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INFLUENCE OF BROMOCRIPTINE PLUS METFORMIN TREATMENT ON GLYCAEMIA AND BLOOD PRESSURE IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

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Abstract

Background and aims: *Bromocriptine is a dopaminergic (D2) agonist that has shown hypoglycemic and normotensive activity in preclinical and clinical studies. The main objective of this study was to investigate the effect of bromocriptine plus metformin on glycaemia and blood pressure in patients with type 2 diabetes mellitus (T2DM).* ***Material and methods:*** *An open-label randomised controlled trial was conducted for three months. It involved two groups (n=10), each containing 2 women and 8 men with an average age of 50 years. One group was given monotherapy (MT) with metformin (850 mg every 12 h) and the other combined therapy (CT) with the same dose of metformin plus an increasing dose of bromocriptine (from 1.25 mg per day to 2.5 mg per day). The parameters monitored were glycaemia, glycated hemoglobin (HbA1c), serum creatinine, blood pressure, and the body mass index.* ***Results:*** *CT was able to significantly decrease the level of glycaemia, HbA1c and diastolic blood pressure, whereas MT had no effect on any of the measured variables.* ***Conclusions:*** *The ability of CT with bromocriptine and metformin to control glycaemia and produce a normotensive effect reaffirms its advantages for controlling T2DM. Further research is needed to improve this therapeutic strategy.*

key words: *Bromocriptine, type 2 diabetes mellitus, glycaemia, glycated hemoglobin, diastolic blood pressure.*

Background and aims

Type 2 diabetes mellitus (T2DM) is the most common type of diabetes and generally occurs in adults [1]. According to the International Diabetes Federation, there are currently around 415 million people with diabetes worldwide, a figure likely to increase to 642 million by 2040 [2]. In 2015, about 11.5 million people suffered from this disorder in Latin America, representing approximately 9.2% of the total affected population in the world [2]. Mexico is second in

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Latin America and sixth in the world in the prevalence of T2DM [3], which has a high morbidity and mortality due to complications like renal failure, blindness, amputations, cardiovascular disease and cerebrovascular events [1].

Initial pharmacological treatment of T2DM is with oral hypoglycemic drugs (OHDs). In developing countries, the biguanide family of pharmaceuticals is most commonly used as an OHD [4,5]. One member of this class of drugs, metformin (ME), represents the first-line therapy because of its capacity to diminish hepatic glucose production and insulin resistance [6,7].

On the other hand, the Food and Drug Administration (FDA) approved bromocriptine (BROMO) in 2009 for control of glycaemia in T2DM patients. This drug is a systemic dopamine (D2) receptor agonist that resets the circadian peak of the dopaminergic signal and exerts its unique insulin-sensitizing effect by causing a shift in caloric intake [8,9]. However, its exact biochemical mechanisms are unknown. A recent meta-analysis showed that BROMO lowers the level of serum of glycated hemoglobin (HbA1c) and fasting plasma glucose (FPG) without affecting the lipid profile or body mass index (BMI) [10]. Other reports have associated BROMO with a decrease in heart attacks as well as cerebrovascular events, evidencing its importance in reducing the risk of cardiovascular disease [11,12].

Insights into the effects of BROMO has led to a growing recognition of the usefulness of combining this dopaminergic agonist with ME or insulin for the control of T2DM [13,14]. It is necessary to continue exploring the best scheme of such a combined treatment for distinct populations. Hence, the aim of the present study was to examine the effects on glycaemia and blood pressure of T2DM patients in Mexico when administering a combined BROMO + ME treatment (versus a monotherapy with ME).

Material and Methods

Study setting and patients

An open-label randomised controlled trial was carried out at the Integral Hospital "Ángel Albino Corzo" (HIAC). T2DM patients from this institution were screened in case their level of HbA1c was poorly controlled by an OHD.

