962). Quali-

tatively all tracings were classified as normal before and after drug ingestion.

Experiment III: Sodium Secobarbital (Seconal Sodium)

Inasmuch as barbiturates have previously been shown to affect smooth-pursuit movements (Rashbass, 1961; Rashbass and Russell, 1961; Norris, 1968), we administered a barbiturate to our subjects as a way of comparing its effect to that of diazepam and CPZ. Sodium secobarbital (Seconal) was administered orally in liquid form, premixed with a base. The dosage was a standard sedative amount of 100 mg (22 mg/ml) and was not adjusted for weight differences.

Subjects[1] were tested at 10-min intervals up to 80 min after ingestion of secobarbital.

Results. Each of the 8 post-drug scores was compared with pre-drug performance by *t*-tests. No significant group difference in the velocity arrest score was detectable until 70 min after drug ingestion ($t = 6.08$, $P < 0.01$). A significant difference was maintained at 80 min ($t = 4.14$, $P < 0.05$), when testing was discontinued. All subjects considered individually showed a significant increase in velocity arrests when under the influence of secobarbital. Fig. 1c contains the group means for the secobarbital trials at 80 min post-ingestion.

Two of the four subjects tested on secobarbital demonstrated the expected barbiturate disruption of smooth pursuit according to the qualitative classification scheme. The other two subjects showed no gross impairment of smooth eye tracking, although the velocity arrest scores revealed a definite increase.

Of the two subjects whose ocular pursuit was interrupted and replaced by saccades under the influence of secobarbital, one began to show deviant tracking 20 min after taking the drug, and it remained so at each subsequent trial; the second subject demonstrated deviant tracking 50 min after drug ingestion, and it remained deviant throughout the remainder of the test. We found evidence of spontaneous nystagmus 80 min after drug ingestion only in one subject. Rashbass (1961) reported the presence of "barbiturate nystagmus" during the post-drug ocular pursuit. No spontaneous nystagmus was detected in the post-drug tests of diazepam and CPZ.

Pre-Drug Scores. The pre-drug velocity arrest score remained the same for all three experiments. A repeated measures analysis of variance of the six pre-drug velocity arrest scores indicates that inter-test differences are not significant ($F = 0.561$, $P =$ n.s.), the mean score for this group of subjects being 3.93 velocity arrests per cycle, with a range of 3.3 to 4.28[2]. All tracings were classified as normal prior to drug administration.

[1] One subject was not available to participate in the secobarbital study.

Experiment IV: Repeated Testing

Serial testing was performed upon one representative subject who had shown no qualitative disruption of his tracking pattern after ingestion of 100 mg of secobarbital. In order to study the longitudinal course of drug effects for an extended period of time, we administered to him on successive weeks 0.284 mg/kg of diazepam, 1.334 mg/kg of CPZ, and 130 mg of secobarbital.

His mean velocity arrest score for 10 pre-drug occasions was 3.73, with a standard deviation of 0.79.

Diazepam Trials. We administered to the subject 0.284 mg/kg of diazepam (about 20 mg). Post-drug testing occurred at 30, 60, 90, 120, 150, 180, 210, 240, 360, 480 min and at 24 hrs. The qualitative tracking patterns were normal for all testing periods. After 30 min, however, the number of velocity arrests increased from the mean of his pre-drug trials of 3.73 to 7.3. It then drops and increases again at 6 hrs. It returned to his pre-drug levels after 24 hrs. Thus, at least for this one subject, 0.284 mg/kg of diazepam increased the number of velocity arrests although it did not produce an abnormal qualitative tracking pattern.

The velocity arrest score at 6 hrs is noteworthy. Baird and Hailey (1972, 1973) reported increases in plasma levels of diazepam up to 90 min, followed by a rapid disappearance from circulating blood for both orally and intravenously administered diazepam. Diazepam then reappears and rises to a second peak at 6–8 hrs after administration. The authors suggested that after initial administration a considerable proportion of diazepam is stored and then after 6 hrs is released into circulation, possibly by participating in an enterohepatic cycle. The velocity arrest curve in our study for 0.284 mg/kg over 24 hrs mirrors the plasma concentration curves reported by Baird and Hailey and the second peak at 6 hrs in our curve may thus be explainable in terms of the effects of a release of diazepam from storage.

Chlorpromazine Trials. One week later we administered 1.334 mg/kg of CPZ. Post-drug testing occurred at 30, 60, 90, 120, 150, 180, 210, 240, 360, 480 min and

[2] Another group of normal subjects ($N = 72$) had a mean of 6.76 velocity arrests per cycle, a statistic which is not significantly different from the mean velocity arrests obtained in the pre-drug trials of the present study.

