Congenital Absence of the Cruciate Ligaments

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Congenital absence of one or both cruciate ligaments is a rare event, and little literature exists regarding this abnormality. Patients with this condition often have associated anomalies. This study looked at 6 subjects with congenital abnormalities often associated with absence of the cruciate ligaments. The subjects were followed by a questionnaire and knee examination. This paper presents results of congenital absence of the cruciate ligaments on knee instability and activities of daily living.

INTRODUCTION

Congenital absence of one or both of the cruciate ligaments is an uncommon occurrence, and has been only sporadically reported in the literature. Most reports are in association with a congenitally short femur or other abnormality, such as congenital dislocation of the knee. A study by Giorgi (1956) looking at morphologic variations in the intercondylar eminence of the knee contained the first mention of congenital absence of the cruciates: one case showed total aplasia of the intercondylar eminence, which Giorgi attributed to a congenital lack of the cruciates. A study by Katz et al. (1967) reported a relationship between congenital cruciate ligament anomalies and congenital dislocation of the knee. This study was the first to report confirmed congenital absence of the cruciate ligaments. Since then, it has been reported in association with a number of congenital abnormalities, [3-8]. Congenital absence of one or both cruciates is usually detected during examination for a separate abnormality, such as congenital dislocation of knee, [2], or preparation for leg-lengthening procedures, [3]. During clinical analysis for the presenting abnormality, ipsilateral instability of the knee is noted, with follow-up tests revealing cruciate ligament insufficiency. This study is intended to add to the existing base of reported cases of congenital absence of one or both cruciate ligaments.

METHODS

Using resources at the IWK Grace Health Centre Orthopaedics Clinic, a list of patients with possible congenital absence of the cruciate ligaments was compiled. These subjects all had associated abnormalities that are often linked to congenital absence of the cruciate ligaments, such as fibular hemimelia and proximal femoral focal deficiencies. A total of 9 patients were identified as having congenital abnormalities associated with congenital absence of the cruciate ligaments. Two of these patients lived a significant distance away and could not be obtained for examination purposes, and 1 patient could not be reached; this left 6 subjects with possible congenital absence of the cruciate ligaments. The subjects were relatively young, ranging in age from 7 to 24 years old. Each subject was asked a series of questions and had his or her knee examined. This was in an effort to clinically determine the presence or absence of the cruciate ligaments and, if absent, any effects this may have had on the subject. The questions included The Knee Society clinical rating system [10] as well as some questions regarding any impact the patient's knee might have had on the subject's life and/or activity levels, associated abnormalities and previous treatments. Each subject signed an informed consent form prior to any investigations.

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Table 1 - Associated Abnormalities As Identified in the Literature

<table>
<thead>
<tr>
<th>Congenital knee dislocation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital leg length discrepancy</td>
</tr>
<tr>
<td>Hypoplastic or absent fibula</td>
</tr>
<tr>
<td>Absent 5th ray of foot</td>
</tr>
<tr>
<td>Dislocation of patella</td>
</tr>
<tr>
<td>Femoral dysplasia</td>
</tr>
<tr>
<td>Congenital talipes equinovarus</td>
</tr>
<tr>
<td>Osteogenic scoliosis</td>
</tr>
<tr>
<td>Bilateral dislocation of hip</td>
</tr>
<tr>
<td>Incomplete sagittal septum</td>
</tr>
<tr>
<td>Proximal femoral focal deficiencies</td>
</tr>
<tr>
<td>Congenital thrombocytopenia</td>
</tr>
<tr>
<td>Genu valgum</td>
</tr>
<tr>
<td>Genu varum</td>
</tr>
<tr>
<td>Absent radius syndrome</td>
</tr>
<tr>
<td>Congenital absence of the menisci</td>
</tr>
</tbody>
</table>

RESULTS

The limited amount of literature regarding absence of the cruciate ligaments indicates the relative rarity of this condition. As well, there were only 9 patients who were suspected of congenital absence of one or both cruciate ligaments in a database of approximately 13000 patients spanning 3 years at the IWK Grace Health Centre Orthopaedics Clinic. From the literature, the most commonly associated abnormalities were congenital knee dislocation and congenital leg-length discrepancies, [2-8]. Table I contains specific conditions that have been reported in cases with congenital absence of the cruciate ligaments.

