EFFECTS OF ACETAZOLAMIDE ON PHYSIOLOGIC AND SUBJECTIVE RESPONSES OF MEN TO 14,000 FEET

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FOREWORD

The research reported in this paper was conducted by personnel of the Physiology Branch under task No. 775801 between April and September 1966. The paper was submitted for publication on 22 June 1967. Portions of this report were presented at the 38th Annual Meeting of the Aerospace Medical Association.

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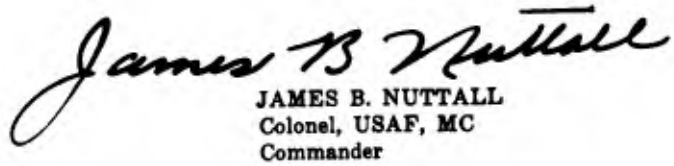
This report has been reviewed and is approved.



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ABSTRACT

A study was carried out to determine the effectiveness of low doses of acetazolamide in ameliorating the symptoms of altitude sickness. Subjects were placed in a low pressure chamber at either 14,000 ft. or 3,000 ft. for 24 hours. Before entering the chamber each subject took a total of 750 mg. of acetazolamide or a placebo. During their 24-hour stay, the subjects filled out a questionnaire designed to evaluate their state of well-being. End-tidal P_{CO_2} was measured, and electrodes were applied for monitoring respiratory pattern and EEG. Subjects were given a ranking of 1 (worst) to 4 (best) comparing individual clinical states. Samples of arterial blood and cerebrospinal fluid were obtained and analyzed for pH, P_{O_2}, P_{CO_2}, CO_2, HCO_3^-, and lactate. Twenty-four-hour urine volumes were analyzed for Na, K, and 17-hydroxycorticosteroids. Acetazolamide significantly lowered arterial and CSF HCO_3^-, arterial and end-tidal P_{CO_2}, and arterial pH. The mean arterial P_{O_2} was higher in those receiving acetazolamide, but the increase was not significant ($P < .10$). Pretreatment with acetazolamide was of sufficient clinical benefit to allow its recommendation prior to altitude exposure.

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I. INTRODUCTION

There have been several attempts to aid altitude acclimatization through the use of metabolic acidifying agents (1, 8). The rationale behind these efforts lies in the assumption that by combating the respiratory alkalosis produced by the hyperventilatory response to hypoxia, a continued increase in ventilation is permitted and the arterial P_{O_2} is raised. Recently, acetazolamide in small amounts has been shown to raise effectively the arterial P_{O_2} of men pretreated with the drug prior to going to altitude (3). This effect was maximum between 24 and 48 hours after reaching an altitude of 14,000 feet. The delay in achieving a maximum drug effect on ventilation and arterial P_{O_2} was thought to correspond to the time necessary for readjustment of the cerebrospinal fluid pH. Accordingly, it was decided to explore further the usefulness of acetazolamide in aiding accommodation to altitude and to examine the mechanisms of its action through a study of blood and CSF acid-base balance.

II. METHODS AND PROCEDURES

Subjects were 47 active duty military men, whose age and surface area are given in table I. All volunteers had passed a standard USAF Class III "flying" physical (9). With one exception, no subject was run more than once. He was used in the 3,000-ft. acetazolamide group and, 4 months later, in the 14,000-ft. placebo group. Although smokers and nonsmokers were equally distributed within the experimental groups, smoking was not permitted. For each experiment, three to four subjects were placed in a low pressure chamber at either 3,000 feet (681 torr) or 14,000 feet (447 torr). The subjects were not told of the altitude, and the chamber was operated so that the difference in the two pressures could not be detected. A total of 750 mg. acetazolamide or a lactose placebo was given orally in a "double-blind" fashion prior to going to altitude. The dose was divided so that two 250 mg. gelatin capsules were taken 12 hours, and one capsule 1 hour, before entering the chamber. The order of presentation of the drug and placebo was random. A normal diet was provided ad libitum, except that sources of caffeine were not given after 5 p.m. so as not to interfere with the sleep measurements. Moderate activity was allowed, but no one was allowed to sleep before 9 p.m.

End-tidal P_{CO_2} sampling was done using a nasal catheter as soon as the chamber had stabilized at its designated altitude and every 2 hours thereafter, except during sleep. After 24 hours at altitude a single sample of arterial blood was obtained from the brachial artery.

