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Bromocriptine — an old drug in a new formulation for the effective treatment of type 2 diabetes

Bromokryptyna — stary lek w nowej formule skutecznym sposobem leczenia cukrzycy typu 2

ABSTRACT

Quick-release bromocriptine mesylate was approved by the Food and Drug Administration (FDA) in May 2009, for the treatment of type 2 diabetes (T2DM). The quick-release formulation of bromocriptine (bromocriptine-QR; Cycloset) represents a novel therapeutic option in T2DM by targeting centrally mediated pathways of glucose metabolism, effecting in reducing plasma glucose, triglycerides, free fatty acid (FFA) levels and eventually cardiovascular events. Randomized controlled trials have shown that bromocriptine-QR lowers glycated hemoglobin by 0.4––0.8% either as monotherapy or in combination with other anti-diabetes medications. Bromocriptine-QR mechanism of action, unique formulation, clinical efficacy and safety, proves it to be a great alternative to current treatments for type 2 diabetes. (Diabet. Prakt. 2011; 12, 5: 175–179)

Key words: bromocriptine, quick release formulation, diabetes, insulin resistance, cardiovascular risk

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Introduction

Despite continual technical progress diabetes remains an as of yet unsolved problem both in the developing and Western worlds. Although the earliest reports mentioning diabetes date from ancient times, it is only in the recent centuries that it has become a serious health issue, and nowadays type 2 diabetes is a growing global pandemic. According to the World Health Organization 346 million people worldwide have diabetes and it is estimated that it will afflict approximately 350 million people by the year 2030 [1, 2].

Our modern lifestyle, changes in eating habits and a decrease in physical activity, together with the related increase in obesity have all contributed to the rise of this pandemic.

Type 2 diabetes (T2DM) 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, and inadequate pancreatic insulin secretion [3].

Once the underlying pathophysiology of T2DM was known various oral hypoglycemic agents had been administered to type-2 diabetic patients to normalize their plasma glucose concentrations, but restoration of normoglycemia is difficult to achieve and requires multiple antidiabetic medications with different mechanisms of action, used in combination to produce a combined effect [4].

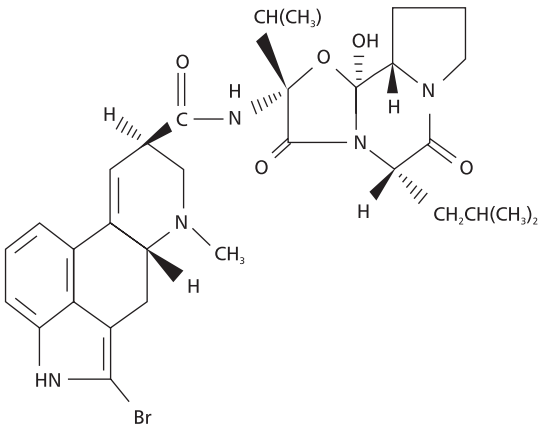

Figure 1. Structure of bromocriptine

There is a clear need for new therapies to treat type 2 patients, that would restore normoglycemia without causing weight gain or hypoglycemia.

Food and Drug Administration approval for bromocriptine mesylate

Nowadays a large number of antidiabetes drugs are available on the market, joined most recently by bromocriptine.

On May 5, 2009, the Food and Drug Administration (FDA), approved bromocriptine mesylate 0.8-mg tablets (*Cycloset*; VeroScience, LLC [marketed with S2 Therapeutics, Inc]) as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus [5].

Bromocriptine is a dopamine D_2 and D_3-agonist which works by activating postsynaptic dopamine receptors in the tuberoinfundibular and nigrostriatal pathways (Figure 1). It also inhibits the secretion of prolactin from the anterior pituitary and is used in the treatment of prolactinoma and in endocrinological disorders [6]. Bromocriptine has been used worldwide for over 20 years to treat Parkinson's disease, macroprolactinoma and other disorders and it has been found to be generally safe.

The quick-release formulation of bromocriptine (bromocriptine-QR; Cycloset) represents a novel therapeutic option in T2DM by targeting centrally mediated pathways of glucose metabolism, with the effect of reducing plasma glucose, triglycerides, Free Fatty Acid (FFA) levels and as a result cardiovascular events [4].

This new 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 postprandial plasma glucose levels, due to the enhanced suppression of hepatic glucose production [7].

Mechanism of action

Seasonal metabolic changes characteristic of migrating birds and hibernating animals were behind the initial idea for using bromocriptine for the treatment of type 2 diabetes. During this period of food shortage these creatures change their metabolism from an insulin-sensitive/glucose-tolerant state to an insulin-resistant/glucose-intolerant state [7]. During transition to the insulin-resistant state, basal lipolytic activity increases to spare glucose utilization by peripheral (muscle) tissues, fat oxidation becomes predominant, and hepatic glucose production and gluconeogenesis rise to supply glucose to the CNS during prolonged periods (seasons) of food deprivation [8, 9]. At the end of the season, these animals revert back to their insulin-sensitive/glucose-tolerant phase and become lean.