Abnormal laxity of the knee is noted upon clinical examination of a subject with congenital absence of one or both cruciate ligaments, [3-6]. Subjects with absent anterior cruciate ligaments show positive anterior drawer and Lachman tests, [3-5][9], medial lateral translational instability, [4][6][7][9], and possible habitual subluxation of the tibia in extension, [4][6]. In cases where the posterior cruciate ligament is absent, subjects exhibit positive posterior drawer signs, [3][8][9]. Of the 6 subjects examined, four had posterior drawer tests of less than 5 mm deviation, and two had deviations of 5 - 10 mm. There were five subjects with anterior drawer tests of 5-10 mm deviation and one with a deviation of greater than 10 mm. Five subjects also had Lachman tests of 5-10 mm deviation and one had a deviation of less than 5 mm. Five of the six subjects had a positive pivot shift. All six subjects had normal range of motion for the knee in question, and 4 of the 6 had less than 5 degrees of mediolateral laxity (the other 2 had 6-9).

In the majority of cases reported with congenital absence of the cruciate ligaments, subjects had no complaints of instability, and even subjects in whom the knee gives way more than once a week are active. Despite the clinically unstable knee, subjects are frequently involved in sports and other strenuous activities with no difficulties, unless precipitated by an associated abnormality, [3-6]. In agreement with this, none of the 6 subjects investigatd claimed to have any problems with regards to knee stability, and 4 subjects were active in athletics, with no limitations. The remaining 2 subjects were active in sports, but found that other factors limited their participation (prosthetic devices and ankle deformity). None of the subjects felt that their knee affected their daily living, nor did any subject find any limitation in walking or stairs. Two subjects mentioned occasional discomfort, although neither would refer to it as pain. One subject mentioned that she thought her knee may have "given way" once, but that it was of no consequence for her. Another mentioned that her knee had locked, but that once again the subject did not feel that it had interfered with her life. A summary of the patients seen during this study is contained in Table II. It is interesting to note that although none of the subjects had intact knees according to objective evaluation, they all had complete function (both values are out of one hundred).

Radiographic findings can be quite useful in differentiating between congenital absence and traumatic effect. Radiographic changes in the subjects missing one or both cruciate ligaments can include: hypoplasia of the intercondylar tubercles (lateral for anterior cruciate; medial for posterior cruciate), [3][4][6]; hypoplasia of the femoral condyles (medial for anterior cruciate; lateral for posterior cruciate), [4-6]; tarsal coalition, [6]; and hypoplasia to aplasia of the intercondylar emi-

Table 2: Patient Characteristics

<table>
<thead>
<tr>
<th>Gender</th>
<th>Age (yrs)</th>
<th>Cruciate(s)</th>
<th>Knee Society Score</th>
<th>Associated Abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>M</td>
<td>13</td>
<td>ACL</td>
<td>92:100</td>
<td>fibular hemimelia, leg length discrepancy, absent 5th ray of foot</td>
</tr>
<tr>
<td>F</td>
<td>21</td>
<td>ACL and PCL</td>
<td>82:100</td>
<td>fibular hemimelia, leg length discrepancy</td>
</tr>
<tr>
<td>F</td>
<td>24</td>
<td>ACL</td>
<td>90:100</td>
<td>proximal femoral focal deficiency, leg length discrepancy</td>
</tr>
<tr>
<td>F</td>
<td>9</td>
<td>ACL and PCL</td>
<td>80:100</td>
<td>fibular hemimelia, leg length discrepancy</td>
</tr>
<tr>
<td>M</td>
<td>6</td>
<td>ACL (R&amp;L)</td>
<td>R - 75:100, L - 89:100</td>
<td>absent 5th ray (upper limb), agenesis of lateral ray (R foot), L fibular hypoplasia, R fibular aplasia, R syndactyly of toes</td>
</tr>
<tr>
<td>M</td>
<td>7</td>
<td>ACL</td>
<td>92:100</td>
<td>absent 5th ray of foot, club foot, fibular hemimelia, leg length discrepancy</td>
</tr>
</tbody>
</table>
nence and corresponding adjustment in the shape of the intercondylar fossa, [3][4][6][8]. Hypoplasia of the lateral femoral condyles has also been accompanied by a valgus deformity, [6]. As well, there have been reports of patellar hypoplasia and absent or hypoplastic tibia being associated with absence of the anterior cruciate ligament [3][4]. Note that while any of the above radiographic changes may occur, they may also accompany each other or not be present at all. Figure I presents a sample knee radiograph from this study. In the image, radiographic changes in the affected (right) knee are evident. Note in particular the hypoplasia of the intercondylar eminence and intercondylar groove.

