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16. Abstract

Decongestants and antihistamines are known to produce effects capable of adversely modifying physiological function and psychomotor task performance. Because of relevance to safe pilot performance, the effects of single doses of two decongestant-antihistamine preparations (Compound A and Compound B), or a placebo on cardiorespiratory responses to two equally spaced +2Gz tests during separate 2-hour exposures at ground level (GL) (1,274 ft MSL) and 12,500 ft chamber altitude were assessed. Postaltitude fatigue was assessed by cardiorespiratory responses to submaximal bicycle ergometry.

Compound A and Compound B appeared to exert no significant detrimental effects on short-duration postaltitude ergometric fatigability. With two exceptions, all combinations of medication, altitude, and +Gz were well tolerated. Two subjects were clearly incapacitated during the first +2Gz test under Compound A at 12,500 ft altitude. It is felt that the +Gz intolerance resulted mainly from an adverse interactive effect of Compound A and altitude on vasomotor and/or chronotropic mechanisms.

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CARDIORESPIRATORY ASSESSMENT OF DECONGESTANT-ANTIHISTAMINE EFFECTS ON ALTITUDE, +Gz, AND FATIGUE TOLERANCES

I. Introduction.

A number of decongestant-antihistamine preparations are currently available for symptomatic treatment of common colds and upper-respiratory allergies. Many of these are available without prescription. Some of the constituent decongestants and antihistamines in these preparations are known to have effects which are capable of adversely modifying both physiological function and psychomotor performance (1,5,6). Because of possible adversity of such effects on safe pilot performance of flight tasks, the use of such medications is considered an aeromedical factor of concern. In a previous study reported from this institute (8), it was determined that the combination of a simulated high altitude and an antihistamine-containing preparation produced a synergistic, detrimental effect on a flight-related psychomotor task.

To provide data especially useful in aeromedical standards development and certification, this study was designed to assess the effects of two decongestant-antihistamine preparations on cardiorespiratory responses to altitude, +Gz, and fatigue testing. A separate, parallel study was conducted to assess psychomotor performance, metabolic, and biochemical responses. The drugs evaluated were: (i) Compound A, the most frequently prescribed medication of this type (13), containing 60 mg pseudoephedrine hydrochloride and 2.5 mg triprolidine hydrochloride (Actifed ®), and (ii) Compound B, a common over-the-counter medication containing 10 mg phenylephrine hydrochloride, 20 mg phenindamine tartrate, aspirin, caffeine, and aluminum hydroxide/magnesium carbonate co-dried gel (Dristan ®).

II. Materials and Methods.

Subjects. Adult, male, paid volunteers were medically examined to insure initial normality. Those medically qualified were given a complete equipment and protocol orientation. This included a 2-minute exposure to lower body negative pressure (LBNP) during 1/2 hour at a chamber altitude of 12,500 ft MSL, and 3 minutes of bicycle ergometry immediately postaltitude at a load of 60 watts (W). During this orientation, gross

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intolerance to altitude, LBNP, or ergometry disqualified the candidate from subsequent participation in the study. Some of the vital statistics of the 12 selected participants are shown in Table 1.

Protocol and Parameters. Each subject underwent one experiment per week for 6 consecutive weeks. Each of the six experimental conditions consisted of combining a ground level (GL) altitude of 1,274 ft MSL or a 12,500 ft chamber altitude with a single dose of Compound A, Compound B, or lactose placebo. All three ingesta were prepared in identical-appearing capsules. Each experiment was conducted completely within an altitude chamber in which the fully instrumented subject remained comfortably seated in an LBNP box and air sealed therein from the waist down. The time sequence for each experiment commenced with ingestion of the capsules and consisted of 20 minutes at GL, 10 minutes of ascent to 12,500 ft, 2 hours at 12,500 ft, 10 minutes of descent to GL, and 8 minutes of pedal ergometry within the LBNP box with no change in the subject's upright, seated position. All time periods remained the same during the experiments conducted completely at GL. Cardiorespiratory data were acquired during the initial 20 minutes at GL, before and during +2Gz LBNP testing (-40 mm Hg LBNP for 2 minutes), at the end of the first and second hours of the altitude period, and before and during the postaltitude bicycle ergometry testing (continuous sequential loads of 30 W for 2 minutes and 60 W for 6 minutes). The average chamber temperature for all experiments during the 2-hour altitude period was 23.5° C.

