The effects of combined treatment with β_1 -selective receptor antagonists and lipid-lowering drugs on fat metabolism and measures of fatigue during moderate intensity exercise: a placebo-controlled study in healthy subjects

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Aims We examined the effects of different combinations of β_1 -selective adrenoceptor blockers and lipid-lowering drugs, on fat metabolism and fatigue during moderate intensity exercise in 14 healthy young volunteers.

Methods The study was a randomized crossover design, each subject completing 5, 90 min walks at 50% of predetermined maximal oxygen uptake (VO_2 max), one following each 3 day treatment period with either: atenolol 100 mg and bezafibrate 400 mg, atenolol 100 mg and fluvastatin 40 mg, metoprolol CR 100 mg and bezafibrate 400 mg, metoprolol CR 100 mg and fluvastatin 40 mg, or placebo.

Results Plasma free fatty acid (FFA) concentration during exercise was significantly reduced on all treatments, in comparison with placebo, $P=0.0001$. Following 90 min of exercise FFA levels were as follows: placebo $573 \mu\text{mol l}^{-1}$ (105–1041), metoprolol CR + fluvastatin $277 \mu\text{mol l}^{-1}$ (0–647), metoprolol CR + bezafibrate $182 \mu\text{mol l}^{-1}$ (0–396), atenolol + fluvastatin $211 \mu\text{mol l}^{-1}$ (0–511), and atenolol + bezafibrate $123 \mu\text{mol l}^{-1}$ (0–352). Total fat oxidation during exercise was also reduced on all treatments in comparison with placebo: 38.1% (2–74), compared with 29.1% (0–61) on metoprolol CR + fluvastatin, $P=0.02$, 26.2% (2–51) on metoprolol CR + bezafibrate, $P=0.002$, 25.5% (3–48) on atenolol + fluvastatin, $P=0.009$, and 22.8% (0–47) on atenolol + bezafibrate treatment, $P=0.0002$. Plasma ammonia concentration was elevated on all treatments during exercise in comparison with placebo. After 90 min of exercise, plasma ammonia levels were as follows: placebo $37 \mu\text{mol l}^{-1}$ (0–84), metoprolol CR + fluvastatin $56 \mu\text{mol l}^{-1}$ (2–110), metoprolol CR + bezafibrate $79 \mu\text{mol l}^{-1}$ (0–167), atenolol + fluvastatin $90 \mu\text{mol l}^{-1}$ (10–170), and atenolol + bezafibrate $100 \mu\text{mol l}^{-1}$ (26–174). In comparison with placebo, metoprolol CR + fluvastatin had the least adverse impact on measures of perceived exertion and the 'feeling scale' during exercise. Metoprolol CR + bezafibrate, atenolol + fluvastatin, and atenolol + bezafibrate treatments had greater adverse effects, particularly on perceived 'cardiorespiratory effort' and 'feeling scale' scores.

Conclusions In healthy volunteers, combinations of β_1 -selective blockers and lipid-lowering drugs were associated with significant reductions in fat metabolism, increased plasma ammonia levels, and raised the perception of effort during exercise, in comparison with placebo. Metoprolol CR + fluvastatin had the least effect, combinations metoprolol CR + bezafibrate and atenolol + fluvastatin had intermediate effects, and atenolol + bezafibrate had the most adverse effect.

Keywords: β_1 -selective blockade, lipid-lowering drugs, fat metabolism, plasma ammonia, perceived exertion, plasma lactate

Introduction

To improve their coronary risk profile, hypertensive or post-myocardial infarct patients with hypercholesterolaemia may be prescribed both β -adrenoceptor blocking drugs and lipid-lowering therapy, and be encouraged to take regular aerobic exercise. However, both non-selective and β_1 -selective blockers have been shown to impair endurance

exercise performance in hypertensive patients [1, 2] and inhibit fat metabolism during exercise in healthy young subjects [3, 4]. A reduction in the availability of free fatty acids for energy production in active skeletal muscle may result in an increased utilisation of carbohydrates, and early fatigue [5, 6]. Lipid-lowering drugs including acipimox [7, 8, 9], and recently, bezafibrate [10], have also been demonstrated to inhibit fat metabolism during moderate intensity exercise. The effects of β -adrenoceptor-blockade in combination with lipid-lowering therapy on fat metabolism and fatigue during exercise are unknown.

