Urinary Excretion of Acetazolamide in Healthy Volunteers After Short- and Long-Term Exposure to High Altitude

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SUMMARY

Acetazolamide is recommended for the prophylaxis of acute mountain sickness symptoms which sets in on climbing to high altitudes (H) above 2,500 m. It is primarily excreted unchanged in urine. In a previous study, we reported on the changes in urinary excretion of meperidine and its metabolite normeperidine on exposure to high altitude. In this study, we investigated the effect on urinary excretion of acetazolamide. The study was carried out in three groups of 12 healthy male volunteers each: at sea level (group LL), these same volunteers the day after arrival at high altitude of 4,360 m (group HA), and subjects residing for ~10 months at high altitude (group HC). Urine was collected for the periods of 0-2, 2-4, 4-8, 8-12, 12-24 and 24-36 h after peroral administration of a single 250 mg dose. Urinary pH was measured and the concentrations of acetazolamide were determined. There were no significant changes observed in the amount of acetazolamide excreted in urine over 36 h. The urinary pH ranged from 4.5 to 7.8 for LL, from 4.2 to 6.9 for HA and from 5.1 to 6.7 for HC. The F_u (fraction eliminated unchanged in urine) was calculated from the amount excreted in 36 h in urine and dose, assuming a bioavailability of 1 based on literature data. No significant changes in F_u were seen. ©1998 Prous Science. All rights reserved

Key Words: Acetazolamide - Pharmacokinetics - High altitude - Mountain sickness

INTRODUCTION

Exposure to high altitude, above 2,500 m, leads to a series of pathophysiologic changes collectively referred to as acute mountain sickness which is defined as the presence of any two or more of the following symptoms: loss of appetite, vomiting, shortness of breath, dizziness or lightheadedness, unusual fatigue, sleep disturbance and headache (1). If not treated promptly, it can progress to more severe condition of high altitude pulmonary edema (HAPE) and high altitude cerebral edema (HACE), which may even be fatal.

Acetazolamide is generally prescribed as the first treatment for relief of acute mountain sickness symptoms (1-4). It is a potent carbonic anhydrase inhibitor and helps relieve the edema which is the primary cause of acute mountain sickness. However, these studies only report the effect on the physiologic parameters and there have been no studies on the effect on the pharmacokinetics of acetazolamide on exposure to high altitude. This information is very important not only for acetazolamide but also for other drugs which are likely to be used by the growing tourist populations at high altitude resorts.

Previously, we reported on the pharmacokinetics and urinary excretion of meperidine and normeperidine, in man, on exposure to high

altitude (5-6). We noted several changes in the disposition of meperidine which started within 24 h of reaching a high altitude of 4,360 m and at least in part appeared to be sustained for more than 10 months.

A brief review of the changes occurring at high altitude is as follows: The hypoxia associated with low barometric pressure at high altitude leads to hyperventilation and fluid accumulation in the brain and lungs. In the initial phase of exposure to high altitude, plasma volume decreases because of loss of total body water and redistribution to extracellular spaces. Erythropoietin is stimulated resulting in increased erythrocyte count and hematocrit. This increased erythrocyte mass may diminish flow through blood vessels.

These pathophysiologic changes associated with exposure to high altitude may significantly alter drug disposition particularly for drugs showing high binding to erythrocytes or plasma proteins (7). Acetazolamide is a weakly acidic drug with a pka of 7.2 and is reported to have a high protein binding of about 93% (8). Increased binding of the drug to erythrocytes and plasma proteins may result not only in a decreased pharmacologic response but also longer elimination half-life.

Elsewhere, we have reported on the influence of short- and long-term exposure to high altitude, on the disposition of acetazolamide in whole blood, plasma and plasma water (9). The purpose of this study was to investigate the effect of short- and long-term exposure to high altitude on the urinary excretion of acetazolamide, in man, after a single, 250 mg peroral dose.

METHODS

Subjects and study design

The study was conducted in three groups of healthy male volunteers recruited from the Chilean Army. The study was approved by the Institutional Review Boards of the University of Cincinnati and the University of Chile and the Chilean Armed Forces. The inclusion parameters included a minimum of 10 months residence at either sea level or high altitude of 4,360 m, completion of physical exam, urinalysis and blood chemistry tests. Exclusion parameters were any deviations outside the established normal range for urine and blood chemistry tests, any previous gastrointestinal, hepatic, cardiovascular, pulmonary or renal disease, previous severe mountain sickness and use of any drug in the 10 days preceding the study.

