Eur Respir J 1998; 12: 1242–1247
DOI: 10.1183/09031936.98.12061242

European Respiratory Journal
ISSN 0903 - 1936

EDITORIAL

Carbonic anhydrase inhibitors and ventilation: a complex interplay of stimulation and suppression

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Inhibitors of carbonic anhydrase (CA) have long been used as respiratory stimulants, most successfully in acute mountain sickness (AMS), but also in chronic obstructive pulmonary disease (COPD) and sleep-disordered breathing syndromes. Although effective, presently available inhibitors have minor annoying side-effects (paraesthesias, mild nausea and gastrointestinal discomfort) that can limit long-term compliance; and in certain cases their use may be hazardous, particularly in those with compromised pulmonary, hepatic and renal function. The overlap in clinical efficacy and side-effects of these drugs is intimately related to the ubiquity of CA in the body, and to the enzyme's many roles in CO_2 transport, acid–base regulation, nitrogen metabolism, fluid secretion and absorption, and ventilatory control.

It is now known that the effect of CA inhibitors on ventilation and ventilatory responsiveness is a complex and not easily predictable summation of CA inhibition in tissues relevant to the control of breathing, including the kidney, red cells, capillary vascular endothelium, brain, and the central and peripheral chemoreceptors [1]. Depending on the dose of inhibitor, duration of dosing and site of inhibition, there can be both inhibitory and stimulatory effects. A good example of this complexity can be found in the present report by WAGENAAR *et al.* [2], who studied the effect of acetazolamide on the hypercapnic ventilatory response in hypoxia.

The development of the presently available CA inhibitors and their application as respiratory stimulants arose from findings in the late 1930s, that sulphanilamide, the first oral sulphonamide antibiotic (and a weak CA inhibitor), caused metabolic acidosis and a compensatory hyperventilation resulting in a higher arterial oxygen tension (P_{a,O_2}). Only several years earlier, the enzyme had been discovered in erythrocytes and, soon thereafter, in many organs including the kidney, where it was established that renal CA inhibition was responsible for the acidosis. Efforts to produce more potent CA inhibitors yielded acetazolamide (Diamox) and several other less commonly used (but still available) sulphonamides, including methazolamide (Neptazane) and diclorphenamide (Daranide). These and even more powerful sulphonamides (benzolamide and ethoxzolamide) with K_i values 2–4 orders of magnitude less than sulphanilamide permitted the investigation of CA function in other tissues. Interestingly and ironically, further drug development in this field led to the serendipitous discovery of the thiazide and high ceiling loop diuretics, which lost CA-inhibiting activity while yielding even greater natriuresis and diuresis than the earlier sulphonamides [3].

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Ventilatory effects of CA inhibitors

When healthy individuals are given conventional doses of acetazolamide (250–500 mg; 3.5–7.0 mg·kg body weight^{-1}), ventilation increases by 10–20% both at rest and during exercise [4]. If a person is hypoxaemic owing to high altitude, lung disease or blunted ventilatory drives, arterial haemoglobin saturation may rise by 3–6% [1, 5]. The metabolic acidosis generated by renal CA inhibition acting on the peripheral and central chemoreceptors is the single strongest contributor to increased ventilation. CA-inhibiting sulphonamides produce an alkaline diuresis by depressing proximal tubular HCO_3^- reabsorption and distal tubular H^+ secretion. Within several hours, the urinary bicarbonate loss results in a reduction in serum bicarbonate that is maximal (4–6 mM decrease) within 24 h and a fall in arterial pH of about 0.05–0.1 units. The ventilatory response generally reduces the arterial carbon dioxide tension (P_{a,CO_2}) by 0.7–0.8 kPa (5–6 mmHg). The metabolic acidosis persists thereafter as long as the drug is administered. CA inhibitors reach high and fully inhibiting amounts in the kidneys owing to an active organic acid secretory mechanism which concentrates these drugs in the urine and renal parenchyma. Thus, complete renal CA inhibition can be achieved at doses that fail to or only partially inhibit intracellular CA elsewhere in the body [6]. Studies with acetazolamide using 250 mg doses probably approach this selectivity [7] and the results appear to be as good as those achieved in studies using higher doses. Furthermore, we and others have shown that benzolamide [8], a highly hydrophilic CA inhibitor with little or no cellular penetrance other than into the kidney, achieves equal improvements in ventilation and gas exchange [9–12].

