# PEDIATRIC PHARMACOTHERAPY

A Monthly Newsletter for Health Care Professionals from the Children's Medical Center at the University of Virginia

Volume 8 Number 9 September 2002

## HMG-CoA Reductase Inhibitors for the Treatment of Hypercholesterolemia in Children and Adolescents

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The treatment of elevated blood lipid levels has been dramatically altered by the introduction of the HMG-CoA reductase inhibitors, also known as the statins, during the last decade. As the use of these agents has become more widespread in adults, investigators have begun to study their effects in pediatric patients. The target pediatric populations for lipid reduction include children with homozygous or heterozygous familial hypercholesterolemia (FH) and children with hypercholesterolemia related to other disease states or congenital syndromes.[1-3]

Mechanism of Action

The enzyme 3-hydroxy-3-methyl-glutaryl-co-enzyme A (HMG-CoA) reductase catalyzes the conversion of HMG-CoA to mevalonate. By competitively blocking this enzyme, the HMG-CoA reductase inhibitors interfere with cholesterol formation. As a result, they decrease total cholesterol, low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (a membrane transport complex for LDL-C), very low-density lipoprotein (VLDL), and plasma triglycerides. They also increase serum concentrations of high-density lipoprotein cholesterol (HDL).[4-9]

Indications

There are currently five drugs within this therapeutic class on the market in the United States: lovastatin, simvastatin, pravastatin, fluvastatin, and atorvastatin. All are indicated for the treatment of hypercholesterolemia in adults. They each carry additional indications, such as treatment of mixed dyslipidemia, hypertriglyceridemia, dysbetalipoproteinemia, heterozygous or homozygous FH, or primary and/or secondary prevention of cardiovascular events. A sixth agent, rosuvastatin, will likely enter the market within the next year.

Although nearly all of the HMG-CoA reductase inhibitors have been used in children, only lovastatin is approved by the Food and Drug Administration (FDA) for use in pediatric patients. On February 21, 2002, the FDA approved the use of lovastatin as an adjunct to diet to reduce total cholesterol, LDL-C, and apolipoprotein B levels in adolescent boys and girls who are at least one year postmenarche who have heterozygous FH. The criteria for use in pediatric patients are based on the National Cholesterol Education Program goals: 1) an LDL-C > 189 mg/dl despite diet therapy or 2) an LDL-C > 160 mg/dl in patients with either a family history of premature cardiovascular disease or two or more risk factors for cardiovascular disease.[5]

Clinical Trials

There are several trials demonstrating the efficacy of the HMG-CoA reductase inhibitors in children and adolescents with heterozygous FH.[10-14] In 1996, Lambert and colleagues conducted a multicenter, randomized, double-blind study of lovastatin in 69 male adolescents with FH.[10] After a 4 week placebo phase, patients were randomized to receive lovastatin at a dose of 10, 20, 30, or 40 mg/day for 8 weeks. All doses effectively reduced total cholesterol (17-29%), LDL-C (21-36%), and apolipoprotein B (19-28%). A dose-response relationship was observed, with improvement up to the 30 mg/day dose. No serious adverse effects were noted. Minor elevations in liver function studies occurred, and three patients had transient, asymptomatic elevations in creatine kinase.

Stein and colleagues found similar efficacy after long-term lovastatin use.[11] In a year-long multicenter trial, 132 boys between 10 and 17 years of age with FH were randomized to receive placebo or lovastatin at doses of 10 to 40 mg/day. LDL-C levels were significantly decreased in the patients receiving lovastatin

(mean 190.9 versus 244.8 mg/dl) and remained at least 25% lower than baseline at the end of 48 weeks. Growth and development were not adversely affected by lovastatin use.

Pravastatin has produced results similar to those seen with lovastatin. In 1996, Knipscheer and coworkers studied pravastatin in 72 children (8-16 years of age) with heterozygous FH.[12] Doses of 5, 10, and 20 mg/day were compared to placebo in this 12-week double-blind, randomized study. Total cholesterol and LDL-C values were reduced in all three treatment groups, with a mean decrease of 24.6% and 32.9%, respectively. Four of the 72 children achieved normal values for age. VLDL and apolipoprotein B also decreased. HDL levels increased only in the 20 mg/day group. No significant adverse effects were noted.

In 1999, Stefanutti and colleagues demonstrated the efficacy of simvastatin in 16 children with FH.[13] All of the children were placed on a low-fat diet for 6 months, then randomized to diet and simvastatin (10 mg/day) or diet alone for an additional 6 months. The authors found a significant improvement with the addition of simvastatin. A recent paper by Vohl et al in *Atherosclerosis* produced further evidence of the efficacy of simvastatin.[14] In this 6-week double-blind trial, 63 children (8-17 years of age) were randomized to receive either 20 mg/day of simvastatin or placebo. Patients were divided by LDL receptor gene mutation. Those with a receptor-negative mutation had an average reduction in LDL-C of 39%, while those with the receptor-defective mutation had a 31% reduction. In both groups, the reduction compared to placebo controls was statistically significant.

