Simvastatin-Associated Memory Loss

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The statins are widely used to treat dyslipidemias. They are generally associated with mild adverse effects, but rarely, more serious reactions may occur. A 51-year-old man experienced delayed-onset, progressive memory loss while receiving simvastatin for hypercholesterolemia. His therapy was switched to pravastatin, and memory loss resolved gradually over the next month, with no recurrence of the adverse effect.
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As an adjunct to dietary modifications, simvastatin commonly is used to treat dyslipidemias to lower elevated total cholesterol, low-density lipoprotein (LDL), apolipoprotein B (Apo B), and triglyceride (TG) levels, and to increase high-density lipoprotein (HDL) levels. Adverse effects are usually mild and include nausea, diarrhea, headache, and elevated hepatic transaminases. More serious side effects include myopathy, which may lead to rhabdomyolysis, hepatitis, and fulminant hepatic failure. Central nervous system (CNS) effects, particularly the propensity to reduce duration of sleep in some patients, has been reported with 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors.[1, 2] We describe a patient who developed memory loss while receiving simvastatin.

Case Report

A 51-year-old white man with a history significant for hepatitis C, coronary artery disease with coronary artery bypass graft and angioplasty with arthrectomy, and lumbar microdiskectomy for lower back pain, was prescribed simvastatin 40 mg at bedtime for hypercholesterolemia. He had no history of smoking or alcohol abuse and no psychiatric history or prior memory loss. He was taking enteric-coated aspirin 325 mg once/day, folic acid 0.4 mg once/day, vitamin C 500 mg once/day, and a multivitamin once/day. He took no other vitamins, herbal products, or dietary supplements.

After approximately 12 months, the patient began to experience slow-onset, short-term memory loss that progressively worsened over the next 3 months. In fact, he had trouble finishing his own sentences as he would forget what he was saying. The memory loss was attributed to simvastatin, which was discontinued; pravastatin 40 mg at bedtime was started. The patient's short-term memory loss resolved completely after approximately 1 month, and he reported no other adverse effects. His cholesterol measurements reached goal levels, and his hepatic transaminase levels were within normal limits.

Discussion

The HMG-CoA reductase inhibitors, also known as the statins, reduce the risk of primary and secondary coronary heart disease and total mortality as shown in large-scale, randomized, controlled clinical trials.[3, 4] Overall, these drugs reduce the risk of major coronary events by 26–36% and reduce the risk of death from any cause by 14–28%.[3] Statins also reduce the risk of angina pectoris and cerebrovascular accidents, and decrease the need for coronary artery bypass grafting and angioplasty.[4–7] The six statins available in the United States (atorvastatin, cerivastatin, fluvastatin, lovastatin, pravastatin, simvastatin) all act primarily by competitively inhibiting HMG-CoA reductase, which is the last regulatory step in the synthesis of cholesterol.[5–7]

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Simvastatin (on formulary at our institution) and pravastatin (nonformulary), along with the other drugs in this class, are well tolerated in the general population. Although the agents are mevinic acid-derivatives and have similar mechanisms of action and the same pharmacologic effect, they have important differences in their chemical structures, which affects their relative lipophilicity. Simvastatin has a methyl substituent attached to the hexahydronaphthalene nucleus, which increases its lipophilicity, whereas pravastatin has a hydroxyl substituent, which increases its hydrophilicity.[8] In addition, simvastatin's closed lactone ring enhances its lipophilicity compared with pravastatin, which is the only statin administered in the hydroxy acid form. A more lipid-soluble closed lactone HMG-CoA reductase inhibitor, such as simvastatin, may have a greater propensity for crossing the blood-brain barrier and affecting CNS activity, even though only very low levels have been found in human cerebral spinal fluid.[8] Pravastatin is the most hydrophilic polar statin, followed in decreasing hydrophilicity by cerivastatin and fluvastatin, atorvastatin, lovastatin, and simvastatin. Cerivastatin and fluvastatin are considered water soluble. Atorvastatin is only slightly water soluble. Lovastatin is more lipophilic, and simvastatin, which is 194 times more lipophilic than pravastatin, is by far the most lipophilic of the statins.[8]

