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TREATMENT OF SLEEP APNEA WITH GLP-1 RECEPTOR AGONISTS AND THEIR EFFECTS ON THE CENTRAL NERVOUS SYSTEM: A LITERATURE REVIEW

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Abstract: Introduction: Obstructive sleep apnea (OSA) is a disorder characterized by episodes of obstructive apneas, hypopneas and/or awakenings, usually caused by upper airway collapse related to respiratory effort. It is common in older men, post-menopausal women and children. Body mass index, obesity and increased abdominal and neck circumference are among the risk factors. The symptoms are daytime sleepiness, wheezing, choking, snoring or interruptions in breathing during sleep. The neurological damage caused by hypoxia includes a high risk of neurovascular complications, structural and metabolic damage. Objective: To analyze the impact of OSA on the central nervous system using drugs analogous to GLP-1 receptors. Methodology: A systematic literature review was carried out by searching for studies in the UpToDate, PubMed, Science Direct and Cochrane databases. Thirteen relevant articles were selected that address both the impacts of OSA and its therapeutic approaches. Results: The pharmacological approach with GLP-1 analogs, such as Liraglutide, has shown promise in the management of OSA, especially in patients with obesity, due to its action in reducing appetite, glycemic control and decreasing body weight. Other drugs such as Tirzepatida have also shown significant benefits, reducing the apnea-hypopnea index and improving cardiometabolic aspects in patients with OSA. Conclusion: The results indicate that drugs analogous to GLP-1 receptors have promising therapeutic potential for the treatment of OSA. However, there is a need for further studies that consider broader variables and different risk profiles. It is also essential to investigate long-term effects, response at different doses and possible interactions with other therapies, in order to better understand the applicability and safety of these drugs in a more diverse spectrum of patients.

Keywords: Sleep apnea, Glucagon-like peptide-1 receptors, Clinical trials.

INTRODUCTION

Obstructive sleep apnea (OSA) is a disorder characterized by obstructive apneas, hypopneas and/or awakenings related to respiratory effort, caused by repetitive collapse of the upper airways during sleep (KLINE, R.L, 2023). OSA is one of the most prevalent respiratory diseases in the world (PATEL, S.R, 2024). It is more common in older men and can affect women, mostly in the post-menopausal context, and children (KLINE, R.L, 2023). Body mass index (BMI), obesity, increased abdominal and neck circumference are among the risk factors.

The most frequent symptoms include daytime sleepiness, wheezing, choking, snoring or interruptions in breathing during sleep. This condition is known to affect the ability to perform daily tasks by causing mostly mild cognitive damage (CASTRONOVO, 2014).

In the midst of the treatment alternatives available, studies indicating the use of Glucagon-Like Peptides (GLP-1) in the treatment of OSA have been emerging. This substance is an incretin, naturally produced by alpha-pancreatic cells, which can be administered peripherally through medication. Its effects include controlling lipid metabolism, increasing thermogenesis from brown adipose tissue, inhibiting gastric emptying and hydrochloric acid secretion, which leads to increased satiety and decreased absorption of glucose into the systemic circulation (MÜLLER, 2019).

OBJECTIVES

The aim of this study is to analyze the potential use of Glucagon-Like Peptides (GLP-1) in the treatment of obstructive sleep apnea (OSA), seeking to understand its effectiveness in reducing the symptoms associated with the condition and its impact on metabolic risk factors. In addition, we intend to investigate the possible neurological damage caused by OSA and assess whether treatment with GLP-1 can help minimize such cognitive impairments.

METHODOLOGY

A qualitative literature review was carried out using the UpToDate, PubMed, Science Direct and Cochrane databases. The search strategies were the health sciences descriptors (DeCS/MeSH) "GLP-1" AND "Sleep apnoea", "Obstructive sleep apnoea" AND "Brain damage", "glucagon like peptide 1" AND "pharmacokinetics", "Obstructive sleep apnea" AND "glucagon like peptide", totaling 160 articles, of which 13 were selected, according to the inclusion criteria: clinical trials, randomized clinical trials, *open access*, published in the last 10 years, in the English language. Duplicate articles, animal studies and discordant articles were excluded from the search. Other articles were also selected on an ad hoc basis, without a defined search strategy.

DEVELOPMENT

EFFECTS OF OSA ON THE CNS

Hypoxia in the central nervous system has an effect on cognitive capacity. Schwartz analyzed the cerebral oxygenation of 26 patients with severe or moderate apnea, aged 20-75, and found that this condition is related to neuro-cognitive and neuronal damage, as well as an increased risk of stroke.

