

# Evaluation of the Ocular Effects of Clonidine Following Therapeutic Use

\*Igwe S.A.<sup>1</sup>, Nwobodo N.N.<sup>2</sup>, Nwadike K.N.<sup>3</sup>, Ebo E.N.<sup>4</sup>, Agbata C.<sup>5</sup>

<sup>1</sup>Department of Pharmacology and Therapeutics, College of Medicine, Enugu State University of Science and Technology, Enugu, Nigeria.

<sup>2</sup>Division of Clinical Pharmacology and Applied Therapeutics, Faculty of Clinical Medicine, Enugu State University of Science and Technology, Enugu, Nigeria. <sup>3</sup>Department of Pharmacology and Therapeutics, College of Medicine, University of Nigeria, Enugu, Nigeria.

<sup>4</sup>School of Optometry, Abia State University, Uturu, Nigeria.

<sup>5</sup>Department of Pharmacology and Toxicology, Faculty of Pharmaceutical Sciences, Nnamdi Azikiwe University, Awka, Nigeria.

## Research Article

### Article Info:

Received on: 26/09/2015  
Accepted on: 25/10/2015  
Published on: 21/11/2015



QR Code for mobile

Literati



### ABSTRACT :

Clonidine hydrochloride is a potent centrally acting antihypertensive agent, having vagotonic effect, lowering blood pressure by stimulating  $\alpha_2$ -receptors in the brain which decreases the peripheral resistance. Apart from its lowering of intra-ocular pressure, no attention has been focused on its effects on any other visual functions. This study was undertaken to investigate the ocular manifestations or signs after therapeutic use of clonidine. Results showed that the pupillary diameter (PD), amplitude of accommodation (AA) and accommodative-convergence/accommodation (AC/A) ratio decreased by 31%, 24.5% and 69% respectively; while the visual acuity (VA) and the near point of convergence (NPC) increased by 65% and 16% respectively. Furthermore, there were significant and varying changes in the phoria status. The net effect of clonidine on visual functions is implosion of vision due to convergence insufficiency and excessive accommodation.

**Keywords:** Accommodation, clonidine, convergence, ocular effects, therapeutic use, visual functions.

## INTRODUCTION:

Clonidine hydrochloride is a potent anti-hypertensive drug closely related chemically to imidazoline, a peripheral vasodilator and  $\alpha$ -adrenergic blocking drug; the sympathomimetics naphazoline and tetrahydrozoline; and antazoline, an antihistamine. It was originally studied as an alpha-adrenergic agonist and was tested for its efficacy as a nasal decongestant<sup>[1]</sup>, while small amounts of the drug given intranasally produced hypotension. Subsequent studies confirmed its therapeutic efficacy as a centrally acting anti-hypertensive agent<sup>[2]</sup>.

Hypertension is not only one of mankind's most common disease but the biggest single causative factor of death. The great majority of cases of hypertension are under the category of essential hypertension of which the clinically distinguished phase is labile hypertension in which the blood pressure is intermittently elevated, followed by a diastolic hypertension in which there is elevation of diastolic pressure whereas systolic hypertension occurs mostly in older patients<sup>[3]</sup>.

Clonidine hydrochloride has become an important antihypertensive drug since its introduction more than three decades ago<sup>[4]</sup>. Clonidine owes its antihypertensive effect to a predominant action on the central nervous system, where it produces a decrease in the sympathetic outflow from the brain<sup>[1]</sup>. Clonidine treats high blood pressure by stimulating  $\alpha_2$ -receptors in the brain, which decreases peripheral

vascular resistance thereby lowering blood pressure. It has specificity towards the presynaptic  $\alpha_2$ -receptors in the vasomotor centre in the brain stem. This binding decreases presynaptic calcium levels, thus inhibiting the release of adrenaline and the net effect is a decrease in sympathetic tone<sup>[5]</sup>. It has also been proposed that the antihypertensive effect of clonidine is due to agonism on the imidazoline receptor, which mediates the sympatho-inhibitory actions of imidazolines to lower blood pressure<sup>[6]</sup>.

Notwithstanding the effects of clonidine indicated above, no report has been documented on its effects on visual functions other than intraocular pressure. The purpose of this study is to evaluate the effects of oral clonidine on some visual functions such as pupil diameter (PD), near point of convergence (NPC), visual acuity (VA) at far and near, amplitude of accommodation (AA), accommodative-convergence/accommodation (AC/A) ratio, distant and near phoria when used therapeutically.

