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Stress responses after treatment of hypercholesterolaemia with simvastatin

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In order to determine whether treatment of hyperlipidaemia with simvastatin impairs exercise stress responses and so may contribute to an excess of suicides and violent deaths, the effects of simvastatin 20 mg daily and placebo on exercise physiology were compared in 19 patients. After 6 weeks of treatment there was no evidence of reduced exercise capacity, or of reduced cortisol or catecholamine responses. It is concluded that treatment of hyperlipidaemia with an inhibitor of HMG-CoA reductase does not significantly modify stress responses, and so the explanation for a possible increase in non-cardiac mortality must be sought elsewhere.

Keywords simvastatin exercise testing cortisol

Introduction

Lowering cholesterol in the primary prevention of coronary heart disease reduces coronary events [1], but it has been suggested that this benefit is balanced by an increased mortality from other causes, especially suicides and violent deaths [2, 3]. Although it has proved difficult to establish a mechanism by which cholesterol reduction could influence non-cardiac mortality [3], cholesterol is an essential precursor of adrenal steroids, and so inhibition of 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase (the rate limiting step in cholesterol synthesis) could affect adrenal steroid production. The effect of exercise, a form of stress to the hypothalamic-pituitary-adrenal axis [4], has not previously been examined, and neither has the effect of HMG-CoA reductase inhibition on catecholamine responses. We therefore set out to examine the effects of simvastatin, a competitive inhibitor of HMG-CoA reductase and a potent lipid-lowering agent [5], on the physiological responses to exercise in a short-term study when compared with placebo.

Methods

Patients attending the Lipid Clinic were considered for entry into the trial if their total serum cholesterol was >7.0 mmol l^{-1} after 3 months of adherence to a diet in which fat contributed 30% to the daily calorie intake. None had angina, or any other reason to stop exercise prematurely (such as musculoskeletal disorders or chronic chest disease). None was receiving drugs which could affect exercise capacity or steroid responses, such as β-adrenoceptor antagonists or prednisolone. All gave written informed consent to the procedures, which had been approved by the Ethics Committee of the Queen's University of Belfast.

After an initial visit for familiarisation with the exercise technique, patients were studied before and after a 2 week single (patient) blind placebo treatment period, and then randomly allocated to receive either simvastatin 20 mg daily or matching placebo on a double-blind basis. The tests were repeated after 6 weeks of treatment. Of the 33 patients initially considered, 14 withdrew for the reasons given below. Results are presented on the 19 patients (11 female) who completed the study. Their mean age was 46 years (range 21–63), height 1.66 m (1.52–1.83) and body weight 67.7 kg (48–85). Six had familial hypercholesterolaemia as defined by the presence of tendon xanthomas in the patient or a first-degree relative. Two had mild hypertension and were receiving indapamide and nifedipine respectively.

At each visit, always in the morning after a 12 h overnight fast, patients rested quietly in the supine position for 1 h after insertion of a teflon cannula into an antecubital vein. Patients then stood on the treadmill for 5 min before withdrawal of blood samples, which were repeated at peak exercise and after 3, 6, 30 and 60 min of recovery in the seated position. Exercise was carried out according to a Bruce protocol modified by an initial 3 min stage at 5% incline and 2.7 km h^{-1}. Ventilation ($\dot{V}E$), oxygen consumption ($\dot{V}O_2$), carbon dioxide production ($\dot{V}CO_2$) and hence respiratory exchange ratio (RER; $\dot{V}CO_2/\dot{V}O_2$) were measured

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throughout exercise [6] using a vane turbine for $\dot{V}E$, a paramagnetic analyser for F_EO_2 and an infrared spectrometer for F_ECO_2. Heart rate, systolic blood pressure and ST segment level (CM5 lead) were recorded at the end of each stage and at peak exercise. Patients were invited to rate their perceived exertion on a non-linear scale of up to 10 points [7], and then return the following day for a further blood sample for creatine kinase (CK) activity.