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We compared the effects of four different β_1 -selective blocker-lipid-lowering drug combinations (atenolol + bezafibrate; atenolol + fluvastatin; metoprolol CR* + bezafibrate; and metoprolol CR* + fluvastatin), in comparison with placebo, on exercise metabolism and fatigue in healthy young men and women. The aim was to determine whether different drug regimens which may be prescribed for patients would have different effects on fat mobilisation and perceived exertion during exercise. The study involves two lipid lowering drugs with differing modes of action, and two different pharmaceutical preparations of β_1 -selective blockers, whose effects on exercise metabolism have been investigated as single treatments, in comparison with placebo, in previous studies [3, 10].

Methods

Subjects

Fourteen healthy normolipidaemic volunteers (seven men and seven women) who were not highly endurance trained, mean age (s.d.) 21.9 (1.9) years, body weight (s.d.) 65.1 (9.8) kg, participated in the study, which was approved by the South Birmingham Health Authority Ethics Committee, and required informed written consent. All subjects had clinical examinations, and normal haematological and biochemical profiles. Cardiovascular fitness was assessed by measurement of maximal oxygen uptake during a graded test to exhaustion on a motorized treadmill, and a workload corresponding to 50% of VO_2 max was determined during a 90 min walking trial during which subjects were familiarised with the protocol.

Experimental design

The study was a double-blind, randomized, crossover investigation, each subject completing five exercise trials; one following each 3 day period of once-daily treatment with either atenolol 100 mg and bezafibrate 400 mg, atenolol 100 mg and fluvastatin 40 mg, metoprolol CR 100 mg + bezafibrate 400 mg, metoprolol CR 100 mg and fluvastatin 40 mg, or placebo. Lipid-lowering (or placebo) tablets were taken after the evening meal, the final dose being taken at 22.00 h on the evening preceding the exercise trial, and β -adrenoceptor-blocker (or placebo) tablets were taken with breakfast, the final dose being taken at 08.00 h on the morning of the exercise trial. Each treatment period was followed by a wash-out period of at least 4 days. Subjects recorded food intake, followed a similar dietary pattern throughout the study, and were instructed to replicate the evening meal preceding each trial. Similarly, subjects were asked to replicate exercise patterns for 3 days preceding each trial.

On exercise trial days subjects arrived at the Clinical Investigation Unit at 08.00 h, having fasted overnight, and

ingested the last tablet of the β -adrenoceptor blocker or placebo treatment before eating a fat free 1 MJ standard carbohydrate breakfast. A cannula was then inserted into a suitable forearm vein and subjects rested for 90 min. Resting blood samples were taken 15 min and 5 min before exercise, and at 15 and 30 min post-exercise. Subjects exercised for 90 min at 50% VO_2 max, during which blood samples, measures of heart rate and perceived exertion ('cardiorespiratory effort', 'leg effort', and 'leg pain') [11]—see Appendix 1, a measure of how subjects were feeling [12]—see Appendix 2, and expired gas samples, were taken every 15 min.

Indirect calorimetry

Oxygen uptake and carbon dioxide excretion were measured using the Douglas bag technique. The percentage of oxygen and carbon dioxide in aliquots of expired gas was measured using a paramagnetic oxygen (Beckmann OM11) and infra-red carbon dioxide meter (Beckmann LB2) previously calibrated with standard gases (BOC Special Gases) certified to an accuracy of 0.05%. Total resistance to flow of the gas collection system was 2.0 cm of water at a constant flow of 200 l min^{-1} , and gas volume was measured at a constant flow using a dry gas meter (Harvard, UK). Oxygen uptake and carbon dioxide excretion were calculated using the Haldane transformation [13], and rates of energy expenditure and the proportion of carbohydrate and fat metabolism calculated using standard equations [14].

Analytical method

Each blood sample (8 ml) was distributed between evacuated septum sealed test tubes ('Vacutainer'®) containing: sodium fluoride and potassium oxalate; lithium heparin; or ethylenediaminetetraacetic acid (EDTA); for subsequent measurement of: plasma glucose (coefficient of variation, CV = 1.6%) [15], lactate (CV = 3.6%) [16], free fatty acids (CV = 2.5%) [17], and triglycerides (CV = 3.6%) [18]; plasma ammonia (exercise samples; CV = 12.7%) [19]; and haemoglobin and haematocrit concentrations, respectively. Samples of approximately 150–200 μl were aliquoted and stored at -70°C . for subsequent analysis on a Cobas Bio® analyser.

