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PPARS - Peroxisome Proliferator Activated Receptor Activators and Fibrates Actions

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ABSTRACT

Peroxisome Proliferator Activated Receptor sits part of the family of nuclear receptors, which has about 50 known receptors, including thyroid hormone receptors, which have the function of regulating metabolism and metabolizing and eliminating substances. These receptors, to act, must be activated by ligands, form a heterodmer with the retinoic acid receptor, recruit activating cofactors, release inhibitory cofactors to which they are bound, and then act on the responsive element of target gene. Three species of peroxisome proliferator activated receptor are known: PPARa, PPARγ and PPARβ (also known as PPARd or β/d). The prototypes of PPARa activators are the derivatives of fibricacid, of which the first representative was clofibrate, used as a lipid-lowering factor in the 1960s and 1970s. Although there may be a small variation among the various fibrates regarding the mechanism of action, these drugs are basically PPARa activators. In the action of fibrates, there is a reduction of triglycerides, with a decrease in the synthesis of VLDL, increase of HDL particles and transformation of small and dense LDL into larger, less dense LDL and with lower atherogenic potential. Fibrates are second-choice substances, and statins are the first for the treatment of hypertriglyceridemia. Fibrates are efficient for the treatment of patients with low HDL-C, decrease macro and microvascular disease of diabetic patients. The recommendation is do not associate gemfibrozil with statins. Other fibrates may be associated, and preference should be given to the association of statins that are not metabolized by CYP3A4: rosvastatin, pravastatin and fluvastatin.

Keywords

Dense LDL lipoproteins; Fibrates; HDL Cholesterol; Hypertriglyceridemia; Peroxisome Proliferator Activated Receptor; Statins.

Abbreviations

Apo A-1: Apoprotein A-1; ApoC-3: Apolipoprotein C-3; CYP3A4: Cytochrome P450 3A4 protein; HDL: High Density Lipoprotein; HDL-C: High Density Lipoprotein Cholesterol; LDL: Low Density Lipoprotein; PPAR: Peroxisome Proliferator Activated Receptor; PPAR-a: Peroxisome Proliferator Activated Receptor-a; PPAR-β: Peroxisome Proliferator Activated Receptor-β; PPAR-γ: Peroxisome Proliferator Activated Receptor-γ; VLDL: Very Low Density Lipoprotein.

Peroxisome Proliferator Agonists Activated Receptor (PPAR)

Using clofibrate in research with rodents, it was observed that the administration of this drug induced the proliferation of hepatic peroxisomes. Although in the human race the Activators of PPAR do not cause an increase in the expression of peroxisomes, the name is maintained by tradition.

PPAR are part of the family of nuclear receptors, which has about 50 known receptors, including thyroid hormone receptors and which have as their function the regulation of metabolism and the metabolization and elimination of substances. These receptors,

to act, must be activated by ligands, form a heterodmer with the retinoic acid receptor, recruit activating cofactors, release inhibitory cofactors to which they are bound, and then act on the responsive element of target gene.

Three species of PPAR are known: PPAR-a, PPAR-γ and PPAR-β (also known as PPAR-d or β/d).

PPAR-a activators: the prototypes of PPAR-a activators are the derivatives of fibric acid, of which the first representative was clofibrate, used as a lipid-lowering factor in the 1960s and 1970s. Due to the profile of side effects, its use has been discontinued, new drugs have been developed and today one can dispose of genfibrozil (although, strictly speaking, this is not a derivative of fibrico acid by a strictly chemical definition, it is classified as a fibrate), fenofibrate, bezafibrate, ciprofibrate and etofibrate.

Mechanism of action of fibrates: although there may be a small variation between the various fibrates regarding the mechanism of action, these drugs are basically PPAR-a activators and act in the genetic control of some important proteins in lipid metabolism, decreasing the expression of apo lipoprotein C-3 (ApoC-3) and increasing the expression of apoprotein A-1 (apoA-1), fatty acid carrier protein, lipoprotein lipase and enzymes that increase fatty acid oxidation [1]. Through the action on these genes, triglycerides decrease, with a decrease in the synthesis of very low density lipoprotein (VLDL), increase of high density lipoprotein (HDL) particles and transformation of small and dense low density lipoprotein (LDL) into larger, less dense LDL and with lower atherogenic potential.

In addition to the improvement of the lipid profile, fibrates have antiatherothrombotic effects, via inhibition of inflammatory mediators, inhibition of coagulation and increased fibrinolysis [2].

Efficacy: the greatest effects of fibrates are on reducing triglycerides and increasing high-density lipoprotein cholesterol (HDL-C). Triglycerides are decreased by an average of 20 to 50% and HDL-C is increased by an average of 10 to 20%; the greatest increases appear when there are very low HDL-C and very high triglyceride levels. In relation to LDL-C, there may be from a slight decrease to an increase; this usually occurs when there is a sharp drop in triglycerides. However, as previously seen, changes occur in LDL particles that take on a less atherogenic form.

