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Effects of simvastatin, bezafibrate and gemfibrozil on the quantity and composition of plasma lipoproteins

Edna Nakandakare, Roberto C. Garcia, Jussara C. Rocha, Giuseppe Sperotto, Helena C.F. Oliveira and Eder C.R. Quintão

Lab. Lipids – (LIM/10) Hospital of the University of São Paulo Medical School, São Paulo (Brazil)

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Summary

Simvastatin, 10–40 mg/d ($n = 11$), bezafibrate, 600 mg/d ($n = 6$), and gemfibrozil, 1200 mg/d ($n = 5$) were administered for 12 weeks after a 4-week placebo period to subjects with initial plasma levels (mg/100 ml, mean ± SD) of cholesterol (346 ± 77), and of triglycerides (180 ± 54). Total LDL-C plasma concentration was lowered 32% by simvastatin and 35% by bezafibrate, but only bezafibrate diminished the triglyceride (41%) and increased HDL-C plasma levels (35%). Plasma lipoprotein fractions obtained by discontinuous gradient ultracentrifugation, namely, VLDL, lighter LDL (LDL-1), heavier LDL (LDL-2) and bulk HDL were chemically analyzed. Simvastatin and bezafibrate significantly diminished the quantity of VLDL and LDL-1 particles, although barely modifying their composition. Neither drug influenced the LDL-2 plasma concentration. Bezafibrate increased the total plasma HDL level little interfering with its chemical composition. Gemfibrozil was the least effective of all drugs but decreased the lipid and protein contents and their ratios in VLDL and LDL-2.

Key words: Simvastatin; Bezafibrate; Gemfibrozil; Lipoprotein ultracentrifugation; Lipoprotein composition; Low density lipoprotein; High density lipoprotein

Introduction

Hypolipidemic drugs with different mechanisms of action on the metabolism of plasma lipoproteins should produce distinct plasma lipoprotein profiles. For example, drugs that primarily inhibit the activity of the enzyme 3-hydroxy-3-methylglutaryl coenzyme A reductase are likely to lower the plasma LDL level through an enhancement of the specific liver LDL receptor number [1–3], whereas the fibrate group of drugs that preferentially lower the plasma triglyceride value, as represented by the VLDL level, should have relatively less influence on the LDL plasma content.

On the other hand, modifications in the lipoprotein quantity and distribution patterns elicited by a certain drug are often dependent upon the

Correspondence to: Dr. Edna Nakandakare, Lab.Lipids – (LIM/10), Hospital of the University of São Paulo Medical School, Av. Dr.Arnaldo, 455-3° A, CEP 01246, São Paulo, Brazil

initial lipoprotein profile as determined by genetic or secondary causes [4,5]. Lipid lowering drugs, in addition to interfering with the quantity of plasma lipoproteins, could modify their size and chemical composition.

In this report it is shown that an HMG-CoA reductase inhibitor (simvastatin) and a fibrate (bezafibrate), although markedly differing in their pharmacological mechanisms of action, have remarkably similar effects on the quantity of VLDL and on the lighter low density lipoprotein particles (LDL-1), barely interfering with the LDL-2 plasma concentration.

Material and methods

Primary hyperlipidemic subjects, 22–66 years of age, joined the study at the out-patient lipid clinic after signing a formal written consent. There were 22 normal weight hyperlipidemic adults (9 men, 13 women). Lipid lowering drugs were administered to all subjects (Table 1) whose cholesterol (346 ± 77), and triglyceride (180 ± 54) levels had been measured over at least 6 weeks of a standard (phase 1) American Heart Association recommended lipid lowering diet [6] before starting the drugs. None of the subjects was obese or had unstable angina, recent heart attacks or diabetes mellitus. Alcohol intake levels were negligible. Their thyroid, liver and renal functions were normal.

