Review Article

Bromocriptine mesylate in type 2 diabetes mellitus: A novel approach

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ABSTRACT

Type 2 diabetes mellitus (T2DM) remains uncontrolled in a large number of patients despite advances in medical treatment. Bromocriptine mesylate is a quick release preparation of bromocriptine, which acts on hypothalamic pathways of glucose metabolism. It represents a novel therapeutic option in the management of T2DM. United States Food and Drug Administration in 2009 approved the use of bromocriptine mesylate in T2DM as an adjunct to diet and exercise. Various clinical trials have demonstrated the efficacy of bromocriptine mesylate in lowering glycosylated hemoglobin by 0.4 to 0.8% as monotherapy or add-on therapy with other antidiabetic agents. Action on central pathways affecting glucose metabolism makes it a great alternative to current modalities of treatment for T2DM.

KEY WORDS: Bromocriptine; Dopamine Agonists; Diabetes; Insulin Resistance

INTRODUCTION

World Health Organization defines diabetes as a metabolic disorder of multiple etiologies characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action or both.[1] The worldwide prevalence of diabetes mellitus is rising like an epidemic and as per International Diabetes Federation projections; approximately 438 million individuals will have diabetes by the year 2030.[2]

PATHOPHYSIOLOGY

The idea of bromocriptine use for the management of type 2 diabetes mellitus (T2DM) came while investigating seasonal metabolic changes in vertebrates and migratory birds. These species develop obesity during hibernation and migration, respectively, as the food accessibility is low. Increased hepatic glucose production and development of insulin resistance in muscle and adipose tissues causes hyperglycaemia thereby glucose is made available for utilization by the brain. At the end of the season, animals revert to the insulin sensitive state and become lean. The net benefit of these changes is improved survival in times of food scarcity. These metabolic changes are controlled by the circadian neuroendocrine rhythms. Animal studies have shown increased serotonin and noradrenergic activity within ventromedial hypothalamus during the insulin resistant phase which returns to normal with insulin sensitive phase. Conversely, dopamine levels are low during the insulin resistant phase and return to baseline in insulin sensitive state. Intracerebral bromocriptine administration leads to a decrease in serotonergic and noradrenergic drive within the ventromedial hypothalamus, resulting in reduced glucose production by liver. Similar neuroendocrine circadian changes are observed in humans and are more pronounced in patients with T2DM. Early morning hypothalamic dopamine levels are low in patients with T2DM leading to increased sympathetic activity, hepatic glucose production, and lipolysis. The final effect is insulin-resistant glucose intolerant dyslipidemic state.[3]

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Bromocriptine mesylate is different from conventional bromocriptine preparation used in the treatment of hyperprolactinaemia and Parkinson's disease. It is a quick release, postsynaptic dopamine receptor agonist which is a predominant neurotransmitter in brain. Cells bearing dopamine receptors are found in the ventral striatum of brain. Administration of bromocriptine mesylate within two hours of awakening restores dopaminergic tone and reduces insulin resistance and blood glucose levels.[4]

BROMOCRIPTINE AND GLYCAEMIC CONTROL

Bromocriptine administration showed improved glucose tolerance and significant reduction in blood glucose in various animal studies which formed the basis for further human testing in T2DM.[5] The first clinical observational trial of bromocriptine was carried out in 1992 in which 33 obese nondiabetic and 15 diabetic individuals were daily administered 1.25 mg and 2.5 mg bromocriptine, respectively, for 6 weeks. In diabetic patients, reduction in fasting blood glucose was 99 mg/dL in insulin group and 65 mg/dL in oral agent group which was found significant.[6]

In a study of 12 nondiabetic obese hyperinsulinaemic, subjects it was found that low dose bromocriptine administration reduces fasting and postprandial blood glucose levels.[7] In a randomized provocative study by Schwartz, insulin-treated T2DM patients were given high-dose bromocriptine mesylate for 12 weeks. Compared with placebo, hemoglobin HbA1c was reduced by 0.7% in the bromocriptine group compared to placebo and was found to be significant.[8]

In Cycloset Safety trial by Florez et al. A subgroup of patients who were using thiazolidinedione alone or in combination with other antidiabetic drugs were analysed. They received daily add-on bromocriptine mesylate for 52 weeks, and the analysis was performed using intent to treat modified and evaluable per protocol basis. Patients with HbA1c of ≥7.5%, bromocriptine treatment resulted in significant reduction in HbA1c and fasting blood glucose when compared with placebo. Diabetics with a HbA1c value of <7.5% who were on bromocriptine showed a greater reduction in HbA1c levels compared to placebo. It was inferred from this study that bromocriptine add-on therapy in early T2DM patients might be beneficial in reducing the postprandial blood glucose levels and the same was suggested by Via et al.[9,10] However, since subgroup analysis by Florez et al. showed benefit in diabetics who were uncontrolled with thiazolidinedione, bromocriptine mesylate might also have usefulness in late diabetes as well. This is further supported by a study of Thomas et al., which concluded that the efficacy of bromocriptine is directly related to the duration of the diabetes.[11]

