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Published Version
doi:10.1155/2015/834903

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Clinical Study

Impact of Bromocriptine-QR Therapy on Glycemic Control and Daily Insulin Requirement in Type 2 Diabetes Mellitus Subjects Whose Dysglycemia Is Poorly Controlled on High-Dose Insulin: A Pilot Study

Erin D. Roe, 1 Bindu Chamarthi, 2 and Philip Raskin 1

1 University of Texas Southwestern Medical Center, Dallas, TX 75235, USA
2 Brigham and Women’s Hospital and Harvard Medical School, Boston, MA 02115, USA

Correspondence should be addressed to Bindu Chamarthi; bchamarthi@partners.org

Received 30 January 2015; Accepted 28 March 2015

Academic Editor: Bernard Portha

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Background. The concurrent use of a postprandial insulin sensitizing agent, such as bromocriptine-QR, a quick release formulation of bromocriptine, a dopamine D2 receptor agonist, may offer a strategy to improve glycemic control and limit/reduce insulin requirement in type 2 diabetes (T2DM) patients on high-dose insulin. This open label pilot study evaluated this potential utility of bromocriptine-QR.

Methods. Ten T2DM subjects on metformin (1-2 gm/day) and high-dose (TDID ≥ 65 U/day) basal-bolus insulin were enrolled to receive once daily (morning) bromocriptine-QR (1.6–4.8 mg/day) for 24 weeks. Subjects with at least one postbaseline HbA1c measurement (N = 8) were analyzed for change from baseline HbA1c, TDID, and postprandial glucose area under the curve of a four-hour mixed meal tolerance test (MMTT).

Results. Compared to the baseline, average HbA1c decreased 1.76% (9.74±0.56 to 7.98±0.36, P = 0.01), average TDID decreased 27% (199±33 to 147±31, P = 0.009), and MMTT AUC 60–240 decreased 32% (P = 0.04) over the treatment period. The decline in HbA1c and TDID was observed at 8 weeks and sustained over the remaining 16-week study duration. Conclusion. In this study, bromocriptine-QR therapy improved glycemic control and meal tolerance while reducing insulin requirement in T2DM subjects poorly controlled on high-dose insulin therapy.

1. Introduction

Maintenance of good glycemic control in type 2 diabetes mellitus (T2DM) patients typically becomes progressively more difficult as the duration of disease lengthens as a result of continuing decline in the capacity of the pancreatic beta cells for appropriate glucose stimulated insulin release, in the presence of insulin resistance [1, 2]. While hyperglycemia in patients with T2DM may be initially managed with oral antidiabetes medications alone, added insulin therapy often becomes necessary with longer duration of disease. This progressive decline in beta cell function amidst a background of insulin resistance, which can be severe in many T2DM patients, particularly with the common concomitant presence of obesity, ultimately results in the need for high doses of insulin in many such patients. While insulin is an effective treatment for hyperglycemia, it carries the potential for undesirable side effects such as hypoglycemia and weight gain, which in turn can lead to a worsening ability to manage diabetes [3–8]. Moreover, chronic high-dose insulin therapy can be difficult to manage from a practical perspective, with inherent challenges related to administration of large doses of insulin, multiple injections, and large volume injections (which could interfere with absorption of the insulin, thus leading to submaximal effect of the administered insulin dose and also adversely impacting patient comfort and compliance) [8–11]. A plausible approach to treating such patients with poor beta cell function and on high-dose daily insulin may be the use of an agent with unique insulin sensitizing properties to improve glycemic control and concurrently reduce the daily insulin requirement. However, the available options for such insulin sensitizing agents that are
safe and effective are very limited. The insulin sensitizers, pioglitazone, has been demonstrated to improve glycemia in insulin-requiring T2DM patients [12–15]; however use of this agent in this setting is associated with significant increased risk for congestive heart failure in addition to weight gain and edema [15–20]. Alternatively, circadian-timed, morning administration of bromocriptine-QR, a quick-release, high absorbing formulation of a potent dopamine D2 receptor agonist, that is approved in the US for the treatment of T2DM appears to be a unique insulin sensitizing therapy with a good safety profile, without risk of weight gain or hypoglycemia and with a potential to reduce adverse cardiovascular risk [21–23]. Available evidence suggests that bromocriptine-QR is a postprandial-weighted insulin sensitizer, promoting glucose disposal following a meal, oral glucose tolerance test, or hyperglycemic-euglycemic clamp [24–27]. Several neurophysiological studies have implicated a role for a diminished circadian peak of dopaminergic activity at the biological clock (suprachiasmatic nucleus [SCN] of the hypothalamus) in the development of insulin resistance [28–34]. Timed bromocriptine-QR administration to restore this diminished circadian peak of dopaminergic activity improves insulin sensitivity [24–27]. Preclinical studies suggest that such effects are mediated via a circadian-time-dependent effect to ameliorate aberrations in hypothalamic activities that potentiate insulin resistance and loss of appropriate fuel sensing mechanisms [28–34]. In humans, this daily peak central dopaminergic activity is believed to occur in the morning circa awakening and to be diminished in T2DM [24, 35]. Consequently, we hypothesized that an additive or supra-additive interaction may exist between bromocriptine-QR and basal plus prandial insulin therapy, with bromocriptine-QR providing the enhanced responsiveness to the exogenous prandial insulin therapy to produce greater postprandial blood glucose lowering with lower insulin requirement. We therefore explored in a small open label pilot study the potential utility of morning bromocriptine-QR therapy to improve glycemic control and daily insulin requirement in T2DM subjects on high-dose (≥65 U/day) insulin therapy that incorporates a prandial insulin administration.