The results obtained showed peripheral and cerebral desaturations that produced brain dysfunctions. In addition, imaging tests showed structural and metabolic damage in OSA patients, and that the risk of stroke is associated with increased intracranial pressure and dysregulation of the autonomic system, which occurs as a result of damage to the endothelium and pressure variations induced by low blood perfusion. Long-term effects have not been tested (SCHWARZ, 2018).

In another randomized clinical trial, morphometry was carried out on 85 patients with severe OSA, aged 30-55. Cognitive and functional deficits were reported, as well as damage to the white matter tracts, due to demyelination and a decrease in axonal caliber, possibly induced by low oxygenation. Areas of ischemia and decreased perfusion were also identified at the level of the small vessels. Despite the damage, it has been suggested that this is a reversible situation if the conditions leading to hypoxia are treated (CASTRONOVO, 2014).

An increase in sympathetic activity associated with OSA, which leads to hypertension, has also been reported. The result was obtained by carrying out MRI scans on 32 patients aged 35-69 with OSA. Abnormalities were identified in the cardiovascular response, which increases the risk of diseases such as stroke. Associated with this effect were structures in the limbic system which, in response to frequent variations in oxygenation, cause excitation of the sympathetic system (FATOULEH, 2014).

PHARMACOLOGICAL APPROACH

Recent studies point to the administration of *Glucagon Like Peptides (GLP-1)* and their derivatives in the treatment of obesity and its complications, including hypertension, type 2 diabetes mellitus, hyperphagia and dyslipidemia, all of which are associated, to a greater or lesser extent, with OSA and hypopnea. These drugs have a mechanism of action based on suppressing appetite and decreasing anabolic activity. Weight loss is a factor that positively influences OSA, which is why drugs that reduce body weight have been gaining prominence in the fight against this condition (BLACKMAN, 2016; JI, 2022).

In a clinical trial conducted by Jiang, 89 patients of both sexes aged 18-75 with T2DM and severe OSA according to the AHI scale were selected. They were given doses of Liraglutide (3.0 mg), combined with the use of CPAP, which reduced the severity of the disorder after 3 months, as well as lowering BMI, improving blood oxygen levels and lowering blood pressure levels (JIANG, 2022).

Blackman found benefits in the use of Liraglutide in patients with moderate or severe OSA. The study selected individuals of both sexes, aged 18-64, diagnosed with OSA, who were not using other medications or interventions, such as CPAP, and excluded patients with diabetes. The doses started at 0.6 mg/day in order to minimize side effects and increased to 3.0 mg over 32 weeks. Most participants reported mild to moderate gastrointestinal effects, which were temporary. The main results were a decrease in BMI, glycemia and a reduction in cardiovascular risk. A reduction in the apnea-hypopnea index (AHI) was observed mainly in patients with mild and moderate conditions. The level of sleepiness, based on the Epworth scale, was not altered (BLACKMAN, 2016).

Other drugs with a similar mechanism of action have also been studied, such as

Mazdutide. Ji selected patients aged 18-75 who were overweight or obese and had at least one comorbidity associated with obesity, including OSA. The compound was found to be safe and highly tolerable. No serious adverse effects were identified. Mild and moderate gastrointestinal and respiratory reactions were reported, but disappeared during the course of treatment. At a dose of 9.0 mg, a decrease in body weight of 11.7% on average over 12 weeks was reported, as well as improvements in various metabolic aspects, also related to apnea. Higher doses showed no significant difference (JI, 2022).

Unsatisfactory results have also been obtained with the use of Liraglutide. Welling reported a statistically unsatisfactory weight loss of -3% over 5.5 months in a 31-year-old obese patient with a genetic obesity disorder, hyperphagia and OSA. The criterion for successful treatment was 5% body mass. Consequently, her OSA and obesity were not resolved. Therefore, a condition that deregulates the appetite mechanism suggests the ineffectiveness of drugs that act on GLP-1 agonist receptors. Therefore, the use of drugs with different mechanisms of action is recommended (WELLING, 2023).

Phase 3 SURMOUNT-OSA clinical trial studies with tirzepatide in adult patients with moderate to severe OSA and obesity demonstrated significant impacts on the clinical parameters evaluated. Participants were divided into two groups: those who were not using positive airway pressure (PAP) therapy at the start of the study, and those who were already on PAP treatment. In both trials, subjects were randomized to receive tirzepatide (at the maximum tolerated doses of 10 mg or 15 mg) or placebo over 52 weeks (MALHOTRA, A, 2024).

