Chapter

Lipid-Lowering Medications

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Abstract

In the last decades, there has been an important progression in the development and assessment of various cholesterol-lowering agents. Until recently, in children under age 10, the focus of treatment has been on dietary and lifestyle adjustments. For children older than 10 years, bile acid-binding resins were also recommended if LDL-C levels remained high after dietary adjustment. However, the lipid-lowering effect of bile acid-binding resins is modest at best and long-term compliance is often poor. In contrast, HMG-CoA reductase inhibitors (statins) are currently widely used in adults and are considered the first choice in the treatment of hypercholesterolemia. In the last few years, several randomized trials have shown that statins are also effective in reducing LDL cholesterol levels in children and seem safe at least in the short term. Another novel development is the cholesterol-lowering agent, ezetimibe, which inhibits cholesterol absorption in the intestine. Although efficacy and safety data in children are still lacking, ezetimibe has a good safety profile in adults, either as monotherapy or in combination with a statin. Lastly, two other classes of lipid-lowering drugs include fibrates and nicotinic acid, but most agree that the side effect profile precludes their use in children except in extreme circumstances. Overall, therapeutic options to lower cholesterol levels in children are expanding.
Introduction

Low-density lipoprotein cholesterol (LDL-C) reduction is a pivotal factor in the prevention of coronary heart disease (CHD). In the last decades, there has been an important progression in the development and investigation of various cholesterol-lowering agents. The most important pediatric target population for lipid reduction includes children with homozygous or heterozygous familial hypercholesterolemia (FH). FH is a common and inherited metabolic disorder of lipoprotein metabolism and it is clinically characterized by elevated levels of total cholesterol (TC) and LDL-C from birth onwards, due to mutations in the LDL receptor gene. Below we will provide an overview of the effects, mechanisms of action, and side effects of various cholesterol-lowering modalities that are used or considered for use in the pediatric population. The following agents will be discussed: bile acid-binding resins, statins, fibrates, nicotinic acid, and ezetimibe (Table 1).

Indications for use of cholesterol-lowering drugs

Currently, pharmacological therapy to lower cholesterol is reserved for children and adolescents over the age of 10 years. The decision to treat with a drug is primarily based on the concentration of LDL-C. The National Cholesterol Education Program (NCEP) recommends that pharmacological therapy be considered in patients whose LDL-C is above 160 mg/dL (4.1 mmol/L) when other cardiovascular disease risk factors are present, or above 190 mg/dL (4.9 mmol/L) when no other risk factors are present. Risk factors include hypertension, diabetes mellitus, obesity, or a strong family history of cardiovascular disease. Pharmacological therapy should be instituted when cholesterol levels remain persistently above the cutoff points despite dietary and other lifestyle intervention. Recently, the NCEP guidelines for adults have become more stringent. This could provide a stimulus for updating the guidelines for children as well. In children and adolescents drug therapy is indicated in both primary and secondary hypercholesterolemia. Primary hypercholesterolemia includes all forms of hypercholesterolemia due to an increase of plasma LDL-C for which there is no identifiable...
Table: Overview of lipid-lowering medication for children.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Available doses</th>
<th>Recommended maximum dose in children</th>
<th>LDL-C reduction (%)</th>
<th>Place of action</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bile-acid binding resins</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Cholestyramine</td>
<td>Sachets of 4 g</td>
<td>24 g</td>
<td>15-20</td>
<td>Bind bile-acids in the intestinal lumen</td>
</tr>
<tr>
<td>Colestipol</td>
<td>Tablet 1 g</td>
<td>20 g</td>
<td></td>
<td></td>
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<tr>
<td>Colesevelam</td>
<td>Sachets of 5 g</td>
<td>nda</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tablet 625 mg</td>
<td>nda</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>HMG-CoA reductase inhibitors (statins)</strong></td>
<td></td>
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<tr>
<td>Atorvastatin</td>
<td>10-20-40 mg</td>
<td>&lt; 40 mg</td>
<td>17-45^c</td>
<td>Inhibit 3-hydroxy-3-methylglutaryl coenzyme reductase and thereby the cholesterol synthesis in the liver.</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>20-40-80 mg</td>
<td>nda</td>
<td></td>
<td></td>
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<tr>
<td>Lovastatin</td>
<td>10-20-40 mg</td>
<td>&lt; 40 mg</td>
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<td></td>
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<tr>
<td>Pravastatin</td>
<td>10-20-40 mg</td>
<td>&lt; 40 mg</td>
<td></td>
<td></td>
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<tr>
<td>Rosuvastatin</td>
<td>10-20-40 mg</td>
<td>nda</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simvastatin</td>
<td>5-10-20-40 mg</td>
<td>&lt; 40 mg</td>
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<td></td>
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<tr>
<td><strong>Fibric acid derivates</strong></td>
<td></td>
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<tr>
<td>Bezafibrate</td>
<td>200-400 mg</td>
<td>400 mg</td>
<td>41^d</td>
<td>Alter the transcription of genes encoding proteins, that control lipoprotein metabolism and vascular inflammation, via peroxisome proliferators-activated receptors (PPAR’s)</td>
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<tr>
<td>Ciprofibrate</td>
<td>100 mg</td>
<td>nda</td>
<td></td>
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<tr>
<td>Clofibrate</td>
<td>60-600 mg</td>
<td>nda</td>
<td></td>
<td></td>
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<tr>
<td>Fenofibrate</td>
<td>54-160 mg</td>
<td>300 mg</td>
<td></td>
<td></td>
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<tr>
<td>Gemfibrozil</td>
<td>600 mg</td>
<td>nda</td>
<td></td>
<td></td>
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<tr>
<td><strong>Nicotinic acid</strong></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Immediate-release</td>
<td>100-250-500 mg</td>
<td>20 mg/kg</td>
<td>30^d</td>
<td>Inhibit hepatic triglyceride synthesis and lipolysis and the hepatic removal of lipoprotein A1</td>
</tr>
<tr>
<td>Extended-release</td>
<td>250-375-500-750-1000 mg</td>
<td>20 mg/kg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long-acting</td>
<td>100-400-500 mg</td>
<td>nda</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>10 mg</td>
<td>10 mg^e</td>
<td>18^e</td>
<td>Inhibit the passage of sterols of dietary and biliary origin across the intestinal wall</td>
</tr>
</tbody>
</table>

