Sibutramine: a safety profile

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Abstract

Sibutramine is one of two anti-obesity agents approved by the National Institute of Clinical Excellence. It inhibits the re-uptake of noradrenaline and serotonin in the brain. By enhancing the sensation of satiety after a meal and reducing the fall in basal metabolic rate which usually occurs during weight loss, sibutramine is a useful aid to achieving weight loss and weight maintenance. Randomised controlled trials have shown that sibutramine 10 mg/day, in combination with diet and exercise, produces and maintains a dose-related weight loss of 5–10% in the majority of obese patients studied. This is accompanied by a range of important health benefits, including improvements in cholesterol and triglyceride levels.

Adverse publicity led to the European Commission's Committee for Proprietary Medicinal Products recently carrying out an in-depth investigation into the use of sibutramine in over 12,000 patients across Europe. Its findings support the use of sibutramine in obesity management, with no causal link found between the use of the drug and mortality. No change has been made to the Summary Product of Characteristics regarding the cardiovascular safety of sibutramine and the drug has been re-instated for use in Italy.

Prescribers should be aware of the cautions surrounding sibutramine use. While it is not advisable for those with a history of coronary heart disease or cardiac arrhythmias, published data reveal that most patients on sibutramine experience a drop in blood pressure and it may be used safely in patients with controlled hypertension. A small number of patients treated may show increases in blood pressure, particularly those who appear to be non-responders. Regular blood pressure monitoring is therefore advised.

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Introduction

Sibutramine (Reductil®) has been available for UK clinicians to prescribe since 2000. It is indicated as adjunctive therapy within a weight management programme for patients with obesity (body mass index [BMI] of 30 kg/m^2 or higher, or for overweight patients with a BMI of 27 kg/m^2 or higher with obesity-related co-morbidities such as type 2 diabetes or dyslipidaemia).

As one of just two licensed weight management agents available on prescription, sibutramine has raised the profile of obesity within the medical profession. The availability of anti-obesity agents has encouraged many in primary care to set up weight management clinics to treat what has historically been considered more a lifestyle issue than a medical condition.

A consequence of sibutramine's mechanism of action is that it may increase the blood pressure (BP) of some individuals, indicating the need for care in selecting appropriate patients for treatment and for ongoing monitoring in those in whom treatment is started. Confidence in sibutramine was dented after the decision by the Italian Health Ministry in March 2002 to suspend the marketing authorisation for the drug in Italy following the deaths of two patients who had been taking it. The

Commissione Unica del Farmaco (CUF) requested a new opinion on the risk/benefit profile of sibutramine from the European Commission's Committee for Proprietary Medicinal Products (CPMP).

The CPMP's rigorous scientific review involved extensive analyses of the 12,000 patients involved in clinical trials of sibutramine, and also included an extensive assessment of the 32 worldwide fatalities of those patients who were being treated with sibutramine since the drug's first launch in 1998. This included a particular focus on cardiovascular safety, in accordance with Italy's referral. Overall, the CPMP found:

- No evidence of a pattern in the causes of death
- In most cases where death occurred, alternative aetiologies and complicating conditions reflecting the known co-morbidities of obesity were present. For example, in one case, the BMI of the subject was recorded as 43 kg/m^2
- In the remaining cases there was insufficient information to identify a cause of death.

Indeed, the reported rate of deaths associated with sibutramine is substantially lower than expected mortality rates reported in epidemiological studies of obese populations. In the Nurse's Health Study,[1] the rate of death was 390 deaths per 100,000 patient years among those patients with a BMI from 29.0 to 31.9 kg/m^2. By contrast, worldwide data from the manufacturer of sibutramine, Abbott Laboratories, show that, until March 2002, there had been 2.13 reports per 100,000 patient treatment years among patients taking the drug.

The CPMP has reaffirmed that sibutramine has a positive risk/benefit profile as a therapy for the treatment of obesity. Its opinion, remains unchanged from the initial opinion issued in November 2000, and no changes have been requested in the cardiovascular wording of the European Summary of Product Characteristics (SmPC).

