LIPID-LOWERING DRUGS: NON-STATIN LIPID LOWERING AGENTS

P3499 Ezetimibe (SCH58235) inhibits cholesterol absorption, reduces plasma cholesterol, and inhibits the development of atherosclerosis in Apo E knockout mice fed a cholesterol-free diet

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Objective: To determine if Ezetimibe (SCH58235), ((1-(4-fluorophenyl)-(3R)-[3-(4-fluorophenyl)-(3S)-hydroxypropyl]-(4S)-(4-hydroxyphenyl)-2-azetidinone) reduces cholesterol absorption and inhibits atherogenesis in apo E knockout (-/-) mice fed a cholesterol-free diet.

Methods: Ezetimibe (0.3, 1, 3, and 10mg/kg/day) was evaluated for inhibition of cholesterol absorption ([14C]-cholesterol/[3H]-sitosterol, 4 day fecal analysis) in apo E +/- and -/- mice. Atherosclerosis and lipoprotein changes were determined in apo E -/- mice fed a semi-synthetic cholesterol free diet alone or containing ezetimibe (5mg/kg) for 6months (n=12/group).

Results: Apo E +/+ and -/- mice absorbed 51.2% and 55.5% of the [14C]-cholesterol, respectively. Cholesterol absorption was inhibited 90% by ezetimibe at 3mg/kg in the apo E -/- mice and >90% at 10mg/kg/day in both apo E +/+ and -/- mice. The plasma cholesterol levels in apo E -/- mice were reduced from 516mg/dl to 178mg/dl by ezetimibe (5mg/kg/day) after 6 months of treatment. The reduction occurred in the VLDL and LDL lipoprotein fractions, while HDL levels were increased by ezetimibe from 27mg/dl to 45mg/dl. Atherosclerotic lesion cross sectional area was reduced 91% by ezetimibe treatment from 0.0436mm2 to 0.0038mm2 ($p<0.05$) in the carotid artery and by 81% in the aorta ($p<0.05$).

Conclusion: Apo E -/- mice have normal cholesterol absorption and ezetimibe has similar activity at inhibiting cholesterol absorption in apo E -/+ and +/- mice. Ezetimibe reduces plasma cholesterol levels, increases HDL, and inhibits the progression of atherosclerosis in apo E -/- mice fed a cholesterol free diet. Ezetimibe may inhibit atherogenesis clinically in individuals consuming restricted cholesterol diets.

P3500 Ezetimibe (SCH58235) localizes to the brush border of small intestinal enterocyte and inhibits entertocyte cholesterol uptake and absorption

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Objective: Ezetimibe, SCH58235 ((1-(4-fluorophenyl)-(3R)-[3-(4-fluorophenyl)-(3S)-hydroxypropyl]-(4S)-(4-hydroxyphenyl)-2-azetidinone) is a potent inhibitor of cholesterol absorption leading to significant decreases in plasma cholesterol levels in cholesterol-fed animals and primary hypercholesterolemic patients. The purpose of this study was to determine the tissue localization and effect of ezetimibe on intestinal cholesterol metabolism.

Methods: An I125 labeled glucuronide of ezetimibe was synthesized for localization studies. Labeled ezetimibe was given intravenously to intact and bile duct cannulated rats and total tissue and autoradiographic localization was determined. The effect of ezetimibe relative to the ACAT inhibitor PD128042 on [C14]-cholesterol enterocyte uptake and absorption was performed in rats following intraduodenal dosing.

Results: The labeled glucuronide of ezetimibe localized primarily in the small intestine 3 hours following intravenous administration. In bile duct cannulated rats the intravenous dose appeared almost entirely in the bile within 3 hours. Small intestinal autoradiography demonstrated that the labeled compound was localized to the brush border of the enterocytes. [C14]-Cholesterol absorption into the plasma and liver was inhibited by both ezetimibe and the ACAT inhibitor PD128042. The uptake of [C14]-cholesterol into the enterocytes was inhibited by ezetimibe and a majority of the [C14]-cholesterol remained in the lumen of the intestine. PD128042 did not inhibit the uptake of [C14]-cholesterol into the enterocytes and it did not increase the amount of [C14]-cholesterol remaining in the intestinal lumen. Therefore, the effect of ezetimibe on inhibiting intestinal cholesterol uptake and absorption occurred prior to cholesterol reaching ACAT for esterification.

Conclusion: Ezetimibe localizes to the brush border of the small intestinal enterocytes, reduces the uptake of cholesterol into the enterocytes, inhibits the absorption of cholesterol, and keeps cholesterol in the lumen of the intestine for excretion.

