Acipimox in combination with low dose cholestyramine for the treatment of type II hyperlipidaemia

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1 This study was designed to examine the effects of acipimox 250 mg three times daily and cholestyramine 4 g three times daily on plasma lipids and lipoproteins in 28 hypercholesterolaemic individuals in a prospective double-blind placebo controlled parallel group fashion.

2 Combined treatment with the two agents produced a mean reduction of 27% in plasma total cholesterol and a 32% fall in LDL cholesterol. Plasma triglyceride was reduced by 13% due to a 38% decrement in VLDL cholesterol.

3 In comparison treatment with cholestyramine alone resulted in a 12% fall in plasma cholesterol and a 15% fall in LDL cholesterol. In this group triglycerides and VLDL showed no significant change.

4 Studies of HDL subfraction mass showed that the addition of acipimox to resin therapy produced a mean increment of 45% in HDL₂.

5 These results demonstrate the effectiveness of such a well tolerated low dosage combination therapy.

Keywords hyperlipidaemia acipimox cholestyramine lipoproteins

Introduction

Hypercholesterolaemia is a major risk factor for coronary artery disease (Kannel *et al.*, 1974; Martin *et al.*, 1986). Recent guidelines for the treatment suggest that a significant number of individuals require therapeutic intervention in addition to dietary measures to achieve satisfactory control of their hyperlipidaemia (Study Group, European Atherosclerosis, 1987). In many cases prescription of a single lipid lowering drug is insufficient to achieve the required treatment goals. Consideration of the mechanisms of action of the available lipid lowering agents permits us to select those combinations which are more likely to be effective than single agent therapy. Cholestyramine, an anion exchange resin, exerts its action by draining the hepatic sterol pool. Some 10–20 g of cholesterol and bile acids are recycled daily via the entero-hepatic circulation. Cholestyramine depletes this pool and induces the hepatic uptake of sterol through the low density lipoprotein (LDL) receptor mediated pathway. Detrimental

effects are also produced by resin therapy. For example, concomitant induction of HMG CoA reductase and phosphatidate phosphohydrolase result in upregulation of both cholesterol (Goldfarb & Pitot, 1972) and triglyceride synthesis in the liver, leading to increased secretion of very low density lipoprotein (VLDL) (Angelin *et al.*, 1981). Although an effective lipid lowering drug in full therapeutic doses, compliance is often poor and generally only lower doses of cholestyramine are well tolerated. Nicotinic acid and its analogues (e.g. acipimox) appear to exert at least some of their actions by inhibiting fat store lipolysis and reducing fasting plasma free fatty acid levels (Carlson *et al.*, 1968). This action limits the supply of free fatty acid substrate to the liver and thus reduces VLDL synthesis. It is logical to expect that combination of these different actions of cholestyramine and acipimox might result in beneficial synergistic effects. Cholestyramine has been shown not to interfere with the absorption of acipimox (De Paolis *et al.*,

1986). In this study a low dose of cholestyramine is used to achieve a high level of compliance in combination with acipimox in a placebo controlled parallel study.

Methods

Subjects

Thirty-two diet resistant hypercholesterolaemic individuals (cholesterol $> 7.0 \text{ mmol l}^{-1}$, triglyceride $< 3.5 \text{ mmol l}^{-1}$ after dietary intervention), were recruited into the study after a period of 3 months lipid lowering dietary control. All patients were maintained on a lipid lowering diet for the 3 months before and during the course of the study. Total fat intake was less than 30% of total calorific intake and cholesterol intake was below 300 mg day^{-1} . Secondary causes of hyperlipidaemia were excluded. Ten patients fitted the clinical criteria for possible familial hypercholesterolaemia (Brown & Goldstein, 1975). All subjects had baseline lipid values measured on three occasions at weeks 0, 4 and 8. After commencing treatment at week 8 lipid parameters were measured at weeks 12, 16 and 20 (i.e. after 1, 2 and 3 months of treatment). Patients were randomly allocated to receive either one acipimox 250 mg capsule three times daily with 4 g cholestyramine (Questran) three times daily or one placebo capsule three times daily with 4 g cholestyramine (Questran) three times daily. Compliance was monitored by capsule and sachet count at each visit. The protocol of the study was approved by the Ethics Committee of Glasgow Royal Infirmary.

