AM 69-12

THE USE OF A TRANQUILIZER (CHLORDIAZEPOXIDE) IN FLIGHT TRAINING

C. E. Melton, Jr.

Marlene Hoffmann

R. H. Delafield

Approved by

J. Robert Dille, M.D.
Chief, Civil Aeromedical Institute

Released by

P. V. Siegel, M.D.
Federal Air Surgeon

July 1969

Department of Transportation

FEDERAL AVIATION ADMINISTRATION

Office of Aviation Medicine

Acknowledgment

The authors express their gratitude to Hoffman-LaRoche, Inc., of Nutley, N.J. for their help and for the Librium (chlordiazepoxide–HC1) and the identical-appearing placebo capsules.

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I. Introduction.

Studies on student pilots undergoing primary flight training have led to the conclusion, based primarily on their heart rates, that the human stress incident to flight training is generally equivalent to that experienced by astronauts or pilots in actual combat.[3] The stress is believed to arise from the fear and anxiety felt by students in the flight situation where there are many unfamiliar elements and where the potential for failure or embarrassment is great. These latter considerations led to the idea that these "tensions" could possibly be alleviated and thus be evaluated by the use of a tranquilizer during the course of student training.

II. Methods.

Eleven male students, ranging in age from 31 to 46 were subjected to a conventional but highly standardized flight syllabus at the Civil Aeromedical Institute (CAMI). All of the subjects had passed the FAA Private Pilot written examination and each possessed a Class II or III medical certificate. All flight training was given in a Cessna 150 airplane by a certificated flight instructor who, aside from casual knowledge of the experiment, was otherwise unrelated to the conduct of the experiment.

For each flight, the subjects were fitted with stainless steel plate ECG electrodes positioned on the lateral chest walls where they were secured with an elastic strap. The skin was cleaned with alcohol prior to attachment of the electrodes and contact with the skin was effected through conductive jelly.

The subjects were requested to collect urine specimens after voiding at bedtime the night before the flight. Specimen #1 consisted of any voidings during the night plus the voiding upon arising in the morning. Specimen #2 consisted of a voiding just prior to flight, specimen #3 was the urine voided in flight and immediately post-flight. Specimen #4 consisted of all the urine voided until bedtime.

Prior to every dual flight, with the exception of the flights that included solo, each student received four capsules that contained 10 mg. of chlordiazepoxide or a placebo. The first capsule was taken at 4:00 PM the day prior to flight, the second at bedtime, the third upon arising, and the fourth 1 hour prior to flight. The contents of the identical-appearing capsules were unknown to the experimenters and the subjects. The code was not broken until the conclusion of the study. The syllabus consisted of 31 flights, with the first solo flight specified on flight 11 and cross-country flights similarly specified on flights 14, 15, 17, 19, 20, and 21. Just prior to each dual flight, each student was examined by a physician who determined the student's fitness for flight.

The leads from the biosensors and from dual microphones, one each for the student and instructor, were connected to appropriate amplifiers, the outputs of which led to three channels of an on-board instrumentation tape recorder. The entire recording system was battery operated. Recordings were taken continuously throughout every flight.

Data reduction was carried out in the laboratory at CAMI. The ECG was processed through a cardiotachometer, rigged so that the R-wave triggered a pulse output that was used to trip a printing digital counter. Print-out, reset, and paper advance functions were controlled by motor-driven notched wheels that activated microswitches every minute. Events were identified by the voice record that was played back over a speaker simultaneously with the ECG. The ECG records were marked according to ongoing activity.

The urine specimens were acidified and frozen until they were analyzed for epinephrine, norepinephrine, 17–OH corticosteroids, and creatinine. All values were referred to 100 mg. creatinine.

Preflight examinations consisted of determinations of oral temperature (to reveal any unsuspected fever), blood pressure, and resting heart rate. Each subject filled out a questionnaire about the amount and quality of sleep the night before, his current subjective feelings, and his physical complaints. Post-flight examinations consisted of determination of blood pressure and the completion of another questionnaire concerning his feelings about the flight, his physical state, and his opinion about whether or not there was an effect of the capsule. The instructor also filled out a questionnaire pertaining to the flight and was asked to record his opinion of whether or not the student showed any effect of the medication.

