LSD-25 and Accommodative Convergence Ratios

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Introduction

Experimentation in both human volunteers and laboratory animals with the psychotomimetic drugs, particularly d-lysergic acid diethylamide (LSD-25), in recent years has revealed that in addition to the more prominent and well-described mental changes there are also decided effects on the autonomic nervous system, as manifested most frequently by mydriasis, increased blood pressure, tachycardia, pilo-erection, hyperthermia, and hyperglycemia.[1,2] It is generally believed that these peripheral autonomic effects are the result of the central action of LSD-25. Some investigators[3] have postulated that the parasympathetic centers are activated by a serotonin system and that the action of LSD-25 is through antagonism to the normal action of serotonin. Others[4] have have felt that LSD-25 causes direct stimulation of mesencephalic and diencephalic sympathetic centers. The mechanism of this central action of LSD-25 on the autonomic system, whether by sympathetic stimulation or by parasympathetic inhibition, has yet to be clarified.

Although LSD-25 is a well-known cause of visual disturbances, no reports indicate an accompanying paralysis of the accommodation mechanism. Accommodation is effected by the contraction of the ciliary muscle, resulting in relaxation of the lens zonules and an increase in the lens thickness. The primary innervation of the ciliary muscle is via the parasympathetic fibers of the third cranial nerve. Cogan[5] has presented clinical evidence that there is perhaps a dual innervation—with the sympathetic system also taking part. More recent investigators[6,7] have shown that sympathomimetic drugs effect a small but detectable decrease in the range of accommodation.

The rate of change of accommodative convergence with the associated change in accommodation, the AC/A ratio, is used to accurately assess accommodation over its full range of action. There are four elements contributing to convergence: fusional, proximal, tonic, and accommodative. By experimentally keeping constant the fusional, proximal, and tonic elements, one may measure the amount of convergence which results from the accommodative stimulus. The AC/A ratio, therefore, is obtained by dividing the change in the lateral phoria in prism diopters by the change in the stimulus to accommodation in diopters. It has been shown that there is a linear relationship between accommodative convergence and accommodation.

The AC/A ratio in the past has been measured by two basic techniques: the variable distance and the gradient methods. In the former method, accommodative stimulus is effected by changes in the fixation distance. On the other hand, by keeping constant the distance of the fixation point and by using varying lenses in front of the eye to change the accommodative stimulus, the gradient method eliminates the influence of proximal

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TABLE 1.—*Accommodative Convergence Ratios—Individual Values*

Subject	Control			LSD-25			Change in Ratio
	No.1	No.2	Average	No.1	No.2	Average	
1	4.4	4.0	4.2	4.7	5.1	4.9	0.7
2	6.0	5.8	6.2	7.3	—	7.3	1.1
3	3.6	4.2	3.9	5.0	4.8	4.9	1.0
4	5.5	6.0	5.75	6.8	6.3	6.4	0.65
5	5.0	5.3	5.15	6.3	—	6.3	1.15
6	3.6	3.8	3.7	4.9	4.9	4.9	1.2
7	4.0	4.7	4.35	6.5	6.8	6.65	2.3
8	5.5	5.5	5.5	6.9	—	6.9	1.4
9	4.8	4.8	4.8	7.0	6.0	6.5	1.7
10	4.3	5.2	4.75	6.7	7.5	7.1	2.35

convergence on the AC/A ratio obtained.[8] Using both methods, early investigations calculated AC/A ratios on just two measurements because of the accepted linearity of the relationship.[9,10] Sloan et al [8] showed that for an accurate determination of the AC/A ratio, multiple measurements with various stimuli to accommodation should be taken. The AC/A ratio then could be calculated on the basis of the best-fitting straight line through numerous points.

The AC/A ratio has been shown to be a relatively stable quantity in a given person.[8,11,12] It is not influenced by changes in pupil size throughout the normal range of pupillary diameters (1.0-10.0 mm).[13] The AC/A ratio, however, will increase decidedly under the influence of parasympathetic antagonists, such as homatropine, which cause marked cycloplegia.[14] Pemberton and Brown [15] showed that orphenadrine citrate (a drug used systemically for relief of muscle spasm and certain clinical manifestations of Parkinsonism) significantly increased the AC/A ratio by means of a mild partial cycloplegia. On the other hand, Sloan et al [8] demonstrated that conjunctival administration of isofluorophate (DFP), an anticholinesterase, consistently reduced the AC/A ratio. This effect on accommodation reflected in the AC/A ratio is undoubtedly due to an increase in the direct parasympathetic stimulation of the ciliary muscle. It was the purpose of this study to evaluate the effect of LSD-25 on the accommodative mechanism of healthy young men by measuring the change in the AC/A ratio.