**DISCUSSION**

The long-term effects on knees of patients with congenital absence of the cruciate ligaments are not completely known [3-5]. The largest concern is whether or not patients will develop the degenerative changes seen in patients who have suffered acute cruciate rupture [3-5]. This is particularly intriguing in that a study by Johannson and Aparisi (1983) contained data on a sixty year old patient with congenital absence of the anterior cruciate ligament who exhibited no significant osteoarthritis. As well, an autopsy performed on an 81 year old male with congenital absence of the cruciate ligaments and a ring meniscus showed no arthritic changes, significant at age 80 [3][5][8]. It has been postulated that the meniscus rather than the anterior cruciate ligament is a better prognosticator of degenerative joint disease, [3][5], and that ring meniscus may be a developmental change attempting to provide more stability [5]. As well, the authors of a study in which 5 patients complained of their knee giving way more than once a week, [4], have suggested that this might lead to the development of degenerative changes similar to those seen in adults who have suffered acute ligamentous disruptions; however, this was only an assumption at the time of their study. Further long term studies are needed to evaluate this area. The current study cannot comment on long term effects because of the young age of the subjects.

Congenital absence of the cruciate ligaments is a relatively rare condition usually associated with other abnormalities. The majority of subjects suffer no ill effects in the short term, and are often active, with no difficulties or restrictions arising from the absence of the cruciate ligament(s). Patients don't have the same demand on the knee because of associated abnormalities, but they do function at a high level. Although these patients are not elite athletes, many engage in competitive sport as associated abnormalities permit. For example, one young male plays in the area hockey league, and the females in their twenties engage in recreational soccer and volleyball. These characteristics are found in both the literature and the results of this study. Finally, due to the dearth of information currently available, further work in determining the long term effects of congenital absence of the cruciate ligaments is indicated.

**REFERENCES**


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ACTIVITIES AND CLINICAL PHARMACOLOGY

LIPITOR (atorvastatin calcium) is a synthetic, lipophilic agent. It is a selective, competitive inhibitor of 3-hydroxy-3-methylglutaryl (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonic acid, which is an early and rate-limiting step in the biosynthesis of cholesterol. LIPITOR lowers plasma cholesterol and lipoprotein levels by inhibiting HMG-CoA reductase and cholesterol synthesis in the liver. Most of the circulating cholesterol is made up of the number of hepatic Low Density Lipoprotein (LDL) receptors on the cell surface for enhanced uptake and catabolism of Low Density Lipoprotein (LDL) cholesterol.

LIPITOR reduces LDL-Cholesterol (LDL-C) and the number of LDL particles, LIPITOR also reduces very Low Density Lipoprotein (VLDL) and triglyceride levels in combination with Statin and triglyceride levels in combination with LDL-C. It also reduces the number of LDL particles (LDL-C) containing particles, but increases High Density Lipoprotein-Cholesterol (HDL-C). Elevated levels of triglycerides (TG) are a risk factor for the development of cardiovascular disease. Elevated levels of lipids protect LDL-C, which are already abnormal, and contribute to increased LDL-C or increased LDC.

Lipitor is rapidly absorbed after oral administration; maximum plasma concentrations occur within 1-2 hours. Lipitor tablets are 95% to 98% bioavailable compared to solutions. Mean distribution of atorvastatin is approximately 381 hours. Atorvastatin is 25% bound to plasma proteins. Approximately 70% of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites. Atorvastatin and its metabolites are eliminated by biliary excretion. Less than 2% of dose of atorvastatin is recovered in urine after oral administration. Mean plasma elimination half-life of atorvastatin is approximately 14 hours, but the half-life of inhibitory activity for HMG-CoA reductase is 23 to 30 hours due to the contribution of longer-lived active metabolites.

INDICATIONS AND CLINICAL USE

Lipitor is indicated in adults as an adjunct to diet in the reduction of elevated total cholesterol, low-density lipoprotein cholesterol, apolipoprotein B, and triglycerides and in the reduction of triglycerides and in the reduction of total cholesterol and triglycerides levels. It is also indicated in the reduction of risk of coronary heart disease in patients with average total cholesterol and triglyceride levels. It also indicates in the reduction of total cholesterol, low-density lipoprotein cholesterol, and triglyceride levels in individuals with primary hypercholesterolemia, type IIa.

- Combined reduced hyperlipidemia (Type IIa), including familial combined hyperlipidemia, regardless of whether cholesterolemia or triglyceridemia are the lipid abnormality of concern;

- Dysbetalipoproteinemia (Type III);

- Hypertriglyceridemia (Type V);

- Familial hypercholesterolemia (homonymous and heterozygous).

For homonymous familial hypercholesterolemia, only LIPITOR should be used as an adjunct to treatment such as LDL apheresis, or monotherapy if such treatments are not feasible.

