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FDA supports the use of Vytorin[®] by Eric Schlegel

In early January 2008, the results from the ENHANCE Trial (Effect of Combination Ezetimibe and High-Dose Simvastatin vs. Simvastatin Alone on the Atherosclerotic Process in Patients with Heterozygous Familial Hypercholesterolemia) were published, causing discussion in the medical world concerning the treatment of high cholesterol.¹

The ENHANCE Trial compared ezetimibe 10mg combined with simvastatin 80mg to simvastatin 80mg alone. The study used Doppler ultrasound to measure carotid artery intima thickness (cIMT) at three sites in patients with heterozygous familial hypercholesterolemia (HeFH) over two years. The researchers predicted a reduction in the progression of atherosclerosis in patients taking the combination tablet as compared to the simvastatin alone. A total 720 patients participated in ENHANCE; 357 randomized to the combination arm and 363 randomized to the simvastatin arm. Change from baseline in mean cIMT was measured and was found to be non-significant in the common carotid, carotid bulb, internal carotid artery, and femoral artery. Average of the mean carotid and femoral IMT values was also not significant. Also, there was no difference in incidence of cardiovascular events such as cardiovascular deaths, nonfatal myocardial infarction, nonfatal stroke, and need for revascularization between the two groups. However, at the end of 24 months, LDL cholesterol decreased 17% more in the combination group compared to the group with simvastatin alone ($p < 0.01$). No difference in treatment related adverse events occurred between the two arms. It is important to note that 81% of the participants enrolled in this trial were previously on aggressive statin therapy. The results from ENHANCE suggested that for patients with very high baseline LDL, there was no benefit in taking a combination ezetimibe/simvastatin as compared to simvastatin alone. While ENHANCE did show a significant difference in LDL reduction, there was no difference in cIMT results. It is important to note that ENHANCE only addressed the surrogate endpoint of intima-media thickness, and was not adequately powered to measure clinical outcomes.²

Due to the concerns raised by the ENHANCE trial, the FDA decided to take a closer look at the data before any conclusions were made regarding the use of ezetimibe/simvastatin. After several months of analyzing the results from ENHANCE, the FDA supports the use of the ezetimibe/simvastatin combination, stating patients should not stop taking this or any cholesterol lowering medication, but rather discuss concerns or questions with their physician. The FDA makes three key points about ENHANCE: 1) many of the patients who were previously on statin or lipid-lowering therapy before the trial had relatively normal baseline cIMT; 2) the two year duration of the trial may not be of adequate length to see a benefit from the combination use on cIMT; and 3) ezetimibe may have some unknown properties that may counteract the benefits of lowering LDL on cIMT.¹

ENHANCE did not change the FDA's position that an elevated LDL cholesterol is a risk factor for cardiovascular disease and that a lower LDL can decrease this risk. While ENHANCE did not show statistical difference in carotid artery thickness, it did show a significant decrease in LDL in the combination group.¹

The FDA is now awaiting the results of an ongoing trial, known as IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial). IMPROVE-IT is studying the effects of ezetimibe/simvastatin combination compared to simvastatin on cardiovascular events such as cardiovascular deaths, major coronary events, and stroke. This trial currently has 18,000 patients and is set to conclude in 2012.¹ It is hoped that additional information will help clarify the relationship between ezetimibe use and clinical outcomes.

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Should oral corticosteroids be used for wheezing in preschool-age children? by Heather Wild

Nearly one third of preschool-age children will experience at least one episode of wheezing before the age of 6. Wheezing episodes in preschool-age children may result in emergency room visits, hospitalizations, and increased health care costs. The most common type of wheezing encountered is termed either “episodic” or “viral” wheezing and is typically associated with viral respiratory infections. Repeated episodes of viral wheezing tend to occur seasonally and most commonly decline over time. Episodic or viral wheeze associated with a viral infection often disappears by six years of age.¹

The current approach to the treatment of acute virus-induced wheezing among preschoolers has been based on the treatment of asthma in school-age children.² In children with classic atopic asthma presenting with a severe acute exacerbation, systemic corticosteroids are often used in the hospital setting to improve symptoms. Children receiving steroids are shown to be discharged earlier from the hospital and are also less likely to be readmitted in the one to three months following admission.³ Accordingly, a short course of oral corticosteroids has been proposed as an effective measure to improve symptoms, prevent emergency room visits and hospitalizations and decrease length of hospital stay in young children with severe wheezing or symptoms of upper respiratory tract infection and a history of severe viral-associated exacerbations.⁴ However, the results of trials specifically addressing the question of efficacy of systemic corticosteroids in young children with acute viral wheezing are contradictory.

Five clinical trials were evaluated which looked at the use of oral prednisolone for viral wheezing in preschool children. The trial by Oommen et al.⁵ looked at the efficacy of parent-initiated oral prednisolone for viral wheeze in children aged 1-5 years. The primary outcome assessed was the 7-day mean day-time and night-time respiratory scores obtained from a parent-completed symptom diary. Investigators concluded there was no clear benefit of a short course of parent-initiated oral prednisolone. In clinical trials conducted by Jartti et al.,^{6,7} and Panickar et al.,² the duration of hospital stay was the primary outcome assessed. The use of oral prednisolone was not associated with a decrease in duration of hospital stay in any of these three trials. Another study conducted by Csonka et al.⁸ was the only clinical trial included in this analysis which demonstrated a statistically significant primary outcome. These findings suggested oral prednisolone effectively reduced disease severity, length of hospital stay, and the duration of symptoms in preschool patients with viral wheeze.