Baseline plasma lipid values were measured at the beginning and at the fourth week of the placebo phase. Thereafter the subjects were administered for 12 weeks one of the 3 lipid lowering drugs in a randomized double-blind study: (1) simvastatin (MK-733), a hydroxymethylglutaryl CoA re-

TABLE 1

CLINICAL DATA AND SERUM LIPIDS OF PATIENTS MEASURED DURING THE PLACEBO PERIOD

Patient	Age (y)	Sex	BMI (kg/m^2)	Chol (mg/dl)	Tg (mg/dl)	Clinical findings
Simvastatin						
1	22	F	18.0	503	138	Xanthomata, FH
2	52	F	24.3	267	90	
3	64	F	20.3	318	214	FH
4	66	F	25.4	292	200	Xanthomata, FH
5	31	F	26.5	343	159	FH
6	60	M	24.8	438	139	
7	61	F	24.8	273	192	
8	56	F	27.6	322	267	
9	55	F	25.3	507	170	CHD, FH
10	45	M	24.8	276	271	Gout, hypertension
11	41	M	28.0	387	263	CHD, Xanthomata
Mean ± SD	50 ± 14		24.6 ± 2.9	357 ± 90	190 ± 60	
Bezafibrate						
12	52	M	20.4	433	169	CHD, Xanthomata
13	60	F	26.4	334	189	
14	38	M	27.2	340	128	Corneal arcus
15	29	M	25.4	265	89	FH
16	57	F	25.3	342	143	Corneal arcus, CHD, hypertension
17	42	F	24.3	289	266	FH
Mean ± SD	46 ± 12		24.8 ± 2.4	334 ± 58	164 ± 61	
Gemfibrozil						
18	31	F	30.0	331	138	Corneal arcus, CHD, FH
19	57	F	27.6	477	224	Xanthelasma
20	47	M	25.4	310	188	Xanthelasma, corneal arcus
21	39	M	25.7	294	141	CHD
22	46	M	25.9	274	181	CHD
Mean ± SD	44 ± 10		26.9 ± 1.9	337 ± 81	174 ± 36	

BMI = body mass index; FH = familial hypercholesterolemia; CHD = coronary heart disease.

ductase inhibitor, administered as single dose before dinner (10–40 mg/day: $n = 11$); (2) bezafibrate, 600 mg/day, divided into 200 mg doses before meals ($n = 6$); (3) Gemfibrozil, 1200 mg/day, divided into 600 mg doses before meals ($n = 5$). Clinical profiles, blood lipid and chemical analyses, were done twice during the placebo period and at weeks 4, 6, 10 and 12 during treatment. The simvastatin doses were adjusted along the course of the study so as to lower LDL-cholesterol to levels below 140 mg/100 ml. At the 6th week, drug distribution was: 10 mg/day ($n = 5$), 20 mg/day ($n = 3$), and 40 mg/day ($n = 3$), average dose being 21 mg/day. None of the drugs elicited adverse side-effects and tolerance was excellent. Blood (20 ml) was drawn after a 12-h fasting into 0.1 ml EDTA solution (8%), sodium azide (5%), and chloramphenicol (0.1%). Cholesterol and triglycerides were measured by enzymatic procedures (Chod-Pap, Boehringer Mannheim Biochemicals, F.R.G. and TG-Enz-Color, Bio-Diagnostica, Brazil). HDL-cholesterol was determined by the enzymatic procedure after precipitation of the lower density lipoproteins with dextran sulfate and magnesium chloride (Wiener Lab., Argentina). This method permitted the estimation of LDL and VLDL-cholesterol by the Friedewald formula [7] in freshly collected samples.

Plasma lipoproteins were isolated by preparative discontinuous density gradient ultracentrifugation [8] at the following density ranges: below 1.006 g/ml (chylomicrons + VLDL), 1.006–1.030 g/ml (LDL-1), 1.030–1.063 g/ml (LDL-2), and 1.063–1.210 g/ml (HDL) [8]. At $d < 1.006$, the fasting plasma should contain VLDL particles only. Fractions were stored in a deep-freezer and analysed in duplicate as a single batch at the end of the study. Cholesterol and triglycerides were quantified by the methods already described; phospholipids by the Bartlett technique [9], and protein by the Lowry method [10]. However, since the HDL fraction contains albumin, the HDL protein content was expressed solely as apo A1 as measured by radial immunodiffusion. The total plasma apo B value was also obtained by immunodiffusion (Daiichi Chemical Co. Ltd., Tokyo, Japan). Data are presented as the mean values of 2 sequential determinations during the placebo phase and at the 10th and 12th week of treatment. Statistical significance of the data was determined by Student's t-test [11].