In clinical trials, LIPITOR (10 mg) significantly improved lipid profiles in patients with a wide variety of hyperlipidemic and dyslipidemic conditions, in 2 dose response studies in mild-to-moderate hyperlipidemic patients (fasting cholesterol levels of 190-290 mg/dL, triglycerides of 150-500 mg/dL, LDL-C of 125-190 mg/dL, and HDL-C of 30-40 mg/dL), and in a recent dose-response study, in patients with hypercylidemia (Type Ia, 10 mg/day of LDL-C 5-8 mmol/L, plasma triglycerides 2-7 mmol/L, and plasma cholesterol 10-15 mmol/L). The results indicated that plasma hypercylidemia (Type Ia) can be used effectively in patients with hypercylidemia (Type Ia).

In a double-blind study involving 24,631 patients with hypercylidemia (Type IIa, 10 mg/day of LDL-C 5-8 mmol/L, triglycerides 2-7 mmol/L, and plasma cholesterol 10-15 mmol/L), the results indicated that plasma hypercylidemia (Type IIa) can be used effectively in patients with hypercylidemia (Type IIa).

In one open-label study involving 24,631 patients with hypercylidemia (Type IIa, 10 mg/day of LDL-C 5-8 mmol/L, triglycerides 2-7 mmol/L, and plasma cholesterol 10-15 mmol/L), the results indicated that plasma hypercylidemia (Type IIb) can be used effectively in patients with hypercylidemia (Type IIb).

In a double-blind study involving 24,631 patients with hypercylidemia (Type IIb, 10 mg/day of LDL-C 5-8 mmol/L, triglycerides 2-7 mmol/L, and plasma cholesterol 10-15 mmol/L), the results indicated that plasma hypercylidemia (Type IIb) can be used effectively in patients with hypercylidemia (Type IIb).

For more details on efficacy by pre-defined classification and pooled data by Fredriksen-type, see PHARMACOREOLOGY, Clinical Studies. Prior to initiating therapy with LIPITOR, secondary causes should be excluded for elevation in plasma lipid levels (e.g., poorly controlled diabetes melitus, hyperparathyroidism, dysadiposopathy, hypothyroidism, and alcoholism), and a lipid profile performed to measure total cholesterol, LDL-C, HDL-C, and TG. For patients with TG ≤400 mg/dL, TG ≥400 mg/dL, or TG ≥500 mg/dL, the dose may be increased or decreased depending on the patient’s response.

CONTRAINDICATIONS

Hypersensitivity to any component of this medication.

Active liver disease or unexplained persistent elevations of serum transaminases exceeding 3 times the upper limit of normal (see WARNINGS).

Pregnancy and lactation (see PRECAUTIONS).

WARNINGS

Pharmacokinetic Interactions

The use of HMG-CoA reductase inhibitors has been associated with severe myalgias, including rhabdomyolysis, which may be more frequent when these agents are co-administered with drugs that inhibit the cytochrome P-450 3A4 enzyme system. LIPITOR is metabolized by cytochrome P-450 3A4 enzyme system, and should be used concomitantly with caution with other agents that inhibit the enzyme (see WARNINGS, Muscle effects and PRECAUTIONS, Drug Interactions and Cytochrome P-450 3A4-interacting drug).

Hepatic Effects

In clinical trials, persistent increases in serum transaminases greater than three times the upper limit of normal occurred in patients who received LIPITOR. When the dosage of LIPITOR was reduced, or when drug treatment was interrupted or discontinued, serum transaminase levels generally normalized within 1 to 2 weeks or if continued with limited administration with rechallenge or other clinical signs or symptoms. Most patients continued treatment with a reduced dose after treatment interruption, and transaminase levels returned to normal. For example, in a randomized, double-blind, placebo-controlled trial, 57% of patients who were treated with LIPITOR 40 mg or 80 mg had liver function test abnormalities. Liver function tests should be performed before the initiation of treatment, and periodically thereafter. Special attention should be paid to patients who have developed elevated serum transaminase levels, and in these patients measurements should be repeated promptly and at more frequent intervals.

If increases in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) exceed 3 times the upper limit of normal and are persistent, the dosage should be reduced or the drug discontinued. LIPITOR should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease or unexplained transient elevations in serum transaminase activities are contraindications to the use of LIPITOR. If such a condition should develop during therapy, the drug should be discontinued.

Precautions

Use in patients with severe renal impairment (creatinine clearance <30 ml/min) is not recommended. In patients with severe renal impairment, LIPITOR should be used with caution. LIPITOR is not recommended for use in patients with severe renal impairment (creatinine clearance <30 ml/min).

