Rimonabant: A new class of drug to fight obesity

Obesity and tobacco abuse, widely recognised as serious health hazards, are increasing in prevalence. Obesity is associated with numerous metabolic complications such as dyslipidemia, type 2 diabetes and cardiovascular diseases. Smoking is a high risk factor for hypertension, lung carcinoma and various other health related problems. The agents that have been used for the treatment of obesity include dexfenfluramine, phentermine, sibutramine and orlistat. Currently, the options for smoking cessation are nicotine patches, gum, lozenges and bupropion. As many of these drugs have serious adverse effects or are unsuitable for maintenance therapy, the search for a novel drug continues.

Rimonabant appears to be a promising drug in an entirely new class called selective cannabinoid (CB1) receptor antagonists. Recent studies have demonstrated the beneficial effects of rimonabant in tackling obesity, smoking cessation and metabolic syndrome. The drug may be approved for treatment of obesity and smoking cessation. Ongoing studies can provide information on its other clinical uses.

Chemistry

Rimonabant (SR141716) is a neurokinin-3 antagonist and selective cannabinoid (CB1) receptor antagonist currently being researched and developed under the proprietary name, Acomplia, by Sanofi-Aventis. The chemical name is N-piperidino-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methylpyrazole-3-carboxamide.

Mechanism of action

Rimonabant is the first in a new class of agents that act by selectively blocking the cannabinoid-1 receptors with resultant central and metabolic peripheral effects, thereby decreasing food intake. Evidence currently exists for two types of cannabinoid receptors: CB1 and CB2. CB1 receptors are present both in the CNS as well as in certain peripheral tissues. The areas in which CB1 receptors are most dense are thought to deal with cognition, motor function and movement. Rimonabant is reported to possess a 1000-fold higher affinity for the CB1 receptor than CB2 receptor. It shows high affinity for the centrally located cannabinoid receptor, while displaying low affinity for the peripherally located receptor. Additionally, it has little or no affinity for non-cannabinoid receptors.

Pharmacokinetic parameters

Rimonabant has demonstrated a long duration of action (8 hours) and good oral bioavailability. Currently, limited information has been published regarding rimonabant’s pharmacokinetic parameters.

Functional in vitro and in vivo studies showed that rimonabant is able to antagonise the pharmacologic effects induced by cannabinoid receptor agonists. It powerfully reduces food intake and increases energy expenditure. It modulates the rewarding properties of food by inhibiting the action of endogenous cannabinoids at specific mesolimbic areas. It alters the variety of signals of peripheral origin (leptin, ghrelin and adiponectin) which modulate the neurochemical activation of hypothalamic neurons and the state of relative energy balance. Rimonabant also inhibits the enzymes involved in lipogenesis. Many rodent model studies have demonstrated a memory enhancing effect due to rimonabant use. Certainly, more information will become available as the drug completes phase III trials.

Preclinical trials

A number of preclinical trials have been conducted on the effects of rimonabant in rodent models. The trials demonstrated that rimonabant treatment was associated with a reduction in intake of highly palatable as well as normal foods in rats. Wiley et al. demonstrated that CB1 antagonist rimonabant dependent decreased food consumption at doses which did not affect motor activity in mice. These trials suggested that rimonabant may affect the actions of endogenous cannabinoids in regulating appetite, or it may directly affect feeding behaviour. In another study, rodents were put on a high fat diet to develop obesity, increase energy intake and insulin resistance. During a five-week treatment period, rimonabant resulted in 48% reduction of food and 20% reduction in body weight. In addition, it helped in correcting insulin resistance.

Clinical trials

Some phase I/II clinical trials have been completed with rimonabant. However, limited information is available regarding these trials. A randomised, double blind, placebo-controlled crossover study assessed the effect of rimonabant on hunger, satiety, food consumption and body weight in obese humans and showed a reduction in their food intake and body weight. The results of phase III studies called RIO (Rimonabant in obesity)Europe, RIO-North America and RIO-Lipids, comparing rimonabant 5, 20 mg and placebo, have indicated significantly more weight loss with rimonabant. (The studies were prospective, randomised, international, multicentre, double blind, placebo-controlled trials.) The RIO-Lipids and RIO-Europe studies showed that the average loss of weight at 12 months was 6.9 and 8.6 kg, respectively, with rimonabant 20 mg/day; 3.1 and 4.8 kg, respectively, with rimonabant 5 mg/day. The RIO-North America trial was a two-year study that enrolled 3040 obese people throughout USA and Canada. The investigations found that those who received the highest...
dose of rimonabant (20 mg) lost >5% of their body weight, while one-third of them lost >10% of their body weight. The results also showed an increase in HDL-C levels with a decrease in atherogenic LDL-C levels. The incidence of metabolic syndrome decreased by nearly one-third and insulin sensitivity was reported as greatly improved.

Rimonabant’s role in smoking cessation will be evaluated in STRATUS-US, STRATUS-EU, STRATUS-WW (prospective, randomised, multicentre, double blind, placebo-controlled) trials. Preliminary results of these trials showed that treatment with rimonabant greatly increases the likelihood of quitting smoking.

Adverse effects

The results of early human trials with rimonabant treatment showed an excellent tolerance among patients, except for some mild gastrointestinal adverse effects at the highest dose administered. Safety data from the preliminary results of the RIO-Lipids, RIO-Europe, RIO-North America and STRATUS-US trials revealed that rimonabant is well tolerated among patients. The most frequently reported adverse effects are nausea, dizziness and upper respiratory infections. Diarrhoea was seen most commonly in the RIO-Europe trial (2.3%, 5.8% and 7% for placebo, rimonabant 5 mg/day and 20 mg/day, respectively).

Advantages

- Rimonabant is reported to increase HDL-C and decrease atherogenic LDL-C levels. The unique property of this drug may, in turn, improve cardiovascular risk factors and metabolic syndrome.
- In addition to weight loss, rimonabant is reported to produce improvement in HbA1c levels and may be helpful in diabetes.
- It also prevents weight gain in persons who are quitting smoking.

Conclusion

Rimonabant, the selective blocker of CB1 receptors, may normalise the activity of the endocannabinoid system, resulting in weight loss, reduced waist circumference, improvement in lipid and glucose metabolism in obese people and may prevent weight gain associated with smoking cessation. The positive effects may, in turn, improve cardiovascular and metabolic risk factors. Future research and the results of ongoing clinical trials of this exciting drug are required to establish its long-term therapeutic implications.

J. Singh, S. Budhiraja
Department of Pharmacology,
Pt. B. D. Sharma PGIMS, Rohtak - 124001, Haryana, India
E-mail: salil_budhi@yahoo.com

References


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