Effect of bromocriptine mesylate in 22 obese T2DM subjects was studied in a double-blinded trial lasting 16 weeks. Bromocriptine mesylate monotherapy significantly reduced HbA1c from 8.7% to 8.1% and fasting blood glucose levels compared to placebo. It was concluded that Bromocriptine improves glycaemic control significantly in T2DM especially in the obese patients.[4]

In a double-blind clinical trial done by Aminorroaya et al., 40 obese diabetics were administered daily 2.5 mg bromocriptine for 12 weeks. Fasting blood glucose and HbA1c were reduced significantly (27 mg/dL and 0.4%, respectively). This study concluded that Bromocriptine improves glycaemic control in obese T2DM patients. No change in body weight was observed in bromocriptine or placebo group.[12]

Cincotta et al. in 1999 conducted 24-week randomized trials of quick release preparation of bromocriptine mesylate in type 2 diabetic patients in a double-blind fashion. One such study, "study L" involved 245 patients with uncontrolled T2DM with HbA1c between 7.8% and 12.5%. Bromocriptine mesylate was added to existing sulfonylurea treatment which resulted in a mean reduction of 18 mg/dL in fasting blood sugar and mean reduction of 0.5% in HbA1c at 24 weeks which was significant. Another similar study, "study K" involved 249 patients with uncontrolled type 2 diabetes with HbA1c between 7.8% and 12.5%. Bromocriptine mesylate was added to existing sulfonylurea treatment which resulted in a mean reduction of 20 mg/dL in fasting blood sugar and mean reduction of 0.6% in HbA1c at 24 weeks which was found significant. A study of bromocriptine mesylate as the single agent in 159 overweight patients with uncontrolled type 2 diabetes was done. The subjects in "study 1" showed a mean reduction of 23 mg/dL in fasting blood sugar and a mean reduction of 0.4% in HbA1c which was found significant. These studies formed the basis for final Food and Drug Administration approval of bromocriptine mesylate in T2DM.[13]

An Indian study to evaluate the safety and efficacy of bromocriptine mesylate was conducted by Ramteke et al. in 2011. In a 12-week double-blind randomized trial, 105 recently diagnosed T2DM patients were classified into 3 groups. In the first group receiving bromocriptine therapy alone, mean reduction in fasting and postprandial blood glucose was not significant at 6-week but was significant at 12-week. In group 2 patients receiving metformin alone, mean reduction in fasting and postprandial blood glucose was significant both at 6 and 12 weeks. Group 3 patients receiving bromocriptine and metformin combination, mean reduction in fasting blood glucose and postprandial blood glucose was significant at 6 weeks but was much more significant at 12 weeks than Groups 1 and 2. Mean reduction in HbA1c at 12 weeks was significant in Groups 1 and 2 but was much more significant in Group 3. Hence, it was inferred from the study that bromocriptine mesylate as an add-on combination therapy is more effective than monotherapy.[14]

Scranton et al. in 2007 conducted 52-week randomized trial to assess the efficacy and safety of bromocriptine mesylate in a double-blind fashion. Uncontrolled 3095 type 2 diabetics with mean HbA1c of 8.3 were started on bromocriptine mesylate as add-on therapy. HbA1c decreased from 0.6% to 0.9% at 24 weeks compared with placebo. The significant reduction in glycaemic parameters in this trial proved the efficacy of bromocriptine.[15]

Kerr et al. conducted a Scopus and Medline search for studies of bromocriptine from 1950 to June 2010 which included more than 4000 diabetic patients. Bromocriptine addition to their therapy showed a mean HbA1c reduction of 0.27%. Patients on placebo therapy showed an increase of 0.48% in HbA1c. Hence, the final conclusion was that bromocriptine is an efficacious adjunctive antidiabetic drug.[16]

In a prospective study conducted by Garg and Chugh, 50 patients with uncontrolled T2DM were started on bromocriptine mesylate as add-on therapy to two oral antidiabetic agents. Patients showed significant decline in fasting, postprandial and HbA1c levels both at 6 and 12 weeks. The net reduction of HbA1c was 1.56% at 12 weeks which was more in diabetics with poor baseline glycaemic control.[17] Ghosh et al randomized T2DM patients into three groups. One group received monotherapy with metformin daily while the other two groups received metformin plus bromocriptine. The difference among these groups was in dosage of bromocriptine given. After 12 weeks of therapy, fasting, postprandial plasma glucose, and HbA1c levels were reduced in all the three groups significantly, but the reduction in these parameters was more pronounced in the group receiving higher dosage of bromocriptine. This showed that bromocriptine reduces glycemic parameters in a dose-dependent manner.[7]