Specific parameters assessed during each experiment consisted of: (i) heart rate (HR) using a single-lead electrocardiogram (ECG), (ii) blood pressure (BP) using automatic auscultative sphygmomanometry, (iii) arterial oxyhemoglobin saturation ($\%HbO_2$) using an ear oximeter (15), (iv) pulmonary ventilation (V_E) using integrated pneumotachometry of expired air, and (v) temporal artery blood flow velocity (TAFV) using a directional Doppler sensor (9). In addition to the above parameters, oxygen uptake (VO_2) was measured during the bicycle ergometry by analysis of quantitatively collected expired air. The CM_5 single lead (2) was used to monitor ECG function. The electrical signal from this ECG lead was fed simultaneously to: (i) an oscilloscope for continuous visual monitoring of the ECG for ischemia and arrhythmia, (ii) a cardiotachometer for

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TABLE 1. Vital Statistics

	Age (yr)	Ht (cm)	Wt (kg)	FRW (%)	Hb (gm %)
X̄	23.1	178.1	75.0	93.8	16.0
SEM	0.9	1.7	3.9	4.5	0.3
r	19-29	166.4-184.8	64.8-103.5	69.3-123.4	14.5-17.3

X̄ = mean. SEM = standard error of the mean. r = range. Age calculated to the nearest completed year. Ht = height in cm measured in stocking feet. Wt = weight in kg measured shirtless and shoeless and corrected for residual clothing weight (14). FRW = Framingham relative weight = (actual weight in kg/{(61.7 + 69.7 (Ht in m − 1.52)} x 100 (4). Hb = hemoglobin concentration in gm %.

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continued indication of HR, and (iii) a standard ECG recorder for scheduled periodic recording. Also continually monitored were the digital readout of $\%HbO_2$ for indication of hypoxemia, and the pulsatile mode of TAFV for flow-reversal indication of imminent loss of consciousness (9). Criteria for immediate termination of any single experiment consisted of strong subjective symptoms of impending syncope (lightheadedness, nausea, and visual tunnelling, grayout, or blackout) accompanied by sustained hypotension and bradycardia, temporal artery flow reversal of at least 5 seconds' duration, and continually falling values of $\%HbO_2$ below 80 percent. The same researcher remained inside the altitude chamber with the subject during each experiment. In the event of incapacitation symptoms, a positive-pressure mask with 100 percent oxygen was immediately available for resuscitation.

A timed, 10-problem addition-subtraction test was administered at the 16th and 32d minutes of each hour of the altitude period solely as a counteraction to the potential soporific boredom of relatively quiet sitting. Talking by the subject was allowed, but not encouraged.

Because a substantial prevalence of drowsiness is known to be among the effects of the antihistamine constituents (6) of Compound A and Compound B, and because drowsiness is capable of adversely affecting psychomotor performance (e.g., piloting an airplane), subjective rating of each subject's state of wakefulness during the 2-hour altitude period was performed by the intrachamber researcher. An arbitrary rating scale was constructed. A rating of 1 was equated to being fully awake (e.g., eyes open, conversive, alert, and attentive); a rating of 2 to being drowsy (e.g., yawning, stretching, nonconversive, drooping eyelids, and periodic eye closings); and a rating of 3 to being asleep (e.g., eyes fully closed for prolonged periods of time along with repetitious head bobbing, body relaxation, and a steady pattern of respiration). A rating of 1, 2, or 3 was assigned for each of three consecutive 6-minute periods during the first and second hours of the altitude period. The six ratings recorded during each experiment were grouped to obtain average values for the first hour, the second hour, and the total 2-hour period.

III. Results.

General. The data for all parameters measured at GL and at 12,500 ft chamber altitude are summarized in Tables 2-9. The data for all parameters measured during the fourth through sixth minutes of the 60-W, 50-rpm ergometry test are summarized in Table 10.

With two exceptions, all combinations of altitude with Compound A, Compound B, or placebo were tolerated without incapacitation during LBNP and postaltitude ergometry. The tolerated combinations, however, were associated with some quantitative differences in response. The two clear-cut incapacitations occurred in association with the combination of Compound A, 12,500 ft altitude, and the first LBNP test.