Calculation and statistical analysis

Data were analysed using repeated measures two factor (time and treatment) analysis of variance (ANOVA), corrected for related means (Greenhouse-Geiser Epsilon), taking $P < 0.05$ to indicate a significant treatment/time interaction effect. One-factor ANOVA determined differences between treatments at individual time points. Results are given as the mean and 95% confidence intervals.

Results

Cardiorespiratory/energy expenditure data

Mean maximal oxygen uptake (VO_2 max) was $52.0 (41\text{--}63) \text{ ml kg}^{-1} \text{ min}^{-1}$ in men ($n=7$), and $43.0 (34\text{--}52) \text{ ml kg}^{-1} \text{ min}^{-1}$ in women ($n=7$).

*Metoprolol CR has been shown to produce an even plasma concentration-time profile over a 24-h period, with a considerably reduced maximum plasma concentration, compared with conventional tablets of metoprolol [21], but is not available in the U.K.

Figure 1 Mean ($\pm$ s.e. mean) heart rate (beats min^{-1}) during 90 min of exercise at 50% VO_2 max on placebo ($-\circ-$), metoprolol CR + fluvastatin ($-\blacksquare-$), metoprolol CR + bezafibrate ($-\triangle-$), atenolol + fluvastatin ($-\bullet-$), and atenolol + bezafibrate ($-\diamond-$) treatment. Placebo compared with all treatments, $P=0.0001$. Metoprolol CR treatments compared with atenolol treatments, $P<0.001$.

Mean heart rate was depressed on all combination treatments in comparison with placebo ($P=0.0001$, $n=14$). Mean heart rate during 90 min of exercise at 50% VO_2 max was; 129 (103–155) beats min^{-1} on placebo, 104 (84–126) beats min^{-1} on metoprolol CR + fluvastatin, 105 (84–126) beats min^{-1} on metoprolol CR + bezafibrate, 95 (84–106) beats min^{-1} on atenolol + fluvastatin, and 97 (85–109) beats min^{-1} on atenolol + bezafibrate treatment. Mean heart rate was higher on metoprolol CR treatments than on atenolol treatments, $P<0.001$ (see Figure 1).

Mean total energy expenditure was similar on all treatments, $P=0.99$ ($G-G=0.97$), but was significantly higher in males; 2985 (2198–3772) kJ compared with females; 2038 (1475–2601) kJ, $P=0.0001$.

Fat oxidation/respiratory exchange ratio (RER)

Fat oxidation increased throughout the 90 min exercise period on all treatments ($P=0.0001$) (see Table 1 and Figure 2). Total fat oxidation was reduced on all combination treatments, compared with placebo; 38.1% (2–74): metoprolol CR + fluvastatin treatment had the least overall effect on fat oxidation, 29.1% (0–61), $P=0.019$, metoprolol

CR + bezafibrate treatment and atenolol + fluvastatin treatments had slightly greater effects, 26.2% (2–51), $P=0.002$, and 25.5% (3–48), $P=0.009$, respectively, and atenolol + bezafibrate treatment produced the most marked reduction in fat oxidation, 22.8% (0–47), $P=0.0002$.

There was also an elevation in the respiratory exchange ratio (RER) on combination treatment in comparison with placebo, $P=0.0011$. In four subjects (one male and three female), the RER (calculated from measurements of expired oxygen and carbon dioxide) was 1.0 or above following 15 min of exercise, suggesting a 'total' reliance on carbohydrate metabolism for energy expenditure. In three of the four subjects, this phenomenon occurred only on atenolol + bezafibrate treatment (the fourth subject had RER values exceeding 1.0 with metoprolol CR + bezafibrate and atenolol + fluvastatin treatments, and a value of 0.98 on atenolol + bezafibrate treatment).

Plasma free fatty acids (FFA)

Mean plasma free fatty concentration (FFA) increased during exercise at 50% VO_2 max on all treatments, $P=0.0001$, but FFA levels, and the increase in FFA concentration with

Table 1 Mean (95% confidence intervals) percentage contribution of fat oxidation to energy expenditure during exercise at 50% VO_2 max on placebo, metoprolol CR + fluvastatin, metoprolol CR + bezafibrate, atenolol + fluvastatin, and atenolol + bezafibrate treatment.