What does this mean for UK clinicians?

The CPMP decision, which is binding on all 15 European Community Member States, means that clinicians may continue to prescribe sibutramine for those patients who suffer from obesity and its consequences. The decision also lends further support to the positive evaluation of sibutramine by the National Institute for Clinical Excellence (NICE).[2]

The NHS is increasingly concerned about obesity. Between 1994 and 1998 in England the proportion of men with a BMI of > 30 kg/m^2 rose from 14% to 17% while the proportion of obese women rose from 17% to 21%.[3] Inevitably, obesity has a direct impact upon healthcare expenditure. Treating obesity costs the NHS £0.5 billion each year in patients care costs, but it costs society a further £2 billion each year in indirect costs such as sickness absence.[4]

Such figures have provided a considerable impetus for the NHS to tackle obesity, not least because it underpins a number of government health strategies such as *The NHS Plan, the Cancer Plan and the National Service Framework for Coronary Heart Disease*, all of which include action to address obesity, diet and nutrition and physical activity.

The need to tackle obesity

Obesity is a serious public health issue, since it is associated with an increased incidence of premature death and chronic diseases. Being overweight or obese substantially increases the risk of hypertension, type 2 diabetes mellitus, coronary heart disease, stroke, gall bladder disease, osteoarthritis, sleep apnoea and other respiratory problems, and certain cancers, particularly those of the endometrium, breast, prostate, and colon.[5,6,7] In the UK, it is estimated that obesity contributes to some 30,000 deaths each year and shortens life expectancy by an average of nine years.[4]

Numerous studies show that intentional weight loss of 5–10%, achieved by dietary and other lifestyle measures, significantly reduces the incidence of morbidity and mortality in obese patients.[8-10] Two recent intervention studies have shown that the risk of diabetes can be halved in middle-aged subjects who take regular exercise and achieve moderate weight loss of around 5%.[11,12]

Consequently, the benefits of moderate weight loss are accepted in national and international guidelines.[13-15] Given that weight loss is difficult to achieve and maintain by lifestyle measures alone, these guidelines also accept the adjunctive role of pharmacotherapy in helping patients to lose weight and maintain weight loss.

The evidence for sibutramine

A series of randomised controlled trials have shown that sibutramine 10 mg/day, in combination with diet and exercise, produces and maintains a dose-related weight loss of 5–10% in the majority of obese patients studied. This is accompanied by a range of important health benefits, including improvements in cholesterol and triglyceride levels.[17,18]

Weight lost during treatment with an anti-obesity drug is usually regained over time once treatment is withdrawn, although typically at a slower rate than the rate of loss while on therapy. The NICE review suggests that, on average, it takes about three additional years to regain the weight that has been lost over a year on sibutramine.[2] This should be considered against the fact that the normal pattern for obese people is one of weight gain at the rate of 1–2 kg per year.

The evidence for sibutramine in controlled hypertension

A number of double-blind, placebo-controlled trials have been derived to evaluate the effects of treating obesity in hypertensive patients controlled with drug therapy. They are summarised below.

In the treatment of obesity in patients with arterial hypertension[19]

One hundred and nine patients attending an out-patient hypertension follow-up clinic with a BMI between 30 kg/m^2 and 50 kg/m^2 were randomised to receive either 10 mg sibutramine or placebo for six months whilst observing a restrictive calorific diet. The sibutramine group showed 6.8 kg weight loss

vs. 2.4 kg for placebo (p<0.001) and also revealed significant decrease in left ventricular mass (LVM) and the LVM index (p=0.002) which was not seen in the placebo group. No difference on impact on BP was seen in either group although an increase in heart rate (78 bpm to 82 bpm) was seen in the sibutramine group (p=0.02).

