Research Article

Effect of Bromocriptine on Peptide YY and Prolactin Hormones in Iraqi Obese Women

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ABSTRACT

Previous preclinical and clinical studies indicated that bromocriptine may have anti-obesity effect by effecting on different hormones such as (peptide YY and prolactin) in the body. Aim of the study is to evaluate the effect of bromocriptine drug on peptide YY hormone which is anorexogenic hormone that inhibit appetite and on prolactin hormone which is metabolic hormone that regulate food intake in Iraqi obese women. Forty obese female age from (18– 50 years) participated in this study (BMI ≥30 Kg/m 2) and they allocated into two groups: group one administrated bromocriptine 2.5mg once daily and group two administrated placebo, both groups continued treatment for eight weeks. Analysis of data revealed that bromocriptine treated group produce a non-significant reduction ($p<0.05$) in peptide YY hormone compared with placebo group but produce significant decrease ($p<0.05$)in prolactin hormone and had a non-significant effect ($P> 0.05$) on ALT and AST enzymes in the liver and serum creatinine and blood urea compared with placebo group we can conclude that bromocriptine had the significant effect on prolactin compared with placebo and bromocriptine produced non-significant effect on peptide YY, liver and kidney function test.

Keywords: Bromocriptine, peptide yy, prolactin, Iraqi obese.

INTRODUCTION

Obesity is a medical condition in which excess accumulation of body fat to the extent that it may have a harmful effect on health. People are generally considered obese when their body mass index (BMI) is over 30 kg/m^2, obesity is most commonly resulted from a combination of increasing in food intake, decreasing in physical activity and genetic susceptibility[1]. A few cases are resulted from genes, endocrine disorders, medications, or mental illness[2]. Obesity increases the probability of infection with various diseases, particularly heart disease, type 2 diabetes, obstructive sleep apnea, certain types of cancer, and osteoarthritis[3]. Peptide YY (PYY) is a short 36 amino acid straight chain protein with chemical structure similar to neuropeptide Y (NPY) and pancreatic peptide (PP). PYY is a GI hormone that increases satiety and consequently reduces food intake[4]. PYY secretion increases in relation to food consumption and is positively related with the meals calorie content[5]. It is synthesized and released from specialized entero endocrine cells called L-cells found in distal GI. Its release is stimulated by intraluminal nutrients, including short-chain fatty acids ,glucose, bile salts, lipids, and amino acids. Regulatory peptides effected on PYY release such as cholecystokinin (CCK), gastrin and GLP-1, vasoactive intestinal polypeptide (VIP)[6]. The proximal gastrointestinal tract through vagal fibers may also contribute in the regulation of PYY release. PYY inhibits many gastrointestinal functions, including secretion of gastric acid, chloride secretion from small intestine and colon, gastric emptying, mouth to cecum transport time, exocrine secretion from pancreas and insulin secretion[6]. The majority of PYY hormone is stored in cells and present in the circulation in the form of PYY (3–36). The hormone PYY3-36 hormone has anorexigenic effects in individuals with normal weight and in individuals with obesity. In a trial done on both obese and lean humans, intravenous administration of PYY3-36 results in appetite reduction and 30% limitation in caloric intake for both groups [7]. The mechanism of anorexogenic effect of PYY is mediated by direct neurons within ARC. The actions of peripheral PYY3−36 on satiety appear to be mediated by a direct action of PYY hormone on the arcuate Y2 receptor, which is a presynaptic inhibitory receptor of NPY neurons, this inhibition decreases ARC NPY expression and release, and also results in increased POMC neuron activity[8]. There is no resistance to PYY was thought to be found in obesity and this was approved by the anorexigenic effect of exogenous PYY3-36 is being completely found in obesity, and this has encouraged chronic administration of PYY for longer term weight loss studies[9].

Human prolactin is a single-chain polypeptide, secreted by the lactotrophs in the anterior pituitary gland. Its secretion is regulated by the hypothalamus and under control of inhibitory effect of mainly dopamin. Prolactin considered as a metabolic hormone, which is locally secreted from adipose tissue. The excess in releasing of prolactin hormone results in increased food intake and body weight in animal models [10].