Tolerated Effects of Compounds A and B at GL. At GL, when the quantitative responses to LBNP and ergometry under Compound A and Compound B were compared with those under placebo, a few statistically significant differences ($P \leq 0.05$) were observed. These are summarized in Table 11. Under Compound A, the $\dot{V}_E$/kg value of the Base 2/GL (defined in Table 1) function was approximately 16 percent greater than the commensurate placebo value. Under Compound B, the $\dot{V}_E$/kg value during the 60-W ergometry load was approximately 12 percent less than the corresponding placebo value. The remaining statistically significant differences were quite small. None of these statistically significant differences indicated any immediate susceptibility to functional incapacitation under each ingestum.

Tolerated Effects of Altitude. The effects of altitude were assessed by statistical comparison of the altitude (12,500 ft) responses under each ingestum to the corresponding responses under the same ingestum at GL. The statistically significant differences are summarized in Table 12. For all three ingesta, all of the altitude %HbO$_2$ values were significantly lower than the corresponding values at GL. As shown in Table 9, all of the altitude %HbO$_2$ values are slightly higher than the generally accepted threshold (85 percent) for minor, but fully compensated hypoxia (11). Many of the altitude HR values were significantly higher than their counterpart GL values. The general range of the observed HR elevations were considered to be reasonable for the altitude and duration employed. However, it should be noted that most of the highest HR values at altitude (see Table 6) were those associated with Compound A.

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TABLE 2. SBP Data

Experimental Condition		SBP (mm Hg)					%Δ SBP			
		GL	Base 1	+Gz 1	Base 2	+Gz 2	Base 1 / GL	Base 2 / GL	+Gz 1 / Base 1	+Gz 2 / Base 2
GL/CA	X̄	112.2	113.6	104.5	114.6	105.1	101.2	102.2	91.9	91.6
	SEM	2.1	2.7	3.1	2.4	3.1	1.2	1.1	1.4	1.6
Alt./CA	X̄	113.6	111.9	107.4	111.3	101.4	98.6	98.3	95.8	91.2
	SEM	1.9	1.6	3.5	1.1	3.2	0.8	2.0	2.3	3.0
GL/CB	X̄	113.0	114.6	107.2	115.7	107.8	101.6	102.5	93.3	93.0
	SEM	2.7	2.5	4.1	2.7	3.5	1.7	1.5	2.1	1.6
Alt./CB	X̄	111.6	114.1	106.0	116.4	106.2	102.2	104.4	93.1	91.3
	SEM	1.3	2.1	2.2	2.0	2.1	1.3	1.8	2.1	1.4
GL/Pl.	X̄	110.4	111.2	104.5	112.0	103.8	100.8	101.7	94.0	92.7
	SEM	1.9	2.5	2.9	2.6	2.8	1.2	0.9	1.8	1.6
Alt./Pl.	X̄	114.2	114.1	108.4	112.1	103.9	100.0	98.2	95.1	92.7
	SEM	2.2	2.3	3.3	2.0	2.9	1.0	1.1	1.6	1.5

SBP = systolic blood pressure in mm Hg. %ΔSBP = percent change in SBP. GL = ground level altitude (1,274 ft MSL). Alt. = 12,500 ft MSL chamber altitude. CA = Compound A. CB = Compound B. Pl. = lactose placebo. $\bar{X}$ = mean. SEM = standard error of the mean. Base 1 = preceding baseline value for the first +2Gz test applied at the end of the first hour of the altitude period. +Gz1 = first +2Gz test applied at the end of the first hour of the altitude. Base 2 = preceding baseline for the second +2Gz test. +Gz2 = second +2Gz test applied at the end of the second hour of the altitude period.

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TABLE 3. DBP Data

Experimental Condition		DBP (mm Hg)					%Δ DBP			
		GL	Base I	+Gz I	Base 2	+Gz 2	Base I / GL	Base 2 / GL	+Gz I / Base I	+Gz 2 / Base 2
GL / CA	X̄	68.1	72.2	73.9	71.6	73.2	106.4	105.7	102.2	102.3
	SEM	2.4	2.5	3.0	2.3	2.4	2.4	2.5	1.3	1.5
Alt. / CA	X̄	69.3	67.5	68.1	69.2	67.0	97.2	99.8	100.9	96.3
	SEM	1.5	2.5	2.7	2.1	3.8	2.1	2.1	2.3	3.5
GL / CB	X̄	68.7	72.6	73.4	73.1	73.8	105.5	106.5	101.3	100.9
	SEM	2.1	3.0	3.1	2.2	2.8	2.2	2.1	2.1	1.9
Alt. / CB	X̄	70.2	70.8	72.7	72.9	71.6	101.2	104.0	102.6	98.0
	SEM	1.6	1.3	2.0	1.6	2.6	1.7	1.2	2.0	2.2
GL / Pl.	X̄	68.6	70.6	71.7	70.6	73.1	102.9	103.1	101.6	103.6
	SEM	1.7	2.2	2.9	2.0	2.4	1.8	2.4	3.0	2.3
Alt. / Pl.	X̄	65.8	69.1	69.0	71.0	70.2	105.6	108.6	99.7	98.9
	SEM	2.7	2.2	2.8	2.2	2.8	2.2	2.3	1.6	2.6

DBP = diastolic blood pressure in mm Hg. All other symbols have been defined in Table 2.

