

Bromocriptine in type 2 diabetes mellitus

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ABSTRACT

Bromocriptine mesylate quick-release was approved by the Food and Drug Administration (FDA) in May 2009, for the treatment of type 2 diabetes. Bromocriptine is thought to act on the circadian neuronal activities in the hypothalamus, to reset an abnormally elevated hypothalamic drive for increased plasma glucose, free fatty acids, and triglycerides in insulin-resistant patients. Randomized controlled trials have shown that bromocriptine-QR lowers glycosylated hemoglobin by 0.4 – 0.8% either as monotherapy or in combination with other anti-diabetes medications. The doses used to treat diabetes (up to 4.8 mg daily) are much lower than those used to treat Parkinson's disease, and apart from nausea, the drug is well-tolerated. The novel mechanism of action, good side effect profile, and its effects to reduce cardiovascular event rates make it an attractive option for the treatment of type 2 diabetes.

Key words: Bromocriptine, circadian rhythm, diabetes, insulin resistance, quick release formulation

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder of multifactorial pathogenesis, caused by insulin resistance, impaired β -cell function, and multiple other metabolic abnormalities. It is characterized by elevated fasting and postprandial plasma glucose concentrations, which result from increased endogenous glucose production, decreased insulin-mediated muscle glucose disposal, and suppression of endogenous glucose release, as well as, inadequate pancreatic insulin secretion. As the underlying pathophysiology in T2DM is being unraveled, our pharmacological repertoire has expanded to target novel pathophysiological mechanisms. Even then, restoration of normoglycemia is difficult to achieve and requires multiple antidiabetic medications with different mechanisms of action, which can be used in combination to produce an additive effect. The development of antidiabetic agents with

novel mechanisms of action is therefore highly desirable.^[1,2]

Bromocriptine is a sympatholytic D2-dopamine agonist that has been recently approved for the treatment of type 2 diabetes. This centrally acting antidiabetic agent has a novel mechanism of action and reduces plasma glucose, triglycerides, Free Fatty Acid (FFA) levels, and possibly cardiovascular events. The utility of bromocriptine in diabetes patients has been recognized, based on its activity in modulating central glucose and energy metabolism pathways.^[3,4] A quick release formulation of bromocriptine, administered within two hours of awakening, is believed to augment low hypothalamic dopamine levels and inhibit excessive sympathetic tone within the central nervous system (CNS), resulting in a reduction in post meal plasma glucose levels, due to enhanced suppression of hepatic glucose production.^[2]

MECHANISM OF ACTION

The idea of using bromocriptine for the treatment of type 2 diabetes came while studying the metabolism of migrating birds. It was noted that they developed seasonal changes in body fat stores and insulin sensitivity. In vertebrates, body fat stores and insulin action are controlled by the temporal interaction of circadian neuroendocrine oscillations. Many vertebrate species develop obesity and insulin resistance

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(IR) during hibernation, migration, and overwintering, when food availability is very low.^[5] During transition to this insulin-resistant state, the basal lipolytic activity increases, to spare glucose utilization by the peripheral tissues and fat oxidation becomes predominant. Hepatic glucose production and gluconeogenesis rise to supply glucose to the CNS during prolonged periods of winter food deprivation.^[5,6] This adaptation helps survival in times of seasonal famine. At the end of the season animals revert to the insulin-sensitive / glucose-tolerant phase and become lean.

Extensive experimental evidence indicates that circadian neuroendocrine rhythms play a pivotal role in the development of these seasonal changes. Specifically, temporal changes in the interaction of two distinct circadian neural oscillations, mediated in part by dopaminergic and serotonergic neurotransmitter activity, with reduced dopaminergic and enhanced serotonergic activity are believed to be responsible for the obese / IR phenotype.^[7-9] These changes in monoaminergic concentrations / activity occur in the suprachiasmatic nuclei (SCN) of the hypothalamus — the mammalian circadian pacemaker — and in the ventromedial hypothalamus (VMH). Within the VMH, multiple studies have documented that both serotonin and noradrenergic levels and activity are increased during the insulin-resistant state and decrease to normal with return to the insulin-sensitive state, in animals that undergo seasonal changes in metabolism. Conversely, dopamine levels are low during the insulin-resistant state and increase to normal following a return to the insulin-sensitive state. Intracerebral bromocriptine administration in insulin-resistant animals leads to a decrease in elevated VMH noradrenergic and serotonergic levels leading to improved insulin sensitivity and reduced plasma glucose and adipocyte lipolysis.^[10-16]

The development of the insulin-resistant state during these periods of seasonal change in animals precisely mimics the changes observed in people with type 2 diabetes and the insulin-resistance syndrome.^[2,17] Data suggests that a decreased hypothalamic dopaminergic tone may be involved in the pathogenesis of insulin resistance. The normal circadian cycle that results in a leaner body in the summer and heavier body in winter is disrupted in humans because of the abundant caloric intake year round resulting in the absence of a lean phase.^[18] Type 2 diabetic individuals are believed to have an early morning dip in the dopaminergic tone, which leads to increased sympathetic activity.^[19] In lean, normal, glucose-tolerant, insulin-sensitive humans, the plasma prolactin concentrations peak at night, during sleep. In contrast, obese insulin-resistant individuals have

elevated (two-fold) day time plasma prolactin levels,^[20] consistent with a reduced dopaminergic tone.