TABLE I

Profile of experimental subjects

Conditions	Number of subjects	Age	BSA(m.²)
3,000 feet			
Acetazolamide	12	24.0 (19-32)	1.88
Placebo	11	25.1 (20-34)	1.94
14,000 feet			
Acetazolamide	12	28.3 (19-38)	1.99
Placebo	12	26.1 (19-36)	1.95
	47	25.7 (19-38)	1.93

Values in parentheses are ranges.

BSA — body surface area in square meters.

The subject was then placed in the left lateral decubitus position and a lumbar puncture done. In an effort to obtain an anaerobic sample, an oil-sealed syringe was used and the dead space displaced with cerebrospinal fluid prior to withdrawing a single 10-cc. sample. During the arterial sampling and lumbar puncture, the end-tidal P_{CO_2} was recorded continuously and the subject instructed to control his breathing so as to adhere to a previously determined baseline level. A 24-hour urine sample was collected while at altitude.

The pH, P_{O_2}, and P_{CO_2} of the arterial blood were measured by appropriate electrodes at an assumed body temperature of 37° C. (2). Microhematocrit measurements were also made. Arterial plasma HCO_3^- was calculated using a pK of 6.09 and a solubility for CO_2 = 0.0308. Standard bicarbonate was calculated from measured pH value of arterial blood equilibrated with 5.72% CO_2 in O_2 (P_{CO_2} = 40 torr).

Cerebrospinal fluid P_{O_2}, P_{CO_2}, and pH were analyzed in O_2, CO_2, and pH electrodes at 37° C. CSF lactate was measured enzymatically (5). In addition to being measured directly, the CSF P_{CO_2} was calculated using values of pK given by Mitchell et al. (10) and a CO_2 solubility of 0.0318 ml./liter/torr at 37° C.

Urine specimens were analyzed for volume, sodium, potassium, creatinine, and 17-hydroxycorticosteroids (17-OHCS). The Technicon AutoAnalyzer was used for determining creatinine. Sodium and potassium were determined by means of a Beckman model DU spectrophotometer equipped with a flame attachment and using an acetylene-O_2 fuel system. Total 17-OHCS was determined by the Reddy method after hydrolysis with β-glucuronidase and ethyl acetate extraction (13).

While in the chamber, each subject was observed and questioned independently by the authors on several occasions. At the conclusion of each run the subjects were ranked as to the state of their well-being against the three others who were with them in the chamber. All subjects were arbitrarily given a rating from 1 to 4 (1 = worst of the particular run; 4 = best) regardless of how well or poorly they were doing. At the bihourly time intervals corresponding to the periods of end-tidal sampling, each subject filled out a 26-item questionnaire devised by Evans (6); this was to evaluate their subjective feelings.

Before going to sleep, each subject was fitted with three Ag-AgCl electrodes across the lower rib cage. These electrodes were connected through appropriate preamplifiers to a Physiograph Six recorder for continuous monitoring of an impedance pneumogram during sleep. Similar electrodes were placed along the left lateral canthus, C_1, P, and O_2 positions of the scalp and attached to a Grass model III-D polygraph for the recording of continuous sleep EEG's.

All of the results were tested using an analysis of variance. In the case of the subjective questionnaire, each question and the two altitudes were treated separately and analyses were done for the effects of drug, time, and the interaction of time and drug.

III. RESULTS

Acetazolamide significantly lowered cerebrospinal fluid (CSF) HCO_3^- at both altitudes (table II). The CSF P_{O_2} was judged unreliable because of the difficulty in ascertaining a definite end point with the oxygen electrode. The values given are means of an estimated peak reading. The failure of acetazolamide to affect significantly CSF P_{CO_2} and pH at altitude is attributed to the difficulty in always obtaining a strictly anaerobic sample. The frequent occurrence of small bubbles when CSF samples were drawn, in spite of all efforts to eliminate this, contributed to higher values of pH and lower values of P_{CO_2} than those reported elsewhere (11, 16). Excellent agreement between measured and calculated P_{CO_2} would indicate that the greatest variability was introduced by sampling technic. The less mobile moiety of HCO_3^- was considered reliable and is, therefore, given more weight in the discussion to follow. CSF lactate was significantly higher at 14,000 feet than at 3,000 feet.