Inclusion and exclusion criteria

Inclusion criteria consisted of a previous diagnosis of T2DM, a patient age of 30-65 years, the administration of a stable dose of OHD (ME at 2 g per day and/or glibenclamide at 15 mg per day) for at least 3 months immediately before the present study, willingness to stop the previous treatment upon being included in the study, and a recent HbA1c test result over 7.5% [15]. All patients accepted to participate by signing informed consent after receiving a detailed explanation of the nature and benefits of the study. Exclusion criteria were patient refusal, insulin therapy, pregnancy, lactation, a clinically significant comorbid condition, allergy to ergot-related or BROMO drugs, or a history of syncope or psychosis.

Study design

The current protocol was reviewed and approved by the hospital Ethics Committee. Eligible T2DM patients were formed into two groups (n=10). One group was prescribed ME tablets (850 mg, Merck, Mexico) every 12 hours. The other group received ME tablets (at the same dosage) plus BROMO (Novartis, Mexico) at a dose that gradually increased from 1.25 mg to 2.5 mg per day.

As a complementary measure we recommended that patients in both groups carry out 3 or 4 sessions per week of moderate aerobic

physical activity with an average duration of 40 minutes per session [16]. Additionally, all participants received nutrition counselling and education, based on the Mexican official norm for the prevention, treatment and control of diabetes [17].

Both drug schemes were implemented for 3 months, with medical appointments programmed each month to monitor diverse clinical aspects, including an evaluation of adherence to treatment by using the Haynes test [18], the possibility of complications related to the medication, and the monitoring of blood sugar by the determination of the fasting plasma glucose [FPG] level (mg/dL).

At the beginning of the study (before treatments) and at the end of 3 months, an evaluation was made of blood pressure, the HbA1c percentage, serum creatinine (mg/dl), and anthropometric measurements (weight in kg and height in cm) for the calculation of the BMI.

Statistical analysis

The SPSS software (version 22.0) was utilized for analysing all data. The effect of each drug scheme on the FPG level was scrutinized with the Kruskal-Wallis test. The post hoc Tukey was applied to examine the differences between the values from each of the monthly evaluations. The parameters assessed before and after the drug treatments were compared with the paired *t* test. All data are expressed as the mean ± standard deviation (SD), and a confidence interval (CI) of 95% was determined in relation to the results of the initial and final evaluations.

Results

Baseline characteristics

Thirty patients with uncontrolled T2DM were screened. Ten patients were eliminated due to one or more of the exclusion criteria. The other 20 participants gave informed consent and were assigned to a treatment in such a way as to assure similar parameters for the two groups, each of which included 2 women and 8 men who had an average age of 50 years and an average time elapsed after their T2DM diagnosis of under 5 years. The initial determination of the BMI revealed that both groups were overweight, a condition unchanged by the respective treatments (see Table 1).

Table 1. Demographic and anthropometric distribution of the patient population before and after the 3-month treatment.

Variables	Before 3-month treatment N=20		After 3-month treatment N=20	
	MT	CT	MT	CT
Female/ Male	2/8	2/8	2/8	2/8
Age (Y)	50.10 ± 13.47	49.40 ± 20.36	50.50 ± 13.47	49.80 ± 20.36
Duration of diabetes (Y)	4.45 ± 2.03	4.50 ± 2.01	4.85 ± 2.03	4.90 ± 2.01
Height (M)	1.54 ± 0.07	1.56 ± 0.08	1.54 ± 0.07	1.56 ± 0.08
Weight (kg)	65.00 ± 13.95	68.17 ± 17.27	65.33 ± 13.44	67.68 ± 16.69
Body mass index (kg/m^2)	27.38 ± 5.05	28.40 ± 5.57	27.54 ± 4.95	28.34 ± 5.56

Data are expressed as the mean ± standard deviation (SD) of each of the studied variables.
Abbreviations: MT = monotherapy; CT = combined therapy; Y = years; M = metros; kg = kilograms.

