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EFFECT OF BROMOCRIPTINE IN DIABETES MELLITUS: A REVIEW

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AUTHORS' CONTRIBUTIONS

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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Review Article

ABSTRACT

Bromocriptine, an antinociceptive D2 receptor agonist, is thought to reorganize an excessively heightened hypothalamic drive for higher fatty acids, plasma glucose, and tri-glycerides in insulin resistant individuals by acting on circadian neuronal activity in the hypothalamus. In May 2009, the bromocriptine mesylate is officially authorized for the cure of people with diabetes. Due to its novel mechanism of action, lower rates of cardiovascular events and good side effect profile it makes an appealing choice for diabetes cure.

Keywords: Bromocriptine; drug interactions; agonist and antagonist.

1. INTRODUCTION

Type 2 diabetes mellitus (T2DM), is a prolonged metabolic condition characterised by decreased cell function and a variety of other endocrine/metabolic disorders. T2DM is characterized by decrease insulin mediated glucose disposal, better blood glucose concentration, which results from raised endogenous glucose synthesis. Due to multifactorial pathogenicity, achieving normal glucose level in body is tough to accomplish and prerequisites combined therapy of antidiabetic medications comprising multiple mechanism of action in order to create a biological effects [1,2]. The patients are also prone for dyslipidemia, obesity, hypertension and metabolic syndrome [3,4]. Furthermore, even if dysglycemia, dyslipidemia, and hypertension have been corrected, T2DM individuals are still at high risk for atherosclerotic cardiovascular problems [5]. As a result, antidiabetic drugs that enhance glycemia while also lowering cardiovascular risk are attractive. Bromocriptine is a sympatholytic dopamine D2 receptor agonist used to treat T2DM. It's a centrally active antidiabetic with a unique method of action that lowers blood glucose, triglycerides, and cholesterol. Fatty acid levels, as well as the possibility of

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cardiovascular events. Bromocriptine's use has been established as a result of its ability to modulate important biochemical pathways [6,7]. Bromocriptine, a potential therapeutic agent to be used for obese patients with T2DM who do not tolerate other diabetes drugs or for patients who require only a small reduction in glycated haemoglobin (HbA1c) to achieve their target. Quick-release medication is given. Bromocriptine, when taken within two hours of waking up, is thought to increase low dopamine levels in the hypothalamus [8].

2. MECHANISM OF ACTION

The Food and Drug Administration (FDA) has authorised bromocriptine, a sympatholytic dopamine D2 agonist, for the cure of T2DM. This mainly acting antidiabetic drug decreases blood glucose, lipid, and fatty acid levels by a unique method. Bromocriptine is distinctive and it mediates its action on metabolism of glucose and lipids. Instead its effects are mediated through dopaminergic tone and sympathetic tone restoration within Central Neural System [9].

Such changes are controlled by mono aminergic concentration levels in the ventromedial hypothalamus (VMH) [10-12]. Comprehensive experimental evidence suggests that in the formation of these seasonal changes circadian neuroendocrine cycles play a crucial role [13-16]. In animals undergoing seasonal variations in metabolism, according to several research published in the VMH. In comparing, dopamine levels have dropped during the insulin-resistant state and return to its original once the animal is returned to the insulin-sensitive state [17-23]. The emergence of the insulin-resistant condition in animals throughout these stages of seasonal shift closely resembles the alterations seen in people with T2DM and insulin-resistance syndrome [24,25]. Evidence suggests that reduced dopaminergic hypothalamic tone is vital for development of insulin resistance. Because of the ample calorie intake throughout the year, the natural circadian cycle leading to a slimmer body in the summer and a larger body in the winter is disrupted in humans, resulting in the lack of a lean phase [26]. Bromocriptine has been demonstrated in several trials to lipoprotein levels, body fat reserves, and limit vascular smooth muscle growth [27,28]. It's thought that those with T2DM experience a morning decrease in dopaminergic tone [29]. Bromocriptine's suggested mechanism of action is summarised in Fig. 1.