The following three groups of 12 volunteers each were created: group L consisted of volunteers living at sea level (military base at Arica, the northernmost city of Chile); group HA comprised of the same subjects as in group L, but after short-term exposure to high altitude. They ascended 1 week after the L study to the military base at Pacollo, in the Andes of North Chile, at 4,360 m. They arrived in the afternoon and the study was performed the following morning. The third group was HC, comprising of subjects who had resided, for at least 10 months, at the study site at Pacollo. The height, body weight and age (mean + SD) were 1.69 ± 0.05 m, 62.5 ± 4.74 kg, and 19.17 ± 0.39 y for L and HA, and 1.69 ± 0.06 m, 65.0 ± 4.94 kg, and 19.75 ± 0.87 y for HC, respectively.

For all groups, the treatment was the same: after an overnight fast with water allowed *ad libitum*, the subjects were provided a standard breakfast at approximately 8 AM, along with standard, measured volumes of water. At approximately 10 AM, a single tablet containing 250 mg of acetazolamide was administered perorally with 200 mL water. During the 3 h prior to dosing and 3 h after dosing, standardized measured volumes of water were provided to the subjects. Urine was collected for the periods 0-2, 2-4, 4-8, 8-12, 12-24 and 24-36 h, after drug administration. The volume of the urine for each collection period was measured and an aliquot frozen for analysis. The pH of the urine was measured immediately upon collection. Blood samples were also collected for a period of 24 h. The results of the blood level evaluation are reported elsewhere (9).

Analytical procedure

All the samples were analyzed for acetazolamide by a high performance liquid chromatography method using an HP 1090 system equipped with a UV detector (Hewlett Packard GmbH and. Biotronik, Germany). A Merck LiChrosphere 60, RP select-B, 125 mm x 4 mm i.d. column was used. The eluent consisted of a mixture of an alkaline phosphate buffer/methanol and acetonitrile. The analyses were eluted by gradient elusion at 30 °C and the effluent was monitored at 263 nm.

The frozen samples were thawed and subjected to an acidic protein precipitation, after which an aliquot was injected onto the HPLC.

Pharmacokinetic analysis

The amount of acetazolamide excreted per collection period was determined from the concentration in urine and the volume of urine excreted. Cumulative urinary excretion was calculated according to standard procedures (10). The urinary pH for each sampling period was plotted and also compared statistically. The fraction of acetazolamide eliminated in the unchanged form in urine was determined by equation 1:

$$F_{el} = \frac{A_e^{(0\text{-}36)}}{D \cdot F}$$

assuming F of 1, as reported in literature (8).

Statistical analysis

Each of the test parameters (urinary pH, $A_e^{(0\text{-}36)}$ and F_{el}) was subjected to a one-way ANOVA. Significant difference was concluded at $p < 0.05$.

RESULTS AND DISCUSSION

Cumulative urinary excretion

The cumulative urinary excretion profiles of acetazolamide, for all three groups, are shown in Figure 1. The individual profiles are shown to emphasize the variability in the data. As can be seen, no significant difference was found in the amount of acetazolamide excreted over the different collection periods for any of the three groups. However, it was observed that the variability in the data was highest for the HA group indicating some physiologic changes occurring which appear to be stabilized on long-term exposure (group HC).