^a the maximum doses that have been studied in children with heterozygous FH. ^b no data available in children and the drug has not been registered for children. ^c effect depends on dose and type of statin. ^d the LDL-C reduction is based on data from only one study in children. ^e there are no data available of ezetimibe in children and the LDL-C reduction of 18% is based on studies in adults. Ezetimibe has been registered for children from the age of 10 years. LDL=Low-density lipoprotein. g=gram, mg=milligram kg=kilogram

Secondary cause. In secondary hypercholesterolemia, the underlying cause should be treated first, with consequent treatment of hypercholesterolemia. Secondary hypercholesterolemia can be caused by a variety of medical conditions including poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemias, obstructive liver disease, certain drug therapy, and alcohol abuse.
Bile acid-binding resins

Indications for use
The currently recommended therapy for hypercholesterolemia consists of bile acid-binding resins (or lovastatin or pravastatin in the US; see section about statins) in children older than 10 years. In adults, the bile acid-binding resin, cholestyramine, is also indicated to relieve pruritus related to bile salts in case of biliary obstruction.

Mechanism of action
Cholesterol that is absorbed in the intestine or synthesized in the liver is eliminated primarily by conversion into bile acids and subsequent excretion in bile. After a fatty meal, bile is secreted into the proximal intestine. A large proportion of bile acids is then reabsorbed and returns to the liver, which represents the enterohepatic circulation. Resins bind to bile acids in the intestinal lumen by forming an insoluble complex that is excreted via the feces. The latter prevents the enterohepatic recirculation of bile acids and increases their excretion. Reduction of the hepatic bile-acid pool leads to an increased oxidation of cholesterol to bile acids, which reduces the hepatocellular cholesterol content. Consequently, hepatic synthesis of cholesterol will increase, but, additionally, LDL receptors on liver cell surfaces will be upregulated. The overall consequence of these changes is a decrease in plasma LDL-C levels.

Dose range and rationale
The available resins are cholestyramine, colestipol, and recently colesvelam in the US, all of which are intended for oral administration. Certain resins are administered as powders mixed with liquid: cholestyramine is available in sachets of 4 g and colestipol in sachets of 5 g. Colestipol is also available in tablets of 1 g. Colesevelam is only available in 625-mg tablets. The powders are taken once, twice, or even sometimes three times daily with meals depending on the dose. Children start with 1 sachet, taken shortly before or with a meal. Subsequently, the daily dose may be increased to 6 sachets, divided into two or more doses. Recommended daily doses of the tablets, albeit in adults, are 2-16 g of colestipol and 3.75 g of colesvelam, taken with meals. However, in practice, doses above 8 g per day do not improve cholesterol levels and are associated with increased side effects. West et al showed that, during eight years of
study, cholestyramine at a dose of 0.4 g/kg/d reduced LDL-C levels by 26 to 44% in 35 children with FH between ages 1.3-17.4 years\(^4\). Also, in a three-week study in 13 children, Farrah et al. showed that cholestyramine, at a dose that was increased daily by 1 g/d up to 16 g/d, reduced cholesterol by about 40%\(^5\). However, many others have shown considerably less efficacy\(^6-10\). In fact, several recent trials using bile acid-binding resins have shown a maximum LDL-C reduction of 20%. In particular, one study of 71 children with FH measured the effect of diet alone or diet plus resin for on average 14.5 months. Fifteen subjects received cholestyramine (0.6 g/kg/d, maximal dose 20 g/d) and two received colestipol (0.6 g/kg/d, maximal dose 20 g/day). Resins reduced LDL-C by about 16% beyond the effects of diet alone\(^11\). Another placebo-controlled trial in 72 FH children, aged 6-11 years, showed that 8 g/d of cholestyramine for one year reduced LDL-C by 17% as compared to 1.4% in the placebo group\(^12\). The same investigators measured the effect of colestipol (10 g/d) in 76 children with FH, aged 10-16 years, in an 8-week placebo-controlled study. A 19.5% reduction in LDL-C levels was achieved in the colestipol group versus a 1% reduction in the placebo group\(^13\). Finally, eight weeks of treatment with cholestyramine in either a tablet or powder form reduced LDL-C by 10% and 15%, respectively, in 38 children with FH aged 10 to 18 years\(^14\). There are no studies in children addressing the efficacy of colesevelam, but, in adults, colesevelam reduced LDL-C by the same amount as the other resins\(^15\). Taking all studies together, the lipid-lowering effect of bile acid-binding resins is at best 15-20%. The maximum decrease in LDL-C is reached after six weeks of resin use.

