Atherosclerosis, 37 (1980) 625—629

CLOFIBRATE RAISES PLASMA APOPROTEIN A-I AND HDL-CHOLESTEROL CONCENTRATIONS

P.J. NESTEL, D. HUNT and M.L. WAHLQVIST

Baker Medical Research Institute, Melbourne; Department of Cardiology, Royal Melbourne Hospital; and Section of Human Nutrition, Deakin University, Geelong, Victoria (Australia)

(Received 9 April, 1980)
(Revised, received 4 June, 1980)
(Accepted 5 June, 1980)

Summary

In 10 hyperlipidaemic subjects who had been satisfactorily treated with clofibrate, stopping treatment led to significant reductions in plasma apoprotein A-I and high density lipoprotein cholesterol concentrations; resumption of treatment significantly raised both. The changes were therefore inversely related to those in the plasma cholesterol and triglyceride levels and were most prominent in hypertriglyceridaemic subjects.

Key words: *Clofibrate — High density lipoproteins*

Introduction

Clofibrate, one of the major lipid-lowering drugs, affects lipid metabolism at several key regulatory points. Among these is the potentiation of lipoprotein lipase [1,2], an enzyme that through its hydrolysis of triglyceride, initiates the cascade of lipoprotein catabolism. High density lipoproteins (HDL) are derived in part through this mechanism [3] and the increase in HDL-cholesterol (the commonest marker of HDL levels), that may occur during clofibrate treatment [4,5], possibly reflects accelerated removal of triglyceride-transporting chylomicrons and very low density lipoproteins (VLDL). The lowered risk for coronary heart disease and coronary atherosclerosis in subjects with increased HDL levels [6,7] has stimulated interest in drugs that may raise HDL, while

This work was supported by a grant from the National Health and Medical Research Council of Australia.

Correspondence to: Dr. P.J. Nestel, Baker Medical Research Institute, Commercial Road, Melbourne, Victoria 3181, Australia.

lowering the concentrations of atherogenic particles such as low density lipoproteins. In this brief report we confirm recent observations that clofibrate treatment may indeed lead to increased HDL-cholesterol levels, and show that this applies also to the concentration of the major HDL apoprotein, A-I, particularly in individuals in whom triglyceride levels are substantially lowered.

Methods

A single-blind trial was conducted in 10 hyperlipidaemic subjects, known to have responded favourably to clofibrate. The subjects had one of several lipoprotein phenotypes (shown in Table 1) which had been satisfactorily controlled with a clofibrate dose 1 g twice daily for the preceding 6 months. These subjects had not responded to diet alone and did not require a second drug. Secondary hyperlipidaemia due to other disorders, excess alcohol intake or oral contraceptive drugs had been excluded.

The design included 2 periods on, and one off clofibrate treatment. Blood samples were obtained in the fasting state twice in 2 weeks before clofibrate was stopped, during the final 2 weeks of a 6-week placebo period and again during the 4th and 6th weeks after clofibrate was resumed. Body weights remained steady and the subjects were instructed not to change dietary habits.

Blood was collected into heparinized tubes. Total cholesterol and triglyceride concentrations were measured by automated methods, HDL cholesterol after other lipoproteins had been precipitated from plasma by the manganese—heparin method [8], and the plasma apoprotein A-I concentration by electroimmunoassay [9].

Results and Discussion

Stopping treatment led to a rise in plasma cholesterol and/or triglyceride concentrations (Table 1). As anticipated, subjects with hypertriglyceridaemia and combined hyperlipoproteinaemia showed the largest increments off treatment with return to satisfactory lipid levels when clofibrate was resumed.

Changes in HDL cholesterol and in plasma apo A-I concentrations reflected those in whole plasma lipids in a reciprocal direction with the exception of hypercholesterolaemic subject no. 5 in whom changes were minimal. Off clofibrate, the falls in HDL-cholesterol were most marked in hypertriglyceridaemic subjects and least in hypercholesterolaemic subjects. The mean differences between the two treatment and the off treatment periods were 7.3 ± 3.3 (SD) mg/dl for HDL-cholesterol and 13.2 ± 8.8 mg/dl for apo A-I, representing differences of 18% and 11% respectively ($P < 0.01$ for both sets of comparisons by paired t-test). The correlation between the changes in HDL-cholesterol and plasma triglyceride was −0.67 ($P < 0.05$), whereas that between the changes in HDL-cholesterol and plasma total cholesterol was −0.49 which was not statistically significant.

