Hypertriglyceridemia

Thomas Dayspring MD, FACP

Fibric Acids (also referred to as fibrates) are amphipathic (one end is hydrophobic and one end hydrophilic) carboxylic acids characterized by the presence of a terminal carboxyl group (COOH). Many use the words polar and nonpolar to describe hydrophilicity where a polar substance is soluble in water whereas a nonpolar substance is not. In actuality the terms hydrophilic and phobic refer to the ability of a molecule to pass through a lipid membrane not its water solubility. Thus amphipathic molecules have one end that is polar and one end that is nonpolar. Cholesterol is an amphipathic molecule as the end with the -OH group at the #3 position is polar and the other end of the molecule with methyl groups is nonpolar. Most fibrates are manufactured and swallowed not as acids but as esters: an ester is an organic acid in which the hydroxyl (-OH) group is replaced by an -O alkyl group which are single chain arrangements of carbon and hydrogen atoms (CH): i.e. methyl, ethyl, etc. A carboxylic acid ester is -COH-OR where R is the specific alkyl group.

Esters are formed in a process called esterification when an alcohol reacts with an acid. Free or unesterified cholesterol is an alcohol with an -OH group at the # 3 position. When it combines with a fatty acid, it is esterified and becomes cholesteryl ester. When glycerol (an alcohol) combines with one, two or three fatty acids (acyl groups) you create, monoacylglycerol, diacylglycerol or triacylglycerol (better known as triglycerides). Triglycerides are thus esters of glycerol.

PPAR-alpha is a nuclear transcription factor or NTF (a protein that enters the nucleus and attaches to DNA causing transcription and creation of messenger RNA ultimately leading to protein synthesis) that potentially regulates hundreds of genes involved with energy expenditure: lipid and lipoprotein synthesis and catabolism, fatty acid regulation and vascular wall biology. Natural ligands for PPAR-alpha are various fatty acids. Certain carboxylic acids have the ability to stimulate PPARs (alpha, gamma and delta). Anything that stimulates a nuclear transcription factor is called an agonist and anything that blocks an NTF is an antagonist. Thus PPAR-alpha stimulators like fibrates are called PPAR-alpha agonists. Interestingly fibrates can also influence other nuclear transcription factors such as liver X receptors (LXR) and ANGPTL and which also play key roles in lipid biology. This seems simple but in reality the process is extremely complex and very tissue specific and it also depends on the presence or absence of multiple other proteins which serve as NTF coactivators or corepressors. For example in the liver, but not in macrophages, fenofibrate (the ester) is an LXR antagonist (important in inhibiting TG synthesis) whereas fenofibric acid (not an ester) has no hepatic LXR antagonist ability on TG synthesis but does have hepatic LXR agonist activity to upregulate ABCA1.

The fibrates that have been most tested in clinical trials and most prescribed are clofibrate (Atromid S), gemfibrozil (Lopid), bezafibrate (not available in US) and fenofibrate (Antara, TriCor and several other names). The newest fibric acid to come on the scene (with considerable efficacy and safety data base) is fenofibric acid (Trilipix). All of these fibrates, except fenofibric acid are administered as esters and have to be converted by hepatic esterases to the carboxylic acid form. The vast majority of fibrate use in the USA is currently fenofibrate as the gemfibrozil is considered to have too many dangerous drug/drug interactions to use safely in combination therapy (severe package warnings). Now in the US, one will have to choose between fenofibrate and fenofibric acid.

