Clinical efficacy of bromocriptine and the influence of serum prolactin levels on disease severity in patients with chronic plaque-type psoriasis

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Received 24 March 2013; accepted 11 April 2013
Available online 18 May 2013

Abstract Background: Psoriasis is a T-cell mediated hyperproliferative cutaneous disease of multifactorial etiology. Prolactin (PRL) has been implicated in the pathogenesis of psoriasis and several studies have pointed to a potential therapeutic role of bromocriptine in psoriasis.

Aim: To assess the clinical efficacy of bromocriptine and the influence of serum prolactin levels on disease severity in patients with chronic plaque-type psoriasis.

Methods: Forty-five patients with chronic plaque-type psoriasis and 45 healthy control subjects were included in the study. The patients were divided into three equal groups; a group treated with narrow-band ultraviolet B (NB-UVB), a group treated with bromocriptine, and a group treated with both NB-UVB and bromocriptine. Serum PRL levels and psoriasis area severity index (PASI) scores were measured before and after a 12-week treatment period.

Results: There was no significant difference in the serum PRL levels between the patients prior to treatment and the controls. Correlations between PASI scores and serum PRL levels before and after treatment were not found.

Abbreviations: PRL, prolactin; NB-UVB, narrow-band ultraviolet B; PASI, psoriasis area severity index.

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Peer review under responsibility of Alexandria University Faculty of Medicine.
Psoriasis is a chronic relapsing T-cell mediated hyperproliferative cutaneous disease of multifactorial etiology that results from polygenic predisposition combined with triggering factors. It affects approximately 2% of the population. Clinically, it is characterized by sharply demarcated erythematous plaques with silvery white scales. Psoriasis can be limited to the skin or can affect extracutaneous sites such as the joints. Treatment is tailored according to the patient’s condition and response to therapy.2

Keratinocyte hyperproliferation and abnormal differentiation, lymphocyte infiltration together with various dermal vascular changes are characteristic findings in psoriasis. T-lymphocytes and their cytokines and chemokines play an important role in psoriasis.3

Stress and hormonal factors have been implicated in the pathogenesis of psoriasis.4 Psoriasis has been reported to worsen at times when hormonal changes such as puberty or menopause occur, and may worsen, improve or remain unchanged during pregnancy and post partum.5 One of the hormones that has been implicated in the pathogenesis of psoriasis is prolactin (PRL), which is one of the major hormonal signals that are upregulated in response to psychological and physical stress.6 PRL was found to have local cytokine-like activities, and to stimulate the proliferation of human keratinocytes in vitro.7

Bromocriptine is a tetracyclic ergoline compound derived from plant alkaloids. It is a strong dopamine D2-receptor agonist that inhibits pituitary secretion of PRL. Bromocriptine has also partial D1-receptor agonist activity, 5-HT2 antagonist effects and mild adrenergic effects.8 Oral doses of 5.0–7.5 mg/day typically cause a marked fall in the concentration of circulating prolactin. Higher doses are used to treat acromegaly and Parkinsonism. Common side effects include nausea, headache, dizziness and fatigue.9 Several studies demonstrated the beneficial effects of bromocriptine on psoriatic skin lesions.10,11 Psoriatic arthritis,12 and autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis, Reiter’s syndrome and uveitis.13

The aim was to assess the clinical efficacy of bromocriptine and the influence of serum prolactin levels on disease severity in patients with chronic plaque-type psoriasis.

2. Materials and methods

This study was approved by the ethics committee of the Alexandria faculty of medicine. An informed consent was signed by all patients and control subjects prior to participation in the study.

Forty-five patients with chronic plaque-type psoriasis and 45 healthy control subjects were recruited in the study. Exclusion criteria were pregnancy, lactation, uncontrolled hypertension, endocrine, renal, hepatic or psychiatric disease.14 Patients receiving medications known to induce hyperprolactinemia such as haloperidol, thioridazine, resperidone, clomipramine, sertraline, fluoxetine, paroxetine, buspirone, metoclopramide, domperidone, alpha-methyldopa, verapamil, cimetidine, ranitidine and fenfluramine15 were excluded from the study and so were patients with known hypersensitivity to bromocriptine or any ergot alkaloid. Patients with serum PRL levels suggestive of prolactinoma (>100 ng/ml) or presenting clinically with galactorrhea, amenorrhea, impotence, decreased libido, headache or visual disturbances were also excluded.

