Lorcaserin: A novel antiobesity drug

Dick B. S. Brashier, A. K. Sharma, Navdeep Dahiya, S. K. Singh, Anjan Khadka

Department of Pharmacology, Armed Forces Medical College, Pune, Maharashtra, India

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ABSTRACT

Obesity is a major co-morbidity with hypertension and diabetes mellitus. There are few drugs for treatment of obesity like orlistat and recentlty approved drug lorcaserin. Lorcaserin has serotonergic properties and acts as an anorectic. It may cause serious side effects, including serotonin syndrome, particularly when taken with certain medicines that increase serotonin levels or activate serotonin receptors. Although, mainstay and first line of approach of treatment will always remain in having low calorie diet and increase in physical activity. Lorcaserin has come as a new hope to achieve success in treating obese patients but still a long road with further extensive research to be undertaken in the treatment of obesity.

Key words: Lorcaserin, obesity, serotonin

INTRODUCTION

Obesity has become a pandemic affecting all strata of society. Man has struggled to overcome this disease and it has been a long battle without much success. Study had shown obesity affecting both developed and developing nations, although prevalence in developed nations were higher (35.2%) as compared to developing nations (19.6%), with total 33% of world population suffering from it.[1] If this trend goes on, by the year 2030 there will be 3.3 billion people suffering from it.[1] Obesity is a major cause of concern for public health specially when co-existing with other comorbid age-related conditions like hypertension and diabetes mellitus.[1] Obesity itself is a single predisposing factor for various illnesses, and affects individuals physically and emotionally in the society. Mainstay for the treatment lies in the intake of low calorie diet and increase in physical activity, which is not possible for everyone, due to lack of motivation. Very few drugs are available for treatment of obesity, last drug approved by Food and Drug Administration (FDA) in 1999 was orlistat, after 13 years a new prescription drug lorcaserin was approved in June 2012 by the FDA.[2] Lorcaserin was initially rejected in October 2010 concerning cancer signals detected in animal studies. Finally, with further research and more data it was approved.[2] Thus, bringing new hope for patients who are obese and specially having other comorbid conditions like hypertension, diabetes mellitus, and arthritis which restrict their option for increased physical activity.

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MECHANISM OF ACTION

It has been found that serotonin plays important role in satiety and hence controls hunger; hence serotonin receptors have become new targets for research in anti-obesity drugs.[3] Intake of food is controlled by satiety center, located in ventromedial nucleus of hypothalamus and hunger center present in lateral hypothalamus.[3] Various inputs from higher centers and

Address for correspondence:
Dick B. S. Brashier, Department of Pharmacology, Armed Forces Medical College, Pune - 411 040, Maharashtra, India.
E-mail: drdickbrashier@gmail.com

gastrointestinal tracts converge in arcuate nucleus, where two types of neurons controlling food intake is present. Firstly, food intake stimulatory group producing agouti-related protein and neuropeptide Y; and secondly, food intake inhibitory group containing cocaine and amphetamine regulated transcript (CART) and pro-opiomelanocortin (POMC) neurons.[3] POMC contains 5-HT 2C receptors, which when activated releases alpha-melanocyte-stimulating hormone (alfa-MSH).[3] Both inhibitory and stimulatory neurons further projects paraventricular nucleus in the hypothalamus.[3] Paraventricular nucleus contains melanocyte 4 receptors (MC4R) that inhibits appetite.[4] In therapeutic doses lorcaserin acts as a selective 5-HT 2C agonist on POMC neurons, which in turn causes release of alfa MSH. Further alfa MSH acts on MC4R in paraventricular nucleus in the hypothalamus, leading to decrease in appetite. In supratherapeutic doses, lorcaserin also acts on 5-HT 2B and 5-HT 2A receptors.[4]

PHARMACOKINETICS

Lorcaserin is rapidly absorbed in gastrointestinal tract and is delayed with fatty meals. Peak plasma concentration is achieved in 1.5-2 h,[5] with half-life of 11h.[5] It is evenly distributed in cerebrospinal fluid and central nervous system.[6] Lorcaserin is 70% plasma protein bound and metabolized in liver, with major metabolite being lorcaserin sulfamate, and its excretion is mainly through urine (92%) and minor excretion through faces.[7]

ABUSE

A small study on 35 recreational poly-drug users was carried out, with single oral dose of lorcaserin 20, 40, and 60 mg; zolpidem 15 and 30 mg; ketamine 100 mg; and placebo was given and subjective and objective parameters were seen after 24 h.[8] Incidence of euphoria with lorcaserin for 20, 40 and 60 mg was 19%, zolpidem had 13-16%, both were similar, whereas with ketamine it was 50%.[8]

DRUG INTERACTIONS

Drugs that interfere with serotonin neurotransmission should be used with caution like, selective serotonin reuptake inhibitors, serotonin norepinephine reuptake inhibitor, and monoamine oxidase inhibitors; which can lead to serotonin syndrome.[9] Serotonin syndrome is caused by toxicity of serotonin in the body which is manifested by sudden onset of various symptoms like increase in blood pressure, shivering, sweating, etc.[9] Drugs like dextromethorphan that are metabolized by cytochrome P450 2D6, which are inhibited by lorcaserin and tends to increase the levels in blood if given together.[6]

CLINICAL TRIALS

Lorcaserin approval was based on data by three main studies; behavioral modification and lorcaserin for overweight and obesity management (BLOOM) study, behavioral modification and lorcarserin for overweight and obesity management in patients of diabetes mellitus type 2 (BLOOM DM) study; and one year nonrandomized trial of lorcaserin for weight loss in obese and overweight adults the BLOSSOM study.