Clofibrate (Atromid S) ----- Active PPAR-α form is clofibric acid
Gemfibrozil (Lopid) --- Active PPAR-α form is gemfibric acid
Fenofibrate (TriCor, Antara, etc) --- Active PPAR-α form is fenofibric acid
Bezafibrate ---- Active PPAR-α form is bezafibric acid
Fenofibric acid (Trilipix) – is the active PPAR-α form

Chemically Trilipix is the choline salt of fenofibric acid. Fenofibric acid is a carboxylic acid which has the ability (without undergoing any further modification) to agonize (stimulate) the nuclear transcription factor PPAR-alpha. Fenofibric acid is an amphipathic molecule with the carboxylic

acid (COOH) moiety being the polar end. When the choline salt enters the intestine it dissociates into choline and fenofibric acid (Trilipix is manufactured as a delayed release tablet of fenofibric acid). Once the choline disassociates, the COO (polar moiety) is exposed. The fenofibric acid is immediately absorbed and starts working (as a PPAR-alpha agonist) inside the enterocyte cell as a ligand recognized by PPAR-alpha. Enterocytes express PPAR-alpha as they are involved with production of proteins involved with the regulation of sterol absorption. Fenofibric acid then enters the blood stream, attaches to albumin and travels to and enters other tissues where PPAR-alpha is expressed (liver, vascular wall, adipocytes, muscles, etc.). The chemical structures of all of these processes and molecules are on my web site www.lipidcenter.com on the Professionals menu, Power Point slide library. A picture of chemical structure can be very enlightening.

Unlike fenofibrate, no hepatic (liver) metabolism is needed to modify the fenofibric acid molecule to render it able to agonize PPAR-alpha. Unlike fenofibric acid, Fenofibrate is packaged and swallowed as a methylethyl ester of fenofibric acid (-CO-CH-2(CH3)). Once absorbed it has to travel via plasma (bound to albumin) to the liver where it undergoes de-esterification (via an hepatic esterase). Once fenofibrate ester looses the ester (is hydrolyzed), via enzymatic cleavage, it becomes fenofibric acid which enters the blood stream, attaches to albumin and travels to tissues where PPAR-alpha is expressed. Fenofibrate (a methylethyl ester of fenofibric acid) is not an active PPAR-alpha agonist, because it has two nonpolar ends, whereas fenofibric acid (an amphipathic carboxylic acid) is. As mentioned above fenofibrate ester can act as an hepatic LXR antagonist.

In its simplest explanation: Antara, TriCor or other branded fenofibrates are prodrugs and Trilipix (fenofibric acid) is the actual active drug (PPAR-alpha-agonist). Fenofibrate requires hepatic metabolism to change into its active amphipathic metabolite, namely fenofibric acid. Trilipix (fenofibric acid) needs no hepatic catabolism to become active (amphipathic), it simply needs to lose its choline salt which it does in the intestinal juices. To be eliminated fenofibric acid returns to the liver and undergoes glucuronidation (made water soluble). Glucuronidated fenofibric acid returned to plasma and is then excreted by the kidney. Fortunately the glucuronidation enzymes fenofibric acid uses are not those used by statins or other drugs (TZDs, ezetimibe) and thus there are no interactions with those drugs. Since fenofibrate becomes fenofibric acid, it (TriCor and others) like fenofibric acid (Trilipix) have no drug-drug interactions other than with Coumadin (warfarin) which because of their protein binding avidity, they displace from albumin.

Theoretically fenofibric acid or Trilipix (the active drug) would be safer than fenofibrate as it requires no liver activation. However we have used fenofibrate for years without experiencing major difficulties. So whether the lack of hepatic activation has any clinical reality is unknown at this time. As we all know fenofibrate has been a very safe drug with no known serious statin interactions. However, Trilipix has significantly more published statin combo safety data than any other fibrate, so its FDA label on combination with a statin is very positive, compared other fibrates including fenofibrate. This may have more medicolegal importance than clinical importance. Certainly no pharmacists should be calling up providers warning them not to use fenofibric acid (Trilipix) with a statin. Also keep in mind the package insert makes that clear. fibrate/statin use, like niacin/statin, use is to be reserved for high or very high risk patients (like T2DM or metabolic syndrome patients) not at goal on statin monotherapy. Academically one would have to say Trilipix is safer when used in combo with a statin as extensive efficacy and safety data published evidence exists whereas it does not for fenofibrate. The FDA label clearly assumes Trilipix is safer when combined with a statin. As a monotherapy several trials (including a very large one) are testament that fenofibrate monotherapy is quite safe.