Results

Table 2 presents plasma lipid levels, HDL-C, VLDL-C and LDL-C as calculated by the Friedewald formula, together with the total plasma Apo A1 and apo B data. When compared to the placebo period, Simvastatin and Bezafibrate were

TABLE 2

PLASMA LIPIDS, LIPOPROTEIN CHOLESTEROL AND APOLIPOPROTEIN LEVELS MEASURED DURING THE PLACEBO PERIOD AND DURING TREATMENT (MEAN DURATION 10–12 WEEKS)

Mean mg/dl ± SD (% variation).

	Chol	VLDL-C	LDL-C	HDL-C	Tg	apo B	Apo A1
Placebo	357 ± 90	38 ± 12	261 ± 94	47 ± 13	190 ± 60	135 ± 30	112 ± 31
Simvastatin	255 ± 77 * (−28%)	34 ± 14	177 ± 83 * (−32%)	47 ± 19	171 ± 69	110 ± 30 * (−19%)	111 ± 28
Placebo	334 ± 58	33 ± 12	258 ± 57	40 ± 10	164 ± 61	125 ± 38	116 ± 15
Bezafibrate	241 ± 46 * (−28%)	19 ± 2 * (−42%)	167 ± 48 * (−35%)	55 ± 10 * (+35%)	96 ± 13 * (−41%)	98 ± 13 * (−22%)	138 ± 30 * (+19%)
Placebo	337 ± 81	35 ± 7	268 ± 68	34 ± 9	174 ± 36	155 ± 26	89 ± 19
Gemfibrozil	304 ± 69	21 ± 8 * (−41%)	246 ± 58	33 ± 12	102 ± 38 * (−41%)	147 ± 19	96 ± 14

Chol = plasma cholesterol; Tg = plasma triglycerides; VLDL-C and LDL-C calculated by the Friedewald formula after precipitation of apo B containing LP.

* $P < 0.01$ according to Student's t-test.

about equally efficient in lowering total plasma cholesterol, LDL-cholesterol, as well as apo B levels. However, Bezafibrate had the additional advantage of being more effective in lowering VLDL-cholesterol and increasing the plasma HDL-C and Apo A1 levels. Gemfibrozil was the least efficient of the three drugs since it significantly reduced only plasma triglyceride and VLDL-cholesterol concentrations, although these effects were as efficient as those of Bezafibrate. However, gemfibrozil may have had some lowering activity on total cholesterol, LDL-C, VLDL-C and apo B levels that did not reach statistical significance only because of the small sample size ($n = 5$).

Table 3 presents the plasma concentrations of cholesterol, triglycerides, phospholipids and protein, together with the total lipid/protein ratios in

TABLE 3

PLASMA CONCENTRATION OF CHOLESTEROL (C), TRIGLYCERIDES (Tg), PHOSPHOLIPIDS (PL), PROTEIN (P) AND RATIO C+Tg+PL/P in VLDL, LDL-1, LDL-2 AND HDL FRACTIONS AFTER PREPARATIVE ULTRACENTRIFUGATION.

Mean mg/dl ± SD (% variation). Mean of 2 analyses/patient were utilized in each period.

