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EDITORIAL

Sibutramine: Balancing weight loss benefit and possible cardiovascular risk

Sibutramine is a tertiary amine, initially developed as antidepressant, which inhibits serotonin, norepinephrine and, to a lesser extent, dopamine re-uptake, without presenting monoamine release activity [1,2]. Sibutramine is rapidly converted into two metabolites, which are 100-fold more powerful than the parent compound [3]. Their half-life is about 14–16 h with a peak concentration after 3–4 h and a plateau from 3 to 7 h [4].

Sibutramine induces weight loss by reducing food intake, due to hypophagic effect mediated by central β_1, α_1, and 5-$HT_{2A/2B/2C}$ receptors [5]. The increase in sympathetic activity due to sibutramine administration causes an increase in β_3-mediated energy expenditure [6,7], though this effect needs confirmation in humans [8]. Its effect is dose dependent [9]. Trials conducted with 10, 15 or 20 mg of oral sibutramine demonstrated significant progressive improvement in weight reduction at higher doses of the drug, when associated with low-calories diet. Nevertheless, the highest dose used in clinical trials, i.e. 20 mg, has not been approved for clinical use. Therapy begins with a dose of 10 mg/OD that will be increased to 15 mg after two weeks. The recommended dose is 15 mg/OD [10].

Weight loss

Compared with placebo, sibutramine increases significantly the number of patients who reach a weight loss $>$ 5% in almost all trials [8,10–20]. Patients achieve the most significant weight loss during the first three months of therapy, but sibutramine reduces the probability of regaining weight in long-term therapy in both continuous and intermittent administration [14].

In a subgroup of the STORM study [21], an abdominal CT scan performed after six months of therapy, demonstrated that sibutramine caused an 18% reduction total abdominal fat by reducing both subcutaneous fat (17%) and total visceral fat (22%) with a consequent significant increase in subcutaneous-to-visceral fat ratio ($p < 0.04$). Kamel et al. [22] estimated changes in intra-abdominal adipose tissue by magnetic resonance imaging during sibutramine 10 mg/day combined with a low-calorie diet: after six months of treatment, the decrease in intra-abdominal fat was greater than the decrease in subcutaneous adipose tissue ($p < 0.01$), both significantly correlated with reduction of weight and BMI.

Similarly to other appetite-suppressant drugs, however, therapy discontinuation causes weight regain, despite this rebound might be less intense in the short-term, due to possible effects of the drug on energy expenditure [1,6,7] or because of a persistent anorectic effect, possibly attributable to a lack of decrease in plasma leptin concentration [23]. This possibility, however, was not confirmed in other studies. During sibutramine therapy, Valsamakis et al. [24] demonstrated a decrease in serum leptin as well as in C-reactive protein (CRP) and resistin while adiponectin levels increased. Extended reviews on beneficial metabolic effects of sibutramine are available [25].

As a medication reducing abdominal fat, sibutramine might be indicated in abdominal obesity and, therefore, the metabolic syndrome. However, there is some concern about the complexity of sibutramine effects, especially on the cardiovascular system, which has blunted wider use of this drug.

Sympathomimetic-mediated cardiovascular side effects

Similarly to, but more potently than other appetite-suppressant drugs, sibutramine inhibits K^+ voltage-gate channels of myocytes [26]. This effect on K^+ channels appears when the channels are already open, similarly to what has been described with fluoxetine. Thus, as with fluoxetine, but in contrast with other inhibitors of serotonin reuptake used as appetite-suppressant drugs, sibutramine does not increase pulmonary artery pressure [27]. However, in contrast with fluoxetine, sibutramine tends to increase systemic pressure and heart rate, both effects attributable to other peripheral actions on sympathetic system.

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In patients treated with sibutramine, titrated up to 20 mg/OD in those failing to lose weight, the two-year STORM trial [12] observed a 4.1-bpm increase in heart rate, 1 mmHg increase in systolic blood pressure and 3 mmHg in diastolic blood pressure, despite the reduction of body weight, expected to decrease blood pressure and heart rate. In contrast with this finding, in the same study, participants on placebo exhibited decreased blood pressure and heart rate that was in fact associated with diet-related weight loss. Apparently contrasting results were obtained in another trial comparing continuous and intermittent therapy with sibutramine 15 mg [14]. In this study, both administration regimens did not yield significant change in blood pressure as compared to a control group, possibly due to the shorter follow-up (44 weeks versus two years in the STORM) but also to the absence of patients treated with higher dose of the drug. In our six-month study [17], using 10 mg/OD, blood pressure decreased with decreasing body weight associated with the sibutramine group, although heart rate increased.