In conclusion, the use of oral corticosteroids in preschool age children with viral wheezing remains controversial. The body of evidence suggests a lack of proven efficacy in using oral corticosteroids in preschool-age children presenting with mild-to-moderate episodic or viral wheezing.

Resources:

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News Clips

- Researchers at the University of Iowa report data suggesting a 200 to 480% increased risk of suffering a stroke within 7 days of hospital discharge for another condition.
- The United States Preventive Services Task Force (USPSTF) recommends all women planning or capable of pregnancy take a daily supplement containing 0.4 to 0.8 mg folic acid.
- Prescription “abandonment”, where a patient fails to pick up a submitted retail prescription, is up approximately 30% since 2006. Experts suggest the economy is playing a large part in this issue.

For more information on these or other news items, please contact the Center for Drug Information & Evidence-Based Practice at 402-280-5100 or druginfo@creighton.edu.

Baclofen for treatment of alcohol withdrawal syndrome by Ka Wan Chiang

Baclofen is a g-aminobutyric acid (GABA_B) receptor agonist used for spasticity control. Recent research has indicated that baclofen may be effective in the treatment of alcohol dependence, in both alcohol withdrawal syndrome (AWS) and maintenance of abstinence.¹

AWS is a clinical problem that occurs in heavy or frequent drinkers who suddenly decrease alcohol consumption or completely cease drinking without seeking professional treatment. Alcohol has depressive effects on the central nervous system, and its prolonged use leads to neuronal compensatory adaptations of the brain. As a result, sudden lowering of the alcohol level causes hyperexcitability of the nervous system, resulting in AWS.^{2,3}

The goal of treatment for AWS is to reduce withdrawal symptoms, prevent complications, and help with long-term abstinence.^{2,3} Clinical evaluation of AWS symptoms can be performed by several standardized scales, including the Clinical Institute Withdrawal Assessment for Alcohol-revised scale (CIWA-Ar).^{1,2} Pharmacological treatment is required for AWS if the CIWA-Ar reaches or exceeds the treatment threshold score of 10.^{1,2} The first-line pharmacologic treatment for AWS are benzodiazepines (BZD). However, long-term use of BZD can lead to tolerance and physical dependence.^{2,3} Therefore, other agents with less habit-forming potential, such as baclofen, are being investigated.^{1,2}

Baclofen is thought to be beneficial in the treatment of AWS by stimulating the GABA_B receptors, resulting in decreased release of excitatory neurotransmitters, such as aspartate and glutamate.¹

Currently, there is limited clinical evidence to support the use of baclofen in acute AWS, although the potential of baclofen for treating acute AWS has been observed. In an open-label clinical study by Addolorato et al. (2002), baclofen rapidly suppressed symptoms of severe AWS.⁴ Five patients with CIWA-Ar scores > 20 were treated with baclofen 10 mg orally administered every 8 hours for 30 days. A rapid decrease of the CIWA-Ar score and marked improvement of AWS symptoms were observed within 1 to 3 hours of baclofen initiation.⁴ No significant side effects were reported in this open clinical study, but three patients reported mild increase in sedation for 30 to 60 minutes following baclofen administration for the first week of treatment. Following this study, Addolorato et al. (2003) reported a case of severe AWS complicated by delirium tremens that was successfully treated with baclofen.⁵ The patient was treated with baclofen 25 mg every 8 hours for 3 days, then 10 mg every 8 hours. Two hours after the first dose of baclofen, the patient's CIWA-Ar score decreased from a baseline score of 25 to 8.⁵ Although the total duration of hospital stay was 14 days, baclofen therapy was continued after discharge for 30 days. AWS and delirium tremens (DT) symptoms did not recur following the drug discontinuation.⁵

The efficacy of baclofen for the treatment of AWS was compared with diazepam in a single-blind randomized study with 37 patients. Patients were randomly assigned to receive baclofen 10 mg three times daily (n=18) or diazepam 0.5 to 0.75 mg/kg/day (n=19), divided into 6 daily doses, then tapered by 25% daily from day 7 to 10. All patients were treated for 10 consecutive days. Both treatments significantly decreased total CIWA-Ar score and CIWA-Ar subscale scores for sweating, tremor, anxiety, and agitation, with no significant differences between the two treatments. No side effects were reported in either treatment group. The investigators concluded that the efficacy of baclofen is comparable with diazepam in the treatment of uncomplicated AWS.⁶

Although available evidence supports the efficacy of baclofen in treating acute AWS, larger randomized studies are required to test the hypothesis that baclofen can reduce symptoms and treat complications of AWS, such as DT. Further comparison between baclofen and the current first-line BZD therapy will be helpful in determining the role of baclofen treatment in acute AWS. However, based on currently available information, baclofen should not be used as monotherapy for the treatment of acute AWS.

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