		Cholesterol	Triglycerides	Phospholipids	Protein	C+Tg+PL/P
Simvastatin ($n = 11$)						
VLDL	Placebo	29.2 ± 3.7	73.7 ± 11.3	34.5 ± 4.2	18.2 ± 1.7	7.3 ± 0.4
	Drug	19.6 ± 3.4 * (−33%)	57.4 ± 12.7 * (−22%)	26.0 ± 4.2 ** (−25%)	13.6 ± 1.9 ** (−25%)	7.2 ± 0.4
LDL-1	Placebo	142.3 ± 23.3	39.3 ± 3.9	99.0 ± 13.5	74.3 ± 11.1	3.9 ± 0.1
	Drug	90.6 ± 9.8 ** (−36%)	40.5 ± 6.5	85.6 ± 10.2	55.8 ± 4.4 * (−25%)	3.9 ± 0.3
LDL-2	Placebo	120.3 ± 13.1	21.4 ± 2.6	84.3 ± 8.6	97.7 ± 7.4	2.3 ± 0.2
	Drug	95.4 ± 11.7	22.6 ± 1.8	69.6 ± 6.9	90.6 ± 10.1	2.2 ± 0.2
HDL	Placebo	30.1 ± 2.4	9.6 ± 0.9	68.6 ± 5.4	88.8 ± 5.7	1.2 ± 0.04
	Drug	30.9 ± 3.0	14.2 ± 1.4 ** (+47%)	71.3 ± 9.9	94.7 ± 8.8	1.3 ± 0.1
Bezafibrate ($n = 6$)						
VLDL	Placebo	30.5 ± 10.0	61.0 ± 21.3	31.3 ± 8.2	17.7 ± 4.1	6.4 ± 0.6
	Drug	11.2 ± 2.7 * (−63%)	23.3 ± 3.8 ** (−62%)	14.2 ± 2.3 * (−55%)	7.7 ± 1.5 ** (−57%)	6.5 ± 0.3
LDL-1	Placebo	150.0 ± 21.6	46.7 ± 6.8	97.3 ± 13.4	79.5 ± 11.7	3.7 ± 0.1
	Drug	100.8 ± 8.7 * (−33%)	27.8 ± 2.5 * (−40%)	81.0 ± 3.8	61.2 ± 4.4 * (−23%)	3.4 ± 0.1 * (−8%)
LDL-2	Placebo	99.8 ± 18.6	18.7 ± 2.8	65.3 ± 9.6	79.7 ± 10.6	2.3 ± 0.1
	Drug	72.0 ± 13.0	12.8 ± 1.5	49.8 ± 6.4	59.3 ± 5.11	2.2 ± 0.2
HDL	Placebo	30.7 ± 3.5	9.5 ± 1.2	67.3 ± 6.5	90.2 ± 11.1	1.2 ± 0.1
	Drug	38.2 ± 3.5 ** (+24%)	11.0 ± 1.2 ** (+16%)	106.6 ± 14.1 ** (+58%)	127.3 ± 12.9 ± * (+41%)	1.2 ± 0.04
Gemfibrozil ($n = 5$)						
VLDL	Placebo	27.6 ± 5.6	84.4 ± 10.0	34.2 ± 4.9	17.8 ± 2.6	8.3 ± 0.4
	Drug	9.0 ± 2.7 * (−67%)	26.0 ± 5.9 ** (−69%)	11.6 ± 2.8 ** (−66%)	7.2 ± 2.1 ** (−60%)	7.1 ± 0.6 ** (−15%)
LDL-1	Placebo	101.2 ± 22.7	32.6 ± 6.2	96.2 ± 24.1	59.6 ± 8.5	3.8 ± 0.5
	Drug	95.8 ± 12.5	28.0 ± 6.1	99.4 ± 8.6	51.6 ± 2.4	4.3 ± 0.2
LDL-2	Placebo	170.0 ± 12.8	28.6 ± 3.0	103.4 ± 6.4	110.4 ± 6.4	2.7 ± 0.1
	Drug	144.4 ± 15.8	20.4 ± 11.2 ** (−28%)	86.4 ± 11.2 * (−16%)	100.2 ± 9.1	2.5 ± 0.1 * (−7%)
HDL	Placebo	27.0 ± 4.2	9.4 ± 1.1	62.8 ± 11.6	83.2 ± 14.6	1.2 ± 0.1
	Drug	26.4 ± 2.9	8.8 ± 0.8	66.2 ± 9.4	86.0 ± 8.3	1.2 ± 0.04

* $P < 0.05$; ** $P < 0.01$, according to Student's t-test.

each lipoprotein fraction. Simvastatin did not alter the total plasma triglyceride concentration; its triglyceride lowering effect in the VLDL fraction apparently was balanced out by a simultaneous gain in triglycerides by the HDL fraction. Nevertheless, the small variation in HDL triglyceride level was insufficient to alter the total HDL lipid content since the lipid/protein ratio did not change upon treatment.