TABLE 1.—Catecholamine and Steroid Excretion for All Subjects

	Specimen 1			Specimen 2			Specimen 3			Specimen 4		
	P*	T*	S*	P	T	S	P	T	S	P	T	S
17 OH CS	0.25	0.24	0.24	0.42	0.43	0.42	0.44	0.42	0.47	0.33	0.29	0.35
mg./100 mg. Creatinine	±0.10	±0.10	±0.10	±0.15	±0.18	±0.11	±0.15	±0.18	±0.15	0.13	0.11	±0.13
Epinephrine	0.66	0.71	0.67	1.50	1.59	1.34	2.11	2.28	2.18	0.95	1.06	1.08
μg./100 mg. Creatinine	±0.50	±0.10	±0.10	±0.11	±0.13	±0.11	±0.15	±0.17	±0.15	±0.86	±0.10	±0.86
Nor-epinephrine	3.98	3.90	3.85	4.39	4.27	4.55	5.08	5.28	5.34	4.59	4.33	4.69
μg./100 mg. Creatinine	±0.27	±0.27.	±0.18	±0.19	±0.19	±0.24	±0.26	±0.28	±0.29	±0.22	±0.18	±0.26

*P=placebo T=tranquilizer S=solo (no treatment) Values are ± SEM

III. Results.

Urine chemistry: Three variables indicative of stress are shown in Table 1. These data show that treatments cannot be differentiated on the basis of the excreted metabolites. There is a distinct increase, however, in the mean values for the variables in the pre- and post-flight specimens. The absolute and percentage changes in metabolite excretion from the (presumably) basal values in the #1 specimen to the (presumably) stressed values in the #3 specimen are shown in Table 2. These data show that the excretion of all the metabolites was increased in the post-flight specimen, but that the increases were about equal for the different treatments, with slightly greater increases in the solo flight specimens.

TABLE 2. Absolute and Relative Differences for Metabolite Excretion in the # 1 and # 3 Specimens

	Placebo	Tranquilizer	Solo
17 OH CS	0.19	0.18	0.23
mg./100 mg. Creatinine	+76%	+75%	+96%
Epinephrine	1.45	1.57	1.51
μg./100 mg. Creatinine	+220%	+221%	+225%
Nor-epinephrine	1.10	1.38	1.49
μg./100 mg. Creatinine	+28%	+35%	+39%

The results by flights for the three metabolites are summarized in Table 3. If the assumption is made that an increase in the amounts excreted reflects the amount of stress, then Table 3 can itself be summarized to show which treatment was associated with greatest stress on each dual flight (Table 4). This tabulation reveals that placebo and tranquilizer were equal in potency.

Table 3.—Excretion of Metabolites for All Subjects by Flights*

Flight#	17 OH CS			Epinephrine			Nor-epinephrine		
	P**	T**	S**	P	T	S	P	T	S
1	0.175 87%	0.061 18%		0.805 111%	1.223 927%		3.143 119%	1.903 37%	
2	0.155 57%	0.094 45%		0.506 62%	2.998 496%		0.386 9%	−1.128 −33%	
3	0.140 54%	0.081 34%		1.228 145%	−0.111 −06%		1.522 39%	2.032 53%	
4	0.158 51%	0.204 88%		1.679 216%	1.807 133%		1.404 38%	1.135 29%	
5	0.223 99%	−0.007 −2%		1.566 273%	0.904 179%		0.334 9%	−0.004 −1%	
6	0.180 64%	0.192 80%		1.8885 262%	1.865 298%		0.624 15%	1.678 39%	
7	0.229 91%	0.120 49%		51.01 128%	2.202 495%		−0.902 −12%	2.436 76%	
8	0.171 89%	0.088 26%		2.094 346%	1.635 560%		1.298 39%	1.685 36%	
9	0.119 36%	0.084 44%		0.968 175%	2.288 401%		1.179 32%	2.336 59%	
10	0.175 95%	0.283 132%		2.031 314%	1.044 165%		1.949 62%	1.686 45%	
11			0.180 77%			2.157 349%			0.131 3%
12			0.211 84%			1.652 248%			2.852 96%
13			0.244 108%			1.645 127%			1.593 32%
14	0.207 78%	0.274 130%		1.977 356%	2.306 471%		0.825 23%	2.469 57%	
15	0.107 47%	1.275 111%		1.640 261%	0.685 128%		−1.428 −25%	0.653 16%	
16			0.228 91%			1.538 349%			1.157 33%
17	0.348 144%	0.212 109%		1.200 174%	1.214 165%		1.250 32%	2.930 72%	
18	0.060 28%	0.253 94%		1.723 268%	1.769 308%		0.486 14%	1.120 44%	
19			0.202 74%			1.683 372%			0.713 20%
20			0.284 130%			1.075 191%			1.358 34%
21	0.182 61%	0.110 58%		0.848 198%	1.892 448%		1.981 39%	1.428 43%	
22			0.283 142%			1.172 225%			1.443 40%
23			0.174 66%			0.841 68%			1.674 46%

