HASTENING RESPIRATORY ACCLIMATIZATION TO ALTITUDE WITH BENZOLAMIDE

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FOREWORD

This report was prepared in the Physiology Branch under task No. 775801. The work was accomplished between October 1966 and May 1967. The paper was submitted for publication on 28 July 1967.

CL 11,366 is the developmental number assigned to benzolamide. The sample of benzolamide used in our experimentation was supplied by Dr. David M. Travis, Department of Pharmacology and Experimental Therapeutics, University of Florida College of Medicine, Gainesville, Fla.

The authors are grateful for the technical assistance of Charles C. Andrews, Jr., Airman Second Class William G. Soucie, and Mrs. Martha E. Kardon; and for the help of the volunteer subjects who endured considerable discomfort to make this study possible.

This report has been reviewed and is approved.

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ABSTRACT

A "double-blind" study involving 72 hours' exposure to a pressure altitude of 14,000 feet (447 torr) was carried out on 23 subjects to ascertain whether benzolamide (CL 11,366) hastened respiratory acclimatization to altitude better than did acetazolamide, another carbonic anhydrase inhibitor previously investigated. Samples of arterial blood, plasma, and cerebrospinal fluid (CSF) were taken at 24 and 72 hours at altitude and analyzed for pH, P_{CO_2}, P_{O_2}, CO_2 content, HCO_3^-, standard HCO_3^-, lactate, Na^+, K^+, and Cl^-. End-tidal P_{CO_2} was measured frequently during waking hours, and CO_2 response curves were measured daily. Three 24-hour urine collections were analyzed for Na^+, K^+, Cl^-, and 17-hydroxycorticosteroids. Subjects filled out questionnaires to evaluate their subjective responses to altitude and were ranked by an observer according to their apparent state of well-being. Changes in physiologic variables were consistent with more rapid respiratory acclimatization, and the subjective data indicated that the drug was helpful in ameliorating acute altitude sickness. Benzolamide was not clearly better in either respect than acetazolamide.

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I. INTRODUCTION

Earlier studies have shown that low doses of the carbonic anhydrase inhibitor, acetazolamide, can assist altitude accommodation (1, 3). The possibility has been raised that this beneficial effect could be enhanced by increasing the dose of the drug (3). Unfortunately, large doses of acetazolamide, in the order of 25 mg./kg. body weight, have produced undesirable side effects similar to those of acute altitude sickness (personal experience of author, S.M.C.). The availability of a newer carbonic anhydrase inhibitor, benzolamide (CL 11,366), has made it possible to give approximately ten times the effective dosage of acetazolamide with respect to renal tubular inhibition of carbonic anhydrase without fear of causing significant enzyme inhibition in the red blood cell (10). Mani and Weinstein (4) have shown that benzolamide improved the performance of rats during hypoxia. This study was carried out to explore the usefulness and mechanisms of action of benzolamide in aiding accommodation of men to altitude.

II. METHODS AND PROCEDURES

Twenty-three active-duty military men were used in this study. The subjects ranged in age from 19 to 37 years and in body surface area from 1.6 to 2.2 $m.^2$ All volunteers had passed a standard USAF Class III physical examination for flying personnel (5). For each experiment, we placed 2 to 4 subjects in a low pressure chamber at 14,000 feet (447 torr) for 72 hours. Benzolamide or a lactose placebo was given orally in a "double-blind" fashion just before subjects went to altitude. The dosage of 500 mg. was divided into 50-mg. gelatin capsules—five being given 12 hours before and five being given 1 hour before entering the chamber. The order of presentation of drug and placebo was random. After a minimum of four weeks each subject was run again with reversal of those receiving drug and placebo. Six subjects served only once. A normal diet was provided ad libitum and moderate activity allowed. Although smokers and nonsmokers were about equal in number, smoking was not permitted during the experiment.

