CLINICAL RESEARCH

Weight loss in obese subjects on a restricted diet given BRL 26830A, a new atypical β adrenoceptor agonist

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Abstract

A double blind placebo controlled study was carried out in 40 subjects newly referred for treatment for obesity to determine the effects of the new thermogenic β adrenoceptor agonist BRL 26830A. The subjects were randomised to receive either BRL 26830A, 200 mg daily for two weeks then 400 mg daily, or placebo for 18 weeks, and all were instructed to follow a 3.35 MJ diet that was low in fat and high in fibre. Weight loss was 15.4 (SD 6.6) kg in subjects given BRL 26830A compared with 10.0 (5.9) kg in those given placebo ($p=0.02$). The relative weight loss was 0.93 (0.39)% a week with BRL 26830A and 0.61 (0.38)% with placebo ($p=0.02$). Urinary excretion of nitrogen was similar in both groups, whereas measurements of skinfold thickness indicated a 4.1 kg difference in the amount of fat lost, suggesting that weight loss with BRL 26830A was mainly from adipose and not lean tissue. BRL 26830A had no effect on resting pulse rate or pressor effects on either diastolic or systolic blood pressure. No significant differences were found between the two groups in serum cholesterol concentration, percentage of high density lipoprotein cholesterol, plasma concentrations of glucose and insulin, the ratio of glucose to insulin, serum concentrations of triiodothyronine and thyroxine, and creatinine clearance. Short term administration of BRL 26830A to six subjects who had taken the drug for 18 weeks showed that the expenditure of energy increased by 11.6% during the second hour after administration, which suggests that BRL 26830A may enhance weight loss thermogenically.

BRL 26830A may be a useful drug in the treatment of obesity.

Introduction

BRL 26830A is a new atypical β adrenoceptor agonist, which in obese rodents increases metabolic rate and causes a reduction in weight by decreasing the body lipid content.¹ It shows a high degree of selectivity for thermogenesis relative to β_1 cardiac or β_2 bronchial effects,^{2,3} and evidence suggests that both brown adipose tissue^{2,4} and skeletal muscle⁵ contribute to this activity. In normal human volunteers BRL 26830A increased the resting metabolic rate and so has potential as an antiobesity agent in man. Indeed, one preliminary report showed that in obese subjects taking a low energy liquid diet BRL 26830A increased weight loss by 42% over six weeks by preventing the fall in expenditure of energy that usually occurs when intake of energy is restricted.⁶ We examined the antiobesity effects of BRL 26830A during 18 weeks in an unselected group of obese subjects eating a diet low in fat and high in fibre.

Subjects and methods

We studied 40 subjects who were newly referred by their general practitioners for treatment for obesity. All were at least 20% in excess of their ideal body weight, defined as that given as an acceptable average in the report of the Royal College of Physicians⁷ based on the weight for height tables of the Metropolitan Life Insurance Company.⁸ At the time of entry to the study they had a stable weight, and none was having treatment to reduce weight; all were in good health and biochemically euthyroid and non-diabetic. They were randomised into two groups for treatment with either BRL 26830A or placebo. Eight subjects defaulted from the study; table I gives the details of all subjects entering and completing the study.

TABLE I—Details before study of all subjects entering and completing study. Values are means (SD)

Treatment group	Ratio of women to men	Age (years)	Weight (kg)	Percentage of ideal body weight	Body mass index (kg/m ²)
<i>Patients entering</i>					
BRL 26830A (n=20)	16:4	42.4 (8.6)	101 (19.9)	179 (38.1)	37.4 (8.0)
Placebo (n=20)	16:4	43.2 (10.0)	100 (22.7)	177 (34.7)	37.0 (7.3)
<i>Patients completing</i>					
BRL 26830A (n=16)	12:4	43.9 (8.3)	102 (21.0)	181 (41.1)	37.7 (8.7)
Placebo (n=16)	12:4	44.9 (10.2)	101 (21.5)	175 (30.3)	36.5 (6.6)

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During the four weeks before the study the expenditure of energy was measured on two occasions by indirect ventilated hood calorimetry. Oxygen consumption and carbon dioxide production were measured by paramagnetic (Taylor, Servomex) and infrared (SS-200, Analytical Development Company Ltd) analyses, respectively. From these data resting metabolic rate was calculated from the formula of Weir and expressed as kJ/min.⁹ Each measurement was made after a 12 hour overnight fast with the subject semirecumbent in a thermoneutral (25-27°C) environment. In premenopausal women energy expenditure was studied in the follicular phase of the cycle. The first measurement of resting metabolic rate was done only to familiarise the subjects with the surroundings, the result being discarded.

