Fibric Acid

Biochemistry

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Fibric Acids

- Fibric Acids, also referred to as fibrates are carboxylic acids that have the ability to interact (agonize or antagonize) with nuclear transcription factors which influence lipid and lipoprotein synthesis and catabolism.

  - PPAR-α, LXR, ANGPTL, SREBP

- Fibrates exist as either acids or as esters. The PPAR-α agonism requires presence of the polar carboxylic acid moiety but LXR antagonism may require the ester moiety.
Fibric Acids (Fibrates)

- **Carboxylic acids** are organic acids characterized by the presence of a carboxyl group, which has the formula \(-\text{C}(=\text{O})\text{OH}\), usually written \(-\text{COOH}\) or \(-\text{CO}_2\text{H}\).

- The **fibrates** are a class of amphipathic carboxylic acids.

  Have hydrophilic (polar) and hydrophobic (nonpolar) properties
Fibrates

- Clofibrate, the prototype of fibric acids derivatives is the ethyl ester of p-chlorophenoxyisobutyrate.
- Gemfibrozil is a nonhalogenated phenoxypentanoic acid and is thus distinct from the halogenated fibrates.
- Fibric acid analogs:
  - Fenofibrate
  - Bezafibrate
  - Ciprofibrate
Esters

- Esters consist of an inorganic or organic acid in which at least one –OH (hydroxyl) group is replaced by an -O- alkyl group.
- Esters can be synthesized in a condensation reaction between an acid and an alcohol in a reaction known as esterification.
- Fatty acid esters form fat and lipids.
Fibrates

F Clofibrate was the first fibrate approved for use in the US in 1967.

F The World Health Organization Trial was published in 1978 and it showed that despite a reduction in cholesterol it did not reduce fatal CV events, although nonfatal infarcts were reduced.

F Total mortality was greater in the clofibrate group, due to multiple causes including cholelithiasis.

F Interpretation of these negative events were clouded by failure to analyze the data according to the intention-to-treat principle.

• A later analysis demonstrated that the apparent increase in noncardiac mortality did not persist in the clofibrate treated patients after discontinuation of the drug Lancet 1984;2:(8403):600-4.
Clofibrate – Clofibric Acid

Ethyl 2-(4-chlorophenoxy)-2-methylpropanoate

Molecular Formula $\text{C}_{12}\text{H}_{15}\text{ClO}_3$
Molecular Weight = 242.698 g/mol

Protein Binding 92-97%
Half Life 18-22 hours
Pregnancy Category C

Hepatic glucuronidation

http://en.wikipedia.org/wiki/clofibrate

Gemfibrozil - Gemfibric Acid

5-(2,5-dimethylphenoxy)-2,2-dimethyl-pentanoic acid

Molecular Formula $C_{15}H_{22}ClO_3$
Molecular Weight = 250.333 g/mol

Protein Binding 95%
Half Life 1.5 hours
Pregnancy Category C
Hepatic CYP3A4 Metabolism

http://en.wikipedia.org/wiki/gemfibrozil
Fenofibrate

1-methylethyl2-[4-(4-chlorobenzoyl) phenoxy]- 2-methyl-propanoate

Molecular Weight = 360.831 g/mol
Molecular Formula C$_{20}$H$_{21}$ClO$_4$

Protein Binding 99%
Half Life 20 hours
Pregnancy Category C

http://en.wikipedia.org/wiki/Fenofibrate
Fenofibrate Tablet Pharmacokinetics

- Fenofibrate is readily absorbed from the gastrointestinal tract
- Following oral administration fenofibrate is rapidly hydrolyzed to by esterases to the active metabolite fenofibric acid
- No unchanged fenofibrate is detected in the serum
- Fenofibric acid is primarily conjugated with glucuronic acid and excreted in the urine
- Neither fenofibrate nor fenofibric acid undergo oxidative metabolism by CYP450 enzymes
  - They are weak inhibitors of CYP2C19, CYP2A6 and mild-moderate inhibitors of CYP2C9 and may potentiate coumarin-type anticoagulants
Fenofibric Acid

In December 2008 the FDA approved a newly developed fibrate that is the choline salt of fenofibric acid. This agent is unique in that it dissociates to free fenofibric acid within the gastrointestinal tract, allowing fenofibric acid to be rapidly and directly absorbed without requiring first-pass metabolism.

In contrast, fenofibrate is an ester of fenofibric acid and requires enzymatic cleavage via first-pass metabolism to form fenofibric acid. Fenofibric acid, the active metabolite of fenofibrate, contains a carboxylic acid moiety instead of an ester moiety and has relatively low potential for interaction with statins.