TABLE 2.—*Accommodative Convergence Ratios—Controls Versus LSD-25*

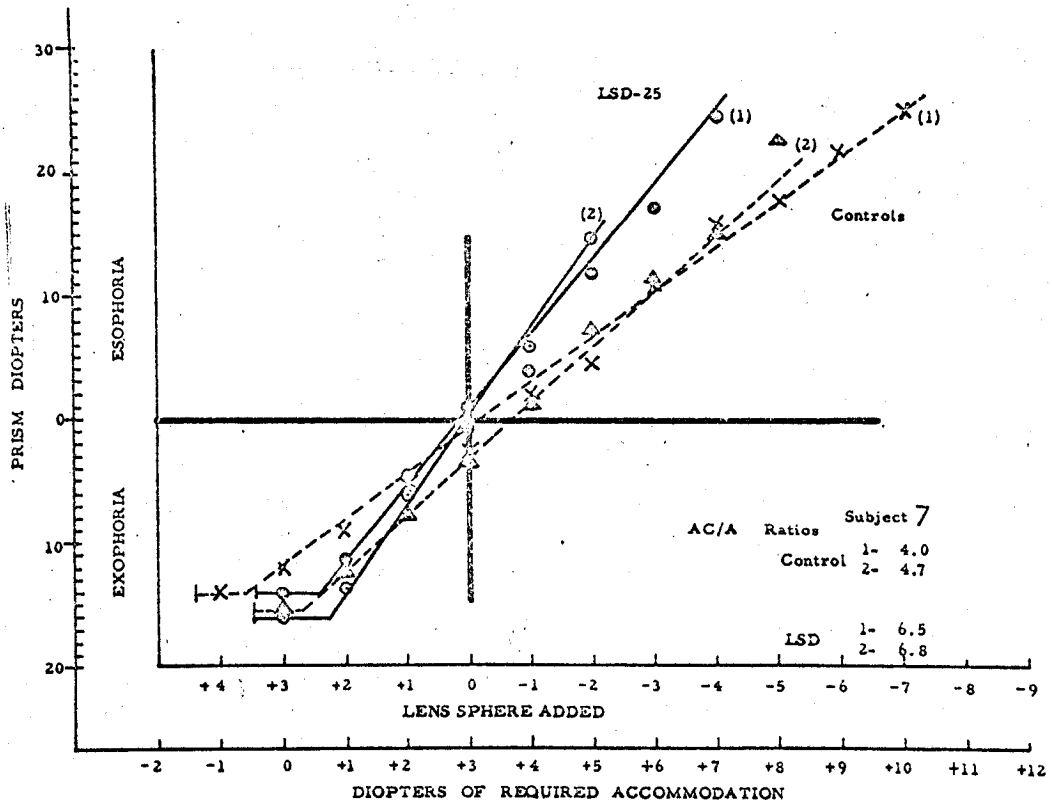
	Mean	Range	Standard Deviation
All controls (20)	4.83	3.6-6.6	0.844
All LSD-25 (17)	6.08	4.7-7.5	0.973
Degrees of freedom	33.819		
t value 4.145			
	Significant at 99%		

Methods

Ten healthy male volunteers, ages 17-24 years, were selected after thorough psychiatric and ocular examinations. The ocular examination included refraction, slit lamp, funduscopy, and tonometry. Only those subjects with relative emmetropia and considered to be psychiatrically "normal" and stable were used.

The AC/A ratio was measured, using the gradient method with a modified phorometer, as previously described by Sloan et al.[8,15] One eye views a point source of light at the center of a small phoria scale at a fixed distance of 33 cm. A white Maddox rod and Risley prism are placed before the other eye. Correction for distance, if indicated, is provided by addition of the necessary lenses to the phorometer. The light source and scale are located at approximately a 20-degree angle below the horizontal plane, in order to correspond to the normal position of the eyes in reading. The subject is instructed to observe the point of light and the adjacent scale markings, trying to keep them in focus at all times. Convex or concave lenses are placed into the lens cells of the phorometer in order to vary the accommodative stimulus given the subject. The first step is the addition of +3 or +4 diopter lenses, in order to eliminate all need for accommodation to focus the normal eye. Successive phoria measurements are then taken by decreasing the lens power in steps of one diopter, working down to a negative lens sufficient to induce the maximum accommodation possible without blurring of the test target.

Measurements of the lateral phoria are made by the prism cover technique. As the eye behind the Maddox rod is periodically uncovered, the subject states whether the streak of light is to the right or left of the point of light. The Risley prism is varied after each exposure until the streak is seen to pass through the point of light when the cover is first removed. Use of the Maddox rod and cover technique eliminates any fusional stimulus to convergence. Since the fixation distance remains unchanged, proximal convergence contributes a con-



Accommodative Convergence Ratios

stant amount to the total convergence and, therefore, has no effect on the change in convergence with the change in accommodation.