After the second determination the thermic response to noradrenaline was measured. A 19 gauge cannula (Venflon) was inserted into a left brachial vein for blood sampling and another into a right brachial vein for infusion of noradrenaline. These were kept patent with 1 ml 3.8% (w/v) sodium citrate BPC. The subjects then rested in the thermoneutral environment for at least 30 minutes before their resting metabolic rate was measured over 20 minutes. Noradrenaline (Levophed, Winthrop) was then infused at 0.1 µg/kg ideal body weight/min for 45 minutes with simultaneous measurement of metabolic rate. We have already shown that this dosage is the maximum that all subjects can receive without undue stress and achieves a plasma noradrenaline concentration of about 5.9 nmol/l.¹⁰ Blood samples were taken at 0, 15, 30, and 45 minutes for estimation of total free fatty acid concentration by a modification of the Wako NEFA-C kit (Alpha Laboratories, Eastleigh) on a Rotochem IIa centrifugal analyser and glycerol concentration by an automated in house enzymatic assay with the Rotochem IIa centrifugal analyser based on the method of Roberts and Smith.¹¹ A 75 g oral glucose tolerance test was performed to confirm that subjects did not have diabetes.

At the start of the study all patients were given careful instruction about a daily diet of 3.35 MJ that was low in fat and high in fibre and asked to continue with this diet throughout the 18 weeks of the study. BRL 26830A, 50 mg four times a day for two weeks and then 100 mg four times a day for 16 weeks, or placebo, eight tablets a day, was prescribed in a double blind fashion. Subjects were reviewed every two weeks and weight, resting pulse rate, blood pressure, and side effects monitored. Skin fold thickness at the suprailiac, subscapular, biceps, and triceps sites¹² was measured before and at the end of the study. The resting metabolic rate was repeated at six, 12, and 18 weeks some 12 hours after the last dosage of BRL 26830A or placebo. The infusion of noradrenaline was repeated only at 12 weeks. At the end of the study six subjects had their metabolic rate measured before and during the two hours after ingesting 100 mg BRL 26830A.

Before the study, at two, six, 12, and 18 weeks, and after the study the following concentrations were measured: glucose by an enzymatic method with Beckman glucose spinchem hexokinase endpoint reagent (Beckman RIIC Ltd, Buckinghamshire), insulin by a magnetic immunoassay (Serono Diagnostic Ltd, London), total thyroxine by an in house macroglol precipitated radioimmunoassay, and total triiodothyronine by an in house double antibody radioimmunoassay. Serum lipid concentrations were assayed with a Cobas Fara analyser; total and high density lipoprotein cholesterol with an enzyme colorimetric method (Boehringer Corporation, London), high density lipoprotein cholesterol after precipitation of low density and very low density lipoprotein cholesterol with phosphotungstate and triglyceride by a colorimetric reaction with iodonitrotetrazolium chloride (Roche Products Ltd, Welwyn Garden City). Routine full blood count, biochemical screening, analysis of urine, and urinary nitrogen and creatinine excretion were also measured at these times.

Ethics and statistics—Ethical approval for this study was given by Tayside Health Board's ethical subcommittee, and fully informed consent was obtained from each subject. The size of the sample was chosen to give at least an 80% chance of detecting a 4.5 kg difference in weight loss between the groups at a 5% level of significance. The STATCALC program was used for statistical analysis. A two tailed Student's *t* test was performed for between group analysis, and 95% confidence limits of estimated differences are shown when appropriate. The cumulative incremental responses were calculated from the area under the response curve. Results are expressed as means (SD) in the text and means (SEM) in the figures.

Results

Four subjects taking BRL 26830A and four taking placebo defaulted from the study. One subject in the group taking BRL 26830A defaulted after feeling unwell with shakiness and rapid weight loss, one defaulted owing to domestic and family problems, another left the country, and no reason could be ascertained for the fourth. In the group taking placebo two subjects defaulted owing to domestic and family problems, and no reason could be ascertained for the other two. Six of the eight defaulted before the sixth week of the study and the two others before the 12th week.

