Surgical vs Conventional Therapy for Weight Loss Treatment of Obstructive Sleep Apnea

Weight loss, combined with other current therapies, can help control and improve symptoms of obstructive sleep apnea (OSA). It is unknown whether the method used to lose weight makes a significant difference in OSA severity.

A two-year, randomized, controlled trial attempted to determine if surgically-induced weight loss was more effective than weight loss from conventional therapy for management of OSA. Patients had a BMI between 35 and 55 kg/m², an apnea-hypopnea index (AHI) of ≥20 events, a recent diagnosis of OSA with recommendations to begin CPAP therapy, and at least three prior significant weight loss attempts. Sixty patients were randomized to either the surgical group (n= 30) or the conventional therapy group (n=30). The conventional therapy group used diet and exercise to lose weight, and the surgical group underwent laparoscopic adjustable gastric banding surgery (LAGB). The primary outcome was the change in AHI at two years compared to baseline. Secondary endpoints included cardiometabolic risk measurements and responses to patient-completed questionnaires.

Mean weight loss was significantly greater in the surgically-induced group compared to the conventional therapy group (between group difference of -22.7 kg, 95% CI -3.1 to -14.3 kg; p< 0.001). This difference in weight loss did not correlate with a significant between-group difference in the change in AHI (-11.5, 95% CI -28.3 to 5.3; p= 0.18). Each treatment group had a significant mean decrease in AHI from baseline, supporting the benefits of weight loss in OSA. The mean AHI at two years was still greater than 30, which indicated that patients, on average, still had severe OSA despite the weight loss. The surgical group had significantly better outcomes than conventional therapy in their changes in waist circumference, metabolic syndrome status, and SF-36 Health Survey categories for physical role, general health, and vitality.

The authors concluded that, while the LAGB group achieved greater weight loss than the diet and exercise group, this difference was not associated with any significant difference in AHI. Weight loss was beneficial in decreasing OSA severity, but the relationship did not appear to be proportional to the amount of weight lost. At baseline, patients were extremely obese based on their BMI and had moderate to severe OSA, which may limit the generalizability of this study. Patients with a lower BMI and/or less severe OSA may experience different results.

CONCLUSION: Although there was a greater mean weight loss after surgical intervention compared to diet and exercise, surgical intervention was no more beneficial in decreasing obstructive sleep apnea (OSA) severity. Therefore, patients should still be counseled on the importance of continuing concurrent therapies, such as CPAP, because weight loss alone is not likely to result in a remission of OSA symptoms.


By Kylie Rauch, Pharm.D. Candidate
This has been the worst year for West Nile virus (WNV) infections in the United States, with a record 3545 cases and 147 deaths reported to the CDC as of September 25, 2012. The reason for this recent outbreak is unknown, but is likely due to warmer temperatures and fluctuations between rainfall and drought. Understanding the transmission, risk factors, symptoms, treatment, and prevention of WNV is an important way to impede the spread of this serious disease.

WNV is spread by a variety of methods, but mosquitoes of the Culex genus are the primary transmission vector. Mosquitoes become carriers of the virus after biting birds, which are a main reservoir for WNV. Due to low viremia levels, it is unlikely that humans, ticks, cattle, or rodents play a substantial role in the spread of the disease. However, WNV can be spread through blood transfusions, organ transplants, and breastfeeding. In 2002, a pregnant woman transmitted WNV to her fetus.

The most important risk factor for WNV infection is exposure to infected mosquitoes. Age and gender do not appear to be an important factor in WNV susceptibility but may influence the development of neuroinvasive disease once infected. After a 2005 WNV epidemic in California, a retrospective observational study identified hypertension and diabetes as possible risk factors for developing neuroinvasive disease once infected. Health departments in California collected case history forms from 880 patients who had suffered WNV illness from May to November 2005. Patients were asked open-ended questions about past medical history. Of the 880 patients, 35% (305/880) had suffered a WNV neuroinvasive illness and 61% (534/880) had suffered West Nile fever (WNF). Compared to patients with WNF, patients with neuroinvasive disease were more likely to be male (OR 1.57, 95% CI 1.18 to 2.09), over the age of 64 (OR 2.24, 95% CI 1.62 to 3.11), have diabetes (OR 4.15; 95% CI 2.63 to 6.55), or have hypertension (OR 2.08; 95% CI 1.44 to 3.01). The authors concluded that these factors were associated with an increased risk of developing neuroinvasive disease. They speculated that the increased risk in these patient populations was because of the impaired immune response in patients with diabetes and a disruption of the blood-brain barrier in patients with hypertension. An important limitation to this study was the low completion rates of the case report forms.

Symptoms of WNV may not appear until up to 14 days post-exposure because the virus has an incubation period ranging from 3-14 days. Up to 80% of patients infected with WNV remain asymptomatic. Most patients who become symptomatic experience WNF, a self-limiting condition characterized by fever, gastrointestinal symptoms, headache, fatigue, weakness, and muscle pain. Rare symptoms reported in patients with WNF include macular rashes, hepatitis, pancreatitis, myocarditis, chorioretinitis, rhabdomyolysis, and cardiac dysrhythmias. Fewer than one percent of patients develop neuroinvasive disease, which leads to meningitis, encephalitis, or paralysis. WNV encephalitis can lead to mild disorientation, movement disorders, flaccid paralysis, coma, and death. Infected patients may suffer long-term physical, functional, and cognitive deficits.