Similarly to simvastatin, bezafibrate diminished the amounts of most of the VLDL and LDL-1 components although, surprisingly, both drugs did not significantly modify the quantity of LDL-2 constituents. Variations in plasma VLDL and LDL-1 concentrations, taken together, explain the lowering of total plasma cholesterol levels by these two drugs, and of triglycerides by Bezafibrate. Although both drugs diminished the plasma concentrations of VLDL and LDL-1 fraction, their lipid/protein ratios remained stable (except for a minor reduction in the LDL-1 ratio on Bezafibrate). These results can only be compatible with a fall in total VLDL and LDL-1 mass in plasma. Bezafibrate must have additionally partially emptied LDL-1 of its fat content, while simultaneously reducing its total mass.

Bezafibrate induced HDL alterations were far more distinct than those secondary to simvastatin, i.e., bezafibrate increased the levels of all HDL components while not disturbing the lipid/protein ratio, a fact that is compatible with a sharp increase in the absolute quantity of HDL particles.

Gemfibrozil did elicit some modifications in the plasma lipoprotein composition in spite of its less potent lipid lowering activity. The drug altered the VLDL fraction by lowering its cholesterol, triglyceride, phospholipid and protein plasma concentrations together with the lipid/protein ratio. In contrast to the ineffectiveness of bezafibrate and simvastatin on LDL-2, gemfibrozil induced a small but significant decrease in the lipid/protein LDL-2 ratio when compared to the placebo period owing to a combined lowering of triglyceride and of phopholipid levels. However, in spite of these modifications in individual lipoproteins, the overall plasma cholesterol lowering efficiency of gemfibrozil was not as distinct as that attained with the other two drugs.

Although the total phospholipid level had not been measured in plasma, its decrease was clearly observed in VLDL after the use of all drugs, and in LDL-2 after the use of gemfibrozil. Phospholipids increased in the HDL fraction under Bezafibrate treatment only.

Discussion

Lipid lowering drugs have complex mechanisms of action on plasma lipoproteins interfering with their rates of production, tissue uptake and exchange of constituentes that simultaneously determine the number and composition of the lipoprotein particles.

Competitive HMG-CoA reductase inhibitors markedly increase the plasma LDL removal rate [1,2] but also are known to impair the LDL production rate [12]. Both mechanisms lower the total plasma cholesterol. In the present study simvastatin significantly reduced the amounts of VLDL and LDL-1, without modifying their lipid/protein ratio. A mild reduction in plasma LDL-2 level did not reach statistical significance. This drug is known to increase the number of high affinity LDL receptors in the liver that are preferentially known to recognize large apo E containing lipoproteins, such as VLDL, and larger and lighter LDL particles [13], with less affinity to the smaller and denser LDL-2 particles [14,15].

Percent distribution of the lipoprotein constituents is presented in Table 4. Simvastatin did not alter VLDL composition. Musliner et al. [16] showed that the larger VLDL particles are removed from plasma faster than the smaller VLDL particles and that a fraction of the latter yields most of the plasma LDL. Our results support their findings in the sense that a faster removal rate of the larger VLDL may also have contributed to reducing the quantity of their direct product, namely LDL-1 particles, but not necessarily that of the LDL-2 particles.This drug modified a little the percent distribution of the LDL-1 constituents, but its influence on LDL-2 composition was negligible (Table 4). On the other hand, HMG-CoA reductase inhibitors may also impair the VLDL production that could additionally interfere with plasma VLDL and LDL levels [17]. Statins are likely to diminish the plasma concentrations of these lipoproteins little interfering

TABLE 4

PERCENT DISTRIBUTION OF THE LIPOPROTEIN CONSTITUENTS (CHOLESTEROL, TRIGLYCERIDES, PHOSPHOLIPIDS AND PROTEIN = 100%) IN EACH PLASMA/LIPOPROTEIN FRACTION

