Medication Induced Poor Sleep And Neurocognitive Consequences In Allergic Rhinitis: A Brief Review

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Abstract

ABBREVIATIONS

AR: Allergic Rhinitis
REM: Rapid Eye Movement
NREM: Non Rapid Eye Movement
SWS: Slow Wave Sleep
TSD: Total Sleep Deprivation
INS: Intra Nasal Steroids

ALLERGIC RHINITIS, ANTIHISTAMINES AND SLEEP EFFICACY

In Allergic Rhinitis (AR) treatment paradigm, the false belief and frequently mistaken practice which obviously contradicts with the current practice guidelines, is the use of antihistamines (H1 blocking agents) to help patients with their allergic symptoms and at the same time promote their sleep(1). AR patients have baseline sleep problem due to impaired upper airway patency during sleep state which leads to sleep fragmentation and the day after, excessive daytime somnolence(1). Blocking H1 receptors in the brain, makes the condition even worse.

Although antihistamines seem sedative, they impair the process of reaching deep sleep stages and would potentially make the patients “REM sleep” deprived. As a result, first-generation antihistamines impair cognitive function of daily living (2,3).

Below, selected notions from the literature on sleep functions (REM and NREM sleep) and the consequence of REM sleep deprivation as a result of shallow non restorative sleep is reviewed.

The role of REM sleep in memory consolidation has recently drawn lot of attention. Higher cortical functions such as cognition, attention, and memory are rapidly affected by REM sleep deprivation. And REM sleep deprivation is something as a rule when anti histamines (1 st generation H1 blockers) are taken(3).We all experience that disrupted sleep is certainly not conductive for attention and learning. So the role of REM sleep in consolidation of mainly procedural memory need not be down played.

Hhistamine cells in the hypothalamic tuberomamillary nucleus is a part of the neural system which regulates arousal (4). The functional attributes of arousal (awareness, movement, mental activity, communication, etc.) are mediated by multiple neural systems including the histaminergic circuitry. The complex system which contributes to the maintenance of the wakefulness arises from the brain stem reticular formation, distributed throughout the brain stem and forebrain. As shown in the purple circuit in Fig.1, histaminergic receptors and mainly H1 type play an important role in this regard.

Functions of brain H1-receptors include regulation of brain activity(3), balance sleep/wakefulness(3), concentration of attention(5), memory(3), learning(3), daily activity(5), appetite (reduction) and activation of serotoninergic system (the secondary anti-depressive effect)(5).

First generation (eg. Chlorpheniramine, Clemastin, Diphenhydramine,etc.)and some sedative second generation(eg.Citrizine) cross blood-brain barrier and block brain H1 receptors, serotonin receptors(5) and central muscarinic cholinergic receptors(3). Even therapeutic doses of first generation antihistamines can cause agitation and sleep disorders in children(5).

First-generation antihistamines inhibits REM sleep (rapid eye movement) and cause rebound syndrome (increase REM number and intensity) that leads to fragmentation of sleep, arrhythmia, tissue hypoxia and sleep apnea,daily somnolence, impairment of daily activity, impairment of

cognitive function, Sleep apnea increases the risk of sudden death(1,3,5).

To elucidate how REM sleep deprivation caused by H1 blockade is damaging to general mental health, we need to go over functions of sleep.

FUNCTION OF SLEEP

Sleep is an essential physiological need without knowing its biological significance. It is a function that cannot be substituted by quiet rest(6).In animal studies 2-3 weeks total sleep deprivation(TSD) is shown to be fatal. REM sleep deprivation produces a similar syndrome with a longer time course(6,7). Chronic partial sleep restriction consequence is on the other hand the invasion of sleep into wakefulness(6,7). Another important outcome of sleep deprivation is impairment of cognitive performance(7).

Some consequences of sleep deprivation (including REM sleep loss) are: lapses in attention, slowed working memory(7), reduced cognitive outputs (learning, memory, executive functions) and depressed mood(8).