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TABLE 4. PP Data

Experimental Condition		PP (mm Hg)					%Δ PP			
		GL	Base 1	+Gz 1	Base 2	+Gz 2	Base 1 / GL	Base 2 / GL	+Gz 1 / Base 1	+Gz 2 / Base 2
GL / CA	X̄	44.1	41.4	30.7	43.0	31.9	95.4	98.7	74.2	74.9
	SEM	2.5	1.6	1.7	1.8	1.5	3.5	2.7	3.3	3.7
Alt. / CA	X̄	44.2	44.7	39.3	42.1	34.4	101.5	96.6	87.6	82.0
	SEM	2.5	2.4	3.6	2.2	4.6	3.5	4.9	6.3	10.7
GL / Cb	X̄	44.3	42.0	33.8	42.6	34.0	94.6	95.8	81.7	80.0
	SEM	1.9	3.0	3.3	2.6	2.3	5.3	3.0	7.3	4.2
Alt. / Cb	X̄	41.4	43.3	33.2	43.5	34.6	105.0	105.1	78.0	79.8
	SEM	1.6	1.8	2.0	2.2	2.3	3.2	3.3	4.8	4.1
GL / Pl.	X̄	41.7	40.6	32.8	41.4	30.7	96.8	99.3	83.7	75.5
	SEM	1.6	2.5	2.0	2.4	1.9	3.0	4.9	6.2	4.8
Alt. / Pl.	X̄	48.4	45.0	39.4	41.1	33.7	93.7	86.1	87.8	82.7
	SEM	2.5	2.4	2.8	1.8	1.5	3.4	3.8	4.7	3.2

PP = pulse pressure (SBP-DBP) in mm Hg. All other symbols have been defined in Table 2.

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TABLE 7. VE/KG Data

Experimental Condition		VE/kg (ml/min/kg)					% Δ VE/kg			
		GL	Base I	+Gz I	Base 2	+Gz 2	Base I' GL	Base 2 GL	+Gz I Base I	+Gz 2 Base 2
GL/CA	X̄	106.7	111.6	131.5	121.4	134.6	104.7	114.0	118.4	109.8
	SEM	5.6	9.2	15.4	8.7	15.4	6.8	6.2	11.9	7.2
Alt./CA	X̄	109.7	119.1	123.1	122.9	139.4	109.5	111.9	103.4	116.6
	SEM	4.6	4.3	9.8	9.7	14.2	4.9	7.6	7.4	12.8
GL/CB	X̄	109.3	106.2	122.3	112.3	114.9	97.6	103.5	114.1	101.0
	SEM	5.3	5.2	13.1	5.6	12.4	2.9	3.8	8.9	6.9
Alt./CB	X̄	111.0	111.9	126.8	118.3	132.2	101.1	107.3	112.6	111.4
	SEM	3.2	4.2	13.0	3.6	11.7	3.5	3.9	9.7	8.7
GL/Pl.	X̄	109.1	103.4	131.9	105.8	134.1	95.7	97.6	125.1	125.5
	SEM	5.4	4.4	18.8	5.6	15.6	3.6	4.5	14.0	10.8
Alt./Pl.	X̄	115.3	112.2	129.2	120.8	132.1	99.9	107.6	114.8	109.8
	SEM	5.8	3.8	10.8	2.3	11.7	5.6	5.7	8.0	10.6

V̇E/kg = pulmonary ventilation expressed in milliliters of expired gas per minute per kilogram body weight (ml/min/kg) at body temperature and pressure, saturated (BTPS) conditions. All other symbols have been defined in Table 2.

