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Singulair and the risk of suicide by Erin Peck

Singulair (montelukast), a leukotriene receptor antagonist, is indicated for the treatment of asthma (in patients ≥ 12 months) and allergic rhinitis (in patients ages ≥ 2 years of age), and the prevention of exercise-induced asthma (in patients ≥ 15 years of age).[1] The Food and Drug Administration (FDA) is investigating a possible association between Singulair use and behavioral disturbances, notably mood changes, suicidal thinking and behavior, and suicide.

In February 2007, Merck, the manufacturer of Singulair, amended its prescribing and patient information to include the adverse effect of suicidal thinking and behavior[2]. In addition, information concerning post-marketing occurrences of tremor, depression and anxiety have also been added to product labeling. Information on these concerns has been included in both patient and prescriber information leaflets. Also, Merck plans to inform prescribers through face-to-face interactions.

The FDA approved Singulair on February 20, 1998. Following approval and upon knowledge of the possible increased risk of suicide, Merck provided information to the FDA on 40 clinical trials. There were no reports of suicide in any of the 11,000 participants involved. Since October 2007, the FDA has received 4 reports of suicide possibly linked to Singulair[3].

The FDA and Merck are evaluating the potential link between Singulair and suicide risk. A detailed analysis of the post-marketing reports is being conducted, and is expected to take up to 9 months to complete. At this time, no causal relationship between suicide and Singulair has been established. It is recommended that prescribers monitor patients taking Singulair for mood or behavior changes, or any signs of suicidal ideation. Patients are advised to speak with their physician before discontinuing Singulair. For the most up to date prescribing and patient information, visit the Singulair website at www.singulair.com.[1]

The FDA will also be reviewing other drugs in the class of leukotriene modifiers, Accolate (zafirlukast) and Zyflo (zileutin), to determine if there is a potential link to suicide as well.[4]

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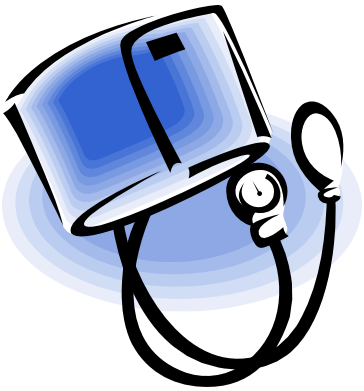
Look for information on the following current topics in upcoming issues of Health Matters

- American Academy of Pediatrics recommendations for treatment of cholesterol in children
- Possible safety concerns with Gardasil
- FDA review of bioequivalence between Wellbutrin XL and the generic equivalent

The benefit of treating hypertension in patients 80 years of age or older
by Megan Kavanaugh



A recent trial was published in the New England Journal of Medicine regarding the effectiveness in treating hypertension in patients 80 years of age or older (Hypertension in the Very Elderly Trial: HYVET). HYVET was a randomized, double-blind, placebo-controlled trial that had 3845 patients enrolled from Europe, China, Australasia, and Tunisia. Inclusion criteria for the study required the patients to be 80 years of age or older with persistent hypertension, defined as a sustained systolic blood pressure of 160 mmHg. Exclusion criteria for the study included a contraindication to use of the trial medications, accelerated hypertension, secondary hypertension, hemorrhagic stroke in the previous 6 months and heart failure requiring treatment with antihypertensive medications. Patients were randomly assigned into two groups: indapamide (sustained release, 1.5mg) or matching placebo. Perindopril (2 or 4 mg), an angiotension-converting enzyme inhibitor, or matching placebo was added on when necessary to achieve the target blood pressure of 150/80 mmHg.

The active treatment group received indapamide (sustained release, 1.5mg). If additional medication was needed to reach the target blood pressure of 150/80 mmHg, perindopril (2 or 4mg) was added to the regimen. Investigators were permitted to adjust the dose of the trial medication as needed during treatment. The primary endpoint of the trial was any stroke (fatal or nonfatal), not including transient ischemic attacks. Secondary endpoints included death from any cause, classified as either cardiovascular or noncardiovascular. All end points were reviewed by an independent committee, unaware of the individual group assignments, using definitions that were predetermined from the protocol. Median follow-up occurred at 1.8 years using an intent-to-treat analysis. In the active treatment group, statistically significant findings included a 39% reduction in the rate of death from stroke (95% CI, 1 to 62); P=0.05), a 21% reduction in the rate of death form any cause (95% CI, 4 to 35; P=0.02), and a 64% reduction in the rate of heart failure (95% CI, 42 to 78; P<0.001). The target blood pressure was reached in 19.9% of patients in the placebo group and in 48% in the active treatment group

Since elevated blood pressure is common in individuals 80 years of age or older, the study provided evidence that blood pressure control is beneficial in reducing the risk of death from stroke, death from any cause, and heart failure in this population.