No topical or systemic forms of treatment were received by the patients for a minimum of 2–6 weeks respectively prior to starting therapy in the study. Patients already receiving treatment for their psoriasis and demonstrating clinical improvement at the time of enrollment were not included in the study and so were patients with a history of recent acitretin intake.

Patients were randomly divided into three equal groups; the first group was treated with narrow-band ultraviolet B (NB-UVB) and received three sessions per week, the second group received bromocriptine in a dose of 5 mg/day. The third group received NB-UVB sessions three times per week and bromocriptine in a dose of 5 mg/day. Two of the patients receiving bromocriptine developed mild nausea and one patient developed headache, but the symptoms were not severe enough to warrant discontinuation of therapy.

In all three groups, treatment was continued for twelve weeks. Serum PRL levels were measured and psoriasis area severity index (PASI) scores were calculated in all patients before starting therapy and at the end of the 12-week treatment period.

2.2. Serum PRL measurement

A morning blood sample was taken from the patients under standardized conditions. In females samples were taken in the premenstrual phase of the cycle. Quantitative determination was done in serum using the ADVIA Centaur® system, which is a two-site sandwich immunoassay using direct chemilumimetric technology, which uses constant amounts of two antibodies. The first antibody, in the Lite Reagent, is a polyclonal goat anti-prolactin antibody labeled with acridinium ester. The second antibody, in the Solid Phase, is a monoclonal mouse.
anti-prolactin antibody, which is covalently coupled to paramagnetic particles. A direct relationship exists between the amount of PRL present in the patient sample and the amount of relative light units detected by the system.

2.3. Psoriasis severity assessment

The degree of disease severity was assessed using PASI score.16 PASI scores were assessed by the same investigator at the beginning and at the end of the 12-week treatment period.

2.4. Statistical analysis

Data were fed to the computer using IBM SPSS software package version 20.0. Qualitative data were described using number and percent. Association between categorical variables was tested using Chi-square test. When more than 20% of the cells have expected count less than 5, correction for chi-square was conducted using Fisher’s Exact test or Monte Carlo correction. Quantitative data were described as median (min—max), as well as mean ± standard deviation. For normally distributed data, parametric tests were applied. If the data were abnormally distributed, non-parametric tests were used. For normally distributed data, comparison between two independent populations was done using independent t-test. When more than two populations were analyzed ANOVA was used. For abnormally distributed data, Mann–Whitney test was used to analyze two independent populations. If more than two populations were analyzed Kruskal–Wallis test was used. Wilcoxon signed-rank test was used to compare between the different periods. Correlations between two quantitative variables were assessed using Spearman coefficient. Significance test results are quoted as two-tailed probabilities. Significance of the obtained results was judged at the 5% level.

3. Results

No significant differences were found between patients and controls regarding the age ($p = 0.138$), sex ($p = 0.109$), skin type ($p = 0.969$) and serum PRL ($p = 0.460$). Patients were randomly divided into three equal groups. In all three groups, patients were age ($p = 0.125$), sex ($p = 0.910$) and skin type ($p = 0.909$) matched.

3.1. Serum PRL levels and disease severity

None of the patients participating in this study had serum PRL levels exceeding the reference range values (non pregnant females: 2.8–29.2 ng/ml, males: 2.1–17.7 ng/ml). There was no significant difference in the pre-treatment serum PRL levels among the psoriatic groups ($p = 0.744$) (Table 1). Correlations between PASI scores and serum PRL levels before ($r = -0.048$, $p = 0.755$) and after treatment ($r = 0.211$, $p = 0.450$) in the group treated with NB-UVB, $r = -0.232$, $p = 0.405$ in the group treated with bromocriptine, and $r = 0.132$, $p = 0.638$ in the group treated with both NB-UVB and bromocriptine) were statistically insignificant.

3.2. Effect of therapy on serum PRL levels

The post-treatment PRL levels were significantly lower than the pre-treatment levels in the groups receiving bromocriptine ($p = 0.001$). Post-treatment serum PRL levels were significantly lower in both groups receiving bromocriptine ($p < 0.001$) than the group treated with NB-UVB alone. The group receiving NB-UVB and bromocriptine had significantly lower post-treatment serum PRL levels than the group treated with bromocriptine alone ($p < 0.001$) (Table 1).

