

## Effects of acetazolamide on cerebral blood flow and brain tissue oxygenation

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**Summary:** Oral administration of 1 g of acetazolamide to 8 normal subjects studied at sea level and in normoxia caused an acute increase in cerebral blood flow (CBF). During the subsequent prolonged oral treatment with 1 g of acetazolamide daily, CBF returned to normal within 2 days. The alveolar CO<sub>2</sub> tension decreased gradually to 70% of the control value, indicating hyperventilation. At sea level hyperventilation will not increase brain oxygenation significantly in normal man, as the arterial oxygen content only increases minimally, while CBF is unchanged. At high altitude the beneficial effects of acetazolamide on the symptoms of acute mountain sickness may well be due to an improved oxygen supply to the brain, as hyperventilation will, at the low ambient PO<sub>2</sub>, cause a significant increase of the arterial oxygen content, while CBF presumably is unaffected by the drug. During hypoxia at high altitude the overall effect of prolonged acetazolamide treatment may thus be equivalent to a descent by several hundred metres.

### Introduction

Acetazolamide has for several years been known to reduce the symptoms of acute mountain sickness, i.e. the cerebral symptoms that many sea-level dwellers experience during the first days or weeks of exposure to high altitude hypoxia.<sup>1–4</sup> The drug increases ventilation<sup>5,6</sup> and also causes a considerable increase in cerebral blood flow (CBF) a few minutes after intravenous injection of the drug.<sup>7–9</sup> Both factors might be of importance for the beneficial effect as both changes would, other factors being equal, tend to augment cerebral oxygen supply. Which one of these two factors is the most important under the conditions of many days of oral acetazolamide taken by mountaineers during acclimatization after abrupt ascent to altitude?

The present study reports sea-level (normoxic) studies of alveolar PCO<sub>2</sub> and CBF during 10 days of oral acetazolamide administration to normal volunteers. This is a baseline study for similar observations at hypoxia.

The intravenous injection of 1 g of acetazolamide results in a prompt increase in CBF.<sup>7</sup> CBF measured in conscious human subjects at sea level increased by about 50% above control values 3 minutes after injection. There was a further rise to about 60% of the control value after 20 minutes. The cerebral oxygen uptake was not affected. This is important, as it

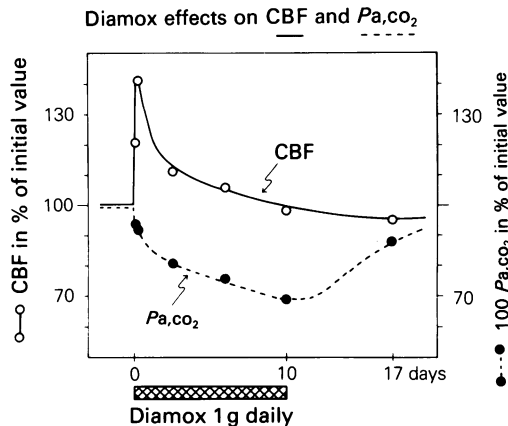
uptake was not affected. This is important, as it permits the calculation of blood flow as the percentage rise in the reciprocal cerebral arterio-venous oxygen difference.<sup>7</sup>

The duration of this response is not known, but in view of the fairly rapid elimination of acetazolamide, complete inhibition of carbonic anhydrase cannot be expected to last for long. It is interesting to note, in contrast, that the intravenous injection of 500 mg of acetazolamide increases CBF only insignificantly during the first 5 minutes<sup>8</sup> with a rise of 30% being seen later.<sup>9</sup> This suggests that in order to obtain a sustained increase of CBF, a high dose of oral acetazolamide would be required.

### Methods and results

Preliminary studies with oral administration are now being performed in our laboratory. Cerebral blood flow has been measured in 8 normal subjects in normoxia at sea level by the intravenous xenon-133 injection method.<sup>10,11</sup> This study showed that a single oral dose of 1 g of acetazolamide increased CBF (40–50%) at 3 hours with only a small decrease in end-expiratory PCO<sub>2</sub>. The following 10 days, 500 mg acetazolamide was taken twice daily. After 2 days CBF had practically normalized but clear cut hyperventilation was evident with alveolar PCO<sub>2</sub> reaching 70% of normal at 10 days (Figure 1).