### Adverse effects

Because bile acid-binding resins are not absorbed, the most common side effects are constipation, abdominal pain, bloating, vomiting, diarrhea, weight loss, and excessive flatulence. It has also been suggested that bile acid-binding resins might impair the absorption of fat-soluble vitamins and folate. Indeed, several studies in children using cholestyramine or colestipol showed a decrease in the plasma levels of folate, carotenoids, and fat-soluble vitamins\(^5,8,12,13,16\). However, if adjusted for cholesterol reduction, only folate and 25-hydroxyvitamin D seemed to be decreased by resin treatment\(^12,13\). Therefore, some advocate folate and vitamin D supplementation during resin treatment. No negative effects were reported in children regarding growth, development, or sexual maturation in any trial of resins\(^10,12,14,17,18\). Also, there were
no effects on liver enzymes or blood count\textsuperscript{12,14}. Nevertheless, due to the difficulty of taking these agents and their side effects, adherence to bile acid-binding resins is poor and there is a high drop-out rate\textsuperscript{4,12,13}. Children may be unwilling to take resins for long periods of time, particularly when the drug is started during adolescence\textsuperscript{4,9}. In one trial, the compliance and efficacy of two forms of cholestyramine resins were studied in 40 children with FH, aged 10-18 years. The children enrolled in a randomized, crossover trial of two eight-week periods of either a tablet or powder form of cholestyramine at a dose of 8 g/d. The mean compliance, as assessed by tablet or powder count, was significantly higher for tablets (61 vs 50\%)\textsuperscript{14}. In another trial with colestipol tablets, adolescents also preferred the tablets to resin granules that they had tried previously\textsuperscript{19}. Adverse effects with colesevelam tablets in adults have been minimal\textsuperscript{15} although there are no studies in children. It remains unknown whether long-term use of the tablets will result in a better compliance as compared to powder.

Pregnancy
The use of cholestyramine or colestipol for hypercholesterolemia in pregnant women has not been adequately evaluated. Because resins are hardly if at all absorbed into the circulation, they are not expected to have untoward consequences for the fetus when administered during pregnancy. Prolonged use of the resins, however, may result in decreased maternal absorption of folate and vitamin D\textsuperscript{20}. These drugs have also been used for the treatment of cholestasis during pregnancy, and no adverse consequences with regards to the fetus were observed. Thus, the use of cholestyramine may be safe during pregnancy\textsuperscript{20,21}. Conversely, the short-term interruption of cholesterol-lowering therapy during pregnancy probably does not influence the development of atherosclerosis. For this reason, we feel that resins should be discontinued during pregnancy and lactation.

Conclusion
Although bile acid-binding resins safely reduce plasma LDL-C levels by approximately 15\%, they are often difficult to take and long-term compliance is poor. Folate and vitamin D supplements should be considered with long-term resin treatment.
Chapter 6

Statins (HMG-CoA reductase inhibitors)

Indications for use
Statins are indicated for the treatment of both primary and secondary hypercholesterolemia. They are effective, safe, and well-tolerated lipid-lowering agents in adults. In fact, adults that are diagnosed with FH are currently undergoing lifelong treatment with statins. Six drugs are currently available within this therapeutic class: atorvastatin, fluvastatin, lovastatin, pravastatin, simvastatin, and recently rosuvastatin. In the US, the Food and Drug Administration (FDA) approved lovastatin in February 2002 for heterozygous FH adolescent boys and girls, the latter who are at least one year post-menarche. The FDA also approved pravastatin in October 2002 for the management of FH in children aged 8 years or older. In Europe, lovastatin is not available and therapy with any other statin is not yet approved for children by the European Agency for the Evaluation of Medicinal Products (EMEA) and, therefore, treatment of hypercholesterolemia in children is restricted to bile acid-binding resins only.

Mechanism of action
Statins inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, thereby blocking the conversion of HMG-CoA into mevalonic acid, the precursor of cholesterol. As cholesterol synthesis is reduced, the expression of the LDL receptors in the liver is upregulated to enhance uptake and catabolism of LDL particles. The effect is a reduced concentration of LDL-C in plasma. Statins also reduce levels of TC and triglycerides, and they increase levels of HDL-C. The mechanism by which statins increase HDL is unknown.

Atorvastatin is a synthetic lipid-lowering agent, which is extensively metabolized to ortho- and para-hydroxylated derivatives and various β-oxidation products. Approximately 70% of the inhibitory activity against HMG-CoA reductase is attributed to these active metabolites. Atorvastatin is metabolized by cytochrome P450 isoform 3A4 and is also highly bound to human plasma proteins.

Fluvastatin is a hydrophilic, synthetic cholesterol-lowering agent. The hydroxyl-metabolites have some pharmacological activity, but reach only a low plasma concentration. It is predominantly metabolized by cytochrome P450 isoform 2C9, with ~20% by cytochrome P450 isoform 3A4. It is also highly bound to plasma proteins.

Lovastatin is isolated from a strain of Aspergillus terreus and administered as an inactive
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lactone. It is readily hydrolyzed in vivo into the corresponding β-hydroxyacid form, which inhibits HMG-CoA reductase. Lovastatin is metabolized by the cytochrome P450 isoform 3A4. It is lipophilic and highly bound to plasma proteins.

**Pravastatin** is administered as an active compound and is not metabolized by cytochrome P450. Metabolites have one-tenth to one-fortieth of the HMG-CoA reductase inhibitory activity of the parent compound. It is relatively hydrophilic, and it is less completely bound to proteins in plasma (~50%).

**Rosuvastatin** is not extensively metabolized; approximately 10% is converted into metabolites which have a HMG-CoA reductase inhibitor activity that is one-sixth to one-half to that of rosuvastatin. Clearance is not dependent on metabolism by the cytochrome P450 isoform 3A4, but principally on conversion by the cytochrome P450 isoform 2C9. It is relatively hydrophilic and highly bound to plasma proteins.