Recently, it has been established that these low doses also inhibit a membrane-bound isozyme (CA IV) located on the luminal plasma-facing aspect of nearly all capillary beds, including the brain and lung [13]. In this location CA IV will be completely inhibited whenever an inhibitor is given. Although other roles are possible [1], the vascular endothelial enzyme provides modest but sufficient catalytic activity to plasma (roughly equal to 1% of red cell CA activity) to prevent end-capillary carbon dioxide tension (P_{CO_2})–pH–HCO_3^- disequilibrium [13]. While the evidence is not entirely consistent, selective capillary vascular endothelial CA IV inhibition appears to impair mildly blood CO_2 uptake and release [14–17] and lead to a local retention of CO_2 in the order of 1–2 mmHg. At the lung, the equivalent effect is a slight increase in the arterial to alveolar (or end-tidal) P_{CO_2} difference of the same magnitude. In the brain and central chemoreceptors, an increase of this magnitude is not trivial given the normal high CO_2 ventilatory responsiveness (1–3 L·min^{-1}·mmHg^{-1}). Support for

an unmeasured additional stimulus (*i.e.* a slight retention of CO_2 in the vicinity of the central chemoreceptors) comes from an analysis of blood gases in subjects taking benzolamide at high altitude, in whom the reduction in P_{a,CO_2} and increase in ventilation is greater than that predicted by the stimuli of arterial hypoxaemia and pH [11].

At higher doses (7–12 mg·kg^{-1}) and independent of whether metabolic acidosis has developed, an additional ventilatory stimulant effect of CA inhibitors arises from partial inhibition of intracellular CA isozymes in red cell and tissues (isozymes CA I and II). Since the extremely efficient exchange of CO_2 between blood and tissues or alveolar gas is dependent on cytoplasmic red cell CA, partial (95–98%) and total inhibition (>99%) of red cell CA will lead to profound retention of CO_2 in all tissues, including the brain [4]. Depending on blood flow–metabolism ratios the normal venous (and/or tissue)–arterial P_{CO_2} gradient can rise with total inhibition from 0.5–0.7 kPa (4–5 mmHg) to over 6.7 kPa (50 mmHg) [4, 16, 18]. In the brain, CO_2 retention in the vicinity of the central chemoreceptors will stimulate ventilation [19, 20] enough to lower the P_{a,CO_2} below normal and blunt the degree of tissue CO_2 retention. Red cell and tissue CA inhibition leads to a unique acid–base status in which arterial blood gases may not reflect the true systemic (tissue) acidotic situation. Arterial hypocapnia may be erroneously assumed to indicate a respiratory alkalosis, when the opposite is true [21], a situation also seen in low cardiac output states [22].

The peripheral and central chemoreceptors contain CA [23, 24], although it is not known which isozymes (intracellular or plasma membrane bound) are present. Inhibition of chemoreceptor CA also contributes to the overall effect of CA inhibitors on breathing but, in contrast to the stimulant systemic acid–base effects described above, depressant effects are often observed in the absence of red cell and renal CA inhibition.

In the brain, central chemoreceptor CA inhibition slows by 50% the rate of rise of ventilation to a hypercapnic challenge [19, 20] by delaying the speed at which a new elevated P_{CO_2} reduces pH in the vicinity of the chemoreceptors. Although local chemoreceptor CA inhibition may also reduce baseline ventilation [25], this is rarely seen *in vivo* because any direct depression is overridden by the powerful opposing stimulant action of local retention of CO_2 from red cell and brain tissue CA inhibition [19, 20, 26] and the metabolic acidosis from renal CA inhibition. With respect to the peripheral chemoreceptors, the findings are somewhat analogous. When direct recordings are taken, CA inhibitors depress baseline carotid nerve sinus activity and slow the rate of change to both hypoxic and hypercapnic challenges by 50–75% [27, 28], but do not alter the steady-state responses.

Over the past decade, Teppema and coworkers [2, 26, 29–32] have provided convincing *in vivo* evidence for si-milar effects of CA inhibitors on ventilation and ventilatory responses. In the present investigation in hypoxaemic cats [2] and in normoxic cats [29] they chose a low dose of acetazolamide, 4 mg·kg^{-1}, administered intravenously and studied ventilatory responses to CO_2 within the first hour to avoid the complicating factors of systemic metabolic and respiratory acidosis. They found that acetazolamide increased ventilation slightly after an initial depression. The drug reduced the gains in both the peripheral and central chemoreflex components to a step change in end-tidal P_{CO_2} and slowed the rate of response. However, they also observed that the apnoeic threshold for CO_2 was decreased (the extrapolated P_{CO_2} at which ventilation ceases). The net effect of these changes (a depressed slope and a shifted apnoeic threshold), shown in their figure 4, is that above a baseline P_{CO_2} of 4.8 kPa (36 mmHg), ventilation is less but below 4.8 kPa, ventilation is greater after CA inhibition. Lastly, they found that 4 mg·kg^{-1} acetazolamide increased the normal arterial to end-tidal P_{CO_2} difference by approximately 0.1 kPa (1 mmHg).