Cholesterol and triglyceride were measured by enzymatic methods on a Cobas Bio centrifugal analyser (Roche) and high density lipoprotein (HDL) cholesterol was measured after manganese-heparin precipitation. Low density lipoprotein (LDL) cholesterol was calculated from the Friedewald formula [8]. Cortisol and aldosterone were measured by solid phase radioimmunoassays (Diagnostic Products Corporation, Los Angeles, USA; between batch CV, 3.3% at 261 pmol l^{-1} and 5.8% at 467 pmol l^{-1} respectively). ACTH was measured by an ELISA method (CIS Ltd, UK; between batch CV 5.5% at 35 pg ml^{-1}). Samples for measurement of catecholamines were mixed with sodium metabisulphite as preservative and chilled. The separated plasma was stored at −70° C until assay by reverse phase h.p.l.c. with electrochemical detection (between batch assay CV—noradrenaline 8.9% at a concentration of 2.95 nmol l^{-1}; adrenaline 6.5% at a concentration of 2.7 nmol l^{-1}).

The values from the first and second visit were averaged and regarded as the baseline. Differences from placebo were assessed by the Mann Whitney U test, and $P < 0.05$ was regarded as significant. Mean values with 95% confidence limits are shown.

Results

Of the 33 patients selected for consideration, nine were unwilling or unable for personal reasons to complete the study, one was sick on the placebo run-in phase, and in one patient the serum cholesterol had fallen to <7 mmol l^{-1} by the time the study started. Six had ECG evidence of myocardial ischaemia during the initial exercise test, despite the absence of angina as a symptom. In three patients, this was of relatively minor degree and the study proceeded. The remaining 19 patients completed the double-blind phase of the trial uneventfully with no reported symptom side-effects.

Simvastatin reduced total serum cholesterol from 9.2 (8.6, 9.8) to 7.1 (6.3, 7.9) mmol l^{-1} (23%) and LDL cholesterol from 7.1 (6.5, 7.6) to 5.0 (4.1, 5.9) mmol l^{-1} (29%) after 6 weeks of treatment. These changes were significant compared with placebo ($P < 0.01$), which had no effect (initial cholesterol 8.6 (8.0, 9.2) mmol l^{-1}). No changes were observed in triglyceride or HDL-cholesterol concentrations in either group. Also measured were creatine kinase levels (CK) and the CK-MB isoenzyme, but no significant changes in either were noted during exercise or 24 h later.

Exercise duration was unchanged after simvastatin (Table 1). Peak $\dot{V}O_2$ was slightly greater in the placebo group prior to treatment, but no change was observed after either treatment. $\dot{V}E$, heart rate and blood pressure responses were unchanged, as was the patient's perception of the severity of the exercise (Borg score).

Table 1 Cardiopulmonary measurements at peak treadmill exercise at baseline (average of visits 1 and 2) and after 6 weeks of treatment (visit 3) with simvastatin 20 mg daily (S; $n = 9$) or placebo (P; $n = 10$). $P\dot{V}O_2$ = peak achieved oxygen consumption; $\dot{V}E$ = ventilation; RER = respiratory exchange ratio; D = difference. Results are shown as means, and as mean differences (95% confidence limits) in the treatment group from placebo

