Prevention of acute mountain sickness by acetazolamide: as yet an unfinished story

SINCE the 1970s, over 200 studies with acetazolamide have shown it safe and 60–80% effective in acute mountain sickness (AMS). Despite much investigation, our understanding of its action in AMS remains incomplete and more complicated than generally taught. This should come as no surprise considering the presence of carbonic anhydrase (CA) in many tissues relevant to high-altitude adaptation or maladaptation. In this issue of the Journal of Applied Physiology, Leaf and Goldfarb (10) provide a fine state-of-the-art review that highlights this complexity and updates the field since last reviewed in 1998 (12).

A brief history of CA and its inhibitors serves to give some perspective on acetazolamide in AMS prevention. Shortly after the discovery of CA in red blood cells in 1932, sulfanilamide, the first nontoxic oral antibiotic, was introduced and noted to have side effects including mild diuresis, metabolic acidosis, and hyperventilation. These were quickly recognized to be a consequence of renal CA inhibition. Following World War II, synthesis of stronger CA inhibitors yielded the 1,000-fold more potent sulfonamide, acetazolamide. Although first used as a diuretic and gastric acid suppressant, by the mid-1950s it found greater efficacy in glaucoma and hydrocephalus. Pulmonologists explored acetazolamide concurrently as a respiratory stimulant for hypoxemic patients with chronic obstructive pulmonary disease in the expectation of improving arterial oxygenation. Albeit effective, patients could not tolerate the worsened dyspnea when forced to breathe more. Kronenberg and Cain (9), however, realized that such ventilatory stimulation might have a significant impact at high altitude in healthy persons and indeed showed better oxygenation and ventilation in subjects at high altitude. Shortly thereafter, Forwand et al. (4) demonstrated that such ventilatory stimulation by acetazolamide could reduce AMS symptoms, and its use for this purpose was established.

How then does acetazolamide work in AMS and what questions remain to be investigated? Leaf and Goldfarb (10) posit that the conventional view by which acetazolamide works is too simplistic. In this model, urinary bicarbonate loss from renal CA inhibition and the resultant mild metabolic acidosis (a ventilatory stimulant) opposes and limits the braking effect of hypoxemia on the full ventilatory response to hypoxia. In essence, acetazolamide simply accelerates the normal bicarbonaturia that would otherwise happen over several days of acclimatization. Although this is clearly not the full story, the renal effect is nonetheless primus inter pares among other possible mechanisms, which include relevant CA inhibition in red blood cells, brain, pulmonary and systemic vasculature, and chemoreceptors.

Leaf and Goldfarb (10) explain how tissue enzyme concentrations and drug penetrance into various tissues rule out any significant effect of clinically useful dosing of acetazolamide (3–5 mg/kg) on red blood cell CO2 transport, cerebral blood flow (CBF), and CA inhibition within the central chemoreceptors. The only caveat with respect to CBF is that if regional brain blood flow changes are heterogeneous, measurements of total CBF may not reflect changes in blood flow in critical areas such as the brain stem. Since tissue pH, PCO2, and PO2 are determined by the metabolic rate of the tissue, its blood flow, and arterial values, blood flow changes will alter ventilatory responsiveness. Another effect of CA inhibition in the brain not mentioned, but conceivably relevant to AMS, is cerebrospinal fluid (CSF) formation. Complete choroid plexus CA inhibition reduces this by 50% and in principle could reduce overall intracranial volume and pressure, which are slightly increased with hypoxia and in AMS and have been proposed as pathogenetic in AMS. However, effective doses of acetazolamide that penetrate the blood-brain barrier, reach the choroid plexus, and depress CSF flow and volume are on the order of 20 mg/kg (18).

Our present understanding of how acetazolamide works points to critical CA inhibition in the brain vascular endothelium, kidneys, and peripheral chemoreceptors interacting with the primary effect of hypoxia to stimulate ventilation. Luminal brain vascular endothelial CA will be fully and immediately inhibited by even very low drug concentrations in blood, causing a small hindrance to normal “tissue-to-blood” transfer such that tissue PCO2 will be elevated by 1–2 Torr (8). A slight CO2 retention in the vicinity of both the central and peripheral chemoreceptors will be sufficient to stimulate ventilation. Acetazolamide (5–7 mg/kg iv) in normoxic humans induces a small increase in ventilation within minutes consistent with endothelial CA inhibition, well before any significant urinary bicarbonate loss or red blood cell drug uptake reaches a critical inhibitory level (13). Thus, in addition to the metabolic acidosis, slight CO2 retention from vascular CA inhibition will help mitigate the suppressant effect of the primary respiratory alkalosis generated by hypoxic hyperventilation and so allow a more complete hypoxic ventilatory response.

Despite the metabolic acidosis, an expected increase in the acute isocapnic hypoxic ventilatory response (HVR) is lacking, indicating that acetazolamide abolishes the H+–O2 interaction in the peripheral chemoreceptors (2, 13, 17). This raises an interesting question as to what could be the advantage of taking a drug at altitude that has inhibitory effects on oxygen-sensing cells. The answer lies in the fact that the ventilatory response to high-altitude hypoxia is essentially poikilocapnic (i.e., hypocapnic). Consequently, any agent abolishing the H+–O2 interaction under these circumstances will blunt the action of a low PCO2 on the hypoxic response and generate more ventilation than would otherwise occur (17). In humans at sea level, acetazolamide has no influence on the peripheral chemoreceptor contribution to the ventilation response on stepwise changes in end-tidal PCO2 (14). It cannot be excluded that, in part, CO2–H+ and O2 follow separate signal-transduction pathways in the carotid bodies. Future studies with acetazolamide are warranted to determine if, despite the absence of an O2–H+ interaction, the carotid bodies may retain their H+ sensitivity.