Lipid and lipoprotein measurements

Cholesterol and triglyceride were measured enzymatically on a centrifugal analyser using kits from Boehringer Mannheim GmbH (Kit No. 310328) and Merk Diagnostica (Kit No. 14341) respectively. Plasma lipoprotein values were determined using the procedure detailed in the Lipid Research Clinics Manual of Laboratory operations (Lipid Research Clinics, 1975). Plasma HDL subfraction masses were determined by analytical ultracentrifugation (Shepherd *et al.*, 1984).

Results

Of the 32 individuals recruited into the study 16 completed treatment with placebo and cholestyramine and 12 completed treatment with acipimox and cholestyramine. Of the four patients who did not complete the study in the acipimox treated

group two patients were unable to tolerate the drug, one patient failed in compliance to both drugs and one patient required incidental surgery which excluded her from further study. Of the 10 patients with possible familial hypercholesterolaemia, coincidentally five were randomised to each treatment group.

Table 1 details the lipid and lipoprotein response to therapy. Treatment with cholestyramine and placebo (placebo group) produced a 12% fall in plasma cholesterol which was accounted for by a 15% fall in LDL cholesterol. Addition of acipimox to this therapy (treatment group) produced a 27% fall in cholesterol giving a total reduction of 32% in LDL cholesterol levels. Treatment with cholestyramine alone resulted in a 7% rise in triglyceride, which though consistent between visits did not reach statistical significance. Combined therapy produced a 13% fall in plasma triglyceride which came from a 38% reduction in VLDL cholesterol. HDL cholesterol did not change significantly with cholestyramine therapy alone. Combination with acipimox resulted in a 6% rise in HDL cholesterol, which was not significant. The influence of the two treatment regimens on HDL subfraction mass is shown in Table 2. Individual patient response to the combined therapy was very variable and no statistically significant changes in HDL subfraction mass could be seen within either treatment regimen. Nonetheless a downward trend in both HDL2 (22%) and HDL3 (11%) seen with cholestyramine alone changed to a 45% increment in HDL2 giving an overall increment of 8% in HDL mass when acipimox and cholestyramine were administered together. Individual patients demonstrated up to a 400% rise in HDL2 with the combined therapy. Comparison of the effects of treatment between the two groups showed relative to the resin alone the combination increased HDL cholesterol ($P < 0.05$, Table 1) and produced a highly significant increase ($P < 0.001$, Table 2) in HDL2 subfraction mass. Figure 1 summarises the changes in plasma lipid and lipoprotein values seen in the treatment and placebo groups.

Discussion

The combination of cholestyramine and nicotinic acid provides one of the most effective lipid lowering therapies available. At present these drugs remain the recommended first choice for treatment of a raised LDL-cholesterol level (The Expert Panel, 1988). Both drugs have been shown to reduce morbidity from ischaemic heart disease in large scale clinical trials (Coronary Drug

Table 1 Effect of acipimox and cholestyramine on plasma lipids and lipoproteins

Visit	Pretreatment			Treatment			Significance Pretreatment vs Treatment	% change	Significance Placebo vs Treatment
	1	2	3	1	2	3			
Cholesterol (mmol l ⁻¹)	9.22	9.41	9.65	7.16	7.35	6.95	0.001	-27	
s.d.	2.22	2.05	2.18	2.09	2.38	2.19			
Triglyceride (mmol l ⁻¹)	2.18	1.86	1.93	1.80	1.81	1.68	0.01	-13	
s.d.	0.71	0.61	0.63	0.84	0.52	0.60			
VLDL cholesterol (mmol l ⁻¹)	0.71	0.57	0.83	0.68	0.79	0.52	0.01	-38	
s.d.	0.34	0.22	0.37	0.43	0.37	0.27			
LDL cholesterol (mmol l ⁻¹)	7.27	7.54	7.37	5.16	5.20	5.03	0.001	-32	
s.d.	2.29	2.28	2.39	2.19	2.22	2.34			
HDL cholesterol (mmol l ⁻¹)	1.25	1.23	1.32	1.43	1.38	1.40	NS	+6	
s.d.	0.27	0.23	0.25	0.38	0.33	0.36			
<i>Placebo group—placebo and cholestyramine</i>									
Cholesterol (mmol l ⁻¹)	8.93	9.09	9.25	8.07	7.95	8.18	0.01	-12	0.01
s.d.	1.22	1.53	1.48	1.44	1.81	2.05			
Triglyceride (mmol l ⁻¹)	1.97	2.23	2.25	2.45	2.45	2.41	NS	+7	0.05
s.d.	0.68	0.73	0.82	1.00	0.91	0.79			
VLDL cholesterol (mmol l ⁻¹)	0.73	0.79	0.98	1.10	0.88	0.97	NS	-1	0.05
s.d.	0.42	0.38	0.52	0.62	0.42	0.42			
LDL cholesterol (mmol l ⁻¹)	6.83	6.93	6.87	5.51	5.64	5.81	0.01	-15	0.01
s.d.	1.32	1.65	1.51	1.63	1.92	2.19			
HDL cholesterol (mmol l ⁻¹)	1.46	1.38	1.40	1.49	1.43	1.38	NS	-1	0.05
s.d.	0.26	0.30	0.31	0.47	0.41	0.36			