In hamsters, inhibition of prolactin secretion by bromocriptine has led to a reduction in fat deposition, without reducing food intake or body weight[10]. In human adipose tissue, Prolactin suppresses lipid storage and adipokine release and also has a paracrine / autocrine function in relation to adiponectin by binding to its receptors[11]. Prolactin cause increment in the expression of adiponectin receptors, a hormone that is secreted by adipose tissue and also increment in insulin sensitivity[12]. In humans, outside pregnancy, the secretion of Prolactin is affected by increasing body weight in adults and children. However, no molecular basis has been found which links Prolactin with an excess of body fat, weight and appetite, although some data propose the involvement of Prolactin with leptin[13]. A role of prolactin in obesity related complications has also been proposed[13]. Bromocriptine is one of dopamine agonist that used for treatment hyper prolactinemia, numerous studies have demonstrated that bromocriptine, the dopamine (DA) D2 receptor (D2R) agonist, produces significant reductions in body fat, in both animals and humans, reduces triglycerides and free fatty acids, increases lean muscle mass, improves glucose intolerance and insulin resistance. In obese humans and animals, defective DA neurotransmission has been described in both[14]. In addition bromocriptine reduces leptin hormone since leptin is secreted by adipose tissue and has a role in appetite regulation by acting on leptin receptors within hypothalmus to promote negative feedback mechanisms it is very important for long term regulation of body weight and it is increased in obesity[15]. There are numerous reports that in the pathological setting, such as sustained hyper prolactinemia, a relatively high rate of obesity is followed by weight loss after normalization of serum prolactin levels with dopamine agonists[16]. On the other hand, drugs that block dopamine D2 receptors increase appetite and result in significant weight gain[17]. Individuals may immortalize pathological eating and strategies aimed at improving dopamine function may be helpful in the treatment of obese individuals[18]. Prolactin is a positive feedback exciter for central dopamine compilation and liberation whereas sustained hyper prolactinemia down-regulates 'normal' effects by reducing central dopaminergic tone[19].

Subjects and Methods

Forty premenopausal obese Iraqi female patients with BMI> 30 kg/m 2 with an age range (18 - 50) were randomly allocated to one of these two groups, group I Includes 16 female patients administrated placebo capsule for 8 weeks in a dose of one capsule administered once daily and group II includes 24 female patients treated for 8 weeks with (bromocriptine) in a dose of one tablet (2.5mg) administered once daily.

Drug and medical history was taken from each patient and excluded diseases such as heart, renal, hepatic diseases, uncontrolled thyroid dysfunction, hyper prolactinemia, polycystic ovarian syndrome and Diabetes mellitus, also excluded women with pregnancy, lactation and women on contraceptive. All participants were advised to take low carbohydrate dietary therapy and median intensity of aerobic exercise for 60 minutes during their treatment for duration of 8 weeks. Blood samples were collected from all the participants at the start of the treatment (baseline samples) and after 8 weeks of starting treatment to measure the possible change in the studied parameters such as hormonal parameter (peptide YY, prolactin), liver and kidney function parameters (AST, ALT, serum creatinine and blood urea). The blood samples were collected in plain tubes and centrifuged at 4000 rpm for 20 minutes and then stored frozen until biochemical analysis, total peptide yy and prolactin measured by enzyme linked immuno sorbent assay (ELISA) (My biosource, USA), liver enzymes (Human, Germany). The results are presented as mean ± SD in two sample T test in the baseline comparison between the two groups and then data were analyzed by using the analysis of covariance (ANCOVA) after adjusted means of both groups the results presented as mean ± SE. The significance level for all tests was taken as P value less than 0.05 and percentage of difference between the baseline and end line was calculated for both groups.

RESULTS

Table 1: Comparison of adjusted effect of treatment for weight and BMI according to covariance.

	Treatment group	Adjusted baseline	Adjusted End line Mean ±SE	Outcome Mean ±SE	P value
Weight (Kg)	Bromocriptne N =24	98.7450	94.234±0.585	-4.511±0.585	0.012
	Placebo N =16	98.7450	96.696±0.719	-2.099±0.719	
BMI (Kg/m^2)	Bromocriptine N =24	39.238	37.460±0.235	-1.778±0.235	0.011
	Placebo N =16	39.238	38.46± 0.288	-0.778±0.288	
N = Number of patients, SE = Standard error					

Table 2: Comparison of adjusted effect of treatment for peptide YY and prolactin hormones according to covariance.

	Treatment group	Adjusted baseline	Adjusted End line (Mean ±SE)	Outcome (Mean ±SE)	P value
Peptide YY (pg/ml)	Bromocriptine N =24	120.64	112.725±2.38	7.920±2.383	0.603
	Placebo N =16	120.64	110.737±2.92	9.908±2.924	
Prolactin (ng/ml)	Bromocriptine N =24	14.827	8.006±0.643	6.822±0.643	<0.001
	Placebo N =16	14.827	13.953±0.791	0.874±0.791	
N = Number of patients , SE = Standard error					

Table 3: Comparison of adjusted effect of treatment for ALT, AST, serum creatinine and blood urea according to covariance.