2.1 Pharmacokinetics

Bromocriptine mesylate is fine crystalline white powder or slightly coloured, with a molecular weight of 750.72 grams/mol and molecular formula of C33H44BrN5O8S.

2.2 Absorption and Bioavailability

(Approximately 65–95 percent of the medicine is absorbed when taken orally.) The maximal plasma concentration is attained in 60 minutes when taken on an empty stomach. Slow absorption of food, and peak plasma levels are reached after 120 minutes in the fed condition [30-32]. Furthermore, as compared to fasting settings, the drug's relative bioavailability is raised by an average of 55–65 percent under fed conditions. Bromocriptine binds to plasma proteins 90–96% of the time [7, 8, 33].

2.3 Metabolism

98% of bromocriptine eaten is excreted by the biliary pathway. Bromocriptine is extensively metabolised in the liver by the cytochrome P450 system, particularly CYP3A4. There are around 20-30 metabolites, but little is known about their biological action. Approximately 93 percent of the absorbed dosage is processed in the first pass [7-10,33].

2.4 Clinical Efficacy

Bromocriptine was studied in over 4300 people to see if it was useful in treating T2DM. The FDA agreed bromocriptine for the cure of T2DM on the basis of the findings of four investigations [34-37]. There was a 24-week monotherapy study, two 24-week sulfonylurea add-on studies, and a 52-week safety trial. Bromocriptine was evaluated as a monotherapy and as an add-on therapy to different anti-diabetes therapies, such as sulfonylurea (SU) and insulin, in these trials.

2.5 Monotherapy

The focus of this study is to determine the characteristics of bromocriptine's safety and efficacy when used as a supplement to diet and exercise. A 24-week systematic clinical study was conducted on 159 people who were type 2 diabetics with insufficient glycemic control and were obese. At the baseline, 69 percent (N= 55) of the 80 bromocriptine individuals attained a maximal dosage of 4.8 milligram daily. The bromocriptine group had 9.0 percent mean HBA1c, whereas the placebo group had 8.8 percent mean HBA1c. This study found that bromocriptine improved fasting plasma glucose levels when compared to a placebo. Fasting plasma glucose (FPG) at the mean baseline was 215 Milligrams/decilitre, compared to 205 Milligrams/decilitre in the placebo arm. The average change in body weight from baseline in the drug group was 0.2 Kilogram, compared to 0.5 Kilogram in the placebo group [38].

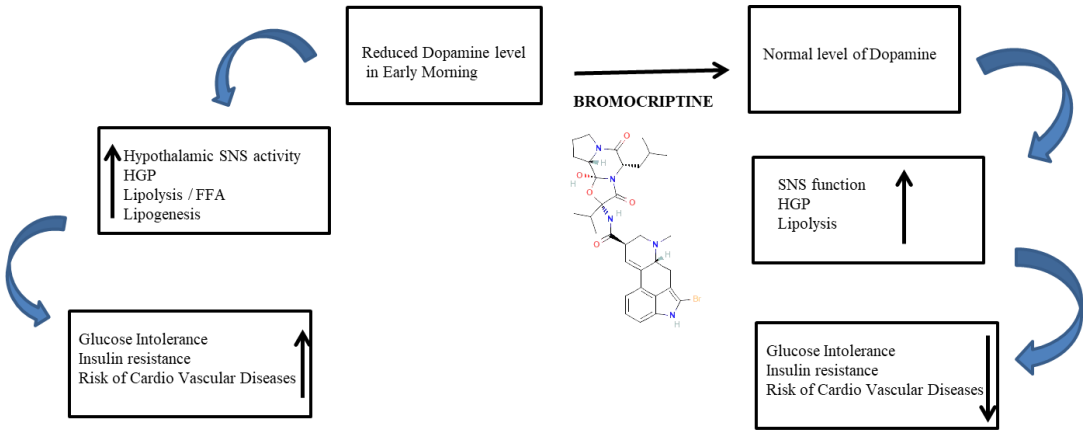

Fig. 1. Mode of action of Bromocriptine which increases the insulin sensitivity and regulate the glucose homeostasis