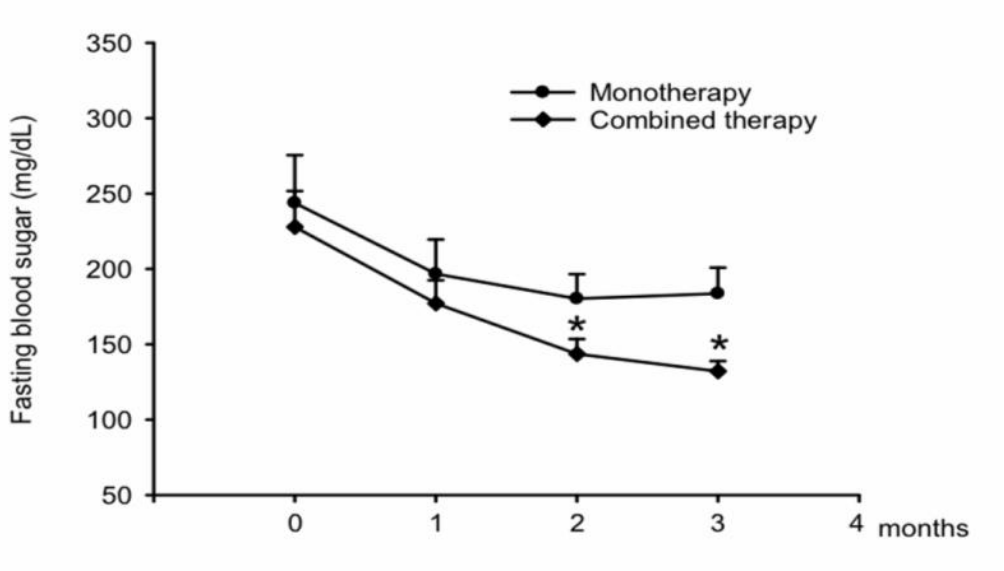

Figure 1. *The mean ± standard error (SE) of the fasting level of glycaemia (mg/dl) during the 3 months of the study, comparing the monotherapy (MT) group with the combined therapy (CT) group. *p<0.05 with respect to the values before treatment.*

Table 2. Metabolic parameters and blood pressure before and after the 3-month treatment.

	Pre-treatment	Post-treatment	Change resulting from treatment [95% IC]	p-value
MT				
Metabolic parameters				
Hemoglobin A_{1C} (% grams)	9.3 ± 1.55	8.7 ± 1.23	↓-0.6 [0.005 - 1.14]	0.05
Serum creatinine (mg/dl)	0.71 ± 0.17	0.77 ± 0.11	↑+0.06 [-0.17 - 0.06]	0.32
Blood pressure				
Systolic blood pressure (mm Hg)	110.0 ± 16.33	113.0 ± 13.37	↑+3[-7.82 - 1.82]	0.19
Diastolic blood pressure (mm Hg)	68.0 ± 7.88	74.0 ± 9.66	↑+6 [-12.91 - 0.91]	0.08
CT				
Metabolic parameters				
Hemoglobin A_{1C} (% grams)	9.0 ± 1.13	8.0 ± 0.78	↓-1.0 [0.08 -1.41]	**0.001**
Serum creatinine (mg/dl)	0.76 ± 0.15	0.76 ± 0.09	[-0.14 -0.14]	1.00
Blood pressure				
Systolic blood pressure (mm Hg)	120.0 ± 21.60	115.0 ± 12.69	↓-5 [-6.80 - 16.80]	0.36
Diastolic blood pressure (mm Hg)	78.0 ± 10.32	69 ± 7.37	↓-9 [1.88 - 16.11]	**0.01**

Data are expressed as the mean ± standard deviation (SD) of each of the studied variables. The numbers marked in bold denote a significant difference when comparing the values of pre- *vs.* post-treatment (the Student's *t* test; p<0.05). Abbreviations: MT = monotherapy; CT = combined therapy.

Whereas the MT did not modify the level of FPG over the four measurement times (Fig. 1; Kruskal-Wallis, H= 9.58; p>0.05), the CT significantly influenced the value of this parameter (Kruskal-Wallis, H= 14.08; p<0.05). In the latter group, the post hoc comparisons showed a significant decrease in the level of glycaemia at the 2nd and 3rd month in relation to

the determination at the beginning of the study (Tukey *p<0.05). During their medical appointments, the participants reported that they either infrequently suffered from nausea, dizziness or constipation, or had no side effects whatsoever resulting from the drug treatments. Overall, the average score for the evaluation of adherence to treatment was 94%.

