Effects of clobazam and clonazepam on saccadic eye movements and other parameters of psychomotor performance

C. H. van der Meyden1, P. R. Bartel1, De K. Sommers2, M. Blom2, and L. C. Pretorius3
1 Departments of Neurology, 2 Pharmacology and 3 Electronic Engineering, University of Pretoria, South Africa

Summary. The effects of two benzodiazepine anticonvulsants clobazam (20 mg) and clonazepam (2 mg) in a variety of psychomotor performance tests were compared in a placebo controlled double-blind acute oral dose study in ten healthy volunteers. Assessments included critical flicker fusion (CFF) threshold, the Sternberg memory scanning and choice reaction time (CRT), peak saccadic velocity (PSV) and visual analogue scales, all previously shown to be sensitive to the effects of benzodiazepines.

Clobazam did not significantly impair saccadic eye movements, CFF threshold, Sternberg memory scanning and CRT compared to placebo. Clonazepam significantly lowered PSV, reduced the CFF threshold, slowed the Sternberg CRT and decreased an alertness factor in the visual analogue scales compared to placebo. Clonazepam significantly increased memory scanning time compared to clobazam. Clobazam was remarkably free of cognitive and psychomotor side-effects.

Key words: clobazam, clonazepam; psychomotor performance, saccades, analogue scales

Clonazepam a 1,4- and clobazam a 1,5 benzodiazepine have both earned a recognized place in the treatment of epilepsy [1–4]. Clonazepam has significant sedative and behavioural side-effects [5, 6], while clobazam is relatively free from psychomotor and cognitive impairment in conventional doses [7–11]. Both drugs have the drawback of the development of tolerance to their anticonvulsant effects [12, 13]. Peak serum levels usually occur 1 to 4 h after oral administration [2, 14]. Benzodiazepines are potentially hazardous due to their effects on driving and motor skills [11, 15, 16]. They impair the speed of performance of simple acts of a repetitive type, and of learning and immediate memory recall, and show relative sparing of established higher mental functions [17]. There is an important relationship between the sedative effect of a drug, the level of arousal and the speed of sensori-motor functioning [18–20].

The aim of the present study was to assess the effects of clonazepam and clobazam on psychomotor function assessed by the following tests: critical flicker fusion (CFF) threshold, a sensitive measure of benzodiazepine sedation [21, 22] and an objective measure of central nervous system arousal, excitability and integration [23]; the Sternberg memory scanning and choice reaction time (CRT) test [24], which measures the speed of sensori-motor functioning after a critical stimulus, and differentiates central (memory scanning and decision making) from peripheral (sensory encoding and distal motor response) processes; the peak velocity (PSV) and duration of saccadic eye movement, which is a sensitive measure of the sedative effect of benzodiazepines and of involuntary pontine reticular formation functioning [25–27]; and the visual analogue scales [28], which afford a subjective but quantifiable rating of mood, alertness and arousal.

Material and methods

Patients and protocol

Ten healthy male volunteers, aged 20 to 25 years, of normal weight and height, were tested in a randomized, cross-over, double-blind, placebo-controlled study. They were requested to abstain from smoking cigarettes or ingesting coffee, tea, cola or alcoholic beverages for 24 h prior to being tested, and they did not take any other medication. Subjects were tested whilst fasting, at the same time in the afternoon, and were familiarized with the tests during a prac-
C. H. van der Meyden et al.: Clobazam and clonazepam effects on saccadic eye movements and visual analogue scale run prior to medication. Each subject was tested before and 1.5 h after the intake of placebo, clobazam 20 mg, and clonazepam 2 mg, and the test results (1.5 h) were compared. The CFF test was administered first, followed by the Sternberg CRT test, the saccadic eye movement recordings and finally the visual analogue scale were completed.

Ethical approval
This was given by an Ethics Committee of the University of Pretoria and written informed consent was obtained from all subjects.

Statistical analysis
The non-parametric Wilcoxon matched-pairs signed rank test was used. Since three pairwise tests (placebo versus clonazepam, placebo versus clobazam and clonazepam versus clobazam respectively) were of interest for each variable, p-values were interpreted at the Bonferroni adjusted significance level of 0.05/3 = 0.017.

Assessment measures
The CFF threshold was determined by combining the method of limits with the two-alternative forced choice method of Salmi [29]. The light stimulus consisted of four, 5 mm square, red light emitting diodes which yielded a target size of 10 mm × 10 mm. The target and the background were delimited by a black border of 1 mm and were mounted behind matt glass. Flickering occurred with a 50% duty cycle and the luminance of the target (average) and the background was 16 cd·mm⁻². The target subtended a visual angle of 3° and the background 15° at the eye. The target and the background were seen in Maxwellian view at optical infinity, through an artificial pupil of 2 mm in diameter. The subject registered responses by means of two push buttons.

The Sternberg CRT test closely followed the design of Oborne and Rogers [24]. The subject had to determine whether a stimulus belonged to a previously memorized set. Four memory set sizes were employed, each consisting of one to four digits. A microcomputer was used to present the digit stimuli and to measure the positive or negative response times. The viewing distance was approximately 60 cm, the stimuli were 1.5 cm in height, subtending a visual angle of approximately 1° 26'. Each digit was presented on the screen for 0.5 s. A trial was defined as a stimulus and a response. A block consisting of 22 trials was used for each memory set size. A 1-min break was allowed between blocks. The memory sets were randomly distributed within the test and each memory set size was tested twice. A practice session preceded the test and consisted of two blocks. Each test session included 2 (each memory set tested twice) x 4 (blocks) x 22 (trials) = 176 trials, of which the first two trials in each block were discarded, leaving 160 trials for analysis. The mean reaction time for each memory set size was determined for the negative, positive and the combined negative and positive (combined mean) responses.

Saccadic eye movements were measured by a microcomputer using original algorithms based on techniques previously described [26, 27, 30-32]. The position and movement of the eyes were measured by electrooculography (EOG) using silver-silver chloride electrodes placed lateral to both outer canthi and with a common reference electrode on the forehead. The EOG was amplified by a DC amplifier (lowpass 50 Hz) and digitized at 400 Hz with 12-bit resolution. The subject viewed the jumping target on a horizontal stimulator bar, which consisted of red light emitting diodes. The saccade test consisted of 42 symmetrical stimulus jumps grouped into three batches, each of 14 jumps. Each batch was separated by a 20 s rest period. The jumps in each batch consisted of 2 amplitudes, the first 7 at a single amplitude and the next 7 at a different amplitude. The first and the eighth saccade of each batch (asymmetrical jumps) were discarded, leaving a maximum of 36 saccades for analysis. The amplitude of the target displacement was 16°, 20°, 25°, 30°, 35° and 40°. Each saccade was processed individually, filtered, checked for artefacts, and then its characteristics were extracted. Saccades were rejected if any of 12 conditions applied, namely inability to calibrate because of artefact or noise, excessively fast or slow reaction time, and a primary saccade which exceeded its allowed maximal duration or velocity. The PSV and saccade duration (ms) were extracted from the processed data. Using nonlinear regression analysis the following exponential curve was fitted to the PSV - amplitude data: $EV = K (1 - \exp (-A/L))$, where EV is eye velocity, A is saccade amplitude (degrees), and K and L are constants returned by the curve fitting program in degrees per second and degrees respectively [30]. The