Treatment	Mean fat oxidation (% contribution to energy expenditure) at time, t , (min)					
	$t15$	$t30$	$t45$	$t60$	$t75$	$t90$
Placebo	24.5 (0–66)	32.4 (0–68)	36.9 (1–73)	41.9 (5–78)	45.2 (9–81)	47.6 (15–78)
Metp + Fluv	21.1 (0–50)	23.4 (0–49)	29.1 (0–62)	31.9 (0–69)*	33.3 (0–67)**	35.9 (2–70)**
Metp + Bez	15.3 (0–35)	21.3 (1–42)	26.4 (0–55)*	31.5 (2–61)*	31.2 (5–57)**	31.6 (8–55)***
Aten + Fluv	19.8 (0–47)	21.3 (0–43)	25.2 (4–46)*	27.0 (4–50)**	31.0 (12–50)**	28.8 (7–51)***
Aten + Bez	15.7 (0–41)	19.6 (1–38)	19.7 (0–42)***	23.8 (0–50)***	25.5 (0–51)***	27.3 (0–57)***

Significant differences compared with placebo: * $P<0.05$; ** $P<0.01$; *** $P<0.001$.

Figure 2 Mean ($\pm$ s.e. mean) percentage contribution of fat oxidation to energy expenditure during 90 min of exercise at 50% VO_2 max on placebo ($\circ$), metoprolol CR + fluvastatin ($\blacksquare$), metoprolol CR + bezafibrate ($\triangle$), atenolol + fluvastatin ($\bullet$), and atenolol + bezafibrate ($\diamond$) treatment. Placebo compared with: metoprolol CR + fluvastatin, $P < 0.05$ metoprolol CR + bezafibrate, $P < 0.01$ atenolol + fluvastatin, $P < 0.01$ atenolol + bezafibrate, $P < 0.001$.

Table 2 Mean (95% confidence intervals) plasma free fatty acid concentration during 90 min of exercise at 50% VO_2 max on placebo, metoprolol CR + fluvastatin, metoprolol CR + bezafibrate, atenolol + fluvastatin, and atenolol + bezafibrate treatment.

Treatment	Mean plasma FFA concentration ($\mu\text{mol l}^{-1}$) at time, t, (min)					
	t15	t30	t45	t60	t75	t90
Placebo	45.9 (0–104)	157 (0–359)	252.4 (0–537)	340 (0–707)	452.4 (15–890)	573 (105–1041)
Metp + Fluv	20.9 (0–75)*	50 (0–106)***	106.8 (0–297)***	145 (0–365)***	206.2 (0–499)***	277 (0–647)***
Metp + Bez	12.3 (0–39)***	30 (0–95)***	50.4 (0–152)***	65 (0–165)***	112.7 (0–247)***	182 (0–396)***
Aten + Fluv	20.7 (0–64)**	43 (0–172)**	65.1 (0–257)***	87 (0–287)***	128.2 (0–343)***	211 (0–511)***
Aten + Bez	9.9 (0–36)**	22 (0–83)***	33.3 (0–113)***	51 (0–157)***	76.9 (0–226)***	123 (0–352)***

Significant differences compared with placebo: * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

time, were significantly reduced on all treatments in comparison with placebo ($P = 0.0001$) (see Table 2 and Figure 3). Of the four combination treatments, metoprolol CR + fluvastatin had the least effect on FFA concentration. Compared to metoprolol CR + fluvastatin, mean FFA concentration was similar on metoprolol CR + bezafibrate, lower on atenolol + fluvastatin, $P = 0.063$, and significantly reduced on atenolol + bezafibrate, $P = 0.0004$. Atenolol + bezafibrate had the most adverse effect on FFA concentration, levels being significantly reduced even in comparison with atenolol + fluvastatin, $P = 0.022$. Plasma FFA levels rose steeply on all treatments immediately post-exercise, but decreased following 15–30 min of rest.

Plasma ammonia

In comparison with placebo, resting plasma ammonia concentration was elevated pre-exercise on atenolol + fluvastatin treatment, $P = 0.041$, and post-exercise on atenolol + bezafibrate treatment, $P = 0.034$. During exercise, plasma ammonia levels were significantly elevated on all

combination treatments in comparison with placebo (see Table 3 and Figure 4). These increases were only moderate on metoprolol CR + fluvastatin treatment (approx $20 \mu\text{mol l}^{-1}$), $P = 0.017$, but substantial on metoprolol CR + bezafibrate (approx 30 – $40 \mu\text{mol l}^{-1}$), $P = 0.0001$, and both atenolol combination treatments (approx 40 – $60 \mu\text{mol l}^{-1}$), $P = 0.0001$. Overall, plasma ammonia levels on metoprolol CR + fluvastatin were considerably lower in comparison with both atenolol + fluvastatin, $P = 0.011$, and atenolol + bezafibrate, $P = 0.003$, but not significantly lower in comparison with metoprolol CR + bezafibrate treatment ($P = 0.23$).