In another study [28] 224 adults were assigned to four intervention groups: lifestyle modification, sibutramine, combination of both lifestyle modification and sibutramine, and sibutramine with brief lifestyle modification counseling. After one year, the combination of lifestyle modification and sibutramine gave the best results in terms of weight loss, with a statistically significant decrease in triglycerides, blood glucose, insulin, LDL cholesterol and a statistically significant increase in HDL-cholesterol. The combination also reduced systolic blood pressure by 4.5 mmHg, which was, however, substantially less than obtained with the sole lifestyle modifications (-8.5 mmHg), despite the latter intervention was less effective in reducing weight. Diastolic blood pressure was reduced only with lifestyle modification (-2.2 mmHg), whereas it was virtually unchanged in the group with combined intervention ($+0.5$ mmHg). Sibutramine also tended to be constantly associated with increased heart rate at the end of the trial. Obese adolescents have also been studied [29]. Sibutramine therapy was associated with greater weight reduction and improvement in plasma glucose, cholesterol, triglycerides, but also with significant increase in heart rate with unchanged blood pressure. Also in this case, however, there was a substantial discrepancy between the level of body weight reduction obtained with sibutramine and the effect on blood pressure and heart rate, as compared to the group on lifestyle intervention.

The effect of sibutramine-induced weight loss has been evaluated also on obstructive sleep apnoea (OSA). The significant weight loss at six months (8.3 ± 4.7 kg, $p < 0.0001$) led to significant amelioration of symptoms and improvement of objective markers of OSA (Respiratory Disturbance Index (RDI)). There was no change in blood pressure, but resting heart rate increased. The authors highlighted that, though most of the improvement was likely due to weight loss, an independent effect of the drug could not be excluded, possibly due to direct neuropharmacological action [30].

Overall taken, these findings suggest that sibutramine has a sympathomimetic effect on both blood pressure and heart rate, and that this effect can be offset, though not completely eliminated, if body weight reduction is significant [31,32].

Is it possible to antagonize cardiovascular side-effect?

To minimize undesired cardiovascular effects, a program of aerobic physical exercise [33] or combination of sibutramine with other medications might be suggested. A combination of sibutramine with ACE inhibitors, has been proposed especially in diabetic patients [11]. In a small group of healthy volunteers, Birkenfeld et al. [34] showed that the sibutramine-induced increase in blood pressure and heart rate can be abolished by metoprolol (25 mg). In this study, despite the increase in blood pressure and heart rate, sibutramine also caused decrease in plasma level of norepinephrine and less response to hand grip and cold pressor test. This finding has been interpreted as a consequence of a possible central clonidine-like activity [34], at least partially offsetting the peripheral effect. This clonidine-like activity might be maximal in obese patients with arterial hypertension, ultimately leading to blood pressure reduction [34]. Similar findings were obtained by Jordan et al. [35], who analyzed data obtained in two clinical trials. This hypothesis has not been confirmed in other studies in obese subjects with arterial hypertension in whom sibutramine administration increased both blood pressure and heart rate, despite its centrally mediated effect [36].

Recently sibutramine therapy has also been associated with favourable effect on endothelial function [37]. There is no information on the potential impact of associated β-blocker therapy on the postulated sibutramine-induced β_3-mediated increase of energy expenditure. Recently a clinical trial, comparing different antihypertensive regimens during sibutramine administration showed that the combination of metoprolol plus hydrochlorothiazide reduces the beneficial effects of sibutramine on weight loss and metabolic parameters if compared with treatment including ACE inhibitors and calcium-channel-blockers [38].