**Simvastatin** is derived synthetically from a fermentation product of *Aspergillus terreus* and is administered as an inactive lactone. It is readily hydrolyzed in vivo into the corresponding α-hydroxyacid form, which inhibits HMG-CoA reductase. Simvastatin is metabolized by the cytochrome P450 isoform 3A4. It is lipophilic and highly bound to plasma proteins.

**Dose range and rationale**

Statins are administered as tablets. The pediatric doses of atorvastatin, lovastatin, pravastatin, and simvastatin that have been investigated range between 10-40 mg/day, with a therapeutic response that reaches a maximum within four to six weeks after start of the treatment.

**Atorvastatin:** In a three-year study with 16 children aged between 10-17 years, 10-40 mg of atorvastatin reduced LDL-C by 45%22. In a larger trial with 187 children of the same age group, 10-40 mg of atorvastatin reduced LDL-C by 40%23. Atorvastatin has not been registered for pediatric use in either the US or Europe.

**Lovastatin:** Two trials assessed the efficacy of lovastatin in children with FH. In 69 boys with a mean age of 12.8 years, eight weeks of treatment of 10 to 40 mg/d lovastatin reduced LDL-C by 21-36%24. In 132 boys aged 10-17 years, lovastatin treatment of 48 weeks in a dosage of 40 mg/d reduced LDL-C by 27% as compared to diet alone25,26. Lovastatin has not been registered for pediatric use in Europe, but has been approved in the US.
**Pravastatin:** Two studies have shown the efficacy and safety of pravastatin in children with FH. In a 12-week placebo-controlled trial, 5-20 mg/d of pravastatin reduced LDL-C by 23-32% in 72 children aged 8 to 16 years. In a two-year safety and efficacy study, 20-40 mg/d of pravastatin reduced LDL-C by 24% as compared to placebo in children aged 8 to 18 years. Pravastatin has not been registered for pediatric use in Europe, but has been approved for pediatric use in the US.

**Simvastatin:** The greatest number of studies in children and adolescents with FH has been carried out with simvastatin. In a short-term placebo-controlled study of six weeks, 20 mg/d of simvastatin reduced LDL-C by 31-38% in 63 children aged 8 to 17 years. LDL-C was reduced by 37% in 32 children younger than 17 years after two years of treatment with 10-40 mg/d simvastatin. In a larger placebo-controlled study, 48 weeks of treatment with 40 mg/d of simvastatin reduced LDL-C by 41% in 173 children aged 10-17 years. In a recent uncontrolled trial, LDL-C was reduced by 25-36% after one year of treatment with lower doses (5-20 mg/d) of simvastatin in 20 children and adolescents. Simvastatin has not been registered for pediatric use either in the US or Europe.

There are no published reports about the efficacy and safety of fluvastatin or rosuvastatin in children.

Thus, the LDL-C-lowering effect of statins in children with FH varies from 21-45%, depending on the dose and type of the statin used.

**Adverse effects**

Statins are well-tolerated by the vast majority of patients. The most common adverse effects observed in adults are: gastro-intestinal symptoms such as constipation, diarrhea, flatulence, dyspepsia, and abdominal pain. Other adverse effects include: myalgia, rash, headache, pruritus, fatigue, and sleep and mood disorders. For most patients, these symptoms resolve within the first month of treatment without having to alter or discontinue the therapy. However, myalgia, even without elevations in creatine phosphokinase (CK), is often a reason to change statin therapy in adults.

All of the above-mentioned side effects have also been reported in the studies of statins in children, but, strikingly, adverse events, whether or not judged to be related to therapy, did not differ between treatment and placebo groups. Some adverse effects did result in discontinuation of the medication in study subjects. One lovastatin-treated subject presented with increased bruising and purpura, but no abnormal
results were found in hematological testing. The investigators did not consider the reason for discontinuation clinically significant or definitely related to study drug. One child on 10 mg/d of simvastatin was discontinued from a study because of the development of infectious mononucleosis, which was considered not drug-related, and one patient on 20 mg/d of atorvastatin was discontinued from the trial due to depression. The depression resulted in hospitalization and the investigators judged this adverse event as possibly related to treatment. Other adverse events during the treatment period were mild or moderate, and resolved spontaneously without interrupting the study medication. Laboratory abnormalities as a result of statin use have been extensively evaluated in adults. Most clinical trials in adults show that statin therapy is associated with an elevation of liver transaminases or CK levels in some cases. The risk for reversible elevation of liver transaminases, defined by alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) levels >3 times the upper limit of normal (ULN), is approximately 1% for all statins, and the prevalence of CK levels >10 times ULN with statin monotherapy is approximately 0.12%. Clinically relevant hepatotoxicity has not been observed, but cases of myositis and myopathy have been reported. Clinically important rhabdomyolysis with statins is rare with an overall incidence of fatal rhabdomyolysis of approximately 0.15 per 1 million prescriptions. Rhabdomyolysis is a clinically and biochemically defined syndrome resulting from skeletal muscle injury and is defined as muscle symptoms with severely elevated CK levels (> 10 x ULN) in conjunction with myoglobinuria. The risk of myopathy or rhabdomyolysis is increased when statins are given together with medication that is metabolized by the same pathway via cytochrome P450 isoform 3A4. Such drugs include cyclosporine, erythromycin, itraconazole, ketoconazole, nicotinic acid, and fibrates, especially gemfibrozil. All statins are metabolized by cytochrome P450 isoform 3A4, except for pravastatin, rosuvastatin, and fluvastatin that are not or only partly degraded through this pathway. Prudence is warranted when these are combined with the above-mentioned medications. Furthermore, drinking grapefruit juice has also been reported to increase the risk of myositis through this mechanism.