The results focused on the change in AHI, which assesses the number of apnea and hypopnea events per hour of sleep. In trial 1, there was an average reduction of 25.3 events per hour with tirzepatide compared to 5.3 events per hour with placebo, resulting in a significant difference of 20 events per hour. In trial 2, the average reduction was even greater, with 29.3 events per hour with tirzepatide versus 5.5 events per hour with placebo, resulting in a difference of 23.8 events per hour. Both results showed a statistically significant improvement with tirzepatide compared to placebo (MALHOTRA, A, 2024).

In addition to AHI, key secondary endpoints included percentage change in body weight, hypoxic load, high-sensitivity C-reactive protein concentration, systolic blood pressure and patient reports of sleep quality and related disturbances. In all these parameters, the use of tirzepatide showed significant improvements compared to placebo, reinforcing its potential benefit not only in reducing the severity of OSA, but also in metabolic and cardiometabolic aspects (MALHOTRA, A, 2024).

The most common adverse events associated with tirzepatide are gastrointestinal in nature, generally mild to moderate in intensity. These results highlight the drug's promising ability to not only treat obesity and improve glycemic control, as commonly observed in previous studies, but also to positively impact the severity of OSA, a condition often associated with obesity and its comorbidities (MALHOTRA, A, 2024).

Glucagon agonists have also been shown to be effective in managing cell damage caused by hypoxia, ischemia, reperfusion syndrome and other complications resulting from oxidative stress (OSS) in the central nervous system. Cortical neurons were protected from cell death by reducing the concentration of markers involved in OE and blocking the glutamate-mediated apoptosis pathway (MÜLLER, 2019; SALCEDO, 2012).

PHARMACOKINETICS

GLP-1 agonist drugs were originally created to control DMT2, but recently they have been taking center stage among weight control drugs. They can be administered through subcutaneous injections or by ingestion, the oral version being approved only for the treatment of DMT2. Its main mechanism consists of mimicking endogenous incretin, binding to its receptors and stimulating insulin secretion and suppressing glucagon secretion, leading to improved glucose homeostasis and a reduction in hyperglycemia. Naturally, glucagon is produced by pancreatic α-cells and has a very short half-life, so its synthetic analogues are produced in order to increase its time of action and its quantity in the body, knowing that it is a dose-dependent drug, and that its administration is directly proportional to its serum level. They are also capable of reducing gastric emptying and appetite by increasing hypothalamic satiety signaling (GUO, 2023; OVERGAARD, 2016, Van HOUT, 2023).

The safety and tolerability of this class of drugs has been demonstrated in several articles. *Semaglutide, Mazdutide, Ecnoglutide, Liraglutide,* among other drugs, both in use and in the testing phase, have demonstrated agreement on these issues. Their effectiveness can depend on factors such as body weight, gender, fractionation, diet and various other metabolic conditions. The main side effects are gastrointestinal, mainly nausea and abdominal distension. Negative effects on other systems have also been reported, but they have been of low severity. The prevalence of these events is dose-dependent, but in all of them the adverse effects were mild or moderate, with no deaths or persistent serious effects. The possibility of them causing liver (BÆKDAL, 2018) and kidney damage has been raised, but recent studies have found no relationship with the use of the drug, except in severe cases of kidney failure (OVERGAARD, 2016; JI, 2022; BLACKMAN, 2016; JIANG, 2022; Van HOUT, 2023).

Evidence suggests that almost 50% of patients who start treatment with a GLP-1 receptor agonist for obesity discontinue therapy within 12 months (PATEL, S.R, 2024).

The main outcome observed between the placebo and control group taking tirzepatide at the 52nd week for patients not using positive pressure treatment is the difference in AHI, as measured by polysomnography. Secondary outcomes include specific hypoxic load, functional outcomes and cardiometabolic markers. The trial includes home sleep tests to record time to improvement for daily physical activity assessment, evaluating exploratory outcomes (MALHOTRA, A, 2024).

CONCLUSION

The results suggest that drugs analogous to GLP-1 receptors have therapeutic potential for the treatment of Obstructive Sleep Apnea, especially in obese or overweight patients. These drugs could help reduce the severity of OSA, improve quality of life and reduce the risk of complications associated with the disease.

However, further studies are needed to evaluate the efficacy of GLIP-1RA in different subgroups of patients, especially with mild OSA, since most of the cases previously analyzed were with patients with moderate or severe OSA.

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