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# THE EFFECTS OF ACETAZOLAMIDE ON PHYSIOLOGIC AND SUBJECTIVE RESPONSES OF MEN TO 24 HOURS AT 14,000 FEET

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There have been several past attempts to aid altitude accommodation through the use of metabolic acidifying agents (1). Recently, acetazolamide has been shown to raise effectively the arterial $P_{O_2}$ of men pretreated with the drug prior to going to altitude (2). 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 cerebrospinal fluid acid-base balance.

## METHODS AND PROCEDURES

For each experiment, four subjects were placed in a low pressure chamber at either 3,000 ft. (681 torr) or 14,000 ft. (447 torr). Each subject consumed either 500 mg. of acetazolamide or a lactose placebo in the form of two 250 mg. gelatin capsules 12 hours prior to entering the chamber. An additional 250 mg. capsule was taken just before going to altitude. The capsules were administered in a double-blind fashion and the order of presentation of the drug and placebo was random. A total of 44 experimental subjects were used. With one exception, no subject was run more than once.

End-tidal $P_{CO_2}$ sampling was done on each subject using a nasal catheter as soon as the chamber had stabilized at its designated altitude and every two hours thereafter, except during sleep. After 24 hours at altitude, a single sample of arterial blood was obtained from the brachial artery. The subject was then placed in the left lateral decubitus position and a lumbar puncture done. A 24-hour urine sample was collected from each subject while he was at altitude.

Lactate, pH, $P_{CO_2}$, $P_{O_2}$, Hct, $HCO_3^-$, std $HCO_3^-$, $CO_2$, $O_2$ sat, and $P_{VO_2}$ were either determined directly or calculated on the blood and CSF samples. The urine specimens were analyzed for volume, $Na^+$, $K^+$, and 17-hydroxycorticosteroids.

Each subject at 14,000 ft. was observed and questioned by the authors. At the conclusion of a run the subjects were numerically ranked as to their state of well-being against the three others who where with them, with a rank of 4 being least sick and 1 being most sick. In addition, each subject filled out a 26-item questionnaire designed to evaluate their subjective responses to the experiment. Before going to sleep at night each subject had electrodes applied for the continuous monitoring of their respiratory pattern by impedance pneumogram and EEG.

## RESULTS

The results of the biological fluid data are given in Table I. Acetazolamide significantly lowered both blood and CSF $HCO_3^-$ under all conditions. In the case of arterial blood, $P_{CO_2}$, pH and std $HCO_3^-$ were also lowered significantly. Arterial $P_{O_2}$ at 14,000 ft. was increased by the drug, but only at a borderline level of significance ($P < .10$). The arterial $O_2$ saturation and $P_{VO_2}$ were significantly raised by acetazolamide at both altitudes ($P < .001$ in both cases). CSF lactate was also increased significantly at 14,000 ft.

Table I. Biological 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 |
| Meas $P_{CO_2}$ (mm. Hg) | 34.3 ± 4.9 | 35.9 ± 2.3 | 41.7 ± 3.4 | 48.0 ± 4.2* |
| Calc $P_{CO_2}$ (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 | 7.340 ± .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 | 7.425 ± .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 ± 1.07** |

Values are means ± 1 S.D. * Denotes probability levels for significant differences between acetazolamide and placebo: * = $P < .05$; ** = $P < .01$. † Denotes that a significant difference ($P < .001$) was present between altitudes but not between acetazolamide and placebo.

The combinations of altitude and drug divided the end-tidal $P_{CO_2}$ determinations into four distinct groups (fig. 1). End-tidal $P_{CO_2}$ decreased significantly over time in both the treated and untreated groups at 14,000 ft., but remained relatively constant at the 3,000-ft. elevation. 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.

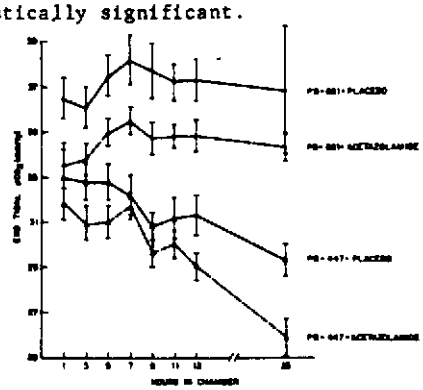

Figure 1. End-tidal $P_{CO_2}$ determinations as a function of time at altitude. Each point represents a mean value ± 1 S.E.M.

