PSYCHOMOTOR EFFECTS OF LOW DOSES OF ACETAZOLAMIDE TO AID ACCOMMODATION OF MEN TO ALTITUDE

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PSYCHOMOTOR EFFECTS OF LOW DOSES OF ACETAZOLAMIDE TO AID ACCOMMODATION OF MEN TO ALTITUDE

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FOREWORD

This report was prepared in the Neuropsychiatry Branch and Biometrics Division under task No. 775504 and was submitted for publication on 9 April 1968. The work was accomplished between May 1965 and December 1967.

The paper-and-pencil skills tests used in this study were developed by Moran and are available in twenty alternate forms from the Hogg Foundation, University of Texas, Austin, Tex.

The data reported here were obtained in a study designed and conducted by Dr. S. M. Cain and Dr. J. E. Dunn II. Charles Andrews, Jr., assisted in psychomotor testing.

This report has been reviewed and is approved.

GEORGE E. SCHAFER
Colonel, USAF, MC
Commander

ABSTRACT

Studies were conducted to evaluate the usefulness of acetazolamide in aiding accommodation to altitude. Three experimental conditions were included in the studies: five men decompressed to a pressure altitude of 14,000 ft. for 6 hours; six men decompressed to 16,000 ft. for 4 hours; and three men decompressed to 14,000 ft. for 5 days. Each subject participated in two runs, one with administration of the drug and the other on placebo, using the usual "double blind" procedure. Despite a scattering of significant psychomotor changes, no substantial evidence was obtained to support the use of this drug for accommodation to altitude

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I. INTRODUCTION

Behavioral and psychomotor changes associated with reductions in oxygenation of the blood are well-known. McFarland (3) summarized these grossly in the following way: deterioration in the quality of complex coordination, appearing initially at an altitude of 10,000 ft.; disturbances of memory and other intellectual functions, occurring at an altitude as low as 10,000 ft.; decrement in compensatory and pursuit tracking performance and increases in reaction time, with significant degradation appearing in the altitude range of 15,000 to 20,000 ft.; changes in judgment and emotional status, occurring at 16,000 to 18,000 ft.; and loss of simple coordination at 17,000 ft. A variety of physiologic adaptive mechanisms come into play as man goes to altitude. Time is a critical parameter in both the appearance of the effects and adaptation to the reduced partial pressure of ambient oxygen.

The U. S. Air Force is interested in the procedure of accommodation to altitude, by pharmacologic manipulation, so that man can maintain normal levels of psychomotor function and work-capacity. Two recent papers from the USAF School of Aerospace Medicine (1, 2) describe the physiologic effect of low doses of acetazolamide in aiding accommodation to altitude. Low doses of acetazolamide apparently result in a correction of respiratory alkalosis, leading to increased ventilation and higher levels of alveolar Po_2 than are usually obtained at a given altitude. In effect, subjects are less hypoxic during the period of accommodation to altitude. Possible mechanisms are discussed in the papers just cited. Psychomotor tests were administered during the second of those two studies (2). This report will be limited to these psychomotor findings.

II. METHODS

Three kinds of altitude studies were carried out: five men[1] were decompressed to a pressure altitude of 14,000 ft. (4,270 m.) for 6 hours; six men were decompressed to 16,000 ft. (4,880 m.) for 4 hours; and three men were decompressed to 14,000 ft. (4,270 m.) for 5 days. Different subjects were used in the three studies. Each subject was exposed to altitude twice; on one run acetazolamide was administered, and on the other, a placebo. The drug and placebo were given in identical gelatin capsules. Each drug capsule contained 250 mg. of acetazolamide. The administration of placebo and drug was randomized for each subject, and the standard "double blind" procedures were followed. For the short-term exposures the subjects were generally run in pairs; however, a subject was not necessarily paired with the same person on both flights. For the 5-day flights the three[2] subjects were run together. In the short-term studies the two flights for a subject were separated by at least two weeks. In the 5-day study the flights were a month apart. The treatment for

[1]There was a sixth subject in these runs, but his physiologic data were grossly out of line and he was dropped from the analysis.

[2]There was a fourth subject in the first 5-day run who was not available for the second run because of unrelated medical reasons.

the short-term studies consisted of two capsules on the evening (around 7 p.m.) before the flight and another capsule in the morning (around 7 a.m.), for a total of 750 mg. of acetazolamide. The treatment schedule was the same in the 5-day study, two capsules the night before and one on the morning of day 1 of the experiment, with a total dosage of 750 mg. of acetazolamide. No further treatment was given.

All subjects took an extensive battery of physiologic tests at ground level on the morning of the test day, and then repeated the tests at altitude. In the 6-hour runs at 14,000 ft., the physiologic battery was repeated at the end of the first and third hour at altitude. In the 4-hour runs at 16,000 ft., this battery was repeated at the end of the first hour at altitude. In the 5-day run at 14,000 ft., the tests were administered at the end of the first hour at altitude on day 1 and repeated at that time on each subsequent day. Complete details on these physiologic procedures are given in the earlier paper (2).