Predictably, acetazolamide’s inhibitory effect on the HVR should be due to peripheral chemoreceptor CA inhibition. However, in the cat, even the more lipophilic inhibitor methazolamide does not reduce the HVR, suggesting that acetazolamide may act by a mechanism other than CA inhibition (15).
as already established for hypoxic pulmonary vasoconstriction (6). Interestingly, antioxidants reverse the inhibitory effects of low-dose acetazolamide on HVR in humans (16). Further studies are needed to establish if antioxidants interfere with the prophylactic effects of acetazolamide and how possibly acetazolamide, either by CA inhibition or by ligation to some other receptor, alters intracellular redox status of the peripheral chemoreceptors.

The contribution of the central chemoreceptors to increased ventilation with acetazolamide is via the stimulatory effect of the metabolic acidosis in raising H+ concentration to counteract the effect of increased ventilation to washout CO2 and raise pH. If a clinically relevant dosing of acetazolamide decreases arterial P CO2 (PaCO2) by \( \sim 7 \) Torr (14, 17) but does not alter CBF (7, 17) or impair blood CO2 transport, then the brain tissue-to-blood P CO2 gradient should not change very much, implying a considerable fall in brain tissue P CO2. However, as mentioned above, brain vascular endothelial CA inhibition will limit this fall to some extent and so lessen the braking effect of increased ventilation to return H+ in the central chemoreceptors to a less acidic state.

Acetazolamide’s actions on respiration and the vasculature suggest how it reduces periodic breathing in sleep at high altitude (5). Dempsey (3) proposed that the “CO2 reserve” (i.e., the difference in PaCO2 between eupnea and the apneic threshold), when combined with “plant gain” (or the ventilatory increase required for a given reduction in PaCO2) and “controller gain” (ventilatory responsiveness to CO2 above eupnea), are the key determinants of breathing stability in sleep. In general, breathing during sleep is made more stable by increases in the CO2 reserve, and reductions in plant and controller gain. Acetazolamide alters all three favorably. First, with elevated arterial Po2 and decreased PaCO2, plant gain will be reduced because larger changes in ventilation are needed to cause equivalent changes in blood gases. Second, a parallel left shift of the CO2 response curve will raise the difference between the prevailing PaCO2 and the apneic threshold (CO2 reserve) and decrease the propensity for apnea. A small rise in brain stem P CO2 with inhibition of vascular CA will have a similar tonic stabilizing influence. Third, due to the higher prevailing Po2, subjects are in a flatter region of the (hyperbolic) hypoxic response curve, resulting in a reduced O2 controller gain. A further reason why acetazolamide reduces ventilatory controller gain in sleep is the abolishment of the CO2-O2 interaction so that responses to hyperventilation-induced combined hypoxia/hypercapnia may be reduced considerably. Finally, it cannot be ruled out that acetazolamide increases the cerebrovascular response to combined hypoxia/hypoxia (17), leading to a dampening influence on subsequent changes in brain stem P CO2. Note that a lowered cerebrovascular CO2 sensitivity may play a role in the genesis of periodic breathing at high altitude (1). Because acetazolamide does not affect the time constant of the peripheral CO2 response (14) or the time course of the HVR (17), we do not believe slower reaction times within the carotid bodies play a significant role in reducing periodic breathing.

Many questions remain to be investigated before we have a complete understanding of acetazolamide protection in AMS. Although not an exhaustive list of experiments and methodological approaches, we believe the following are several key directions to pursue.

1) Regional brain blood flow, pH, metabolic rate, and oxygenation (such as with magnetic resonance imaging and spectroscopy) in areas of brain involved in respiratory control need to be performed in humans in conjunction with ventilation, ventilatory responses, and arterial blood gas measurements. Dose-response experiments with acetazolamide in normoxia and hypoxia, combined with plasma measurements of total and free drug levels, are needed to better calculate the degree of red blood cell and tissue CA inhibition. Although not presently available for humans, analogs of acetazolamide, lacking CA inhibiting activity, will be useful in animals to test whether and how much of the effect of acetazolamide is due to CA inhibition or to some other action on O2 and CO2 sensing and responsiveness.

2) Studies of acetazolamide in conscious and sleeping chemoreceptor-intact animals are needed, both in normoxia and hypoxia, in which central and peripheral chemoreceptor contributions can be gauged by isolating the drug and/or systemic acid-base changes to either the central or peripheral chemoreceptors. This can be done by isolating the circulation to the carotid bodies and perfusing them with appropriately conditioned blood (11).

3) The contributions of the renal metabolic acidosis and diuresis of acetazolamide to the protection with acetazolamide in AMS need to be explored by using other mild diuretics to achieve the same magnitude of diuresis as acetazolamide and/or using acetazolamide but preventing bicarbonate and sodium losses by carefully calibrated replacement.

REFERENCES


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