See footnotes on following page.

Table 3.—Continued

Flight #	17 OH CS			Epinephrine			Nor-epinephrine		
	P**	T**	S**	P	T	S	P	T	S
24			0.222 92%			1.546 392%			0.646 16%
25	0.215 95%	0.325 152%		1.562 157%	2.179 670%		1.493 40%	0.840 30%	
26			0.293 145%			2.157 389%			2.813 77%
27			0.150 52%			1.089 132%			1.864 44%
28			0.240 89%			1.826 300%			1.758 52%
29	0.168 63%	0.224 113%		0.984 181%	2.197 332%		1.062 60%	1.656 34%	
30	0.182 60%	0.190 79%		2.092 290%	1.568 250%		2.623 89%	2.459 92%	
31	0.262 136%	0.106 38%		1.478 355%	0.581 32%		2.545 76%	−1.931 −29%	

*The top number in each rank represents the absolute difference between the # 1 and # 3 specimens. The percentages represent the relative change. Positive numbers mean that the amount in the # 3 specimen was increased over the resting value in the # 1 specimen; negative numbers mean that there was a decrease in the amount excreted in the # 3 specimen.
**P=Placebo T=Tranquilizer S=Solo (no treatment)

Table 4. Summary of Data in Table 3

Flight #	17 OH CS	Epinephrine	Nor-epinephrine
1	P*	T*	T
2	P	T	P
3	P	P	T
4	T	P	T
5	P	P	P
6	T	T	T
7	P	T	P
8	P	T	T
9	T	T	T
10	T	P	T
14	T	T	T
15	T	P	P
17	P	P	T
18	T	T	P
21	P	T	P
25	T	T	P
29	T	T	T
30	T	P	P
31	P	T	P
	P>9/19 T>10/19	P>7/19 T>12/19	P>9/19 T>10/19

*P=Placebo
T=Tranquilizer

Heart rate: The average heart rates over the entire syllabus are about the same for both the treatment and no-treatment flights. However, the previously-observed increases in heart rates from the beginning of training to solo and again at the end of the syllabus[3] are evident also in this study (Table 5). The average heart rate on flight 10, just prior to solo, is higher for the placebo group than for the tranquilizer group but the large variance renders the difference insignificant.

Table 6 is a comparison of heart rates during maneuvers traditionally held to be among the most stressful for students. There is scarcely any difference in the averages for the tranquilizer and placebo groups, except for short-field landings which show the placebo group to be about one standard deviation greater than the tranquilizer group. The values obtained on solo flights are consistently higher than those obtained on dual flights, as previously found in another study.[3]

Table 7 shows resting heart rates for all subjects by treatment prior to flights. It is evident from these figures that there is no difference for the three treatments.