In the treatment of obese patients with hypertension controlled with beta blockers[20]

Sixty-one obese patients with controlled hypertension entered this 12-week, multi-centre, double-blind, placebo-controlled, randomised study. Patients were all on concurrent beta blocker therapy (with or without thiazides). All patients had a BMI in the range of 27–40 kg/m^2. All received dietary advice with exercise and behavioural recommendations, with patients randomised into either placebo or incremental sibutramine dosing (5–20 mg daily). The sibutramine group exhibited significantly more weight loss after 12 weeks (4.2 kg *vs.* 0.3 kg in placebo, p<0.001). Mean supine and standing BPs were not statistically significant between placebo or sibutramine groups at any point during the study. A small but significant increase in pulse rate was observed in the sibutramine group (mean increase of 5.6 bpm from baseline, p<0.001).

Efficacy and safety in obese hypertensives controlled with angiotensin-converting enzyme inhibitors (ACE)[21]

Two-hundred and twenty obese hypertensives controlled with ACE inhibitors (with or without thiazides) were enrolled into a 52-week, multi-centre, double-blind, placebo-controlled, randomised study. All adults had a BMI, in the range of 27–40 kg/m^2 and were randomised in a 2:1 ratio to either sibutramine or placebo for the 52-week study. All were given a standardised programme of dietary advice with exercise and behavioural recommendations. After 52 weeks sibutramine patients had lost significantly more weight than those on placebo (4.5 kg *vs.* 0.4 kg, p<0.05). Small increases in both BP (mean 3 mmHg, p<0.004 for diastolic and p<0.0497 for systolic) and pulse rate (increase of 5.7 bpm from baseline) were seen in the sibutramine group. The authors concluded that in obese patients with well controlled BP sibutramine achieves effective weight loss without compromising good control.

Using sibutramine in practice – managing the cardiovascular side effects

Sibutramine acts centrally to increase satiety, reduce hunger and to limit post-dieting decline in energy expenditure. Since it acts by inhibiting the re-uptake of serotonin and noradrenaline and by stimulating the sympathetic nervous system, cardiovascular effects are to be expected.

In patients with uncomplicated obesity, treatment may result in dose-dependent increases in heart rate and BP, particularly during the initial phase of treatment. However, trials (1–2 years duration) revealed virtually no change in systolic BP in patients treated with sibutramine 10 mg and the average increase in BP in patients treated with sibutramine 15 mg is around 1 mmHg.[18] Furthermore, BP actually falls in the majority of patients who achieve a weight loss of more than 5%.

Sibutramine is not contraindicated in patients with well-controlled hypertension, in whom treatment is safe and effective.[21-23] When used at 10 mg, there is a decrease in systolic BP.[22]

There are three 'keys' to the safe and effective use of sibutramine:

- Observe the recommended exclusion criteria – currently accepted exclusion criteria include recent myocardial infarction, coronary artery disease, congestive heart failure, tachycardia, peripheral arterial occlusive disease, arrhythmias and cerebrovascular disease.
- Monitor BP and heart rate – every two weeks in the first three months, once-monthly between months four and six, and thereafter at intervals of three months.
- Adhere to the withdrawal criteria – withdraw sibutramine if i) resting heart rate increases by 10 bpm; ii) systolic/diastolic BP increases by 10 mmHg on two consecutive visits; iii) if BP is > 145/90 mmHg on two consecutive visits in patients with previously well-controlled hypertension; or iv) if there is progressive dyspnoea, chest pain or ankle oedema.

Recognising the benefits not only of weight loss, but weight maintenance is key to prescribing any pharmacological agent for weight loss. While prescribers should follow the Summary of Product Characteristics with all drugs, it is particularly important with any new agent, such as sibutramine. Doing so should enable identification of patients for whom sibutramine is not suitable while permitting the majority of patients to gain clinical benefit from treatment of their obesity.

Key messages

- Sibutramine can achieve a dose-related weight loss of 5–10% in obese patients in combination with diet and exercise
- Sibutramine has been approved as an anti-obesity agent by the National Institute for Clinical Excellence. It is supported by the European Commission's Committee for Proprietary Medicinal Products
- Sibutramine can be associated with dose-dependent increases in heart rate and blood pressure, and should not be used in certain groups of patients, such as those with coronary heart disease or cardiac arrhythmias. It can be used safely in patients with controlled hypertension

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