Hiperprolaktinemide Total Antioksidan Düzey: Bromokriptin Tedavisinin Etkileri

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ÖZET:

Amaç: *Çalışmanın amaçları i) hiperprolaktinemik kadınlarda total antioksidan düzeyini(TAD) ii) bromokriptinin bu grupta antioksidan etkisinin olup olmadığını araştırmaktı.*

Materyal ve Metod: *Yirmi-dört hiperprolaktinemik kadın ve 20 sağlıklı kontrol grubu çalışmaya dâhil edildi. Kan örnekleri çalışma ve kontrol gruplarında folliküler fazda toplandı. Bromokriptin tedavisi alan hiperprolaktinemik kadınlarda 8 hafta sonra kan örnekleri tekrar alındı. FSH, LH, östradiol (E2), prolaktin ve total antioksidan düzeyi ölçüldü.*

Sonuçlar: *Serum LH, E2 ve TAS düzeyleri hiperprolaktinemik kadınlarda kontrollere kıyasla anlamlı derecede düşük ve prolaktin ise anlamlı derecede yüksekti. Serum FSH düzeyleri gruplar arasında değişiklik göstermemekteydi. Hiperprolaktinemik kadınlarda bromokriptin kullanımından sonra FSH, LH ve E2 düzeylerinde anlamlı bir değişiklik yoktu. Fakat bromokriptin tedavisinden sonra hastalar TAS da anlamlı bir yükselme ve prolaktin düzeylerinde anlamlı bir düşme gösterdi.*

Tartışma: *Çalışmamızda, TAS düzeylerinin hiperprolaktinemik hastalarda anlamlı düzeyde düşük olduğunu ve bromokriptinin antioksidan kapasitesiyle koruyucu etkisinin olduğunu gösterdik. O, sadece hiperprolaktinemik hastalarda prolaktin düzeyini düşürmede çok etkili bir ajan değil, fakat aynı zamanda bu grup hastalarda antioksidan aktiviteyi artıran bir ajandır.*

Anahtar Kelimeler: Hiperprolaktinemi, total antioksidan düzey, bromokriptin

SUMMARY:

Total antioxidant status in hyperprolactinemia: effects of bromocriptine therapy

Objective: *The aims of the study were to evaluate i) total antioxidant status (TAS) in women with hyperprolactinemia ii) whether bromocriptine had an antioxidant property in that group of patients.*

Materials and Methods: *Twenty-four hyperprolactinemic women and 20 healthy control group were enrolled in the study. Blood samples were collected from the study and control groups during the follicular phase. Blood samples were collected again from hyperprolactinemic women on bromocriptine therapy after 8 weeks. FSH, LH, estradiol (E2), prolactin and TAS were measured.*

Results: *Serum LH, E2 and TAS levels were significantly lower and prolactin was significantly higher in hiperprolactinemic women than in controls. Serum FSH levels did not differ between the groups. There were no significant differences in FSH, LH and E2 levels after bromocriptine use in hyperprolactinemic women. However, after treatment with bromocriptine the patients demonstrated significant increase in TAS and significant decrease in prolactin levels.*

Discussion: *In this study, we demonstrated that TAS levels were significantly lower in patients with hyperprolactinemia and bromocriptine had protective effect with its antioxidant capacity. It is not only a very effective agent for lowering prolactin levels in hyperprolactinemic patients, but also increases antioxidant activity in that group of patients.*

Key words: *Hyperprolactinemia, total antioxidant status, bromocriptine*

INTRODUCTION

Hyperprolactinemia is one of the most common endocrine disorders of the hypothalamic-pituitary axis (1). However, the prevalence of hyperprolactinemia varies in different patient populations, with for example, approximately 0.4% in an unselected normal population; 5% in family planning clinic populations; up to 17% of women with reproductive disorders (1). It is characterized by amenorrhea, infertility and galactorrhea with an increased risk of long-term complications including osteoporosis (1). Oxidative stress arises as a consequence of excessive production of reactive oxygen species (ROS) and impaired antioxidant defense mechanisms (2). Interest in the relationship between inflammation and oxidative stress has increased dramatically in recent years. Inflammation and oxidative stress share a common role in the etiology of a variety of chronic diseases (3,4). It has been reported that hyperprolactinemia is associated with low grade inflammation (5). Serum levels of markers of inflammation were increased in hyperprolactinemic patients (5). However, oxidative stress in women with hyperprolactinemia has not been adequately studied.