TABLE II

Biologic fluid variables

	14,000 ft.		3,000 ft.	
	Acetazolamide	Placebo	Acetazolamide	Placebo
Cerebrospinal fluid				
P_{O_2} (mm. Hg)	34.7 ± 6.2	32.7 ± 3.3	42.3 ± 5.7	41.3 ± 10.2
Measured P_{CO_2} (mm. Hg)	34.3 ± 4.9	35.9 ± 2.3	41.7 ± 3.4	48.0 ± 4.2*
Calculated P_{CO_2} (mm. Hg)	34.2 ± 4.2	36.3 ± 2.7	41.4 ± 1.7	47.0 ± 4.5†
pH	7.376 ± .035	7.387 ± .033	7.359 ± .017	7.360 ± .012
Lactate (mg. %)‡	18.4 ± 3.0	19.8 ± 3.0	13.4 ± 1.3	12.4 ± 1.1
HCO_3^- (mM./liter)	19.04 ± 0.69	20.72 ± 1.00†	22.30 ± 0.85	25.09 ± 0.60†
Arterial blood				
P_{O_2} (mm. Hg)	46.6 ± 5.3	41.8 ± 3.0	86.4 ± 7.3	80.1 ± 7.2*
P_{CO_2} (mm. Hg)	26.6 ± 1.7	30.5 ± 2.7†	34.8 ± 2.7	38.2 ± 2.5†
pH	7.423 ± .030	7.466 ± .042†	7.351 ± .020	7.420 ± .028†
HCO_3^- (mM./liter)	17.42 ± .09	22.30 ± 1.50†	19.55 ± 1.66	25.09 ± 1.58†
Std. HCO_3^- (mM./liter)	19.99 ± .06	23.66 ± 1.20†	20.32 ± 1.00	24.37 ± 1.00†

Values are means ± 1 S. D.

Probability levels for significant differences between acetazolamide and placebo:

*$P < .05$;

†$P < .01$.

‡A significant difference ($P < .001$) was present between altitudes but not between acetazolamide and placebo.

Arterial blood P_{CO_2}, pH, HCO_3^-, and standard HCO_3^- were lowered significantly by acetazolamide (table II). Arterial P_{O_2} was increased at both altitudes, but only at a borderline level of significance at 14,000 feet ($P < .10$).

The combination of altitude and drug divided the end-tidal P_{CO_2} determinations into four distinct groups. As can be seen in figure 1, end-tidal P_{CO_2} decreased significantly over time in both the treated and untreated groups at 14,000 feet ($P < .01$), but remained relatively constant at the 3,000-ft. altitude. This decrease was more pronounced in the acetazolamide-treated group with a sharp fall-off occurring after 7 hours in the chamber. The apparent rise in the end-tidal P_{CO_2} levels in three of the four groups at the seventh hour could not be related to any single event, such as food intake or initiation of an experimental procedure. It was not found to be statistically significant.

The incidence of pattern breathing as recorded by means of the impedance pneumogram was significantly higher ($P < .001$) at 14,000 feet than at 3,000 feet (table III). In this report, pattern breathing was considered to be any respiration showing a rhythmic sequence of hyperpnea followed by apnea and persisting for at least 5 minutes. Classic Cheyne-Stokes respiration was not observed. On several occasions, pattern breathing was followed by awakening, but this was not a constant finding. Heart rates were recorded randomly on individual subjects throughout the night and showed only the expected slowing during sleep. Acetazolamide had no effect on the incidence of pattern breathing.

Acetazolamide produced a significant diuresis and kaluresis both at 3,000 feet and 14,000 feet (table IV). The drug did not affect sodium excretion. Altitude alone did not increase urinary potassium loss. This is consistent with the fact that the plasma HCO_3^-

