Pearls & Oy-sters: Treatment of central sleep apnea with topiramate

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PEARLS

- Cheyne-Stokes breathing (CSB) is a type of central sleep disorder commonly associated with heart failure, cerebrovascular disease, or renal failure.
- At least 3 consecutive cycles of cyclical crescendo/decrecendo change in breathing amplitude is required with 5 or more central apneas or hypopneas per hour of sleep or a cyclical crescendo and decrecendo change in breathing amplitude that has a duration of 10 minutes or more.¹
- Treatment options include noninvasive mechanical ventilation and medication therapy.
- Medications with carbonic anhydrase inhibiting action, such as topiramate, may be effective for central sleep apnea, and provide benefit in patients with associated comorbidities, such as epilepsy or migraine.

OY-STER

- Not considering alternative medical treatment of central sleep apnea may limit therapeutic options for these patients and result in avoidable trials of noninvasive mechanical ventilation leading to high costs and possible poor compliance.

CASE REPORT A 67-year-old man with a history of epilepsy, cardiac failure, alcohol dependence, and hypercholesterolemia underwent a polysomnogram (PSG) study because of snoring and observed apnea during sleep. Body mass index was recorded at 25.9 kg/m². Medications included metoprolol, valsartan, simvastatin, phenytoin, valproate, and levetiracetam. Prior echocardiogram had shown an ejection fraction of 35%. PSG showed an overall Central Apnea Index (CAI) of 18, with 18 central apneas/hour, 7 hypopneas/hour, 0 mixed apneas/hour, and 0 obstructive apneas/hour (figure 1). Central apneas displayed a crescendo-decrecendo pattern, consistent with CSB. Because of recurrent seizures, topiramate was added to the medication regimen, with a titration schedule

to 100 mg twice per day. After 5 months, a second PSG for titration with adaptive servo-ventilation was obtained. Baseline portion of the study (about 90 minutes) showed a significant decrease in number of central apneas, with an overall CAI of 0, with 0 central apneas/hour, 12 hypopneas/hour, 0 mixed apneas/hour, 0 obstructive apneas per hour of sleep, and resolution of the Cheyne-Stokes pattern of breathing (figure 2).

DISCUSSION Breathing is an unconscious process initiated in the brainstem and regulated by monitoring levels of carbon dioxide (and, to a lesser extent, oxygen) in the blood. Chemoreceptors detect the partial pressure of carbon dioxide and adjust minute ventilation accordingly. Elevated carbon dioxide levels result in a rapid feedback response to increase ventilatory rate and subsequently reduce the carbon dioxide level in the blood. In the awake state, the PCO₂ is kept around 40 mm Hg. In sleep the level is dependent on sleep stage but it is typically around 45 mm Hg.

Sleep apnea is a common, undertreated disorder which increases the risk of cardiovascular disease, hypertension, and stroke.² Sleep apnea is classified into central or obstructive depending on the absence or presence of inspiratory effort, respectively. CSB is a type of central breathing disorder in sleep associated with cardiac (particularly heart failure), renal, or neurologic disease. It occurs in non-REM sleep and is also more common at high altitude and in patients with Arnold Chiari type 1 malformation.

CSB is typified by cyclical waves of breathing that becomes progressively faster (crescendo) then progressively slower (decrecendo) to the point respiration is abnormally low (a hypopnea) or arrested (an apnea). By definition, at least 3 consecutive cycles of cyclical crescendo/decrecendo change in breathing amplitude is required with 5 or more central apneas or hypopneas per hour of sleep or a cyclical crescendo and decrecendo change in breathing amplitude that has a duration of 10 minutes or more.¹

Figure 1 Representative 7-epochs polysomnogram before topiramate initiation in supine position during non-REM

Periodic central apneas (orange dotted box) with crescendo-decrescendo pattern (orange dotted circle) are seen. Majority of arousals (*) coincide with peak of the crescendo. ABDM = abdominal belt; C = central; CHIN = chin EMG; EOG = electrooculogram; F = frontal; FLOW = nasal air flow; LLEG = L leg; M = mastoid; O = occipital; PRES = nasal pressure; SNOR = snore channel; RLEG = right leg; sPO₂ = oxygen saturation; THOR = chest belt.

The pathophysiology of CSB is not fully understood; however, the proposed “loop-gain concept” suggests the fault lies with an overly sensitive monitor-and-response mechanism.³⁻⁵

The loop gain, a term borrowed from engineering, describes the stability of a system calculated as the ratio of a response size to a disturbance size. In ventilation, the response to CO₂ is the “controller gain” and the “plant gain” is the blood gas response to change in ventilation. The length of the cycle will depend upon the time between detection and time lag to produce a corrective response, the “feedback gain” (reliant upon the hemodynamics of the body). The loop gain of this system is therefore the ratio of controller, plant, and feedback gain.⁵

When the controller is overly sensitive the threshold to evoke a change is more easily attained. This then results in a feedback loop correcting the abnormal carbon dioxide levels detected. If there is oversensitivity at the plant gain then this may result in overcompensation of the ventilatory response and lead to respiratory instability—an inappropriately sized response to an inappropriately detected disturbance. The overall unstable system therefore would manifest itself as a cyclical fluctuation in breathing, as seen in CSB.