Bromocriptine mesylate, an ergot derivative, is a sympatholytic dopamine D₂ receptor agonist that can exert inhibitory effects on a serotonin turnover in the central nervous system. Quick-release bromocriptine given once in the morning, is believed to reset the circadian clock permanently stuck in a winter rhythm.^[2] This means there occurs a re-setting of the abnormally elevated hypothalamic drive for increased plasma glucose, triglycerides, and free fatty acid levels in fasting and postprandial states in insulin-resistant patients [Figure 1].

PHARMACOKINETICS

The structural formula of bromocriptine is shown in Figure 2. Bromocriptine mesylate is a white or slightly colored, fine crystalline powder with a molecular formula

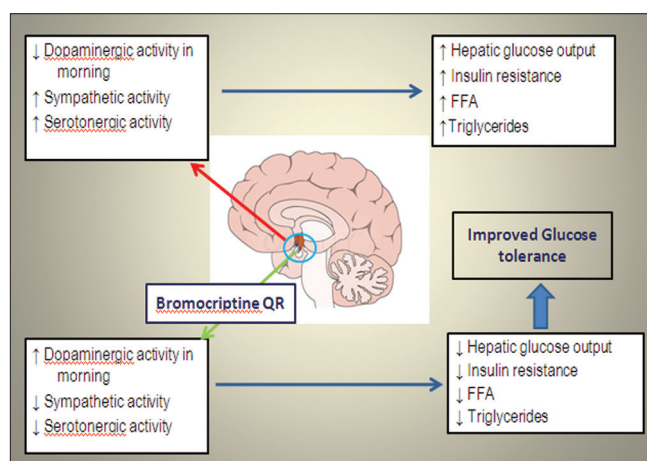


Figure 1: Potential mechanisms of the action of Bromocriptine, to improve glucose tolerance

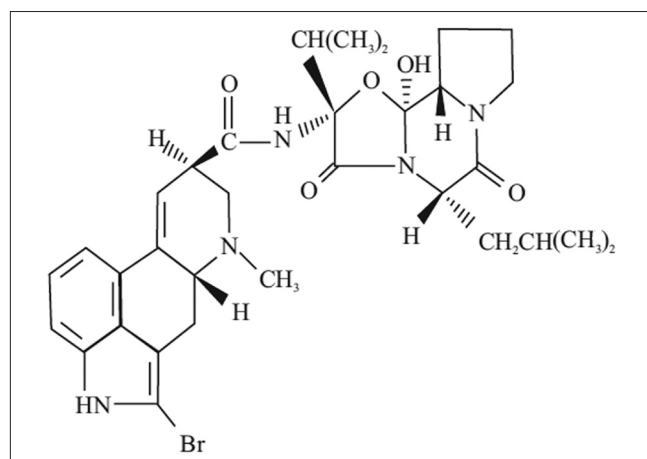


Figure 2: Structure of bromocriptine

of $C_{32}H_{40}BrN_5O_5 \cdot CH_4SO_3$ and a molecular weight of 750.72.

ABSORPTION AND BIOAVAILABILITY

When administered orally, approximately 65 – 95% of the drug is absorbed. Due to extensive hepatic extraction and first-pass metabolism, approximately 7% of the dose reaches the systemic circulation. Under fasting conditions the time to maximum plasma concentration is about 60 minutes. Absorption is delayed by food and peak plasma levels are achieved at 120 minutes in a fed state. Also, the relative bioavailability of the drug is increased under the fed as compared to fasting conditions, by an average of approximately 55 – 65%. Bromocriptine is 90 – 96% bound to plasma proteins.^[2,4,21]

METABOLISM

Bromocriptine mesylate is extensively metabolized in the gastrointestinal tract and liver. Metabolism by CYP3A4 is the major metabolic pathway. Most of the absorbed dose (approximately 93%) undergoes first-pass metabolism. The major route of excretion of bromocriptine is in the bile, with the remaining approximately 2 – 6% of an oral dose excreted via the urine. The elimination half-life is approximately six hours.^[2,4,21]

POSODOLOGY

The recommended dose is 1.6 mg to 4.8 mg, administered once daily, within two hours after waking in the morning. It should be taken with food to potentially reduce the gastrointestinal side effects such as nausea. Bromocriptine mesylate should be initiated at one tablet (0.8 mg) and increased by one tablet per week until a maximum daily dose of six tablets (4.8 mg) or until the maximal tolerated number of tablets, between two and six per day, is reached. No pharmacokinetic studies have been conducted in subjects with renal and hepatic impairment, and it should be used with caution^[2,4,21] in such patients.

