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BRIEF REPORT

Cabergoline treatment in men with psychogenic erectile dysfunction: a randomized, double-blind, placebo-controlled study

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The effectiveness of cabergoline in 50 men with psychogenic erectile dysfunction was investigated in a 4-month, randomized, placebo-controlled, double-blind study with validated psychological tests, and prolactin, follicle-stimulating hormone, luteinizing hormone and testosterone serum levels. Cabergoline treatment was well-tolerated and resulted in normalization of hormone levels in most cases. In the cabergoline-treated group, significant interactions between prolactin and testosterone serum concentrations were observed. Erectile function improved significantly. Sexual desire, orgasmic function, and the patient's and his partner's sexual satisfaction were also enhanced. Cabergoline may be an effective and safe alternative agent for men with psychogenic ED.
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Introduction

The dopamine agonist cabergoline is a synthetic drug, with a long half-life[1] and a high affinity for D2 receptors, that is indicated for treatment of Parkinson's disease and hyperprolactinemic disorders.[1,2] Dopamine agonists such as apomorphine, ropirinole and cabergoline were observed to increase penile erection and libido in patients with Parkinson's disease.[3]

Krueger *et al.*[2] demonstrated that cabergoline induced an acute modification of prolactin plasma levels in healthy men that may be a possible factor modulating their sexual drive and function. De Rosa *et al.*[4] reported normalization of serum prolactin and preserving gonadal function in hyperprolactinemic men after 6 months of cabergoline treatment.

The aim of this study was to examine whether cabergoline exerts a significant beneficial influence compared to placebo on sexual drive and functioning in patients with psychogenic erectile dysfunction (ED), and on quality of life in patients and their sexual partners.

Methods

Participants

Men ($n = 88$) over 18 years old who were subjectively suffering from chronic stress, and anxious or depressive mood, and were subjectively unable to attain and maintain a penile erection sufficient to permit subjectively satisfactory sexual intercourse, and who were living in a stable, monogamous, heterosexual partnership, and had attempted sexual intercourse at least once during the previous 4 weeks were recruited from the general population via advertisements.

Exclusion criteria were psychotic disorders, organic ED (including smoking, hypertension and diabetes as risk factors for ED, and diagnosed in previous medical and urological examinations), the current use of cabergoline, other dopamine agonists, any kind of current anti-ED treatment, current use of antidepressants, antianxiety drugs or psychotherapy, an TICS-screening-scale of <50, and an erectile

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function score of >25 (assessment-section).[5] Potential subjects were also excluded if they were severely somatically ill, actively suicidal or abusing alcohol or drugs. Thirty-eight subjects were excluded.

Sample size was estimated as described by Muellner.[6] This resulted in a group size of $n=50$ (2×25) patients.

Subjects underwent a physical, psychiatric and laboratory examination. If a serum prolactin level $\geqslant50$ ng/ml was found, magnetic resonance imaging (MRI) examination was arranged.

Assessment

The study was performed using the Hamilton Depression Rating Scale (HDRS),[7] the Hamilton Anxiety Rating Scale (HARS),[8] the Trier Inventory for the Assessment of Chronic Stress (TICS),[9] and the following self-administered questionnaires: the International Index of Erectile Function (IIEF),[5] the Erectile Dysfunction Effect on Quality of Life (ED-EQoL),[10] and the Sexual Functioning Questionnaire for the female partner (SFQ).[11]

Design

The study was conducted between 2004 and 2005. Randomization was carried out confidentially: 25 test subjects would be treated with the active drug (Cab-G) and 25 with a placebo (PG).

Subjects received blinded medication in numbered boxes twice weekly (Monday and Thursday), which was either a constant 0.5 mg of cabergoline (cf. 1) or a matching placebo for 4 months. The presence of side effects was assessed with a non-structured questionnaire. Both subjects and clinicians were blinded.

Subjects were seen and tested upon admission to the study and after the first, second, third and fourth month of treatment. Seven subjects (Cab-G: $n=3$; PG: $n=4$) dropped out.