TABLE 8. TAFV Data

Experimental Condition		TAFV(cm/s)					%△ TAFV			
		GL	Base I	+Gz I	Base 2	+Gz 2	Base I / GL	Base 2 / GL	+Gz I / Base I	+Gz 2 / Base 2
GL / CA	X̄	4.7	4.6	3.0	5.1	3.5	100.3	110.5	63.9	67.6
	SEM	0.4	0.4	0.4	0.5	0.4	8.5	9.3	3.9	3.8
Alt. / CA	X̄	5.1	5.0	3.3	5.4	4.1	95.5	101.7	67.3	74.7
	SEM	0.6	0.8	0.6	0.8	0.8	7.1	6.3	5.8	6.5
GL / CB	X̄	4.9	5.0	4.1	5.7	4.7	102.0	122.4	83.2	83.2
	SEM	0.5	0.6	0.5	0.5	0.4	4.8	10.6	2.6	3.0
Alt. / CB	X̄	5.4	4.9	3.6	5.3	3.9	90.2	97.0	74.5	74.6
	SEM	0.5	0.6	0.5	0.7	0.6	4.7	7.0	4.0	3.7
GL / Pl.	X̄	5.0	5.2	4.2	5.0	4.0	106.9	99.9	77.3	76.8
	SEM	0.5	0.6	0.6	0.7	0.6	9.7	10.8	5.3	3.4
Alt. / Pl.	X̄	5.2	4.9	3.5	5.0	3.6	94.4	96.4	70.9	70.3
	SEM	0.3	0.4	0.3	0.5	0.5	5.2	7.1	3.7	3.6

TAFV = temporal artery blood flow velocity in centimeters per second (cm/s). All other symbols have been defined in Table 2.

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TABLE 9. %HbO$_2$ Data

Experimental Condition		%HbO$_2$					%△ %HbO$_2$			
		GL	Base I	+Gz I	Base 2	+Gz 2	Base I / GL	Base 2 / GL	+Gz I / Base I	+Gz 2 / Base 2
GL/CA	X̄	96.7	97.0	96.4	96.8	97.0	100.3	100.1	99.4	100.2
	SEM	0.3	0.3	0.5	0.2	0.3	0.2	0.3	0.4	0.3
Alt./CA	X̄	96.8	86.7	89.1	87.0	89.2	89.6	89.9	102.7	102.6
	SEM	0.3	1.2	1.7	1.3	1.6	1.1	1.3	1.3	1.1
GL/Cʙ	X̄	95.8	96.5	95.9	96.4	96.1	100.7	100.6	99.5	99.8
	SEM	0.3	0.3	0.4	0.3	0.4	0.2	0.1	0.2	0.2
Alt./Cʙ	X̄	96.3	87.1	89.5	88.0	89.9	90.5	91.4	102.7	102.1
	SEM	0.3	0.8	0.8	0.5	0.8	0.9	0.6	0.9	0.7
GL/Pl.	X̄	96.9	97.1	97.1	97.1	97.2	100.3	101.2	99.9	100.2
	SEM	0.3	0.2	0.2	0.3	0.3	0.2	0.2	0.2	0.2
Alt./Pl.	X̄	96.8	86.9	89.9	87.8	90.0	89.8	90.7	103.4	102.5
	SEM	0.2	0.5	0.6	0.6	0.7	0.5	0.6	0.6	0.7

%HbO$_2$ = arterial oxyhemoglobin saturation expressed in percentage. All other symbols have been defined in Table 2.

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TABLE 10. Ergometry Data

Experimental Condition		SBP (mm Hg)	DBP (mm Hg)	PP (mm Hg)	AP (mm Hg)	$\dot{V}O_2$/kg (ml/min/kg)	HR (bpm)	TAFV (cm/s)	$\dot{V}E$/kg (ml/min/kg)	%HbO2
GL / CA	X̄	127.9	67.1	60.8	87.4	11.6	100.8	4.5	304.3	96.7
	SEM	2.3	3.3	3.7	2.5	0.4	4.5	0.6	12.9	0.3
Alt. / CA	X̄	128.8	62.7	66.2	84.7	13.1	102.7	6.5	329.6	96.8
	SEM	1.5	1.8	3.2	0.9	0.5	2.7	1.0	16.9	0.6
GL / CB	X̄	130.9	67.5	63.4	88.6	13.0	95.0	5.3	294.0	96.3
	SEM	2.2	2.6	2.3	2.2	0.8	3.9	0.5	11.5	0.5
Alt. / CB	X̄	129.9	66.0	63.9	87.3	13.2	99.6	6.4	329.0	97.3
	SEM	3.2	2.8	2.9	2.6	0.5	3.1	0.8	10.9	0.3
GL / Pl.	X̄	130.3	65.8	64.5	87.3	11.9	96.8	6.3	332.3	97.2
	SEM	3.1	2.4	3.3	2.1	0.5	3.8	0.6	11.3	0.3
Alt. / Pl.	X̄	134.5	67.3	67.3	89.7	13.0	98.4	6.1	326.5	97.0
	SEM	3.4	3.4	2.3	3.2	0.6	3.7	0.8	10.4	0.3