Psychomotor testing was conducted after resting following each physiologic test period. The psychomotor battery consisted of four paper-and-pencil skills tests, compensatory tracking, simple reaction time, and hand-steadiness. The paper-and-pencil tests consisted of placing dots in small circles (RPM-A), adding three sets of two-digit numbers (RPM-NF), circling four-letter words in rows of letters (RPM-SC), and crossing out a number in rows of numbers (RPM-PS). Subjects were required to work as rapidly as possible. We used the test manual time limits, which are short enough (from 1½ to 3 minutes) so that subjects cannot finish. In the tracking task, the target signal was a 30-c.p.m. sine wave. Each trial last 1 minute and was followed by 15 seconds of rest; eight trials were run without interruption during each testing period. The measure of performance was time-off-target in 0.01 second, using a standardized on-target band adjusted to yield off-target times around 50% under ground-level, nonstressed condition. In the hand-steadiness task, subjects held a stylus in each of a series of successively smaller holes (from ½ to $^{3}/_{32}$ in. diameter) for 10 seconds, and then had 10 seconds of rest before proceeding to the next hole. Pacing lights kept the subjects on a rigid schedule. The measure of performance was total number of contacts with the sides of the holes. In the reaction time task, subjects depressed a "ready" switch until a light came on, then moved that finger as rapidly as possible to depress a second switch. There were ten successive trials. The measure of performance was mean response time. Figure 1 shows the psychomotor test equipment. Total

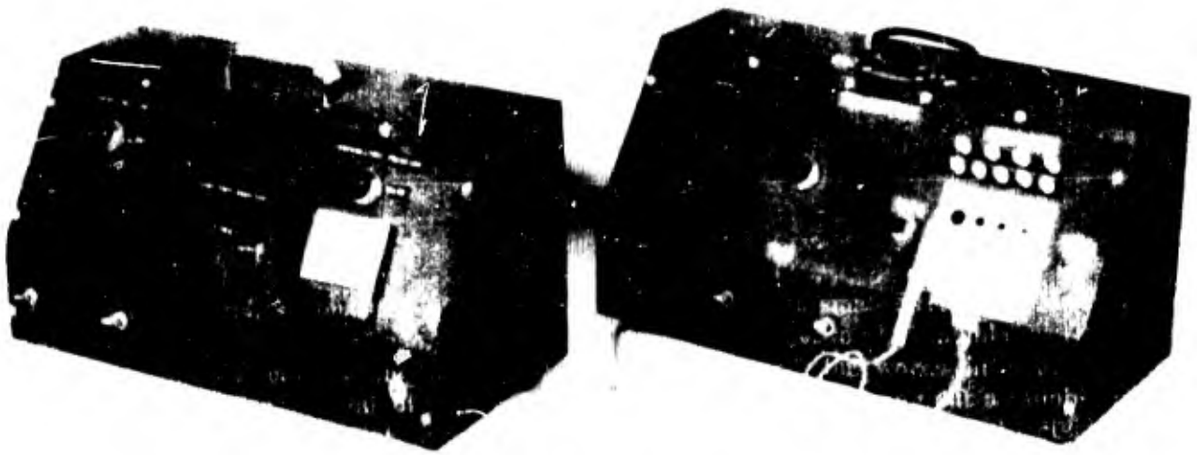

FIGURE 1

Psychomotor test equipment.

test time for the entire battery was approximately 30 minutes. Subjects were trained to an asymptote prior to the experimental sessions, using half-hour training sessions. Three or four such training sessions were sufficient to achieve asymptote.

III. RESULTS

One score for each subject during each session on each test was used for the analysis. For those tests involving several trials, a mean was computed. An analysis of variance of the general form indicated in table I was computed for each of the variables for the short-term flights. When the psychomotor tests involved multiple trials, the mean of the several trials was used in the analysis. The probabilities for the tests in the analyses of variance are given in table II. In the body of the paper, tests with probabilities less than .05 will be termed as statistically significant and those for which $.05 < P < .10$ will be termed as borderline.

TABLE I

General form of the analyses of variance computed for the data from the short-term studies at 14,000 and 16,000 ft.

Source of variation	Degrees of freedom	
	14,000 ft.	16,000 ft.
Subjects	4	5
Treatment	1	1
Subject x treatment	4	5
Time	—	—
Time 1 vs. other	1	1
Time 2 vs. time 3	1	1
Time x subject	8	10
Time x treatment	—	—
Time 1 vs. other x treatment	1	1
Time 1 vs. time 3 x treatment	1	1
Error	8	10

When treatment as a source of variation is statistically significant for a variable, it indicates that the mean of the placebo observations for that variable is different from the mean of the measurements made during the acetazolamide treatment. The variation among the time means can be divided into that associated with the difference between the ground-level mean and the mean at altitude, and that associated with the difference between the means of the two measurements made at altitude. Time 1 vs. other compares the mean of the ground-level measurements with the mean of the altitude measurements. Time 2 vs. time 3 compares the means of the two times at altitude.

The test of significance for the time x treatment interaction indicates whether the response over the three times for a variable is the same regardless of the treatment (placebo or acetazolamide). In particular, the interaction of time 1 vs. other x treatment indicates whether the difference between the mean of the ground-level measurements and the mean of the two altitude measurements is the same for acetazolamide and placebo. The interaction of time 2 vs. time 3 x treatment indicates whether the difference between the means of the two times at altitude is the same regardless of treatment.