Fibrates, therefore, should be used in cases of hypertriglyceridemia or combined family hyperlipemia, and their use is especially recommended in cases of very high triglycerides at risk of pancreatitis and in the treatment of dyslipidemia associated with diabetes mellitus and metabolic syndrome.

The clinical efficacy of fibrates can be confirmed by the results of some large studies:
VA-HIT: [3] secondary prevention study with genfibrozil, which showed reduction in chonovascular events and stroke in men with low HDL-C.
BECAIT: [4] this angiographic study showed that, in patients treated with bezafibrate, dyslipidemia improved, fibrinogenemia reduced, coronary atherosclerosis progression decreased, and coronary events reduced.
LOCAT: [5] secondary prevention angiographic study in men undergoing myocardial revascularization surgery and with low HDL-C, showing that genfibrozild slowed the progression of coronary atherosclerosis and the formation of lesions in the veins used in revascularization.
DAIS: [6] secondary, angiographic prevention study with the use of fenofibrate compared with placebo in patients with type 2 diabetes, which showed a reduction in angiographic progression of coronary atherosclerosis in patients receiving fenofibrate.
Helsinki Heart Study: [7] primary prevention study in men with dyslipidemia, showing reduced risk for corony events especially in overweight patients.
FIELD: [8] study with the use of phenofibrate, controlled by placebo, in diabetic patients, showing that in the group of patients receiving fenofibrate there was a very mild improvement in dyslipidemia, which was statistically not significant, but with a statistically significant decrease in the incidence of macro and microvascular diseases. However, there was an excess of mortality not significant in the treated group.

It has also been shown that the use of the association of fenofibrate with sinvastatin in patients with triglycerides > 204 mg/ml and HDL-C < 34 mg/dl, in patients with well-controlled diabetes, led to a significant reduction in the number of amputations [9].

Safety and tolerability: although in some studies with fibrates there is a non-significant excess of mortality in the group with active treatment, it can be concluded that the safety margin for the use of fibrates is well established in patients at high risk for cardiovascular disease and pancreatitis.

These drugs are generally well tolerated and the side effects presented are rare, and can be mentioned: epigastric pain or burning, flatulence, headache, anxiety, fatigue, vertigo, sleep changes, myalgia, loss of libido and alopecia. Although there was an excess of biliary lithiasis with clofibrate, this is not seen with the other drugs in the group. Myopathy rarely occurs, which can sometimes progress to rhabdomyolysis. Risk factors for the development of myopathy are: renal failure, hypoalbuminemia, association with vastatins or other substances metabolized by cytochrome P450 3A4 protein (CYP3A4) or that would instill it, such as cyclosporine, antifungal agents, or erythromycin. Among the fibrates, the one that most causes myopathy when in association, especially with vastatine, is genfibrozil.

Eventually, elevation of hepatic transaminases may occur, which should be determined 30 days after the start of therapy and sequentially at intervals of 4 to 6 months.

Dosage: genfibrozil should be administered at a dose of 1,200 mg in 2 taken, half an hour before breakfast and dinner. The dose of micronized fenofibrate ranges from 67 to 200 mg in a single daily

dose, accompanied by a meal. Bezafibrate is used in a single dose of 400 mg as a slow-release tablet. Ciprofibrate is used at a dose of 100 mg/day, in a single dose with a meal. Etofibrate is used in the single daily dose of 500 mg.

It is important to remember that concomitant administration of bile resins and antacids leads to a decrease in the absorption of fibrates.

Contraindications: fibrates are contraindicated in severe liver or kidney dysfunctions and in patients with a history of biliary lithiasis. Should be avoided in diabetic nephropathy, pregnancy and lactation.

In summary, the considerations about fibrates are summarized in:
- Fibrates are substances of choice for the treatment of hypertriglyceridemia.
- Fibrates are efficient for the treatment of patients with low HDL-C.
- Fibrates decrease macro and microvascular disease of diabetic patients.

Do not associate genfibrozil with statins. Other fibrates may be associated, and preference should be given to the association of statins that are not metabolized by CYP3A4: rosvastatin, pravastatin and fluvastatin.

PPAR-g agonists: although PPAR-g agonists are drugs of use in the treatment of type 2 diabetes mellitus because they are sensitizing to insulin action, this action of reducing insulin resistance may be accompanied by improvement of metabolic syndrome and diabetes dyslipidemia. However, it should always be remembered that the primary indication of these drugs is for the treatment of type 2 diabetes.

In the PROactive study, [10] with the use of pyoglitazone in diabetic patients with cardiovascular disease (very high risk), in addition to a lower incidence of myocardial infarction, which was statistically significant, there was a reduction in triglycerides and a slight increase in HDL-C in the group that received pioglitazone in relation to the placebo group.

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