The data summarized in this table represent the "steady state" mean values obtained during the fourth through sixth minutes of the 60-W, 50-rpm pedal-ergometry load. $\dot{V}O_2$/kg = oxygen uptake per kilogram body weight (ml/min/kg) at standard temperature and pressure, dry (STPD) conditions. All other symbols have been defined in Table 2.

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TABLE 11. Statistically Significant Effects of
Compound B and Compound A at GL

| | GL | | ERGOMETRY | |
	GL/Pl. vs. GL/Cb	GL/Pl. vs. GL/Ca	GL/Pl. vs. GL/Cb	GL/Pl. vs. GL/Ca
TAFV				* 60W
$\dot{V}_E$/kg		* Base 2/GL	* 60W	
% HbO2	* GL, +Gz1, +Gz2			

* = statistically significant difference at the level of $P \leq 0.05$.
All symbols have been defined in Tables 2, 7-9.

TABLE 12. Statistically Significant Effects of Altitude

| | ALTITUDE | | | ERGOMETRY | | |
	GL/Ca vs. Alt./Ca	GL/Cb vs. Alt./Cb	GL/Pl. vs. Alt./Pl.	GL/Ca vs. Alt./Ca	GL/Cb vs. Alt./Cb	GL/Pl. vs. Alt./Pl.
SBP			* Base2/GL			
DBP	* Base1/GL					
PP	* +Gz1		* GL, Base2/GL			
AP	* Base1/GL, Base2/GL					
$\dot{V}O_2$/kg				* 60W		
HR	* Base2/GL	* Base1, Base2, Base1/GL, Base2/GL	* Base2, Base1/GL, Base2/GL			
TAFV						
$\dot{V}_E$/kg			* Base 2		* 60W	
% HbO2	* Base1, +Gz1, Base2, +Gz2, Base1/GL, Base2/GL, +Gz1/Base1, +Gz2/Base2	* Base1, +Gz1, Base2, +Gz2, Base1/GL, Base2/GL, +Gz1/Base1, +Gz2/Base2	* Base1, +Gz1, Base2, +Gz2, Base1/GL, Base2/GL, +Gz1/Base1, +Gz2/Base2			

* = statistically significant difference at the level of $P \leq 0.05$.
All symbols have been defined in Tables 2-10.

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With Compound A ingestion, some of the altitude values of mean arterial pressure (AP) and diastolic blood pressure (DBP) were significantly less than their counterpart GL values, and one of the altitude values of pulse pressure (PP) was greater than its GL counterpart. With placebo ingestion, two of the altitude values of PP and one of systolic blood pressure (SBP) were significantly displaced. These displacements did not appear to reflect any vulnerability to incapacitation.

With respect to the effects of altitude on immediately subsequent ergometry, only two statistically significant differences were observed. Under Compound A, the postaltitude value of $\dot{V}O_2$/kg was approximately 13 percent greater than that of the corresponding period at GL. Under Compound B, the postaltitude value of $\dot{V}_E$/kg was approximately 12 percent greater than that of the corresponding period at GL.

<u>Tolerated Effects of Compounds A and B at 12,500 Ft Altitude</u>. Since placebo ingestion is assumed to represent the condition of no medication, it is logical that the responses to placebo ingestion combined with altitude exposure should constitute the baseline for quantitatively comparing the effects of Compound A or Compound B combined with altitude. The relatively few statistically significant differences arising from this comparison are summarized in Table 13. Under Compound B, three of the PP functions were smaller than the corresponding placebo values, and one of the SBP functions was greater than its corresponding placebo value. Under Compound A, two of the AP functions and two of the DBP functions were smaller than their respective counterpart placebo values. Although not statistically significant, one should note in Tables 5 and 6 that the altitude AP values during both LBNP tests under Compound A were less than the corresponding values under the Compound B and placebo ingesta, while the HR values under Compound A, altitude and LBNP were greater than the corresponding values under Compound B and placebo.