Elevation of CK levels was also observed in some children participating in statin trials. Such CK elevations fluctuated between 3x ULN and 5x ULN, without any clinical symptoms of myalgia, myositis, or rhabdomyolysis. The investigators of the studies in question could not find a relationship with the study medication, and mostly
attributed the CK elevation to excessive exercise and sports. All these laboratory abnormalities returned to normal without interruption of the study drug. In a study on the efficacy and safety of pravastatin, one child had an asymptomatic, but extreme, CK elevation of 16,400 U/L after 168 days of therapy, receiving either pravastatin or placebo. Within one week after cessation of the study drug, the CK level fell to normal and, thereafter, the study drug was reintroduced. At the end of the trial, the child was found to be in the placebo group. One child on simvastatin, who concomitantly received erythromycin, showed a CK increase of more than 10x ULN without muscle symptoms. The level returned to normal after discontinuation of the antibiotic. In the pediatric studies, no clinical symptoms of myositis, myopathy, or rhabdomyolysis were reported.

Some trials showed increased levels in liver enzymes, ALT and AST, in the active treatment group as compared to the placebo group. One child on simvastatin experienced several elevations <3x ULN as well as one elevation >3x ULN. Those elevations were considered drug-related, but not clinically significant. Therapy was interrupted for 10 days and levels returned to normal. Two children treated with atorvastatin (10-20 mg/d) had an AST elevation of >3x ULN and one had an ALT elevation of >3x ULN, whereas no placebo-treated patients had such elevations. None of the children discontinued the study medication. In an uncontrolled study using lovastatin, statistically significant, but minor and clinically unimportant, increases of 2 and 3 U/L of AST levels over baseline were observed during treatment with 30 mg/d and 40 mg/d lovastatin, respectively. ALT levels were not changed. In other controlled studies, there were no differences between the statin and the placebo group with respect to liver enzyme changes. In summary, discontinuation of statin treatment due to hepatic transaminase or CK elevation was rare in all pediatric studies. In most cases, such elevations decreased to normal spontaneously without changing or interrupting the study medication.

Since cholesterol is the precursor of adrenal and gonadal steroids, inhibition of cholesterol synthesis by HMG-CoA reductase inhibitors may affect steroidogenesis, which, in turn, may affect growth and/or sexual maturation of treated children. Most pediatric statin trials evaluated steroid hormone levels. However, results were variable. One uncontrolled study showed that 10 mg/d of lovastatin significantly increased plasma levels of cortisol and that 40 mg/d of lovastatin significantly reduced
cortisol levels\textsuperscript{24}. Other trials did not observe any changes in the levels of plasma cortisol\textsuperscript{25,27,28,31}. Similarly, for dehydroepiandrosterone sulphate (DHEAS), children treated with lovastatin showed significantly increased plasma levels \textsuperscript{24,25}, whereas simvastatin at a dose of 40 mg/d was shown to significantly reduce levels of DHEAS in treated children\textsuperscript{31}. In view of the fact that statins inhibit cholesterol synthesis, an increase of steroid hormones levels was totally unexpected and could not be explained by the investigators. In the case of simvastatin, the decrease of DHEAS was small and the investigators did not observe a deviation in growth or sexual development. Therefore, no clinical significance was attributed to the effects on DHEAS\textsuperscript{31}. In contrast, in the pravastatin trial, no changes were found in the levels of DHEAS\textsuperscript{28}. Furthermore, statins did not affect levels of estradiol in girls or testosterone in boys, or the levels of gonadotrophic hormones, lutropin and follicle-stimulating hormone (FSH)\textsuperscript{28,31}. No significant deviations were observed for sexual maturation or growth in any of the studies\textsuperscript{23,28,31}. In conclusion, statins do not appear to have clinically meaningful effects on hormone levels, growth, or sexual maturation in children.

Pregnancy

Infants with malformations following \textit{in utero} exposure to lovastatin and simvastatin have been described in reports, but a causal relationship between the drug and the defects has not been established. There is one case report of a pregnant women taking multiple medications, including fluvastatin, with good outcome\textsuperscript{20,39}. Recently, Edison and Muenke reviewed 178 cases of first-trimester statin exposure reported to the FDA from 1987 through 2001. After the exclusion of cases involving first-trimester elective or spontaneous abortions (46 and 42 cases, respectively), there were 20 reports of malformation, including five severe defects of the central nervous system and five unilateral limb deficiencies. All of these cases were associated with lipophilic statins. The authors concluded that these findings support the need for controlled epidemiological studies evaluating the potential teratogenic effects of statins\textsuperscript{40}. Experimental animal studies with these agents do not indicate a substantial teratogenic risk. Only exposure of pregnant rats to very high doses of lovastatin resulted in skeletal abnormalities and gastroschisis in the offspring, while pre-and post-natal administration of atorvastatin to pregnant rats produced developmental abnormalities in their offspring\textsuperscript{20,41}. Because the interruption of cholesterol-lowering medication should have
no untoward consequences for the long-term treatment of hypercholesterolemia, the use of statins during pregnancy should be discontinued. Women taking these agents before conception should ideally stop the therapy before becoming pregnant and certainly on recognition of pregnancy. Accidental use of the drugs during gestation, though, apparently has no known consequences for the fetus

**Conclusion**

Statins seem safe and have been shown to effectively lower cholesterol levels in pre- and post-pubertal children. If children are started on statin therapy, they should be seen at regular intervals by a lipid specialist or pediatrician experienced in lipid disorders. Growth, sexual development, and levels of liver enzymes should be monitored frequently. Because statins increase the risk for myopathy or rhabdomyolysis, CK levels should be evaluated as well. Patients and their families should be instructed to immediately report symptoms of muscle pain, myalgia, weakness, or the appearance of dark urine. In such cases, CK levels should be assessed and, if more than 5 x ULN, therapy should be discontinued. If CK levels return to normal, therapy may be reinstituted at a lower dose.