Drug Interactions

Concomitant Treatment with Other Lipid-lowering Agents: Combined drug therapy should be approached with caution as information from controlled studies is limited.
**Title:** Bile Acid Sequestrants:  
**Patients with mild to moderate hypercholesterolemia, LDL-C reduction was greater when NPTORI 10 mg and colesevelam 20 g were administered (*p*<0.001) than when either drug was administered alone (35% for NPTORI and 22% for colesevelam).  
**Patients with severe hypercholesterolemia (LDL-C reduction was similar (35%) when NPTORI 40 mg and colesevelam 20 g were coadministered when combined with NPTORI 40 mg alone. Plasma concentrations of cholesterol were lower (approximately 30%) when NPTORI 40 mg plus colesevelam 20 g were coadministered compared with NPTORI 40 mg alone.**  
However, the combination drug therapy was less effective in lowering the triglycerides than NPTORI monotherapy in both types of hypercholesterolemic patients (see PHARMACOLOGY: Clinical Studies). When NPTORI is used concurrently with colchicine or any other agent, an interval of at least 2 hours should be maintained between the two drugs, since the absorption of NPTORI may be impaired by the wax.  
**Fibric Acid Derivatives (Gemfibrozil, Fenofibrate, bezafibrate) and Nicotin (Nicotinic Acid).** Although there is no experience with the fibric acid derivatives concurrently with colchicine and nicotinic acid, the benefits and risks of such combined therapy should be carefully considered. The risk of myopathy with concurrent treatment in these drugs and nicotinic acid should be considered before therapy (see PHARMACOLOGY: Contraindications and Nicotinic Acid).  
**Coarskin Anticongestants:** NPTORI has no clinically significant effect on prothrombin time when administered to patients receiving chronic warfarin therapy (see SELECTED BIBLIOGRAPHY).  
**Digeoxin:** Concentrations in multiple doses of Digeoxin and digoxin decreased modestly-substantially plasma-digoxin concentrations by approximately 20%. Patients taking digoxin should be monitored closely and appropriately.  
**Oral Contraceptives:** Concentration of NPTORI with an oral contraceptive, containing 1mg norethindrone and 0.05 mg ethinyl estradiol, increased plasma concentrations: AUC, t1/2, and ethinyl estradiol by approximately 30% and 20%, respectively. These increases should be considered when used in these drugs and oral contraceptives.  
**Antacids:** Administration of aluminum and magnesium based antacids, such as Maalox™ TC Suspension, with NPTORI decreased the absorption of NPTORI by approximately 30%. LDL-C reduction was not altered but the triglyeride lowering effect of NPTORI may be affected.  
**Cimetidine:** Administration of cimetidine with NPTORI did not alter plasma concentrations of LDL C lowering efficacy of NPTORI. However, the triglyceride-lowering effect of NPTORI was reduced from 35% to 26%.  
**Cytochrome P-450-mediated Interactions:** Allopurinol is metabolized by the cytochrome P-450 isomerase, CYP 3A4. Ethamylzol, a CYP 3A4 inhibitor, increased allopurinol plasma levels by 40%. Concentration of CYP 3A4 inhibitors, such as grapefruit juice, are reduced by approximately 20% plasma concentrations of allopurinol may be increased by these drugs.  
**Antipyrine:** Antipyrine was used as a non-specific model for drugs metabolized by the microsomal hepatic enzyme system (cytochrome P-450 system). NPTORI had no clinically significant effect on the pharmacokinetics of antipyrine, thus interactions with other drugs metabolized via the same cytochrome isoenzymes are not expected.  
**Erythromycin:** In healthy individuals, plasma concentrations of erythromycin increased approximately 40% with coadministration of NPTORI and erythromycin, a known inhibitor of CYP 3A4 (see WARNINGS, Pharmacokinetic Interactions, Doseage and Administration). Concomitant use should be administered concurrently with antiepileptic agents and estrogen replacement therapy without evidence to date of clinically significant adverse interactions. Interaction studies with other antiepileptic agents have not been conducted.  
**Patients with Severe Hypercholesterolemia:** Higher drug dosages (80 mg) may be required for some patients with severe hypercholesterolemia (including familial hypercholesterolemia) who are also severely proteinuria impacted or are concurrent being administered Dicyclan or CYP 344 inhibitors (see WARNINGS, Pharmacokinetic Interactions, Doseage and Administration).  
**Drug/Laboratory Test Interactions:** NPTORI may elevate serum transaminase and other liver function tests (from skeletal muscle). In the differential diagnosis of chest pain in a patient on therapy with NPTORI, cardiac and noncardiac fractions of these enzymes should be determined.  
**AVERSE REACTIONS**  
NPTORI is generally well-tolerated. Adverse reactions have usually been mild and transient. In controlled clinical studies (placebo-controlled comparative studies with placebo and active compounds), 3% of patients reported experiencing adverse events while taking NPTORI.  
**Gastrointestinal**  
- Constipation: 1 1  
- Diarrhea: 1 1  
- Dyspepsia: 1 1  
- Flatulence: 2 1  
- Nausea: 2 1  
**Nervous System**  
- Headache: 2 1  
- Miscellaneous**  
- Pain: <1 1  
- Myalgia: 1 1  
- Apathy: 1 1  