CO_2 response curves on 9 of the subjects were determined immediately before they went to altitude and in the afternoon of the first, second, and third days at 14,000 feet. In the determination of the ground-level CO_2 response curves, each subject breathed mixtures containing approximately 1.5%, 3%, and 5% CO_2 in O_2 through a diluter demand regulator connected to a respiratory non-rebreathing valve for a 10-minute period. A sampling port close to the mouth was connected to a Beckman model LB-1 CO_2 analyzer in series with an Esterline-Angus recorder (model S-601-S). Gas samples were withdrawn during the breathing period by a Beckman microcatheter sample pump at a rate of 500 cc./min. After a 10-minute stabilization period, the subjects at end-expiration were switched to a Collins 120-liter gasometer and their expired air collected for 3 minutes. $\dot{V}E$ was corrected for temperature and the amount of gas withdrawn through the sampling circuit. End-tidal P_{CO_2} was taken as the average value during the last 30 seconds of the collection period. The curves at 14,000 feet were determined in an identical fashion except that the gas mixtures used were approximately 3%, 5%, and 7% CO_2 in

O_2. Considerable effort was made to have the subjects achieve a steady state before beginning the collection period. They were encouraged to occupy their time by reading or watching television during the procedure.

End-tidal P_{CO_2} was routinely sampled from a nasal catheter as soon as the chamber had stabilized at 14,000 feet and every 2 hours thereafter, except during sleep. After 24 and 72 hours at altitude, samples of arterial blood were obtained from the brachial artery. In addition, 10 cc. of venous blood were withdrawn. The subjects assumed a sitting position, and a lumbar puncture was done. An oil-sealed syringe was used and the dead space displaced with cerebrospinal fluid (CSF) before withdrawing a single 8-cc. sample. During the arterial sampling and lumbar puncture, the end-tidal P_{CO_2} were recorded continuously and the subjects were instructed to control their breathing so as to adhere to a level determined immediately before the insertion of any needles. Three 24-hour urine samples were collected while the subjects were at 14,000 feet.

P_{CO_2}, P_{O_2}, pH, HCO_3^- concentration, and standard HCO_3^- were measured or calculated for arterial blood. Except for standard HCO_3^-, the same were measured in CSF as well as lactate and Cl^- levels. Na^+, K^+, and Cl^- were measured in venous plasma and in 24-hour urine samples; 17-hydroxycorticosteroid was measured in the latter. All Cl^- determinations were made by electrometric titration (2). Other methods and calculations have been stated previously (3).

While the subjects were in the chamber, the authors ranked them relative to their apparent state of well-being and asked them to fill out a questionnaire designed to evaluate their subjective feelings in an identical manner to that used in earlier experiments (3). In addition, we asked them to compare the two runs as to their state of well-being. All of the results were tested using an analysis of variance.

III. RESULTS

Benzolamide significantly lowered cerebrospinal fluid (CSF), calculated P_{CO_2}, and HCO_3^- at both 24 and 72 hours (table I). All of the other significant changes in the CSF were ascribed to an effect of time at altitude rather than drug; calculated P_{CO_2}, lactate, and HCO_3^- decreased by the end of 72 hours while pH and P_{O_2} rose. The 24-hour values for the P_{CO_2} and pH in the untreated subjects were similar to those obtained by Severinghaus et al. (8) after 2 days at 12,470 feet. Excellent agreement was found between the directly measured value of P_{CO_2} in CSF and that calculated from the measured values of pH and CO_2 content. A significant difference between groups, however, was evident only in the calculated P_{CO_2} and must, therefore, be accepted with caution as a demonstrable drug effect.

Arterial blood P_{CO_2}, pH, HCO_3^-, and standard HCO_3^- were lowered significantly by benzolamide at both 24 and 72 hours (table I). Arterial P_{O_2} was significantly higher at both time periods in the drug-treated group. In addition, the 72-hour values for arterial P_{O_2} were higher than the 24-hour values in both the treated and untreated groups. Some hemoconcentration was noted by the end of the study in that the arterial hematocrit increased in both subject groups by 72 hours, but the increase was not statistically significant ($.05 < P < .10$). In the venous blood the serum chloride increased in the benzolamide group at both 24 and 72 hours, and the serum potassium decreased between 24 and 72 hours in the treated subjects (table II).