NON-DIABETIC USES OF BROMOCRIPTINE

Bromocriptine preparations used for type 2 diabetes are quick release tablets of 0.8 mg strength. They are different from the conventional bromocriptine tablets of 2.5 mg or 5 mg used in other indications.

Bromocriptine is used in various indications, and by diverse medical specialties. It is used by endocrinologists for the management of pituitary adenomas, by gynecologists for suppression of lactation, by neurologists in Parkinson's

disease and restless legs syndrome, and by cardiologists as a treatment for peripartum cardiomyopathy. Psychiatrists find that it improves anhedonia in depressed patients.^[18]

CLINICAL EFFICACY AND SAFETY IN DIABETES

Bromocriptine has been studied in more than 4300 patients, evaluating its efficacy in the treatment of type 2 diabetes. The results of four studies have served as the basis for the FDA approval of RR-bromocriptine in the treatment of T2DM [Table 1].^[22-25] A 24-week monotherapy trial, two, 24-week add-on to sulfonylurea trials, and a 52-week safety trial have been carried out. In these studies bromocriptine-QR has been studied as monotherapy and as an add-on therapy to sulfonylurea (SU) treatment, as well as, in a large safety study in which bromocriptine-QR (BR) was added to various anti-diabetes treatments, including insulin. In all the four clinical trials, the subjects assigned to treatment with bromocriptine-QR received an initial dose of 0.8 mg, which was increased by 0.8 mg each week for six weeks (4.8 mg / day final dose), if no intolerance occurred, or until the maximum tolerated dose of > 1.6 mg / day was reached.

MONOTHERAPY TRIAL

This trial was designed to evaluate the efficacy and safety of bromocriptine-QR as an adjunct to diet and exercise. It was a 24-week, double-blind, placebo-controlled study that enrolled 159 overweight adults with type 2 diabetes and inadequate glycemic control. Of the 80 subjects in the bromocriptine group, 69% (N = 55) achieved the maximum daily dose of 4.8 mg. Mean HbA1c at baseline was 9.0% in the Cycloset group and 8.8% in the placebo group. Bromocriptine improved HbA1c and fasting plasma glucose compared to the placebo. The 24-week change from baseline was -0.1 in the bromocriptine arm and 0.3 in the placebo arm (a -0.4 difference from placebo; $P < 0.05$). The mean baseline fasting plasma glucose (FPG) (mg / dl) was 215 in the bromocriptine arm and 205 in the placebo arm. At 24 weeks, the adjusted mean change from placebo was -23 ($P = 0.005$). The mean change from baseline in body weight was +0.2 kg in the bromocriptine group and +0.5 kg in the placebo group.^[22-25]

COMBINATION THERAPY

Study L: This 24-week, randomized, double-blind, placebo-controlled trial enrolled 249 subjects with type 2 diabetes and inadequate glycemic control (HbA1c 7.8 – 12.5%) on sulfonylurea therapy. The study was designed to evaluate the safety and glycemic efficacy of bromocriptine when added to stable sulfonylurea therapy versus placebo plus

Table 1: Summary of four studies that served as the basis for the FDA approval of RR-bromocriptine for the treatment of T2DM

	Arm 1	Arm 2	HbA1C (%) Baseline	HbA1C (%) Change from baseline	Overall HbA1C difference b / w 2 arms	FPG (mg / dl) Baseline	FPG (mg / dl) Change from baseline	Overall FPG difference b / w 2 arms
Study 1	Br N = 80	PI N = 79	Br - 9%	Br - - 0.1	- 0.4*	Br - 215	Br - 0	- 23**
			PI - 8.8%	PI - 0.3		PI - 205	PI - 23	
Study L	Br+SU N = 122	PI + SU N = 123	Br - 9.3%	Br - - 0.1	- 0.5*	Br - 216	Br - 10	- 18**
			PI - 9.4%	PI - 0.4		PI - 227	PI - 28	
Study K	Br+SU N = 122	PI + SU N = 127	Br - 9.3%	Br - - 0.4	- 0.6*	Br - 220	Br - 3	- 20†
			PI - 9.4%	PI - 0.3		PI - 226	PI - 23	
Study 4#†								
a. Adjunct to 1-2 OHA	Br N = 376	PI N = 183	Br - 8.3%	Br - - 0.4	- 0.5 ^			
			PI - 8.4%	PI - 0.0				
b. Adjunct to MF + SU	Br N = 177	PI N = 90	Br - 8.3%	Br - - 0.5	- 0.5 ^			
			PI - 8.3%	PI - 0.0				