In addition to their use in FH, the HMG-CoA reductase inhibitors have been studied for the management of elevated serum lipids in children with nephrotic syndrome, after cardiac transplantation, in Niemann-Pick disease type C, and in Smith-Lemli-Opitz syndrome.[15-18]

Adverse Effects

The HMG-CoA reductase inhibitors are well tolerated by most patients. The most commonly reported adverse effects in adult and pediatric trials include: headache (2-12% of subjects), dizziness or asthenia (0.5-3%), insomnia and paresthesias (0.5-2%), nausea and/or vomiting (2-7%), diarrhea or constipation (1-6%), abdominal discomfort (1-5%), rash and pruritus (1-4%), and myalgia or arthralgia (1-3%). For most patients, these symptoms resolve within the first month of treatment without altering or discontinuing therapy. In clinical trials of adults, 1-3% of subjects withdrew because of adverse effects, most often for elevations in serum transaminases and unremitting adverse gastrointestinal symptoms.[4-9,19]

Elevations in serum transaminases ($\geq$ 3 times the normal limit) have been reported in 0.5-2% of patients on HMG-CoA reductase inhibitors. This adverse effect appears to be dose-related and can often be reversed with a reduction in dose. Despite the frequency of transaminase increases, progression to hepatic failure is rare. It is recommended that liver function tests be done prior to starting therapy, within 12 weeks of initiation, and on a 6 to 12 month basis thereafter. Serum transaminases should also be evaluated after dosage adjustments.[4-9,19,20]

All of the HMG-CoA reductase inhibitors are capable of producing myopathy. While most patients exhibit only mild, transient muscle aches during treatment, approximately 0.8-1% of patients will develop severe myositis, with significant muscle weakness and elevations in creatine kinase (CK). Rarely, myositis will progress to rhabdomyolysis, and may be complicated by acute renal failure secondary to myoglobinuria. In August 2001, Bayer voluntarily withdrew cerivastatin (Baycol®) from the market because of its higher association with serious myopathy, including rhabdomyolysis, relative to the other agents in the class. At the time of cerivastatin's withdrawal, the FDA had received 31 reports of patient death due to rhabdomyolysis, 12 of which involved combined therapy with gemfibrozil. It is estimated that as many as 100 deaths may have occurred world-wide. The FDA reports a relative risk of fatal rhabdomyolysis with cerivastatin 16 to 80 times that of any other HMG-CoA reductase inhibitor. There appears to be no significant difference in risk among the remaining agents.[20]

Patients and their families should be instructed to immediately report symptoms of muscle pain, tenderness, or weakness, as well as the appearance of dark or brown urine. In patients with symptoms, CK levels should be assessed and therapy discontinued if CK levels are greater than 10 times normal. If needed, therapy may be resumed at a reduced dose once CK levels have returned to normal. Milder symptoms and smaller CK elevations may not require discontinuation of therapy. The utility of a baseline CK measurement is still being debated, but routine monitoring of CK in the absence of symptoms is not recommended. The risk of myopathy is known to be increased with higher doses and in patients receiving concomitant therapy with gemfibrozil and other fibrates or

drugs which block the metabolism of the HMG-CoA reductase inhibitors.[4-9,19,20]

Rare, serious adverse effects with the HMG-CoA reductase inhibitors include peripheral neuropathy and hypersensitivity reactions. Photosensitivity has also been reported, and patients should be instructed to minimize sun exposure. The HMG-CoA reductase inhibitors are contraindicated in pregnancy. Although there are no specific reports of teratogenicity in humans, administration to pregnant animals resulted in skeletal malformations in their offspring. Adolescent girls and young women taking HMG-CoA reductase inhibitors should be counseled about the need for contraception.[4,21,22]

Drug Interactions

There are a number of drug interactions with the HMG-CoA reductase inhibitors (Table).[4] The clinical significance of these interactions varies within the class, especially those interactions mediated through inhibition of the cytochrome P450 3A4 isozyme. For specific recommendations, refer to the product prescribing information.[5-9]

Table. HMG-CoA Reductase Inhibitor Drug Interactions

| *Interacting Agent* | *HMG-CoA Reductase Inhibitor* | *Outcome* |
|---|---|---|
| antacids | atorvastatin | ↓ conc. of atorvastatin |
| azole antifungals<br>clarithromycin<br>cyclosporine<br>erythromycin<br>grapefruit juice<br>nefazodone<br>protease inhibitors | all<br>-more significant with<br>lovastatin<br>simvastatin<br>atorvastatin | ↑ conc. of statin with ↑ risk of myopathy |
| amiodarone<br>gemfibrozil<br>niacin (rare)<br>verapamil | all | ↑ risk of myopathy |
| bile acid sequestrants (cholestyramine, colestipol) | all | ↓ absorption (take statin 1 hr before or 4 hours after) |
| cimetidine<br>ranitidine<br>omeprazole | fluvastatin | ↑ conc. of fluvastatin |
| diclofenac | fluvastatin | ↑ conc. of diclofenac |
| digoxin | lovastatin<br>pravastatin | ↑ conc. of digoxin |
| glyburide | fluvastatin | ↑ conc. of glyburide |
| isradipine | lovastatin | ↓ conc. of lovastatin |
| oral contraceptives | atorvastatin | ↑ conc. of oral contraceptives |
| phenytoin | fluvastatin | ↑ conc. of both |
| rifampin | fluvastatin | ↓ conc. of fluvastatin |
| warfarin | lovastatin<br>simvastatin | ↑ PT/INR |