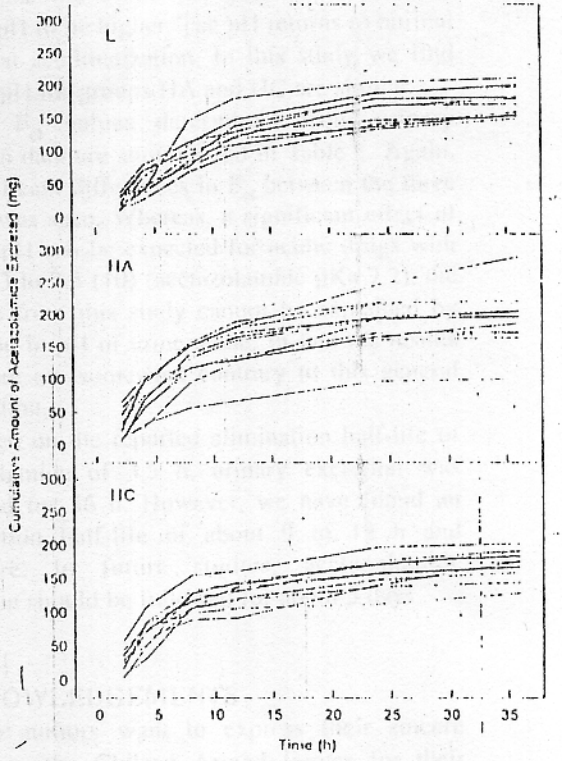

FIG. 1. Cumulative amount of acetazolamide excreted unchanged in urine for the three study groups (L, at sea level; HA and HC, after short- and long-term exposure to high altitude).

The urinary pH values for the different collection periods of the three study groups are shown in Figure 2. The urinary pH ranged from 4.5 to 7.8 for group L, from 4.2 to 6.9 for group HA, and from 3.1 to 6.7 for group HC. The urinary pH for group L was significantly higher than that for groups HA and HC for the first 4 h after dosing. Also, the urinary pH for group HC was significantly lower than those of groups L and HA

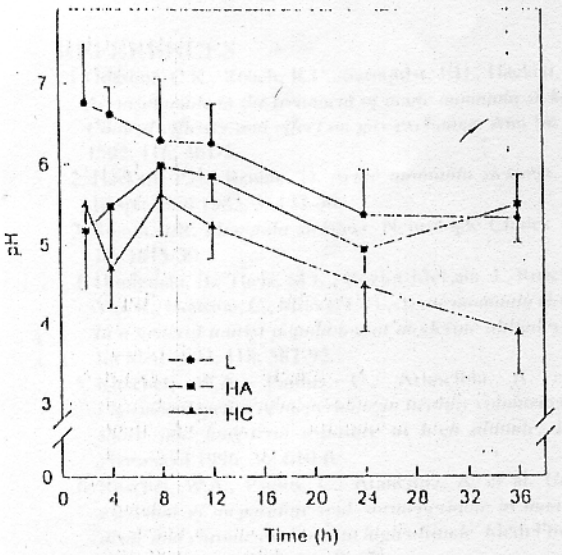

FIG. 2. Mean ± SD urinary pH profiles for the subjects at sea level (L), after short- (HA) and long-term (HC) exposure to high altitude.

36 h after dosing. This is an interesting observation which is contrary to the findings reported in the literature and to our previously observed results (6), where the pH is usually higher after short-term exposure to high altitude. Due to the physiologic changes, more bicarbonate is excreted in the urine to stabilize the blood pH and this causes the urinary pH to be higher. The pH returns to normal values on acclimatization. In this study we find that the pH for groups HA and HC are similar.

The F_{el} values determined from urinary excretion data are summarized in Table 1. Again, no significant differences in F_{el} between the three groups was seen. Whereas, a significant effect of urinary pH can be expected for acidic drugs with pKa of 3 to 7.5 (10) (acetazolamide pKa 7.2), the findings from this study cannot be explained by alteration in pH of urine alone. In fact the results seen here are somewhat contrary to this general observation.

Based on the reported elimination half-life of acetazolamide of 3.5 h, urinary excretion was followed for 36 h. However, we have found an elimination half-life of about 9 to 12 h and therefore, in future studies, acetazolamide excretion should be followed for about 5 days.

ACKNOWLEDGEMENTS

The authors want to express their sincere thanks to the Chilean Armed Forces for their support, transportation and housing at the investigation site to facilitate this study, and to Dr. J. Wallner for lab assistance.

TABLE 1. Fraction of acetazolamide excreted unchanged in urine (F_{el}).

Subject	F_{el}		
	L	HA	HC
1	0.736	0.891	0.704
2	0.689	0.876	0.809
3	0.807	1.162	0.699
4	0.791	0.823	0.731
5	0.612	0.695	0.575
6	0.724	0.787	0.512
7	0.717	0.829	0.671
8	0.598	0.796	0.770
9	0.626	0.657	0.759
10	0.845	0.401	0.636
11	0.642	0.749	0.739
12	0.617	0.686	0.664
Mean	0.700	0.779	0.689
SD	0.084	0.178	0.084

No significant differences at $p = 0.05$.

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