BROMOCRIPTINE AND OBESITY

Obesity is a very common association with T2DM, and up to 80% diabetic patients are obese. Bromocriptine mesylate reduces body fat stores by improving insulin sensitivity and inhibiting lipogenesis. Improvement in body mass index in obese individuals by increased hypothalamic dopaminergic tone is supported by a study of Wang et al. in 2001. This study showed that body mass index is inversely related to status of dopamine receptors in the brain.[18] One randomized double-blinded placebo controlled study by Cincotta et al. in 1996 enrolled 17 nondiabetic obese individuals who were started on calorie restricted diet and administered daily bromocriptine mesylate over a period of 18 weeks. The bromocriptine mesylate group demonstrated significant weight loss but noted no change in fasting blood glucose compared with placebo plus diet.[19] Obese postmenopausal females treated with daily oral bromocriptine showed a decline of 11.7% in total body fat and reduction in body weight. Hyperglycaemia was reduced in 15 diabetic patients treated with bromocriptine resulting in euglycaemia.[6] One randomized clinical trial of bromocriptine was conducted in 13 obese diabetic patients by Wasada et al. in a double-blind fashion. After 30 weeks, there was no significant change in body fat.[20] The effects of bromocriptine on body weight and visceral fat are quite complex and would require studies specifically designed for testing the same.

BROMOCRIPTINE AND LIPID PROFILE

Bromocriptine reduces plasma free fatty acids and serum lipids by increasing hypothalamic dopaminergic tone when administered early in the morning. Kamath et al. in 1996 demonstrated a significant reduction in concentration of plasma free fatty acids and cholesterol in obese subjects after bromocriptine mesylate administration without a change in body weight.[21] A 24 weeks randomized controlled trial by Cincotta et al. in 1999 showed a significant reduction in plasma free fatty acids and triglycerides after administration of bromocriptine mesylate in obese T2DM patients.[22]

BROMOCRIPTINE AND HYPERTENSION

The data on the effect of bromocriptine in hypertension is limited only to one animal study done by Ezrokhi et al. Bromocriptine administration in hypertensive rats showed a reduction in systolic and diastolic blood pressures along with a reduction in plasma glucose levels.[23] None of the human studies till date have shown any significant reduction in blood pressure.

POSOLOGY

Following oral ingestion, bromocriptine mesylate tablet is dissolved rapidly. Peak plasma concentration is achieved within 60 minutes. Drug absorption is delayed by food and peak plasma levels are achieved after 120 minutes. Bromocriptine is extensively metabolized in the liver and is excreted in bile. Due to hepatic first pass metabolism, less than 10% of ingested drug reaches systemic circulation. It is highly protein bound. The recommended daily dose is between 1.6 mg and 4.8 mg depending on the individual tolerability. It is preferably taken in the morning within two hours after waking up with food to reduce gastrointestinal side effects. Bromocriptine mesylate should be started as one tablet of 0.8 mg daily and gradually up-titration of dose on a weekly basis should be done. It should be used with caution in liver and renal diseases. Compliance is improved by once daily dosage.[3]

SAFETY AND ADVERSE EFFECT PROFILE OF BROMOCRIPTINE

It should not be used in type 1 diabetics, lactating mothers and patients with allergy to ergot drugs. Concomitant usage with

ergot drugs increases the likelihood of adverse effects such as nausea, vomiting and fatigue. Orthostatic hypotension may occur on starting the treatment in patients who are already taking other antihypertensive drugs. Serious side effects are rare at the dosages recommended in diabetic patients. Clinical data and safety profile of bromocriptine mesylate in T2DM is available from 2 to 6 month trials (study K and study L) and a 1-year safety trial by Scranton et al.[13] Nausea and vomiting have been the most common side effects reported. Headache, fatigue and dizziness are the other adverse effects of bromocriptine mesylate. These side effects are more likely to occur on starting the treatment, hence weekly up-titration of the dose is recommended. In the 1-year safety trail by Scranton et al. which included 3070 patients, side effects were reported in 8.5% in the bromocriptine mesylate group and 9.6% of placebo group. hypoglycaemia incidence was not increased in bromocriptine group compared to placebo. Severe hypoglycemia occurred in 0.5% of bromocriptine mesylate users. Overall, bromocriptine mesylate demonstrates good safety and tolerability.[24]

CONCLUSION

Bromocriptine mesylate denotes a novel antidiabetic drug in view of its unique action on hypothalamic centers. The available clinical data corroborates a moderate clinical efficacy of bromocriptine mesylate when used singly or in combination with other antidiabetic drugs. Some studies have shown benefit in terms of moderate weight reduction with a beneficial effect on lipids as well. However, larger randomized controlled trials of longer duration need to be undertaken to assess efficacy and safety profile and will further delineate bromocriptine mesylate use in T2DM.

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