The following additional adverse events were reported in clinical trials, not all events listed below have been associated with a causal relationship to NPTORI therapy. Muscle cramps, myalgia, myasthenia, parasthesia, peripheral neuropathy, pancreatitis, hepatitis, cholestatic jaundice, anemia, vomiting, alopecia, pruritus, rash, impotence, hyperglycemia, and hypoglycemia.  
**Pharmacokinetic experience:** Very rare reports of severe myopathy with or without rhabdomyolysis have been reported (see WARNINGS, Muscute Effects, PREDICATION, PAECAE, and Drug Interactions). Isolated cases of lactic acidemia and severe lactic acidosis (including lactic acidosis and severe acidosis) that may have no causal relationship to NPTORI have also been reported.  
**Pharmacological observations:** see PREDICATION.  
**Laboratory Tests:** Increases in serum transaminase levels have been noted in clinical trials (see WARNINGS).  

**SYMPTOMS AND TREATMENT OF OVERTOXICITY:**  
There is no specific treatment for NPTORI overdosage. Should an overdose occur, the patient should be treated symptomatically and supportive measures instituted as required. Due to possible drug binding to plasma proteins, hemodialysis is not expected to significantly enhance atorvastatin clearance.  

**DOSAGE AND ADMINISTRATION:**  
Patients should be started on a reduced cholesterol lowering diet (at least equivalent to the American Heart Association (AHA) Step 1 diet) before receiving NPTORI, and should be continued on this diet during treatment with NPTORI. If appropriate, a program of weight control and physical exercise should be implemented.
A foundation in asthma control

THEATPICAL CLASSIFICATION
Gestures may have been divided into the treatment of bronchial asthma.

INDICATIONS AND CLINICAL USE:
1. Patients who require inhaled steroids.
2. In patients for whom a reduction of systemic steroids is desired.

CONTRAINDICATIONS:
1. States of asthma; not to be used in primary treatment of acute episodes of asthma or in patients with moderate to severe chronic asthma.
2. Patients with a history of bronchitis treatment intractable, or they may need inhalations that are usually not required.

DOSAGE AND ADMINISTRATION:
1. In patients with bronchial asthma, PULMOCORT should be used as a bronchodilator treatment ineffective, or they may need inhalations that are usually not required.

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ADVERSE REACTIONS

BAYCOL® (cerivastatin sodium) is generally well tolerated. Adverse events have usually been mild and transient. In 1934 patients treated in placebo-controlled clinical studies investigating doses of BAYCOL® compared to 2.5% for placebo. Of these 1394 patients, 880 were treated for 21 years. Approximately 21% of patients participating in placebo-controlled clinical studies of BAYCOL® 0.2 or 0.3 mg/day and reported to be possibly, probably, or definitely drug-related are shown in the following table.

<table>
<thead>
<tr>
<th>Associated Adverse Events Reported in ≥1% of Patients in Placebo-Controlled Clinical Trials of 0.2 and 0.3 mg BAYCOL*</th>
<th>Placebo %</th>
<th>BAYCOL %</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n = 541)</td>
<td>(n = 1394)</td>
<td></td>
</tr>
<tr>
<td>GASTRINOSTINAL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Nausea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Constipation</td>
<td>1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>NERVOUS SYSTEM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

Ophthalmological Observations: See PRECAUTIONS. Effect on Lens.

Laboratory Tests: Increases in serum transaminases and CPK have been noted in clinical trials (see WARNS/NGS).

The following effects have been reported with drugs in this class. Not all of the effects listed have necessarily been associated with cerivastatin therapy: myopathy, muscle cramps, myasthenia, myoglobin, arthralgia, dysfunction of certain cranial nerves (including alteration of taste, impairment of extraocular movement, facial paresis), insomnia, depression, paresthesia, hepatitis, cholestatic jaundice, fatigue change in liver, creatine (rare), hyperkalemia (rare), anemia, vomiting, aspiration pneumonia, pancreatitis, loss of libido, erectile dysfunction, progression of cataracts (femur opacities), epistaxis epistaxis.

Novernmental (irregularity, angioneurotic, lupus erythematosus-like syndrome, polymyalgia rheumatica, vasculitis, purpura, thrombocytopenia, leukopenia, hemorrhagic anemia, positive ANA, eosinophilia, eosinophilia, arthralgia, urticaria, zanthia, photosensitivity, fever, rash, flushing, malaise, dyspepsia, toxic epidermal necrolysis, urticaria multiiforme including Stevens-Johnson syndrome.

