ORIGINAL ARTICLE

Cabergoline Effect on Blood Sugar in Type 2 Diabetic Patients with Oral Agent Failure

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SUMMARY

Ergot-derived dopamine D2 receptor agonists are the usual treatment of hyperprolactinemia and Parkinson's disease and recently bromocriptine has been approved for the treatment of type 2 diabetes. The aim of this study was the evaluation of short-term effect of cabergoline in poorly controlled diabetic patients with oral agent failure who refused insulin therapy.

Methods: This study was performed in 17 overweight women and men with type 2 diabetes with persistent hyperglycemia in spite of treatment with maximum dose of sulfonylurea, metformin and pioglitazone. 10 patients (group I) randomized to be treated with cabergoline 0.5 mg weekly for 3 months and 7 patients (group II) with placebo. Fasting and postprandial plasma glucose concentration and HbA1c measured in beginning and end of the study.

Results: FBS decreased from 210.70± 21.29 to 144.90± 26.56 mg/dl in cabergoline group whereas it decreased in placebo group insignificantly. Postprandial blood glucose decreased from 264.2±28 mg/dl to 203.6±34.34 mg/dl in cabergoline group whereas it increased in placebo group insignificantly.HbA1c decreased in cabergoline group from 8.48±0.44 to 7.7±0.11 whereas in control group it increased insignificantly from 8.7±0.33 to 8.8±0.16.

Conclusion: Cabergoline improves glycemic control in type 2 diabetic patients with oral agent failure. It reduces both fasting and postprandial plasma glucose levels and causes 0.45–1.11 reduction in HbA_{1c}.

KEY WORDS:
Cabergoline, Diabetes, Dopaminergic agonists

INTRODUCTION

Type 2 diabetes is a worldwide important health problem that will afflict about 350 million people by the year 2030[1,2]. Although dramatic advances in the pharmacologic treatment of diabetes occurred in recent years, medical interventions in order to find new medications continue. Ergot-derived dopamine D2 receptor agonists like bromocriptine and recently cabergoline have been used for the treatment of hyperprolactinemia and Parkinson's disease[3,4]. Bromocriptine also was effective in reducing A_{1c} Hemoglobin (HbA_{1c}) in type 2 diabetes in short term clinical trials[5,6]. Recently a quick release formulation of bromocriptine (Cycloset) has been approved by the US Food and Drug Administration for the treatment of type 2 diabetes mellitus[7]. There is also a report about the effect of cabergoline in treatment of hyperglycemia in patients with Cushing syndrome[8]. The aim of this study was the evaluation of short-term effect of cabergoline in poorly controlled diabetic patients with oral agent failure who refused insulin therapy.

MATERIALS AND METHODS

This study performed in 17 overweight women and men with type 2 diabetes with persistent hyperglycemia in spite of treatment with maximum dose of sulfonylurea, metformin and pioglitazone (Table I). All of these patients were candidate for insulin therapy but they denied injecting insulin. Exclusion criteria were severe comorbid states, HbA_{1c} > %10 and migraine headache. 10 patients (group I) randomized to treat with cabergoline 0.5 mg weekly for 3 months and 7 patients (group II) with placebo. The patients did not receive any other medications and remained on routine diet and exercise to exclude any effect of changes in life style on the primary outcome measurements. Fasting plasma glucose concentration (FBS) and HbA_{1c} measured in beginning and end of the study. Adhesion to medical therapy and clinical adverse events at follow-up visits searched for by monthly office visits. Statistic analysis performed by SPSS software (version 11.5, Inc Chicago, IL, USA). The student t-test and paired t test used as indicated and P value less than 0.05 considered significant.

The study registered in clinicaltrial.gov; identifier NO is NCT 01459601.The Endocrine Research Committee of Mashhad University has reviewed all aspects of the research and has approved the protocol. There is not any conflict of interest for the investigators.

RESULTS

All of the patients completed the study without major adverse effects. 1 patient in the cabergoline group complained of mild nausea and dizziness in first 2 weeks of study, but these symptoms resolved spontaneously in the next weeks.