Recent studies have reported that ergot derived dopamine agonists such as bromocriptine, cabergoline and quinagolide are recommended as first line medical therapy for hyperprolactinemia (6). Bromocriptine stimulates dopamine D2-type receptors on lactotroph cells of the anterior pituitary to reduce prolactin secretion. It is also able to both antagonize and stimulate dopamine D1-type receptors, resulting in mild adrenal side effects (6). Bromocriptine has the longest history of use for the treatment of hyperprolactinemia and is well established as a safe and effective therapy (7,8). Since it is highly generalized, bromocriptine is an inexpensive treatment for hyperprolactinemia. Bromocriptine has potent antioxidant properties in brain and has been widely used as a free radical scavenger in the treatment of Parkinson's disease. In addition, it has neuroprotective effects (9). The antioxidant property of bromocriptine in plasma in hyperprolactinemic patients remains unclear.The aims of the study were to evaluate i) total antioxidant status (TAS) in women with hyperprolactinemia ii) whether bromocriptine had an antioxidant property in that group of patients.

MATERIALS AND METHODS

Twenty-four hyperprolactinemic women were enrolled in the study. All the patients had normal thyroid function. None of the patients had taken dopamine agonists or any estrogen or progestogen therapy, supplemental vitamins or oral steroids within the 2 months prior to the study. Patients with a preexisting medical condition or with evidence of any inflammatory disease like urinary infection, anemia and smokers were excluded. The controls were matched for age and body mass index (BMI).

Blood sample collection

All of the participants were treated effectively with 5 mg bromocriptine resulting in suppression of prolactin levels usually to normal and none of them were excluded from the study. Blood sampling was repeated on two occasions during the follicular phase before bromocriptine treatment and after 8 weeks of therapy. Blood samples were collected at 9:00 and 11:00 a.m. after an overnight fast. The samples were centrifuged within 2 h after withdrawal and assessed on the same day.

Measurement of total antioxidant status in plasma

Total antioxidant status (TAS) of plasma was determined by using an automated measurement method, developed by Erel (10). In this method, the hydroxyl radical, the most potent radical, is produced via Fenton reaction and consequently the colored dianisidinyl radical cations, that are also potent radicals, are produced in the reaction medium of the assay. Antioxidant capacity of the added sample against these colored potent free radical reactions is measured as totally. The assay has got excellent precision values, within and between precision values was lower than 3%. The results were expressed as mmol Trolox equivalent/L.

Hormone assays

Serum levels of FSH, LH, prolactin, estradiol (E_2) were measured by electrochemiluminescent immunoassay (Roche, E170, Mannheim, Switzerland). Intra and interassay coefficients of variation were less than 2.6% and 3.6% for FSH, less than 1.2% and 2.0% for LH, less than 1.2% and 5.5% for prolactin and less than 3.3% and 4.7% for E_2 respectively.

Statistics

Results were expressed as mean ± S.D. for all continuous variables. Differences among study and control groups were assessed by using Student's t test. The effect of bromocriptine treatment in patients with hyperprolactinemia was evaluated by paired sample t test.

RESULTS

Patient characteristics were shown in **Table1.** There were no significant differences in terms of age and BMI between the groups. Hormone profiles of hyperprolactinemic patients and normal controls were summarized in **Table2.**

Table 1. Clinical characteristics of the study population

	Hyperprolactinemia (n=24) (mean ± SD)	Controls (n=20) (mean ± SD)	*p*
Age (year)	25.8 ± 3.3	25.9 ± 4.4	NS
BMI (kg/m²)	21.8 ± 2.5	21.4 ± 2.0	NS
Years since diagnosis of hyperprolactinemia (year)	1.6 ± 0.7	-	

BMI: body mass index

Table 2. Hormone profile of hyperprolactinemic patients compared with normal controls and in a subgroup of women with hyperprolactinemia before and during hormone replacement therapy

	Hyperprolactinemia (n= 24)	Controls (n= 20)	Treated hyperprolactinemia (n=24)	
			Pretreatment	Posttreatment
FSH (mIU/mL)	5.8 ± 1.7	5.2 ± 1.3	5.8 ± 1.7	5.5 ± 1.5
LH (mIU/mL)	4.3 ± 1.3[a]	5.4 ± 1.9	4.3 ± 1.3	4.8 ± 1.6
E_2 (pg/mL)	46.1 ± 14.9[b]	59.8 ± 16.6	46.1 ± 14.9	49.5 ± 10.2
Prolactin (ng/mL)	66.0 ± 15.1[c]	12.0 ± 4.0	66.0 ± 15.1[d]	16.2 ± 4.2
TAS (mmolTrolEq/L)	1.1 ± 0.1[c]	2.2 ± 0.5	1.1 ± 0.1[d]	2.4 ± 0.5