The increase in ventilation probably represents the small stimulus of CO_2 retention from vascular endothelial CA IV inhibition. The initial depression of ventilation is possibly a transient effect of the usual alkalinity of acetazolamide solutions. The reduction in the hypercapnic peripheral chemoreflex component can be explained by direct inhibition of peripheral chemoreceptor CA, either membrane-bound CA IV directly in contact with plasma or cytosolic CA II at sufficiently low concentration that the intracellular penetrance of 4 mg·kg^{-1} acetazolamide gives near complete inhibition. The reduction in the central chemoreflex component is not as readily explained. Since access of drugs such as acetazolamide to the central chemoreceptors is limited by the blood–brain barrier, reduction of the central chemoreflex component cannot be attributed to CA inhibition in the central chemoreceptors. The authors hypothesize that brain capillary endothelial CA IV inhibition alters cerebral blood flow regulation in response to a hypercapnic challenge. In a previous model analysis [2], which incorporated an altered relationship with CA inhibition between P_{a,CO_2} (the measured variable in ventilatory testing) and brain tissue P_{CO_2}–pH (the true stimulus to the central chemoreceptors), they were able to predict the ventilatory responses observed in hypercapnic–normoxic cats.

It is unclear how brain vascular capillary CA IV inhibition leads to an altered P_{a,CO_2}–brain tissue P_{CO_2} difference. The explanation favoured by the authors is that CA IV inhibition may cause brain blood flow to increase to a greater extent with a hypercapnic challenge than in the absence of inhibition. This would blunt the rise in brain tissue P_{CO_2} occurring with the same increase in P_{a,CO_2} and could explain an apparent decreased central chemoreflex component. At this time, very little is known about CA and brain blood flow regulation, or whether vascular smooth muscle contains CA. Although a global increase in baseline cerebral blood flow occurs with very high-dose CA inhibitors [33, 34], this was not observed with the more conventional doses used clinically [35] or in the present study by Wagenaar *et al.* [2]. However, given the very high ventilatory sensitivity to CO_2, even small changes in global and regional brain blood flow may be important. Therefore, it will be critical that investigators studying the control of breathing develop means by which cerebral blood flow (ideally in the vicinity of the chemoreceptors) can be measured simultaneously with ventilatory measurements.

There is some evidence for peripheral and central chemoreceptor depression with CA inhibitors in humans. If acetazolamide (7 mg·kg^{-1}) is given *i.v.*, there is no change in the slope of the hypercapnic ventilatory response (HCVR) and no increase at all in ventilation with mild hypoxia in the first hour before a metabolic acidosis develops [36]. In contrast, with dosing over 24 h, by which time a metabolic acidosis is established, HCVR is increased [9, 36–38] and the hypoxic ventilatory response (HVR) is either

unchanged [10, 39] or increased [38, 40]. In addition, the rate of response to a hypercapnic stimulus is reduced by half, both before and after a metabolic acidosis develops [36].

Clinical application of CA inhibitors as respiratory stimulants

How, then, can one incorporate the considerable complexity of CA involvement in the control of ventilation described above into an understanding of how the CA inhibitors work in humans: what doses should be used, for what indications and when are they contra-indicated? With the rare exception of acute *i.v.* administration (acute glaucoma, rapid urinary alkalinization for drug ingestion and correction of severe metabolic alkalosis) a renal metabolic acidosis will always be present and will constitute the most important stimulus to greater ventilation. Adding to this stimulation will be the additional ventilatory drive arising from vascular endothelial CA IV inhibition and any partial red cell or tissue CA inhibition causing CO_2 retention and brain respiratory acidosis. Opposing but never overcoming these stimulatory effects will be the direct suppressant effects of CA inhibition on chemoreceptor sensitivity and rate of response.

The dose of acetazolamide sufficient to generate a renal effect without significant respiratory effect (*i.e.* red cell and tissue CA inhibition) is <5 mg·kg^{-1} (250–350 mg) given every 8–12 h. This dose also inhibits vascular endothelial cell membrane CA IV and peripheral chemoreceptor CA. Although higher doses may increase ventilation further as respiratory acidosis develops, this comes at the expense of impairing CO_2 transport [4] and even ventilation–perfusion ($\dot{V}_A/\dot{Q}$) matching in the lung [41]. In healthy individuals this can be readily tolerated and even maximal exercise is possible with partial red cell CA inhibition [1, 4], since the necessary compensatory hyperventilation does not exceed maximal voluntary ventilation (MVV) capacity. However, complete red cell CA inhibition with acetazolamide (>20 mg·kg^{-1}) limits exercise endurance in animals and probably humans, based on model calculations that predict prohibitively high ventilation (exceeding MVV) and profound muscle CO_2 retention at submaximal exercise, *i.e.* 50% maximal oxygen consumption ($\dot{V}_{O_2,max}$) [4, 18].