	Treatment group	Adjusted baseline Mean ±SE	Adjusted End line Mean ±SE	Outcome (Mean±SE)	P value
ALT (U/l)	Bromocriptne N =24	15.5	12.58±0.76	-2.9±0.76	0.666
	Placebo N =16	15.5	13.12±0.94	-2.39±0.94	
AST (U/l)	Bromocriptine N =24	17.57	15.19±0.98	-2.87±0.98	0.284
	PlaceboN =16	17.57	16.9±1.2	0.08±1.2	
Serum Creatinine (mg/dl)	Bromocriptine N =24	0.917	0.945±0.034	0.028±0.03	0.393
	Placebo N =16	0.917	0.898±0.042	0.02±0.042	
Blood Urea mg/dl) (	Bromocriptine N =24	30.1	30.8±1.4	0.697±1.42	0.372
	Placebo N =16	30.1	28.7±1.75	-1.36±1.74	
N = Number of patients , SE = Standard error					

In table (1, 2 and 3) after adjustment means of different parameters for the bromocriptine group and placebo group according to the covariance analysis there is significant reduction P value <0.05 in weight, BMI and prolactin in bromocriptine group compared with placebo group but there is a non-significant difference P value > 0.05 between the two groups for peptide YY, ALT, AST, serum creatinine and blood urea.

DISCUSSION

Bromocriptin which is dopamine receptor agonist has anti-obesity effect by different ways. Patients in this study were obese premenopausal females with normal prolactin levels. The analysis of data in the present study indicated that the group of patients treated with bromocriptine 2.5 mg once daily for 8 weeks combined by diet and exercise produced significant weight loss and decrease in BMI and (P < 0.05) compared with placebo group combined by diet and exercise according to analysis of covariance with percentage of reduction 4.5% and 4.5% respectively.

In the current study bromocriptine produced significant weight loss compared with placebo and this agrees with Cincotta *et al.* that found bromocriptine produced significant reduction in body weight and body fat compared with placebo when used for 18 weeks[20]. The current study agreed with study accomplished by Meier *et al*. that shows that bromocrptine decrease total body fat and decrease body weight by 2.5% when used for 6 weeks[21]. Bromocriptine may decrease body fat by decreasing insulin stimulating hepatic lipogensis, and also by inhibiting lipolysis that lead to free fatty acid re esterfication[20]. Bromocriptine increase dopaminergic tone and decrease prolactin level that may reduce lipogenesis lead to decrease body fat [22], In obese humans and animals defective dopamine neurotransmission was found, imaging studies indicated that obese individuals have decreased D2 receptor in stratium and genetic

studies have also shown individuals have decreased D2R binding in stratium carrying the taq 1A1 allele of the D2R gene'. Reduced dopamine signal transduction may lead to decreased energy expenditure and overeating such as in obesit[14]. Animal's studies suggested that dopamine receptors activation result in decreasing the or exogenic effect of ghrelin[23], this may explain the anorexogenic effect of dopamine agonist such as bromocriptine. Previous study by Kok P *et al*. confirmed that bromocriptine treatment decreases leptin hormone level in obese women, since leptin is secreted by adipose tissue and has a role in appetite regulation by acting on leptin receptors within hypothalamus to promote negative feedback mechanisms which is very important for long term regulation of body weight and obesity[15].

Table 4: Percentage of difference for the two groups.

		% of difference
weight	Bromocriptine N24	↓4.5%
	Placebo N16	↓2%
BMI	Bromocriptine N24	↓4.5%
	Placebo N16	↓2%
Peptide YY	Bromocriptine N24	↓ 6.6%
	Placebo N16	↓ 8%
prolactin	Bromocriptine N24	↓ 46%
	Placebo N16	↓ 5.8%
ALT	Bromocriptine N24	↓18.7%
	Placebo N16	↓15%
AST	Bromocriptine N24	↓16%
	Placebo N16	↓0.45%
Serum creatinine	Bromocriptine N24	↑3%
	Placebo N16	↓2%
Blood urea	Bromocriptine N24	↑2.3%
	Placebo N16	↓4.5%

