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COMMENTARY

Acetazolamide for central sleep apnea: teaching an old drug new tricks?

Commentary on Ni Y-N, Yang H, Thomas RJ. The role of acetazolamide in sleep apnea at sea level: a systematic review and meta-analysis. *J Clin Sleep Med*. 2021;17(6):1295–1304. doi:10.5664/jcsm.9116

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Acetazolamide is an old drug. A very old drug. In fact, the method by which it may be synthesized (along with a number of other molecules related to 5-membered heterocyclic sulfonamides having at least 3-hetero atoms) was patented in 1951, one year after I was born. The genesis for synthesizing acetazolamide and its related molecules was the discovery that sulfanilamide exhibited activity (albeit weak) as a carbonic anhydrase inhibitor, and the resulting diuretic property prompted its experimental use in heart failure in the late 1940s. Thus, the impetus existed to determine whether other heterocyclic sulfonamides could be identified that exhibited more potent carbonic anhydrase inhibitor activity and consequently might find use in the treatment of human disease. Indeed, several such molecules were synthesized; at least 8, including acetazolamide, have been available clinically although not all are as closely related to sulfonamides.

Carbonic anhydrase is a conserved zinc metalloprotease present in both prokaryotes and eukaryotes and has many isoforms.[1] Human cells contain only carbonic anhydrase α-isoforms, and there are actually 14 of these; α-isoforms of carbonic anhydrase are ubiquitous in cells throughout the human body and may be cytosolic, membrane-bound, mitochondrial, or secretory. Moreover, although it is primarily considered to catalyze the reaction $HCO_3^- + H \leftrightarrow CO_2 + H_2O$, it seems to serve important functions seemingly unrelated to this activity, including roles in adipogenesis (it regulates PPARγ2 expression) and gluconeogenesis.

Acetazolamide is a nonspecific CAI and could potentially affect all isoforms in all cells and in various ways. It is no surprise, therefore, that acetazolamide has found uses that are both on-label (edema resulting from heart failure or drug-induced; epilepsies; glaucoma) and off-label (intracranial hypertension, hypercapnia, and/or weaning from mechanical ventilation in patients with chronic obstructive pulmonary disease; obesity hypoventilation syndrome; methotrexate toxicity; contrast-induced nephropathy; nephrolithiasis), most of which may be attributed to the primary mechanism of action and some perhaps to other effects.[2,3] The use of acetazolamide in disorders of respiration has always been attributed to promoting bicarbonate excretion in the proximal tubule of the kidney by means of the above reaction. However, attention should be paid to the diverse actions of this drug when inconsistent results emerge from its use in studies of sleep-disordered breathing.

In this issue of the *Journal of Clinical Sleep Medicine,* Ni et al[4] have performed the difficult task of identifying published reports of acetazolamide employed for the treatment of obstructive sleep apnea (OSA) or central sleep apnea (CSA) in patients at or close to sea level. They rightly limited their meta-analysis to studies of reasonably high-quality methodology: 6 randomized controlled trials using either a placebo or another drug as a control, and 9 studies in which patients acted as their own controls ("pre- and post-acetazolamide"). Unfortunately, even after culling the most methodologically challenged reports, they were still left with a *gemisch* of 15 publications that varied in methodology, sufficient numbers of patients, results stated as only "sleep apnea" but not specifically CSA or OSA, and reports involving a broad variety of clinical scenarios including heart failure,[3] spinal cord injury,[1] and opioid use.[1] Eight articles reported exclusively on CSA (including the studies of spinal cord injury and opioid use), and only 2 studies were limited to patients with OSA. One of the 15 articles included the use of continuous positive airway pressure and was excluded, leaving 14 to be incorporated into the meta-analysis. Moreover, the studies were heterogeneous with respect to the outcomes reported; only 6 reported the central apnea index and one-half or fewer reported oxyhemoglobin saturation variables or respiratory-related arousal indices.

