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Original Research Article

Effects of Oral Diazepam on Visual Functions of Healthy Nigerian Volunteers

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Abstract
Objectives: Diazepam, a benzodiazepine is used clinically for its anxiolytic, sedative-hypnotic, muscle-relaxant effects, and when used therapeutically, little or no attention is paid to its ocular effects or manifestations.
Methods: The ocular manifestations or signs after therapeutic ingestion of diazepam on visual functions were determined in ten healthy young adult volunteers. The following visual functions were assessed: pupil size, amplitude of accommodation, near point of convergence, visual acuity at near and far, as well as distant and near phoria.
Results: Revealed that diazepam has no effect on the pupil diameter, as well as near and distant visual acuity, while the near point of convergence and the amplitude of accommodation increased by 51% and 13.4% respectively. However, the phoria status tended towards orthophoria thereby enhancing existing heterophoria.
Conclusion: Consequently, there is need for close monitoring to avoid negative effects on vision following prolonged use of diazepam.
Keywords: Diazepam, sedative-hypnotic, therapeutic effects, visual functions

1.Introduction
Diazepam, a benzodiazepine, is a sedative-hypnotic drug with anxiolytic, muscle relaxant autonomic, calming, sleep inducing and anticonvulsant properties. Most important effects of the drug are exerted on the central nervous system, and these include reduction of anxiety and aggression, sedation and induction of sleep, reduction of muscle tone and coordination as well as anticonvulsant effect[1,2,3]. Benzodiazepine as a group reduces the time taken to get to sleep and increases the total duration of sleep, reduces muscle tone by a central action that is independent of their sedative effect. Members of the group have anticonvulsant activity and are generally more effective against chemically-induced convulsions than against electrically-induced ones[4]. Diazepam is selectively analgesic and causes transient analgesia following intravenous administration[5]. This study deals with the effects of diazepam, a member of benzodiazepine group on visual functions in the process of accomplishing its therapeutic effects.

2. Patients and Methods
2.1 Subjects
Ten healthy young adult volunteers of either sex whose ages ranged between 35 and 40 years (mean 36.6±1.56) and body weight 60-68 kg, were screened and selected from those who attended the optometry outreach organized by the School of Optometry, Abia State University, Uturu, Nigeria.
2.2 Study Design
Each volunteer was interviewed separately and information on socio-demographic data, medical history was obtained and informed verbal consent elicited. Each volunteer was further subjected to screening, ocular and visual examination by the optometrist, to ensure ocular health that is, refractive errors or ocular pathologies which might introduce

errors in the study. Additionally, each volunteer (subject) had a normal near point of convergence (NPC) of 8-10cm before the study. Subjects had initial measurements of the pupil size (pupil diameter), visual acuity (VA) at far and near, the amplitude of accommodation (AA), the near point of convergence (NPC), phoria status and tonometry before commencement of protocol so as to establish their initial values. Furthermore, each volunteer served as his or her own control. This study was approved by the Health Research Ethical Committee of the University involving such studies. Differences, between the initial values of the visual parameters or functions and those observed after drug administration (diazepam) were regarded as the effect of the drug on the particular visual function or parameter. Preliminary studies had shown that following oral administration of diazepam (benzodiazepine) effects manifest within 30 minutes and may last for more than 60 minutes. The pupilliometer was used for the measurement of the pupil diameter, while the meter rule was used for the NPC. The Snellen distance chart and the reduced Snellen chart were used for the measurement of VA and the phoria. The phoropter and its accessories were used for the assessment of the amplitude of accommodation. Diazepam, by Roche 10mg, light blue scored tablet marked "Roche 10^{TM}" was used for the study.

2.3 Measurements

Before the commencement of the measurements the subjects were properly instructed and educated on each procedure.

a. Pupil size (pupil diameter): The pupillary diameter of each subject was measured using a pupillometer. Each value was measured three times and the average determined and the value expressed in mm.
b. Visual acuity (VA): The VA at both far and near were measured using standard illuminated Snellen optotypes at the normal measuring distance of 6m and 0.4m for far and near respectively.
c. Near point of convergence (NPC): The NPC was measured with subjects fixating at the tip of a pencil positioned initially at 40cm, then adjusted towards the subject until the subject reports diplopia. The distance between the position of the doubling and the central plane of the subject was measured with the meter rule in centimeters to give the NPC.
d. Amplitude of accommodation (AA): The AA was accomplished using the minus and subjects were positioned behind the phoropter was accomplished using the minus lens to the blur method, the subjects were positioned behind the phoropter and gaze directed on the standard reading material of size 0.62m at 0.33m distance. Minus lenses were added in 0.25D steps binocularly until a complete blur of the letters gazed at was achieved. The value of the amplitude of accommodation is the amount of lens added to achieve blur plus +2.50D and is expressed in diopters (D).
e. Phoria. The fixation target used for assessing the phoria was a vertical line of letters placed at 0.40m for near and a Snellen optotype at 6m for far. A 6-base up prism to separate the target vertically was placed before the eye of the subject. The 15-base-in prism was gradually reduced while asking the patient to report when the images have aligned vertically. The remaining base-in prism while alignment was achieved was recorded as the amount of phoria exhibited by the patient. This was done at near distance of 0.4m with the target using a reduced 6/6 letters and measurements taken.

Thereafter, 10mg diazepam, light-blue scored tablet marked "Roche 10^{TM}" was administered orally to the subjects. Each subject received 50ml of potable water to hasten dissolution of the tablets, and the above measurements were repeated after 20 and 30 minutes respectively.

2.4 Statistical Analysis

This was carried out using GraphPad Prism version 4.0 and results presented in tabular form.