Peptide YY hormone is anorexogenic (appetite inhibiting hormone) secreted in response to meal and has a role in short term regulation of food intake. In the present study fasting total peptide YY both (peptide YY 1-36, peptide YY 3-36) measured before starting the treatment program and after 8 weeks, the analysis indicated that there was non-significant change in peptide YY (Pvalue >0.05) between the bromocriptine group plus diet and exercise and the placebo group plus diet and exercise, where peptide YY decrease in both groups after weight loss with percentage of reduction 6.6% in bromocrptine group and 8% in placebo group. The non-significant change of fasting peptide YY between the two groups cannot be explained on bases of amount of weight loss or use of bromocriptine but possibly to the reduction of caloric intake, or it may be due to limited number of patients within each group, which may affect the results of peptide YY. Previous studies suggested that in obese individuals there are low levels of fasting and postprandial peptide YY which may result from decrease the synthesis and release of peptide YY leading to decrease satiety that may contribute to obesity[24], also obese individuals show sensitivity toward peptide YY anorectic effect which means, there is no peptide YY resistance as leptin resistance that found in obesity[25], there is multiple opinions about the levels of peptide YY after weight loss , some studies confirmed that peptide YY concentration increases after weight loss in children such as by Roth *et al.*[26], and also by Hill *et al.* who noticed increase in fasting peptide YY levels after weight loss[27]. Another studies showed no changed in level of peptide YY after weight loss such as by Moran *et al*.[28] the only limitation is it is done on overweight not obese, and also by Gueugnon *et al.* which showed no change in peptide YY after weight lossin adolescents[25]. But another previous studies showed a decrease in peptide YY levels after weight loss and this may agree with the current study that showed peptide YY decrease after weight loss in both groups, as Sumithran *et al.*[29] show in men and postmenopausal women and also Essah *et al.* that found after weight loss fasting peptide YY level decrease after weight loss and the level of peptide YY is independent on weight loss degree[30] as had been noticed in the current study.

The reduced level of peptide YY after weight loss is represent one of physiological compensatory mechanism of the body in an attempt to increase appetite [(31)] in order to maintain body weight and regain the weight loss. The limitations of current study including measurement of total peptide YY rather than peptideYY3-36 but this is closely correlated to total peptide YY[32].

Bromocriptine drug is D2 receptor agonist that inhibits the release of prolactin from pituitary gland used for treatment hyper prolactinemia that mainly associated with prolactinoma. In the current study the prolactin levels of obese females was within normal level, but after treatment with bromocriptine, prolactin decreased significantly (P<0.001) compared with placebo group with percentage of difference of 46% in bromocriptine group compared with 5.8% in placebo group. The level of prolactin after treatment with bromocriptine remains within normal range.

Previous studies confirmed that there is a relationship between high prolactin level and visceral fat mass[33], since high prolactin hormone may stimulate obesity by lipogenesis stimulation and reduction of CNS dopaminergic tone, bromocriptine increase dopaminergic tone that may reduce lipogenesis by decreasing prolactin level leading to decrease body fat[22]. Obese female patients in this study have normal level of prolactin. The possibility of relative hyper prolactenimia (even with normal mean prolactin) still a probable explanation, so further studies needed to determine the effect of lowering normal prolactin levels on body weight.

Alanine aminotransferase (ALT) is liver specific enzyme whereas aspartate aminotransferase (AST) is found in many tissues such as liver, kidney, heart, brain and muscle. These two enzymes used as indicator for liver function test[34] and both serum creatinine and urea give indication for kidney function. Treatment with bromocriptine produced a non-significant change (P >0.05) in ALT, AST, serum creatinine, and urea compared with placebo group, this indicated that bromocriptine 2.5 mg once daily for 8 weeks had no harmful effect on both the kidney and liver since bromocriptine metabolized in the liver and small amount of bromocriptine is excreted from kidney. Patients in this study has normal liver and renal function test before starting treatment. Bromocriptine in the current study produced reduction in both ALT and AST with percentage of reduction 18.7% and 16% respectively this effect on liver enzymes may be attributed to decrease abdominal fat that accumulated in hepatic tissue(nonalcoholic fatty liver), as weight decrease in bromocriptine group. A study on genetically obese and diet induced rodents indicated that bromocriptine may had therapeutic effect on a non-alcoholic fatty liver disease associated with obesity by decreasing hepatic lipid accumulation, glucose tolerance, mitochondrial oxidative stress and by decreasing obesity[35]. Future study is required to evaluate the action of bromocriptine on fatty liver associate with obesity.

CONCLUSION

Bromocriptine had significant effect on weight and BMI compared with placebo, Bromocriptine produced significant reduction in prolactin hormone, but it had no effect on peptide YY hormone and had no harmful effect on both liver and kidney function compared with placebo in Iraqi obese women.

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