Br: Bromocriptine mesylate, PI: Placebo, SU: Sulfonylurea, OHA: Oral antidiabetic medications, RR: Rapid release, *P*-value calculated by ANOVA; **P* = 0.05, ***P* = 0.005, *P*-value calculated by ANOVA; †*P* < 0.001, ***P* = 0.02; ‡*P* = 0.006, †patients in the 'metformin + sulfonylurea only' subgroup are also counted in the 'adjunct to 1 - 2 oral anti-diabetic medications', ^ subgroup *P*-value is based on an ANCOVA model with treatment and center as fixed effects, and baseline HbA1c as covariates; ^*P* < 0.001, #Subgroup analyses of glycemic efficacy for patients who had inadequate glycemic control (baseline HbA1c ≥ 7.5%)

sulfonylurea. The mean baseline HbA1C was 9.3% in the bromocriptine arm and 9.4% in the placebo arm. At 24 weeks, the adjusted mean from baseline was - 0.4% and 0.3 for bromocriptine and placebo, respectively, (- 0.6 difference; *P* < 0.001). The baseline FPG was 220 mg / dl in the bromocriptine arm and 226 mg / dl in the placebo arm. At 24 weeks, the adjusted mean change from baseline was 3 mg / dl and 23 mg / dl, respectively, (- 20 difference; *P* = 0.006). The mean change from the baseline in body weight was + 0.9 kg in the bromocriptine group and + 0.5 kg in the placebo group.^[22-25]

Study K: This 24-week, randomized, double-blind, placebo-controlled trial enrolled 245 subjects with type 2 diabetes and inadequate glycemic control (HbA1c 7.8 - 12.5%), on stable sulfonylurea therapy, who were randomized to add-on therapy with either bromocriptine or placebo. Of the 122 subjects in the bromocriptine group, 91 (75%) achieved the maximum dose of the study drug. Mean change from baseline in body weight was + 1.4 kg in the bromocriptine group and + 0.5 kg in the placebo group. The mean baseline HbA1C was 9.3% in the bromocriptine arm and 9.4% in the placebo arm. At 24 weeks, the adjusted mean from the baseline was - 0.1 and 0.4% for bromocriptine and placebo, respectively, (- 0.5 difference; *P* < 0.001). The baseline FPG was 216 mg / dl in the BR arm and 227 mg / dl in the placebo arm. At 24 weeks, the adjusted mean change

from baseline was 10 mg / dl and 28 mg / dl, respectively (- 18 difference; *P* = 0.02).^[22-25]

BR ADD-ON TO VARIOUS ORAL ANTI-DIABETIC AGENTS: 52-WEEK SAFETY TRIAL

This randomized, double-blind, placebo-controlled safety trial enrolled approximately 3,000 subjects with type II diabetes receiving various anti-diabetic therapies (mean baseline HbA1c 8.3%). Approximately 70% of the subjects assigned to treatment with bromocriptine reached a maximum daily dose of 4.8 mg. The least-squares mean change in HbA1c from baseline to week 24 was 0.0% with BR and + 0.2% with placebo. Subjects receiving bromocriptine, compared to placebo, experienced a significant improvement in HbA1c when it was used as an adjunctive therapy to one to two oral antidiabetic medications, including the subgroup of patients treated only with background metformin + sulfonylurea. The mean change in body weight for the glycemic efficacy subgroup from baseline to week 24 was - 0.1 kg with BR and + 0.1 kg. The mean change in body weight for the entire study population from baseline to week 52 was + 0.2 kg with BR and + 0.1 kg with placebo.^[22-26]

Three other RCTs have evaluated the utility of bromocriptine therapy for the treatment of T2DM and / or obesity [Table 2].

Table 2: Published randomized controlled trials of Bromocriptine in diabetes / obesity

	Subjects	Arm 1	Arm 2	Br dosage	Duration (weeks)	Change in FPG (mg / dl)	Change in HbA1c (%)	Change in weight (kg)
Cincotta <i>et al.</i>	Obese with IGT	Br N = 8	PI N = 7	1.6 - 2.4 mg / day	18	Br improved glucose tolerance	-	- 6.3 - Br - 1.5 - PI
Pijl <i>et al.</i>	Obese T2DM	Br N = 15	PI N = 7	4.8 mg daily	16	- 18 - Br + 36 - PI	- 0.6 - Br + 0.6 - PI	+ 0.04 - Br + 0.9 - PI
Aminorroaya <i>et al.</i>	Obese T2DM	Br N = 20	PI N = 20	2.5 mg daily	12	- 27 - Br - 2 - PI	- 0.4 - Br + 1.1 - PI	No change