Plasma triglycerides

Plasma triglyceride levels rose by approximately 10 mg dl^{-1} on all treatments during exercise, $P = 0.0001$, declining to pre-exercise values by 30 min post-exercise. Compared with placebo, plasma triglycerides were significantly reduced on both bezafibrate treatments (metoprolol CR + bezafibrate, $P = 0.012$, and atenolol + bezafibrate, $P = 0.037$), at rest and

Figure 3 Mean ($\pm$ s.e. mean) plasma free fatty acid concentration at rest (-15 and -5 min, before exercise and $+15$ and $+30$ min, post-exercise), and during exercise at 50% VO_2 max for 90 min ($t15$ – $t90$), on placebo ($-\circ-$), metoprolol CR + fluvastatin ($-\blacksquare-$), metoprolol CR + bezafibrate ($-\triangle-$), atenolol + fluvastatin ($-\bullet-$), and atenolol + bezafibrate ($-\diamond-$) treatment. Placebo compared with all treatments, $P < 0.001$.

Table 3 Mean (95% confidence intervals) plasma ammonia concentration during 90 min of exercise at 50% VO_2 max on placebo, metoprolol CR + fluvastatin, metoprolol CR + bezafibrate, atenolol + fluvastatin, and atenolol + bezafibrate treatment.

Treatment	Mean plasma ammonia concentration ($\mu\text{mol l}^{-1}$) at time, t , (min)					
	$t15$	$t30$	$t45$	$t60$	$t75$	$t90$
Placebo	39.8 (0–44)	41.8 (8–76)	37.1 (0–82)	41.8 (0–97)	41.6 (6–78)	37.3 (0–84)
Metp + Fluv	58.6 (0–152)	65.0 (6–124)*	61.1 (19–104)*	61.9 (15–109)	55.2 (0–114)	55.9 (2–110)
Metp + Bez	52.8 (0–107)	70.7 (16–126)**	78.6 (4–153)***	75.8 (5–147)**	70.7 (6–135)**	78.9 (0–167)***
Aten + Fluv	66.8 (24–109)	80.6 (30–132)***	98.6 (13–184)***	90.2 (27–153)***	84.1 (12–156)***	90.2 (10–170)***
Aten + Bez	72.3 (11–134)**	85.1 (22–148)***	89.8 (22–158)***	91.8 (30–154)***	98.0 (10–186)***	99.6 (26–174)***

Significant differences compared with placebo: * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

during exercise, but not on fluvastatin treatments (metoprolol CR + fluvastatin, and atenolol + fluvastatin). For example, at $t60$, plasma triglyceride concentrations were; 74 mg dl^{-1} (22–126), 71 mg dl^{-1} (23–119), 74 mg dl^{-1} (22–126) on placebo, metoprolol CR + fluvastatin, and atenolol + fluvastatin, respectively, and 52 mg dl^{-1} (22–82) and 54 mg dl^{-1} (16–92) on metoprolol CR + bezafibrate and atenolol + bezafibrate treatments.

Plasma lactate

Plasma lactate levels were not significantly elevated above placebo levels on any combination treatment. For example, at $t45$, plasma lactate levels were: 1.1 (0.47 – 1.7) mmol l^{-1} , 1.0 (0.47 – 1.6) mmol l^{-1} , 1.0 (0.39 – 1.6) mmol l^{-1} , 1.2 (0.37 – 2.0) mmol l^{-1} , and 1.1 (0.47 – 1.8) mmol l^{-1} , on placebo, metoprolol + fluvastatin, metoprolol + bezafibrate, atenolol + fluvastatin, and atenolol + bezafibrate treatments, respectively.

Perceived exertion

Cardiorespiratory effort, leg effort, leg pain Mean scores for perceived cardiorespiratory effort (CE) during exercise were lower on placebo compared with all other treatments. CE was highest on atenolol treatments, although in comparison with placebo, this difference was only statistically significant on atenolol + fluvastatin ($P = 0.018$), and not on atenolol + bezafibrate treatment ($P = 0.11$). CE was also high on metoprolol CR + bezafibrate treatment compared with placebo ($P = 0.044$), but not significantly so on metoprolol CR + fluvastatin ($P = 0.154$) (see Table 4).