2.6 Combination Therapy

In the bromocriptine group, 91 (75%) of the 122 individuals received the maximal dose of the study medicine. In the bromocriptine and placebo groups, the average change in physical weight from baseline was 1.4 Kilogram and 0.5 Kilogram, respectfully. In the bromocriptine and placebo arms, the mean baseline HbA1c was 9.3 percent and 9.4 percent, respectively. At 24 weeks, the modified mean change from baseline was 0.1 percent for bromocriptine and 0.4 percent for placebo (-0.6 difference; P-value 0.001). The baseline FPG in the BR arm was 216 Milligrams/decilitre, while the placebo arm had 227 Milligrams/decilitre. These adverse effects were typically minor and only occurred on occasion. Thirteen percent of treated patients withdrew owing to side effects, compared to three to five percent of placebo-controlled subjects (P-value 0.01). In both the bromocriptine-QR and placebo groups, there was no increase in severe side effects (2.4 vs. 4.3 percent, respectively) [34-38].

2.7 Safety Test

The overall safety and cardiovascular safety of this innovative T2DM medication were assessed in this 52-week, randomised, double-blind, multicenter experiment. In line with standard diabetic management, 3,095 individuals with T2DM were randomly allotted to one of two groups: bromocriptine-QR or placebo (diet regulated only or with up to two medications for diabetes, insulin inclusive). The probability of any significant adverse event (SAE) was the all-cause safety end goal. In the bromocriptine-QR group, 176 (8.6%) participants experienced SAEs compared to 98 cases (9.6%) in the placebo group (HR 1.02 [96 percent one-sided Confidence Intervals 1.27]). In the bromocriptine-QR group, fewer participants reported a CVD end goal than in the placebo group (37 cases [1.8 percent] vs. 32 cases [3.2 percent]) (HR 0.60 [95 percent two-sided Confidence Intervals 0.35-0.96]) [39,40].

2.8 Contraindications

Bromocriptine is contraindicated in Type 1 diabetes, syncopal episodes, and psychosis. It can cause hypotension in persons with syncopal migraines. It has the potential to make nursing women stop producing milk. It should not be used in people who are hypersensitive to ergot-related medicines or bromocriptine. It might induce adverse reactions, especially after commencement or dosage escalation, thus patients receiving anti-hypertensive medicines should exercise caution. In persons with severe psychotic illnesses, it should not be administered [38].

2.9 Interactions

Bromocriptine serum concentrations will be reduced by CYPA4 inducers and increased by CYP3A4 inhibitors [26]. Bromocriptine's effectiveness can be reduced by dopamine receptor antagonists such as neuroleptics or metoclopramide, and vice versa. Because bromocriptine mesylate is highly complex, it may raise the unbound fraction of other highly protein-bound therapies taken at the same time, lowering efficacy and raising the risk of side effects. It is not suggested to use ergot-related drugs within six hours after taking bromocriptine.

2.10 Utility in India

Bromocriptine's particular mechanism should make it a helpful medicine in the treatment of depressed, insulin resistant, and overweight individuals in Indian

T2DM patients, many of whom are stressed by living in a dopaminergic environment [40].

3. CONCLUSION

Bromocriptine is a drug with a distinctive mode of action in the cure of T2DM. Bromocriptin-QR has a modest clinical effectiveness whether taken as a monotherapy or in combination with others, according to published clinical data, with HbA1c reductions ranging from 0.4 to 0.7 percent. Bromocriptine-QR can also help you lose weight and lower your risk of heart disease. Other benefits include the absence of hypoglycemia and a low risk of negative effects. Drugs that are powerful CYP3A4 inhibitors, inducers, or substrates should be used with caution when co-administered.

COMPETING INTERESTS

Authors have declared that no competing interests exist. The encouragement and support from Bharath Institute of Higher Education and Research, Chennai, is gratefully acknowledged.

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