Weight loss was increased in the group taking BRL 26830A compared

FIG 1—Mean (SEM) weight loss in subjects taking BRL 26830A (—) and placebo (---). *p = 0.02.

with the group taking placebo (fig 1). In those subjects who completed the trial weight loss at six weeks was 8.6 (3.4) kg with BRL 26830A compared with 6.3 (2.4) kg with placebo, and at 12 weeks it was 13.0 (5.3) kg compared with 8.9 (4.7) kg. By 18 weeks the respective weight losses were 15.4 (6.6) and 10.0 (5.9) kg, the mean difference of 5.4 kg having a 95% confidence interval of 0.8 to 9.9 kg (*t* = 2.42, *p* = 0.02). From all available data on weight loss, including those from defaulters, the regression coefficient of log_e (weight) on time was calculated to give the overall rate of relative weight loss. Comparing rates between groups gave a relative weight loss of 0.93 (0.39)% a week for subjects taking BRL 26830A and 0.61 (0.38)% a week for subjects taking placebo (*t* = 2.40, *p* = 0.02).

Skinfold thickness (sum of four sites) also decreased more in subjects taking BRL 26830A (39 (11) mm) than in those taking placebo (26 (15) mm) (*p* < 0.01). Urinary nitrogen excretion was not increased in subjects taking BRL 26830A (fig 2); indeed, at two weeks the fall in urinary nitrogen excretion with BRL 26830A was greater than that with placebo, the mean difference being 2.6 g/24 h (95% confidence interval -0.2 to 6.0, *t* = 1.94, *p* = 0.06), although at other times no significant differences existed between the groups.

Table II shows resting metabolic rates during the study. At six weeks the

FIG 2—Mean (SEM) urinary excretion of nitrogen in subjects taking BRL 26830A (—) and placebo (---).

TABLE II—Mean (SD) resting metabolic rates and cumulative noradrenergic thermic responses in subjects treated with BRL 26830A and placebo

Time (weeks)	Resting metabolic rate (kJ/min)		Noradrenergic thermic response (kJ)	
	BRL 26830A	Placebo	BRL 26830A	Placebo
Before study	5.35 (0.74)	5.22 (1.03)	21.8 (13.7)	16.6 (14.8)
6	5.27 (0.80)	4.84 (0.80)		
12	5.00 (0.74)	4.99 (1.05)	17.5 (13.9)	21.4 (10.4)
18	5.11 (1.00)	4.98 (1.12)		

fall was greater in the group taking placebo, the mean difference being 0.30 kJ/min (95% confidence interval -0.04 to 0.66, $t=1.80$, $p=0.08$); no significant differences were found between the groups at 12 and 18 weeks. The mean thermic response to noradrenaline infusion decreased after 12 weeks in subjects taking BRL 26830A but increased in those taking placebo, although the differences were not significant. BRL 26830A had no effect on resting pulse rate or pressor effects on either systolic or diastolic blood pressure (table III).

TABLE III—Mean (SD) resting pulse rates and sitting blood pressure measurements in subjects treated with BRL 26830A or placebo

Time weeks	Pulse (/min)		Systolic blood pressure (mm Hg)		Diastolic blood pressure (mm Hg)	
	BRL 26830A	Placebo	BRL 26830A	Placebo	BRL 26830A	Placebo
Before study	78 (8)	76 (7)	129 (12)	127 (18)	84 (8)	83 (7)
0	85 (9)	79 (9)	134 (9)	127 (13)	82 (9)	81 (9)
2	75 (9)	76 (13)	122 (17)	124 (13)	79 (8)	80 (8)
6	76 (8)	70 (12)	120 (16)	125 (12)	79 (8)	82 (12)
12	76 (11)	73 (8)	116 (15)	121 (8)	76 (11)	80 (8)
18	75 (8)	75 (8)	116 (16)	119 (12)	78 (8)	79 (8)

TABLE IV—Mean (SD) high density lipoprotein cholesterol, plasma glucose, and insulin concentrations and ratio of glucose to insulin in subjects treated with BRL 26830A or placebo

Time weeks	High density lipoprotein cholesterol (%)		Glucose (mmol/l)		Insulin (mU/l)		Ratio of glucose to insulin	
	BRL 26830A	Placebo	BRL 26830A	Placebo	BRL 26830A	Placebo	BRL 26830A	Placebo
Before study	23.3 (6.6)	21.9 (6.1)	4.9 (0.4)	5.0 (0.6)	19.3 (6.5)	18.2 (6.6)	0.27 (0.06)	0.30 (0.11)
2	26.5 (7.7)	22.6 (6.2)	5.0 (0.5)	5.2 (0.5)	15.9 (3.7)	19.0 (8.0)	0.33 (0.08)	0.31 (0.10)
6	26.0 (7.4)	23.0 (6.4)	5.1 (0.4)	5.4 (0.5)	18.1 (4.1)	22.0 (10.0)	0.30 (0.06)	0.28 (0.10)
12	24.7 (7.0)	22.5 (6.3)	4.6 (0.5)	5.0 (0.4)	15.8 (3.4)	18.2 (4.2)	0.30 (0.07)	0.28 (0.05)
18	24.7 (6.0)	21.5 (5.7)	4.8 (0.3)	5.0 (0.4)	14.8 (2.2)	15.4 (3.6)	0.33 (0.05)	0.34 (0.06)