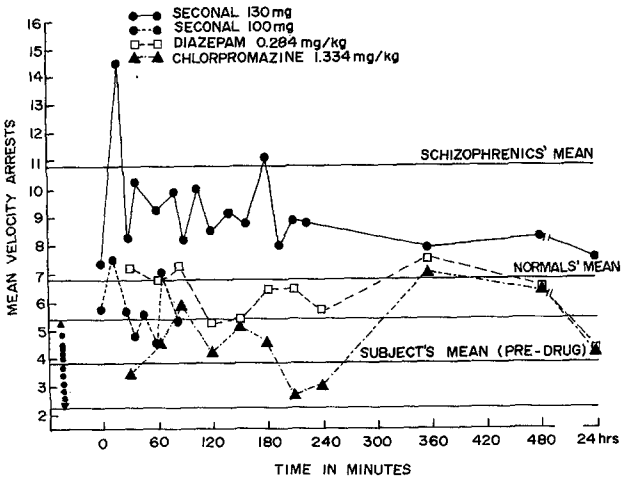

Fig. 2. Mean velocity arrest scores per cycle for one subject in serial-testing after ingestion of 0.234 mg/kg of diazepam, 1.334 mg/kg of CPZ, and 130 mg of secobarbital. The values for the 100 mg trials of secobarbital are also shown. The subject's own pre-drug scores are shown as are the limits of $\pm$ 2 σ from his own mean. The mean scores of 72 normal subjects and 75 schizophrenic subjects are also shown for comparison

24 hrs. All of the qualitative tracking patterns were normal. The number of velocity arrests showed no statistically significant increase over pre-drug levels.

Although the number of velocity arrests remains well within normal levels and there are no significant qualitative disturbances in the eye tracking, the number of velocity arrests increases at 90 min, subsides to a low at 210 min and rises to its highest point at 360 min. In these respects, the CPZ curve resembles that of diazepam and suggests that the behavioral effects in the form of velocity arrests may be correlated with changes in plasma concentrations of CPZ. Although to our knowledge no studies have appeared showing storage and release of CPZ 6 hrs after an initial dose, this present result would strongly suggest such a process. We are currently undertaking a serial study of plasma levels of phenothiazine and their association with eye-tracking behavior.

Secobarbital Trials. One week later we administered 130 mg of secobarbital. We tested this subject 10 and 20 min post-drug and at 15-min intervals thereafter until 4 hrs post-drug, and then at 6, 8, and 24 hrs. At 20 min there is a significant rise in velocity arrests, both for the 100 and 130 mg dosages. For the 130 mg trial, the velocity arrest score remains elevated even after 24 hrs. Barbiturate-induced nystagmus was present in all recordings from 20 min to 24 hrs, though in decreasing amounts over time.

Fig. 2 shows the composite representation of the effect of all 3 drugs on velocity arrests for this subject. It is unmistakable that secobarbital disrupted eye tracking and raised the number of velocity arrests to the level reported for schizophrenic patients (Holzman *et al.*, 1974). Although diazepam produced an increase in velocity arrest scores, the increase is not greater than that of the average of a large group of normal subjects.

Comment

This study demonstrates that orally ingested single doses of 0.071, 0.142, and 0.284 mg/kg diazepam, and 0.667 and 1.334 mg/kg CPZ produce neither significant changes in the velocity arrest measure of eye-tracking performance, nor deviant qualitative changes in smooth eye tracking in nonpatient subjects. 100 mg of secobarbital, however, produced a significant group change in both measures. 130 mg of secobarbital, moreover, produced eyetracking disruption which, in the single subject tested, remained impaired 24 hrs later.

The disruption of smooth-pursuit eye movements by the barbiturate is not attributable to the sedative action of the drug.

All subjects experienced extreme drowsiness and lethargy—indeed they were allowed to stretch out and sleep and then they had to be awakened from sleep to perform the task—following administration of both dosages of CPZ and following the two larger dosages of diazepam. It thus seems likely that the dysfunction of smooth eye tracking under barbiturates is not referable to their general sedative action or to attentional interference with task efficiency, but rather to the sites of action of the drugs and to the specific neurological pathways they involve (*cf.* Rashbass, 1961).

With respect to the effects of barbiturates on smooth-pursuit movements, our findings are congruent with those of Rashbass and his colleagues (*e.g.*, Rashbass, 1961) who demonstrated the specificity of barbiturate action in respect to various oculomotor mechanisms. Rashbass, however, utilized the intravenous administration of 100 mg of sodium thiopentane (Pentothal) in contrast to our use of oral administration. The difference probably accounts for the slower appearance of effects of the drug on smooth-pursuit movements in our group of subjects and may account for the failure of two subjects to show grossly impaired tracking, although they experienced a sedative effect and showed an elevation in velocity arrest scores. Conclusive statements concerning dosage-effects cannot be made in the absence of drug blood-level data.