2. Methods

2.1. Subjects and Study Design. Ten subjects with T2DM treated with high-dose insulin [total daily insulin dose (TDID) ≥ 65 units/day] and metformin (1-2 g in divided doses) were recruited from the outpatient primary care and diabetes clinics at Parkland Memorial Hospital or through self-referral at the Clinical Diabetes Office at the University of Texas Southwestern Medical Center in Dallas, TX, and assigned to bromocriptine-QR therapy (see below for dosing regimen). Patients between ages 30 and 65 years with the clinical diagnosis of T2DM on multiple daily injections of insulin (MDI insulin) plus metformin and HbA1c between 7.5 and 12.0% were eligible. Major exclusion criteria for study participation were pregnancy, lactation, type 1 diabetes, elevated serum creatinine over 1.5 mg/dL, elevated liver function tests above 3-fold the upper limit reference range, and a recent history of substance abuse. In addition, patients with a risk of hypotension, recent blood donation in the past 30 days, syncopal migraines, gastroparesis, autonomic neuropathy, hypoglycemia unawareness, uncontrolled mental illness and/or psychosis, and variable sleep patterns (e.g., shift workers) were excluded. Five additional patients with similar demographics as the bromocriptine-QR treated group were recruited under the same study protocol only as a reference for glycemic control achievable only by increasing insulin dose (i.e., absent bromocriptine-QR therapy). In this pilot study design, this reference group was not randomized nor placebo-treated nor able to serve as an active comparator for efficacy due to allowance of insulin dose change during the study and of too small N to serve as a control group for noninferiority testing. The study protocol was approved by the institutional review board (IRB) of the University of Texas Southwestern Medical Center, Dallas, TX, and all participants provided written informed consent prior to enrollment. The study protocol was registered with ClinicalTrials.gov (Identifier: NCT01474018).

2.2. Treatment Paradigm. Patients continued baseline treatment with metformin (1-2 gm in divided doses) and MDI insulin (either premixed human 70/30 insulin twice daily or basal-bolus regimen with basal insulin glargine [rDNA origin; Lantus, Sanofi, Paris, France] and insulin aspart [rDNA origin; Novolog, Novo Nordisk, Bagsvaerd, Denmark] at each meal). Bromocriptine-QR was titrated weekly according to a schedule used in previous studies and detailed on the FDA-approved package insert; 1 tablet (0.8 mg) is taken within 2 hours of waking for the first week and each week thereafter; an additional tablet is added until a maximum tolerated dose of two to six tablets (1.6 to 4.8 mg, resp.) during week six was achieved. Patients were contacted by phone each week during the titration period to inquire about hypoglycemia and potential side effects, primarily nausea, headache, and dizziness. If intolerable side effects were encountered, the patient was instructed to reduce the dose to the highest previously tolerated dose and continue taking this dose through the remainder of the 24-week trial. Metformin dose was held constant. Insulin was titrated according to good clinical practice to target an HbA1c ≤ 7.0%, while minimizing hypoglycemia.