Products and Dosing Recommendations

Lovastatin (Mevacor® or generic) is available in 10, 20, and 40 mg tablets. The recommended starting dose for adolescents (10-17 years of age) and adults requiring a 20% or greater reduction in LDL-C is 20 mg given once daily. Titration may continue up to 40 mg/day in adolescents and 80 mg/day in adults, given in one or two divided doses. Patients requiring a smaller reduction in LDL-C should begin therapy at 10 mg/day. Patients taking cyclosporine or with severe renal dysfunction should begin therapy with a lovastatin dose of 10 mg/day, with a maximum of 20 mg/day after titration.[5]

Simvastatin (Zocor®) is available in 5, 10, 20, 40, and 80 mg tablets. In adults, the recommended starting dose is 20 mg given once daily. The dosage range is 5-80 mg/day, given in 1 to 3 divided doses. In adults with homozygous FH, a higher starting dose of simvastatin is recommended, either 40 mg/day given once daily or 80 mg/day given in two or three divided doses. In patients taking cyclosporine or with severe renal dysfunction (creatinine clearance < 30 ml/min), the initial dose should be 5 mg/day, with a maximum of 10 mg/day.[6] Doses of 10 to 20 mg/day have been used in children with FH or nephrotic syndrome.[13-15] In two infants with Smith-Lemli-Opitz syndrome, simvastatin doses of 0.2-1 mg/kg/day were found to be effective.[18]

Pravastatin (Pravachol®) is available in 10, 20, 40, and 80 mg tablets. The initial adult dose is 40 mg/day. The dose may be increased to a maximum of 80 mg/day, if needed. The initial dose should be reduced to 10 mg/day for patients with significant renal or hepatic dysfunction or in patients taking cyclosporine.[7] In pediatric patients, effective pravastatin doses have ranged from 5 to 20 mg/day.[12,17]

Fluvastatin (Lescol®) is available in 20 and 40 mg capsules and an 80 mg extended-release product (Lescol XR®). In adult patients, therapy should begin with a dose of 40 to 80 mg/day. A lower dose of 20 mg/day may be used in patients requiring less than a 25% reduction in LDL-C levels. Since less than 10% of a fluvastatin dose is excreted unchanged, no dosage adjustment is needed for patients with renal dysfunction.[8]

Atorvastatin (Lipitor®) is available in 10, 20, 40, and 80 mg tablets. The recommended starting dose in adults is 10 or 20 mg/day, with a treatment range of 10-80 mg/day. No adjustment is necessary in patients with renal dysfunction.[9] There are no pediatric dosing recommendations for fluvastatin and atorvastatin at this time.

All of these agents may be taken without regard to meals, although lovastatin concentrations are greater when taken with food. HMG-CoA reductase inhibitors may be taken at any time of day, but it is recommended that once daily doses be given in the evening to coincide with the natural peak in cholesterol synthesis. Dosage adjustments for the HMG-CoA reductase inhibitors should be made at monthly intervals.[4-9]

Summary

The HMG-CoA reductase inhibitors have had a significant impact on the prevention of cardiovascular disease in adults. They effectively reduce cholesterol, as well as other byproducts of cholesterol synthesis, and are generally well tolerated. Based on their success in adults, investigators are now evaluating their potential in children with familial hyperlipidemia or dyslipidemias associated with other disease states. While the results of short-term trials look promising, more longitudinal studies are needed to clarify the role of HMG-CoA reductase inhibitors in the pediatric population.

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## Pharmacology Literature Review

Drug information software for PDAs

Clinical pharmacists at St. Louis College of Pharmacy reviewed nine drug information software programs for personal digital assistants (PDAs). The authors rated the systems on breadth and dependability, as well as ease of use. The LexiComp Platinum package received the highest rating, followed in order by Trascon's Pharmacopoeia, MosbyDrugs, ePocrates, Davis's Drug Guide for Physicians, PDR 2001, Physician's Drug Handbook, A to Z Drug Facts, and mobileMicromedex. Exact rankings are provided, as well as cost, memory size, and frequency of updates. Enders SJ, Enders JM, Hostad SG. Drug information software for Palm operating system personal digital assistants: breadth, clinical dependability, and ease of use. **Pharmacotherapy 2002;22:1036-40.**

## Formulary Update

The Pharmacy and Therapeutics Committee met on 8/23/02. No Formulary actions were taken.


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