The test which bears most directly on the question of acetazolamide aiding in the acclimatization to altitude is the interaction of the comparison between ground level and altitude performance with treatment. One expects a decrement in performance at altitude with no treatment (placebo) and hopes for no decrement in performance at altitude when the subjects receive acetazolamide. This sort of response should lead to a statistically significant test for the source of variation, time 1 vs. other x treatment (as detailed in figure 1).

Short-term runs at 14,000 ft.

The results from the tests in the analyses of variance for the data from the 14,000-ft. study are shown in table II. The mean values for time x treatment are given in table III.

TABLE II

Summary of the statistical tests in the analyses of variance

Study	Source of variation	Variable						
		RPM-A	RPM-NF	RPM-SC (Adj)	RPM-PS(Adj)	Tracking	Reaction time	Hand-steadiness
14,000-ft.	Time	< .005	—	—	—	—	—	—
	Time 1 vs. other	< .001	—	—	—	—	—	—
	Time 2 vs. time 3	—	—	—	—	—	—	—
	Treatment	—	—	< .005	—	< .005	—	< .025
	Time x treatment	—	—	—	—	—	—	(< .10)
	Time 1 vs. other x treatment	—	—	—	—	—	—	< .05
	Time 2 vs. time 3 x treatment	—	—	—	—	—	—	—
16,000-ft.	Time	< .001	< .005	(< .10)	< .001	(< .10)	—	—
	Time 1 vs. other	< .001	< .001	—	> .005	< .025	—	(< .10)
	Time 2 vs. time 3	—	—	< .05	< .001	—	—	—
	Treatment	—	—	—	—	—	—	—
	Time x treatment	—	—	(< .10)	(< .10)	—	—	—
	Time 1 vs. other x treatment	(< .10)	—	—	—	—	—	—
	Time 2 vs. time 3 x treatment	—	—	(< .10)	(< .10)	—	—	—
5-day	Treatment	—	(< .10)	—	—	—	—	—
	Time	< .001	< .05	(< .10)	< .005	< .01	< .05	
	Treatment x time	—	—	—	—	—	—	—

Adj—Adjusted.

F-ratios in parentheses only approached statistical significance.

TABLE III

Mean values from the 14,000-ft. study

Variable and treatment	Time			
	Ground level	Alt. 1	Alt. 2	Mean
RPM-A				
Placebo	140.2	113.2	99.6	117.67
Acetazolamide	140.6	122.2	119.2	127.33
Mean	140.4	117.7	109.4	122.50
RPM-NF				
Placebo	47.8	46.6	47.2	47.20
Acetazolamide	46.0	48.6	48.2	47.60
Mean	46.9	47.6	47.7	47.40
RPM-SC(Adj)				
Placebo	30.6	31.6	34.8	32.33
Acetazolamide	39.0	41.6	37.8	39.47
Mean	34.8	36.6	36.3	35.90
RPM-PS(Adj)				
Placebo	114.2	111.2	108.4	111.27
Acetazolamide	108.4	113.0	113.0	111.47
Mean	111.3	112.1	110.7	111.37
Tracking				
Placebo	2,060	2,164	2,118	2,114
Acetazolamide	1,930	1,940	1,896	1,922
Mean	1,995	2,052	2,007	2,018
Reaction time				
Placebo	39	38.4	37.6	38.33
Acetazolamide	35.8	35.4	35.6	35.60
Mean	37.4	36.9	36.6	36.97
Hand-steadiness				
Placebo	95.8	119.2	106.2	107.07
Acetazolamide	80.8	69.4	72.4	74.20
Mean	88.3	94.3	89.3	90.63

Adj—Adjusted.

Time was statistically significant only for the variable RPM-A. This significance seems to be due entirely to the difference between the level of performance at ground level and that at altitude. The level of performance for RPM-A was significantly lower (see table III) at altitude.

For three variables (RPM-SC, tracking, and hand-steadiness), the difference between the two treatment means was statistically significant. The level of performance was significantly lower with acetazolamide for tracking and hand-steadiness, but significantly higher (see table III) for RPM-SC.

Only the hand-steadiness test showed any interaction between treatment and time, and in this case it was because the difference between the mean of the ground-level measurements and the mean of the altitude measurements was not the same for the two treatments (time 1 vs. other x treatment). Examination of the mean values (table III) shows that with placebo the level of performance for hand-steadiness increased between ground level and altitude, whereas with acetazolamide it decreased between ground level and altitude. Only hand-steadiness gave any indication that acetazolamide aided accommodation to altitude.

Short-term runs at 16,000 ft.

The results of the statistical tests of significance from the analyses of variance for the data from the 16,000-ft. runs are also shown in table II. The mean values for the data from the 16,000-ft. study are given in table IV.