As is standard practice in a meta-analysis, the authors analyzed the studies for bias. Six had no bias in attribution, detection, or reporting, whereas 9 were found with high bias in selection, performance, and detection. In addition, significant heterogeneity was found in both the CSA and OSA investigations. Given the large degree of heterogeneity, the authors appropriately utilized a random-effects method to compute mean differences; because they did not use the Cochrane term *standardized mean difference,* they were presumably reporting the absolute difference between the mean values of the outcome measure(s) of the incorporated studies—that is, the estimates of

the difference in the outcome measure(s) when studies are combined not just by weighting based on the within-study variance but also by the between-study variance. This is an important difference because in using this methodology, studies with large numbers of patients but high variance are not given undue influence compared to studies with smaller numbers of patients but low variance.[5,6]

Despite these considerations, the authors reported results that were significant, if perhaps not clinically significant, with respect to the primary outcome. Acetazolamide reduced the apnea-hypopnea index (AHI) by a mean difference of 16 events/h for the 14 studies overall. However, patients with CSA showed the greatest effect (mean decline in AHI of 23 events/h and in central apnea index of 12 events/h; this result included 2 of the 3 heart failure groups) followed by those with unclassified sleep apnea or mixed OSA and CSA (mean decrease of 8 events/h). Studies enrolling only patients with OSA showed no significant improvement in AHI overall; whereas mean AHI was reduced by 10 events/h, the 95% confidence interval bracketed 0 (–33 to +13). Clearly, the reduction in AHI reported for the group as a whole was attributable to patients with CSA and those with mixed CSA/OSA or unclassified sleep apnea; one would likely presume that the latter group included patients with a high proportion of CSA. Absent this information, it is not possible to assess the validity of this particular finding. One must also interpret these findings in the context of the baseline values of AHI to judge whether the reductions reported overall and for CSA were clinically meaningful. Focusing on CSA (the most relevant finding), the authors tabulated baseline AHIs as reported in the analyzed articles as varying between 18 events/h and 78 events/h; in this context, the small (but significant) mean difference in AHI on acetazolamide seems far less impressive. Whether these were clinically meaningful results seems doubtful. Admittedly, the individual study results (Table S1 in their study) enumerating reductions in the central AHI seemed more promising. However, acting on the results of individual studies defeats the whole purpose of a meta-analysis, which considers the number of patients in each study and the variance of the data in each study (using the random-effects method) and weights the mean difference accordingly.

Other findings of interest included a reduction in the respiratory arousal index (but only by a mean of < 1 event/h) for the group overall and improved oxygenation overall but not when the OSA and CSA studies were examined independently. Event duration did not change with acetazolamide therapy. Interestingly, acetazolamide improved total sleep time by a mean of 26 minutes and sleep efficiency by a less impressive 5%. High heterogeneity was once more present in all of the above analyses. Finally, as expected from the known primary mechanism of acetazolamide treatment, arterial pH, pCO_2, and HCO_{-3} all decreased, but with high heterogeneity involving the first 2 metrics. The mean reduction in HCO_{-3} was an impressive but expected 5.65 mEq/L.

Acetazolamide is thought to suppress hyperventilatory CSA through 2 different mechanisms. The first relates to the apneic threshold during sleep, which, has been measured to be approximately 33–35 mmHg, perilously close to normal eupneic $PaCO_2$ and even closer in hyperventilatory settings such as heart failure, in individuals with a particularly robust ventilatory response to CO_2, and at high altitude. The difference between $PaCO_2$ and the apneic threshold for $PaCO_2$ is termed the CO_2 reserve, and when this value is small, minor perturbations in $PaCO_2$ can result in CSA. Paradoxically, although acetazolamide induces a metabolic acidosis and stimulates ventilation, Nakayama et al[7] showed (in dogs) that although the drug causes a fall in arterial $PaCO_2$, it also dramatically reduces the apneic threshold for $PaCO_2$ during sleep. In fact, it causes a widening of CO_2 reserve, an effect that has been attributed to an increase in "background" ventilatory drive. The decrease of the apneic threshold for $PaCO_2$, out of proportion to the decrease in $PaCO_2$ induced by acetazolamide, stabilizes breathing and reduces the tendency for CSA to occur.