No specific treatment exists for WNV infection. Patients with more serious symptoms may require supportive treatment in a hospital, such as intravenous or respiratory therapy. High-dose ribavirin and interferon-α2b were shown to be effective in vitro, but no randomized, controlled trials have been conducted in humans. A human vaccine for WNV is currently being investigated by Acambis Inc. and Baxter/Immunovia.

Prevention is a key component to avoiding WNV transmission. The CDC currently recommends the following measures to reduce the risk of infection:

- Use insect repellent containing an EPA-registered active ingredient (DEET, picaridin, oil of lemon eucalyptus, or IR3535) when spending time outdoors.
- Since mosquitoes are most active at dusk and dawn, remember to apply insect repellent and to wear long sleeve shirts and pants during these times. Consider staying indoors when mosquitoes are active.
- Use window and door screens and keep them in good repair to keep mosquitoes out of the house.
- Emptying standing water eliminates mosquito breeding sites. Throw out standing water from flower pots, buckets, and barrels. Change water in pet dishes often, and replace bird bath water weekly. Drill holes in tire swings to drain any excess water. Keep children’s wading pools empty and on their sides when not in use.

WNV infections are on the rise in the United States, and 2012 has been the worst year to date. Knowing the transmission, symptoms, risk factors, treatment, and prevention of WNV can help curb the recent increase in infections. While most patients infected with the virus will remain asymptomatic, WNV can lead to WNF, meningitis, encephalitis, coma, or death. Neuroinvasive disease risk factors include age over 64, male gender, and diabetes or hypertension. While there is currently no treatment or vaccine for WNV, patients can prevent disease by avoiding infected mosquitoes.

By Doug Huntington, Pharm.D. Candidate

(references on page 4)
Stribild™ for HIV Infection

Stribild™, also known as the “Quad” pill, was approved by the FDA on August 27, 2012, and is the first single-tablet, integrase-inhibitor-based regimen that can be taken once daily.1,3 This drug is a combination of elvitegravir 150 mg (EVG), cobicistat 150 mg (COBI), emtricitabine 200 mg (FTC), and tenofovir disoproxil fumarate 300 mg (TDF).2,4 It has been approved for antiretroviral-naïve adults as a complete antiretroviral treatment regimen and should not be administered with other antiretroviral medications.2

Two studies have compared the safety and efficacy of Stribild™ (EVG/COBI/FTC/TDF) to already established antiretroviral regimens.2,3 These were 48-week, phase 3, randomized, double-blind, non-inferiority studies in treatment-naïve adults diagnosed with HIV. Patients had a plasma HIV RNA concentration ≥5000 copies/mL. Patients were excluded if they had been recently diagnosed with a new AIDS-defining disorder or serious infection. The primary endpoint in both studies was the achievement of viral suppression at week 48. Viral suppression was defined as an HIV RNA concentration <50 copies/mL. Secondary endpoints included the change in CD4 cell count and the emergence of resistance. Safety data was collected from all patients from the time they received their first dose of study drug until 30 days after their last dose.2,3

The first study compared EVG/COBI/FTC/TDF to a regimen of co-formulated efavirenz 600 mg, emtricitabine 200 mg, and tenofovir disoproxil fumarate 300 mg (EVF/FTC/TDF).2 Patients were randomized to receive either EVG/COBI/FTC/TDF (n=348) or EVF/FTC/TDF (n=352) once daily. Viral suppression was achieved in 305 patients (87.6%) receiving EVG/COBI/FTC/TDF compared to 296 patients (84.1%) in the comparator group (between-group difference of 3.6%, 95% CI -1.6% to 8.8%). At week 48, patients in the EVG/COBI/FTC/TDF group had a significantly higher mean increase in CD4 cell count (239 cells/µL) than the comparator treatment (206 cells/µL; p=0.009). In both treatment groups, eight patients (2%) developed a resistance mutation to their treatment drug.2 The majority of reported adverse events were mild to moderate.2 More patients in the EVG/COBI/FTC/TDF group experienced nausea (p=0.016), and more patients receiving the comparator regimen experienced dizziness (p=0.001), abnormal dreams (p=0.001), insomnia (p=0.031), and rash (p=0.009).2

The second study compared EVG/COBI/FTC/TDF to a regimen of ritonavir 100 mg, atazanavir 300 mg, and emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg (ATV/RTV+ FTC/TDF).3 Patients were randomized to receive either EVG/COBI/FTC/TDF (n=357) or ATV/RTV+FTC/TDF (n=358) once daily. Viral suppression was achieved in 316 patients (89.5%) receiving EVG/COBI/FTC/TDF compared to 308 patients (86.8%) receiving the comparator treatment (between-group difference of 3.0%, 95% CI -1.9% to 7.8%). At week 48, the mean increases in CD4 cell counts were similar in both groups (207 cells/µL and 211 cells/µL for the EVG/COBI/FTC/TDF group and comparator group, respectively). Five patients receiving EVG/COBI/FTC/TDF and zero patients in the comparator group developed a resistance mutation. Adverse events included diarrhea, nausea, upper respiratory tract infections, headache, and fatigue.2 These events were generally mild to moderate and occurred equally in each group. Ocular icterus occurred more frequently in the EVG/COBI/FTC/TDF group (51 vs. 2 cases; p=0.001).3