TABLE IV

Mean values from the 16,000-ft. study

Variable and treatment	Time			
	Ground level	Alt. 1	Alt. 2	Mean
RPM-A				
Placebo	145.83	95.83	89.83	110.50
Acetazolamide	136.33	103.67	94.83	111.61
Mean	141.08	99.75	92.33	111.06
RPM-NF				
Placebo	32.50	29.17	25.00	28.89
Acetazolamide	35.33	30.00	31.17	32.17
Mean	33.92	29.58	28.08	30.53
RPM-SC(Adj)				
Placebo	31.17	29.00	29.50	29.89
Acetazolamide	29.17	28.50	36.67	31.44
Mean	30.17	28.75	33.08	30.67
RPM-PS(Adj)				
Placebo	109.33	109.17	73.17	97.22
Acetazolamide	105.00	104.83	90.50	100.11
Mean	107.17	107.00	81.83	98.67
Tracking				
Placebo	2,720.0	3,780.0	3,966.7	3,488.9
Acetazolamide	2,873.3	3,363.3	3,840.0	3,355.9
Mean	2,796.7	3,571.7	3,903.3	3,423.9
Reaction time				
Placebo	39.17	40.00	38.17	39.11
Acetazolamide	39.33	44.50	50.00	44.61
Mean	39.25	42.25	44.08	41.86
Hand-steadiness				
Placebo	84.50	103.83	117.17	101.83
Acetazolamide	78.33	90.17	104.17	90.89
Mean	81.42	97.00	110.67	96.36

Adj—Adjusted.

Statistical significance ($P < .05$) or borderline significance ($P < .10$) was found for the variation between the time means for all the variables except reaction time and hand-steadiness. For three of the variables (RPM-A, RPM-NF, and tracking), the comparison between the ground-level measurement and the average of the altitude measurements explained this significant time variation. With RPM-A and RPM-NF the level of performance decreased at altitude, but with tracking it increased (table IV). The significant time variation for RPM-SC was because the mean of the first altitude measurements was significantly lower than the mean of the second altitude measurements. The mean of the altitude measurements of RPM-PS was significantly lower than the mean of the ground-level measurements; however, this was because the mean of the second altitude measurements was significantly lower than the mean of the first altitude measurements (table IV). The comparison of ground level with altitude was at the borderline of significance for hand-steadiness, with the mean of the altitude readings being higher than the mean of the ground-level readings. The difference between the treatment means was not statistically significant for any of the variables.

Three variables (RPM-A, RPM-SC, and RPM-PS) gave some indication of an interaction between treatment and time, but in all cases the test was of borderline significance. Time 1 vs. other x treatment was statistically significant only for RPM-A, for which the level of performance decreased less at altitude for the acetazolamide measurements than for the placebo measurements. The same pattern held for this variable in the 14,000-ft. study, but the statistical testing in that study was not even of borderline significance. The effect of the time x treatment interaction for both RPM-SC and RPM-PS was because the difference between the two altitude means was not the same for placebo and acetazolamide (time 2 vs. time 3 x treatment). For RPM-SC the two altitude means were nearly the same for placebo, but the second altitude mean was substantially higher than the first altitude mean for acetazolamide. For RPM-PS the second altitude mean was lower than the first altitude mean for both placebo and acetazolamide; however, for placebo, the decrease in level of performance between the first and second altitude measurements was greater than that for the acetazolamide measurements. It should be emphasized again that these last few tests discussed were all at the borderline of statistical significance.

The hand-steadiness data from the 14,000-ft. study showed a statistically significant interaction of time 1 vs. other x treatment that could be explained by an increase in level of performance between ground level and altitude for placebo, but a decrease for acetazolamide. This interaction was not near significance for the hand-steadiness data from the 16,000-ft. study. These means showed a pattern (table IV) of increasing between ground level and altitude for placebo, and a lesser increase for acetazolamide. Thus, the patterns between the two studies showed some similarity.

Five-day study

Analyses of variance were computed for the data from the 5-day study. Since no measurements were made at ground level in this study, it was not possible to compare ground level vs. altitude as was done with the data for the short-term studies (time 1 vs. other).

The results from the analyses of variance are shown in table II. The mean values are given in table V.

The test of treatment means was not statistically significant for any of the variables, but was at the borderline of significance for RPM-NF. The mean for acetazolamide was higher than the mean for the measurements taken during placebo treatment for the variable.

The variation associated with time was statistically significant for all but two variables—namely, RPM-SC and hand-steadiness—and was of borderline significance for RPM-SC. Four of the variables (RPM-A, RPM-NF, RPM-

TABLE V

Mean values from the 5-day study

Variable and treatment	Day					
	1	2	3	4	5	Mean
RPM-A						
Placebo	137.00	131.67	160.00	138.67	168.00	147.07
Acetazolamide	126.00	139.67	144.33	147.67	164.00	144.33
Mean	131.50	135.67	152.17	143.17	166.00	145.70
RPM-NF						
Placebo	34.33	36.67	37.33	38.33	36.67	36.67
Acetazolamide	34.33	37.00	40.00	42.00	40.33	38.73
Mean	34.38	36.83	38.67	40.17	38.50	37.70
RPM-SC(Adj)						
Placebo	31.67	36.00	40.67	38.00	39.33	37.13
Acetazolamide	34.00	33.00	40.67	39.00	30.33	35.40
Mean	32.83	34.50	40.67	38.50	34.83	36.27
RPM-PS(Adj)						
Placebo	94.67	94.00	111.33	116.67	81.33	99.60
Acetazolamide	88.00	101.00	103.33	93.00	91.33	95.33
Mean	91.33	97.50	107.33	104.83	86.33	97.47
Tracking						
Placebo	3,500.0	3,203.3	2,800.0	2,240.0	2,443.3	2,837.3
Acetazolamide	2,690.0	2,876.7	2,330.0	1,853.3	2,470.0	2,444.0
Mean	3,095.0	3,040.0	2,565.0	2,046.7	2,456.7	2,640.7
Reaction time						
Placebo	35.13	35.13	39.80	29.43	32.53	34.41
Acetazolamide	37.73	32.77	34.07	31.53	28.23	32.87
Mean	36.43	33.95	36.93	30.48	30.38	33.64
Hand-steadiness						
Placebo	26.33	35.67	46.00	32.33	38.33	35.73
Acetazolamide	35.00	38.67	23.33	28.33	25.67	30.20
Mean	30.67	37.17	34.67	30.33	32.00	32.97

Adj—Adjusted.