**Fibric-acid derivatives (fibrates)**

**Indications for use**

Fibric-acid derivatives or fibrates are indicated for use in the treatment of combined (mixed) hyperlipidemia or hypertriglyceridemia. In these conditions, the drugs decrease triglyceride levels and/or increase HDL levels. Fibrates are also indicated for the treatment of familial dysbetalipoproteinemia to reduce lipoprotein remnant concentrations and prevent coronary artery disease. A variety of fibrates are available worldwide: bezafibrate, ciprofibrate, clofibrate, fenofibrate, and gemfibrozil; however, the availability of fibrates varies between countries. They are rarely prescribed for children, because no randomized controlled studies exist with these compounds in a pediatric population. Safety and efficacy, therefore, are unknown.

**Mechanism of action**

The fibrates have a complex mechanism of action that includes multiple effects on
both the synthetic and catabolic pathways of triglyceride-rich particles. They are synthetic ligands for nuclear receptors such as peroxisome proliferator-activated receptors (PPARs), thereby altering the transcription of genes encoding proteins that control lipoprotein metabolism and vascular inflammation. For example, the expression of the enzyme, lipoprotein lipase (LPL), which catalyzes the hydrolysis of chylomicrons and VLDL, is increased. The activation of LPL also results in the transfer of cholesterol-rich surface lipids from VLDL to HDL, leading to an increase of circulating levels of HDL-C.

Fibrates may also decrease dense LDL particles in hypertriglyceridemic patients and convert them into larger, buoyant, and potentially less atherogenic forms.

Dose range and rationale
Fibrates are administered in tablet or capsule form with a meal. In adults, the dose of the fibrates varies from 100-900 mg/d, depending on the particular type. In children, data on the optimal dose are lacking as only a very few studies have evaluated the efficacy and safety of fibrates in hypercholesterolemic children. One uncontrolled trial demonstrated that intake of 100-300 mg/d of fenofibrate significantly reduced TC and triglyceride levels by 22% and 39%, respectively, as compared to baseline after three months of treatment. Another controlled trial over six months in 14 children with FH aged 4-15 years using bezafibrate at a dose of 10-20 mg/kg/d reduced TC and triglycerides by 22% and 23%, respectively, and increased HDL-C levels by 15% as compared with placebo. Finally, a three-month intervention with bezafibrate (2 x 200 mg/d) in seven children with FH aged 5.3-10.8 years showed that TC, LDL-C, and triglycerides were reduced by 32%, 41%, and 36%, respectively, and HDL-C levels were increased by 17%.

Thus, these studies suggest that fibrates may be effective lipid-lowering agents for children, particularly for elevated triglycerides, but the number of subjects studied to date is too small to establish or even estimate the long-term safety and efficacy of these compounds.

Adverse effects
In adults, the most common side effects of fibrates are gastrointestinal such as nausea and distention, diarrhea, vomiting, and dyspepsia. Furthermore, rash, urticaria, pruritus, headache, and elevated CK levels have been described. Other, more severe, but rare
adverse effects include: myalgia, myositis, and rhabdomyolysis. An association has been documented between clofibrate and an increased prevalence of gallstones. Myopathy is uncommon with the use of fibrate monotherapy, but the risk increases when these agents are combined with statins. Therefore, the combination therapy of statins and fibrates should be avoided in children and adolescents.

None of the above described adverse effects has been reported in the few trials in children, but those were short-term trials and the number of children was small. Wheeler et al. reported a transient rise in alkaline phosphatase in one patient, probably due to an incurrent illness, and an unexplained increase in ALT in another patient. Steinmetz et al. showed that AST and ALT levels increased 2- to 5x during three months of fenofibrate treatment in 4 out of 17 children. On the other hand, Becker et al. did not observe liver enzyme elevations in the bezafibrate trial. Regular monitoring of liver function should be advised in children if therapy with fibrates is instituted.

Pregnancy

Experience with fibrates during pregnancy is very limited in humans and insufficient data are available for risk assessment. In a surveillance study conducted between 1985 and 1992, 15 newborns had been exposed to gemfibrozil during pregnancy. One structural brain anomaly and an infant with Pierre-Robin syndrome were reported. In rats and rabbits, reproductive studies have been conducted with doses that were 0.2 to 18 times the maximum recommended human dose. All of these animal studies demonstrated that high doses in rats increased the incidence of congenital malformations, the rate of abortion, fetal death, and tumors. Based on these animal results, fibrates should not be used during pregnancy and lactation.