2.3. Measurements. HbA1c levels and total daily insulin dose requirements were assessed at enrollment and weeks 8, 16, and 24. HbA1c was measured using high performance liquid chromatography in the UTSW Clinical Diabetes Laboratory. At baseline and week 24, a four-hour mixed meal tolerance test (MMTT) was performed in the fasting state with antidiabetic treatments withheld prior to and during the MMTT to evaluate the impact of bromocriptine-QR therapy upon fasting and postprandial blood glucose levels. Antidiabetes medications were withheld prior to and during the MMTT to assess the impact of bromocriptine-QR on endogenous insulin-mediated glucose disposal without interference/confounding of results from a potentially changed exogenous insulin dose requirement during the study period. A four-hour challenge was selected to better quantify
the glucose profile which does not normalize within 3 hours in patients with T2DM. A mixed carbohydrate/fat meal was simulated with Boost concentrate 1 gm/kg carbohydrate equivalent ingested over 5 minutes. Glucose levels were measured at 0, 15, 30, 60, 90, 120, 150, 180, and 240 minutes following ingestion. The area under the curve (AUC) for postprandial glucose response [total (0–240 minutes) and postabsorptive (60–240 minutes)] was calculated.

2.4. Statistics. Statistical analyses were performed to assess within group pre- versus posttreatment differences. Analyses of the study endpoints used the modified intention-to-treat population of subjects defined as those having at least one postinitiation HbA1c data point utilizing the last observation carry forward method for missing data. Statistical analyses were performed using SPSS Version 19.0 (Armonk, NY: IBM Corp.). The change over time in the HbA1c level and the total daily insulin dose requirement were analyzed by repeated measures analysis of variance (ANOVA). Paired, two-tailed t-tests were performed for pre- versus post-8- and 24-week comparisons of HbA1c, total daily insulin dose requirement, and the 24-week AUC of postprandial (0–240 and 60–240 minutes) blood glucose during the MMTT. Statistical significance was accepted at the $P < 0.05$ level. Data are presented as mean and standard error of the mean (SEM).

3. Results

Of the 10 subjects recruited, two withdrew consent prior to the first HbA1c data point assessment and a third patient was lost to follow-up after the week 8 visit assessment, while on 1.6 mg/day of bromocriptine-QR. Seven subjects completed the study. Of the seven subjects that completed the study, five achieved the maximum bromocriptine-QR dose of 4.8 mg daily and 2 subjects stopped dose titration at 1.6 mg daily due to nausea and headaches and continued this dose for the duration of the study. Statistical analyses were performed on the 8 subjects with a postinitiation HbA1c value. All 5 patients in the reference group completed the study. The study subjects were predominantly black and Hispanic and obese. The baseline demographics of the study subjects are displayed in Table 1. There was an overall significant decrease in HbA1c ($P = 0.004$, ANOVA) (Figure 1(a)) and total daily insulin dose ($P = 0.001$, ANOVA) (Figure 1(b)) over the 24-week bromocriptine-QR treatment period. Following 24 weeks of bromocriptine-QR therapy, the average HbA1c decreased by 1.76% compared to the baseline (from 9.74±0.56 to 7.98±0.36, $P = 0.01$) (Figure 1(a)). Two of the 8 patients achieved an HbA1c less than 7.0% (from 8.3% to 6.9% and 11.3 to 6.7%, resp.). Furthermore, this improvement in HbA1c was accompanied by a concurrent reduction in the average daily insulin requirement by 27% (TDID from 199±33 to 147±31, $P = 0.009$) (Figure 1(b)). The decline in HbA1c and in the TDID were observed at 8 weeks of treatment with average Alc decreasing by 1.86% (from 9.74±0.56 to 7.88±0.29, $P = 0.01$) with a concurrent 28.6% reduction in average daily insulin requirement (TDID from 199 ± 33 to 142 ± 27, $P = 0.01$) and were sustained over the remaining 16-week study duration (Figures 1(a) and 1(b)). The bromocriptine-QR induced improvement in HbA1c was associated with a significant reduction in mixed meal tolerance test postprandial glucose AUC tested during the postabsorptive phase (AUC$_{60-240}$, 32% reduction, $P = 0.04$) (Figure 2). The MMTT AUC$_{0-240}$ also showed a trend of reduction in glucose levels that approached but did not achieve statistical significance (29% reduction, $P = 0.057$). There was no significant difference from baseline in the fasting glucose checked at initiation of the MMTT (conducted in the absence of any antidiabetes medications on the day of testing) (fasting glucose 243±31 mg/dL at baseline versus 229±16 mg/dL at 24 weeks).