High altitude

Prevention and treatment of AMS is the leading and best-defined indication for CA inhibitor use, now that a topical inhibitor (dorzolamide) is available for glaucoma [42]. A recent meta-analysis of the available randomized, double-blind, placebo-controlled trials using acetazolamide (250–500 mg *b.i.d.* or *t.i.d.*, usually started the day before ascent) showed a 60% reduction in AMS incidence [43]. The efficacy did not differ significantly between the high and low dose range. Recently, several groups have shown that AMS, once established, can be treated with the same doses [44–46].

The efficacy of CA inhibitors is the result of ventilatory stimulation and better arterial oxygenation driven by the metabolic acidosis and the slight CO_2 retention from vascular CA IV inhibition and any partial red cell CA inhibition. These effects override any negative effect of direct peripheral and central chemoreceptor CA inhibition on overall ventilation and ventilatory responsiveness. The decreased responsiveness of the peripheral chemoreceptors to changes in oxygen tension (P_{O_2}) and P_{CO_2} alluded to above appears to have a beneficial effect during sleep on periodic breathing, an annoying and sleep-depriving phenomenon very commonly observed at high altitude. Studies using acetazolamide [39, 47] have demonstrated a marked reduction (60–80%) in sleep-related periodic breathing and improved arterial oxygenation.

Periodic breathing is a repetitive cycle of hyper- and hypoventilation initiated by hypoxic stimulation of the peripheral chemoreceptors sufficient to reduce P_{a,CO_2} and cause a central chemoreceptor-mediated reduction in ventilation. As ventilation declines and P_{a,O_2} falls again, the peripheral chemoreceptors are reactivated to provoke hyperventilation and initiate another cycle of periodic breathing. CA inhibitors interrupt this ventilatory control instability by increasing the tonic output of the central chemoreceptors and lowering their apnoeic threshold, thus rendering them less responsive to periodic reductions in arterial P_{CO_2}. In addition, inhibition of CA in the peripheral chemoreceptors reduces both the magnitude of hypoxic and hypercapnic sensitivity and the rate at which these signals arrive at the respiratory controller. Consistent with this concept is the fact that peripheral chemoreceptor stimulants such as almitrine aggravate periodic breathing at high altitude [39]. Whether a reduction in periodic breathing *per se* during sleep at high altitude by CA inhibitors is important in reducing AMS has not been established but may be questioned in the light of a study that found no differences in the amount of periodic breathing between those with and without AMS [48]. Other benefits attributed to CA inhibitors in altitude adaptation include mild diuresis, increased cerebral blood flow and reduced cerebral spinal fluid formation, but they have never been adequately investigated. Based on animal studies and a few studies in humans, these effects are probably insignificant and negligible com-pared with the ventilatory stimulation and improved oxygenation (reviewed in [1]).

Sleep-disordered breathing

Several syndromes of sleep-related disordered breathing are responsive to CA inhibitors. Both central sleep apnoea and the obesity–daytime hypoventilation syndrome can be treated effectively with acetazolamide in doses similar to those effective in AMS and high-altitude periodic breathing [49–51]. Since the aetiology of these conditions appears to be an overall depressed central drive to breathe, the metabolic acidosis following even low-dose acetazolamide (250 mg·day^{-1}) is sufficient to increase the overall tonic output of the respiratory controller, augment breathing and improve the quality of sleep [51].

The treatment of obstructive sleep apnoea is principally directed toward mechanical means of maintaining upper airway patency during sleep [52], since this condition is dominated not by central ventilatory drive but rather by insufficiency activation of pharyngeal dilator muscles to oppose the natural tendency of the soft tissues above the larynx to collapse with the negative intraluminal pressures

that develop during inspiration. However, in selected patients who do not tolerate or respond to surgical treatment and/or continuous nasal positive airway pressure, a CA inhibitor may be useful [51, 53–56]. Occasionally, CA inhibitors may worsen upper airway obstruction by stimulating greater efforts of the inspiratory muscles (diaphragm and intercostals) than the pharyngeal dilators [57] or convert a predominant central apnoeic condition to one of obstructive apnoea [58].