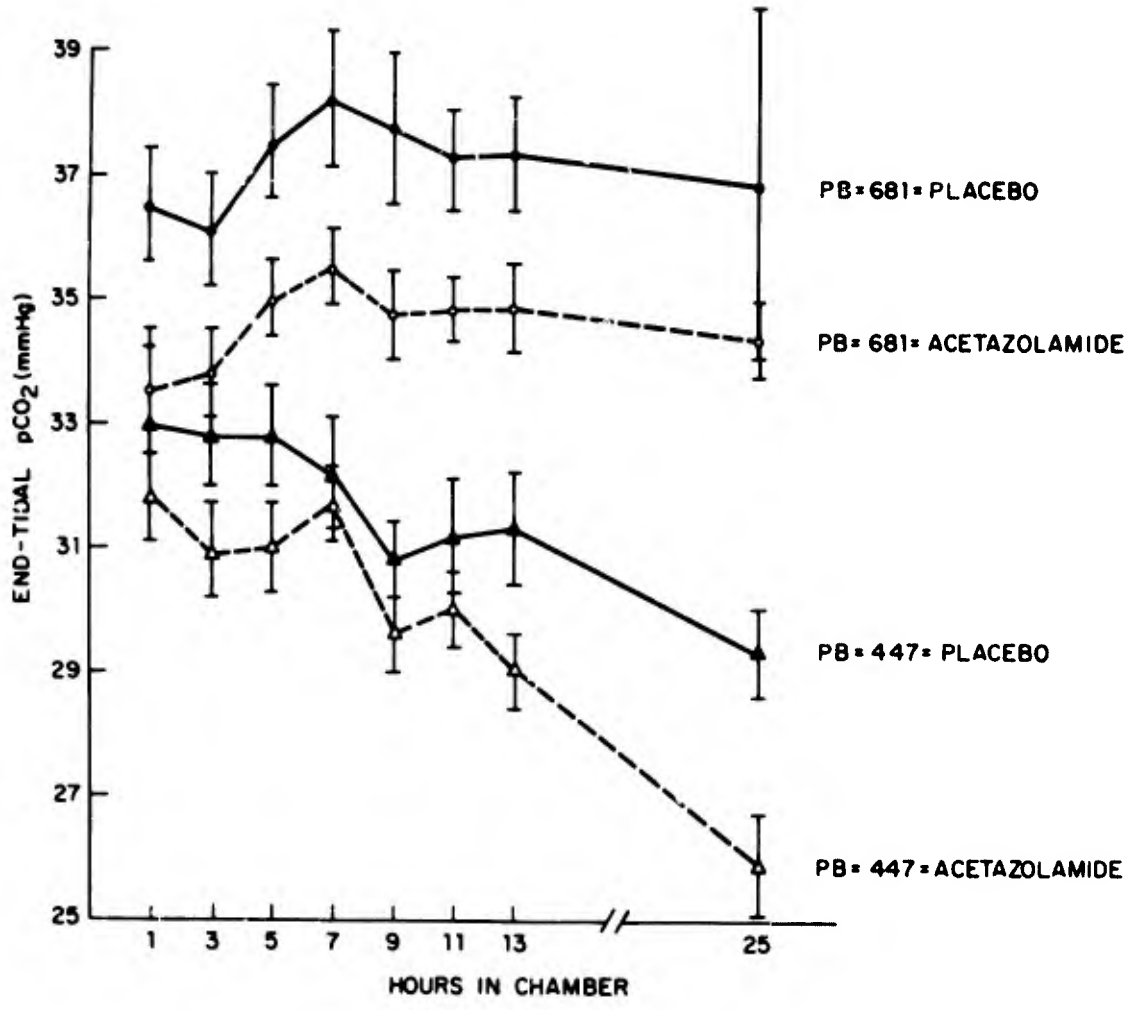

FIGURE 1

End-tidal P_{CO_2} determinations as a function of time at altitude. Each point represents a mean value ± 1 S.E.M.

was not significantly affected by changing the chamber altitude. The only significant difference seen in the urine data between 14,000 feet and 3,000 feet was in the 17-OHCS excretion which was higher at altitude. The urine volumes tended to be higher at 3,000 feet. This was probably a reflection of higher fluid intake. No effort was made to control food, fluid, or salt intake which was assumed to be adequate prior to the experiment. Anorexia was frequently observed at altitude along with nausea and vomiting. The volume of vomitus was not recorded, but considerable potassium may have been lost by this route.

The sleep EEG data are summarized in table V. The records were scored for stages of sleep according to the method of Dement and Kleitman (4). By this method, the stages can be interpreted as follows: stage 0—awake; stage —drowsy; stages 2, 3 and 4—progressively deeper stages of sleep; REM—rapid eye movement stage indicative of dreaming. The subjects receiving acetazolamide at 14,000 feet

did have, on the average, more total sleep, as well as more sleep in the deeper stages, than the untreated subjects at 14,000 feet; but, this was not a statistically significant finding. Technical difficulties were considerable and artifacts were numerous. The fact that the subjects at 3,000 feet failed to sleep any longer than those at 14,000 feet indicates that no conclusion should be drawn on the basis of these data.

The results of the clinical ranking of the subjects in the 14,000-ft. runs are summarized in figure 2. Those who showed definite objective signs of being sick, such as vomiting or complete inability to cooperate in the experiment, were given a ranking of 1. The difference between a 2 and a 3 ranking was quite arbitrary in most cases. If only those subjects given either rankings of 1 or 4 are considered, acetazolamide had a significantly beneficial effect ($P < .05$). Although the subjects at 3,000 feet were not ranked, there was one case of nausea and vomiting in this group. This was accompanied by fever, myalgia, and the presence of two sick family members at home; it was, therefore, attributed to a viral illness unrelated to the conditions of the experiment.