For the evaluation of prolactin, follicle-stimulating hormone (FSH), luteinizing hormone (LH) and testosterone serum levels (automated chemiluminescence-immunoassay system IMMULITE 2000) blood samples were taken on two consecutive days (Tuesday and Wednesday) in the morning between 0730 and 0830, the average value being taken for statistical analysis. Subjects were asked to maintain sexual abstinence starting 24 h before the first, and ending after the second blood sample was taken. Blood samples were taken in a separate sound-attenuated room with relaxing background music. At 30 min before sampling, an i.v. cannula was inserted into a forearm vein of the non-dominant arm. After the relaxation interval, the blood was taken and centrifuged. All samples of each participant were assayed in duplicate for a particular hormone within the same assay. The intra-assay and inter-assay coefficients of variation were between 2.4 and 6.4%. Normal ranges were 2.1–17.7 ng/ml prolactin, 2.3–8.3 ng/ml testosterone, 1.4–18.1 mlU/ml FSH, and 1.5–9.3 mlU/ml LH.

Data analysis

We used the statistical program SPSS, Version 11.0. 1 (SPSS Inc., Chicago, IL, USA). Multivariate analysis was performed using a repeated measures analysis of variance to analyze differences between the two groups and interactions in the course of time. The differences between the initial and final point was analyzed on the basis of contrasts. The significance levels were corrected by Bonferroni. Significance levels of parameters that did not pass the sphericity assumption for conducting a repeated measures analysis were adjusted by the Greenhouse-Geisser epsilon. The treatment results were reported in accordance with the intent-to-treat principle.[6]

Ethics

The study was planned and conducted in accordance with the Declaration of Helsinki and ethical laws pertaining to the medical professions, and its design was approved by the clinic's 'Ethikkommission' (the German equivalent of the Committee on Human Subjects). The study was conducted independently of any institutional influence and was not funded.

Results

There were no relevant differences in the mean age (years) (Cab-G:39. 3 ± 15.3; PG:38.8 ± 12.9; CG:38.1 ± 13.4), ED duration (Cab-G:7.4 ± 3.1 months; PG:6.2 ± 2.5 months), HDRS (Cab-G:19.1 ± 5.2; PG:19.9 ± 5.0; CG:6.4 ± 3.5), HARS (Cab-G:21.2 ± 4.9; PG:21.5 ± 5.3; CG:8.5 ± 3.8), Excessive Social Stress Scale of TICS (Cab-G:64.1 ± 15.2; PG:66.9 ± 14.5; CG:28.7 ± 8.1) and body mass index (BMI) (Cab-G:26.1 ± 5.9; PG:26.9 ± 5.4; CG:21.6 ± 3.1) between the Cab-G and PG at the time of study entry. Two patients (Cab-G: $n=2$; PG: $n=0$) were examined by MRI. No prolactinomas were diagnosed.

Moderate baseline hyperprolactinemia was found in 38 ED patients (Cab-G: $n=18$; PG: $n=20$). Table 1 summarizes the effects of treatment over the course of the entire study. In the Cab-G the repeated measure analysis shows a significant ($P<0.001$) interaction between prolactin and testosterone serum concentrations (PG: $P=0.135$). The repeated measure analysis did not yield any significant difference in the time course for high baseline prolactin ($P=0.094$) or low baseline

Table 1 Changes in the prolactin, FSH, LH and testosterone serum levels, the International Index of Erectile Function (IIEF), the Erectile Dysfunction Effect on Quality of Life (ED-EQoL) questionnaire, and the questionnaire for female partner from the Sexual Functioning Questionnaire (SFQ)

