Spotlight on Fibrates

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As presented at the Drug Update & Practical Therapeutics Course, November 8, 2002.

In this article:

Andrew's visit

Andrew, 68, comes to you for a routine physical examination. He has abdominal obesity with a waist circumference of 100 cm, a body mass index of 30, and an average blood pressure of 150/95 mmHg. His lipid profile shows:

- Total cholesterol 4.2 mmol
- High-density lipoprotein cholesterol (HDL-C) 0.7 mmol
- Low-density lipoprotein cholesterol (LDL-C) 2.5 mmol
- Triglycerides 4.3 mmol/L

Management should include:
- Testing him for diabetes
- Starting a fibrate to improve his low HDL level
- Adding a statin if the LDL level remains high

For Andrew's followup, please go to page 154.

Fibric acid derivatives (fibrates) have been used to treat dyslipidemia since 1962, when clofibrate was first used. Certain fibrates are currently available in Canada (Table 1).

Their mode of action remains complex and incompletely understood. Fibrates do alter gene transcription by activation of transcription factors belonging to peroxisome proliferator-activated receptors (PPARs) in the liver cell.[1] Fibrates are PPAR-alpha mediators. These actions lead to the enhancement of catabolism of triglyceride remnants, reduction of serum triglyceride levels, and increased synthesis of apo A-IA and apo-II which tends to raise high-density lipoprotein cholesterol (HDL-C).

When should I prescribe fibrates?

The 2000 Canadian working group on dyslipidemias recommendations suggest the use of fibrates in patients who have not responded adequately to lifestyle modification and diet.[2] These

Fibrates

Table 1
Fibrates available in Canada

Name	Formulation and dose
Clofibrate:	
• Atromid-S®	No longer used much
Gemfibrozil:	
• Lopid®	600 mg twice daily 30 minutes before morning and evening meals
Fenofibrate:	
• Lipidil®	300 mg daily in divided doses
• Lipidil Micro® (prolonged release)	200 mg once daily
• Lipidil Supra® (a micronized preparation using a lower dose to achieve therapeutic blood levels)	160-200 mg once daily
Bezafibrate:	
• Bezalip®	200 mg, 2-3 three times a day
• Bezalip-SR®	400 mg daily
Ciprofibrate: (special release only)	Not readily available

patients should have high triglyceride levels and/or low HDL-C levels and normal low-density lipoprotein (LDL-C) levels, or in combination therapy with 3-hydroxy-3-methylglutaryl coenzyme A (HMG Co-A) reductase inhibitors (statins) in patients with elevated LDL-C and high triglyceride/low HDL-C levels.[1,2]

Clinical situations where fibrates are used include:

- Patients with very high triglyceride levels (typically over 11 mmol/L to 12 mmol/L) who are at risk of acute pancreatitis.
- Patients with the "metabolic syndrome" (insulin resistance). These subjects are characterized by abdominal obesity, insulin resistance manifested as hypertension, glucose intolerance or diabetes mellitus, dyslipidemia typically comprising a lipid pattern of low HDL-C, and elevated triglyceride levels.[3]
- Patients on combination therapy, with statins (*e.g.,* commonly in patients with familial combined dyslipidemia who have elevation of both LDL-C and triglyceride levels).

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How effective are fibrates?

Fibrates reduce serum triglyceride levels by 35% to 50%. The greater the initial triglyceride elevation, usually the better the response. Fibrates elevate HDL-C levels by 15% to 25% (both actions more than with statins). In addition, fibrates may have a modest effect on reducing LDL-C levels by up to 20% (less than with statins) in some responders, but paradoxically can elevate LDL-C in some (especially if the triglyc-

Andrew's followup

Andrew has:

- Abdominal obesity
- Hypertension
- Low high-density lipoprotein cholesterol (HDL-C)
- A high triglyceride level

These are typical findings in someone with the so-called "metabolic syndrome" of insulin resistance.[3] Andrew should be tested for diabetes.

It is reasonable to start him on a fibrate to try to increase his HDL-C in view of the results of the VA-HIT study[11] Alternatively, a statin may also be reasonable in view of the results of the Heart Protection Study.[12] Drug therapy should be started immediately if he is shown to be diabetic.[2]

VA-HIT: Veterans Affairs high-density lipoprotein Intervention Trial

erides are significantly lowered).[4] Fibrates also modify LDL-C particles qualitatively, from small dense LDL particles to the larger and, therefore, less atherogenic forms. In addition fibrates have a variable effect on lipoprotein (a) levels, reduce fibrinogen and plasminogen 1 levels, reduce platelet activity, may increase homocysteine levels (fenofibrate, bezafibrate), and reduce uric acid. The clinical significance of these latter effects, however, is uncertain.

Although these actions are theoretically attractive for reducing cardiovascular risk, the clinical data regarding benefit of fibrates use is not as robust as with the statins. All clinical trials of fibrates to date suggest benefit in reducing cardiovascular disease, but reduction of total mortality has not been demonstrated (Table 2).[5-11]

Among the most positive studies on fibrates to date is the VA-HIT study.[11] This was a secondary prevention study which treated 2,531 male patients. The patients, aged 64 to 67, had coronary artery disease and were given gemfibrozil or placebo for 5.1 years (mean). These patients had:

- low HDL-C (0.8 ±0.1 mmol)
- modestly elevated triglyceride (1.8±0.8 mmol)
- "normal" LDL-C (2.9±0.6 mmol)

levels.