Pharmacokinetic variability also contributes to the differences among the statins. After oral administration, only about 5% and 17% of the doses of simvastatin and pravastatin, respectively, reach the general circulation as active drug.[6, 7] This low bioavailability is due to incomplete absorption and extensive first-pass hepatic metabolism. Both drugs undergo extensive hepatic metabolism. Simvastatin is an inactive prodrug that requires hepatic activation through hydrolysis to β-hydroxyacid, an active inhibitor of HMG-CoA reductase. Other hepatic metabolites are 6-hydroxy, 6-hydroxymethyl, and 6-exomethylene (as well as other derivatives). Pravastatin is inherently active and undergoes extensive first-pass hepatic metabolism to its primary metabolites—the 3-α-hydroxy isomer and the 3-α-, 5-β-, and 6-β-trihydroxy metabolite. Unlike simvastatin's metabolites, pravastatin's metabolites are not active in the inhibition of HMG-CoA reductase.[6, 7]

Simvastatin is highly protein bound (95%) compared with pravastatin (43–55%). Both simvastatin and pravastatin potently inhibit cholesterol synthesis in liver cells. Pravastatin is unique in that it is the only statin that undergoes selective uptake into hepatocytes. Due to its low lipid solubility, a carrier-mediated transport process specific to hepatocytes is necessary for cellular uptake.[8] Simvastatin has passed the blood-brain barrier in in vitro studies, whereas pravastatin does not distribute into cerebrospinal fluid. Both drugs undergo significant biliary excretion, with 60% of simvastatin and 71% of pravastatin appearing in the feces after oral administration. Thirteen percent of simvastatin and 20% of pravastatin are excreted renally. Neither compound is significantly affected by renal dysfunction, and dosage reductions are not necessary in patients with mild to moderate renal insufficiency.[6, 7]

Statins generally are tolerated better than other lipid-lowering drugs. However, mild, transient gastrointestinal disturbances and muscle aches occurred, and hepatitis, myopathy, rash, insomnia, disturbing or vivid dreams, and difficulty sleeping or concentrating were reported rarely. Dysfunction of certain cranial nerves (resulting in alteration of taste, impairment of extraocular movement, and facial paresis), tremor, dizziness, vertigo, memory loss, paresthesia, peripheral neuropathy, peripheral nerve palsy, psychiatric disturbances, anxiety, insomnia, and depression were reported during clinical trials.[1, 5–7] Memory loss associated with the statins is listed in the manufacturers' product information.[6, 7, 9–12]

Two clinical trials were designed to evaluate the effect of simvastatin or pravastatin on cognitive function. One study compared the effects of these agents on measures of CNS activity: electroencephalogram (EEG) evoked potentials, mood, sleep, or cognitive performance.[13] This double-blind, placebo-controlled, crossover study randomized 25 healthy volunteers to 4 weeks each of simvastatin 40 mg, pravastatin 40 mg, and placebo in random order. Each treatment period was followed by a 4–6-week washout period. Cognitive function was evaluated by the digit symbol substitution test, and no statistically significant differences were found between treatment groups. The study had 90% power to detect differences at the 0.05 significance level. Subjects reported significantly greater difficulty falling asleep while receiving simvastatin compared with pravastatin but neither differed from placebo. The investigators concluded that neither drug exerts significant

CNS effects compared with placebo on EEG evoked potentials, mood, sleep, or cognitive performance after 4 weeks.

Another study used a double-blind, crossover design to evaluate changes in cognitive function after treatment with simvastatin or pravastatin.[14] Thirty-six patients with hypercholesterolemia were randomized to simvastatin 20 mg, pravastatin 40 mg, or placebo taken with the evening meal for 4 weeks, followed by a 1-week washout period. Patients then were crossed over to receive one of the other treatments for 4 weeks. Objective tests to evaluate cognitive function, such as the digit symbol substitution, auditory vigilance, selective reminding word recall, choice reaction time, and finger tapping, were done at baseline and after 2 and 4 weeks of treatment. The study had 80% power to detect a difference between any two treatments of six substitutions in the digit symbol substitution test. There was no statistically significant difference in cognitive function after 4 weeks in each active treatment group compared with placebo.

Our patient developed slowly progressive memory loss while receiving simvastatin. The onset of this reaction occurred after approximately 12 months of exposure to simvastatin, and continued to worsen over the next 3 months. Studies evaluating simvastatin's CNS side effects are few and of relatively short duration. If memory loss is a rare and delayed effect of simvastatin, it may not have manifested during the 4-week duration of these studies. To our knowledge, this is the first reported case of simvastatin-associated memory loss. It is not possible to establish causality of memory loss with simvastatin in our patient, as he was not rechallenged. However, on dechallenge the patient's symptoms slowly resolved, and he tolerated pravastatin without a similar reaction. Therefore, we believe that our patient's symptoms had a possible association with simvastatin.

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