### MATERIALS AND METHODS

Twenty healthy adult volunteers whose ages ranged between 25 and 30 years (mean  $26.7 \pm 0.45$ ) and body weight 55 to 65kg (mean  $61.8 \pm 1.36$ ) were screened and selected from those who attended the optometry outreach organized by the School of Optometry, Abia State University, Uturu, Nigeria. Informed verbal consent was elicited and each volunteer interviewed separately and information

\*Corresponding author:

Igwe S.A

Department of Pharmacology and Therapeutics, College of Medicine, Enugu State University of Science and Technology, Enugu, Nigeria.

E-mail: nwsuigwe@yahoo.com

doi: 10.15272/ajbps.v5i49.743

Conflict of interest: Authors reported none

submit your manuscript | www.jbiopharm.com



on sociodemographic data and medical history obtained. Each volunteer was further subjected to screening and visual examination by the optometrist to rule out ocular conditions, that is refractive errors or ocular pathologies which might introduce bias in the study. Additionally, routine blood pressure measurement was undertaken for each volunteer, and only those volunteers whose mean blood pressure was  $\leq 120/80$  mmHg after 3 consecutive measurements enlisted in the study.

This study was approved by the Ethical Review Committee of Abia State University. Subjects had initial measurements of the pupil diameter (PD), visual acuity (VA) at far and near, near point of convergence (NPC), amplitude of accommodation (AA), accommodative-convergence/accommodation (AC/A) ratio, distant and near phoria and tonometry before commencement of protocol so as to establish their initial values. Furthermore, each volunteer or subject served as his or her own control.

#### Measurements:

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

- Pupil Diameter (PD): The pupillary diameter of each subject was measured using a pupilometer. Each value was measured three times and the average determined and the value expressed in mm.
- 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 vision respectively.
- 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 metre rule in centimeters to give the NPC.
- Amplitude of Accommodation (AA): The AA 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 0.250 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 + 2.500 and is expressed in diopters.
- Phoria: The fixation target used for assessing the phoria was a vertical line of letters placed at 0.40m for near and 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 subject. This was done at near distance of 0.4m with the target

using a reduced 6/6 letters and measurements taken.

- Accommodative-Convergence/Accommodation (AC/A) Ratio: AC/A ratio was measured by determining the phoria at far, then repeated with the addition of +1.00D or -1.00D lens. The difference in both phoria measured was recorded as the accommodative-convergence/accommodation (AC/A) ratio in fraction.

#### Drug Administration

Oral clonidine 100mg was used and dispensed as *Catapres*<sup>TM</sup>. The study lasted for five days during which clonidine was administered in the following manner:

Day 0	-	1.2mg/day
Day 1	-	1.2mg/day
Day 2	-	1.2 mg/day
Day 3	-	1.2mg/day
Day 4	-	Drug free.

The measurements of the visual functions were repeated each day at 10.00am before drug administration. This is to avoid diurnal variations. On day 4 (D4) following drug administration, only measurements of the visual functions were taken.

Differences between the initial values of each visual function and the values obtained for the particular visual function after drug administration was regarded as the effect of the drug on the particular visual function and the result expressed in percentage.

#### Drugs and Equipment

Lignocaine 0.4% (*Xylocaine*<sup>TM</sup> from Astra-Zeneca, India), Clonidine 100mg (*Catapres*<sup>TM</sup> from Boehringer-Ingelheim, India), Pupilometer, Pen torch, Optical rule, Snellen's chart, Sphygmomanometer, Phoropter with its accessory and Schiötz tonometer.

**Data analysis:** The data generated from the study were arranged in tabular form. Difference between the initial value prior to drug administration and that obtained at end of the study was taken as the change induced by clonidine on the particular visual function and the value expressed in percentage.

#### RESULTS

The results of the present study are presented in Tables I-VI.

Table I, depicted the effects of clonidine on the pupil diameter. It revealed a 31% reduction in the pupil size which is a miotic effect.

Table II shows the overall effects of clonidine on the visual acuity of the study group and shows that 65% of the group had their VA improved at far while near VA remained constant throughout the study group.

