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Specific Oculomotor Deficit After Diazepam

II. Smooth Pursuit Eye Movements

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Abstract. Changes in smooth pursuit eye tracking of horizontal sinusoidal target movement before and after up to 10 mg oral diazepam were measured electrooculographically in diazepam-naive humans. Diazepam produced a dose-dependent reduction in gain of pursuit eye movements at target frequencies of 0.4–1.6 Hz. Cross-correlation of eye and track was significantly reduced at most frequencies showing gain reduction after 10 mg diazepam. Eye-target phase relationship was not systematically altered by drug. Visual inspection of smooth pursuit tracking records showed reduced peak-to-peak amplitude of eye tracking along with replacement of smooth pursuit with saccadic pursuit, especially after 10 mg. Changes in smooth pursuit eye tracking after diazepam were similar to those changes reported in the literature associated with olivopontocerebellar atrophy and were quite unlike the changes in smooth pursuit after opiates, as previously reported. The role of cerebellar benzodiazepine binding sites in diazepam disruption of eye tracking was discussed.

Key words: Diazepam – Benzodiazepine – Smooth pursuit eye tracking – Oculomotor response – Humans – Drugs

Diazepam selectively alters saccadic eye movements in humans (Aschoff 1968; Gentles and Thomas 1971; Aschoff and Becker 1973; Aschoff et al. 1975; Stern et al. 1974; Jürgens et al. 1979; Rothenberg and Selkoe 1981). In the present paper we demonstrate that diazepam causes specific changes in another measure of oculomotor control, namely, smooth pursuit. This paper shows that diazepam decreases the gain of smooth pursuit and decreases the cross-correlation between the eye track and the target track. We contrast these effects with the effects of methadone, a synthetic narcotic analgesic, on smooth pursuit.

Materials and Methods

The procedures used in this experiment are mostly the same as those reported before (Rothenberg et al. 1980a; Rothenberg and Selkoe 1981). The following summary includes the differences in methods between this and the previous reports. Nonsmoking, low drug-using subjects, ages 21–40 years, with normal pursuit eye movements were tested before and after 0, 5, and 10 mg oral diazepam on a number of oculomotor tests. Each dose was at least 1 week from the previous one and order of dosage was completely counterbalanced over subjects. Electrooculograms (EOG) were led from nonpolarizable silver-silver chloride electrodes pasted on the inner and outer canthi of the dominant eye. EOG signals were amplified by a system with response from DC to 100 Hz (3 dB down), digitized at 200 Hz and stored on disk.

The subject viewed the target, a small green dot subtending 5 min of visual arc, monocularly while seated with chin and forehead supports 37 cm from a television monitor with a fast-decay P24 phosphor. The position of the dot on the screen was changed sinusoidally in time by a wave-form generator. The periodicity of the sinusoidal forcing function driving the stimulus was set to within ± 1 ms of the intended value.

Visual Tests: Calibration and Pursuit. The stimulus was directly in front of the viewing eye at the start of each test.

Because EOG voltage is not linearly related to eye position, three consecutive calibration tests were run immediately prior to the pursuit tests to allow transformation of EOG voltage into eye position data. The target was displaced fixed distances to the left and right of the center position and the subject moved the eye as accurately as possible towards the target at each position. At the center position and at each displaced position the subject pressed a button to indicate when the eye was directly on the target.

Horizontal pursuit tests were run at sinusodial forcing function frequencies of 0.2, 0.4, 0.6, 0.8, 1.0, 1.2, 1.6, and 2.0 Hz. Peak-to-peak amplitude of target excursion was ±5° about the center position. Testing continued at each frequency until at least six consecutive artifact-free cycles of eye movement were recorded, which in no case took more than 12 cycles. Rests were provided between testing at each frequency. Instructions to the subject stressed smooth and accurate tracking.

Calibration curves were constructed from the EOG voltage recorded when the eye was at each target position averaged over the three calibration tests. EOG voltage was sampled for a 100 ms epoch starting 75 ms before the subject's button press at each target position. The EOG voltage difference recorded between the center position and the displaced position of the target was plotted against target position and a third-order polynomial regression was determined for the plots. The regression equation was used to convert EOG voltage recorded during the pursuit tests to eye position.

