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SLEEP BREATHING PHYSIOLOGY AND DISORDERS • CONFERENCE REPORT

Pharmaceuticals are back in the Game for OSA Treatment

Highlights from the 2019 American Thoracic Society (ATS) Conference in Dallas, Texas, and 2019 Affiliated Professional Sleep Societies Meeting (APSS) in San Antonio, Texas

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From the ATS 2019

Pharmaceuticals for sleep apnea

Once upon a time, elder statesmen in medicine might remember, before continuous positive airway pressure (CPAP) was invented almost 40 years ago, investigators tried to cure sleep apnea with medications: progesterone, theophylline, acetazolamide, and others. Then, this treatment approach was long forgotten. A charming prince came on a white horse and… No, seriously, it seems that pharmaceuticals are back in the game!

Why is there a resurgent interest in pharmaceuticals for sleep apnea? Clinicians may be experiencing frustration with the inability to improve adherence to the mechanical forms of treatment for sleep apnea, even though adherence rates are as high as with medications for other chronic diseases. Perhaps knowledge about the role of loop gain in sleep apnea is stimulating efforts to interrupt this maladaptive physiology. It may be the understanding that central apneas and mixed sleep apnea are difficult to treat with CPAP or might even worsen. A number of abstracts at the 2019 ATS Conference in Dallas, Texas, dealt with pharmaceutical treatment of the different forms of sleep apnea.

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Acetazolamide is under focus not only because it suppresses central apneas but also reduces loop gain, both triggered by vacillating CO_2 levels with unstable respiration during sleep.

Christopher Schmickl, Bob Owens, and Atul Malhotra from the University of California San Diego presented a meta-analysis of trials with acetazolamide in sleep apnea. Assessment of 11 studies showed that acetazolamide had an 83% effect size on the apnea-hypopnea index (AHI) with a significantly larger effect on central apneas compared with obstructive apneas, but still a clear effect on obstructive apneas. The effect of acetazolamide was dose-dependent up to 500 mg and then plateaued above that dosage.

A poster presented by Safwan Badr and Sushmita Chowdhuri from Detroit, Michigan, described an investigation on the effect of acetazolamide on cerebrovascular responsiveness to CO_2 in older adults with sleep-disordered breathing (SDB). Elderly persons ordinarily have physiologically reduced CO_2 responsiveness. This unresponsiveness may be caused by alterations of CO_2 sensor cells in the peripheral and central chemoreceptors. The reduced CO_2 responsiveness leads to respiratory instability during non-REM sleep. By keeping CO_2 levels high, acetazolamide can stabilize respiration. In five elderly patients, CO_2 responsiveness increased and apneic threshold decreased significantly with acetazolamide 500 mg. AHI decreased from a mean of 25 to 7 events per hour. The authors concluded that further trials with more patients are needed to delineate effects of acetazolamide in elderly patients with SDB.

Using benzodiazepines for hypoxia-induced periodic breathing is not a new idea. Prior studies have shown the positive effect of temazepam on hypoxia-induced periodic breathing and a decrease in acute mountain sickness. The effect of benzodiazepines is the opposite of stimulating substances such as acetazolamide or theophylline. Benzodiazepines suppress respiratory drive in hypoxia and lower loop gain. It is not clear

if benzodiazepine receptor agonists, the so-called Z-substances, zolpidem and zopiclone, have the same effect on suppressing respiratory drive and lowering loop gain. Recently, two papers have been published in the journal *Sleep* suggesting that zolpidem does have this effect on respiratory drive. Mehdi Eshraghi from Wayne State University in Detroit, Michigan, presented a poster on the improvement of central sleep apnea in patients with idiopathic central sleep apnea using zolpidem in a placebo-controlled cross over trial. The 10 patients received zolpidem one night and placebo on another night in random order. With zolpidem 5 mg, the AHI improved significantly and the controller gain decreased significantly. While the results were promising, the authors stated that the sample size was too small to reach definitive conclusions and that further trials are needed to substantiate these findings.

Asynchronous ramp ventilation

David Rappaport of the Mount Sinai Health System, New York, New York, presented a poster on the so-called asynchronous ramp ventilation. The hypothesis is that an extended pressure ramp in adaptive servo-ventilation (ASV) may be more comfortable for patients and decrease $TcPCO_2$ more than regular ASV in patients with chronic hypercapnic hypoventilation. During a 15-s cycle in ASV, the pressure increases from baseline to a set maximum. A lower inspiratory pressure will be needed at the start of inspiration but the patient can begin an inspiration at any time point of the cycle that feels most comfortable. Using this asynchronous ramp ventilation, $TcPCO_2$ was lowered in nine elderly patients by an average of 2.2 mmHg.

From Sleep 2019

Claustrophobia is no excuse for CPAP non-adherence

Claustrophobia is one of the most common excuses offered by patients for not being willing to use a nasal mask for CPAP. However, it is hard to conceive why a mask covering only the nose and leaving the eyes unencumbered would have the same effect as being enclosed in a tight space, nor are there good scientific data to substantiate claustrophobia as a legitimate descriptor. Swallowing air, feeling pressure, and discomfort on the skin and cheek bones are understandable, but claustrophobia is difficult to grasp. A group from the Henry Ford Hospital in Detroit, Michigan, presented a poster at Sleep 2019 in San Antonio, Texas, supporting the claustrophobia thesis with a validated claustrophobia questionnaire in 114 newly diagnosed patients with obstructive sleep apnea (OSA). The data showed no overall correlation between a positive result in the claustrophobia questionnaire and non-adherence to nasal CPAP. Only one of 15 items on the questionnaire, the item (feeling anxious if being in a bathroom or kitchen cabinet under the sink for more than 15 min) was a statistically significant predictor of CPAP non-adherence.

A more discerning cognitive performance and attention test

The psychomotor vigilance test (PVT) is the most recognized vigilance test in sleep medicine. Hans van Dongen, a specialist for vigilance testing in pilots and astronauts at Washington State University in Spokane, Washington, presented a new vigilance test that measures a subject's ability to change focus from one task to a more important task if needed. To highlight the relevance of this measure for difficult driving situations, Dr. van Dongen showed an example from a black box recording of a commercial airplane crash. In the recording, one could clearly hear that the pilot focused on a minor problem and was unable to shift his attention to the more deadly problem of rapid loss of altitude. In the new vigilance test, subjects are required to press a green (go) button when presented with four different two digit numbers and a red (no go) button for four other number combinations. During the test, the number combinations signaling appropriate red and green responses change. The subject is informed about this change, but the test requires substantial focus to keep from sticking to the prior number signals. Very small sleep deficiencies have a profound effect on the performance of this vigilance testing.

Does CPAP reduce blood pressure?

The Apnea Positive Pressure Long-term Efficacy Study (APPLES) from the Harvard Sleep Laboratory at Brigham and Women's Hospital in Boston, Massachusetts, investigated the effect of CPAP on blood pressure reduction in patients with OSA. Sogol Javaheri presented a poster with data from 1101 patients randomized to receive therapeutic CPAP or sham CPAP. Differences in blood pressure response between the groups were marginal. Patients on therapeutic CPAP showed a reduction of 2 mmHg in the diastolic pressure only. One limitation of the study was that the baseline pressure was low in both groups at the start of the study, perhaps because patients were already receiving antihypertensive medications. These results do not support the effectiveness of CPAP to reduce blood pressure in patients with OSA.