Clofibrate treatment, therefore, influenced HDL-cholesterol and plasma apo A-I concentrations in the direction of reduced coronary risk. These changes occurred whenever total triglyceride levels fell, in line with the known inverse relationship between VLDL and HDL concentrations, which is believed to

TABLE 1

CHANGES IN WHOLE PLASMA LIPIDS, IN HDL-CHOLESTEROL AND IN PLASMA APO A-I CONCENTRATION WITH AND WITHOUT CLOFIBRATE TREATMENT

Subject	Sex	Age (yr)	Weight (kg)	Lipoprotein [a] phenotype	Plasma cholesterol [b]			Plasma triglyceride [b]			HDL-cholesterol [b]			Plasma A-I [b]		
					On	Off	On	On	Off	On	On	Off	On	On	Off	On
1	M	55	71	Combined hyperlipoproteinaemia	301	333	287	191	223	202	63	56	63	135	114	123
					289	361	277	182	238	196	61	57	64	128	116	127
2	M	51	64	Hypercholesterolaemia	295	348	302	45	70	59	44	39	50	131	119	122
					286	333	289	46	78	63	44	40	49	124	107	124
3	M	34	82	Hypertriglyceridaemia	238	263	256	131	321	166	37	29	38	127	115	126
					242	281	244	149	295	143	36	33	41	125	119	130
4	M	49	76	Combined hyperlipoproteinaemia	281	338	291	141	269	179	41	29	39	121	105	119
					269	354	284	162	285	169	43	34	40	117	106	118
5	F	39	57	Hypercholesterolaemia	293	361	311	82	105	91	47	44	45	138	133	141
					292	349	309	76	110	81	46	44	47	140	139	140
6	F	63	65	Combined hyperlipoproteinaemia	262	308	246	132	264	168	76	61	67	168	132	166
					237	321	248	128	281	162	79	52	62			
7	M	53	75	Hypertriglyceridaemia	258	280	254	140	410	187	37	35	35	130	115	143
					249	271	256	151	340	112	38	33	48	132	121	140
8	M	58	88	Hypertriglyceridaemia	212	260	206	300	920	370	28	10	26	112	103	115
					216	244	208	400	850	318	24	24	26	97	111	119
9	M	57	70	Hypertriglyceridaemia	269	388	269	216	1152	243	47	34	43	141	132	143
					284	335	296	288	684	270	48	36	45	139	129	147
10	M	30	90	Hypercholesterolaemia	281	312	296	99	108	99	40	37	39	124	113	124
					277		292	108		90	40		40	119		124

[a] As defined on the basis of lipoprotein lipids in WHO Bulletin [10]: combined hyperlipoproteinaemia = Type 2B; hypercholesterolaemia = Type 2A; hypertriglyceridaemia = Type 4.

[b] Values in mg/dl (2 values during each period).

reflect the activity of the lipoprotein lipase system [11]. Since HDL are partly derived from surface material shed from catabolized VLDL (and chylomicrons), a high rate of VLDL catabolism leads to low VLDL and high HDL concentrations [11]. Clofibrate, which is known to stimulate lipoprotein lipase activity [1,2], might therefore be expected to raise HDL as a consequence of increased VLDL-triglyceride removal.

The inverse correlation between VLDL (or triglyceride) and HDL-cholesterol concentrations is well known, occurring both at low levels of triglyceride removal, as in severe (Type 5) hyperlipoproteinaemia [12], in diabetic hyperlipidaemia [13], and at high levels of triglyceride utilization as found in highly fit athletes [11]. The effects of clofibrate that appear to be mediated in this way have been reported previously with respect to the HDL-cholesterol concentration [4,5], although a recent study from Norway failed to find such an effect [14]. The present data extend this conclusion to the plasma apo A-I concentration, which, being the major apoprotein of HDL, possibly indicates an increase in HDL particle number.