It also has adverse effects on endocrine function and metabolic and inflammatory responses. Behavioral lapses during performance are due to appearance of micro-sleeps which ranges from 0.5 to 10 seconds in duration often leading to full blown sleep .This has been viewed as “wake state instability”(9,10). Although the most immediate unavoidable effect of sleep deprivation is cognitive impairment, the entire body benefits from sleep. In addition to cognitive impairments, sleep loss is proven to cause cardiovascular diseases, mainly hypertension(11).

Non-REM Sleep functions

NREM sleep gives the brain rest. Slow Wave Sleep (SWS) activity may reflect the average strength of cortical synapses which would increase during wakefulness as a result of plastic processes and decreased during sleep due to sleep dependent mechanisms of synaptic downscaling(12-14).

ENERGY CONSERVATION

Sleep may be adaptive by which we conserve energy. Specifically, NREM sleep is associated with reduced brain energy expenditure(17).Sleep time may be related to defense against oxidative stress. A high metabolic rate results in generation of high levels of reactive oxygen species(ROS) by mitochondria(17,21).

Sleep deprivation (Including NREM sleep loss) in accompanied by increased oxidative stress and evidence of membrane disruption in the hippocampus, sub cortical brain regions and peripheral tissues(18-21).

HORMONE SECRETION

Growth Hormon(GH) secretion occurs in pulses throughout the day. But after sleep onset, there are large bursts of GH secretion associated with SWS.GH secretion during SWS can amount to two-third of the total GH secreted in children(15-17). Sleep is necessary to normalize synapses to a baseline level that is sustainable and ensures cellular homeostasis(17).

REM Sleep functions

The features of REM sleep include EEG desynchronization, rapid eye movements, ponto geniculo occipital (PGO) waves, skeletal muscle atonia, erection in male and dream state. Throughout the sleep cycle REM sleep follows N3 which is considered as the deepest stage of sleep in humans(17).

Neuronal activity is high during REM sleep. This may be a clue that REM sleep state is involved in the brain growth during early development period(13-17). Getting up from a more alert stage has substantial advantage over confused state. One of the functions of REM sleep could be to release from NREM sleep to wakefulness(1).

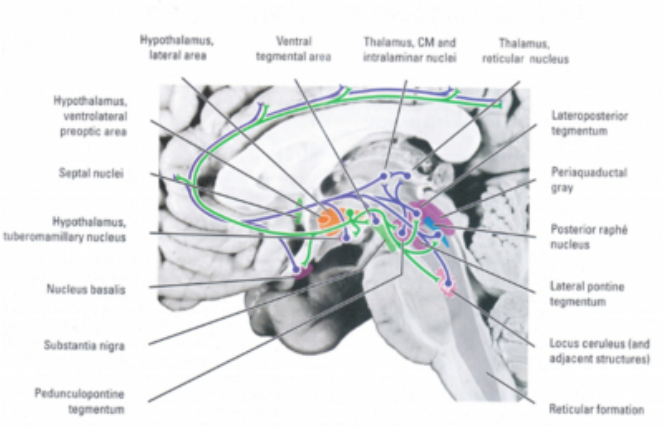
COMMENTS

Although systemic steroid treatment may be associated with decreased SWS, increased sleep onset latency and increased wakefulness after sleep onset(22), INS of low systemic bioavailability (i.e. less that 0.1% for Mometasone Furoate, for instance) does not negatively affect sleep architecture and efficacy(23).

In conclusion; to stay away from devastating cognitive consequences caused by poor sleep and mainly lacking REM and phase 3 NREM function of sleeping state, which is considered as an effect when first generation (Chlorpheniramine, Clemastin,etc) and some second generation anti-histamines (eg.Citrizine) are used, and based on current practice guide lines; the use of sedative antihistamines rather than intranasal steroids as first choice in treatment of allergic rhinitis does not seem to be an appropriate decision making in pharmacotherapy.

Figure 1

Figure 1 : Arousal and sleep pathway. Courtesy of Dr.Thomas A.Woolsey, The definitive guide to the human brain; 3rd.ed.; John Wiley &Sons;,Inc.ISBN:978-0-470-0847-6. 2008: 215



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