		Before	*After*
Exercise time (s)	S	718 (606, 830)	713 (593, 833)
	P	720 (635, 805)	715 (620, 810)
	D	−2 (−131, 126)	−2 (−143, 138)
$P\dot{V}O_2$ (ml min^{-1} kg^{-1})	S	30.6 (26.7, 34.6)	28.9 (25.5, 32.2)
	P	32.9 (27.5, 38.4)	30.9 (25.7, 36.1)
	D	−2.3 (−8.7, 4.1)	−2.1 (−8.0, 3.9)
$\dot{V}E$ (l min^{-1})	S	71.2 (51.9, 90.5)	69.2 (49.6, 88.8)
	P	71.1 (57.2, 84.9)	69.4 (55.7, 83.1)
	D	0.1 (−21.6, 21.7)	−0.2 (−21.7, 21.3)
Heart rate (beats min^{-1})	S	171 (164, 178)	168 (157, 179)
	P	167 (157, 177)	166 (156, 176)
	D	4 (−8, 15)	2 (−12, 15)
Systolic blood pressure (mm Hg)	S	184 (171, 197)	182 (172, 191)
	P	188 (179, 196)	193 (179, 207)
	D	−4 (−18, 10)	−11 (−27, 5)
RER ($\dot{V}CO_2/\dot{V}O_2$)	S	1.11 (1.02, 1.20)	1.13 (1.04, 1.22)
	P	1.08 (1.03, 1.13)	1.10 (1.03, 1.17)
	D	0.03 (−0.05, 0.11)	0.03 (−0.08, 0.14)
Borg score	S	3.8 (2.5, 5.1)	3.6 (2.1, 5.0)
	P	4.9 (3.7, 6.1)	4.4 (3.1, 5.7)
	D	−1.1 (−2.8, 0.5)	−0.8 (−2.6, 0.9)

Cortisol levels at rest and during exercise (Table 2) were lower at the follow-up visit in both treatment groups, as were levels of ACTH. However, resting cortisol levels were higher after active treatment ($P < 0.05$ compared with placebo) and the exercise response unimpaired—the increase from resting levels to 30 min after exercise was 33% after placebo and 30% after simvastatin. Peak ACTH levels coincided with peak exercise, but cortisol and aldosterone levels were greater 30 min later. Changes in aldosterone levels are more difficult to interpret as levels were higher in the simvastatin group before treatment, but again there did not seem to be any impairment of the response to exercise (increase of 51%). No significant changes were observed in the responses of noradrenaline, or adrenaline (not shown).

Discussion

Simvastatin produced the expected reduction in total and LDL-cholesterol levels, with no adverse effects. In contrast to previous studies [9, 10], no increase in CK levels was observed 24 h after exercise. Cortisol and ACTH levels were lower in both treatment groups at the follow-up visit, indicating reduced hypothalamic-pituitary drive, but the basal level of cortisol was greater in the active treatment group, and the response to exercise stress appeared to be preserved.

Table 2 Effect of simvastatin 20 mg daily (S; $n = 9$) or placebo (P; $n = 10$) on steroid and noradrenaline responses to exercise before and after 6 weeks of treatment. D = difference. * = $P < 0.05$ compared with placebo. Results are shown as means, and as mean differences (95% confidence intervals) in the treatment group from placebo