Laboratory Abnormalities: elevated transaminases, alkaline phosphatase, y-glutamyl transpeptidase, and bilirubin, thyroid function abnormalities.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

The maximum single oral dose of cerivastatin sodium received by healthy volunteers and patients is 0.8 mg. No specific recommendations concerning the treatment of an overdose can be made. Should an overdose occur, it should be treated symptomatically and supportive measures should be undertaken as required.

The ability of cerivastatin and its metabolites to be dialyzed in humans is not known.

DOSEAGE AND ADMINISTRATION

The patient should be placed on a standard cholesterol-lowering diet (at least equivalent to the American Heart Association (AHA) Step 1) diet before receiving BAYCOL® (cerivastatin sodium) and should continue on this diet during treatment with BAYCOL®. If appropriate, a program of weight control and physical exercise should be implemented.

The recommended starting dose is 0.2 mg once daily in the evening. The recommended dosing range is 0.2-0.3 mg as a single dose in the evening. BAYCOL® may be taken with or without food since there are no apparent differences in the lipid lowering effects of BAYCOL® administered with the evening meal or at bedtime.

Doses should be individualized according to the recommended goal of therapy and the patient's response. Since the maximal effect of a given dose of BAYCOL® is seen within 4 weeks, periodic lipid determinations should be performed at this time and the dosage adjusted to the patient's response to therapy and established treatment guidelines.

Consideration should be given to reducing the dosage of BAYCOL® if cholesterol levels fall below the targeted range, such as that recommended by the Second Report of the U.S. National Cholesterol Education Program (NCEP) and/or the Canadian Consensus Conference Guidelines.

Severe Hypercholesterolemia: In patients with severe hypercholesterolemia, higher dosages (0.3 mg/day) may be required (see WARNS/NGS: Muscle Effects; PRECAUTIONS; DRUG INTERACTIONS).

Consultant Therapy: See PRECAUTIONS; DRUG INTERACTIONS.

Dosage in Patients with Renal Insufficiency: See PRECAUTIONS.

PHARMACEUTICAL INFORMATION

Drug Substance: Cerivastatin sodium
Chemical Name: 1-[1-(3,5-diethyl-4-hydroxy-phenyl)-3-(4-Hydroxyphenyl)-2,6-disopropyl-5 methoxy methyl-phenyl-3-y1]-3,5-dimethylhex-6-enoate
Molecular Formula: C34H39NO12Na
Molecular Weight: 541.5

Description: Cerivastatin sodium is a white to almost-white amorphous powder (hyphosphate). It is soluble in water, methanol and ethanol. The pick is 5.3 and pKa is 4.4 determined using a pH 7.4 buffer. The partition coefficient of cerivastatin was determined in octane/phosphate buffer pH 7.4 (P = 0.3) and octanol-water partition coefficient of cerivastatin was determined in octanol/phosphate buffer pH 7.4 (P = 0.3). At room temperature, Cerivastatin remains soluble up to 200°C. At higher temperatures, the active ingredient decomposes without melting.

Composition: BAYCOL® (cerivastatin sodium) tablets contain 0.2 or 0.3 mg of cerivastatin sodium.

Nonmedicinal Ingredients: crospovidone, magnesium stearate, macrogel pharmaceutical grade 25%, sodium hydroxide, hydroxypropyl methylcellulose, polyethylene glycol 4000, titanium dioxide, and ferric oxide.

Stability and Storage Recommendations: The tablets should be stored between 15° and 25°C. Dispense in tight containers.

AVAILABILITY OF DOSAGE FORMS

BAYCOL® (cerivastatin sodium) is supplied as 0.2 mg and 0.3 mg tablets. The different tablet strengths can be identified as follows.

<table>
<thead>
<tr>
<th>Strength</th>
<th>Colour</th>
<th>Marking</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.2 mg</td>
<td>light yellow-brown</td>
<td>203 on one side, 200 MCS on the other</td>
</tr>
<tr>
<td>0.3 mg</td>
<td>yellow brown</td>
<td>284 on one side, 300 MCS on the other</td>
</tr>
</tbody>
</table>

Nonmedicinal ingredients: crospovidone, magnesium stearate, macrogel, povidone 25%, sodium hydroxide, hydroxypropyl methylcellulose, polyethylene glycol 4000, titanium dioxide, and ferric oxide.

BAYCOL® is supplied in bottles of 100 tablets.

The tablets should be stored at room temperature (15° to 25°C).

Product monograph available on request.