SC, and RPM-PS) showed a tendency to increase with time or to increase and then fall off. Two of them (tracking and reaction time) tended to decrease with time, and tracking gave some indication of rising after decreasing over the first 4 days.

The time x treatment interaction was not statistically significant for any of the variables.

Since the subjects were on a treatment regimen for the entire 5 days, both the test of treatments and the test of the treatment x

time interaction would bear on whether acetazolamide was effective in hastening acclimatization to altitude. Because only a single variable (RPM-NF) gave any indication of a response to acetazolamide and that test was only at the borderline of significance, these data give essentially no indication that acetazolamide would be effective in hastening the acclimatization.

Figures 2 through 8 present mean scores for each test in the battery on each of the three different altitude exposures. The scores which have been plotted are those given in tables III through V. The figures show that the differences which exist are limited largely to differences between treatments or to changes associated with being decompressed, rather than to treatment variations associated with the critical interaction, time 1 vs. other x treatment.

IV. DISCUSSION AND CONCLUSIONS

It is apparent that there is no substantial evidence in the psychomotor data that acetazolamide aided accommodation. There are occasional suggestions that the drug may have been of some assistance in the arithmetic task (RPM-NF) and in hand-steadiness and aiming (RPM-A) tasks, the latter two being somewhat different aspects of eye-hand coordination.

The altitudes used in this study were within the range in which psychomotor changes appear, but at levels where these changes would

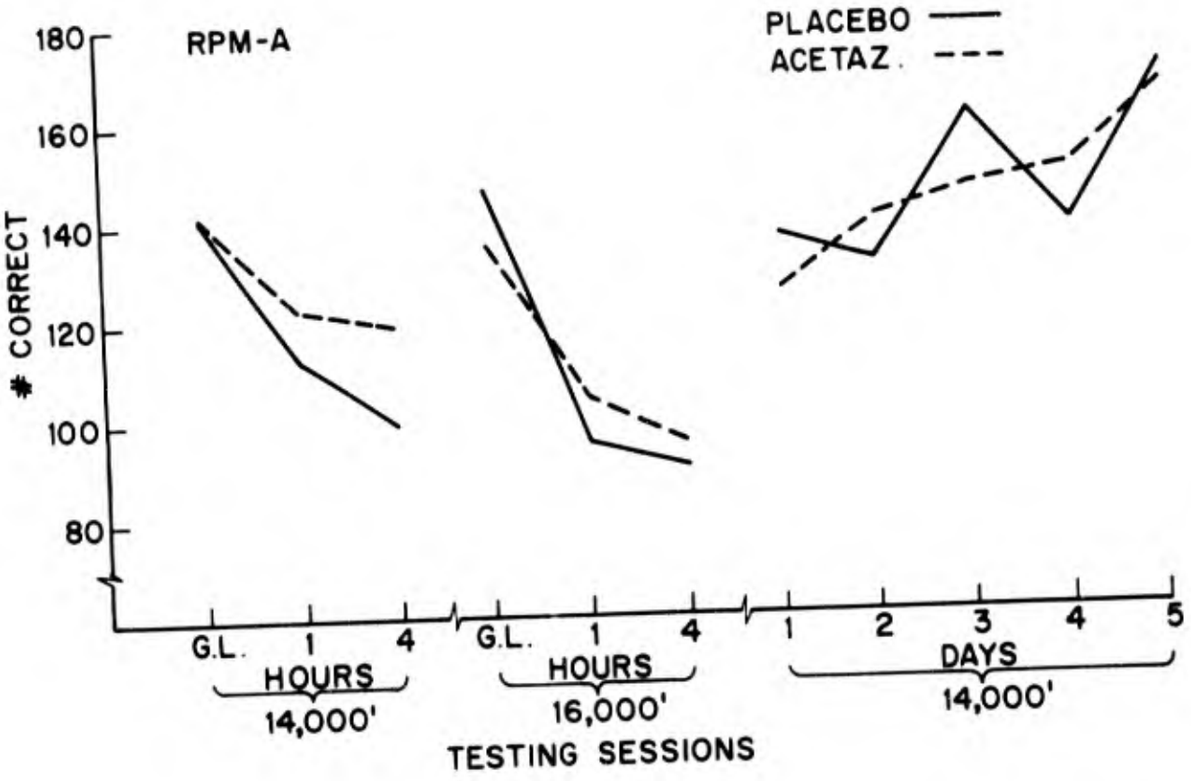

FIGURE 2

Mean scores on the aiming task (RPM-A), with subjects pooled.