Table 5.—Heart Rate Averages by Flights

Flight #	Tranquilizer N	Tranquilizer Heart Rate Mean	Tranquilizer Heart Rate S D	Placebo N	Placebo Heart Rate Mean	Placebo Heart Rate S D	Solo (No Treatment) N	Solo (No Treatment) Heart Rate Mean	Solo (No Treatment) Heart Rate S D
1	5	89.98	16.34	6	86.45	11.34			
2	6	91.34	13.71	5	95.03	18.13			
3	5	104.54	20.34	6	94.64	12.75			
4	6	94.98	12.74	5	103.58	28.77			
5	5	96.61	27.10	6	95.61	10.98			
6	6	101.87	13.43	5	104.79	24.31			
7	5	104.82	19.68	3	105.69	8.04			
8	6	99.00	10.11	5	107.24	18.55			
9	3	119.31	23.55	5	107.47	12.51			
10	6	101.49	12.76	4	110.81	26.72			
11							11	108.19	16.91
12							11	111.62	15.54
13							10	111.28	13.66
14	5	105.04	21.52	6	98.33	6.90			
15	6	95.01	7.77	5	101.75	18.03			
16							11	102.79	12.59
17	5	108.86	16.08	3	93.83	8.39			
18	4	88.73	3.94	4	104.95	26.56			
19							8	107.11	20.00
20							8	105.26	11.39
21	2	89.41	6.19	2	119.97	14.49			
22							7	94.78	16.12
23							8	95.36	10.20
24							9	95.74	11.85
25	4	92.46	18.21	2	91.04	35.55			
26							8	99.12	11.93
27							9	100.00	16.51
28							9	103.46	13.57
29	5	110.57	22.67	3	112.90	17.52			
30	4	103.22	9.83	4	104.26	10.81			
31	5	115.02	20.27	5	106.41	10.72			
	Avg. 100.65			Avg. 102.36			Avg. 102.89		

Table 6. Heart Rates During Selected Events

Event	Tranquilizer	Placebo	Solo (No Treatment
Stalls	101±17	102±18	107±16
Landings	106±13	106±15	116±15
Short-field takeoff	103±15	103±11	116±22
Short-field landings	94±15	109±13	118±18
First solo	X	X	119±18
Cross-wind landings	109±7	102	------------

Table 7. Resting Heart Rates

Subject No.	Tranquilizer	Placebo	Solo (No Treatment)
1	81	78	81
2	80	81	78
3	107	106	105
4	95	95	99
5	92	98	103
6	87	92	90
7	97	95	94
8	78	83	82
9	83	84	83
10	99	97	93
11	101	98	98
Avg. ±S.E.	91±3	92±3	91±3

IV. Discussion.

It is obvious from these data that the tranquilizer, chlordiazepoxide, had no observable effect in alleviating the stress of flights, for there was no apparent difference in urinary metabolite excretion or heart rate values between placebo- and tranquilizer-treated subjects. Several reasons for this lack of effect can be envisioned. First, the drug may not have been given in sufficient amounts, though the usual 10-mg. dosage was used. Secondly, it was not possible to treat the subjects continuously with the drug, because of the prohibition against flying solo while on drug treatment; at least 24 hours were allowed to pass from the time of the last capsule until solo flight was undertaken. A sufficiently high blood level may not have been attained for an effect to be seen. (If continuous dosage had been possible, it would have been necessary to design the study with tranquilizer-treated and placebo-treated groups of subjects, thus requiring many more subjects than was technically feasible.) Thirdly, a more potent drug could have been used. Chlordiazepoxide was chosen because of its relative freedom from side effects identifiable by the subjects. The subjects and the instructor were asked to give an opinion as to what species of capsule they had been given. The students were correct 37–58% of the time and the instructor was correct 40–67% of the time. The student and instructor agreed 60–100% of the time.

Stress was evident, however, both in the urinary excretion of "stress metabolites" and in the heart rates. The excretion of catecholamines and 17–OH CS was increased in the pre- and post-flight specimens over the values in the early morning and evening specimens. Demos, Hale, and Williams[1] have published values for excretion of these metabolites by Air Force pilots flying a variety of missions and have compared those values with control values obtained from laboratory workers and administrative personnel. The solo values in specimen #3 presented in Table 1 compare with those published by Demos *et. al.*[1] for F–102 pilots, as shown in Table 8.

TABLE 8.—Comparison of Student Pilot Data (#3 Specimen) with Demos, *et. al.* Data on F–102 Pilots and Controls [1]

	Students	F–102	Controls
17–OH CS	0.47	0.49	0.39
Epinephrine	2.18	1.60	0.74
Nor-epinephrine	5.34	5.38	2.85

V. Conclusions.

This study demonstrates once again that civilian private pilot training is an experience comparable in stressfulness to much of the most hazardous flying done by military pilots. The use of a mild tranquilizer during the training of civilian pilots apparently has a negligible effect in mitigating the stress. However, it should be pointed out that the drug had no unfavorable effect on the student's performance that was apparent to the instructor. In this respect, chlordiazepoxide is similar in effect to meprobamate used in an earlier study[2].

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