The effect on the NPC are depicted in Table III showing 16% increase. However, Tables IV and V depict values for AA and AC/A ratio obtained during the study and indicate 24.5% and 69% reduction in AA and AC/A ratio respectively at the end of the study. Table VI depicts the results of the phoria status of the population, in which at far 35% were orthophoric at the end of the study while another 35% were esophoric and the remaining 30% of the study

group were exophoric to varying degrees. However, at near, 95% of the subjects were exophoric at different degrees and only one subject (5%) demonstrated esophoria. Furthermore, in the exophoric state two subjects (10%) remained unchanged while another subject (5%) changed from 2 eso

to 4 exo and another single subject converted from ortho to 1 exo position.

**TABLE I: INITIAL AND FINAL PUPIL SIZE IN (MM) AFTER ADMINISTRATION OF CLONIDINE**

S/NO	INITIAL PUPIL SIZE (MM)	FINAL PUPIL SIZE (MM)
1.	3.0	2.0
2.	3.0	2.0
3.	4.0	3.0
4.	2.0	1.0
5.	3.0	2.0
6.	3.0	2.5
7.	3.0	2.0
8.	3.0	2.0
9.	4.0	3.0
10.	2.0	1.0
11.	3.0	2.0
12.	3.0	2.0
13.	4.0	3.0
14.	3.0	2.0
15.	2.5	2.0
16.	2.0	1.5
17.	3.0	2.0
18.	3.0	2.5
19.	3.0	2.0
20.	2.0	1.0
TOTAL	58.5	40.5

**TABLE II: VISUAL ACUITY AT FAR AND NEAR BEFORE AND AFTER CLONIDINE ADMINISTRATION**

S/NO	VISUAL ACUITY AT FAR				VISUAL ACUITY AT NEAR			
	BEFORE		AFTER		BEFORE		AFTER	
	OD	OS	OD	OS	OD	OS	OD	OS
1.	6/6	6/6	6/5	6/5	N.5	N.5	N5	N5
2.	6/6	6/6	6/5	6/6	N.5	N.5	N5	N5
3.	6/5	6/5	6/5	6/5	N.5	N.5	N5	N5
4.	6/5	6/5	6/4	6/5	N.5	N.5	N5	N5
5.	6/6	6/6	6/6	6/6	N.5	N.5	N5	N5
6.	6/6	6/6	6/6	6/6	N.5	N.5	N5	N5
7.	6/4	6/5	6/4	6/5	N.5	N.5	N5	N5
8.	6/6	6/6	6/6	6/5	N.5	N.5	N5	N5
9.	6/5	6/5	6/5	6/4	N.5	N.5	N5	N5
10.	6/5	6/5	6/4	6/4	N.5	N.5	N5	N5
11.	6/6	6/6	6/5	6/4	N.5	N.5	N5	N5
12.	6/5	6/4	6/4	6/5	N.5	N.5	N5	N5
13.	6/6	6/6	6/5	6/5	N.5	N.5	N5	N5
14.	6/5	6/5	6/4	6/4	N.5	N.5	N5	N5
15.	6/6	6/6	6/5	6/5	N.5	N.5	N5	N5
16.	6/5	6/6	6/4	6/5	N.5	N.5	N5	N5
17.	6/6	6/6	6/6	6/6	N.5	N.5	N5	N5
18.	6/6	6/6	6/5	6/5	N.5	N.5	N5	N5
19.	6/6	6/6	6/6	6/6	N.5	N.5	N5	N5
20.	6/5	6/4	6/4	6/4	N.5	N.5	N5	N5

TABLE III: INITIAL AND FINAL VALUES OF NEAR POINT OF CONVERGENCE (NPC) IN CM AFTER CLONIDINE ADMINISTRATION

S/NO	INITIAL NPC (CM)	FINAL NPC (CM)
1.	10.0	13.0
2.	11.0	12.0
3.	11.5	14.0
4.	8.0	8.5
5.	9.0	11.0
6.	7.0	9.0
7.	10.0	11.5
8.	9.0	10.5
9.	11.0	11.5
10.	8.5	10.5
11.	9.0	11.0
12.	7.0	9.0
13.	6.5	8.0
14.	11.0	12.0
15.	9.0	10.0
16.	7.0	8.0
17.	7.5	8.0
18.	8.0	9.0
19.	10.5	11.0
20.	8.0	10.0

TABLE IV: INITIAL VALUES OF AMPLITUDE OF ACCOMMODATION (AA) IN DIOPTERS (D) AND FINAL VALUES AFTER ADMINISTRATION OF CLONIDINE