Mean perceived leg effort and leg pain scores were slightly higher on all combination treatments in comparison with placebo, but there were no significant differences (see Table 4).

Feeling scale Mean scores on the 'feeling scale' during exercise at 50% VO_2 max were significantly lower on all

Figure 4 Mean ($\pm$ s.e. mean) plasma ammonia concentration at rest (-15 and -5 min, before exercise and $+15$ and $+30$ min, post-exercise), and during exercise at 50% VO_2 max for 90 min ($t15$ – $t90$), on placebo ($-○-$), metoprolol CR + fluvastatin ($-■-$), metoprolol CR + bezafibrate ($-△-$), atenolol + fluvastatin ($-●-$), and atenolol + bezafibrate ($-◇-$) treatment. Exercise samples: placebo compared with: metoprolol CR + fluvastatin, $P<0.05$ metoprolol CR + bezafibrate, $P<0.0001$ atenolol + fluvastatin, $P<0.0001$ atenolol + bezafibrate, $P<0.0001$.

Table 4 Mean (95% confidence intervals) scores for perceived cardiorespiratory effort (CE), leg effort (LE), and leg pain (LP), and 'feeling scale' scores during exercise at 50% VO_2 max at time $t90$ (90 min), on placebo, metoprolol CR + fluvastatin, metoprolol CR + bezafibrate, atenolol + fluvastatin, and atenolol + bezafibrate treatment.

Treatment	CE	LE	LP	Feeling scale
Placebo	2.5 (0–5.8)	2.7 (0–6.4)	2.2 (0–6.3)	1.4 (–1.9–+4.7)
Metp + Fluv	2.8 (0–5.9)	3.4 (0.7–6.1)	2.7 (0–6.2)	0.6 (–2.9–+4.1)
Metp + Bez	3.1 (0–7.4)	3.7 (0–8.0)	3.0 (0–8.3)	0.3 (–3.7–+4.2)
Aten + Fluv	3.4 (0–7.7)	3.3 (0–7.4)	2.9 (0–7.8)	0.1 (–4.4–+4.6)
Aten + Bez	3.5 (0–7.6)	3.8 (0–8.3)	3.2 (0–8.5)	–0.3 (–4.2–+3.6)

treatments i.e. subjects felt worse, in comparison with placebo; metoprolol CR + fluvastatin, $P=0.049$; metoprolol CR + bezafibrate, $P=0.03$; atenolol + fluvastatin, $P=0.007$; atenolol + bezafibrate, $P=0.002$. Feeling scale scores were particularly low on atenolol combination treatments, and subjects felt slightly better on metoprolol CR + bezafibrate in comparison. Of the four combination treatments, metoprolol CR + fluvastatin had the least adverse effect on feeling scale scores and were significantly higher compared with atenolol + bezafibrate, $P=0.044$ (see Figure 5 and Table 4).

Discussion

In this randomized, crossover study, we investigated the effects of 3 days' treatment with different combinations of β_1 -selective receptor antagonists and lipid-lowering drugs, in comparison with placebo, on exercise metabolism and fatigue during moderate intensity exercise in healthy young men and women. We wanted to compare the effects of two different lipid lowering drugs, to compare the effects of two β_1 -selective blocker preparations one producing very marked and the other producing modest β -adrenoceptor blockade,

and we wanted to assess the impact of giving the two types of drug in combination. We did not wish to compare metoprolol with atenolol.

Mean heart rate was reduced on all β -adrenoceptor blocker treatments during exercise at 50% VO_2 max (by approximately 25 – 30 beats min^{-1}) but was reduced by approximately 9 or 10 beats min^{-1} more on atenolol 100 mg than on metoprolol CR 100 mg treatment ($P=0.001$). Although comparable doses of atenolol and metoprolol CR were employed in the study, and they are both β_1 -selective, the pharmacokinetics of the two preparations are different. The plasma concentration of conventional release atenolol peaks at approximately 2 – 4 h [20] which was the time of the exercise session, whereas 'controlled release' metoprolol produces a more even plasma concentration-time profile over a 24 h period [21, 22]. Thus the lower exercise heart rate on atenolol 100 mg, compared with metoprolol CR 100 mg, was expected [23].