The first cycle of eye and target position data at each frequency was discarded to avoid contamination of the measures by start-up transients. The following five to ten cycles of artifact-free eye and target position data at each frequency were analyzed by a discrete fast Fourier transform (Aho et al. 1974) in epochs of 1,024 points. Since two to six epochs of data were required to contain the minimum of five cycles of eye movement at the slower pursuit frequencies, the measures reported below for frequencies of 0.6 Hz and below are the averaged values of all epochs analyzed at each frequency. Power spectra were computed for trarget and eye position data. The ratio of the power in the target spectrum to power in the eye position spectrum at the frequency of stimulation was computed to derive the gain of pursuit tracking at each frequency. Phase information at each frequency was also derived from the Fourier calculation. The cross-correlation function between target and eye position at each frequency was computed by shifting the target and eye movement data one sample at a time over a ±90° range. The maximum of the cross-correlation function at each frequency was determined. These data were entered into a three-way analysis of variance (ANOVA) for repeated

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measures (Armor and Couch 1972) (predrug versus postdrug, 0, 5, or 10 mg dose, and eight frequencies). Subsequent ANOVAs were run with subsets of the data as indicated by the previous analyses.

Results

Mean gain, phase, and maximum cross-correlation across all subjects at the eight frequencies are plotted in Figs. 1–3. Predrug and postplacebo functions for smooth pursuit were similar to those reported previously (Rothenberg et al. 1980a). There were significant reductions in gain and cross-correlation and increases in phase lag as a function of frequency ($F = 113.878$, $df = 7, 35$, $P < 0.001$ for gain; $F = 20.299$, $df = 7, 35$, $P < 0.001$ for cross-correlation; and $F = 47.529$, $df = 7, 35$, $P < 0.001$ for phase) as cited in the literature.

There was a significant decrease in smooth pursuit gain as a function of dose and drug ($F = 4.518$, $df = 2, 10$, $P = 0.041$ for dose; and $F = 5.353$, $df = 2, 10$, $P = 0.027$ for the dose by predrug/postdrug interaction). Further analyses showed that only the postdrug dose effect was significant ($F = 10.488$, $df = 2,10$, $P = 0.004$). Matched t-tests indicated that 5 mg diazepam significantly reduced gain only at 0.4 Hz ($t = 2.649$, $df = 5$, $P = 0.046$), while 10 mg diazepam significantly reduced gain at pursuit frequencies of 0.4, 0.6, 0.8, 1.0, 1.2, and 1.6 Hz when compared to gain after placebo ($t = 2.067$, $df = 5$, $P = 0.094$; $t = 2.319$, $df = 5$, $P = 0.069$; $t = 4.274$, $df = 5$, $P = 0.008$; $t = 11.008$, $df = 5$, $P < 0.001$; $t = 4.253$, $df = 5$, $P = 0.009$; and $t = 8.334$, $df = 5$, $P < 0.001$ for the six frequencies, respectively).

Significant changes were found in smooth pursuit stimulus-response cross-correlation as a function of drug ($F = 9.483$, $df = 1, 5$, $P = 0.028$ for predrug/postdrug effect). Matched t-tests showed that predrug versus postdrug change in cross-correlation was significant for 10 mg diazepam at pursuit frequencies of 0.6, 1.0, 1.2, and 1.6 Hz ($t = 2.731$, $df = 5$, $P = 0.042$; $t = 2.898$, $df = 5$, $P = 0.034$; $t = 2.199$, $df = 5$, $P = 0.80$; and $t = 5.180$, $df = 5$, $P = 0.004$ for the four frequencies, respectively).

There were no consistent drug or dose effects of diazepam upon phase of smooth pursuit.

Discussion

Diazepam reduced the amplitude (gain) of smooth pursuit eye tracking at all but the highest and lowest frequencies tested. Furthermore, for most of the frequencies with reduced amplitude of eye movement, diazepam reduced the correspondence between the stimulus track and the eye track (cross-correlation). The apparent lack of diazepam action at 2.0 Hz may be accounted for by the general failure of smooth pursuit at this frequency even without drug. Amplitude of tracking is considerably reduced at 2.0 Hz and smooth pursuit is mostly replaced by saccadic tracking, both predrug and postplacebo. At 0.2 Hz the effects of diazepam are not significant. Although there is much variability between subjects in response to diazepam at this frequency, with some subjects showing pronounced decreases in gain, this result may indicate that the effects of diazepam upon smooth pursuit eye tracking are dependent on stimulus velocity. This possibility is reinforced by the finding that smooth pursuit fails at lower stimulus frequencies following administration of 10 mg diazepam and is replaced by saccadic pursuit.