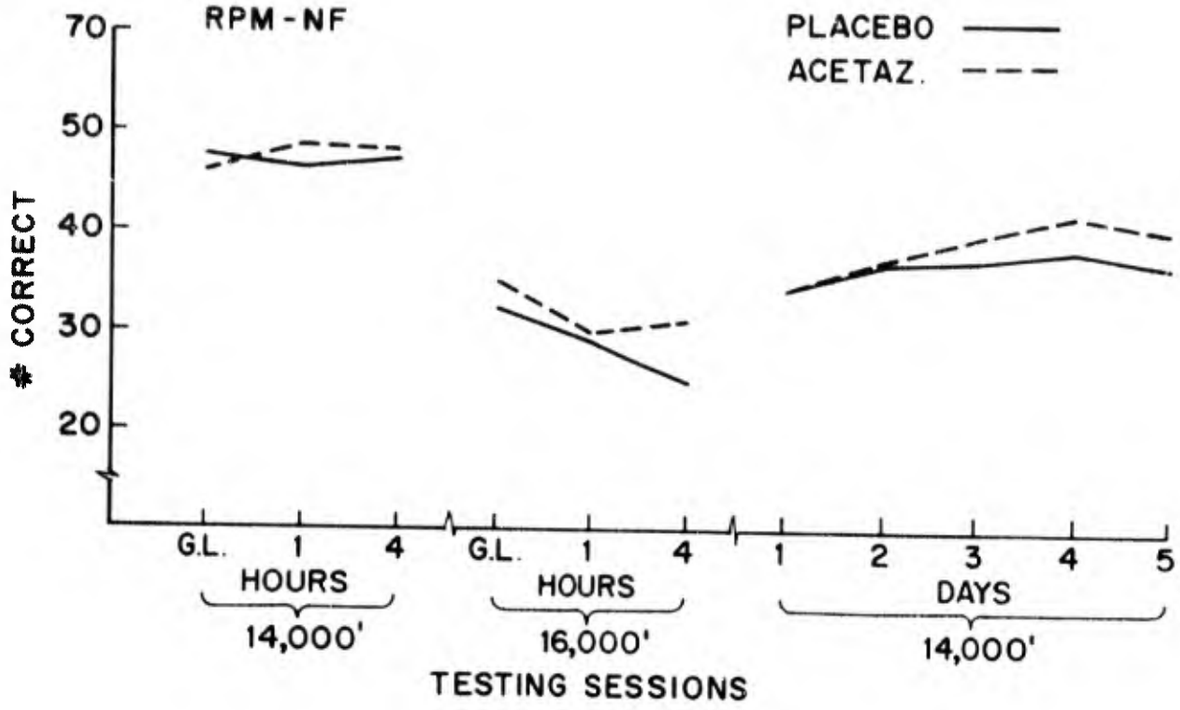

FIGURE 3

Mean scores on the arithmetic task (RPM-NF), with subjects pooled.

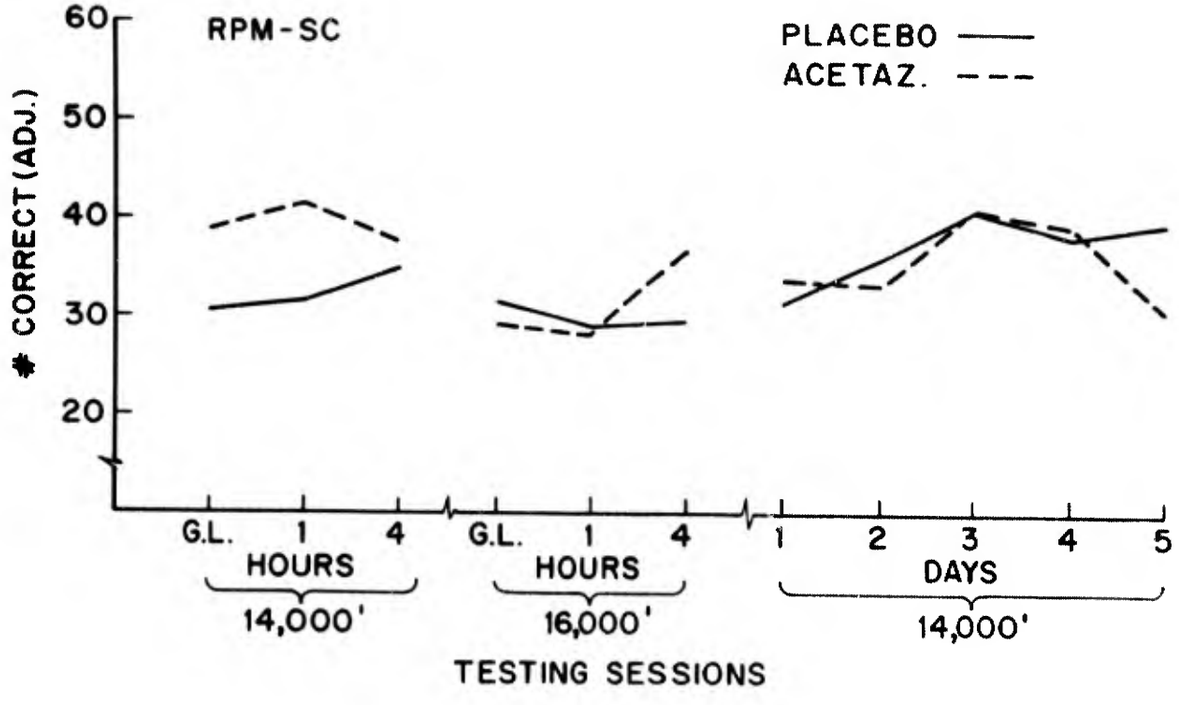

FIGURE 4

Mean scores on the speed of closure task (RPM-SC), with subjects pooled.