In the analysis of the questionnaires, the only item showing a statistically significant difference between acetazolamide and placebo was eye fatigue, which was worse in the treated group at both altitudes. There were many significant differences in the remaining 25 items because of time and altitude. In general, these could have been predicted in that the subjects at 14,000 feet tended to develop altitude sickness and, the longer they remained at altitude, the sicker they became. The subjects at 14,000 feet were nauseated, became less lively, developed dizziness, became progressively unhappy, developed headaches, became less active, slept poorly, experienced heart pounding, and were generally less refreshed. The 3,000-ft. group also became less happy and energetic with time, but did not report the specific disagreeable symptoms that those at 14,000 feet encountered.

TABLE III

Incidence of pattern breathing

	Pattern breathing	No pattern breathing
3,000 ft.		
Acetazolamide	1	11
Placebo	0	12
	1	23
14,000 ft.		
Acetazolamide	7	5
Placebo	9	2
	16	7

TABLE IV

Twenty-four-hour urine variables

	14,000 ft.		3,000 ft.	
	Acetazolamide	Placebo	Acetazolamide	Placebo
Potassium (mEq./24 hr.)	110.3 ± 24.1	66.4 ± 20.0†	137.6 ± 23.1	61.1 ± 26.9†
Sodium (mEq./24 hr.)	216.5 ± 74.9	183.0 ± 90.0	220.1 ± 81.8	242.8 ± 73.6
17-OHCS‡ (mg./24 hr.)	7.3 ± 2.5	7.2 ± 4.9	4.6 ± 3.4	4.1 ± 1.6
Volume (cc./24 hr.)	1,910 ± 23	1,279 ± 18*	2,049 ± 15	1,544 ± 20*

Values are means ± 1 S. D.

Probability levels for significant differences between acetazolamide and placebo:

*$P < .05$;

†$P < .001$.

‡A significant difference ($P < .01$) was present between altitudes but not between acetazolamide and placebo.

TABLE V

Minutes in each stage of sleep

	14,000 feet		3,000 feet	
	Acetazolamide	Placebo	Acetazolamide	Placebo
Stage 0	29 ± 34	96 ± 84	25 ± 27	19 ± 13
Stage 1	56 ± 45	86 ± 45	46 ± 37	49 ± 45
Stage 2	212 ± 113	113 ± 55	110 ± 86	109 ± 79
Stage 3	54 ± 54	59 ± 52	51 ± 61	38 ± 75
Stage 4	22 ± 47	11 ± 34	21 ± 26	24 ± 29
REM	12 ± 15	3 ± 3	3.5 ± 8	3.5 ± 5
Artifact	72	75	202	150
2 + 3 + 4 + REM	295 ± 97	175 ± 90	195 ± 137	202 ± 147
Total sleep*	368 ± 34	273 ± 92	231 ± 140	251 ± 161

Values are means ± 1 S. D.

Stages were determined from EEG records.

*See text for explanation.

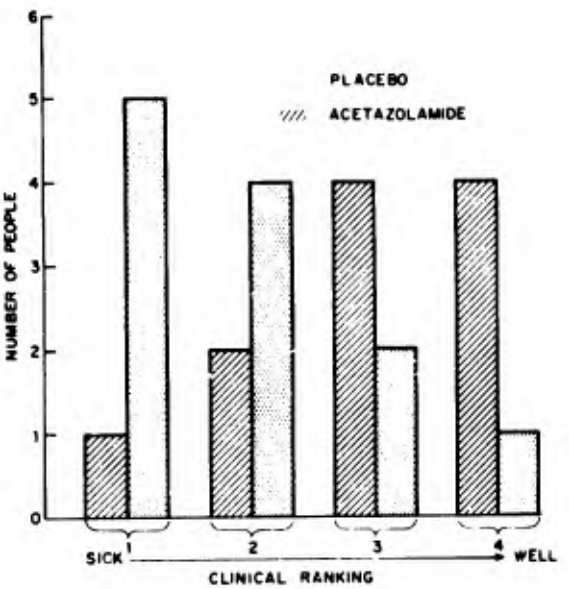

FIGURE 2

Clinical rankings of the 23 subjects at 14,000 feet.

IV. DISCUSSION

The present study has again demonstrated the ability of low doses of acetazolamide to lower significantly arterial blood pH, HCO_3^-, standard HCO_3^-, and blood and alveolar P_{CO_2}. Arterial P_{O_2} was also increased but this was significant only at the 3,000-ft. altitude. These results are similar to those obtained by Cain and Dunn (3) in their short exposure studies. The effects of altitude alone on cerebrospinal fluid found in the untreated group—namely, loss of HCO_3^- and accumulation of lactate—are comparable to those noted by Severinghaus and co-workers (15). The notable new information provided by this study was the combined effect of low doses of acetazolamide and hypoxia on CSF composition and its relation to arterial blood.