P3501 BAY 13-9952 (implitapide): pharmacodynamic effects of a new microsomal triglyceride transfer protein (MTP) inhibitor on plasma lipids and adipose tissue in animals

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Objective: BAY 13-9952 has shown to potently inhibit the MTP-activity and secretion of apoB-containing particles in vitro. Animal studies should demonstrate the pharmacological profile of this new therapeutic principle and the pharmacodynamic effects of BAY 13-9952.

Methods: The intestinal effects on TG absorption and postprandial (pp) TG rise were investigated after oral olive oil loading in rats. The hepatic VLDL secretion was studied after intravenous injection of the lipoprotein lipase inhibitor Triton WR 1339 and determination of plasma TG. Lipid lowering effects (TG and CHOL) of BAY 13-9952 were investigated in genetically hypertriglyceridemic fa/fa-Zucker rats and dogs, and effects on adipose tissue in obese Zucker rats.

Results: The intestinal TG absorption and pp plasma TG rise was reduced by 50% with 0.3 mg/kg body weight p.o.(ED50-value). The hepatic VLDL secretion in rats was decreased by 50% after 1 mg/kg body weight p.o. After acute administration to fa/fa-Zucker rats, BAY 13-9952 effectively reduced plasma TG and CHOL concentrations by 50% after 1.5 mg/kg and TG up to 80% after 4.5 mg/kg b.w. In subchronic 4-week studies only 0.5 mg/kg b.w./day reduced the TG levels by 84%. In feeding experiments for 4 weeks 45 ppm BAY 13-9952 administered in normal lab chow reduced the perirenal and epididymal fat by 22%. The same dose, administered in a high caloric diet to female obese Zucker rats decreased the perirenal fat accumulation by 38%. BAY 13-9952 was also active in dogs: In subchronic studies, 4 mg BAY 13-9952/kg b.w. lowered plasma TG levels by 60%.

Conclusion: In acute and subchronic rat and dog studies, BAY 13-9952 effectively reduced pp serum TG rises as well as fasting plasma TG and CHOL concentrations, and additionally the accumulation of fat in adipose tissue. This pharmacological approach of inhibiting MTP-activity and secretion of apoB-containing particles may offer a new therapeutic principle for the treatment of combined hyperlipidemia and arteriosclerosis.

P3502 Fenofibrate, but not atorvastatin treatment increases homocystein levels in patients with combined hyperlipidaemia

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Objectives: It has been recently reported in small clinical trials, that treatment with fibrates increased total serum homocysteine (tHCY) level, while simvastatin did not influence it. The effect of atorvastatin (A) and fenofibrate (F) on the levels of total serum homocysteine in patients with combined hyperlipidaemia has not been compared yet. To assess the influence of fibrates and statins on serum tHCY levels we analysed the whole group of patients enrolled into randomised, cross-over trial comparing both drugs (Fenofibrate versus Atorvastatin Trial, FAT).

Methods: 29 non-smoking males (mean age 47.2 ± 7.8 years, mean BMI 27.7 ± 2.7) with combined hyperlipidaemia, without any other disease or medication, were randomised to treatment with 10 mg of atorvastatin o.d. or 200 mg of micronised fenofibrate o.d. The medication was crossed over after 10 weeks. Patients were asked to remain on the same diet during all study period. Fasting blood samples were taken at the baseline, in the middle and at the end of the trial and were processed immediately. Total serum homocysteine was determined with HPLC method.

Results: are presented in the Table and are expressed as percentual change of mean values against baseline. Paired t-test was used for comparison of pre-, post and between treatment values. P less than 0.05 was considered significant.

	baseline	F-fibrate (%)	A-statin (%)	F v A
Cholesterol	7.54 mmol/L	- 12.1 ***	- 27.9 ***	***
Triglycerides	5.41 mmol/L	- 49.7 ***	- 32.2 **	**
Serum tHCY	12.4 umol/L	+ 36.5 ***	- 0.7 NS	***
Serum creatinine	96.7 umol/L	+ 10.7 ***	- 0.6 NS	***

* p less than 0.05, ** p less than 0.005, *** p less than 0.0005

Conclusion: F was more efficient than A in reduction of triglycerides levels. A was more efficient than F in reduction of total cholesterol levels. In agreement with previous report we found, that F treatment caused a significant increase of serum tHCY level, associated with significant increase of serum creatinine level. Either serum tHCY or creatinine level did not change after A treatment.