These changes are mediated in part by dopaminergic and serotonergic neurotransmitter activity, with reduced dopaminergic and enhanced serotonergic activity and are believed to be responsible for the obese/IR phenotype [10–12]. 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) [7, 13].

These neurogenic and metabolic changes are consistent with the so called "thrifty gene" hypothesis. Thrifty genes are genes which enable individuals to efficiently collect and process food to deposit fat during periods of food shortage. Conversion to the obese, insulin-resistant state provides a survival advantage. Such development of the insulin-resistant state during these periods of seasonal change precisely mimics the type 2 diabetic and the insulin-resistance syndrome: insulin resistance in muscle and liver, accelerated hepatic glucose production/gluconeogenesis, hyperglycemia, adipocyte insulin resistance and increased lipolysis, enhanced fat oxidation, increased plasma FFA and triglyceride levels, and obesity [7, 14, 15].

Type 2 diabetic patients tend to have an early morning dip in the dopaminergic tone, which leads to increased sympathetic activity [16]. In non-obese, normal, glucose-tolerant, insulin-sensitive individuals, the plasma prolactin concentrations peak at night, during sleep. On the other hand obese insulin-resistant individuals have elevated (two-fold)

Table 1. QR Bromocriptine mechanism of action versus diabetes type 2 status

Type 2 diabetes	QR bromocriptine
↓ Dopaminergic tone → ↑ Sympathetic activity	↑ Hypothalamic dopamine
↑ Plasma glucose	↓ Insulin resistance
↑ Free fatty acid levels (FFA) levels	Improves glycemic control and dyslipidemia
↑ Triglycerides	↓ Free fatty acid levels (FFA) levels

day time plasma prolactin levels [17] consistent with a reduced dopaminergic tone.

Bromocriptine mesylate is a sympatholytic dopamine D2 receptor agonist that effects are mediated via resetting of dopaminergic and sympathetic tone within the central nervous system (CNS) [13]. When administered in the early morning at the start of the light phase, a new quick release (QR) formulation of bromocriptine appears to act centrally to reset circadian rhythms of hypothalamic dopamine and serotonin and improve insulin resistance [9], as well as glycemic control and dyslipidemia — without change in body weight in type 2 diabetic and obese nondiabetic humans [17, 18]. Bromocriptine seems to work as a powerful tool, reversing the unnaturally elevated hypothalamic drive for increased plasma glucose, triglycerides, and free fatty acid levels, in fasting and postprandial states in insulin-resistant patients [4] (Table 1).

Posology

FDA approved bromocriptine mesylate 0.8-mg tablets may be used as monotherapy or as adjunctive therapy to sulfonylurea, metformin/sulfonylurea, and single or dual oral hypoglycemic agent therapies.This drug has been developed by Vero Science Inc, under the trade name Cycloset [5]. Cycloset differs from traditional bromocriptine formulations, such as Parlodel, in its quick release that provides peak concentrations within 60 min. The starting dose is 0.8 mg/day and can be titrated to a maximum of 4.8 mg/day. Cycloset is administered as a once daily dose within 2 h of awaking and it reduces the elevated prolactin levels [17, 19, 20] and is thought to restore dopaminergic activity. 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. Adverse events associated with the use of Cycloset may include: nausea, dizziness, fatigue, headache, vomiting, diarrhoea and constipation.

It should not be used to treat type-1 diabetes or diabetic ketoacidosis. There is limited efficacy data in combination with thiazolidinediones and efficacy has not been confirmed in combination with insulin [21]. The drug is contraindicated in patients with known hypersensitivity to bromocriptine or ergot-related drugs. It is also contraindicated in patients with syncopal migraine. Bromocriptine increases the likelihood of a hypotensive episode among patients with syncopal migraine. Loss of consciousness during migraine may reflect dopamine receptor hypersensitivity. Bromocriptine is a dopamine receptor agonist, and may, therefore, potentiate the risk for syncope in these patients [21, 22]. It is also contraindicated in nursing women as Bromocriptine may inhibit lactation.

CYCLOSET trials

The CYCLOSET safety trial was a 52-week, placebo-controlled study that included patients treated only with diet therapy or with other anti-diabetic medications. A total of 3,070 patients were randomized to CYCLOSET (titrated to 1.6 to 4.8 mg daily, as tolerated) or a placebo. The study population had a mean baseline age of 60 years (range 27–80) and 33% were 65 years of age or older. The mean baseline body mass index was 32 kg/m^2. The mean duration of diabetes at baseline was 8 years and the mean baseline HbA_{1c} was 7.0% with a mean baseline fasting plasma glucose of 142 mg/dL. At baseline, 12% of patients were treated with diet only, 40% were treated with one oral anti-diabetic agent, 33% were treated with two oral anti-diabetic agents, and 16% were treated with insulin alone or insulin in combination with an oral anti-diabetic agent. At baseline, 76% of patients reported a history of hypercholesterolemia, 75% reported a history of hypertension, 11% reported a history of revascularization surgery, 10% reported a history of myocardial infarction, 10% reported a history of angina, and 5% reported a history of stroke. Forty-seven percent of the CYCLOSET-treated patients and 32% of the placebo-tre-

ated patients prematurely discontinued treatment. 24% of the CYCLOSET-treated patients and 15% of the placebo-treated patients discontinued the study due to adverse events. This between-group difference was driven mostly by gastrointestinal adverse events, particularly nausea [21].