Both studies found that once-daily Stribild™ was non-inferior to both comparator regimens and was generally well tolerated in treatment-naïve HIV patients. The once-daily dosing and single-tablet formulation of Stribild™ may help encourage patient compliance. Post-marketing data will give a better idea of the effectiveness and safety of Stribild™ in non-controlled environments.

By Kylie Rauch, Pharm.D. Candidate

REFERENCES:
Since inhaled glucocorticoids appear to reduce growth velocity in children only during initial treatment, it has been hypothesized that children exposed to inhaled glucocorticoids eventually catch up in height to their counterparts. This retrospective, observational cohort study of patients enrolled in a previously conducted randomized placebo-controlled trial assessed whether glucocorticoid therapy in prepubertal children affected height later in life.

In the original CAMP trial, 1041 children, aged 5-13 years old, with mild to moderate asthma were randomly assigned to receive either budesonide 200 mcg twice daily, nedocromil 8 mg twice daily, or placebo twice daily for 4.5 years. Height was measured using a stadiometer every six months during the initial trial and once or twice a year for the next eight years. The primary endpoint in the observational follow-up study was the mean difference in adult height between patients who were exposed to budesonide in childhood and those who did not receive glucocorticoids. Height measurements were obtained for 943 of the original CAMP trial participants, and an imputation strategy was used to determine the probable height of 98 participants who were lost to follow-up.

In the original CAMP study, two years of budesonide treatment resulted in a 1.3 cm adjusted mean height deficit compared to the placebo group (95% CI -1.7 to -0.9). At the end of the CAMP trial, patients on budesonide treatment had only a 1.2 cm deficit (95% CI, -1.9 to -0.5). These results may have contributed to the original conclusion that inhaled glucocorticoids retard growth instead of suppressing growth. In this observational study, patients who had been treated with budesonide as children had a statistically significant lower adjusted mean adult height of 1.2 cm compared to the placebo group (171.1 cm vs. 172.3 cm; p=0.001). A major limitation of both the original and observational study was the use of a 400 mcg daily budesonide dose, which may have been excessive for mild to moderate asthma. The clinical significance of the height difference between groups is minimal.

**CONCLUSION:** High-dose inhaled glucocorticoid therapy (budesonide 200 mcg twice daily) in prepubertal children resulted in a statistically significant average height deficit of 1.2 cm that persisted into adulthood.


By Doug Huntington, Pharm.D. Candidate

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### West Nile Virus (from page 2)

**REFERENCES:**

Adult exercise improves overall health and can decrease the risk of type 2 diabetes. A dose-response effect of exercise on overall health has been observed in adults. Some trials have shown that exercise can also reduce metabolic risk factors in children, but recommendations for exercise dose do not exist because of a lack of dose-response information in children. A randomized placebo-controlled study compared the effects of two different doses of exercise on diabetes risk in overweight and obese children who were also sedentary.

The goal of this study was to determine the effect of different doses of aerobic exercise on several factors associated with diabetes risk, including fitness, insulin resistance, and body fat. Subjects were included if they were overweight or obese (BMI > 85th percentile) and had no medications or health conditions that would prevent exercise or affect the results of the study. Patients (n=222) were randomized to participate in either 20 minutes of exercise five times weekly (low dose; n=71), 40 minutes of exercise five times weekly (high dose; n=73), or no exercise (n=78) for 13 weeks. The intensity of exercise was the same between both exercise groups. The primary endpoints included insulin AUC, body fat, visceral fat, and fitness. A secondary endpoint was fasting blood glucose.

Insulin AUC, body fat percentage, and visceral fat decreased significantly more in both exercise groups compared to control (p=0.01 to 0.03 for low dose; p≤0.001 to 0.01 for high dose). There was not a statistically significant difference between the high dose and low dose groups in any outcome. Fasting blood glucose levels were not significantly decreased in any group. The authors concluded that insulin resistance and total body and visceral fat were improved by high intensity exercise in sedentary children who were also overweight or obese.

Minor adverse events were similar among the groups. There was one major adverse event in the low dose group (a foot fracture). Limitations of the study include the lack of blinding of participants. The two exercise groups were given a snack with each workout that was not given to the control group. This variable may have had unwanted effects on one or more of the outcomes.

CONCLUSION: High intensity exercise (either 20 minutes or 40 minutes five times weekly) for 13 weeks resulted in decreased diabetes risk (measured by insulin resistance and body fat) in children who were overweight or obese. The differences in insulin AUC and body and visceral fat were not significant between the 20-minute and 40-minute groups.


By Amy Wetch, Pharm.D. Candidate