Br: Bromocriptine mesylate, PI: Placebo, FPG: Fasting plasma glucose, IGT: Impaired glucose tolerance

Cincotta *et al.*, conducted a double blind, placebo-controlled trial of bromocriptine-QR in 17 obese subjects with impaired glucose tolerance, who were instructed to follow a moderate hypocaloric diet. Patients were randomized to daily treatment with bromocriptine-QR (1.6 – 2.4 mg / day) or placebo at 0800 hours, over an 18-week treatment period. Daily dosages ranged from 1.6 to 2.4 mg in the eight patients who received RR-bromocriptine. After 18 weeks of follow-up, the bromocriptine-QR group demonstrated significant weight loss of 6.3 ± 1.5 kg ($P < 0.01$) and had a 46% decrease in the area under the serum glucose curve during an oral glucose tolerance test ($P < 0.02$) compared to the baseline. No changes were noted in the placebo group.^[27]

Pijl *et al.*, studied the effect of a quick-release bromocriptine formulation on glucose homeostasis and insulin sensitivity in obese type 2 diabetic subjects. Twenty-two obese diabetic subjects were randomized to receive a quick-release formulation of bromocriptine ($n = 15$) or placebo ($n = 7$) in a 16-week double-blind study. Bromocriptine significantly reduced the HbA1c (from 8.7 to 8.1%, $P = 0.009$) and FPG (from 190 to 172 mg / dl, $P = 0.02$) levels, whereas, these variables increased during placebo treatment (from 8.5 to 9.1%, NS, and from 187 to 223 mg / dl, $P = 0.02$, respectively). The differences in HbA1c and fasting glucose levels between the bromocriptine and placebo groups at 16 weeks were highly significant. The mean plasma glucose concentration during OGTT was significantly reduced by bromocriptine (from 294 to 272 mg / dl, $P = 0.005$), whereas, it increased in the placebo group.^[28]

Aminorroaya, conducted a double-blind placebo-controlled clinical trial in 40 obese patients with type-2 diabetes (aged 32 – 70 years). Patients were randomly allocated to receive bromocriptine (2.5 mg daily) or placebo for three months. The FPG level decreased in the bromocriptine-treated group from 10.59 ± 0.42 to 9.06 ± 0.41 mmol / l (mean \pm SEM; $P < 0.01$), whereas, in the placebo group it was not changed, 10.69 ± 0.52 and 10.6 ± 0.57 mmol / l, respectively. The HbA1c concentration was reduced in the bromocriptine-treated group from 9.9 ± 0.3 to 9.5

$\pm 0.2\%$ ($P = 0.06$), whereas, it increased in the placebo-treated group from 10.2 ± 0.3 to $11.3 \pm 0.6\%$ ($P < 0.05$). The differences in HbA1c (1.8%, $P < 0.01$) and FPG (1.55 mmol / l, $P < 0.05$) levels between the bromocriptine and placebo groups at three months were significant. No changes in body weight or BMI occurred during the study in either the placebo or bromocriptine-treated group.^[29]

To summarize, bromocriptine-QR causes a small reduction in FPG and HbA1C, which can translate into a modest improvement in diabetes control. In addition it has a beneficial impact on body weight. However the results have not been consistent and further large scale trials are warranted.^[30]

The Cycloset Safety Trial, a 52-week, randomized, double-blind, multicenter trial, evaluated the overall safety and cardiovascular safety of this novel therapy for type 2 diabetes. A total of 3,095 patients with type 2 diabetes were randomized 2 : 1 to bromocriptine-QR or placebo, in conjunction with the patient's usual diabetes therapy (diet controlled only or up to two anti-diabetes medications, including insulin). The all-cause-safety end point was the occurrence of any serious adverse event (SAE), with a hazard ratio (HR) non-inferiority margin of 1.5. In a pre-specified analysis, the frequency of cardiovascular disease (CVD) events, defined as a composite of myocardial infarction, stroke, coronary revascularization, and hospitalization for angina or congestive heart failure was evaluated, using modified intent-to-treat analysis. The frequency of SAEs was comparable between the treatment arms. Compared with patients in the placebo arm, fewer patients taking bromocriptine-QR experienced a cardiovascular end point. In the bromocriptine-QR group, 176 (8.6%) people reported SAEs compared to 98 (9.6%) in the placebo group (HR 1.02 [96% one-sided CI 1.27]). Fewer people reported a CVD end point in the bromocriptine-QR group versus the placebo group (37 [1.8%] versus 32 [3.2%], respectively) (HR 0.60 [95% two-sided CI 0.35– 0.96]). Nausea was the most commonly reported adverse event in the bromocriptine-QR group.^[26]