S/NO	INITIAL AA (D)	FINAL AA (D)
1.	6.50	5.00
2.	5.75	4.00
3.	6.75	5.00
4.	7.00	5.50
5.	5.50	4.00
6.	6.00	4.50
7.	5.75	4.50
8.	5.00	4.00
9.	6.50	4.50
10.	6.75	5.00
11.	6.50	5.25
12.	6.50	5.00
13.	5.50	4.50
14.	6.50	4.00
15.	6.50	5.00
16.	7.00	5.00
17.	5.50	54.50
18.	6.00	4.50
19.	6.50	5.25
20.	6.00	5.00
TOTAL	124.5	94

S/NO	INITIAL AC/A RATIO	FINAL AC/A RATIO
1.	1	0
2.	2	1
3.	3	2
4.	1	1
5.	1	0
6.	1	-1
7.	2	1
8.	3	2
9.	2	1
10.	1	0
11.	1	-1
12.	2	1
13.	4	3
14.	2	1
15.	3	2
16.	1	1
17.	1	0
18.	1	-2
19.	2	1
20.	1	-2
TOTAL	35	11

TABLE VI: INITIAL PHORIA STATUS AT FAR AND NEAR BEFORE AND AFTER CLONIDINE ADMINISTRATION

S/NO	PHORIA AT FAR		PHORIA AT NEAR	
	BEFORE	AFTER	BEFORE	AFTER
1.	2eso	Ortho	7 exo	5 exo
2.	2 eso	1 eso	6 exo	4 exo
3.	3 eso	1 eso	3 eso	2 eso
4.	1 exo	12 exo	7 exo	5 exo
5.	½ exo	1 exo	6 exo	6 exo
6.	2 exo	1 exo	5 exo	4 exo
7.	3 eso	Ortho	6 exo	5 exo
8.	1 exo	X exo	8 exo	7 exo
9.	Ortho	1 eso	7 exo	6 exo
10.	1 eso	Ortho	6 exo	6 exo
11.	2 eso	2 eso	6 exo	4 exo
12.	2eso	Ortho	6 exo	5 exo
13.	2 eso	Ortho	7 exo	5 exo
14.	3 exo	4 exo	5 exo	2 exo
15.	4 eso	2 eso	Ortho	1 exo
16.	2 eso	Ortho	6 exo	4 exo
17.	2 eso	1 eso	6 exo	4 exo
18.	1 eso	Ortho	7 exo	5 exo
19.	Ortho	1 eso	2exo	4 exo
20.	1 exo	12 exo	7 exo	6 exo

## DISCUSSION

Clonidine reduces sympathetic outflow centrally and has vagotonic effect which enhances its sensitivity to carotid sinus stimulation. Reduction in sympathetic outflow would increase the parasympathetic activities leading to the observed side effect of miosis. The suppression of sympathetic outflow results in the lowering of the blood pressure which in effect will make for better vision because hypertension damages the retina which is the vision house of the individual. Clonidine can also be used in the treatment of Tourette syndrome<sup>[7]</sup>. It can be used to ease withdrawal symptoms associated with long term use of narcotics, alcohol, benzodiazepine and nicotine<sup>[8]</sup>. It can alleviate opioid withdrawal symptoms by reducing the sympathetic nervous system response such as tachycardia and hypertension as well as reducing sweating, hot and cold flushes and general restlessness<sup>[9]</sup>. The sedation effect is also useful, although its side effects include insomnia thus exacerbating an already common feature of opioid withdrawal<sup>[10]</sup>. Clonidine has several off-label uses such as sleep disorders and hyperarousal caused by post-traumatic stress disorder<sup>[11]</sup>.

In the present study clonidine caused pupillary constriction, a miotic effect and a reduction of 31% of the pupil size thereby reducing the amount of light reaching the retina. This miosis is in line with the vagotonic effect of clonidine which enhances sensitivity of carotid sinus stimulation. Oral clonidine significantly improved VA from 6/6 to 6/4 and 6/5 indicating that the drug tends to increase vision at far, whereas it did not affect near vision; showing that the drug induces good vision at far and maintains the extent of VA at near. This property might be of benefit to individuals with raised intraocular tension. The relationship between the pupil size and the VA is such that dilated pupil and constricted pupil less than 2mm tend to reduce the acuity whereas not more than 3mm pupil size tends to reduce the amount of light entering the eye thereby increasing the VA. Clonidine increased the NPC by 16% from an initial value of  $8.92 \pm 0.05\text{cm}$  to a final average of  $10.35 \pm 0.06\text{cm}$  (16% rise). This shows that the drug causes more convergence thereby creating better vision at near and in this study the VA at near remained unchanged. The amplitude of accommodation (AA) 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 refractive status of the individual, previous use of the ciliary muscles and age. In the present study there was a reduction in the AA (25%) which would lead to receding near point of clear vision. Low accommodation can be induced by several factors such as age, systemic diseases and in the present study, it is due to drug-induced side effect of clonidine. The subjects demonstrated accommodative insufficiency because the final value of AA in diopters was less than the initial value and these subjects had difficulty in reading and demonstrated transient presbyopia<sup>[12]</sup>. Clonidine reduced the AC/A ratio by 69% which will pre-