	Chol	Tg	Phospho-lipids	Protein
Simvastatin ($n = 11$)				
VLDL				
Placebo	19.3	46.0	22.3	12.4
Drug	17.4	46.8	23.2	12.6
LDL-1				
Placebo	39.0	12.0	28.3	20.7
Drug	33.3 **	14.6 *	30.9 **	21.2
LDL-2				
Placebo	36.6	6.5	25.8	31.1
Drug	33.9	8.3 **	25.0	32.8
HDL				
Placebo	5.3	4.9	34.7	45.1
Drug	14.7	7.0 *	33.3	45.0
Bezafibrate ($n = 6$)				
VLDL				
Placebo	21.7	40.9	23.4	14.0
Drug	20.0	39.6	26.2 *	14.2
LDL-1				
Placebo	40.0	12.7	26.1	21.2
Drug	36.9 *	10.3 **	30.2 *	22.6
LDL-2				
Placebo	37.3	7.2	24.9	30.6
Drug	35.8	6.7	25.8	31.7
HDL				
Placebo	15.5	4.9	34.4	45.2
Drug	13.6 **	4.0 *	37.2	45.2
Gemfibrozil ($n = 5$)				
Placebo	16.1	52.3	20.8	10.8
Drug	16.2	49.1	22.1	12.6 *
LDL-1				
Placebo	34.3	11.4	32.1	22.2
Drug	34.3	10.7	36.1 *	18.9
LDL-2				
Placebo	41.4	7.0	25.0	26.9
Drug	41.1	5.8	24.4	28.7 *
HDL				
Placebo	15.0	5.4	34.3	45.3
Drug	14.1	5.1	34.7	46.1

* $P < 0.05$; ** $P < 0.01$.

with the percent distribution of their constituents as shown in Table 4.

The reason for the HDL-triglyceride gain elicited by simvastatin is unknown. It may ultimately have resulted from a shifting of lipid components among the plasma lipoproteins that may be ascribed to the activity of the lipid transfer proteins [18].

The bezafibrate induced drop in plasma VLDL or LDL-1 concentration was remarkable, although the lipid/protein ratio was not modified in the VLDL fraction, and was decreased by only 8% in the LDL-1 range (Table 3). In comparison, modifications in VLDL and LDL-1 compositions, although significant, were of relatively lesser magnitude (Table 4). Bezafibrate seemingly did not significantly boost a specific hydrolysis of the VLDL-triglyceride content by the lipoprotein lipase activity, since this mechanism of action should primarily lower the VLDL triglyceride content. Instead it appears that Bezafibrate simultaneously impaired the rate of VLDL production and stimulated its removal in the liver. However, stimulation of VLDL triglyceride depletion would most likely be observed in hypertriglyceridemics rather than in the present types IIa and IIb.

Similarly to simvastatin, bezafibrate did not influence the quantity or composition of LDL-2. LDL plasma level is the outcome of the VLDL delipidation cascade in plasma [19] and of VLDL and LDL uptake by common high affinity liver apo B-E receptors. Depending on the degree and type of hyperlipidemia those metabolic processes could be independently influenced by bezafibrate [4,20] leading to the formation of different species of LDL particles.

Bezafibrate increased the total amount of plasma HDL without interfering with the lipid/protein HDL ratio, and slightly modified the HDL composition (Table 4). The origin of HDL is rather complex. For instance, HDL components exchange with other lipoproteins, notably chylomicrons and VLDL [18,21]. As fatty acids leave these large lipoproteins, cholesterol, proteins, phospholipids and even triglycerides may shift to HDL. Consequently bezafibrate may lead to the formation of a greater quantity of HDL but not necessarily to its enrichment in lipid constituents. In fact, as shown in Table 3, the total lipid/protein ratio of HDL did not change on bezafibrate. In short, since this drug interferes simultaneously with the rate of VLDL synthesis, splanchnic uptake, and delipidation rates in plasma, it will probably likely determine changes in the level and

composition of each plasma lipoprotein according to the type and degree of hyperlipidemia.

Gemfibrozil did substantially reduce the plasma triglyceride but not the cholesterol concentration. This drug significantly lowered the amount of VLDL but only reduced the contents of triglycerides and phospholipids in LDL-2 (Table 3). In contrast to the two other drugs, gemfibrozil modified the VLDL and LDL lipid/protein ratio, and had no effect either on the quantity or the composition of HDL, a finding that does not agree with other reports [22,23]. However, the smaller sample size in the gemfibrozil group made it less likely that significant effects on the lipoprotein lipid levels were observed in this group as compared to the other two drugs.

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