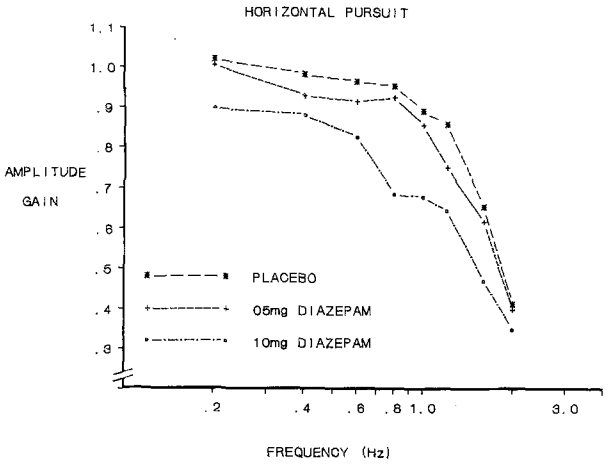

Fig. 1. Mean postdrug gain of smooth pursuit. Change in gain was dose-related

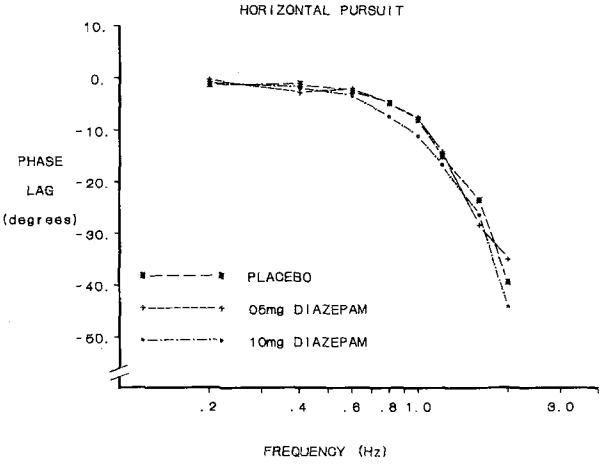

Fig. 2. Mean postdrug phase of smooth pursuit. Changes in phase were not significant

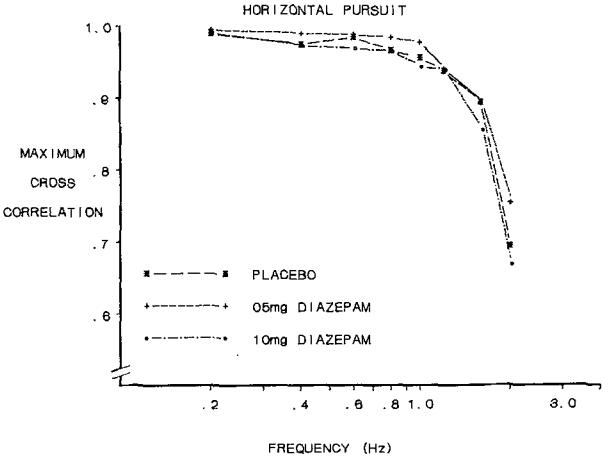

Fig. 3. Mean postdrug maxima of cross-correlation between eye and target motion in smooth pursuit. There were significant pre-drug versus post-drug changes in cross-correlation at some frequencies with 10 mg diazepam

Figure 4a shows the typical progression of smooth pursuit failure as a function of dose of diazepam. Peak amplitude of tracking decreases and there is a progressive increase in saccadic tracking as the dose increases. This pattern of deficit after diazepam may be related to the pattern of benzo-