dispose to convergence insufficiency causing doubling of vision at near. The drug appears to reduce the central demand for accommodative innervations and hence reduce the amount of convergence induced by accommodation<sup>[13]</sup>. In table VI, the effects of oral clonidine on the phoria status of the subject are displayed. For the distant phoria, there was 45% reduction in esophoria, 25% reduction in exophoria and a decrease of 35% in orthophoria while 10% of the study group showed increase in both esophoria and exophoria. This shows that the reduction in esophoria at far will predispose to better vision at distance. For the near phoria, oral clonidine caused 80% decrease in exophoria, 5% reduction in esophoria and 5% increase in exophoria while 10% had their exophoria static at the end of the study. This indicates that oral clonidine created more exophoria at near, making vision much better but the miosis would make the fusional reserve insufficient for the exercise.

We conclude that although clonidine lowers both systemic and intraocular pressure appreciably, the drug induces convergence insufficiency and excessive accommodation which must be taken into consideration during assessments or tests of visual functions in patients on clonidine therapy.

## REFERENCES :

1. Parker K, Bruntone L, Goodman LS, et al. Central acting agents that interfere with adrenergic neurons. In: Goodman and Gilman, eds. *The Pharmacological Basis of Therapeutics*. McGraw-Hill, New York; 2006: 854-55.
2. William O. *Principles of Medicinal Chemistry*. 3<sup>rd</sup> edition, Ronal Press, New York; 1981.
3. Wang IJ, Ramachandran SV. Epidemiology of uncontrolled hypertension in the United States. *Circulation* 2005; 112:1051-57.
4. Alvin S, Myrth P. Antihypertensives. In: *Nursing Pharmacology*, 2<sup>nd</sup> edition, Yake Medical Books, New York; 1991: 743-58.
5. Shen H. *Illustrated Pharmacology Memory Cards*. PharMnemonics: Minireview; 2008: ISBN1-5954-101-1.
6. Reis OJ, Piletz JE (1997): The imidazoline receptor in control of blood pressure by clonidine and drugs. *Am J Physiol* 1997; 273(5): R1569-71.
7. Egolf A, Coffey BJ. Current pharmacotherapeutic approaches for the treatment of Tourette syndrome. *Drugs of Today* 2014; 50(2): 159-79.
8. Fitzgerald PJ. Elevated norepinephrine may be a unifying etiological factor in the abuse of a broad range of substances: alcohol, nicotine, marijuana, heroin, cocaine and caffeine. *Substance Abuse* 2013; 7:171-83.
9. Gianini AJ. *Drugs of Abuse*. 2<sup>nd</sup> edition, Practice Management information, Los Angeles; 1997.
10. Gianini AJ, Extein I, Gold MS, et al. Clonidine in mania. *Drug Development Research* 1983; 3(1): 101-5.
11. Zoegemjprm AA, Roepke S, Schommer NC, et al. Clonidine improves hyperarousal in border-line personality disorder with or without co-morbid post traumatic stress disorder: a randomized, double-blind, placebo controlled trial. *J Clinical Psychopharmacology* 2009; 19(2): 170-3 .
12. David B. *Clinical Manual for Optometry Students*. Mosby; 1980.
13. Igwe SA, Nwobodo N, Ibeawuchi I. The effects of miotics on accommodative convergence/accommodation ratio of Nigerian youths. *World Journal of Pharmaceutical Sciences* 2015; 3(4): 702-5.

Cite this article as:

Igwe S.A, Nwobodo N.N, Nwadike K.N, Ebo E.N, Agbata C. Evaluation of the Ocular Effects of Clonidine Following Therapeutic Use. *Asian Journal of Biomedical and Pharmaceutical Sciences*, 5(50), 2015,10-15.