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Overview of the ENHANCE trial by Nancy Xiong

With the publication of the Effect of Combination Ezetimibe and High-Dose Simvastatin vs. Simvastatin Alone on the Atherosclerotic Process in Patients with Heterozygous Familial Hypercholesterolemia (ENHANCE) trial and media exposure, many patients are not sure if they should continue taking Vytorin. There are limited studies comparing monotherapy statin to combination statin therapy. The most recent study, the ENHANCE trial, was published in the April 2008 issue of the *New England Journal of Medicine*.

The ENHANCE trial was a two-year, prospective, randomized, double-blind, active comparator, multicenter study that enrolled 720 adults between the ages of 30 and 75 years, who were diagnosed with heterozygous familial hypercholesterolemia (HeFH) and had LDL-C greater than 210 mg/dL. HeFH is a single-gene disorder and occurs in approximately 1 in 500 persons[7]. There was a screening phase, a single-blind placebo run-in period of 6 weeks in which all lipid-lowering drugs were discontinued, and a double-blind study period of 24 months. Measurements of cholesterol, triglycerides, apolipoprotein and C-reactive protein were obtained at baseline, 6, 12, 18 and 24 months. Baseline values were obtained at the end of the run-in period. 357 patients received 80 mg of simvastatin plus 10mg of ezetimibe, and 363 patients received 80 mg of simvastatin plus placebo. The primary outcome was the change in the mean intima-media thickness (IMT) of the carotid and femoral arteries. The four key secondary outcomes were 1) the incidence of regression in the mean carotid artery IMT from baseline, 2) the incidence of patients with new carotid-artery plaques of more than 1.3mm, 3) the change from baseline in the mean maximal carotid artery IMT and 4) the change from baseline in the average mean IMT of the carotid and common femoral arteries.

B-mode ultrasonographic imagesof the IMT in the carotid and femoral arteries were surrogate markers used to assess the progression of atherosclerosis. A surrogate endpoint is an endpoint that is obtained sooner, at lower cost or less invasively than the true endpoint for a health outcome, and is used to make conclusions about the effect of interventions on the true endpoint[1]. The appropriateness of IMT as a surrogate marker for heart disease has been questioned[3]. In addition, the validity of surrogate endpoints requires a prospective study that is adequately powered in order to demonstrate that the endpoint is able to predict future events[3].

The ENHANCE trial results showed that the changes in mean IMT of the carotid and femoral arteries, the primary endpoint, were not statistically significant (P=0.29). However, the trial showed statistically significant (P<0.01) reductions in LDL, triglycerides and C-reactive protein (CRP). The difference between the two groups in reductions in levels were a 16.5% mean reduction of LDL cholesterol, a 6.6% median reduction of triglycerides and 25.7% in the median reduction of CRP, respectively. Even though the overall incidence of cardiovascular events was similar between both groups in the ENHANCE trial, the trial did not have enough patients to reliably test whether treatment with Vytorin reduces the risk of cardiovascular events compared to simvastatin/placebo .

The Food and Drug Administration[6] released a statement before the study was published, urging patients to talk to their doctors if they have any questions about the ENHANCE trial. The American Heart Association[5] stated that statins are the only drug class for lowering cholesterol, for which there is evidence that heart attacks are prevented and life extended with their use. Patients who need to lower their cholesterol should continue taking the medications because discontinuing them can increase their health risks. Additionally, the American College of Cardiology recommendations are: 1) to achieve targets of LDL and HDL cholesterol (per current guidelines) with the use of statins plus drugs that have shown clinical benefits when added to statins, 2) use ezetimibe (Zetia) in patients who don't achieve target levels with statins and 3) avoid drawing conclusions, as the trial did not assess clinical outcomes[4].

In summary, the ENHANCE trial showed no significant changes in the intima-media thickness of patients with familial hypercholesterolemia in the Vytorin group compared to the simvastatin group. However, there were significant reductions in LDL, triglycerides, and CRP. Since the study was not adequately powered to assess the incidence of atherosclerotic events and a surrogate end-point was used, validity was not sufficient. From a pharmacoeconomic standpoint, there is much interest in this subject due to the cost discrepancy between the two products. The cost of Vytorin is approximately $3 per pill, as compared to the cost of generic simvastatin at $1 per pill[3].