In testing diazepam and CPZ we were surprised to find an increase in velocity arrests 6 hrs post-drug administration. There is a strong possibility that this

second phase effect may be related to pharmacokinetic processes. That is, the eye-tracking response may be sensitive to the storage and subsequent release of diazepam and the findings with respect to CPZ have provoked us to undertake blood measures. Attention focused on later phase effects might have implications for the therapeutic regulation of these drugs. We should note, however, that these effects may be contingent upon single rather than on multiple doses.

The question of an impact from chronic and large doses of phenothiazines (including Parkinsonian side effects) on eye-tracking performance is not addressed by this study. We are preparing an animal model for studying these issues. This current study, however, does present evidence that single doses of diazepam in 0.071, 0.142, and 0.284 mg/kg and CPZ in 0.667 and 1.334 mg/kg have no discernible effects on eye-tracking parameters that have been shown to be of clinical interest. Secobarbital, on the other hand, has clear effects on these parameters.

References

Baird, E. S., Hailey, D. M.: Delayed recovery from a sedative: Correlation of the plasma levels of diazepam with clinical effects after oral and intravenous administration. Brit. J. Anaesth. **44**, 803–808 (1972)

Baird, E. S., Hailey, D. M.: Plasma levels of diazepam and its major metabolite following intramuscular administration. Brit. J. Anaesth. **45**, 546–547 (1973)

Benitez, J. T.: Eye-tracking and optokinetic tests: Diagnostic significance in peripheral and central vestibular disorders. Laryngoscope (St. Louis) **80**, 834–848 (1970)

Bochenek, Z., Ormerod, F. C.: The inhibitory action of certain substances on the response to vestibular stimulation. J. Laryng. **76**, 39–44 (1962)

Corvera, J., Lombardo, L., Torres, G. C.: Alteraciones nistagmograficas en lesiones del tallo cerebral. Neurol. Neurocir. Psiquiat. (Mex.) **7**, 77–86 (1966)

Curry, S. H.: The determination and possible significance of plasma levels of chlorpromazine in psychiatric patients. Aggressologie **9**, 1–5 (1968)

Curry, S. H., Marshall, J. H. L.: Plasma levels of chlorpromazine and some of its relatively nonpolar metabolites in psychiatric patients. Life Sci. **7**, 9–17 (1968)

Curry, S. H., Davis, J. M., Janowsky, D. S., Marshall, J. H. L.: Factors affecting chlorpromazine plasma levels in psychiatric patients. Arch. gen. Psychiat. **22**, 209–215 (1970)

Foster, L. B., Frings, C. S.: Determination of diazepam (Valium) concentrations in serum by gas-liquid chromatography. Clin. Chem. **16**, 177–179 (1970)

Holzman, P. S., Proctor, L. R., Hughes, D. W.: Eye-tracking patterns in schizophrenia. Science **181**, 179–181 (1973)

Holzman, P. S., Proctor, L. R., Levy, D. L., Yasillo, N., Meltzer, H. Y., Hurt, S. W.: Eye-tracking dysfunctions in schizophrenic patients and their relatives. Arch. gen. Psychiat. **31**, 143–151 (1974)

Jung, R., Kornhuber, H. H.: The oculomotor system, pp. 452–454. M. B. Bender, ed. New York: Harper & Row 1964

von Noorden, G. K., Thompson, H. S., Van Allen, M. W. Eye movements in myotonic dystrophy: An electrooculographic study. Invest. Ophthal. **3**, 314–324 (1964)

Norris, H.: The time course of barbiturate action in man investigated by measurement of smooth tracking eye movement. Brit. J. Pharmacol. Chemother. **33**, 117–128 (1968)

Rashbass, C.: The relationship between saccadic and smooth tracking eye movements. J. Physiol. (Lond.) **159**, 326–338 (1961)

Rashbass, C., Russell, G. F. M.: Action of a barbiturate drug (Amylobarbitone sodium) on the vestibulo-ocular reflex. Brain **84**, 329–335 (1961)

Schwartz, M. A., Koechlin, B. A., Postma, E., Palmer, S., Krol, G.: Metabolism of diazepam in rat, dog, and man. J. Pharmacol. exp. Ther. **149**, 423–435 (1965)

de Silva, J. A. F., Schwartz, M. A., Stefanovic, V., Kaplan, J., D'Arconte, L.: Determination of diazepam (Valium) in blood by gas liquid chromatography. Analyt. Chem. **36**, 2099–2104 (1964)

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