The second mechanism involves a decrease in plant gain associated with the hypocapnia induced by acetazolamide. Ventilation is governed by a negative feedback control system, and excessive values of loop gain (the product of controller gain and plant gain) will destabilize ventilatory control and result in periodic breathing, eg, CSA. Hypocapnia moves the relationship between minute ventilation and $PaCO_2$ to a different position along the "metabolic hyperbola," graphically depicted in the seminal article by Berger et al.[8] This curve describes the relationship between changes in minute ventilation and $PaCO_2$; as $PaCO_2$ moves further into the hypocapnic range, changes in minute ventilation result in smaller than usual changes in $PaCO_2$. Thus, the increased background drive produced by acetazolamide induces high minute ventilation and low $PaCO_2$, reduces plant gain and thus loop gain, and stabilizes breathing.[9]

The meta-analysis by Ni et al[4] is not the only such study examining the effects of acetazolamide on sleep apnea at sea level; I was able to identify a total of 5. Two addressed OSA specifically,[10,11] 2 examined the effect on both OSA and CSA,[12,13] and only 1 focused exclusively on CSA.[14] No meta-analysis of acetazolamide in patients with OSA or CSA resulting from opioid medication appears in the published literature. Unfortunately, 1 meta-analysis examining both OSA and CSA included several investigations performed at high altitude and is not comparable to that of Ni et al[13]; it seems from examining the other four references that the others excluded reports of studies at high altitude. None of these 5 studies specifically excluded patients with heart failure, and 1 included only patients with heart failure.[12] With respect to OSA, Mason et al[10] analyzed only 1 study, which reported a substantial (and most likely clinically meaningful) decrease in AHI with acetazolamide; unfortunately, only 10 patients were enrolled. Gaisl et al[11] excluded reports that were not randomized controlled trials and identified only 1 such trial, which showed a modest decrease in AHI (10 events/h) in the 44 randomized patients. Wongboonsin et al[12] performed their analysis to yield a standardized mean difference, and therefore one cannot easily convert this result to a change in AHI. However, the AHI for CSA and OSA combined yielded what is considered a significantly large standardized mean difference of –1.06 and for CSA alone of –1.10.[15] They did not separately report a standardized mean difference for OSA, and one can most likely infer that the fall in overall AHI was predominantly the result of the effect of acetazolamide on CSA. Moreover, their meta-analysis was limited to patients with heart failure, and although not explicitly

stated these patients seemed to primarily suffer from heart failure with reduced ejection fraction. Finally, another meta-analysis examined multiple treatment modalities for CSA and found only 1 report of the use of acetazolamide, preventing a meta-analysis focusing specifically on acetazolamide.[14] Performed to develop practice parameters under the auspices of the American Academy of Sleep Medicine, this document concluded that acetazolamide might be an "option" for the treatment of primary CSA and could be "considered" for use in patients with heart failure.

In the final analysis, what can we conclude about the possible use of acetazolamide in sleep apnea? First, it seems not to be useful for OSA. Second, it seems to have a modest beneficial effect in CSA associated with several clinical scenarios, specifically heart failure, where it has the modest additional advantage of contributing to diuresis, and in primary CSA, assuming that such an entity exists.[16] However, the emphasis is on "modest." That acetazolamide is useful for CSA at high altitudes is undisputed, with evidence available from a number of studies and 1 meta-analysis.[17] On the other hand, acetazolamide is by no means a benign medication with respect to significant adverse effects, many of them common: paresthesia, nausea, fatigue, and headache, to name a few. The information that the meta-analysis by Ni et al[4] contributes to how we manage CSA points to the fact that there are better choices available and that the drug has no role in the treatment of OSA.

CITATION

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DISCLOSURE STATEMENT

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