In both groups serum cholesterol and triglyceride concentrations decreased during the 18 weeks, but with no significant differences between them. The percentage of high density lipoprotein cholesterol increased in the subjects taking BRL 26830A, but again with no significant differences between the groups (table IV). BRL 26830A had no deleterious effect on glucose tolerance as determined by fasting plasma glucose concentration, insulin concentration, and the ratio of glucose to insulin. Serum triiodothyronine concentration was lower at all time points in both groups compared with values before the study, being 2.00 (0.45) nmol/l before the study and 1.67 (0.43) nmol/l at 18 weeks in the group taking BRL 26830A and 1.86 (0.32) nmol/l and 1.52 (0.30) nmol/l, respectively, in the group taking placebo; no significant differences were found between the two groups. Serum thyroxine concentration did not change in either group. Creatinine clearance decreased in both groups from 139 (38) ml/min before the study to 82 (31) ml/min at 18 weeks in subjects taking BRL 26830A and from 133 (48) ml/min to 79 (29) ml/min in those taking placebo. No other biologically important changes were detected in the full blood count or in the biochemical analysis of serum and urine.

The only side effects of treatment with BRL 26830A that were regularly observed were shaky hands and tremulousness. Twelve subjects experienced these symptoms at some time during the 18 weeks; in nine subjects they were classified as slight, in two as moderate, and in one as severe. These symptoms tended to occur about one hour after subjects took the drug, lasted from 30 minutes to one hour, and became less common after the first two weeks of the study. No patient had to be withdrawn from the study because of the severity of side effects. Only one subject taking placebo reported slightly shaky hands. No other side effects were identified.

Each of the six subjects studied after an oral dose of 100 mg BRL 26830A showed a rise in metabolic rate with a mean rise of 11.6% (95% confidence interval 9.5 to 13.5%, $t=15.1$, $p=0.001$) during the second hour (fig 3). Systolic and diastolic blood pressure did not increase significantly in the two hours after the dose was given.

Discussion

Treating obesity with drugs is not generally favoured and is often reserved for complicated obesity or for special circumstances such

as before elective surgery. This attitude however, is perhaps prejudiced by past experience with the abuse of amphetamines and because long term treatment may be required. Additionally, the anorectic agents currently in use have appreciable undesirable side effects: those that act on catecholaminergic pathways, such as diethylpropion, give rise to sympathomimetic side effects, and fenfluramine, which acts on the serotonergic system, may result in pulmonary hypertension and also depression, especially on withdrawal of the drug.¹³ Thus considerable interest in the new thermogenically active β adrenoceptor agonists as potential anti-obesity agents is not surprising.

In our study BRL 26830A was given to an unselected group of obese subjects and resulted in significantly more weight loss than placebo. The additional 5.4 kg lost after 18 weeks represents a mean weekly additional weight loss of 0.3 kg. Although the results were significant, it is important to comment on the magnitude of the benefit. In 1971 the Food and Drug Administration reported on over 7000 subjects who took part in 170 double blind placebo controlled studies. In over 90% of these studies active treatment with anorectic drugs resulted in greater weight loss than treatment with placebo, and the mean additional weekly weight loss attributable to treatment was 0.23 kg.¹⁴ Our results compare

favourably with that analysis, especially given that many of those studies were short, often being for only four weeks. Furthermore, the rate of weight loss in our subjects taking BRL 26830A was similar to the best rate obtained by Stunkard *et al* in their comprehensive study of fenfluramine and behaviour therapy.¹⁵ It seems that treatment with BRL 26830A confers a clinically significant advantage on weight reduction.

Thyroid hormones were previously used to treat obesity, but as well as raising the metabolic rate they also resulted in loss of lean body mass when used in pharmacological doses¹⁶⁻¹⁸ and so are not now recommended. Although our study's protocol did not include sophisticated measurements of body composition, the decrease in skinfold thickness and the similar urinary excretion of nitrogen with BRL 26830A and placebo suggest that the additional weight loss was from adipose tissue, which agrees with data from animal

FIG 3—Mean (SEM) rise in metabolic rate in six subjects in response to 100 mg oral BRL 26830A.

studies.¹ From the differences in skinfold thickness at 18 weeks we estimate that BRL 26830A resulted in the loss of 4.1 kg (95% confidence interval 1.2 to 6.9, $t=2.92$, $p<0.01$) more body fat than placebo, which, within the limitations of the technique, is roughly an actual difference in weight loss of 5.4 kg.¹²