Benzolamide produced a significant kaluresis during the first 2 days at altitude but not during the third day (table III). The 17-hydroxycorticosteroid (17-OHCS) excretion was higher in the placebo group during all 3 days. In addition, the 17-OHCS excretion of both groups increased during the second day but returned to the first day's levels on the last day of the study. All of the other significant changes in the urine variables were related to a marked decrease in the excretion in both drug and placebo groups. The one exception to this uniform decrease was in the 72-hour potassium excretion in the placebo group, which was essentially identical to the 48-hour value.

TABLE I

Mean values ± 1 S.E.M. of variables measured in arterial blood and CSF

	24 hours		72 hours	
	Benzolamide	Placebo	Benzolamide	Placebo
Cerebrospinal fluid				
Po_2 (mm. Hg)*	29.7 ± 1.8	27.8 ± 1.7	32.2 ± 1.6	31.4 ± 1.7
Meas. Pco_2 (mm. Hg)	38.0 ± 1.0	38.7 ± 0.8	36.3 ± 0.9	37.2 ± 0.8
Calc. Pco_2 (mm. Hg)†	37.3 ± 1.0	40.8 ± 0.9‡	35.2 ± 0.9	36.5 ± 0.9‡
pH*	7.357 ± .008	7.348 ± .008	7.362 ± .008	7.373 ± .008
Lactate (mg. %)†	17.4 ± 0.6	18.2 ± 0.5	15.8 ± 0.5	17.1 ± 0.6
HCO_3^- (mmoles/liter)†	20.26 ± 0.21	21.41 ± 0.20§	19.44 ± 0.20	20.24 ± 0.20§
Chloride (mEq./liter)	130.3 ± 1.0	128.7 ± 0.6	131.1 ± 0.8	129.2 ± 0.7
Arterial blood				
Po_2 (mm. Hg)	45.6 ± 1.6	41.1 ± 1.4‡	49.3 ± 1.5	44.4 ± 1.5‡
Pco_2 (mm. Hg)	26.7 ± 0.9	28.5 ± 0.7‡	25.8 ± 0.8	27.3 ± 0.9‡
pH	7.437 ± .008	7.493 ± .006§	7.445 ± .008	7.501 ± .007§
HCO_3^- (mmoles/liter)	18.11 ± 0.50	22.33 ± 0.35§	17.94 ± 0.45	21.47 ± 0.40§
Std. HCO_3^- (mmoles/liter)	21.33 ± 0.31	25.06 ± 0.26§	21.33 ± 0.32	24.27 ± 0.25§
Hematocrit (%)	45.6 ± 1.0	41.1 ± 0.9	49.3 ± 1.0	44.4 ± 1.0

Differences between the 24- and 72-hour values for both benzolamide and placebo:
*$P < .05$.
†$P < .01$.

Differences between benzolamide and placebo:
‡$P < .05$.
§$P < .01$.

TABLE II

Mean values ± 1 S.E.M. of Na^+, K^+, and Cl^- in venous plasma

	24 hours		72 hours	
	Benzolamide	Placebo	Benzolamide	Placebo
Sodium (mEq./liter)	143.2 ± 0.7	143.4 ± 0.6	143.7 ± 0.5	143.9 ± 0.7
Potassium (mEq./liter)*	4.6 ± 0.9	4.5 ± 0.8	4.3 ± 0.6	4.4 ± 0.7
Chloride (mEq./liter)	113.4 ± 0.7	109.7 ± 0.7†	113.6 ± 0.6	110.8 ± 0.7†

*Difference ($P < .05$) between the 24- and 72-hour values for benzolamide, but not placebo.
†Difference ($P < .01$) between benzolamide and placebo.