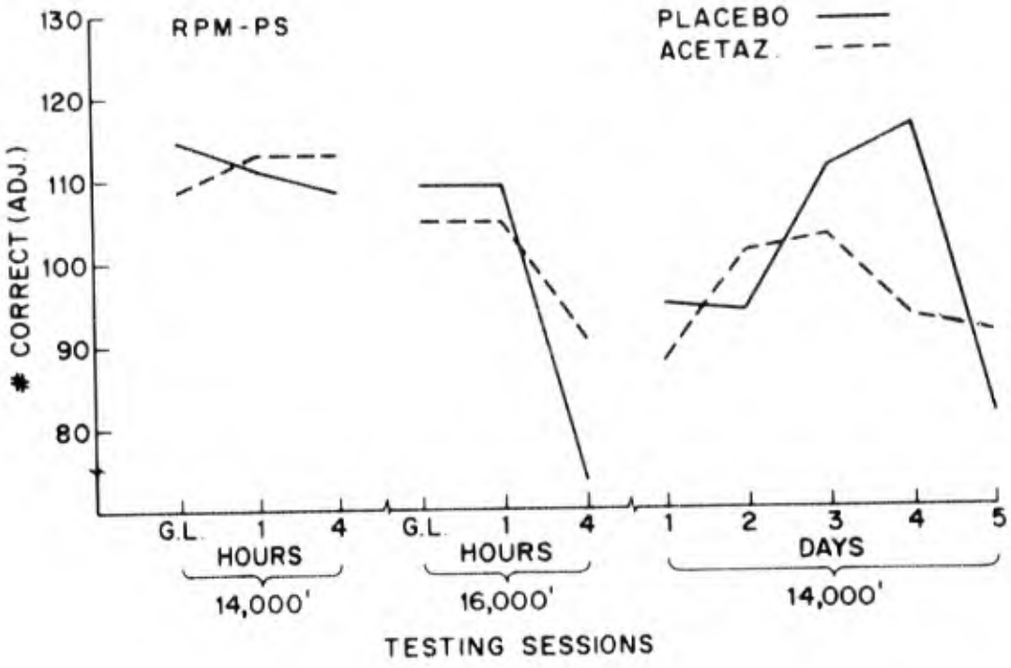

FIGURE 5

Mean scores on the perceptual speed task (RPM-PS), with subjects pooled.

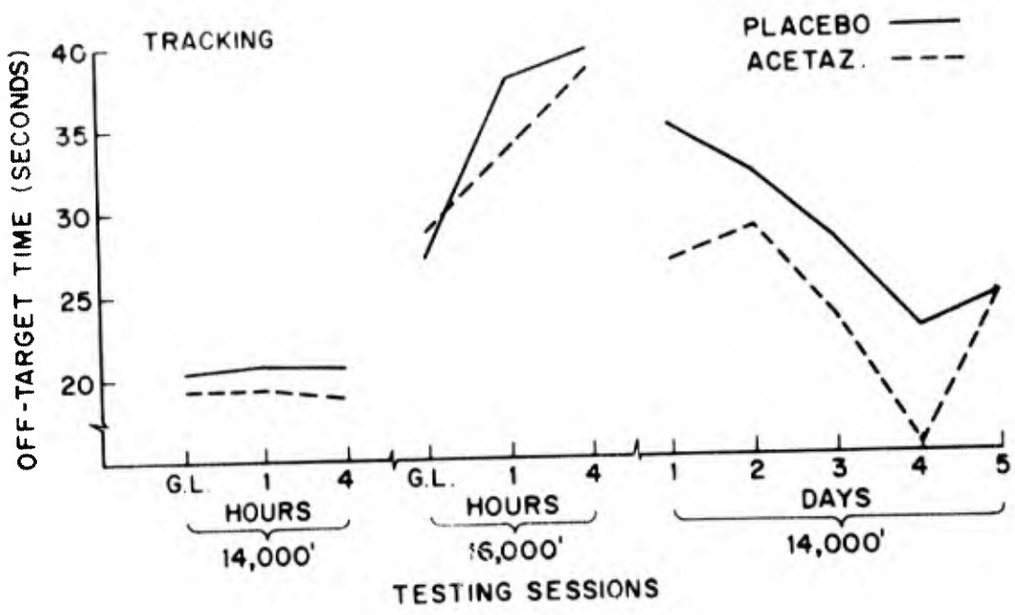

FIGURE 6

Mean scores on the compensatory tracking task, with trials averaged and subjects pooled.