In contrast, in the reference group, where the treat-to-target goal could be achieved only by raising the insulin dose, a nonstatistically significant 1.08% Alc drop from baseline (from 9.68±0.74 to 8.6±0.62; $P = 0.19$) with no change in fasting or postprandial glucose response during the mixed meal tolerance test was observed over the 24-week study period, while subjects increased the average total daily insulin dose by 26% from 105±41 to 135±49 units.

4. Discussion

This pilot study is the first demonstration of an effect of morning bromocriptine-QR therapy to improve glycemic control while enabling a reduction in total daily insulin dose requirement in T2DM subjects whose glycemia was inadequately controlled (HbA1c > 7.5%) on metformin plus high-dose (TDID insulin ≥ 65 units/day) MDI insulin therapy. Addition of bromocriptine-QR therapy to high-dose basal plus prandial insulin regimens resulted in a significant 1.76% HbA1c reduction with a concurrent 27% reduction in daily insulin dose requirement. Such a response to bromocriptine-QR was also coupled to a 32% improvement in the MMTT glucose levels conducted in the absence of any insulin dosing. Contrariwise, increasing the daily insulin dose by 26% from 105 to 132 U/day was without significant

<table>
<thead>
<tr>
<th>Table 1: Baseline demographics of the study subjects.</th>
<th>Bromocriptine-QR treatment group ($N = 8$)</th>
<th>Reference group ($N = 5$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>46 ± 3</td>
<td>54 ± 3</td>
</tr>
<tr>
<td>Gender (% female)</td>
<td>88</td>
<td>40</td>
</tr>
<tr>
<td>Race</td>
<td>63% B; 25% H; 12% W</td>
<td>60% B; 40% H; 0% W</td>
</tr>
<tr>
<td>Weight (lbs)</td>
<td>252.3 ± 20</td>
<td>227.2 ± 17.4</td>
</tr>
<tr>
<td>BMI</td>
<td>46.2 ± 5.9</td>
<td>37.1 ± 5.3</td>
</tr>
<tr>
<td>Duration of diabetes (years)</td>
<td>13.7 ± 2.2</td>
<td>12.6 ± 3.5</td>
</tr>
<tr>
<td>HbA1c</td>
<td>9.74 ± 0.56</td>
<td>9.68 ± 0.74</td>
</tr>
<tr>
<td>Total daily dose of insulin (units)</td>
<td>199 ± 33</td>
<td>105 ± 41</td>
</tr>
</tbody>
</table>

*Mean does not include one double amputee subject. B: black; H: Hispanic; W: white; BMI: body mass index.*
improvement in glycemic control in the reference group. Although not specifically tested, these findings support a potential insulin sensitizing effect of bromocriptine-QR in this subject population, which is in agreement with previous preclinical and clinical studies suggesting a postprandial-weighted insulin sensitizing effect of this therapy [24–27, 36, 37]. It should be noted that, in the present study, the MMTT was conducted in the absence of any antidiabetes agent including insulin on the day of the test. Given previous study results demonstrating bromocriptine-QR’s effect to improve postprandial insulin sensitivity, its effect on the MMTT would be expected to have been even greater if conducted in the presence of exogenously administered prandial insulin even at its reduced dose after 24 weeks of bromocriptine-QR therapy. In agreement with the present findings and this tenet are the observations that timed bromocriptine therapy improved maximally insulin stimulated glucose disposal during a euglycemic-hyperinsulinemic clamp in severely insulin resistant T2DM subjects on oral antidiabetes agents [25]. Moreover, in insulin resistant animals, the effect of exogenous insulin administration on glucose disposal and glucose tolerance AUC glucose and insulin were each markedly enhanced in animals pretreated with timed daily bromocriptine administration for a two-week period. Such bromocriptine-QR treatment in animals also improves glucose disposal during a hyperglycemic-hyperinsulinemic clamp [26, 27, 36, 37]. By extension, combination of bromocriptine-QR therapy with prandial insulin secretagogues, such as the incretin-mimetics, may also produce similar additive or supra-additive effects as indicated in preclinical studies [38].