The resting metabolic rate was measured after a 12 hour fast and without treatment on the morning of the study to determine any long term adaptive changes in energy expenditure induced by BRL 26830A. At six weeks the resting metabolic rate had fallen in the subjects taking placebo but was maintained in those taking BRL 26830A. A previous study found the energy expenditure measured over 20 hours to be maintained during six weeks' treatment with BRL 26830A and a liquid diet compared with a fall of 15.5% with the liquid diet and placebo.⁶ At 12 and 18 weeks in our study no significant difference in resting metabolic rate was found between the groups, which might be explained by the effects of BRL 26830A diminishing with time or by uncounselled changes in dietary intake. None the less, a beneficial effect on weight loss was maintained for 18 weeks. The acute thermic effects of BRL 26830A after a dose is taken rather than long term adaptive changes are probably most important, as shown by an 11.6% rise in expenditure of energy in the six subjects after their usual dose of BRL 26830A at the end of 18 weeks' treatment.

The thermic response to infusion of noradrenaline did not increase after 12 weeks in the group treated with BRL 26830A, suggesting that the thermic effect of the infusion of noradrenaline did not adapt in the long term to the drug. This is interesting because the thermic response to a single oral dose of ephedrine increased by 475% after 12 weeks' continuous treatment.¹⁹ The reason for this may be that BRL 26830A acts on expenditure of energy in a different manner from noradrenaline. In retrospect, we should have measured the long term adaptive changes in the thermic response to a single dose of BRL 26830A in all our subjects, but this would have jeopardised the double blind design of the study. In any case, BRL 26830A has already been shown to raise the metabolic rate when given short term and the effect is enhanced after continuous treatment (C Zed, personal communication).

That no effects were found on resting pulse and blood pressure confirms that BRL 26830A is relatively inactive at cardiac β_1 receptors. Notably, the drug had no deleterious effects on serum lipid concentrations or glucose tolerance. Indeed, BRL 26830A may increase sensitivity of insulin both in mice²⁰ and in healthy men.²¹ Serum triiodothyronine concentration decreased in both groups owing to diminished intake of carbohydrate,^{22,23} there being no evidence that BRL 26830A stimulates peripheral conversion of thyroxine to triiodothyronine.

Creatinine clearance fell substantially in both groups. Although some of the multiple 24 hour urine collections could feasibly have been missed by subjects, we found no fall in the mean volumes of the 24 hour urine collections. The safety profile of BRL 26830A was partly assessed by monitoring the full blood count and results of serum and urinary biochemical tests, which showed no biologically important changes.

Although the side effects of shaky hands and tremulousness were common, they were generally mild, corresponding with peak plasma concentrations (Beecham Pharmaceuticals, personal communication). Whether these side effects would be abolished by a slow release preparation has yet to be determined. Further studies with more patients are required to evaluate BRL 26830A fully and to give adequate data on weight changes after the drug has been stopped. The exact mechanism of action of BRL 26830A in humans is as yet undetermined but is probably not by means of brown fat for brown fat's energetic relevance in adults is slight.²⁴ The site of action may be skeletal muscle, which has already been shown to be one site of the drug's thermic activity in rats.⁵

We conclude that BRL 26830A may be a useful drug in the treatment of obesity.

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ONE HUNDRED YEARS AGO

WE understand that there is a wide-spread feeling of dissatisfaction among London surgeons with the way in which the institution called St. Thomas's Home is conducted. It will be remembered that the easternmost block of St. Thomas's Hospital has been converted into a home hospital for paying patients; for an inclusive charge of eight shillings a day, they are provided with board, lodging, drugs, skilled nursing, and the services of a highly competent resident medical officer. It is alleged that no supervision whatever is exercised over the admission of patients, and that no inquiry is made as to their social or pecuniary circumstances. A very strong feeling exists that, under the guise of charity, a great injustice is being done to the medical profession, whose patients are, by extensive advertising, induced to enter St. Thomas's Home. It is said to be the practice, in surgical cases which are not treated by the resident medical officer, to call in some member of the St. Thomas's Hospital staff, who has to be satisfied with a reduced fee. Obviously the mere fact that many persons avail themselves of these facilities is no proof that they are deserving objects of this various charity. There are in London a considerable number of nursing homes, which afford, at various rates, the advantages of a home hospital to patients who can there be treated by their own medical men, and there is a general opinion that a public charity like St. Thomas's Hospital ought not to go out of its way to compete for private patronage, and interfere with the ordinary relations existing between medical men and their patients.

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