However, the mechanism by which timed bromocriptine reduces cardiovascular events in type 2 diabetic patients remains to be defined. Bromocriptine has been shown in some studies to reduce free fatty acids, lipoprotein concentrations, body fat stores, and to inhibit vascular smooth muscle proliferation.^[31,32] In animal studies, bromocriptine has been shown to attenuate the effect of CNS sympathetic overactivity on the vasculature, and a direct inhibitory effect of bromocriptine on mitogen-stimulated proliferation of rat vascular muscle cells and human aortic smooth muscle cells has been demonstrated *in vitro*.^[33-35]

In the monotherapy and add-on to sulfonylurea trials (29), side effects that occurred more commonly in bromocriptine-QR versus placebo were nausea (26 vs. 5%), asthenia (15 vs. 8%), constipation (11 vs. 4%), dizziness (11 vs. 6%), and rhinitis (8 vs. 5%). In general, these side effects were mild and transient. Thirteen percent of the treated subjects withdrew because of adverse events compared to three to five percent of the placebo-treated subjects ($P < 0.01$). There was no increase in serious adverse events in the bromocriptine-QR and placebo groups that were compared (2.4 vs. 4.3%, respectively). There was no difference in the incidence of hypoglycemia between the two groups in any trial.^[22-25]

In the Cycloset Safety Trial, adverse events (AEs) occurred in 89% of the bromocriptine-QR-treated and 83% of the placebo-treated patients. AEs were not commonly reported as severe in either treatment group (17% of the events were reported as severe on bromocriptine-QR compared to 14% on placebo). More patients discontinued bromocriptine-QR than placebo, due to an adverse event (24% vs. 11%, respectively). The most commonly reported adverse event among patients who discontinued bromocriptine-QR was nausea (7.6% bromocriptine-QR vs. 1% placebo). The only AEs that occurred at a frequency rate of at least 5% and were numerically greater in the bromocriptine-QR arm were nausea, vomiting, dizziness, headache, and diarrhea. Nausea was the most common adverse event, (32.2% in bromocriptine-QR vs. 7.6% in placebo). A majority of the commonly occurring adverse events attributed to bromocriptine-QR occurred during the initial titration phase, were dose-related, and transient in nature (mean duration of 14 days). After the initial titration phase, the commonly occurring adverse events were reported at a frequency similar to that observed in the placebo-treated arm.^[26]

CONTRAINDICATIONS

Contraindications to bromocriptine include type 1

diabetes, syncopal attacks, and psychosis. It can precipitate hypotension in patients with syncopal migraines and inhibit lactation in nursing women. It should not be used in patients with hypersensitivity to ergot-related drugs or bromocriptine. It can cause orthostatic hypotension and syncope, particularly upon initiation or dose escalation so caution is advised in patients taking anti-hypertensive medications. It should not be used in patients with severe psychotic disorders

DRUG INTERACTIONS

Bromocriptine is metabolized by the CYP4A pathway. CYP4A inducers will therefore reduce the serum concentration of bromocriptine. On the other hand, drugs that are CYP3A4 inhibitors, will increase bromocriptine concentration.^[18] Bromocriptine mesylate, is highly bound to serum proteins and may increase the unbound fraction of other concomitantly used highly protein-bound therapies (e.g., salicylates, sulfonamides, chloramphenicol, and probenecid), which may alter their effectiveness and risk for side effects. Concomitant use of dopamine receptor antagonists, such as neuroleptics (e.g., phenothiazines, butyrophenones, thioxanthenes), or metoclopramide may diminish the effectiveness of bromocriptine and vice versa. In combination with ergot-related drugs it may increase the occurrence of ergot-related side effects such as nausea, vomiting, and fatigue, and may also reduce the effectiveness of these ergot therapies when used to treat migraines. The concurrent use of these ergot agents within six hours of bromocriptine is not recommended.

UTILITY IN INDIA

Bromocriptine is a dopamine modulator, and as such, may have greater utility in clinical situations with sustained dopaminergic hyperactivity.

Modern India is a fast progressing nation, and may be called an 'adrenergic country,' or, more specifically, a 'dopaminergic society'. Even as phasic dopaminergic activity is good (as demonstrated by animals who need to survive harsh winters), sustained or tonic hyperdopaminergicism, may be non-physiological or counterproductive, and result in lifestyle diseases such as diabetes mellitus.