As was expected, acetazolamide produced a significant diuresis and kaluresis at both 3,000 ft. and 14,000 ft. The drug did not affect sodium excretion. 17-OHCS excretion was higher

at altitude, but showed no difference between treated and untreated groups.

The incidence of pattern breathing as recorded by means of the impedance pneumogram was significantly higher ($P < .001$) at 14,000 than at 3,000 ft; however no difference was found between treated and untreated subjects. The 14,000-ft. group reported more symptoms suggestive of altitude sickness on their questionnaires, but no difference was noted between acetazolamide and placebo. Those who received acetazolamide at 14,000 ft. slept more on the average than the controls, but this was not statistically significant. The results of the clinical rankings in the 14,000-ft. runs are summarized in figure 2.

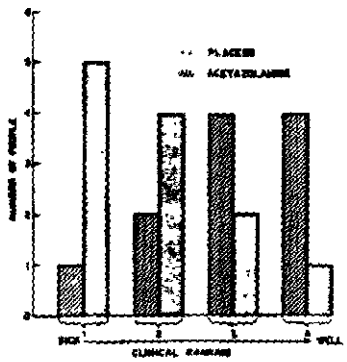

Figure 2. Clinical rankings of subjects at 14,000 ft.

## DISCUSSION

The present study has again demonstrated the ability of low doses of acetazolamide to lower significantly blood pH and $HCO_3^-$; blood and alveolar $P_{CO_2}$; and CSF $HCO_3^-$. The data on CSF and plasma $HCO_3^-$ tends to support the concept advanced by Severinghaus and his co-workers (3) that the reduction in CSF $HCO_3^-$ is accomplished to a large extent by means of an active transport mechanism (fig. 3). A high coefficient of correlation was found between CSF $HCO_3^-$ and alveolar $P_{CO_2}$ (fig. 4).

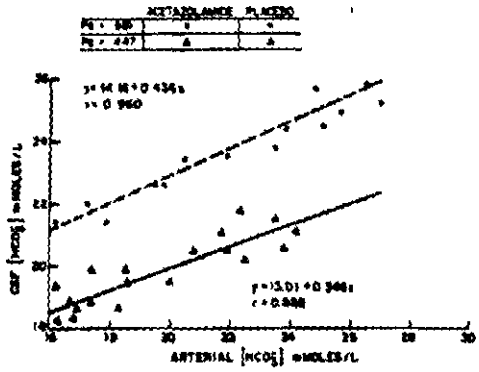

Figure 3. CSF $HCO_3^-$ vs. arterial $HCO_3^-$.

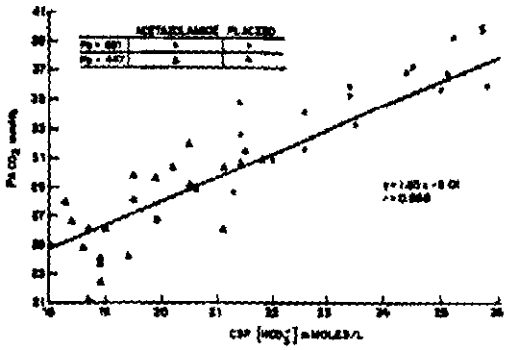

Figure 4. CSF $HCO_3^-$ vs. alveolar $P_{CO_2}$.

The subjects receiving acetazolamide failed to show a clear-cut advantage over the controls as far as their objective and subjective testing was able to determine. Unfortunately, considerable individual variation was encountered and, although a definite trend was established in favor of the drug, this failed to attain any statistical significance. For example, the difference between rankings of 2 and 3 on the clinical ranking scale was quite arbitrary at best. An individual subject might change from a 2 to a 3 and back again several times during the flight. If just the 1 and 4 groups are considered, acetazolamide does demonstrate a statistical advantage ($P < .01$).

In spite of the fact that the present study has failed to establish acetazolamide as providing definitive protection against altitude sickness, we recommend its use prior to altitude exposure. If one considers that even a modest amelioriation of symptoms 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 had virtually no side effects in the dosage given, there seems to be no reason for withholding the drug.

## REFERENCES


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