Fenofibric Acid

2-[4-(4-Chlorobenzoyl)phenoxy]-2-methylpropanoic acid; 2-[4'-
(p-Chlorobenzoyl)phenoxy]-2-methylpropionic acid

Molecular Weight = 318.76
Molecular Formula C₁₇H₁₅ClO₄

Protein Binding 99%
Half Life 20 hours
Pregnancy Category C

http://www.chemblink.com/products/42017-89-0.htm
Fenofibric Acid

Unlike fenofibrate, fenofibric acid contains a carboxylic acid moiety instead of an ester moiety.

This polar moiety plays an important role in the formation of a rare acid-to-ketone hydrogen-bond-type packing interaction. The lack of an isopropyl group in fenofibric acid aligns the carboxyl group on the same side as the ketone carbonyl group; this conformation may play an important role in discrimination between the acid and the fenofibrate molecule in molecular recognition.

http://journals.iucr.org/c/issues/2005/02/00/sq1185/sq1185bdy.html
Unlike fenofibrate, fenofibric acid contains a carboxylic acid moiety instead of an methylethyl ester moiety.

Choline is a quarternary saturated amine with the chemical formula \((\text{CH})_3\text{N}^+\text{CH}_2\text{CH}_2\text{OH}^-\), where \(X^-\) is a counterion such as chloride.

**Choline Salt of Fenofibric Acid**

Unlike fenofibrate, fenofibric acid contains a carboxylic acid moiety instead of an methylethyl ester moiety.
Choline is a quarternary saturated amine with the chemical formula \((\text{CH})_3\text{N}^+\text{CH}_2\text{CH}_2\text{OHX}^-\), where \(X^-\) is a counterion such as chloride.

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Fenofibrate vs Fenofibric Acid

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Fenofibric Acid

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Fenofibrinic Acid

Alignment of the sp2 ketone moiety (the C4/C7/O1/C8 plane) of fenofibrinic acid and the corresponding plane in the fenofibrate molecule reveals that the carboxyl moiety is positioned almost on the same side as the ketone carbonyl group in fenofibrinic acid.

This conformation may facilitate the formation of intermolecular C – O --- H - O hydrogen bonding over the carboxyl OH dimer. However, the carboxyl moiety of the fenofibrate molecule is located away from the ketone carbonyl group, at the back of the molecule.

This conformation may be due to steric effects and packing interactions, which are caused by the presence of the isopropyl group. This phenomenon may play a significant role in distinguishing fenofibrinic acid as an activator of PPAR over fenofibrate. In general, if polar groups, such as the carbonyl and carboxyl groups in fenofibrate and fenofibrinic acid, are involved in the formation of specific interactions with their target molecules, the orientation of these moieties will alter the binding affinities.

A dimer of fenofibric acid, showing the rare acid-to-ketone hydrogen bonding pattern. The symmetry operator \((-x, -y, 1-z)\) was used to generate atoms labeled with the suffix \(A\).

A packing diagram of fenofibric acid, in the orthorhombic space group \(Pbca\), viewed along the \(a\) axis.

“Zig-Zag” Stacking Pattern unique to \(FFA\), not seen with \(fenofibrate\)

Fibrate Esters vs Fibrate Acid

F The fenofibrate ester is rapidly converted into the carboxylic acid form by esterases in the liver and plasma. It has been assumed that the pharmacologically relevant form of fenofibrate is the acid form due to its specificity for PPAR-α and the lack of detectable ester in the plasma.

F The fibrate esters bound only to the LXRs, whereas the fibric acids were specific for PPARs.

F The ester/acid moiety acts as a switch that determines LXR versus PPAR-α affinity, yet the remaining portion of the ligand seems to have relatively little impact on this selectivity.

F Fenofibrate ester, antagonizes LXR and represses lipogenic gene expression in liver, but not members of the ABC transporter gene family (ABCA1, ABCG5, and ABCG8).

Fibrate Esters vs Fibrate Acid

F Not only does the fibrate class of hypolipidemic compounds function through activation of PPAR-α, leading to induction of genes that control fatty acid -oxidation; they also decrease SREBP1 and FAS gene expression by antagonizing LXR-mediated transcription.

F Fibrate esters display LXR partial agonist/antagonist activity that is dependent on the target gene context. This data ascribes a novel regulatory function to the clinically utilized fibrate drugs and have therapeutic implications for identification of compounds that increase cellular cholesterol efflux through LXR yet counteract the accumulation of triglycerides by utilizing a promoter-selective mode of action.