TABLE III

Mean values ± 1 S.E.M. of variables measured on 24-hour collections of urine

	24 hours		48 hours		72 hours	
	Benzolamide	Placebo	Benzolamide	Placebo	Benzolamide	Placebo
Sodium (mEq./24 hr).	185.0 ± 17.1	173.9 ± 12.8	99.0 ± 15.0	140.5 ± 10.2	91.2 ± 13.1	126.0 ± 5.6
Potassium (mEq./24 hr.)	69.0 ± 4.8	41.5 ± 3.5*	50.5 ± 4.5	35.5 ± 3.3*	36.7 ± 5.0	39.7 ± 3.7
Chloride (mEq./24 hr.)	126.0 ± 14.3	126.7 ± 11.2	99.1 ± 9.7	93.1 ± 8.3	91.6 ± 8.5	90.6 ± 8.0
17-OHCS (mg./24 hr.)	4.4 ± 0.6	5.4 ± 0.4†	6.1 ± 0.7	6.7 ± 0.5†	4.7 ± 0.5	5.6 ± 0.3†
Volume (cc./24 hr.)	1,702 ± 142	1,196 ± 164	1,196 ± 110	1,024 ± 108	921 ± 72	986 ± 65

All the variables for both drug and placebo decreased significantly ($P < .05$) over time, with the exception of drug and placebo chlorides and placebo potassium between 48 and 72 hours.

Differences between benzolamide and placebo:

*$P < .01$.

†$P < .05$.

The end-tidal P_{CO_2} fell significantly ($P < .001$) during the course of the study in both the treated and untreated subjects (fig. 1). This drop was fairly linear during the first 2 days at altitude, with a leveling off occurring during the third day and a slight rise at the very end of the study. The slopes of the two curves followed each other very closely, with the benzolamide curve always below that of the placebo. This difference due to the drug was not significant ($.05 < P < .10$).

The effect of altitude on the CO_2 response curves was to shift these to the left and upward

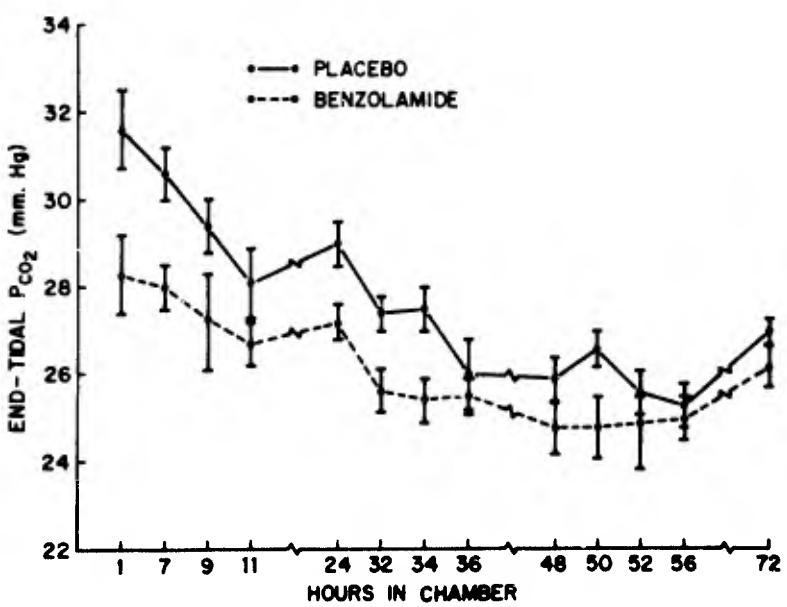

FIGURE 1

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

(fig. 2). This change in the position of the curves occurred more rapidly and was more pronounced in the benzolamide-treated subjects, so that the placebo curves lagged behind the drug curves by a full 24 hours. In general, a greater ventilatory response was achieved by the benzolamide-treated subjects to the same level of inspired P_{CO_2}.