Pappenheimer and Severinghaus and their co-workers have shown the importance of the cerebrospinal fluid in the regulation of respiration (11, 16). Severinghaus et al. (16) have demonstrated that early accommodation to altitude is largely mediated through an active process which regulates CSF hydrogen ion concentration. This process which involves active transport of HCO_3^- ions out of the CSF occurs within 24 hours after ascent and serves to counteract partially the inhibitory effect on ventilation of the respiratory alkalosis produced by the peripheral chemoreceptors in

response to low P_{O_2}. The change in slope of the end-tidal P_{CO_2} curves after 7 hours at 14,000 feet (fig. 1), indicates that this might be the amount of time necessary for transport to occur. Eventually, a more complete adjustment of blood and CSF acid-base balance is achieved by the elimination of HCO_3^- through the kidney over a period of several days or weeks. Hypothetically, the administration of low doses of a carbonic anhydrase inhibitor, such as acetazolamide, prior to altitude exposure should hasten this entire process by increasing renal HCO_3^- excretion. This early HCO_3^- loss would have three possible effects. First, it would lower plasma pH, thereby reducing the inhibitory effect on ventilation of the respiratory alkalosis and permitting the peripheral chemoreceptors to respond more fully to low P_{O_2}. Secondly, it would establish a greater diffusion gradient between CSF and plasma HCO_3^-. Thirdly, it would have a direct effect on the central chemoreceptors by lowering the pH of the blood and interstitial fluid surrounding them (11).

The data obtained on CSF and plasma HCO_3^- support Severinghaus' concept that the early reduction in CSF HCO_3^- at altitude is accomplished to a large extent by means of an active transport mechanism. At a given altitude there is a linear relationship (fig. 3) between CSF and arterial HCO_3^- with the slope of the calculated regression line being very similar to that obtained by Fencl et al. (7) during chronic metabolic acidosis and alkalosis. The slope of the 14,000-ft. or 447-torr line was