Table 2
Summary of fibrate clinical trials

Primary Prevention

- WHO Study (clofibrate)- reduction in cardiovascular events but an increase in cholelithiasis as well as excess deaths (non-cardiac) in the clofibrate-treated patients during the treatment period. Debate continues as to the validity of this latter observation, as excess deaths have not been seen in all other subsequent trials using other fibrates.[5]
- Helsinki Heart Study (gemfibrozil)-positive reduction in cardiovascular risk in a subset of patients with mixed hyperlipidemia, without significant differences in coronary or all-cause mortality.[6]

Secondary Prevention

- LOCAT (gemfibrozil): Positive beneficial angiographic outcome[7]
- BCAIT (bezafibrate): Positive beneficial angiographic outcome[8]
- DAIS (fenofibrate): Positive beneficial angiographic outcome[9]
- BIP (bezafibrate): Trend to clinical benefit, especially in subset of patients with high triglycerides and whose high-density lipoprotein levels increased[10]
- VA-HIT (gemfibrozil): Benefit in cardiovascular outcomes but not total mortality[11]

Pending

- FIELD (results due about 2004): Micronized fenofibrate vs placebo given to dyslipidemic diabetic patients—planned 8,000 patients equally between both sexes, and at least 20% who have had myocardial infarctions.

WHO: World Health Organization
LOCAT: Lopid Coronary Angiography Trial
BCAIT: Bezafibrate Coronary Atherosclerosis Intervention Trial
DAIS: Diabetes Atherosclerosis Intervention Study
BIP: Bezafibrate Infarction Prevention
VA-HIT: Veterans Affairs high-density lipoprotein Intervention Trial
FIELD: Fenofibrate Investigation Event Lowering in Diabetes

Fibrates

Of the patients, 25% were diabetic, and 57% had hypertension. In comparison to those given placebo, patients treated with gemfibrozil showed a 6% increase in their HDL-C levels, 31% decrease of triglyceride levels, and a negligible change in LDL-C levels. Coronary heart disease death (-23%, p=0.006) and nonfatal myocardial infarction (-22%, p=0.07) were significantly reduced with gemfibrozil, but not total mortality.

Table 3

Checklist for fibrate-statin combination therapy

- The patient should have normal renal function.
- The patient should not be receiving another drug that could increase blood concentrations of either the statin or fibrate.
- The patient is intelligent enough to recognize and report symptoms of myopathy.
- You should start with an intermediate dose of the statin in combination therapy.
- Creatine phosphokinase (CPK) should be measured as baseline before combination therapy, and as needed in followup (typically together with liver enzymes every four to six months).
- Monitoring should be increased every time a dose of either statin or fibrate is increased, or if other drugs that may interact with these lipid lowering drugs are added to the patient's medications.
- If CPK exceeds 10 times the upper limit of normal (or in patients with myopathy symptoms), discontinue combination therapy and wait for resolution of symptoms and CPK values. Reconsider whether to reinitiate therapy with either drug at a lower level.
- If there is no response to combination therapy in 8-12 weeks then combination therapy should be discontinued.

Adapted from: Gotto A, Pownall HJ, Simpson S: *Manual of Lipid Disorders* (3rd Edition) 2003. Pub. Lippincott, Williams & Wilkins.

Though significant benefit in clinical cardiovascular endpoints were seen (that appear unrelated to LDL-C lowering, such as seen in statin trials), debate continues as to whether the results reflect the benefit of HDL-C elevation, or that of qualitative change to LDL-C particles (or both) by fibrates.

Although diabetics showing lipid profiles (such as those in VA-HIT patients) will likely benefit from fibrates, many statin trials have also demonstrated benefit for diabetic patients. For example, in the Heart Protection Study, which involved a large number of diabetic patients, simvastatin was shown to be of benefit even at low LDL-C levels.[12] The real question is whether fibrates parallel this benefit, or increase this benefit when used in combination with a statin.

What are the possible side-effects?

Fibrates are generally well tolerated. Uncommon side-effects include:

- upper gastrointestinal disturbances,
- headache,
- anxiety,
- fatigue,
- vertigo,
- sleep disorders,
- myalgia,
- loss of libido,
- alopecia, and
- dose-related asymptomatic transaminase rise.[4]

Unlike observations with the earlier fibrate clofibrate,[5] no increase in cholelithiasis was reported in the five years of use of gemfibrozil in the VA-HIT trial. Patients should however be advised of the need for regular monitoring of liver enzymes.[4]

Because they are protein bound as well as metabolized via the hepatic cytochrome P450 CYP3A4 system, fibrates may interact with other drugs using these systems including:

- statins,
- warfarin,

- grapefruit juice (enhances levels and toxicity),
- oral hypoglycemic agents,
- metformin and the sulphonylureas (increases hypoglycemia), and
- cyclosporin (reduces level).

Fibrates are renally excreted and doses should be reduced in the elderly and in patients with renal insufficiency or avoided entirely in those with severe hepatic or renal dysfunction.

How are fibrates used with statins in dyslipidemia?

Fibrates are also used (often very effectively) in combination with statins in patients with elevated LDL-C and high triglyceride/low HDL-C levels when statin therapy alone has not corrected all the lipoprotein abnormalities. Risk of coronary events remains high in these patients. Though treatment with fibrates of these residual abnormalities is recommended,[2] evidence for benefit of this recommendation is presently weak. Combination therapy of this nature increases the risk for myopathy and rhabdomyolysis, most cases having been reported with gemfibrozil-lovastatin combination therapy.[4]

A practical checklist can be used when considering fibrate/statin combination therapy (Table 3). CME

Net Readings

1. MedicineNet.Com: www.medicinenet.com
2. Lipids Online: www.lipidsonline.org

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