Bromocriptine is the first drug for treatment of diabetes to be approved under the FDA's new guidelines where no increased cardiovascular risk could be reported in clinical trials [23, 24].

In the above mentioned 52-week, double-blind, placebo-controlled safety trial, treatment with quick-release formulation of bromocriptine did not increase the risk of a composite of myocardial infarction, stroke, hospitalization for unstable angina, congestive heart failure, and revascularization surgery (hazard ratio, 0.58; 95% confidence Interval, 0.35–0.96).

The incidence of the above was 1.5% among patients receiving bromocriptine and 3% among patients receiving placebo. Bromocriptine reduces the incidence of diabetic cardiovascular complications in patients with type-2 diabetes and improves glycemic control in those patients who did not achieve HbA_{1c} of less than 7.5% with metformin plus a sulfonylurea [4, 25].

Another large, randomised, double-blind placebo-controlled study was conducted in which Ergoset (Ergo Science Corporation product) was given once daily at 8 am up to 4.8 mg maximum dose for 24 weeks as adjunctive therapy to sulphonylurea (485 subjects) to obese Type 2 diabetics held on a weight- maintaining diet. Treatment efficacy parameters included change from baseline in glycated haemoglobin A(1c) (HbA_{1c}), fasting and postprandial serum glucose, insulin, triglyceride and free fatty acid levels. Baseline glycated haemoglobin, fasting glucose, insulin, triglyceride and free fatty acid levels did not differ between treatment groups and on average were 9.4 +/– 0.05%, 222 +/– 2 mg/dl, 24 +/– 1 μU/ml, 248 +/– 11 mg/dl, and 850 +/– 32 μEq/l, respectively. A similarly designed study of Ergoset as monotherapy in Type 2 diabetics (154 subjects) with similar baseline clinical characteristics was conducted. Addition of Ergoset treatment to sulphonylurea reduced percent glycated HbA_{1c} by 0.55 ($p < 0.0001$) (approximately 1.0 for responders, 65% of population), fasting and postprandial glucose by 23 and 26 mg/dl ($p < 0.0002$), fasting and postprandial triglycerides by 72 and 63 mg/dl ($P < 0.005$) and fasting and postprandial free fatty acids by 150 and 165 μEq/l ($p < 0.05$), relative to placebo. Twelve percent of all Ergoset subjects, compared to 3% of placebo subjects, withdrew from the study due to adverse events. The most common events causing withdrawal were nausea, dizziness, asthenia, and rhinitis (representing 4.5, 3.3, 2.0, and 0.8% of the total Ergoset populations, respectively). The incidence of serious adverse events did not differ between Ergoset- (3.4%) and placebo- (4.3%) treated subjects. Ergoset as monotherapy also improved glycaemic control (0.56 HbA_{1c} decrease relative to placebo after 24 weeks of treatment; $p < 0.02$). Once daily Ergoset treatment improves glycaemic control and serum lipid profile and is well-tolerated in obese Type 2 diabetics [17].

Other advantages of Cycloset include: absence of hypoglycemia (since insulin secretion is not stimulated); weight neutrality; elimination of the need for dose adjustment in patients with moderate renal insufficiency; lack of edema and congestive heart failure, and good side effect profile [17].

Ongoing study commitments

- VeroScience has agreed to a deferred pediatric feasibility study: A Randomized, Double-Blind, Controlled Study To Assess the Use and Effectiveness of Cycloset in Children Aged 10 to 16 With a Diagnosis of Type 2 Diabetes Mellitus
  Final Protocol Submission Date: No later than November 30, 2010, Study Completion Date: No later than October 31, 2012, Final Study Report Submission Date: No later than March 31, 2013
- VeroScience has agreed to a deferred clinical efficacy and safety study: A Pivotal, Randomized, Double-Blind, Controlled, Efficacy and Safety Study of the Use of Cycloset for the Treatment of Type 2 Diabetes Mellitus in Children Aged 10––16 years with a Diagnosis of Type 2 Diabetes Mellitus *Final Protocol Submission Date: No later than August 31, 2013, Study Completion Date: No later than February 28, 2015, Final Study Report Submission Date: No later than July 31, 2015*

Conclusions

Despite proven efficacy of bromocriptine and its unique mechanism of action, this drug is not generally prescribed to type 2 diabetic patients since there is not enough documented evidence supporting its general use — possibly due to it being unregistered for use in diabetes in the European Union including Poland. This is in contrast to extensive research and marketing of new anti-diabetic drugs such as GLP analogues, DPP-4 inhibitors and Sodium-glucose transporter-2 inhibitors (SGLT2). Detailed studies of bromocriptine would identify

the patients who would most benefit from its unique mechanism of hypoglycemic action.

Nevertheless the outcomes of ongoing trials remain pending despite our hope that it will be approved for the European Union market.

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