Potential cardiovascular benefits

Paralleling reduction of body weight, and opposing to the reported side effects, sibutramine therapy is also associated with reduction of left ventricular (LV) mass (M), a potent marker of cardiovascular outcome [39,40]. Zannad et al. [16] studied 185 obese patients divided into three groups (placebo, 10, and 20 mg sibutramine). Mean changes of LVM index (LVM/height) were similar in placebo (-3.0 ± 11.9 g/m, $n = 56$), sibutramine 10 mg (-4.4 ± 10.7 g/m, $n = 61$), and sibutramine 20 mg (-4.3 ± 10.9 g/m, $n = 56$), but difference from baseline values was significant only in the groups treated with sibutramine. In another randomized placebo-controlled study including patients with arterial hypertension [17], we showed that the sibutramine treated group had a significantly greater decrease in LVM than placebo, due to greater weight loss, and greater LV mass at baseline, because of a higher proportion of hypertensive subjects.

The reduction of LVM in our study was substantially sustained by the greater reduction of LV end-diastolic diameter (a crude indicator of preload), probably as a consequence of weight loss related diuresis, a characteristic also evident in Zannad's study with the 20 mg dose

[16]. In our study, this volume effect was also combined with the weight-loss-dependent slight reduction of blood pressure, probably facilitated by the baseline blood pressure that was higher than in Zannad's study. The coincidence with a pronounced weight loss (10%) should also be considered important, consistent with the evidence that LV mass substantially decreases when weight loss is significant [40—42].

These two studies did not show increase in blood pressure except for Zannad's sibutramine 20 mg group, an increase, however, which did not reach statistical significance.

There is also evidence of favourable metabolic changes associated with sibutramine-induced weight loss, including decrease in VLDL-cholesterol, triglycerides and uric acid, increase in HDL-cholesterol and improvement in glycemic control [13,18,19]. In particular, Fujioka et al. [18] showed that in type 2 diabetic patients, sibutramine reduced HbA1c and fasting plasma glucose, in relation to the decrease in body weight. Correlation between diabetic control and changes in body weight was not evident in the placebo group.

Balancing evidence

Obesity should be considered as a major cardiovascular risk factor [43] tracking hypertension, diabetes, dyslipidemia and, eventually, the metabolic syndrome. It is associated with increased LVM, an extraordinarily potent marker of preclinical cardiovascular disease, predicting 2.5-fold higher risk of cardiovascular events [39]. Weight reduction is the first and most important objective to reduce obesity-associated comorbidities and, therefore, cardiovascular risk.

Unfortunately sibutramine has significant unfavourable effects on cardiovascular system that should be considered as potentially offsetting, at least in part, a long-term benefit. At this time, there is no evidence of improvement in event-free survival, especially when an efficacious weight loss is not achieved. In weighting advantages and disadvantages of therapy with sibutramine, considerations should be, therefore, developed on both long-term benefits in high-risk patients and the possibility to combine medications able to balance sibutramine-induced increase in blood pressure and heart rate, two very adverse reactions to the drug administration. Although there are trials that did not show increase in blood pressure and heart rate, attention should be paid to the fact that the successful weight loss achieved in these studies could be expected to track more substantial blood pressure reduction and decrease in heart rate than obtained with sibutramine, as suggested in other trials without pharmacologic intervention [44] and studies on the reduction of sympathetic drive tracked by weight loss [45]. Combination of sibutramine with β-blockers might be promising to antagonize heart rate increase, but the possible block of β_3-receptors might decrease the effect of sibutramine.

At present, sibutramine is an effective appetite-suppressant drug, reducing body weight, and potentially affecting positively some, but not all, cardiovascular risk factors [46]; however, it cannot be prescribed in patients with high cardiovascular risk, according to licensing recommendations. The SCOUT study [47] was designed to verify safety of sibutramine use in high cardiovascular risk patients, in consideration of the fact that the positive effect of the drug on metabolic parameters could counterbalance and overwhelm the increase in sympathetic activity that might be pharmacologically controlled.

Preliminary data from the 6-week lead-in period of the SCOUT study [48] confirm previous reports: decrease in systolic and diastolic blood pressure parallels the reduction in body weight, but pulse rate is increased (all $p < 0.001$). Death occurred in a rate at least comparable to (and possibly less than) that reported in other studies with similar populations (HOPE, ASCOTT-LLA).

In the balance between visible benefits and potential risks of sibutramine treatment, we should consider that cardiovascular risk might discourage the use of the medication, but also that reduction of body weight in severe obesity might be mandatory especially in those patients with high-risk profile. The results of the SCOUT study will be extremely relevant to resolve a conundrum that in the meantime remains to the doctors' wisdom.

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