Although most of the postaltitude ergometry responses under Compound A or Compound B differed quantitatively from those under placebo, none of the differences were statistically significant. However, the directional displacements of the data in Table 10 were compatible with the general conclusion that the ergometric response under Compound A or Compound B was less efficient than the response under placebo.

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TABLE 13. Statistically Significant Effects of Compound B and Compound A at Altitude

	ALTITUDE		ERGOMETRY	
	Alt./Pl. vs. Alt./C$_B$	Alt./Pl. vs. Alt./C$_A$	Alt./Pl. vs. Alt./C$_B$	Alt./Pl. vs. Alt./C$_A$
SBP	* Base 2/GL			
DBP		* Base 1/GL, Base 2/GL		
PP	* GL, Base 1/GL, Base 2/GL			
AP		* Base 1/GL, Base 2/GL		

* = statistically significant difference at the level of $P \leq 0.05$. All symbols have been defined in Tables 2-5.

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Incapacitation. As mentioned previously, two subjects suffered clear-cut incapacitation at altitude under Compound A. Both incapacitations occurred during the first LBNP test. The LBNP test was terminated immediately without allowing each incapacitation to progress to frank syncope because both subjective and objective evidence clearly indicated the otherwise certainty of this outcome. Since an oral breathing valve was in place during each LBNP test, each subject's hand signals indicated his subjective judgment of impending syncope. Subjectively, facial blanching was concomitantly evident. Objectively, the Doppler's pulsatile signal indicated a marked diminution of forward blood flow in the temporal artery, and the $\%HbO_2$ meter indicated a decreasing saturation. Via concomitant microphonic communication, the "outside" technicians reported severe drops in both BP and HR. Upon each subject's hand signal, the LBNP was immediately terminated, the mouthpiece and nose clip were removed, and the standby mask source of 100 percent oxygen was instituted. Since rapid assessment of each subject's monitored functions indicated that impending syncope had been reversed, but an appreciable degree of hypotension and bradycardia still persisted, controlled descent to GL was initiated while 100 percent oxygen breathing was continued. All monitored functions indicated a return to normal ranges shortly thereafter. Each subject appeared to be fully recovered by the time descent was completed. Retrospectively, each subject reported that progressive symptoms of nausea, lightheadedness, visual tunnelling and grayout, and approaching syncope had occurred. Both subjects were detained and examined medically for complete return to functional normality prior to their release.

Drowsiness During the Altitude Period. The results of the subjective assessment of degree of wakefulness during the 2-hour altitude period are summarized in Table 14. It is of interest to note that Compound A at both altitudes was associated with a greater degree of drowsiness than was either Compound B or the placebo. Of further interest is the observation that, under Compound A, the degree of drowsiness was greater at altitude than at GL, with a greater difference between altitude and GL drowsiness occurring during the first hour than during the second hour. This first-hour difference, however, was not statistically significant. The only statistically significant difference which emerged was in the category of the effect of medication at altitude. The degree of drowsiness during the first hour at 12,500 ft under Compound A was significantly greater (P = 0.03) than its degree under placebo.

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TABLE 14. State of Wakefulness

		First Hour	Second Hour	Two-Hour Total
GL/CA	$\bar{X}$	2.25	2.12	2.19
	SEM	0.27	0.24	0.25
Alt./CA	$\bar{X}$	2.42	2.20	2.25
	SEM	0.25	0.25	0.24
GL/CB	$\bar{X}$	1.71	1.50	1.60
	SEM	0.24	0.24	0.21
Alt./CB	$\bar{X}$	1.89	1.86	1.88
	SEM	0.24	0.23	0.21
GL/Pl.	$\bar{X}$	1.76	1.52	1.64
	SEM	0.24	0.22	0.18
Alt./Pl.	$\bar{X}$	1.69	1.89	1.79
	SEM	0.22	0.26	0.23

A rating of 1 = fully awake. A rating of 2 = drowsy. A rating of 3 = asleep. See text for supplemental subcriteria for each rating. All symbols have been defined in Table 2.