Conclusion

Although fibrates reduce TC, LDL-C, and triglyceride levels, long-term safety data are lacking in children. Therefore, fibrates are not recommended for lipid-lowering therapy in hypercholesterolemic children, except in extreme cases of severe hypertriglyceridemia when other therapies fail to control lipoprotein levels.
Nicotinic acid (Niacin)

Indications for use
Niacin or nicotinic acid is used as adjunctive therapy in addition to diet and other measures to lower elevated serum cholesterol and triglycerides in patients with type II, III, IV, or V hyperlipoproteinemia, and also to increase HDL-C. However, in children, nicotinic acid is rarely used for the treatment of either hypertriglyceridemia or hypercholesterolemia. Furthermore, nicotinic acid or niacin should not be confused with niacinamide or nicotinamide, another subtype of vitamin $B_3$. Niacinamide does not lower cholesterol levels. Nicotinic acid is also used for the prophylaxis and treatment of pellagra.

Mechanism of action
Nicotinic acid is a water-soluble B vitamin. The mechanism by which nicotinic acid affects lipids and lipoproteins is not entirely clear, but probably involves several pathways. It inhibits hepatic triglyceride synthesis which results in increased intracellular apoB degradation and subsequent decreased secretion of VLDL and LDL particles. In addition, it decreases the mobilization of fatty acids from adipose tissue to the liver by inhibiting the lipolysis of triglycerides. Furthermore, it has been suggested that nicotinic acid inhibits the hepatic removal of LP-A1 with a consequent rise of HDL-C$^{49,50}$.

Nicotinic acid undergoes saturable, first-pass metabolism via two pathways. In one pathway, nicotinic acid is conjugated with glycine, whereas the other pathway involves a number of general oxidation/reduction reactions that produce nicotinamide. High doses or immediate-release nicotinic acid will quickly saturate the non-conjugative metabolic pathway, forcing a large fraction of the nicotinic acid dose to be metabolized by the conjugative system$^{51}$.

Dose range and rationale
Nicotinic acid is orally administered as a tablet. There are three types of nicotinic acid preparation: immediate-release, long-acting, and extended-release. Immediate- and extended-release nicotinic acids have been approved by the FDA for the treatment of dyslipidemia. Long-acting formulations are labeled with a variety of names such as “time-release” or “sustained-release,” and are not approved by the FDA$^{51}$. The extended-release nicotinic preparation has been developed in an attempt to minimize
side effects of the immediate-release nicotinic acid.
In adults, nicotinic acid reduces plasma cholesterol and triglyceride levels at doses of 1-3 g/d\(^{52-55}\). Studies on the use of nicotinic acid in children are lacking. Only one trial has been conducted in 21 hypercholesterolemic children\(^{56}\). Nicotinic acid treatment in daily doses of 1200-2250 mg reduced TC by 23% and LDL-C by 30%, whereas daily doses of <1000 mg were less effective in cholesterol-lowering\(^{56}\). In adults, nicotinic acid also increases HDL-C levels by 17-30%\(^{52,55}\); however, it did not improve HDL-C levels in the 21 children included in this trial\(^{56}\).
Nicotinic acid may be used in a limited number of high-risk pediatric patients, but should only be prescribed to these patients by a lipid specialist and only when bile acid-binding resins and/or statins are not adequate, or if statin treatment is not possible.

**Adverse effects**

The most frequent side effects of nicotinic acid are cutaneous vasodilatation and flushing. Because of this, the use in adult patients is limited. To overcome this major obstacle to nicotinic acid, long-acting formulations of niacin have been developed, but nearly all of these formulations enhance the inherent hepatotoxicity of plain or unmodified nicotinic acid\(^{57}\). The FDA-approved extended-release nicotinic acid is associated with one-fourth of the flushing and, therefore, improves patient compliance, and produces less hepatotoxicity than other long-acting formulations\(^{57}\). Pretreatment with aspirin about half an hour before intake of nicotinic acid may blunt flushing and could be considered a necessary concomitant medication if there are no contraindications. Other adverse effects of nicotinic acid in adults are dry skin, pruritus, hepatotoxicity, hyperglycemia or diabetes, and hyperuricemia or even gout.

The only study with nicotinic acid in 21 children showed that, although treatment with nicotinic acid was efficacious in lowering LDL-C, adverse events were common. Flushing was present in 71% of the children. Other less prominent adverse events were itching, abdominal pain, nausea, vomiting, headache, and constipation. No patients had life-threatening or irreversible adverse events. Due to the frequent side effects, discontinuation of medication was very common in the children. Furthermore, it was not possible to assess the long-term safety of nicotinic acid because only two patients were followed for more than 18 months. Thus, adverse events are very common and, as yet, long-term safety of high doses has not been established in children.
Myopathy is uncommon in niacin monotherapy, but the risk increases when niacin is given in combination with other lipid-lowering medication such as statins. When symptoms compatible with myopathy are reported, CK levels should be monitored and the drug discontinued.

Pregnancy
The recommended daily dietary allowance for nicotinic acid is 17 mg in pregnancy and 20 mg during lactation, whereas the lipid-lowering dose of 1000-3000 mg/d is 100 times higher. Nicotinic acid is converted in humans to niacinamide, which is actively transported to the fetus. Doses used for lipid-lowering revealed adverse effects for the fetus in animal studies. Furthermore, niacin is actively excreted in human breast milk. Therefore, nicotinic acid should be discontinued during pregnancy and lactation.

Conclusion
Although niacin or nicotinic acid treatment might be efficacious for the treatment of hypercholesterolemia in children, adverse events are common. Furthermore, long-term safety of high doses of nicotinic acid has not been established in this age group. Therefore, treatment with nicotinic acid should be reserved for the closely supervised treatment of severe hypercholesterolemia by a lipid specialist. In fact, nicotinic acid should only be prescribed when bile acid-binding resins and/or statins are not adequate or if statin treatment is not possible.