3. Results

The ocular effects of diazepam were early in onset and manifested as common complaints of drowsiness, a central effect. However, this was overcome by engaging the participants (subjects) in ambulatory activity within the clinic which served as supplemental physical activity while the study lasted.

Pupil size (diameter): Diazepam has no effect on the pupil diameter as the mean diameter remained unchanged throughout the study.

Near point of convergence (NPC): The mean initial value of NPC before the study was 8.55± 2.12 cm and following ingestion of diazepam, (10mg), the value became 12.91 ± 2.15 cm or 51% increase as shown in Table 1.

Visual acuity (VA): The VA at both far and near before the commencement of protocol remained unchanged until the end of the study.

Amplitude of accommodation (AA): The mean initial value of the AA was 7.01± 1.06 and following drug administration, the mean value changed to 7.95± 1.51 D or 13. 4% increase as shown in Table 2.

Phoria: At the commencement of the study, 30% of the subjects were orthophoric (normal) and exophoric

(divergent) respectively, while the remaining subjects (40%) were esophoric (convergent). However, following diazepam administration, 60% of the study population became orthophoric as all the exophoric subjects had been converted to orthophoria while those who were initially orthophoric remained unchanged. Similarly those esophoric subjects remained unchanged (40%) and were more esophoric (convergent). On the whole there was enhancement of existing heterophorias as shown in Table 3.

Table 1: Changes in NPC following oral administration of Diazepam (10mg)

S/N	Initial Value (cm)	Value 20 Mins After Drug Adminstration (cm)	Value 30 Mins After Drug Administration (cm)
1.	10	12	13
2.	8	11	11
3.	10	13	13
4.	8	10	10
5.	8	11	11
6.	10	15	15
7.	10	13	13
8.	12	14	14
9.	10	13	13
10	9	12	12

Table 2: Changes in AA Following oral administration of Diazepam (10mg)

S/N	Initial Value (D)	Value 20mins After Drug Adminstration (D)	Value 30 Mins Later (D)
1.	8.50	6.25	6.25
2.	8.20	9.20	9.20
3.	9.50	10.00	10.00
4.	6.00	7.00	7.00
5.	7.00	8.00	8.00
6.	7.00	7.50	7.50
7.	9.50	10.00	10.00
8.	8.00	9.00	9.00
9.	6.25	6.50	6.50
10	7.75	8.50	8.50

Table 3: Changes in phoria status following oral administration of diazepam 10mg

S/N	Initial Phoria Value	Phoria Value 20 Mins After Drug Administration	Phoria Value 30 Mins Later
1.	Ortho	Ortho	Ortho
2.	Ortho	Ortho	Ortho
3.	2 exo	Ortho	Ortho
4.	5 eso	11 eso	11 eso
5.	Ortho	Ortho	Ortho
6.	2 exo	Ortho	Ortho
7.	1 eso	4 eso	4 eso
8.	3 eso	7 eso	7 eso
9.	2 exo	Ortho	Ortho
10.	4 eso	6 eso	6 eso

4. Discussion

The effects of diazepam, a benzodiazepine, virtually result from actions on the central nervous system even when high doses are taken. The most prominent of these effects are sedation, hypnosis, decreased anxiety, muscle relaxation and anti-convulsant activity. It affects activities at all levels of neuroaxis, some of the effect of the drug are indirect[6,7]. It decreases sleep latency when first used and diminishes the number of awakening and time spent in the stage of wakefulness[8,9]. Much attention has been paid to the effects of the drug on REM (rapid eye movement) sleep. Members of the group increase REM latency that is, time from onset of spindle sleep to the first REM burst. The frequency of eyeball movement during REM is decreased and the time spent on REM sleep is shortened[10]. However, nothing has been said about

the resultant visual effects (defects) following their therapeutic use.

In the present study, diazepam increased the NPC and the AA without affecting the pupil size (diameter) and the VA at both far and near, but subjects were still able to read 6/5 line of the far Snellen chart and the N5 line of the near chart even after the administration of the drug. The resolving power of the eye was not in any way affected by the ingestion of 10mg diazepam.

As the pupil diameter was not affected, it portends that the drug has no effect on either of the pupillary muscles–sphincter and dilator pupillae even though the drug has muscle relaxant properties[11]. Furthermore, the amount of diazepam reaching the eye may not be sufficient to cause any effect on the pupil size because the drug effect on any tissue or organ depends on the pharmacokinetic profile of the drug and in this case the bioavailability, which is low since diazepam was administered orally.

As there is no direct blood supply to the lens, the amount of diazepam reaching this ocular structure is reduced and this accounts for lack of effect on the VA. On the other hand, the NPC had some deviation from normal which showed that patients taking diazepam demonstrate convergence in-sufficiency which would predispose them to asthenopic symptoms when near work is being done. However, this effect is not manifested because of sedative-hypnotic properties of diazepam.

The amplitude of accommodation (AA) which represents the maximum amount of accommodation which the eye is capable of tolerating and the ability of the eye to effect this, is influenced by various factors such as the refractive status of the subjects, previous use of the ciliary muscles and the general ocular health of the subject. In the present study, there was an increase in AA (13.4%), however, the increase was not enough to affect the vision of the subjects.

Diplopia, due to paresis of the extra ocular muscles has been reported with diazepam[12] and in the present study, there were changes in the phoria status and the trend showed that subjects who were exophoric (divergent) initially became orthophoric (normal) after diazepam (drug) administration while the orthophoric subjects remained so and the esophoric (convergent) became more esophoric. In other words, this finding shows an enhancement of existing heterophoria following oral administration of diazepam.

Finally it should be noted that in long-term use of diazepam, patients should be under close monitoring to guard against abnormal or excessive changes in AA, NPC and phoria in order to avoid their negative effects on vision.

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