In the analysis of the data from the questionnaire, the only item showing a significant difference between drug and placebo was "headaches." The subjects receiving placebo had a definitely greater tendency to develop headaches than did the treated subjects ($P < .05$). Two other items gave a borderline test for a significant difference between drug and placebo ($.05 < P < .10$). The drug-treated subjects got less sleepy and had drier noses than the placebo group. Many of the answers on the questionnaire exhibited a significant change over time. In general, these changes could have been predicted in that the longer the subjects stayed in the chamber, the unhappier they became. All of the subjects were happiest and most lively just after reaching altitude than at any other time in the flight.

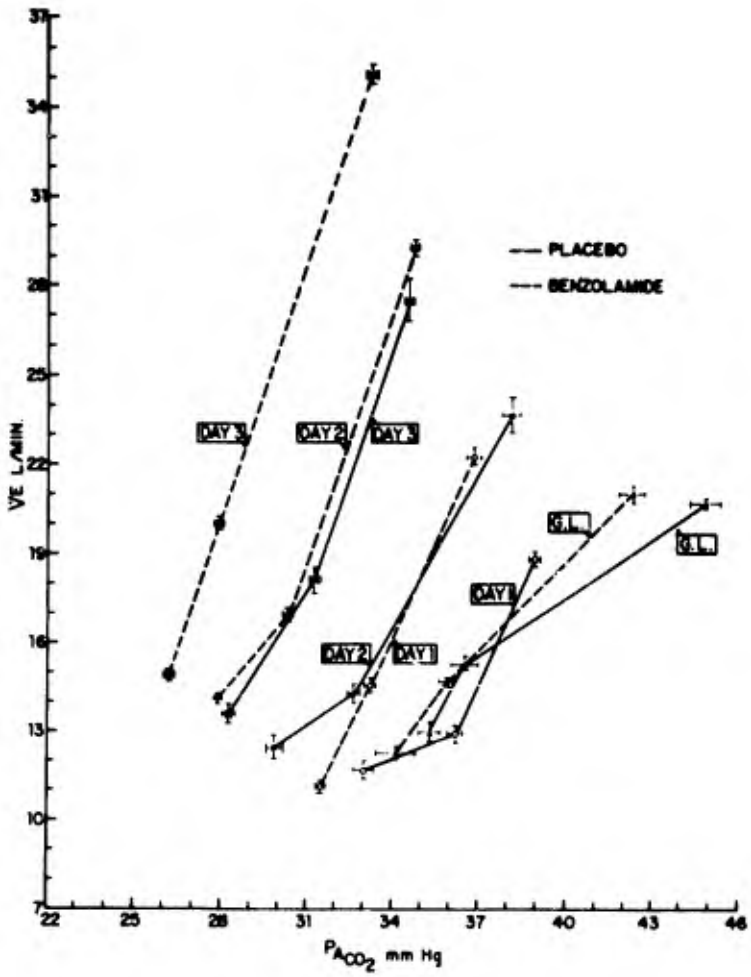

FIGURE 2

Average CO_2 response curves. Each point represents a mean value ± 1 S.E.M.

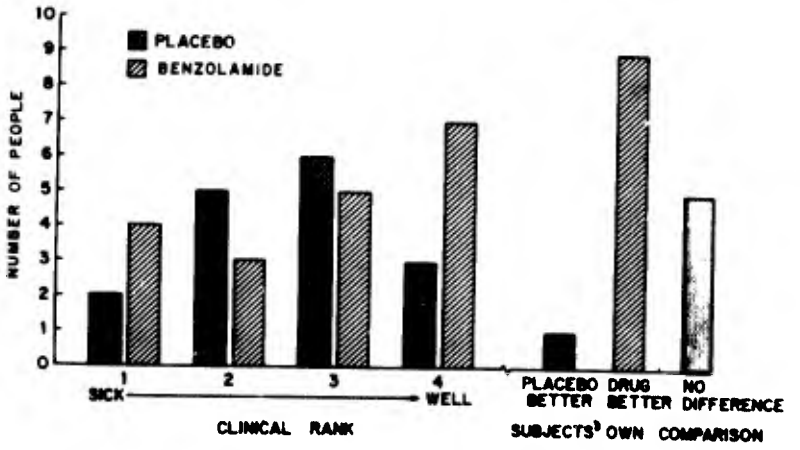

FIGURE 3

Clinical rankings and subjects' own evaluation of the flights.