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**Figure 1** Cerebral blood flow (CBF) and arterial  $PCO_2$  ( $Pa,CO_2$ ) during and after acetazolamide administration.

## Discussion

Acetazolamide inhibits carbonic anhydrase both in the erythrocytes and in the cells of the tissues. Blocking the erythrocytes will cause tissue  $PCO_2$  to increase relative to arterial  $PCO_2$  so that the venous blood can leave the tissue with an increased  $PCO_2$ , in order for  $CO_2$  to be eliminated at its normal rate. Inhibition of tissue carbonic anhydrase may enhance tissue acidosis beyond the level indicated by the tissue  $PCO_2$ . If, as suggested by Severinghaus & Coté<sup>12</sup> and by Heuser *et al.*,<sup>13</sup> carbonic acid and not  $CO_2$  is the end product of metabolism, then carbonic acid must accumulate in order for the uncatalysed reaction to proceed at the same rate as the catalysed reaction.

Both the physiological parameters that we studied are controlled by intracellular pH at normoxia. Ventilation is controlled by pH in the brain stem's respiratory centres and cerebral blood flow by the pH of smooth muscle cells in brain arterioles. The time course of the acetazolamide-induced increases in ventilation and in CBF were distinctly different. Ventilation was found to increase gradually over the 10 days of medication. The 30% decrease in alveolar  $PCO_2$  at the end of the study corresponds to a 50% increase in alveolar ventilation. The progressive increase in ventilation suggests a progressive acidosis in the chemosensitive areas of the brain stem. This might be due to slowness of acetazolamide accumulation in the brain, if indeed tissue anhydrases must be inhibited to obtain the full acidotic response. The brain stem has a high rate of metabolism and would

therefore require a considerable rise in tissue carbonic acid in order for  $CO_2$  to be formed at the same rate as normally.

In view of the sustained increase of ventilatory drive the brevity of the CBF increase was a surprise. After a few days CBF returned to its normal level. This suggests that pH in the arteriolar smooth muscle cells had become normalized also. The gradual reduction in arterial  $PCO_2$  may be important in this respect. It should be noted that the smooth muscle cells are much less active metabolically than brain tissue. Thus, inhibition of the local carbonic anhydrase will not produce nearly as much carbonic acid acidosis in the arteriolar wall as in the brain tissue.

The results we obtained at sea level show that in normoxia prolonged acetazolamide administration to normal man hardly influences brain oxygenation and CBF is normal despite hyperventilation. The 30% decrease in alveolar  $PCO_2$  must correspond to a decrease of arterial  $PCO_2$  from 40 to 28 mm Hg. Hence arterial  $PO_2$  also rises by about 12 mm Hg; this will only increase arterial oxygen content minimally because of the shallowness of the oxygen saturation curve at these pressures.

In prolonged exposure to hypoxia no data on acetazolamide effects on arterial  $PCO_2$  or CBF are available. But, assuming the same directional changes are superimposed on the hypoxic responses, then a considerable effect on brain oxygenation must be predicted because increasing the alveolar  $PO_2$  will augment arterial oxygen content considerably, due to the steepness of the saturation curve at hypoxic  $PO_2$  values. The values published by Gill *et al.*<sup>14</sup> on alveolar air composition at high altitude imply that, if other factors remain equal, then a 50% increase in ventilation induced by acetazolamide will correspond to an acute descent by approximately 1000 metres.

Despite reservations on extrapolating to hypoxic conditions the present study suggests that carbonic anhydrase inhibitors should be commenced several days before abrupt ascent to altitude; that it should be continued throughout the stay and that a compound and dose should be used which inhibits the anhydrase in both erythrocytes and brain cells. Much further work should be carried out to clarify these and other points. The techniques described are atraumatic and could be used in the field. It is important as high mountain climbing and trekking has become so popular; why mar the pleasure with unnecessary discomfort and risk!

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