		Before	*After*
Cortisol (nmol l^{-1})			
Rest	S	334 (270, 398)	292 (215, 369)
	P	265 (213, 317)	209 (174, 244)
	D	68 (−7, 144)	83 (8, 158)*
Peak	S	376 (283, 469)	298 (205, 391)
	P	303 (221, 385)	211 (165, 257)
	D	73 (−41, 187)	87 (−6, 179)
+ 30 min	S	534 (380, 688)	417 (270, 564)
	P	423 (302, 545)	312 (190, 434)
	D	111 (−67, 290)	105 (−71, 280)
+ 60 min	S	424 (287, 561)	316 (198, 434)
	P	325 (231, 419)	239 (173, 305)
	D	99 (−52, 249)	77 (−45, 199)
ACTH (ng l^{-1})			
Rest	S	17.2 (13.4, 21.0)	15.7 (13.0, 18.4)
	P	16.9 (12.6, 21.2)	16.5 (11.1, 21.9)
	D	0.3 (−5.1, 5.7)	−0.8 (−6.6, 4.9)
Peak	S	69.5 (24.5, 114.5)	44.7 (−2.7, 92.1)
	P	49.3 (24.6, 74.0)	30.2 (13.7, 46.7)
	D	20.3 (−25.7, 66.2)	14.5 (−29.7, 58.6)
+30 min	S	43.5 (22.4, 64.6)	34.0 (5.5, 62.5)
	P	36.6 (19.2, 54.0)	20.8 (14.9, 26.7)
	D	7.0 (−18.1, 32.0)	13.2 (−12.1, 38.5)
+60 min	S	19.1 (13.6, 24.6)	16.1 (10.9, 21.3)
	P	19.5 (13.1, 25.9)	15.3 (11.7, 18.9)
	D	−0.3 (−8.2, 7.6)	0.8 (−4.9, 6.5)
Aldosterone (pmol l^{-1})			
Rest	S	469 (276, 662)	437 (224, 650)
	P	325 (155, 495)	304 (173, 435)
	D	144 (−92, 381)	133 (−92, 359)
Peak	S	833 (538, 1128)	690 (329, 1051)
	P	555 (270, 840)	521 (316, 726)
	D	277 (−103, 658)*	170 (−202, 542)
+ 30 min	S	1018 (697, 1339)	851 (485, 1217)
	P	582 (271, 893)	562 (379, 745)
	D	436 (23, 849)*	289 (−76, 653)
+ 60 min	S	735 (500, 970)	603 (368, 838)
	P	371 (186, 556)	349 (237, 461)
	D	364 (91, 637)*	254 (22, 485)*
Noradrenaline (nmol l^{-1})			
Rest	S	5.5 (3.9, 7.1)	4.1 (3.0, 5.2)
	P	4.9 (3.8, 6.0)	4.1 (2.8, 5.4)
	D	0.6 (−1.1, 2.4)	0 (−1.7, 1.7)
Peak	S	26.0 (16.9, 35.0)	18.4 (7.4, 29.4)
	P	20.1 (14.6, 25.6)	16.2 (10.5, 21.9)
	D	5.8 (−3.7, 15.3)	2.2 (−8.6, 13.1)
+ 3 min	S	12.6 (8.2, 17.1)	10.7 (2.7, 18.7)
	P	9.1 (7.3, 10.9)	7.1 (5.4, 8.8)
	D	3.5 (−0.7, 7.7)	3.6 (−2.8, 10.0)
+ 6 min	S	8.9 (6.2, 11.5)	7.8 (2.3, 13.3)
	P	6.4 (5.2, 7.6)	5.0 (3.8, 6.2)
	D	2.4 (−0.1, 5.0)	2.8 (−1.6, 7.2)

Studies in mononuclear leucocytes from normal subjects treated with lovastatin indicate that a reduction in steroid synthesis is balanced by induction of enzyme activity [11]. In patients treated with inhibitors of HMG-CoA reductase, the response of serum cortisol to tetracosactrin (ACTH) injection is either slightly blunted [12] or unaffected [13–16]. It would appear therefore that such treatment does not affect steroid production, whether the stimulus is ACTH or stress.

Two major intervention trials [17, 18] have shown an excess of deaths in the active treatment group due to violence or suicide, and this is widely quoted as evidence of the potentially harmful effects of cholesterol reduction. However, detailed examination of the individual deaths from these trials [19] has shown little evidence to suggest that the lipid-lowering treatment was responsible, and the numbers involved are small. There remains the problem of establishing how cholesterol reduction could produce such an effect.

Monkeys fed a low fat diet become more aggressive [20], and in man low serum cholesterol concentrations may be associated with antisocial behaviour [21]. It has been suggested that a fall in serum cholesterol reduces brain serotonin (5-HT) levels, producing a personality change [22]. Some epidemiological data support the concept that lower cholesterol levels are associated with violent deaths [23], but other surveys have failed to establish the link [24–27].

From our observations we conclude that there is no evidence to support the hypothesis that treatment of hyperlipidaemia with a HMG-CoA reductase inhibitor such as simvastatin impairs the response to stress and so contributes to a possible increase in suicides and violent death. An explanation must therefore be found elsewhere, although it is still possible that the apparent increase in such deaths is fortuitous, and so the results of current major primary prevention trials with these drugs are awaited with interest.

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