The fact that heart rate was reduced on all combination treatments ($P=0.0001$), and plasma triglyceride concentration was reduced on both bezafibrate treatments (metoprolol CR + bezafibrate, $P=0.012$, and atenolol + bezafibrate,

Figure 5 Mean ($\pm$ s.e. mean) reported 'feeling scale' (see Appendix) scores during exercise at 50% VO_2 max for 90 min (t_{15} – t_{90}), on placebo (○), metoprolol CR + fluvastatin (■), metoprolol CR + bezafibrate (△), atenolol + fluvastatin (●), and atenolol + bezafibrate (◇) treatment. Placebo compared with: metoprolol CR + fluvastatin, $P < 0.05$ metoprolol CR + bezafibrate, $P < 0.05$ atenolol + fluvastatin, $P < 0.01$ atenolol + bezafibrate, $P < 0.01$.

$P = 0.037$), during exercise in comparison with placebo, indicates that 3 days' treatment was sufficient to produce significant pharmacological changes in these normolipidaemic subjects.

The steady increase in the mean plasma concentration of free fatty acids observed during exercise on placebo ($35 \mu\text{mol l}^{-1}$ at rest to $573 \mu\text{mol l}^{-1}$ at t_{90}) in this study is commonly observed [24, 25] and results primarily from an increase in the rate of lipolysis [25]. With this rise in FFA the respiratory exchange ratio (RER), declines indicating that a greater proportion of the energy was being supplied by oxidation of fat [24, 25]. Following 90 min of exercise at 50% VO_2 max, fat oxidation was providing more than 50% of the required energy in seven subjects.

Atenolol + bezafibrate treatment had the most significant adverse effect on fat metabolism (fat oxidation, plasma free fatty acid concentration) during exercise at 50% VO_2 max, metoprolol CR + bezafibrate, and atenolol + fluvastatin had moderate effects, and metoprolol CR + fluvastatin treatment had the least effect in comparison with placebo.

In a previous study [10], fluvastatin was shown to have no adverse impact on fat metabolism in comparison with placebo, so we conclude that reduced FFA availability and fat oxidation on the combination treatment metoprolol CR + fluvastatin is largely attributable to the effects of metoprolol CR. A blockade of predominantly β_1 -adrenergic receptors in adipocytes by metoprolol CR [26] would reduce adenylate cyclase activity (since the stimulation by catecholamines is blocked), and lead to a reduced availability of cyclic AMP to activate lipolysis. Since metoprolol CR 100 mg has a low even plasma concentration profile [23], its effects on β_2 -receptors is minimal [23].

Conventional release atenolol may lose some β_1 -selectivity during the peak phase of plasma concentration [27, 23] and

may thus exert anti-lipolytic effects via β_2 -receptors [28] both within muscle [26], and within adipose tissue [29], in addition to a β_1 -mediated inhibition of lipolysis in adipose tissue. This might explain the greater adverse effect of atenolol + fluvastatin on fat metabolism compared with metoprolol CR + fluvastatin.

The effects of metoprolol CR and bezafibrate and those of atenolol and fluvastatin on fat metabolism were comparable. This suggests that the benefits of metoprolol CR over atenolol were lost when metoprolol was given with the lipid-lowering drug bezafibrate—which has been shown to have an adverse effect on fat metabolism during exercise, unlike fluvastatin [10]. Clofibrate [30, 31, 32] has also been shown to reduce fasting FFA levels in humans. Carlsson *et al.* [31] found that high concentrations of clofibrate decreased the rate of triglyceride lipolysis in rat adipocytes, and postulated that this may be related to a decrease in intracellular cyclic AMP concentration, which controls the activity of the hormone-sensitive triglyceride lipase system [33].

Plasma ammonia levels during exercise were higher on all combination treatments than on placebo. Mean plasma ammonia concentration was slightly elevated on metoprolol CR + fluvastatin treatment, higher on metoprolol CR + bezafibrate and even higher on both atenolol + fluvastatin and atenolol + bezafibrate treatments.

It was recently demonstrated that despite significant reductions in plasma FFA availability and fat oxidation on bezafibrate, there was no significant elevation in plasma ammonia concentration above placebo level [10]. However, there is evidence for heightened plasma ammonia levels during exercise on β -adrenoceptor blockade [34, 35]. It is postulated, therefore, that increased ammonia concentration on combination treatment, in comparison with placebo, is related primarily to β -adrenergic receptor blockade,

particularly blockade of intramuscular β_2 -receptors (atenolol at peak plasma concentration). An inhibition of intramuscular lipolysis [26] and glycogenolysis [36] via β_2 -receptors might, theoretically, 'force' an increase in the activity of alternative energy production pathways.