Values above are means for all patients in each group. Significance between pretreatment and treatment values tested by the Wilcoxon paired test between pretreatment Visit 3 and treatment Visit 3.
Significance between different treatments tested by the Mann-Whitney unpaired test between the results for the two groups at treatment Visit 3.

Project, 1975; Lipid Research Clinics, 1984). The combined drug treatment has been shown to be effective in heterozygous familial hypercholesterolaemia (Kane *et al.*, 1981; Packard *et al.*, 1980). The combination of colestipol and niacin will induce regression of xanthomata and atherosclerotic lesions (Azen *et al.*, 1987). Nicotinic acid provides additional increments in HDL-

cholesterol which may importantly contribute to the beneficial effects of this agent (Grundey *et al.*, 1989). Combined administration of nicotinic acid and cholestyramine has been shown to produce reductions of up to 45% in serum cholesterol and 55% in LDL-cholesterol by treatment regimens requiring either 20 g of colestipol or 16 g cholestyramine as well as 3 g nicotinic acid or equivalent

Table 2 Effect of acipimox and cholestyramine on HDL subfraction mass

Subject	Treatment group				Placebo group			
	HDL2 (mg dl ⁻¹)		HDL3 (mg dl ⁻¹)		HDL2 (mg dl ⁻¹)		HDL3 (mg dl ⁻¹)	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1	46	26	155	150	87	64	195	194
2	11	4	182	141	94	77	307	214
3	18	34	178	207	47	48	206	206
4	27	44	246	254	49	53	313	245
5	118	155	215	186	38	26	217	154
6	26	30	165	181	65	44	274	232
7	66	94	279	239	30	30	205	194
8	36	150	240	203	110	48	260	219
9	50	95	245	190	41	84	180	296
10	57	51	201	166	34	29	223	236
11	45	46	216	312	108	95	302	231
12	38	50	189	280	101	83	320	299
13					53	15	237	171
14					33	19	164	194
15					183	118	348	225
16					15	14	139	152
Mean	44.8	64.9	209.3	209.1	68.0	52.9	243	216.4
s.d.	28.0	48.4	37.7	52.4	43.2	31.2	62.5	42.1
Sign. of change within group		NS		NS		NS		NS
% change		+45		+0		-22		-11

Significance of different response between treatments HDL2 = $P < 0.001$ HDL3 = NS Total HDL = $P < 0.05$
Significance of changes within group tested by the Wilcoxon paired test.
Significance of different response between treatments tested by the Mann-Whitney unpaired test.

Figure 1 Summary of lipoprotein changes between treatment group (acipimox and cholestyramine) and placebo group (placebo and cholestyramine): ■ treatment group pretreatment, ▨ treatment group post-treatment, ▤ placebo group pretreatment, □ placebo group post treatment.

(Kane *et al.*, 1981). At these drug dosages side effects become a major barrier to treatment and without close supervision compliance often fails.