The results of the clinical ranking and the subjects' own evaluation of their flights are shown in figure 3. Those who showed definite objective signs of altitude sickness such as vomiting or complete inability to cooperate in the experiment were given a ranking of 1, while those having no signs were ranked as 4, with the difference between rankings of 2 and 3 being quite arbitrary. Although the ranking was done at the end of every 24-hour period at altitude, only the first 24-hour ranking was considered in reporting the results because reactions to the spinal tap and arterial puncture frequently complicated the clinical picture after the first day. Benzolamide did not appear to be advantageous on the basis of clinical rankings, but it was highly beneficial ($P < .01$) according to the subjects' own estimation of their feelings. This evaluation was made at the end of the second flight when we asked the subjects to write a comparison of the two flights in their own words. If answers were equivocal, the placebo flight was listed as being better; the drug flight was listed as better only when answers were definitely favorable.

IV. DISCUSSION

Severinghaus et al. (8) have shown that active transport of HCO_3^- from the CSF occurs during the first 24 hours at altitude. Subsequent to this period, the HCO_3^- of cerebrospinal fluid continues to fall in a passive manner following the constantly decreasing plasma HCO_3^- which is being excreted through the kidneys. This loss of HCO_3^- partially compensates for the alkalosis produced by the drop in P_{CO_2} of CSF. In the current study both HCO_3^- and calculated P_{CO_2} fell significantly as anticipated between the 24- and 72-hour samples in the untreated subjects. The decrease in calculated P_{CO_2} was of proportionately greater magnitude than the HCO_3^- loss in that the pH rose to a moderate degree. Benzolamide was expected to accentuate the changes found in the untreated subjects by enhancing the unloading of plasma HCO_3^- through the renal tubules; this expectation proved to be correct as shown by the difference in the 72-hour drug and placebo results (table I). The mean HCO_3^- and P_{CO_2} of cerebrospinal fluid in the benzolamide-treated subjects at the end of 72 hours were lower than those found by Severinghaus et al. in untreated volunteers after 8 days at an altitude of 12,470 feet. Admittedly, this comparison may not be justified as the difference between 12,470 and 14,000 feet may be important physiologically. The increase in pH in the drug-treated group between 24 and 72 hours amounted to an average of only 0.005 of a pH unit, probably not a

physiologically significant amount. This is contrasted with the 0.025 pH unit rise in the placebo group. The lowering of CSF pH contributes to, or at least detracts less from, the ventilatory stimulus provided by hypoxia, thereby increasing arterial P_{O_2}.

The 24-hour values for CSF lactate reported in this study are comparable to those found by us earlier (3) and by Severinghaus et al. (8) in altitude experiments. Our earlier study showed that the rise in CSF lactate occurring during the first 24 hours at altitude accounts for less than one-third of the HCO_3^- loss in CSF. Plum and Posner (6), using severely hyperventilated and hypoxic dogs, found that lactate played a much greater role in the early regulation of CSF pH. The fact that CSF lactate fell significantly between 24 and 72 hours in both our treated and untreated subjects, even though HCO_3^- was also dropping (table I), would indicate that the effect of lactate on HCO_3^- concentration in CSF lessens considerably after the first 24 hours at altitude. The observed drop in lactate may reflect an improved state of cerebral oxygenation. This is further borne out in the increased arterial P_{O_2} at the end of 72 hours and the fact that the benzolamide-treated subjects with a higher mean arterial P_{O_2} also had a lower mean CSF lactate than did the untreated subjects. This relationship between CSF lactate and arterial P_{O_2} was not seen in the subjects studied by Severinghaus et al. (8) between the second and eighth days at altitude; as previously noted, that study was done at 12,470 feet (3,800 meters), and the higher altitude which our subjects experienced may be important from the standpoint of cerebral hypoxia.