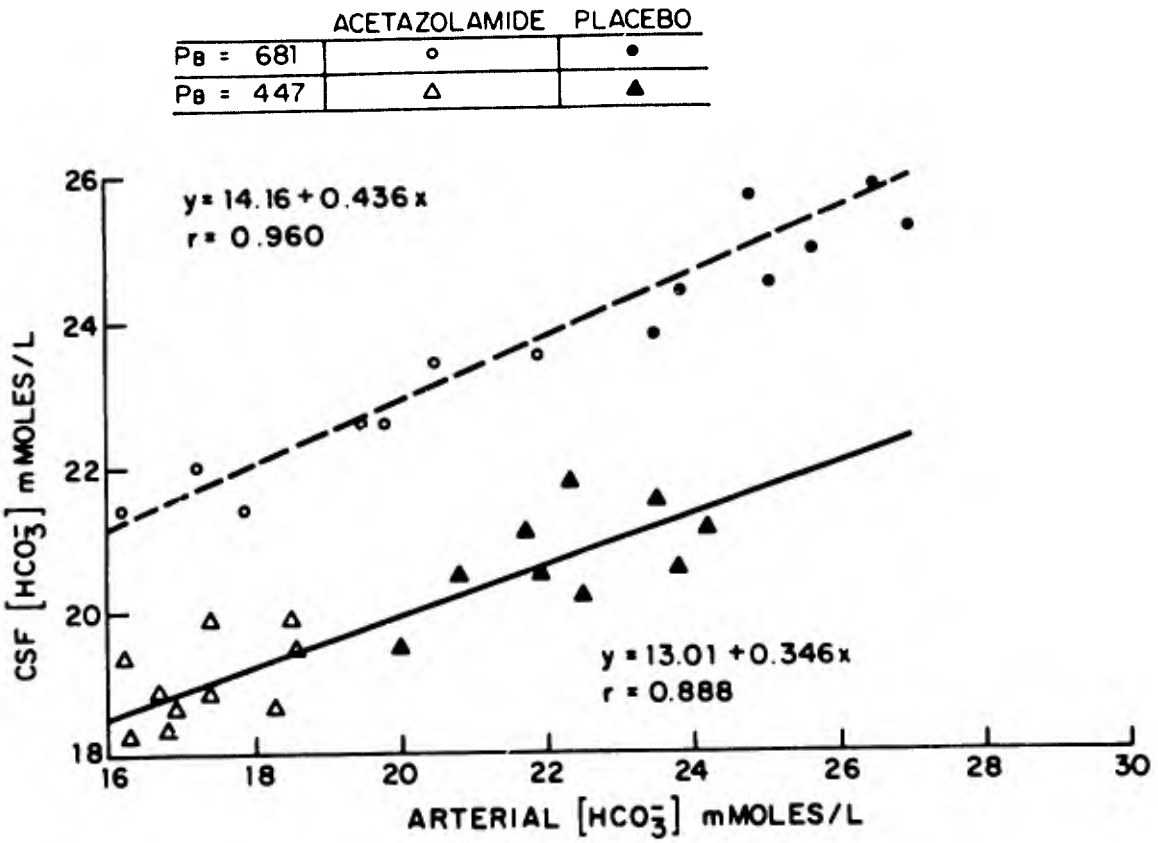

FIGURE 3

Cerebrospinal fluid bicarbonate vs. arterial bicarbonate.

almost the same as that of the 3,000-ft. or 681-torr line, but the entire line was displaced downward by about 3 mM./liter. The increase in CSF lactate at 14,000 feet accounted for less than one-third of this displacement. This contribution of lactate to the restoration of a normal CSF pH, was considerably less than that found by Plum and Posner (12); however, their study involved severely hyperventilated and hypoxic dogs and the results are probably not directly comparable. The amount of displacement not accounted for by the rise in CSF lactate, therefore, might reasonably be attributed to the active transport mechanism operating during the 24-hour exposure.

The fact that the CSF and arterial bicarbonate values obtained at the two altitudes from the acetazolamide-treated individuals fell along the same lines as the placebo points indicated that the drug had no direct effect on the CSF composition but exerted its action primarily by lowering plasma HCO_3^-.

The significantly lower $P_{A_{CO_2}}$ found in the treated group (fig. 1) implied that acetazolamide augmented the increase in ventilation at altitude. Although, on the average, this increased ventilation raised the arterial P_{O_2} only 5 torr at the 14,000-ft. altitude and was not significant statistically, it may have been important physiologically. Arterial O_2 saturations, as determined from the Severinghaus blood O_2 dissociation nomogram (14), were significantly higher in the treated groups at both altitudes ($P < .001$). The lowering of the arterial pH produced by the drug should also have enhanced the unloading of O_2 at the tissues and increased the mixed venous P_{O_2}. By assuming an arteriovenous difference in O_2 content of 5 vol. % and a normal O_2 capacity of 20 vol. %, the mixed venous P_{O_2} can be read from the nomogram. In the placebo-treated individuals at 14,000 feet, the mixed venous P_{O_2} was 26.2, on the average, whereas it averaged 28.6 in those given acetazolamide. The difference was statistically significant ($P < .001$).

Acetazolamide produce a significant diuresis at both 3,000 and 14,000 feet (table IV). The difference in urine volume between treated and untreated individuals of about 600 cc./24 hours at 14,000 feet, together with the reduced intake at altitude, might have been sufficient to produce mild dehydration. Smith and Crowell (17) have shown that hemoconcentration at altitude may slow blood flow sufficiently to hinder accommodation; therefore, fluids should probably be encouraged when the drug is used under these circumstances. Most of the urine HCO_3^- was excreted in the form of $KHCO_3^-$. Cain and Dunn (3) demonstrated that the serum K^+ remains within normal limits in similar experiments; however, a significant depletion in total body potassium may occur through intracellular loss before any change can be detected in extracellular K^+. In addition, the subjects exposed to the 14,000-ft. altitude frequently suffered from anorexia and vomiting, thereby reducing their K^+ intake while greatly increasing K^+ loss. The desirability of giving individuals treated with acetazolamide a supplement of potassium while at altitude should be considered.

The objective and subjective data relating to the efficacy of acetazolamide in ameliorating altitude sickness were difficult to interpret. The altitude chamber that was used was approximately 20 feet long, 8 feet wide, and 8 feet high. The floor space was largely occupied by two double bunks, chairs, and other assorted paraphernalia. One can well imagine that the sight of someone vomiting from altitude sickness in one corner of the chamber would be enough to nauseate everyone, regardless of how they were being affected by the altitude. Several men reacted violently with severe headache and vomiting within 2 to 3 hours after going to altitude, only to eventually settle down and have an uneventful stay while their chambermates, who began in good spirits, would be awake all night with altitude sickness. This behavior made clinical ranking difficult. In cases where an individual's rank changed from 1 (sick) to 4 (well) during the course of a flight, his nighttime ranking was given the most weight.