Control AC/A ratios were determined before and then at least one week after a given subject had received a dose of LSD-25. Each of the ten subjects received LSD-25 once, and seven of the ten received it on two occasions. Individual doses were picked at random in a double blind fashion. Subjects receiving LSD-25 twice received the same dose each time. The doses of LSD-25 administered to the subjects varied from approximately 0.7γ to 2.8γ/kg.

AC/A ratios were measured on each subject approximately three hours after administration of the LSD-25. Pupil size in an evenly illuminated room was estimated by means of a low-powered microscope. Various mental examinations and psychological tests were performed during the course of the LSD-25 effects but are not within the scope of this paper.

Results

The mental effects in the subjects under LSD-25 ranged from minimal thought and visual disturbances to overt hallucinations, depending on the dose of LSD-25 received. Those having maximal mental disturbances had some difficulty concentrating and cooperating for the AC/A ratio determination; but with patience, repeated directions, and continual encouragement from the examiner, they were able to do so. Mydriasis was noted in all. Tachycardia and rise in blood pressure were inconstant findings, observed at all dose levels.

The Figure shows the contrasting control and LSD-25 AC/A ratios in subject 7. The ordinate plots the lateral phoria measurement in prism diopters; and the abscissa gives the stimulus induced by the specific spherical lens added in diopters, and the diopters of accommodation required by the stimulus for clear image. A straight line plots the AC/A ratio, using the various points obtained during one examination.*

* Alpern et al[16] have termed this the stimulus AC/A ratio as contrasted to the response AC/A ratio. This distinction is made because in clinical practice it is assumed that the amount of actual accommodation is equal to the amount of accommodative stimulus presented.

As can be seen, the variations in individual points from the linear relationship of the AC/A ratio is no greater under the effects of LSD-25 than in the controls. Therefore, although the measurements were difficult to obtain in those subjects with severe mental disturbances under LSD-25, the values themselves apparently have the same accuracy as the controls.

The AC/A ratios of the entire group are listed in Table 1. Control values ranged from 3.6 to 6.6 units, and were repeatable in a given subject, with variation ranging from 0.0 units to a maximum of 0.9 units. This compares favorably with the reproducibility in a given subject reported by Sloan et al.[8] LSD-25 values in subjects receiving the same dose twice had variations ranging from 0.0 to 1.0 unit. The range of all the LSD-25 values was from 4.8 to 7.5 units. The difference between the average values for the control and LSD-25 AC/A ratios is given in the last column of Table 1. Under the influence of LSD-25, the AC/A ratio showed an increase of 0.7 to 2.35 units. There was no correlation between individual changes in the AC/A ratio, the dose of LSD-25, or the pupil dilation.

Table 2 shows the tabulation of the mean, range, and standard deviation of all the controls contrasted to all the LSD-25 values. The difference in the two groups has a significance at the 99% level.

Comment

These results show that there is a small but definitely detectable increase in the AC/A ratio in humans under the influence of LSD-25. This presumably is due to partial cycloplegia. More central stimulation, therefore, is necessary to cause a given amount of accommodation. This increased stimulation, traveling on similar neural pathways, causes an increase in the corresponding convergence. There was no correlation between the dose of LSD-25 and the increase in the AC/A ratio. It is possible that in a much larger group of subjects a correlation of this sort could be demonstrated.

The fact that these results indicate an LSD-25 effect on the ciliary muscle is of particular interest. The central action of LSD-25 on the autonomic nervous system is a complicated one. To think of this purely on the basis of sympathetic stimulation or parasympathetic inhibition is probably a great over-simplification. These reported changes in the AC/A ratios indicate that the ciliary muscle is affected by the action of LSD-25. Whether these changes are due to sympathetic or parasympathetic effects can not be ascertained.

Summary

The effect of various doses of LSD-25 on the AC/A ratios of ten healthy young men was studied by the gradient method.

There was a small but definite increase in the AC/A ratios under the influence of LSD-25 compared to the control ratios. This increase is due to a partial cycloplegia.

Some sort of action by LSD-25 on the central autonomic centers is probably involved.

Dr. Louise Sloan of The Wilmer Institute, The Johns Hopkins Hospital, Baltimore, and Major James S. Ketchum of United States Army Chemical Research and Development Laboratories, Edgewood Arsenal, Md, gave advice and criticism.

Generic and Trade Names of Drugs

Orphenadrine citrate—Norflex.
Isoflurophate—Floropryl.

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