Energy is produced by the hydrolysis of adenosine triphosphate (ATP) to adenosine diphosphate (ADP), and ATP is resynthesised from the breakdown of energy substrates. A shortage of energy substrates may reduce the reformation of ATP and lead to increased ADP and adenosine monophosphate (AMP) levels, increased adenylate kinase activity which activates AMP deaminase [37], resulting in the deamination of AMP to inosine 5'-monophosphate (IMP) and ammonia [38]. However, there is a lack of evidence for an increase in adenine nucleotide degradation during moderate exercise intensities [39], but some evidence that the rate of AMP deamination, and ammonia production, during high intensity exercise may be enhanced on propranolol [40].

Plasma ammonia levels of 70–100 $\mu\text{mol l}^{-1}$ measured on combination treatment in this study would normally be associated with plasma lactate levels exceeding 10 mmol l^{-1} [41], an indication of intracellular acidosis—which may activate AMP deaminase [41], but mean plasma lactate concentration did not exceed 1.2 mmol l^{-1} on any treatment. Therefore, it is possible that in response to a reduced availability of fat as an energy source, a compensatory increase in the deamination of branched-chain amino acids (BCAA) may have occurred, resulting in increased ammonia production [42].

Treatment with a β_1 -selective blocker (particularly atenolol) + a lipid-lowering drug significantly increased the perception of effort (cardiorespiratory effort and a non-significant trend for heightened leg effort), and subjects reported 'feeling worse' (particularly on atenolol treatments) on all combination treatments, compared with placebo.

Increased plasma ammonia concentration is related to the development of local (muscle) fatigue [43], and may exert an influence in the central nervous system, leading to a heightened perception of fatigue [44]. Other factors which could, theoretically, contribute to the increased perception of effort on beta-blocker treatments include; i) an increased stroke volume—a compensatory mechanism as a result of reduced heart rate [45], ii) a localised build-up of products of metabolism, such as plasma ammonia or lactate [46], due to inadequate blood flow in working muscle resulting from β_2 -receptor blockade in peripheral veins [47], and iii) a constriction of the bronchi as a result of β_2 -receptor blockade [48]. The adverse effect of bezafibrate on fat metabolism may exacerbate any fatigue mechanisms related to insufficient energy production resulting from beta-blockade.

There was an apparent relationship between elevations in plasma ammonia levels on combination treatments during exercise, heightened perceived cardiorespiratory exertion (and leg effort/pain), and reduced 'feeling scale' scores, in that treatments with least impact on plasma ammonia had least impact on the perception of effort, and those which increased ammonia had most effect. Since elevated plasma ammonia concentration has been associated both with local fatigue [43] and central fatigue [44], raised ammonia levels on atenolol

treatments may contribute significantly to the heightened perception of fatigue and reduced 'feeling scale' scores.

Atenolol and lipid-lowering drug combination treatments did have adverse effects on lipid metabolism, plasma ammonia levels, and feelings of fatigue during exercise but a non-selective β -adrenoceptor-blocker, such as propranolol, would have produced a much greater effect on such measures [4]. The findings from this study suggest that the potential cumulative effect of propranolol and lipid-lowering therapy (particularly bezafibrate) on exercise metabolism and fatigue may be particularly severe. In fact, it may be advisable for patients who are on conventional release beta-blockers such as atenolol and propranolol to exercise at least five hours after taking a tablet to avoid the adverse effects on exercise metabolism associated with β_2 -adrenoceptor blockade.

To summarise, in healthy volunteers, combinations of β_1 -selective blockers and lipid-lowering drugs were associated with significant reductions in fat metabolism, increased plasma ammonia levels, and raised the perception of effort during exercise, in comparison with placebo. Metoprolol CR + fluvastatin had the least effect, combinations metoprolol CR + bezafibrate and atenolol + fluvastatin had intermediate effects, and atenolol + bezafibrate had the most adverse effect.

This work was supported by Astra Pharmaceuticals (Germany) Ltd.

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(Received 19 March 1996,
accepted 11 October 1996)

Appendix 1

Borg II Scale [11]

0	Nothing at all
0.5	Very, very weak
1	Very weak
2	Weak
3	Moderate
4	Somewhat strong
5	Strong
6	
7	Very strong
8	
9	
10	Very, very strong

Appendix 2

'Feeling Scale' [12]