In a fast changing society such as India, stress is an inevitable part of life. Stress, mediated by the autonomic nervous system, specifically dopamine, has to be tackled if comprehensive management of diabetes is to be achieved. Dopamine is important as it is the predominant catecholamine found in the central nervous system.^[36]

The novel mechanism of bromocriptine should make it a useful drug for Indian patients with type 2 diabetes, many of whom experience the stress of having to survive in a dopaminergic society. It should find a place in the management of obese, depressed, 'less mobile', insulin-resistant patients.^[36] No wonder, then, that high levels of interest have been documented by Indian physicians attending continuing medical education programs, regarding the use of bromocriptine.^[37]

A large scale, multicentric, prospective, open labeled trial is underway to assess the efficacy and safety of bromocriptine in India.

CONCLUSIONS

Bromocriptine represents a novel agent with a unique mechanism of action in the management of T2DM. The available clinical data demonstrate a modest clinical efficacy for bromocriptine-QR with HbA1c reduction of 0.4–0.7% when used as a monotherapy or in combination with other OADs. However, the results of the studies that serve as the basis for the FDA approval of bromocriptine-QR, for the treatment of T2DM, have not been published yet and critical evaluation of the study design and results of these studies is required. Bromocriptine-QR may also cause weight loss and reduce cardiovascular event rate. Other advantages include the absence of hypoglycemia and a good side effect profile. Large trials to confirm the potential benefits of RR-bromocriptine in T2DM are warranted. Caution is advised when co-administering drugs which are strong inhibitors, inducers, or substrates of CYP3A4 (e.g., azole antimycotics, HIV protease inhibitors).

REFERENCES

1. DeFronzo RA. Banting Lecture: From the triumvirate to the ominous octet: A new paradigm for the treatment of type 2 diabetes mellitus. *Diabetes* 2009;58:773-95.
2. DeFronzo RA. Bromocriptine: A sympatholytic, d2-dopamine agonist for the treatment of type 2 diabetes. *Diabetes Care* 2011;34:789-94.
3. Kerr JL, Timpe EM, Petkewicz KA. Bromocriptine mesylate for glycemic management in type 2 diabetes mellitus. *Ann Pharmacother* 2010;44:1777-85.
4. Via MA, Chandra H, Araki T, Potenza MV, Skamagas M. Bromocriptine approved as the first medication to target dopamine activity to improve glycemic control in patients with type 2 diabetes. *Diabetes Metab Syndr Obes* 2010;3:43-8.
5. Cincotta AH. Hypothalamic role in the insulin resistance syndrome. In: Hansen B, Shaffrir E, editors. *Insulin Resistance Syndrome*. London: Taylor and Francis; 2002. p. 271-312.
6. Holt RI, Barnett AH, Bailey CJ. Bromocriptine: Old drug, new formulation and new indication. *Diabetes Obes Metab* 2010;12:1048-57.
7. Meier CA. Circadian rhythms regulate the expression of the thrifty genotype/phenotype. *Diabetes Rev* 1996;4:464-87.
8. Grewal E. Bromocriptine: The new frontier in type 2 diabetes. Available at http://www.ijcci.info/flash/oct10/Diabetes_summit/Dopamine%20The%20new%20frontier%20in%20type2.swf. [Last accessed on 2011 May 1].
9. Southern LL, Cincotta AH, Meier AH, Bidner TD, Watkins KL. Bromocriptine-induced reduction of body fat in pigs. *J Anim Sci* 1990;68:931-6.
10. Erminioc P. Ergot compounds and brain function: Neuroendocrine and neuropsychiatric aspects. In: Goldstein ML, editor. *Advances in Biochemical Psychopharmacology*. New York: Raven; 1980. p. 41-62.
11. Luo S, Meier AH, Cincotta AH. Bromocriptine reduces obesity, glucose intolerance and extracellular monoamine metabolite levels in the ventromedial hypothalamus of Syrian hamsters. *Neuroendocrinology* 1998;68:1-10.
12. Luo S, Luo J, Cincotta AH. Suprachiasmatic nuclei monoamine metabolism of glucose tolerant versus intolerant hamsters. *Neuroreport* 1999;10:2073-7.
13. Luo S, Luo J, Meier AH, Cincotta AH. Dopaminergic neurotoxin administration to the area of the suprachiasmatic nuclei induces insulin resistance. *Neuroreport* 1997;8:3495-9.
14. Luo S, Liang Y, Cincotta AH. Intracerebroventricular administration of bromocriptine ameliorates the insulinresistant/ glucose-intolerant state in hamsters. *Neuroendocrinology* 1999;69:160-6.
15. Cincotta AH, MacEachern TA, Meier AH. Bromocriptine redirects metabolism and prevents seasonal onset of obese hyperinsulinemic state in Syrian hamsters. *Am J Physiol* 1993;264:E285-93.
16. Cincotta AH, Schiller BC, Landry RJ, Herbert SJ, Miers WR, Meier AH. Circadian neuroendocrine role in age-related changes in body fat stores and insulin sensitivity of the male Sprague-Dawley rat. *Chronobiol Int* 1993;10:244-58.
17. De Fronzo RA, Ferrannini E. Insulin resistance: A multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. *Diabetes Care* 1991;14:173-94.
18. Kalra S, Kalra B, Agrawal N, Kumar S. Dopamine: The forgotten felon in diabetes. *Recent Pat Endocr Metab Immune Drug Discov* 2011;5:61-5.
19. Luo S, Luo J, Cincotta AH. Chronic ventromedial hypothalamic infusion of norepinephrine and serotonin promotes insulin resistance and glucose intolerance. *Neuroendocrinology* 1999;70:460-5.
20. Cincotta AH, Meier AH, Cincotta M Jr. Bromocriptine improves glycaemic control and serum lipid profile in obese Type 2 diabetic subjects: A new approach in the treatment of diabetes. *Expert Opin Investig Drugs* 1999;8:1683-707.
21. Kvernmo T, Hartter S, Burger E. A review of the receptor-binding and pharmacokinetic properties of dopamine agonists. *Clin Ther* 2006;28:1065-78.
22. Prescribing information. Cycloset (bromocriptine mesylate). Research Triangle Park, NC: VeroScience LLC; 2009.
23. Available from: <http://www.centerwatch.com/drug-information/fda-approvals/drug-etails.aspx?DrugID=1020>. [Last accessed on 2011 May 1].
24. Scranton RE, Gaziano JM, Cincotta A. Cycloset (bromocriptine mesylate accelerated absorbing) therapy improves glycemic control in type 2 diabetes (T2D) subjects failing thiazolidinedione (TZD) therapy [abstract]. *American Diabetes Association 69th Annual Meeting*; 2009. p. 481.
25. Scranton RE, Gaziano JM, Ruddy D, Ezrokhi M, Cincotta A. A randomized, double-blind, placebo-controlled trial to assess safety and tolerability during treatment of type 2 diabetes with usual diabetes therapy and either Cycloset or placebo. *BMC Endocr Disord* 2007;7:3.