References:
Dalhousie Medical Journal Instructions for Authors

The Dalhousie Medical Journal will consider manuscripts in English which deal with any aspect of medicine including basic science, clinical medicine, surgery, medical education, medicolegal affairs, medical humanities and public health. An accompanying cover letter signed by all authors should state that the manuscript has not been published by another journal, nor is it under consideration by another journal.

Six (6) copies of the text, in addition to the original, are required. A camera ready copy of all figures, line drawings and graphs are required as well as six additional copies which may be high quality photocopies. If a submission is accepted the author should then make any changes requested by the reviewers and submit a 3.5 inch disk containing two (2) copies of the manuscript: one copy should be in MS Word 6.0, Wordperfect 6.1 or MS Word for MacIntosh 6.0 (or earlier versions), and the other copy should be in Rich Text Format (RTF). References should be listed at the end of the paper and end-note functions should not be used.

Manuscripts should be printed on standard 22x28 cm (letter-sized) paper. Submissions should be 3000 words (approximately 15 pages double spaced) or less. This word limit does not include references or figures. Longer submissions may be considered with prior permission from the Associate Editor-Reviews and the Editor-in-Chief. Pages should be numbered consecutively.

Title page: The title page must include the following information: 1) authors’ full names, degrees and affiliations 2) first author biography 3) mailing address 4) e-mail address 5) phone number (home and work). The following information should be included if applicable: 1) pager number 2) Tupper Box # 3) fax number 4) year in educational program. To facilitate the anonymous peer review process, the title page should be the only page containing the authors names.

Abstract: The abstract should appear on the second page and should be no longer than 250 words. It should state the purpose of the paper, basic procedures, main findings and the principal conclusions.

Text, Acknowledgements: These should conform to the Uniform requirements for manuscripts submitted to biomedical journals (CMAJ 1994;150:147-154). These are on reserve in Dalhousie University’s Kellogg Library under reserve call #971.

References: References are to be numbered in the order they appear in the text. The reference section should be located after the acknowledgements at the end of the text, following the sample formats given below. Complete information should be given for each reference, including titles of journal articles, names of all authors and editors, and inclusive pagination.

Journal article

Chapter in book

Book

Tables: Tables should be numbered in the order in which they are referred to in the text. Each should have a brief title. Column headings and descriptive matter in tables should be brief.

Figures: Each figure should be planned to fit into either one or two columns of text. Photographs and illustrations must be black and white and of good quality. Figures should be numbered in the order in which they are referred to in the text. Labelling should be limited to the essential components of a figure. Figure captions should be typed on a separate page at the end of the manuscript. Electronic copies of photographs and illustrations are preferred in TIFF or PICT format (resolution should be 600 dpi), and in separate files. MS PowerPoint (97 or earlier versions) is also acceptable. Attention should be given to be certain the graphics have adequate resolution.

Drug Names: Both proprietary (generic) and trade names should be given for all drugs mentioned in the text.

Submission: Send manuscripts to:

Associate Editor, Reviews
Dalhousie Medical Journal, Box 398
Sir Charles Tupper Medical Building
Dalhousie University, Halifax
Nova Scotia, Canada
B3H 4H7

Manuscripts can also be dropped into the DMJ dropslot in the door to room 2L-B8 (DMSS storage room) in the Sir Charles Tupper Building (Link) Dalhousie University.
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We plan to purchase a scanner, fax machine and printer or printer/copier. In addition, we must pay for a variety of services including: phone and long-distance service, Internet service, and equipment maintenance. Continued support from patrons will allow for the operation and expansion of the Publication Office.

With your support the DMJ will continue to develop both into a forum for research relevant to the health of Atlantic Canadians and as an international forum for the highest quality medical and graduate student research. To become a Patron of the DMJ please send a cheque for $50.00 to the address on the adjacent form. You will be acknowledged as a “Patron of the DMJ” in each of the two following issues.

We would be happy to have any other support that faculty, or other physicians might like to provide. This may take the form of editorial assistance, or submission of research/review papers. We look forward to hearing from you.

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SJRH is a major affiliate of the Dalhousie University School of Medicine with 60-70 residents and medical students each year, doing core and elective rotations in virtually every medical and surgical discipline. It is home to the NB Heart Centre providing leading edge cardiology and cardiac surgery services for patients throughout the province. In addition, it is a recognized leader in such areas as Neurosciences, Oncology, Plastic Surgery, Paediatrics, Diagnostic Imaging, Emergency Medicine, Family Medicine teaching, pre-hospital and home care. The facility was the first to be designated as an accredited tertiary trauma centre in Atlantic Canada and is a leader in telemedicine applications.

All inquiries and applications, with references and résumés should be directed to the attention of:

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