	Prolactin (ng/ml)[a]	*FSH (mlU/ml)*[a]	*LH (mlU/ml)*[a]	*Testosterone (ng/ml)*[a]	*Erectile function (IIEF)*[a]	*Sexual desire (IIEF)*[a]	*Orgasmic function (IIEF)*[a]	*Satisfaction with intercourse (IIEF)*[a]	*Overall satisfaction (IIEF)*[a]	*ED-EQoL*[a]	*Partner Questionnaire (SFQ)*[a]
Initial evaluation											
Cab-G ($n=25$)	31.9±17.8	6.6±4.1	4.1±1.9	4.2±1.2	16.5±5.1	4.8±2.1	5.2±2.0	5.7±1.9	4.4±1.4	31.1±12.6	5.5±1.9
PG ($n=25$)	32.0±15.1	6.2±3.9	4.2±1.8	4.1±1.5	16.4±5.2	4.6±1.6	4.4±1.6	5.0±1.8	4.4±1.5	33.6±11.0	6.0±1.5
Final evaluation											
Cab-G ($n=25$)	4.9±3.2	9.2±4.0	6.3±1.3	7.4±1.3	24.8±5.0	8.3±1.8	8.8±2.2	11.4±2.5	8.0±1.5	14.2±6.9	10.2±1.5
PG ($n=25$)	31.0±15.1	6.5±3.7	4.4±1.6	4.0±1.3	19.5±5.4	6.6±1.5	6.2±1.6	7.6±1.5	5.3±1.5	24.0±10.7	7.6±1.5
Repeat measures analysis *P*	<0.001	0.044	0.008	<0.001	0.014	0.008	0.004	0.002	<0.001	0.016	0.006
DI (Initial/final evaluation)	−27.0/−1.0	2.6/0.3	2.2/0.2	3.2/−0.1	8.3/3.1	3.5/2.0	3.6/1.8	5.7/2.6	4.0/0.9	−16.9/−9.6	4.7/1.6
95%-CI	[−32.1;−20.0]	[1.8;2.8]	[1.4.1;2.3]	[2.0;4.4]	[4.6;8.6]	[0.9;3.2]	[1.2;3.6]	[2.0;6.3]	[2.0;3.3]	[−21.6;−3.2]	[2.4;5.8]
P	<0.001 (*t*-test)	<0.001 (*t*-test)	<0.001 (*t*-test)	<0.001 (*t*-test)	<0.001 (*t*-test)	<0.001 (*t*-test)	<0.001 (*t*-test)	<0.001 (*t*-test)	<0.001 (*t*-test)	<0.001 (*t*-test)	<0.001 (U-test)

Abbreviations: Cab-G, cabergoline-treated group; PG, placebo group; DI, difference in change between the two groups; 95%-CI, its 95% confidence interval.
[a]Mean±s.d.

testosterone ($P=0.642$) with respect to favorable treatment.

Nausea (Cab-G: $n=5/25$; PG: $n=3/25$), dizziness (Cab-G: $n=4/25$; PG: $n=2/25$), constipation (Cab-G: $n=3/25$; PG: $n=2/25$), and headache (Cab-G: $n=3/25$; PG: $n=2/25$) were reported as side effects.

Comments

At 4 months of treatment with cabergoline resulted in normalization of prolactin, FSH, LH and testosterone levels in most cases. Erectile function, namely the ability to achieve and maintain an erection in a manner sufficient for sexual intercourse, improved significantly. Sexual desire, orgasm function and the patient's and his partner's sexual satisfaction were also enhanced. These results support the findings from previous studies.[1,2]

Several of ED patients in our trial had elevated baseline prolactin levels. Stress and psychiatric disorders, which may disturb central neurotransmitter pathways involved in sexual function, have been reported to cause increased prolactin levels and consequently ED.[12] Prolactin release may modify dopaminergic systems within the central nervous system that are responsible for controlling sex drive and refractoriness.[13] Besides a short-loop feedback to tuberoinfundibular dopaminergic neurons regulating pituitary prolactin release, peripheral prolactin may be able to affect dopaminergic neurons in the nigrostratial and mesolimbocortical system and the medial preoptic area.[13] Cabergoline induces a reduction of prolactin plasma levels, with a possible subsequent improvement of testosterone concentration, may have an overall effect on sexual drive and function.[2,4]

Most of our patients tolerated cabergoline relatively well, which seems to conform with observations from other investigations.[1,3]

Conclusion

The possible efficacy of cabergoline in the treatment of men with psychogenic ED could be demonstrated. These data corroborate the hypothesis that besides a neuroendocrine reproductive reflex, prolactin reduction following cabergoline treatment may be one factor modulating acute sexual drive and behavior. The effects of cabergoline-induced reduction of prolactin level may have a clinical impact for the application of dopamine agonists in the treatment of psychogenic ED.

However, the relatively small number of patients limits the extent to which the results of this study can be generalized. Further trials with optimized doses are therefore necessary.

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