26. Gaziano JM, Cincotta AH, O'Connor CM, Ezrokhi M, Rutty D, Ma ZJ, *et al.* Randomized clinical trial of quick-release bromocriptine among patients with type 2 diabetes on overall safety and cardiovascular outcomes. *Diabetes Care* 2010;33:1503-8.
27. Cincotta AH, Meier AH. Bromocriptine (Ergoset) reduces body weight and improves glucose tolerance in obese subjects. *Diabetes Care* 1996;19:667-70.
28. Pijl H, Ohashi S, Matsuda M, Miyazaki Y, Mahankali A, Kumar V, *et al.* Bromocriptine: A novel approach to the treatment of type 2 diabetes. *Diabetes Care* 2000;23:1154-61.
29. Aminorroaya A, Janghorbani M, Ramezani M, Haghghi S, Amini M. Does bromocriptine improve glycemic control of obese type-2 diabetics? *Horm Res* 2004;62:55-9.
30. Wasada T, Kawahara R, Iwamoto Y. Lack of evidence for bromocriptine effect on glucose tolerance, insulin resistance, and body fat stores in obese type 2 diabetic patients. *Diabetes Care* 2000;23:1039-40.
31. Kamath V, Jones CN, Yip JC, Varasteh BB, Cincotta AH, Reaven GM, *et al.* Effects of a quick-release form of bromocriptine (Ergoset) on fasting and postprandial plasma glucose, insulin, lipid, and lipoprotein concentrations in obese nondiabetic hyperinsulinemic women. *Diabetes Care* 1997;20:1697-701.
32. Meier AH, Cincotta AH, Lovell WC. Timed bromocriptine administration reduces body fat stores in obese subjects and hyperglycemia in type II diabetics. *Experientia* 1992;48:248-53.
33. Zhang Y, Cincotta AH. Inhibitory effects of bromocriptine on vascular smooth muscle cell proliferation. *Atherosclerosis* 1997;133:37-44.
34. Franchi F, Lazzeri C, Barletta G, Ianni L, Mannelli M. Centrally mediated effects of bromocriptine on cardiac sympathovagal balance. *Hypertension* 2001;38:123-9.
35. Liang Y, Cincotta AH. Increased responsiveness to the hyperglycemic, hyperglucagonemic and hyperinsulinemic effects of circulating norepinephrine in ob/ob mice. *Int J Obes Relat Metab Disord* 2001;25:698-704.
36. Kalra S. Bromocriptine: A Revolution in Diabetes Care? *Int J Clin Case Investig* 2010;1:2.
37. Das AK, Kalra S. Bromocriptine in diabetes management: Knowledge and attitudes of Indian physicians. *Int J Clin Case Investig* 2011;2:5.

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