IV. Discussion.

Generally, nonsyncopal cardiorespiratory responses to 2 minutes of -40 mm Hg of LBNP (+2Gz) in the upright, seated position (Tables 2-9) are quite similar to those correspondingly measured during human centrifugation studies (3-9). In order to retain a functionally useful degree of consciousness during the legward LBNP shift of blood volume (12,16), sufficient blood flow at the cerebral level must be maintained. The data in Tables 2-9 reflect the delicate, dynamic rebalancing of cardiorespiratory functions to achieve this end. In order to maintain an AP sufficient to perfuse the cerebrum, an arterial vasoconstrictor response appears to maintain the DBP in the face of a sustained decrease in SBP. As reflected by the decreased PP, the diminished cardiac stroke volume (12,16) caused by decreased venous return is compensated by a sustained increase in HR. This compensation provides a decreased, but maintained cardiac output (12,16), which is temporarily adequate to maintain a marginally sufficient cerebral blood flow. As reflected in Table 7, increased pulmonary ventilation serves as an adjunct aid to venous return. The maintenance of cerebral blood flow at this time is objectively reflected by the AP, TAFV and $\%HbO_2$ data in Tables 5, 8, and 9 respectively.

That the maintenance of adequate cerebral perfusion during the 2-minute LBNP test at 12,500 ft altitude is sufficiently, but precariously balanced, is reflected by the two incapacitations that occurred under Compound A. That Compound A appears to confer the greatest +Gz vulnerability of the three ingesta is evidenced by the fact that the AP was lowest (Table 5) and the HR was highest (Table 6) in those subjects who tolerated the LBNP at altitude under Compound A. Since no incapacitations occurred during the GL experiments, the altitude must have played some role in increasing orthostatic vulnerability under Compound A. The role of altitude is probably not a direct effect of hypoxia, per se, on cerebral mechanisms of circulatory control, because the observed drops in $\%HbO_2$ associated with untolerated LBNP followed rather than preceded the collapse of the sustaining BP and HR responses. Besides arterioconstriction (12,16), venoconstriction (7) is also known to occur in response to +Gz stress. Although the venoconstriction aids in returning blood to the heart, the resulting increase in venous resistance partially impedes the volume flow of venous return. This partly explains the necessity of an increased

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HR to maintain cardiac output and cerebral perfusion. If the
arterial and venous constrictor responses during LBNP are not
sufficient to allow the HR response to sustain the cerebral
blood flow above a critical threshold value, then incapaci-
tation and syncope ensue. The ensuing loss of consciousness
is due to cerebral hypoxia resulting from lack of blood flow
rather than the concomitant value of arterial $\%HbO_2$ because:

(i) useful consciousness during maintained cerebral perfusion
is known to be sustainable at arterial $\%HbO_2$ levels much lower

(ii) than the lowest arterial $\%HbO_2$ value (77 percent) observed

in our data during both incapacitations; and (ii) no syncopal
threshold was ever approached in our experiments without a
preceding Doppler indication of markedly reduced blood flow
at the cerebral level of the temporal artery. At this writing,
the exact mechanism by which Compound A and 12,500 ft altitude
interacted to compromise the delicate balance between the
compensatory vasomotor and chronotropic responses to +2Gz
stress remains obscure. However, it is possible that the
known drowsiness and hypotensive adverse effects of the type
of antihistamine (6) found in Compound A may have contributed
to the observed incapacitations. In adjunct observations, both
subjects who became incapacitated exhibited marked somnolence
(rating of 3) during most of the first three rating periods
prior to the initiation of the first LBNP test. This somno-
lence persisted despite the temporary arousing intervention
of two equally spaced math tests. It is possible that this
degree of somnolence indirectly reflected a dulling of feedback
sensory mechanisms necessary for elicitation of adequate
compensatory vasomotor and chronotropic responses. It may be
coincidental, but the greatest averaged degree of drowsiness
for all 12 subjects in this study occurred around the end of
the first hour at 12,500 ft altitude under Compound A, and
the first hour somnolence rating (see Table 14) under the latter
conditions was significantly greater (P = 0.03) than the com-
mensurate degree of drowsiness under placebo.

It is important to stress that, uninterrupted, both inca-
pacitations would have resulted in frank syncope. The imminence
of this syncope was reflected by the fact that during the two
incapacitations, the transient lowest values for SBP and HR
were 58 mm Hg and 58 bpm respectively for the one subject and
65 and 56 for the other. Logically, syncope in a pilot during
flight is incompatible with flight safety. If the +Gz and
altitude conditions of this study possess in-flight relevance,

then piloting an airplane under similar conditions during Compound A medication could compromise safe flight.

The results of the postaltitude ergometry testing indicated that 3 hours after initial ingestion, Compound A or Compound B had no significant detrimental effect on short-duration physical-work fatigue.

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