BLOOM STUDY

It was a multicentric, double-blinded study having two primary end points. Firstly, assess weight loss of lorcaserin at the end of 1st year and secondly assess ability of the drug to maintain weight loss at the end of 2nd year.[10] A total of 3,182 obese males or females aged between 18 and 65 years were enrolled, who were able to perform exercise, and had body mass index (BMI) 30-45 kg/m^2 (obese) with or without comorbid conditions or 27-29.9 kg/m^2 (overweight) with at least one treated or untreated comorbid condition (hypertension, cardiovascular disease).[10] Patients were randomly assigned into three groups, one having lorcaserin 10 mg once a day, second twice a day, and third a placebo group.[10] Results showed at 1 year 47.5% in lorcarserin group and 20.3% in placebo group lost 5% or more of body weight.[10] At the end of 2nd year weight loss was maintained by 67.9% patients who continued to receive lorcarserin, whereas 50.3% could maintain weight loss who received placebo.[10]

BLOOM DM STUDY

It was a randomized, placebo-controlled clinical trial enrolling 604 patients with type II diabetes mellitus treated with metformin, sulfonylureas, or both, in age group 18-65 years having glycated hemoglobin (HbA1c) of 7-10% and BMI between 27 and 45%.[11] Three groups were randomly assigned lorcaserin 10 mg once a day, twice a day, and placebo. Primary end points were efficacy and safety of lorcaserin in diabetic patients in weight loss, whereas secondary end point was evaluation of glycemic control. Results showed loss of body weight more than 5% in 37.5, 44.7, and 16.1% patients in lorcaserin 10 mg once a day, twice a day, and placebo, respectively.[11] Secondary end point showed decrease in glycated hemoglobin of 0.9 ± 0.06, 10 ± 0.09, and 0.4 ± 0.06% in lorcaserin 10 mg twice a day, once a day, and placebo, respectively.[11]

BLOSSOM STUDY

Again in 1 year study enrolling 4008 patients between 18

and 65 years with BMI between 30 to 45 kg/m^2 (obese) or 27-29.9 kg/m^2 (overweight) with related comorbid conditions were randomly assigned 2:1:2 as lorcaserin 10 mg twice a day, once a day, and placebo.[12] Primary end points were proportion of patients showing decrease in body weight of 5% or more, mean change in body weight and proportion of patients showing decrease in body weight of 10% and more. Results showed 5% or more decrease in body weight, that is, 47.2, 40.2, and 25% in lorcaserin 10 mg twice a day, once a day, and placebo, respectively.[12] Mean change in body weight was 5.8, 4.7, and 2.8% in lorcaserin 10 mg twice a day, once a day, and placebo, respectively.[12] Whereas, patients achieving 10% and more decrease in body weight was 22.6, 17.4, and 9.7% in lorcaserin 10 mg twice a day, once a day, and placebo, respectively.[12]

ADVERSE EFFECTS, CONTRAINDICATIONS, AND SPECIAL POPULATION

Most common adverse reactions seen were nausea, vomiting, constipation, diarrhea, fatigue, upper respiratory tract infection, urinary tract infections, back pain, headache, dizziness, and rash.[10-12] As lorcaserin affects serotonin receptors, serotonin syndrome can be precipitated with drugs or herbal products that affects levels of serotonin neurotransmitters like selective serotonin reuptake inhibitors (SSRIs).[13] Attention and memory deficit were seen in 1.9% patients receiving lorcarserin as compared to 0.5% in placebo.[12] Patients should be monitored for developing signs and symptoms of depression or worsening of already preexisting depression, especially for developing suicidal tendencies.[14] Patients having regurgitant valvulopathy in mitral or aortic valves have increased expression of 5-HT 2B receptors,[14] as seen in supratherapeutic doses lorcaserin can activate 5-HT 2B which can lead to valvulopathies. Patients should also be monitored for hypoglycemia, specially who are diabetics as weight loss increases tendencies of precipitating hypoglycemia.[11] Priapism has being reported in preclinical studies, but not seen in clinical trials.[15] Decrease in white blood cells and red blood cells were seen in 0.4 and 1.3%, respectively as compared to placebo 0.2 and 1.2%.[10] Lorcaserin has also shown to increase prolactin levels moderately in some patients.[10] Lorcaserin is contraindicated in pregnancy and falls in category X, as weight loss cannot be monitored in pregnancy.[16] Its not known if its excreted in human milk.[16] It is not studied in patients below 18 years so pediatric data is not present.[16] No dose adjustment is required with mild to moderate renal and hepatic diseases.[16]

PRESENT STATUS

After first rejection in October 2010, FDA finally approved lorcaserin on 27th June 2012.[17] It is available as 10 mg film-coated tablets, taken twice daily, with or without food for 12 weeks. If weight is not decreased by 5% or more, treatment should be discontinued.[17]

CONCLUSION

A new drug for treating obesity has come as a new hope to achieve success in treating obese patients. Although, mainstay and first line of approach of treatment will always remain in having low calorie diet and increase in physical activity, due to its natural physiological way to lose weight. As obesity is associated with other comorbid conditions like hypertension, diabetes mellitus, arthritis, and depression clubbed with day-to-day stress of modern life affecting both physical and emotional well-being, it becomes very difficult to attain a level of motivation to follow natural way to lose weight. Therefore, a new treatment is a welcome for medical fraternity, especially after more than a decade, but it is still a long road with further extensive research to be undertaken for developing a definite treatment for obesity. Lorcaserin seems to be a new challenging molecule, but time will give the answer, as to where this new molecule stands in treatment of obesity.

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