Available evidence suggests that timed bromocriptine therapy improves insulin sensitivity and dysglycemia by correcting hypothalamic activity aberrations that potentiate insulin resistance ([30], reviewed in [31]). In normal insulin sensitive states, hypothalamic fuel sensing neurons detect the meal-associated rise in plasma and brain levels of glucose and free fatty acids and, via the neuroendocrine axis, send signals to the peripheral tissues to improve insulin-stimulated glucose disposal, reduce hepatic glucose output, and reduce adipose tissue lipolysis [39–43]. However, in insulin resistant states, such hypothalamic fuel sensing is diminished and consequently these hypothalamic directed responses to produce the above effects in the periphery are also diminished. Resultantly, such hypothalamic aberrations are causative in the insulin resistance and contribute to postprandial hyperglycemic dysglycemia. Importantly, recent studies indicate

Figure 1: Effect of bromocriptine-QR therapy on HbA$_1c$ (Panel (a)) and total daily insulin dose (TDID) (Panel (b)) over 24 weeks in subjects on metformin plus high-dose basal-bolus insulin therapy at baseline.

Figure 2: Effect of bromocriptine-QR therapy on mixed meal tolerance test postprandial glucose area under the curve (AUC) over 24 weeks in subjects on metformin plus high-dose basal-bolus insulin therapy at baseline.
a role for diminished hypothalamic dopaminergic activity in such aberrant hypothalamic fuel sensing [28, 30, 31, 34, 36, 37, 44–46].

Neurophysiological studies of hypothalamic regulation of fuel metabolism in normal and insulin resistant states indicate that central dopaminergic activities modulate insulin sensitivity as follows. In insulin resistant states, the normal daily peak in dopaminergic activity at the biological clock (hypothalamic SCN) is diminished and reinstating this peak with systemic, central, or direct (to the SCN itself) dopaminergic agonist reverses the insulin resistance ([28, 36, 37, 44–45], Cincotta and Luo unpublished data). It has been observed that such reductions in hypothalamic dopaminergic activity in insulin resistant states are coupled to elevations of noradrenergic and serotonergic activities at the ventromedial hypothalamus (VMH) and elevated Neuropeptide Y and corticotropin releasing hormone levels at the hypothalamic paraventricular nucleus (PVN), in which neurophysiological alterations have been shown to markedly potentiate insulin resistance in part via a concurrent loss of appropriate hypothalamic fuel sensing (as discussed above) and an elevation of sympathetic tone in the periphery [30–34, 46]. Timed daily administration of bromocriptine to reestablish the daily peak in SCN dopaminergic activity also reverses the VMH and PVN abnormalities described above [30, 37, 46] and improves postprandial insulin resistance (even via its intracerebroventricular administration) [26, 30, 45]. Additionally, a large and growing body of evidence implicates functional roles for decreased mesolimbic dopamine activity in the onset of insulin resistance [47–52] and this neural center is also under the influence of the SCN (reviewed in [53]). Restoration of the circadian peak in central nervous system (hypothalamic) dopaminergic neuronal activity may represent a potential therapeutic target to improve glycemic control in T2DM patients requiring high-dose basal-bolus insulin therapy.

Limitations of this study include the small sample size and no direct measure of insulin sensitivity or beta cell function. However, the significant findings noted in this small pilot study indicate that a trial with a larger sample size and assessing beta cell function and insulin sensitivity is warranted.

In conclusion, bromocriptine therapy in T2DM patients on high-dose insulin and with poor glycemic control improved glycemic control and meal tolerance while simultaneously allowing for a reduction in the daily insulin dose requirement.

Conflict of Interests

Dr. Roe and Raskin have no conflict of interests regarding the publication of this paper. Dr. Chamarthi is a consultant to VeroScience, LLC.

Acknowledgments

The study drug (bromocriptine-QR) was provided by VeroScience, LLC. The funding sources for this study were VeroScience, LLC, and S2 Therapeutics Inc.

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