If raised HDL-cholesterol and plasma A-I levels are indeed an index of reduced risk for coronary heart disease [6,7], then any effect of clofibrate through this mechanism might be mediated through improved clearance of VLDL. The significance of raised triglyceride concentrations as an independent risk factor is less secure than that for total cholesterol but cannot be ruled out [15]. The reduction in non-fatal heart attacks with clofibrate treatment, shown to occur in younger men with more severe degrees of hyperlipidaemia [16], may partly reflect more efficient catabolism of lipoproteins.

Acknowledgement

The authors thank Ms M. O'Connor for technical assistance.

References

1 Taylor, K.G., Holdsworth, G. and Galton, D.J., Clofibrate increases lipoprotein-lipase activity in adipose tissue of hypertriglyceridaemic patients, Lancet, ii (1977) 1106.
2 Nikkilä, E.A., Huttunen, J.K. and Enholm, C., Effect of clofibrate and postheparin plasma triglyceride lipase activities in patients with hypertriglyceridaemia, Metabolism, 26 (1977) 179.
3 Tall, A.R. and Small, D.M., Plasma high density lipoproteins, New Engl. J. Med., 299 (1978) 1232.
4 Wilson, D.E. and Lees, R.S., Metabolic relationships among plasma lipoproteins — Reciprocal changes in very low and low density lipoproteins in man, J. Clin. Invest., 51 (1972) 1051.
5 Wallentin, L., Lecithin : cholesterol acyl transferase and high density lipoproteins in plasma during dietary and clofibrate treatment of hypertriglyceridaemic subjects, Atherosclerosis, 31 (1978) 41.
6 Rhoads, G.G., Gulbrandsen, C.L. and Kagan, A., Serum lipoproteins and coronary heart disease in a population study of Hawaii Japanese men, New Engl. J. Med., 294 (1976) 293.
7 Jenkins, D.J., Harper, R.W. and Nestel, P.J., Severity of coronary atherosclerosis related to lipoprotein concentration, Brit. Med. J., 2 (1978) 388.
8 Albers, J.J., Arnick, G.R. and Cheung, M.C., High density lipoprotein quantitation, Lipids, 13 (1978) 926.
9 Currey, M.D., Alaupovic, P. and Duennan, C.A., Determination of apolipoprotein A and its constitutive AI and AII polypeptides by separate electroimmunoassay, Clin. Chem., 22 (1976) 315.
10 Classification of hyperlipidaemias and hyperlipoproteinaemias, Bull. Wld. Hlth. Org., 43 (1970) 891.
11 Nikkilä, E.A., Taskinen, M., Rehunen, S. and Harkonen, M., Lipoprotein lipase activity in adipose tissue and skeletal muscle of runners — Relation to serum lipoproteins, Metabolism. 27 (1978) 1661.
12 Greenberg, B.H., Blackwelder, W.C. and Levy, R.I., Primary Type V hyperlipoproteinaemia, Ann. Int. Med., 87 (1977) 526.

13 Kennedy, A.L., Lappin, T.R.J., Lavery, T.D., Haddan, D.R., Weaver, J.A. and Montgomery, D.A.D., Relation of high-density lipoprotein cholesterol concentration to type of diabetes and its control, Brit. Med. J., 2 (1978) 1191.
14 Enger, S.C., Erikssen, J., Johnsen, V., Samuelsen, A., Herbjornsen, K. and Laws, E.A., The effect of clofibrate on high density lipoprotein and total cholesterol in patients with coronary heart disease, Artery, 4 (1978) 28.
15 Gotto, Jr., A.M., Status report: Plasma lipids, lipoproteins and coronary artery disease, Atheroscler. Rev., 4 (1979) 17.
16 A co-operative trial in the primary prevention of ischaemic heart disease using clofibrate, Brit. Heart J., 40 (1978) 1069.