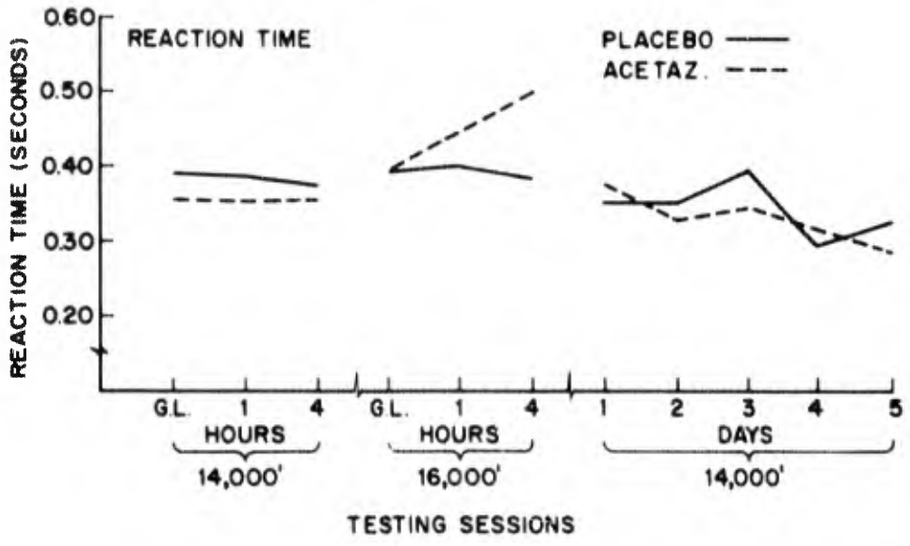

FIGURE 7

Mean scores on the reaction time task, with trials averaged and subjects pooled.

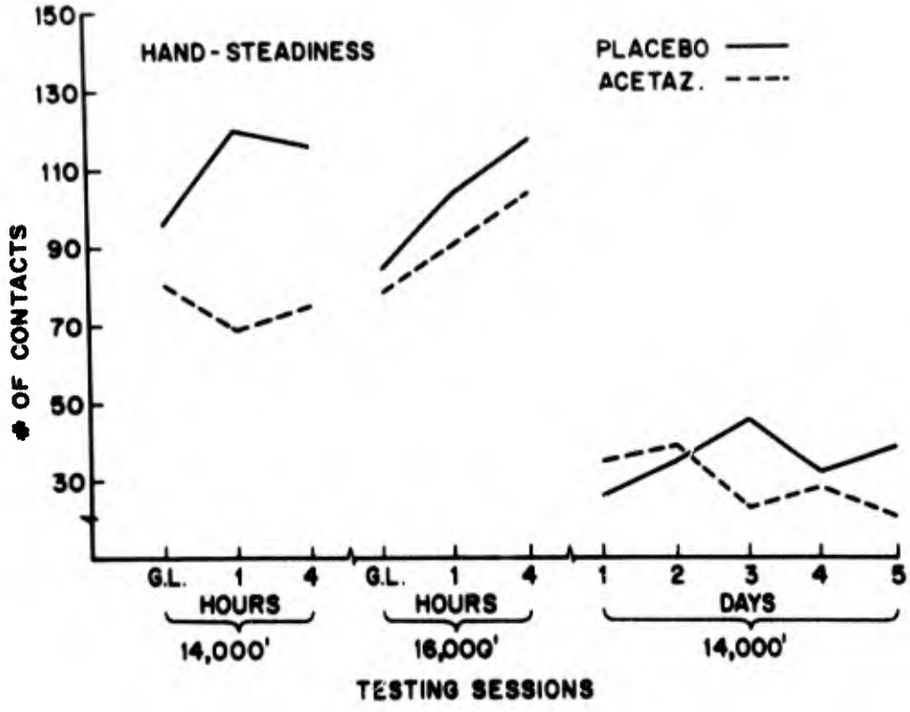

FIGURE 8

Mean scores on the hand-steadiness task, using an average for each subject and pooling subjects.

likely be minimal. It is not surprising that tests directed at small changes, in a study involving small numbers of subjects, failed to yield evidence that supported the value of acetazolamide in acclimating to altitude. The physiologic changes provided, at best, only qualified support for the utility of this drug in altitude accommodation. This study appears to be another instance in which a joint physiologic-psychologic study involving only moderate physiologic insult yielded only a limited number of significant physiologic changes and no important psychomotor changes.

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11. SUPPLEMENTARY NOTES	12. SPONSORING MILITARY ACTIVITY
	USAF School of Aerospace Medicine Aerospace Medical Division (AFSC) Brooks Air Force Base, Texas

13. ABSTRACT

Studies were conducted to evaluate the usefulness of acetazolamide in aiding accomodation to altitude. Three experimental conditions were included in the studies: five men decompressed to a pressure altitude of 14,000 ft. for 6 hours; six men decompressed to 16,000 ft. for 4 hours; and three men decompressed to 14,000 ft. for 5 days. Each subject participated in two runs, one with administration of the drug and the other on placebo, using the usual "double blind" procedure. Despite a scattering of significant psychomotor changes, no substantial evidence was obtained to support the use of this drug for accommodation to altitude.

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Security Classification

14 KEY WORDS	LINK A		LINK B		LINK C	
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Pharmacology						
Altitude acclimatization						
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