Sleep-related periodic breathing (Cheyne–Stokes breathing) occurring in congestive heart failure may also be treated with acetazolamide [59]. Analogous to the destabilizing oscillations in P_{a,O_2} and P_{a,CO_2} in high-altitude periodic breathing, the ventilatory instability of these patients is the result of their low cardiac output slowing the immediate sensing of changes in ventilation by the central and peripheral chemoreceptors. These delays can initiate an overreaction by the respiratory controller, which can be dampened by generating a metabolic acidosis and slowing the response of the chemoreceptors to arterial blood gas fluctuations.

Hypoxaemic lung disease

Shortly after the introduction of acetazolamide into clinical practice in the 1950s, several papers and letters reported improved arterial oxygenation with CA inhibition in patients with hypoxaemic lung disease, mostly in COPD. These uncontrolled studies were usually on small numbers of patients and were soon followed by reports of no benefit or more rarely deterioration (reviewed in [60]). Although largely out of favour, as are most respiratory stimulants in this group of patients [61], subsequent data have appeared that warrant cautious reconsideration of CA inhibitor treatment.

Three more recent trials totalling nearly 50 patients with stable severe COPD, characterized by a forced expiratory volume in one second (FEV_1) below 45% predicted, arterial hypoxaemia (P_{a,O_2} <7.3 kPa (55 mmHg)) and CO_2 retention (P_{a,CO_2} >6.7 kPa (50 mmHg)), used a low dose of acetazolamide, 250 mg twice daily [62–64]. No adverse effects were reported and the mean fall in P_{a,CO_2} was 0.8 kPa (6 mmHg) with a 1.3 kPa (10 mmHg) rise in P_{a,O_2}. These results could be sustained during 5 months of therapy [63]. Sleep quality and arterial oxygenation during sleep were also improved with therapy, in part owing to an elimination of sleep-related apnoeas. Although in one study [62], nonresponders to acetazolamide (P_{a,CO_2} falling <0.7 kPa (5 mmHg)) had more severe obstruction (FEV_1 ~24% pred *versus* 42%) than responders, this correlation between FEV_1 (over a range of 20–40% pred) and magnitude of response could not be demonstrated by others [63].

CA inhibitors may also be particularly helpful in those patients in whom metabolic alkalosis from any cause (*e.g.* diuretics, corticosteroids, nasogastric suction) depresses ventilation and slows weaning from mechanical ventilation [65–69]. Other possible benefits include a rightward shift in the oxyhaemoglobin dissociation curve that improves tissue O_2 unloading [1, 7]. In addition, a mild diuresis improves cardiac function and gas exchange in congestive heart failure and cor pulmonale.

It is very clear, however, that in patients with advanced lung disease, CA inhibitors have a narrow therapeutic index since significant red cell and pulmonary CA inhibition may develop even with low dosing, as a result of either slower drug metabolism when renal function is decreased or the use of other drugs that may alter plasma protein binding of these drugs. Any patient with mild or occult renal insufficiency is also at risk of developing a much greater drug-induced metabolic acidosis (HCO_3^- <15 mM) than in those with normal renal function [70]. The benefits of CA inhibitors stem from the renal effect of mild metabolic acidosis which, at a dose of acetazolamide of 4–5 $mg \cdot kg^{-1}$, is virtually maximal. The ventilatory stimulation that this affords is accompanied by insignificant effect on red cell CO_2 transport and efficiency of CO_2 elimination by the lungs [7, 41]. Above this dose and the concentrations it achieves, CO_2 retention can be anticipated and the extra ventilation necessary to limit or prevent it may cause respiratory muscle fatigue. These factors explain the occasional serious respiratory decompensation in acutely ill patients with long-standing lung disease given a CA in-hibitor, sometimes in combination with other drugs that adversely affect lung function [71, 72].

In general, it is best to avoid carbonic anhydrase inhibitors in patients with very severe obstruction and carbon dioxide retention (forced expiratory volume in one second <25% predicted and arterial carbon dioxide tension >8 kPa (60 mmHg)). A test that may be helpful in determining whether a patient will benefit from a respiratory stimulant is whether they can lower their arterial carbon dioxide tension by >0.7 kPa (5 mmHg) with a short period of voluntary hyperventilation [73]. If a respiratory stimulant is indicated or another condition requires a carbonic anhyd-rase inhibitor and the patient can lower their arterial carbon dioxide tension with voluntary hyperventilation, then a dose no greater than 250 mg acetazolamide should be used and close monitoring of clinical symptoms, blood gases and renal/hepatic function is warranted. Lastly, any patient with severe lung disease who is hospitalized for an acute exacerbation of their disease or other severe illness should never receive carbonic anhydrase inhibitors, unless ventilatory assistance is already provided.

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