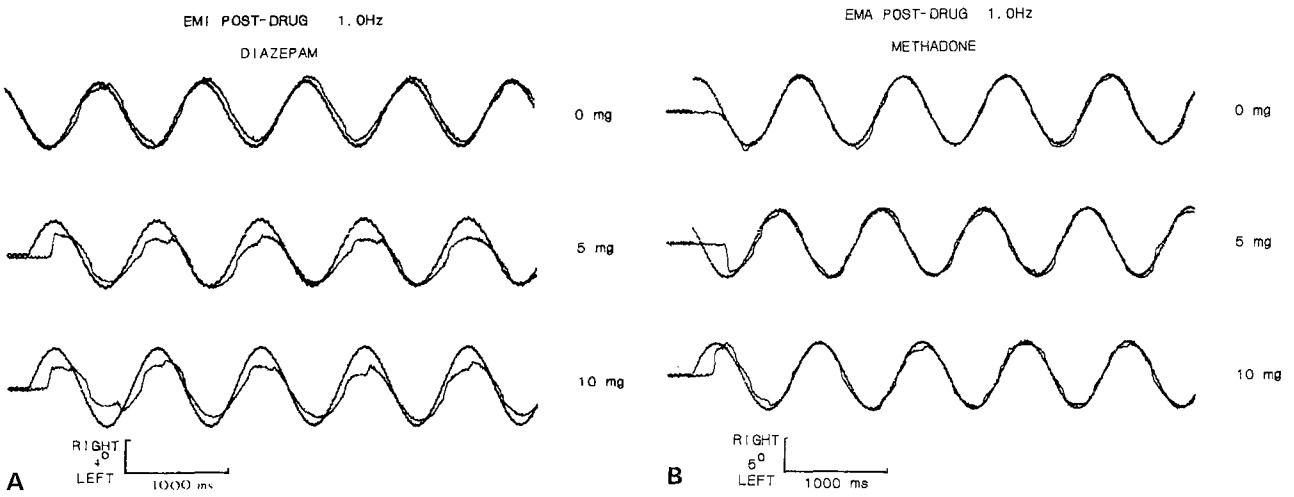

Fig. 4. Typical change in smooth pursuit as a function of dose diazepam (**A**) and methadone (**B**). Note larger reduction in amplitude and replacement of smooth pursuit with saccadic pursuit after diazepam

diazepine binding sites in the visual CNS. Benzodiazepines bind densely in frontal and occipital cortical areas and in vermal and floccular cerebellar areas (Speth et al. 1978; Möhler and Okada 1978), occupying binding sites in brain areas important to oculomotor control. We have previously demonstrated the correlation of diazepam and opiate binding site distribution in visual CNS with specific deficits in saccade function after diazepam and opiate (Rothenberg and Selkoe 1981; Rothenberg et al. 1980b). Figure 4b shows that alteration of smooth pursuit by methadone, a synthetic opioid analgesic, is markedly different from that produced by diazepam. Specifically, the reduction in amplitude is less severe than that seen after diazepam and there is almost no evidence of replacement of smooth pursuit by saccadic pursuit.

We have previously noted the similarity between diazepam alteration of saccadic eye movements and the changes in saccades produced by alcohol and olivopontocerebellar atrophy (OPCA) (Rothenberg and Selkoe 1981). The effects of alcohol (Drischel 1968; Wilkinson et al. 1974; Guedry et al. 1975; Flom et al. 1976) and OPCA syndrome (Baloh et al. 1975; Avanzini et al. 1979) upon smooth pursuit are qualitatively similar to the effects of diazepam on smooth pursuit as well. While alcohol has rather widespread action in the CNS, the areas affected in OPCA are largely confined to the pontine and olivary regions of the brain stem, and the granular and Purkinje cells of the cerebellum (Königsmark and Weiner 1970; Brown 1975). The similarity between diazepam and OPCA effects on smooth pursuit becomes more interesting in light of the localization of benzodiazepine binding sites to granular and molecular leyers of the cerebellum (Young et al. 1980), areas that receive input from climbing and mossy fibers derived from olivary and pontine regions of the brain stem. The data on diazepam binding site pattern in the cerebellum, the similarity of the drug's effect of OPCA syndrome, and the possibility that the diazepam deficit in smooth pursuit may be related to stimulus velocity, suggest the importance of investigating the effects of diazepam on the vermal and floccular Purkinje cells, which are modulated by target or eye velocity (Kase et al. 1979; Noda and Suzuki 1979).

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