In this study a new nicotinic acid derivative, acipimox, was studied. At the dosage of 750 mg a day side effects of flushing and nausea were minimal and the drug was well tolerated, with good compliance. When used alone in type II hyperlipidaemia acipimox has been shown to produce modest reductions in serum total cholesterol of between 7–18% but more marked effects on other lipids have been seen. HDL-cholesterol has been increased between 8–18% and triglyceride levels have been reduced by up to 43% (Capurso *et al.*, 1987; Crepaldi *et al.*, 1988). In our study, combination of acipimox with a low dose of cholestyramine (12 g day⁻¹) produced a dramatic improvement giving a total 27% fall in plasma cholesterol and 32% decrement in LDL cholesterol. The rise in triglyceride and VLDL seen with cholestyramine alone was reversed by coadministration of acipimox which gave a 13% fall in triglyceride and 38% fall in VLDL cholesterol. As

in the study of acipimox alone a 6% rise in HDL cholesterol was seen. The rise in HDL mass related to an increase in the HDL2 subfraction. Individual patients showed widely differing responses to treatment in this subfraction. In one patient greater than a 400% rise in HDL2 mass occurred. Nicotinic acid is known to increase the HDL2 subfraction mass (Packard & Shepherd, 1987) and raise the plasma concentration of apolipoprotein AI, the major structural protein in HDL. A previous study of apolipoprotein AI kinetics (Shepherd *et al.*, 1979) during nicotinic acid therapy has shown that the circulating mass of the protein rises because of a reduction in its catabolism. The ratio of apo A-I to apo A-II increases, implying that the ratio of HDL2/HDL3 particles has risen.

These drugs therefore offer the combined benefits of a good lipid lowering effect and a well tolerated regimen. Beneficial changes in triglyceride metabolism and a rise in HDL cholesterol and HDL2 mass are important additional advantages.

References

- Angelin, B., Bjorkhem, I. & Einarsson, K. (1981). Influence of bile acids on the soluble phosphotidic acid phosphatase in rat liver. *Biochem. Biophys. Res. Comm.*, **100**, 606–612.
- Avogaro, P., Crepaldi, G., Descorich, G. C., Diferri, T., Musatti, L., Postiglione, A., Sirtori, C. R., Strano, A. & Ventura, S. (1988). Plasma lipid lowering activity of acipimox in patients with type II and type IV hyperlipoproteinemia. *Atherosclerosis*, **70**, 115–121.