Ezetimibe
Indications for use
In adults, ezetimibe is indicated, as an adjunct to diet, as monotherapy or in combination with statins in patients with primary hypercholesterolemia to reduce TC and LDL-C and in patients with homozygous sitosterolemia to reduce elevated plant sterol levels. Ezetimibe monotherapy has recently been approved for the treatment of children with FH from the age of ≥10 years old.
Mechanism of action

Ezetimibe is a novel cholesterol absorption inhibitor that prevents the absorption of cholesterol and plant sterols at the brush border of the small intestine by inhibiting the passage of sterol of dietary and biliary origin across the intestinal wall. Two target mechanisms for this drug have recently been proposed, namely the Niemann-Pick C1 Like 1 protein (NPC1L1)\textsuperscript{58} and the annexin-caveolin 1 complex\textsuperscript{59}, both seemingly associated with the regulation of intestinal sterol metabolism. The inhibition of cholesterol absorption reduces the overall delivery of cholesterol to the liver, thereby promoting the synthesis of LDL receptors with a subsequent reduction of LDL-C. Ezetimibe is rapidly absorbed and studies in bile-duct cannulated rats show that intraduodenal delivered ezetimibe undergoes rapid and extensive metabolism to its phenolic glucuronide in the intestine. In the portal vein, more than 95\% of ezetimibe is already glucuronidated\textsuperscript{60}. The absorbed glucuronide is taken up by the liver from the portal blood and excreted into the bile. Back in the intestinal lumen, the glucuronidated ezetimibe repeatedly inhibits cholesterol absorption. It is re-absorbed itself, indicating enterohepatic recycling\textsuperscript{61}. In plasma, ezetimibe exhibits more than 90\% plasma protein binding. In vivo experiments in humans assessing the effect of ezetimibe on the activity of drug-metabolizing enzymes revealed no effect on the activity of the cytochrome P450 (CYP) isoenzymes CYP1A2, CYP2C8/9, CYP2D6, or CYP3A4\textsuperscript{62}.

Dose range and rationale

Ezetimibe is administered as a tablet. In adults, the dose of ezetimibe for all indications is 10 mg/d whether prescribed as monotherapy or in combination with a statin. There are no reports on the efficacy and safety of ezetimibe in children, and ezetimibe can only be prescribed as monotherapy. One study with 18 adults with mild-to-moderate hypercholesterolemia showed that a two-week course of treatment with 10 mg/d of ezetimibe inhibited the fractional absorption of cholesterol by 54\% relative to placebo. This inhibition was associated with an 89\% increase in cholesterol synthesis. These changes led to a 22.3\% reduction of plasma LDL cholesterol concentrations\textsuperscript{63}. Other phase II, as well as phase III, placebo-controlled studies conducted in 432 and 1719 adult patients with primary hypercholesterolemia, respectively, showed that daily intake of 10 mg of ezetimibe lowered LDL-C by approximately 18\%\textsuperscript{64-66}. The maximum effect on LDL-C levels is reached within two weeks of initiation of treatment\textsuperscript{63}. 

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Furthermore, 10 mg/d of ezetimibe significantly and progressively reduced plasma plant sterol concentrations as compared to placebo in 30 sitosterolemia patients of who four were younger than 18 years. This confirms that ezetimibe also inhibits the intestinal absorption of plant sterols. Combination therapy of ezetimibe with statins may offer an advantage over monotherapy. Moreover, the addition of 10 mg/d of ezetimibe to a low dose of a statin can avoid the risk of potentially serious adverse effects associated with the use of a high dose of a statin. Studies on the combination therapy in adults are promising, but, in children, no studies addressing the efficacy or safety of ezetimibe alone or in combination with statins have been carried out.

Adverse effects

In adults, ezetimibe is well tolerated and has a good safety profile. Based on the pooled analyses of 432 adults in two larger phase II studies over 12 weeks, viral infection (8%), headache (9%), arthralgia (3%), and upper respiratory tract infections (1%) were the most commonly observed adverse events and occurred with the same frequency as in placebo recipients. Also in the phase III studies, the most frequently reported events were headache, upper respiratory tract infection, and back pain (4-11%) with similar frequency between the placebo and ezetimibe treatment groups. No clinically significant differences between placebo and ezetimibe were reported in the results of safety laboratory tests, vital signs, electrocardiograms, and cardiopulmonary and general physical examinations. Ezetimibe is, therefore, a safe lipid-lowering agent that may be useful in patients who do not tolerate first-line treatment with statins. Furthermore, administration of 10 mg/d of ezetimibe had no adverse effect on the lipid-soluble vitamins A, α- and β-carotene, and D, or α- and γ-tocopherol, and it did not adversely affect the production of steroid hormones. However, it is unknown whether ezetimibe is also well-tolerated in children as efficacy and safety data are still lacking.

Pregnancy

Since ezetimibe is a novel drug, its effect on the human fetus is unknown, and treatment during pregnancy should be avoided.
Conclusion

Ezetimibe, either as monotherapy or in combination with statins, might be beneficial to lower cholesterol levels in children with primary hypercholesterolemia who do not reach the target levels on statin therapy alone, and in children with homozygous sitosterolemia to reduce elevated sitosterol and campesterol levels. However, studies in children are urgently required to establish both long-term efficacy as well as safety.

Summary

There are increasing options for pharmacological treatment of dyslipidemias in children and adolescents. Clinicians who use these medications in pediatric patients should be familiar with their indications, dosing, and side effects. Data on long-term safety and efficacy are still lacking. It will be important for investigators to perform such studies to increase confidence in their use.
Lipid-Lowering Medications

References


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