Post-treatment data

Upon comparing the parameters before and after monotherapy, it can be appreciated that there was no significant change in the HbA1c percentage (t= 2.24; p=0.05), the level of serum creatinine (t= -1.03; p>0.05), or the systolic (t= -1.40; p>0.05) or diastolic blood pressure (t= 1.96; p>0.05).

With CT, a significant reduction was found in the HbA1c percentage (t= 5.47; p<0.001) and in diastolic blood pressure (t= 2.86; p<0.05), whereas the levels of serum creatinine (t=-1.75; p>0.05) and systolic blood pressure (t=0.95; p>0.05) remained unchanged (see Table 2).

Discussion

The adherence of the patients to each of the two treatments was considered adequate, based on the criteria of Haynes [18], which helps rule out a possible bias in the results derived from the administration of MT and CT. The adequate adherence to treatment and the lack of desertion from the present study is in accordance with the scarcity of reports of adverse effects related to a CT that includes BROMO.

On the other hand, the significant decrease in glycaemia and the HbA1c percentage found with this CT treatment confirms the results of some studies with a similar therapeutic scheme [19,20]. However, the average value of HbA1c in the CT group (8%) only approached the optimum level (≤ 7%). The inability to reach the 7% threshold may be related to the short treatment time employed (3 months), taking into account that the duration of the treatment with BROMO was longer in other studies (4-8 months) [20,21].

In agreement with some reports demonstrating the greater vulnerability of T2DM patients to the development of cardiovascular disease [23-26], three participants in each group of the current clinical trial had a diastolic blood pressure ≥ 90 mmHg (data not shown). This reaffirms the importance of following the new guidelines of the American Diabetes Association, whose objective for T2DM patients is to maintain the systolic blood pressure < 140 mmHg and diastolic blood pressure < 90 mmHg [22].

The present hypotensive activity of CT concurred with previous results from BROMO treatment in preclinical as well as clinical trials [27,28]. Such an effect has been explained as the capacity of this dopaminergic agonist to induce a sharp reduction in plasma norepinephrine by means of the interaction of BROMO with the D2 receptors, which are widely distributed in the peripheral nervous system (PNS) [29,30]. Indeed, the hypotensive effect of administering BROMO has been able to diminish the number of deaths due to cardiovascular disorders [11,12,31]. Hence, it is essential to continue investigating the effects of BROMO on the cardiovascular system in order to provide the basis in the not too distant future for including this drug in therapy for some cardiovascular diseases associated with T2DM.

Regarding insulin resistance (IR), this parameter reportedly decreases when employing some OHDs (e.g., thiazolidinediones), either as the primary treatment or a co-adjuvant for controlling T2DM and its possible associated complications [32,33]. Various studies on BROMO have described its capacity, alone or combined with ME, to improve sensitivity to insulin [13,20,34].

A certain association has been established between the disruption of the circadian rhythm of T2DM patients [35-37] and an increase in IR [38,40], which coincides with the demonstrated ability of BROMO to normalize the circadian cycle [41,42] and reduce IR [33,43]. Further research is needed on the application of BROMO therapy to better understand its mechanisms and effects. Such information may lead to its improved clinical administration to treat T2DM.

Limitation

It is important to recognize some limitations of the current contribution that might have had some influence on the results, including the relatively small number of patients in each group, the low participation of women, the short treatment time for the two drug regimens, and the lack of evaluation of adherence to the diet and physical exercise program that was recommended. Despite these limitations, the present findings provide clear evidence of the advantages of CT with BROMO, and thus represent another step towards the possible inclusion of BROMO in therapy for the control of T2DM in Mexican patients.

Conclusions

Multiple advantages were herein shown by the CT with BROMO plus ME when administered to T2DM patients for the control of metabolic, endocrine and cardiovascular parameters.

Although the therapeutic advantages of BROMO have been reproduced in distinct clinical trials, further research is necessary on the outcome of BROMO treatment in different populations whose genetic variability could favour or modify the therapeutic use of this drug.

Conflicts of interest. Authors have no conflicts of interests regarding this paper.

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