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Resistant Hypertension: An overview of etiology, diagnosis and treatment
by Gyliane Fouche

In a scientific statement published in April 2008, the American Heart Association (AHA) defines resistant hypertension as blood pressure that remains above goal in spite of the concurrent use of optimal doses of three antihypertensive agents of different classes, with one of these being a diuretic.[1] Although its prevalence is unknown, clinical trials suggest that resistant hypertension is quite common. [1] Older age, obesity, diabetes, chronic kidney disease (CKD), and left ventricular hypertrophy (LVH), are strong predictors of treatment resistance. Genetic factors play a role as well but have not been widely studied. In evaluating patients with severe hypertension, care must be applied to identify true treatment resistance. Pseudoresistance must be ruled out by assessing patients' treatment adherence and blood pressure measurement technique.[1]

Studies have shown that certain lifestyle factors and classes of medications contribute to treatment resistance.[1] It is to be noted that obesity, excessive dietary sodium intake, and heavy alcohol intake are strong contributors to treatment-resistant hypertension. Nonsteroidal anti-inflammatory drugs (NSAIDs) are associated with significant fluid retention, increases in blood pressure, and/or kidney disease.[2] The use of corticosteroids can also result in fluid retention and significant increases in blood pressure. Other medications shown to worsen blood pressure include decongestants, amphetamine-like stimulants, oral contraceptives, and herbal products containing ephedra.[1, 3]

Resistant hypertension is frequently linked to secondary causes. Among the most common secondary causes are obstructive sleep apnea, primary aldosteronism, renal parenchymal disease, and renal artery stenosis. Other less common secondary causes of hypertension include pheochromocytoma, Cushing's syndrome, hyperparathyroidism, aortic coarctation, and intracranial tumors.[1] The likelihood of finding secondary causes of hypertension is greater in older patients.[1]

Resistant hypertension is almost always a result of a variety of factors and treatment regimens will be influenced by these factors. Nonpharmacological recommendations include weight loss, dietary salt restriction, and moderation of alcohol intake. Patients already on antihypertensive therapy have been found to reap the greatest benefits from weight loss. The results of long-term studies on weight loss indicate that a 10-kg weight loss is associated with an average 6.0-mm Hg reduction in systolic and a 4.6-mm Hg reduction in diastolic blood pressure.[4] Dietary restriction to less than 2300 mg of sodium in 24 hours is ideally recommended, and daily intake of alcohol is recommended not to exceed one or two drinks per day. A meta-analysis of studies on the effects of routine aerobic exercise on blood pressure suggests that a regular aerobic exercise regimen produces average reductions of 4-mm Hg in systolic and 3-mm Hg in diastolic blood pressure.[1]

Patients with resistant hypertension usually have inappropriate volume expansion, which makes the use of a diuretic essential in maximizing blood pressure control. A long-acting thiazide is appropriate for most patients. Studies have shown chlorthalidone to be the preferred agent due to its superior efficacy compared with hydrochlorothiazide. It is, however, available in few fixed-dose combinations and requires more than once-daily dosing. A loop diuretic such as torsemide or furosemide may be helpful in patients with underlying chronic kidney disease. Studies have shown that the use of two antihypertensive agents from different classes significantly improved blood pressure control. Combination therapy that included a diuretic was consistently found more effective. Data on the efficacy of specific combinations of three or more agents is limited. Therefore, recommendation of specific multidrug combinations is empiric.[1] Pharmacological treatment combining agents with different mechanisms of action seem appropriate. A combination of an ACE inhibitor or ARB, a calcium channel blocker, and a thiazide diuretic has been found effective and generally well tolerated. Ultimately, however, combination therapy should be tailored to the individual specific needs, taking into consideration contributing factors, history of adverse events, and patient financial limitations. Medications that are known to interfere with blood pressure control, such as NSAIDs, should be avoided or be used at the lowest effective dose in patients with resistant hypertension. Patient compliance should be encouraged by the use of long-acting combination agents that allow for once daily dosing.[1]

More studies are needed to better identify underlying mechanisms of treatment resistance and to assess the efficacy of specific multidrug regimens. However, patients with resistant hypertension usually have concomitant disease processes which limit the type and duration of experimental interventions. Differentiation of subgroups based on etiologies is necessary to identify respective causes of treatment resistance and to develop specific treatment strategies. Much progress needs to be made in this direction and in identifying underlying genetic causes of resistant hypertension.[1]

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Creighton University Center for Drug Information & Evidence-Based Practice
2500 California Plaza
Omaha, NE 68178

Contact us:
Telephone: 402-280-5100
800-561-3728

Fax: 402-280-5149

Email: druginfo@creighton.edu

Editor:

Amy Friedman Wilson, PharmD.
Director, Center for Drug Information & Evidence-Based Practice