Other difficulties were encountered in attempting to measure sleep. Ventilation and cooling requirements produced a constant noisy

air flow through the chamber. This, added to uncomfortable double bunks, the presence of electrodes on the chest and scalp, and the strangeness of the situation made sleeping difficult. In addition, the technical difficulties involved with the taking of the sleep EEG's were almost unsurmountable. One interesting EEG phenomenon that was noted with some frequency was that awakening would be immediately preceded by a prolonged bout of pattern respiration. This sequence of events may be what actually occurs in individuals who awaken at altitude with severe dyspnea.

In view of the ability of acetazolamide to affect favorably all of the parameters customarily associated with altitude accommodation, some speculation as to why those subjects receiving the drug failed to demonstrate an unequivocal advantage seems warranted. The correction of hypoxia by the administration of O_2 will prevent the appearance of any symptoms of altitude sickness. Exactly how much the arterial Po_2 has to be raised to achieve this goal is not known. Obviously the average 5-torr rise obtained in this study was insufficient. Since it is doubtful if any pharmacologic agent would induce an increase of arterial Po_2 much greater than 5 torr during the first 24 hours at altitude, one wonders if all efforts to aid altitude accommodation by means of drugs must not end in failure. Of course, the desirable extracellular acid-base changes produced by acetazolamide may not be reflected on the intracellular level, but the enhanced renal excretion of potassium and HCO_3^- produced by the drug should have increased intracellular H^+ concentration. The quantitative role of the peripheral chemoreceptors in total respiratory drive during short exposures to altitude is another major unknown factor (15). A third possibility is that increasing the dosage of acetazolamide might achieve more uniform benefit. Large doses, however, in the order of 25 mg./kg. body weight produce undesirable side effects similar to those of acute altitude sickness (personal experience of SMC). The dosage level used was sufficient to induce significant acid-base changes, eye fatigue, diuresis, and renal potassium loss and, therefore, was probably large enough for our purpose. Newer carbonic anhydrase inhibitors with selective renal action might prove to be more suitable for aiding altitude accommodation (18). The necessity of readministering the drug during longer stays at altitude should also be considered.

In spite of the fact that, in this study, acetazolamide did not prevent altitude sickness in all the treated subjects, we recommend its use prior to altitude exposure on the basis of the clinical rankings of groups 1 and 4. Those subjected to a study of this type seem to fall in one of three groups. A small percentage will not be adversely affected by the altitude. A slightly larger number will be made ill no matter what preventives they take. Finally, the majority will be helped to some degree by prior administration of the drug. If one considers that even a modest amelioration of altitude sickness might make the difference between being prostrate with vomiting and being able to function in a reasonable fashion, anything that can achieve this difference is probably worthwhile. When this small but definite benefit is coupled with the fact that acetazolamide is nontoxic and has virtually no side effects in the dosage used, there seems to be no reason for withholding it. This is especially true when acetazolamide is contrasted with other agents used for this purpose, such as NH_4Cl with its attendant gastric irritation and somewhat unphysiologic mechanism. Certainly the optimal combination of drugs and their methods of administration have not yet been found. Until they are, we feel that acetazolamide remains the best drug currently available for this purpose.

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13. ABSTRACT

A study was carried out to determine the effectiveness of low doses of acetazolamide in ameliorating the symptoms of altitude sickness. Subjects were placed in a low pressure chamber at either 14,000 ft. or 3,000 ft. for 24 hours. Before entering the chamber each subject took a total of 750 mg. of acetazolamide or a placebo. During their 24-hour stay, the subjects filled out a questionnaire designed to evaluate their state of well-being. End-tidal P_{CO_2} was measured, and electrodes were applied for monitoring respiratory pattern and EEG. Subjects were given a ranking of 1 (worst) to 4 (best) comparing individual clinical states. Samples of arterial blood and cerebrospinal fluid were obtained and analyzed for pH, P_{O_2}, P_{CO_2}, CO_2, HCO_3-, and lactate. Twenty-four-hour urine volumes were analyzed for Na, K, and 17-hydroxycorticosteroids. Acetazolamide significantly lowered arterial and CSF HCO_3-, arterial and end-tidal P_{CO_2}, and arterial pH. The mean arterial P_{O_2} was higher in those receiving acetazolamide, but the increase was not significant ($P < .10$). Pretreatment with acetazolamide was of sufficient clinical benefit to allow its recommendation prior to altitude exposure.

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