TAS: total antioxidant status E2: estradiol

[a] $p<0.05$ hyperprolactinemia versus controls

[b] $p<0.01$ hyperprolactinemia versus controls

[c] $p<0.0001$ hyperprolactinemia versus controls

[d] $p< 0.0001$ treated hyperprolactinemia pretreatment versus posttreatment

Serum LH, E_2 and TAS levels were significantly lower and prolactin levels were significantly higher in hyperprolactinemic women than in the control group. Serum FSH levels did not differ between the groups. There were no significant differences in FSH, LH and E_2 levels after bromocriptine use in hyperprolactinemic group. However, after treatment with bromocriptine the patients demonstrated significant increase in TAS and significant decrease in prolactin levels.

DISCUSSION

In this study, we found that TAS was lower in hyperprolactinemic women than in healthy controls. Moreover, TAS was significantly increased in these patients after 8 weeks of bromocriptine use. ROS play important roles in many physiological processes; however, if the amount of ROS exceeds the capacity of the ROS-suppressing machinery, oxidative stress occurs. Antioxidants act as first line defense against ROS in all cellular compartments. Blood contains many antioxidant molecules. Concentrations of all these antioxidants in serum can be measured separately, but this procedure is time- consuming, labor intensive and requires complicated techniques (10). TAS reflects the total antioxidant activity in serum (10). TAS which acts against free radicals can be used as an indicator of oxidative stress. It is proposed that oxidative stress precipitates the range of pathologies that currently are thought to afflict the reproductive function (2). This was the first study that showed that the level of TAS was significantly lower in hyperprolactinemic patients than in healthy controls. The mechanism was unclear, but it might be related to increased inflammation (3,4) that could lead to oxidative stress and depletion of serum levels of antioxidants in that group of patients (5,11). It has been reported that inflammatory markers were increased in hyperprolactinemia (5,12). High sensitive C-reactive protein, an inflammatory marker, was significantly higher in hyperprolactinemic patients than in healthy subjects (12). Another inflammatory marker homocysteine was also found to be elevated in that group of patients (12).

Bromocriptine has an antioxidant capacity (13). Recent studies have suggested that bromocriptine directly scavenge hydroxyl and/or nitric oxide (NO) radicals (14, 15). It has positive effects superoxide dismutase, catalase and glutathione, the major endogenous antioxidants in brain (16). In addition, bromocriptine induces neuroprotection in rat mesencephalic neurons by its antioxidant effect via a D2- receptor-dependent pathway (9). Thus, the antioxidant properties of bromocriptine as well as other ergot-derived drugs may both directly and indirectly participate in the neuroprotection of dopaminergic neurons. We demonstrated that TAS was significantly increased in hyperprolactinemic patients after 8 weeks of bromocriptine administration and bromocriptine had also an antioxidant activity in plasma. FSH concentration was not significantly different in hyperprolactinemic patients than in controls. However, LH and E2 levels were significantly lower in hyperprolactinemia compared with healthy subjects. It has been reported that hyperprolactinemia is associated with low levels of LH (17,18). It is effective in suppressing basal LH secretion in rats (19). Hyperprolactinemia affects ovarian steroidegenesis by blocking aromatisation in granulosa cells (20). Direct inhibition of E2 by granulosa cells in the midfollicular phase has been demonstrated (21). Hyperprolactinemic patients had no significant different levels of FSH, but lower levels of serum E2 compared with healthy controls in another study that also supported our findings (18).Hormonal changes after treatment with bromocriptine were also evaluated. There were no significant differences in FSH, LH and E2 levels before and after treatment with bromocriptine. Studies have also reported that FSH, LH and E2 did not vary after bromocriptine use (22).It was important to establish normal thyroid function in the hyperprolactinemic group. Hyperprolactinemia is associated with primary and subclinical hypothyroidism (23, 24) which is in turn associated with increased levels of oxidative stress (25, 26). However, in this group of patients, the concentrations of thyroid stimulating hormone (TSH) were normal.

In conclusion, we demonstrated that TAS was significantly lower in patients with hyperprolactinemia and bromocriptine had protective effect with its antioxidant capacity. This study suggests that bromocriptine stimulates antioxidant mechanisms in plasma indicating its strength as a valuable antioxidant. It is not only a very effective agent for lowering prolactin levels in hyperprolactinemic patients, but also reduces oxidative stress in that group of patients. Due to its antioxidant and antiprolactinemic properties, bromocriptine can safely be used hyperprolactinemic patients.

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