3.3. Effect of therapy on disease severity

There was no significant difference in the pre- or post-treatment PASI scores ($p = 0.073$, $0.345$, respectively) among the psoriatic groups. Post-treatment PASI scores were significantly lower than pre-treatment values in each of the three treated groups (Table 2). There was also no significant difference in the number of responders and non-responders among the treated groups ($p = 0.104$) (Table 3). There was, however, a trend toward significance ($p = 0.55$) on comparing the number of responders and non-responders in the group treated with bromocriptine alone and the group treated with both NB-UVB and bromocriptine.

4. Discussion

Several studies have pointed to the possible role of PRL in the pathogenesis of psoriasis. Some authors found serum PRL levels to be significantly higher in psoriatic patients compared to normal control subjects.17,18 Some psoriatic patients were even found to be hyperprolactinemic.17 A significant correlation between serum prolactin levels and PASI scores was also detected, suggesting that PRL may serve as a useful marker for disease activity.18 Other investigators, however, did not find a correlation between serum PRL levels and PASI scores, nor did they find serum PRL levels to be significantly higher in psoriatic patients compared to healthy controls.19,20

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Pre- and post-treatment serum PRL levels in the treated groups.</th>
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<tbody>
<tr>
<td></td>
<td>Narrowband group ($n = 15$)</td>
</tr>
<tr>
<td>Pre-treatment Prolactin (ng/ml)</td>
<td>6.7 (2.7–11.4)</td>
</tr>
<tr>
<td>Post-treatment Prolactin (ng/ml)</td>
<td>6.8 (5.0–15.0)</td>
</tr>
<tr>
<td>$p_2$</td>
<td>0.078</td>
</tr>
</tbody>
</table>

$p_1$: $p$ value for Kruskal Wallis test.
$p_2$: $p$ value for Mann–Whitney test.
Data are expressed as median (min–max).
$^*$ Statistically significant at $p \leq 0.05$. 
El-Khateeb et al. did not find a correlation between PASI scores and PRL levels in lesional and non-lesional skin. They found, however, PRL levels in lesional skin to be significantly higher than non-lesional skin and serum of psoriatic patients, which led to the assumption that locally produced PRL in psoriasis lesions rather than circulating PRL levels may play a role in the pathogenesis of psoriasis. In our study none of the patients were hyperprolactinemic. Serum PRL levels were not significantly higher in psoriatic patients compared to control subjects. We did not find a significant correlation between PASI scores and serum PRL levels before or after treatment. These findings led us to question the hypothetical role of circulating PRL in the pathogenesis of psoriasis and its value as a marker for disease activity.

Bromocriptine has long been investigated for its immunosuppressive properties, which may be related to its ability to lower circulating PRL levels or to its direct suppressive effect on B and T cells. Several studies reported the efficacy of bromocriptine in the treatment of psoriasis and psoriatic arthritis. 

Bromocriptine was also reported to improve psoriasis in three patients whose disease worsened with the development of prolactinoma and relapsed when bromocriptine was discontinued. It was also reported to improve psoriatic arthritis in a case of hyperprolactinemia. In our study we found bromocriptine, either alone or in association with NB-UVB, to be effective but not superior to NB-UVB in the treatment of chronic plaque-type psoriasis. We did not find bromocriptine or the combination of NB-UVB and bromocriptine to be superior to NB-UVB in the treatment of psoriasis, nor did we find a correlation between serum PRL levels and disease severity. Further placebo-controlled studies of longer duration and with larger sample size are required to confirm our findings.

5. Conclusion

Our data suggest that bromocriptine may have a role in the treatment of chronic plaque-type psoriasis in the absence of hyperprolactinemia, and that NB-UVB may have an additive effect to bromocriptine on serum PRL levels. We did not find bromocriptine or the combination of NB-UVB and bromocriptine to be superior to NB-UVB in the treatment of psoriasis, nor did we find a correlation between serum PRL levels and disease severity. Further placebo-controlled studies of longer duration and with larger sample size are required to confirm our findings.

References