- Azen, S. P., Blankenhorn, D. H., Cashin-Hemphill, L., Johnson, R. L., Nessim, S. A. & Sanmarco, M. E. (1987). Beneficial effects of combined colestipol niacin therapy on coronary atherosclerosis and coronary venous bypass grafts. *J. Am. med. Ass.*, **257**, 3233–3240.
- Bedford, D. K., Caine, E. A., Packard, C. J. & Shepherd, J. (1984). Ultracentrifugal subfraction of high-density lipoprotein. *Analyst*, **109**, 347–351.
- Brown, M. S. & Goldstein, J. L. (1975). Familial hypercholesterolemia. Genetic, biochemical and pathophysiological considerations. *Adv. Intern. Med.*, **20**, 273–296.
- Browner, W. S., Hulley, S. B., Kuller, L. H., Martin, M. J. & Wentworth, D. (1986). Serum cholesterol, blood pressure, and mortality: implications from a cohort of 361,622 men. *Lancet*, **ii**, 933–936.
- Capurso, A., Ciancia, D., Larezzari, M., Mogavero, A. M., Pamlisano, S., Resta, F., Siciliani, G., Taverniti, R. D. & Tommaso, M. (1987). Effect of acipimox and pantethine on serum lipids and apoproteins in patients with Type II hyperlipoproteinemia. *Curr. Ther. Res.*, **42**, 1216–1223.
- Carlson, L. A., Oro, L. & Ostman, J. (1968). The effect of nicotinic acid on plasma lipids in patients with hyperlipoproteinemia during the first week of treatment. *Atherosclerosis*, **8**, 667–677.
- Castelli, W. P., Gordon, T., Kannel, W. B., McNamara, P. M. (1974). Serum cholesterol, lipoproteins, and the risk of coronary heart disease: The Framingham Study. *Ann. int. Med.*, **74**, 1–12.
- Celotti, F., De Paolis, C., Farina, R., Pianezzola, E., Pontiroli, A. E. & Valzelli, G. (1986). Lack of pharmacokinetic interaction between cholestyramine and acipimox, a new lipid lowering drug. *Br. J. clin. Pharmacol.*, **22**, 496–497.
- Cleeman, J. I., Goodman, D. S., Grundy, S. M. & Rifkind, B. M. (1989). The place of HDL in cholesterol management. *Arch. int. Med.*, **149**, 505–510.
- Coronary Drug Project (1975). Clofibrate and niacin in coronary heart disease. *J. Am. med. Ass.*, **231**, 360–381.
- Crepaldi, G., Avogaro, P., Descovich, G. C., DiPerri, T., Postiglione, A., Sirtori, C. R., Strano, A., Ventura, S. & Musatti, L. (1988). Plasma lipid lowering activity of acipimox in patients with type II and type IV hyperlipoproteinemia. *Atherosclerosis*, **70**, 115–121.
- De Paolis, C., Farina, R., Pianezzola, E., Valzelli, G., Celotti, F. & Pontiroli, A. E. (1986). Lack of pharmacokinetic interaction between cholestyramine and acipimox, a new lipid lowering drug. *Br. J. clin. Pharmacol.*, **22**, 496–497.
- Freedman, D. D., Havel, R. J., Kane, J. P., Malloy, M. J., Phillips, N. R., Rowe, J. S., Tun, P. & Williams, M. L. (1981). Normalisation of low density lipoprotein levels in heterozygotes familial hypercholesterolemia with a combined drug regimen. *New Engl. J. Med.*, **304**, 251–258.
- Goldfarb, S. & Pitot, H. C. (1972). Stimulatory effect of dietary lipid and cholestyramine on hepatic HMG CoA reductase. *J. lipid Res.*, **13**, 797–801.
- Gotto, A. M., Packard, C. J., Patsch, J. R., Shepherd, J. & Taunton, O. D. (1979). Effect of nicotinic acid therapy on plasma high density lipoprotein subfraction distribution and composition and on apolipoprotein A metabolism. *J. clin. Invest.*, **63**, 858–867.
- Grundy, S. M., Goodman, D. S., Rifkind, B. M. & Cleeman, J. I. (1989). The place of HDL in cholesterol management. *Arch. int. Med.*, **149**, 505–510.
- Kane, J. P., Malloy, M. J., Tun, P., Phillips, N. R., Freedman, D. D., Williams, M. L., Rowe, J. S. & Havel, R. J. (1981). Normalisation of low density lipoprotein levels in heterozygous familial hypercholesterolemia with a combined drug regimen. *New Engl. J. Med.*, **304**, 251–258.
- Kannel, W. B., Castelli, W. P., Gordon, T. & McNamara, P. M. (1974). Serum cholesterol, lipoproteins, and the risk of coronary heart disease: The Framingham Study. *Ann. int. Med.*, **74**, 1–12.
- Lipid Research Clinics Program (1984). The Lipid Research Clinics Coronary Primary Prevention Trial results: 1. reduction in incidence of coronary heart disease. *J. Am. med. Ass.*, **251**, 351–364.
- Lipid Research Clinics Program Manual of Laboratory Operations (1975). Vol I. DHEW Publication No. (NIH 75-628 (1975)). Government Printing Office, Washington DC.
- Lorimer, A. R., Morgan, H. G., Packard, C. J., Shepherd, J. & Stewart, J. M. (1980). Combined drug therapy for familial hypercholesterolemia. *Artery*, **7**, 281–289.
- Martin, M. J., Hulley, S. B., Browner, W. S., Kuller, L. H. & Wentworth, D. (1986). Serum cholesterol, blood pressure, and mortality: Implications from a cohort of 361,622 men. *Lancet*, **ii**, 933–936.
- Packard, C. J. & Shepherd, J. (1987). Effect of diet and drugs on high density lipoprotein metabolism. *Atherosclerosis Reviews*, **16**, 181–206.
- Shepherd, J., Caine, E. A., Bedford, D. K. & Packard, C. J. (1984). Ultracentrifugal subfractionation of high density lipoprotein. *Analyst*, **109**, 347–351.
- Shepherd, J., Packard, C. J., Patsch, J. R., Gotto, A. M. & Taunton, O. D. (1979). Effect of nicotinic acid therapy on plasma high density lipoprotein subfraction distribution and composition and on apolipoprotein A metabolism. *J. clin. Invest.*, **63**, 858–867.
- Study Group, European Atherosclerosis Society (1987). Strategies for the prevention of coronary heart disease: A policy statement of the European Atherosclerosis Society. *Eur. Heart J.*, **8**, 77–88.
- The Expert Panel (1988). Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults. *Arch. int. Med.*, **148**, 36–69.

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