Treatments for CSB have therefore centered on stabilizing this feedback system and dampening the loop gain.⁶

In heart failure the effective circulation is impaired (the feedback gain). Patients with heart failure usually have PCO₂ levels in the lower range of normal and are hypoxemic (the plant gain), which may itself result in apnea through pulmonary vasoconstriction and hypoventilation. Depression of the respiratory rate may also be due to chronically elevated adenosine levels (the controller gain). These alterations may explain why CSB is frequently seen in heart failure.

Treating heart failure modifies the loop gain and consequently results in a reduction of CSB. This can be achieved with noninvasive ventilation (NIV) or medical therapy. NIV requires persistent adherence. A large cohort study showed patients used NIV for an average of only 3.6 hours on a daily basis after 1 year.⁷ It is also contraindicated in some neurologic diseases, unstable arrhythmias, and anatomic deformities. The bulky hardware, high initial costs, requirement of titration, and feelings of claustrophobia may also result in noncompliance.⁸ NIV can be modified with the use of adaptive servo-ventilation, but neither NIV or adaptive servo-ventilation have been shown to improve long-term mortality in patients.

Pharmacologic therapy for central sleep apnea includes medications such as theophylline and acetazolamide. Theophylline is a phosphodiesterase-5 inhibitor and a competitive adenosine antagonist.⁹ Theophylline may also change the response sensitivity to carbon dioxide or reverse hypoxia-induced hypoventilation. Despite its unclear mechanism of action it has been shown to reduce the number of central apneas and hypopneas per hour. The disadvantage is the association with arrhythmia and drug-drug interactions.

Acetazolamide may improve central sleep apnea through its action of carbonic anhydrase inhibition.^{3,4} By inducing a metabolic acidosis through loss of bicarbonate, the apneic threshold increases. This therefore reduces the frequency an abnormal gas level is detected by the controller, thereby improving the stability of the system.

Topiramate is an effective and safe treatment of headache, mood disorders, and epilepsy.¹⁰ The exact mechanism of action of topiramate is unknown; however, it is a partial carbonic anhydrase inhibitor. It acts multifactorially through the blockade of sodium channels and kainate/AMPA receptors, enhancement of γ -aminobutyric acid (GABA)ergic transmission. We may postulate that topiramate provided a beneficial action on central sleep apnea through its function as a carbonic anhydrase inhibitor, similar to acetazolamide. To this effect, we can speculate that other antiepileptic drugs with similar mechanisms of action, such as a zonisamide,¹⁰ may also be beneficial for the treatment of central apneas.

Figure 2 Representative 7-epochs polysomnogram after 5 months after topiramate initiation in supine position during non-REM

Prior noted central apneas are not seen; some hypopneas are noted (one is illustrated by the orange dashed box). Electrode placements are based on the International 10-20 system (odd numbers left, even numbers right; ABDM = abdominal belt; C = central; CHIN = chin EMG; EOG = electrooculogram; F = frontal; FLOW = nasal air flow; LLEG = L leg; M = mastoid; O = occipital; PRES = nasal pressure; SNOR = snore channel; RLEG = right leg; sPO₂ = oxygen saturation; THOR = chest belt).

No other medications than those listed were administered to the patient between the 2 PSGs, suggesting that topiramate reduced the prevalence of CSB. There are limitations of this case report that must be noted. One limitation that was not addressed in our study was the inability to define the hypopneas as central or obstructive. These require an esophageal probe, intercostal EMG, or calibrated respiratory inductance plethysmography, but these were not used in our study. No follow-up echocardiogram was performed to rule out spontaneous improvement in circulation independent of the topiramate. However, the patient routinely follows up with cardiology and he was stable from the cardiac standpoint. Further studies including discontinuation of topiramate and reevaluation to assess for recurrence of CSB may strengthen these findings.

Nevertheless, in patients with headaches, mood disorders, or epilepsy who are found to have central sleep apneas, treatment with topiramate is a consid-

eration. Using medication that can be multi-effective against several comorbidities provides the most cost-effective outcome and aims to improve patient compliance by limiting the necessary lifestyle adjustments and adherence to a larger than needed polypharmacy.

AUTHOR CONTRIBUTIONS

Concept and design: Drs. Vendrame, Montouris, and Auerbach. Acquisition of data: Drs. Vendrame, Montouris, and Auerbach. Analysis and interpretation of data: Drs. Vendrame and Auerbach. Drafting of the manuscript: Dr. Westwood. Critical revision of the manuscript for important intellectual content: Dr. Vendrame. Supervision: Dr. Auerbach.

DISCLOSURE

Dr. Westwood serves on the advisory board for *OnExamination*, an online *British Medical Journal* learning resource. Dr. Vendrame serves on the editorial board of *Neurology and Neurophysiology*. Dr. Montouris serves on scientific advisory boards for UCB, Sepracor, and Eisai Inc.; and has served on speakers' bureaus for and received speaker honoraria from GlaxoSmithKline, UCB, Pfizer Inc, and Eisai Inc. Dr. Auerbach reports no disclosures.

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Neurology 2012;78:e97-e99

DOI 10.1212/WNL.0b013e318250d7bf

This information is current as of April 16, 2012

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