The gradual decrease in plasma HCO_3^- that occurs during the process of altitude accomodation has been noted in other studies (1, 8). The effect of the carbonic anhydrase inhibitors, benzolamide and acetazolamide, is to speed up this process by approximately 24 to 48 hours at 14,000 feet. This effect is shown by comparing the 3-day benzolamide data from this study and the 5-day placebo data of Cain and Dunn (1), who observed an increase in plasma HCO_3^- between the third and fifth day in their acetazolamide-treated subjects. Although this increase was not enough to raise the acetazolamide value above that of the placebo, the possibility that additional doses of drug need to be administered between the third and fifth day should be considered. Some indication that this might also be true for benzolamide is given by both the end-tidal P_{CO_2} curves (fig. 1), which started to rise on the morning of the third day, and by the absence of any drug effect on urine volume and K^+ excretion after 48 hours (table III).

The fact that urinary K^+ loss was significantly greater in the benzolamide-treated subjects during the first 48 hours would indicate that it was the principal cation accompanying the increased HCO_3^- excretion induced by the drug. The mean difference of about 3.5 mEq./liter in serum Cl^- concentration between benzolamide and placebo-treated subjects was matched by an identical but opposite difference in serum HCO_3^-. The higher excretion of 17-OHCS in the placebo group suggests that the placebo-treated subjects found altitude to be more stressful since production of this hormone is indicative of stress. Benzolamide did produce a greater urine volume on the average during the first 48 hours, but this diuretic effect was not statistically significant. The marked decrease in the rate of excretion of almost all of the urine constituents is probably due to the lesser oral intake once the subjects entered the chamber. A moderate amount of dehydration was present by the third day. This is reflected in the low urine volume and an increase of borderline significance in arterial hematocrit. Since hemoconcentration may be detrimental to altitude accommodation (9), every effort should be made to insure adequate fluid intake during altitude exposure.

The CO_2 response curves also support the concept that benzolamide speeds up the normal process of accommodation (fig. 2). Severinghaus et al. (7) have shown that the medullary chemoreceptors are set by the HCO_3^- concentration in CSF to operate at different P_{CO_2} levels at altitude than at ground level. This phenomenon also occurred in our study, as

illustrated by the shift of the CO_2 response curves upward and to the left with increasing time at altitude. The resetting of the central chemoreceptors apparently was 24 hours slower in the placebo group than in the benzolamide-treated subjects.

The difficulty in having outside observers accurately assess someone else's state of well-being is illustrated in figure 3. In the ranking, little separation was obtained between drug and placebo. This is contrasted with the subjects' clear-cut preference for the drug flights. Part of this difficulty lies in the interposition of spinal taps and arterial punctures during the course of the experiment. Certainly, the presence of a spinal headache would serve to confuse the clinical picture. For this reason, we feel that the subjects' own evaluation should be given the most weight, particularly since the evaluations are supported by the results of the subjective questionnaire and the 17-OHCS excretion.

Before undertaking this study, we believed that benzolamide might prove to be a better drug than acetazolamide for ameliorating altitude sickness because of its selective site of action in the renal tubule. The data obtained did not justify this hope. Both drugs produce about the same magnitude of physiologic changes and, as might be expected, about the same level of subjective response. Although neither drug is completely effective in preventing the signs and symptoms of acute altitude sickness, this study with benzolamide offers additional evidence that pretreatment with carbonic anhydrase inhibitors does aid some subjects in that respect and certainly hastens respiratory acclimatization to altitude.

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