FBS decreased from 210.70± 21.29 to 144.90± 26.56 mg/dl (P =0.00) in cabergoline group whereas it decreased insignificantly in the placebo group from 222.0±28.34 to 210.00±25.43 (p=0.69).

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Table I: Baseline demographic and characteristics of subjects in cabergoline and placebo group

	Placebo	cabergoline	p
Number	7	10	
Male/Female	2/7	4/6	
Age	50.6 7.2	54.2	0.856
Weight (kg)	72.6 11.1	71.2 9.6	0.817
FBS (mg/dl)	210.70± 21.29	222.0±28.34	
Postprandial BS (mg/dl)	264.2±28	281±25.7	
HbA_{1c}	8.48±0.44	8.7±0.33	

Postprandial blood glucose decreased from 264.2±28 mg/dl to 203.6±34.34 mg/dl (P =0.00) in cabergoline group whereas it increased insignificantly in the placebo group from 281±25.7 mg/dl to 293±44mg/dl (p=0.9).

HbA1c decreased in the cabergoline group from 8.48±0.44 to 7.7±0.11(P = 0.00) whereas in control group it increased insignificantly from 8.7±0.33 to 8.8±0.16 (P=0.5).

The differences in HbA_{1c} and fasting glucose levels between the cabergoline and placebo group at the end of the study were significant.

No changes in body weight occurred during the study in either placebo- or bromocriptine-treated subjects. One patient in cabergoline group complained of mild nausea and dizziness in first 2 weeks of study, but these symptoms resolved spontaneously in next weeks.

DISCUSSION

Dopamine receptor agonists do not have a specific receptor for metabolic actions and their effects are mediated via resetting of dopaminergic and sympathetic tone within the CNS. Metabolism of mammalian species living in the wild changes during seasons of food deprivation by increment in both serotonin and noradrenergic levels in the suprachiasmatic and ventromedial nuclei of the hypothalamus[9]. By this way, an insulin resistant state appears that increases fat oxidation and spares glucose utilization in peripheral tissues. Based on animal studies bromocriptine administration increases dopamine and decreases noradrenergic and serotonergic levels in hypothalamus and by this way improves insulin sensitivity in peripheral tissues and suppress glucose production in liver[10-13]. In type 2 diabetic patients there is an early morning dip in dopaminergic tone and twofold elevation in day time plasma prolactin levels [5, 14]. Administration of dopaminergic agonists in diabetic patients improves glucose profile without increasing plasma insulin levels by restoring dopaminergic activity and reducing prolactin levels [5,15-16]. Recently a quick release formulation of bromocriptine (Cycloset) has been approved by the US Food and Drug Administration for the treatment of type 2 diabetes mellitus [7]. In a 16-week double blind, placebo-controlled study in obese type 2 diabetic subjects treated with Cycloset for 16 weeks, HbA1c and fasting plasma glucose decreased significantly [17]. Cycoset also could reduce HbA1c by 0.7% in insulin-treated type 2 diabetic subjects [18]. Cabergoline is a long acting dopamine agonist that is administered once or twice a week and has much less tendency to cause nausea than bromocriptine [3-4]. There is a report about the effect of cabergoline in decreasing of blood glucose in Cushing syndrome [8] but there is no study about the effect of cabergoline in diabetic patients.

We treated patients with type 2 diabetes with oral agent failure who denied insulin injection, with cabergoline and showed significant reduction in FBS and HbA1c after 3 month. There are some reports about association of cabergoline with valvular heart disease in Parkinson disease [19-20]. This association is dose-dependent, and does not occur with lower doses of cabergoline (0.5 to 1.5 mg/day) that usually use in treatment of hyperprolactinemia[21]. We used also low dose of cabergoline. Side effects were uncommon. Nausea and dizziness occurred transiently in only 10% of patients that was less than bromocriptine in similar studies [10].

CONCLUSION

Cabergoline improves glycemic control in type 2 diabetic patients with oral agent failure. It reduces both fasting and postprandial plasma glucose levels and causes 0.45–1.11 reduction in HbA_{1c}.

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