VIDENTES

Improvement of Psoriasis Vulgaris With Oral Nickel Dibromide

A possible connection between nickel and the pathogenesis of psoriasis is indicated in at least 2 diverse studies.1,2 Bromide absorption has been proposed as a beneficial factor in psoriasis treatment at the Dead Sea, and bromide salts were found to have an antiproliferative effect on cell growth in cultures.3 A pilot study was designed to evaluate the effect of oral nickel and bromide therapy on psoriasis vulgaris.

Subjects and Methods. This was a 2-period (12 weeks in each period), placebo-controlled, crossover study with a 48-hour washout between periods (the biological half-life of serum nickel ranges from 11-28 hours).4 Patients were evaluated at baseline and every 4 weeks thereafter. Eligible patients with at least 5% body surface area of plaque-type psoriasis were recruited from the clinic (Steven A. Smith, MD, Dermatology PC, Tulsa, Okla) patient database. Patients were instructed to discontinue all psoriasis treatments at least 2 weeks before and throughout the study. The study monitor assigned patients as they enrolled to 1 of 2 treatment groups (ie, placebo treatment before active intervention or active intervention before placebo) in an alternating manner, except for the last 5 patients, who were assigned to the second group to introduce more patients undergoing active treatment in the first period. Both patients and the clinical investigator (S.A.S.) were blinded to the assignment scheme.

The active study medication consisted of nickel dibromide dissolved in distilled water; the placebo consisted of distilled water with 0.45% sodium chloride. There were no distinguishable differences in appearance or taste. Dosage of the active study medication was 0.015 mg/kg per day of nickel and 0.041 mg/kg per day of bromide. Patients were instructed to take the medication orally in the early morning, 1 hour prior to eating, for maximum absorption.4

In light of the pilot status of this study, a simplified 5-point global assessment scale (worse, 0 through improved markedly, 4) was used by both the patient and clinical investigator. Standardized photographs were taken of the whole body (front and back) and of a selected regional area documenting the most severe involvement. The same evaluations were performed at 4-week intervals. A blinded independent physician (V.B.) evaluated the photographs based on a 7-point scale (markedly worse, 1 through markedly improved, 7). Intervention efficacy was determined by a significant (α=.05) improvement in the psoriatic condition from baseline. The incidence and severity of adverse events as well as significant changes from baseline in results of the routine serum chemistry profile, complete blood cell count, and urinalysis were used to monitor safety. Data were analyzed using the paired and independent t test (for laboratory values), Wilcoxon matched pairs test (for treatment effects), and Mann-Whitney U test (for period and carryover effects).

Since the potential for large variability of gastrointestinal nickel absorption exists* and since it has been postulated that there might be greater improvement among patients who absorb more nickel, active-treatment patients were divided into 2 subgroups (high and low) with the overall mean serum nickel level as the dividing point. Efficacy parameters for the 2 serum nickel subgroups and the placebo group were then compared.

Results. Twenty-three patients matched for age and sex were enrolled in the study. There were no significant differences between baseline surface area involvement of psoriasis and erythema-thickness scale involvement between the active intervention and placebo groups. Nine patients were assigned to group 1 (placebo before active intervention) and 14 patients to group 2 (active intervention before placebo). Twenty-two patients completed the entire 24-week study. The period and carryover effects of the efficacy variables were not significant (α=0.05; Table), indicating that there was no statistically significant carryover effect of the study medication from the first period to the second.

A summary of the analysis of treatment effects is listed in the Table. The global psoriatic condition of patients receiving active medication tended to remain stable or improve and the condition of patients taking the placebo tended to worsen (the study was conducted during fall and winter). A statistically significant improvement in patients taking the active medication vs patients taking the placebo was found for the self-assessed score (P=.03), the clinical investigator's assessed score (P=.03), and the independent physician's assessed score from photographs (P=.04; Table; Figure 1 and Figure 2).

<table>
<thead>
<tr>
<th>Treatment Effects*</th>
<th>Placebo Group</th>
<th>Active Treatment Group</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>Median</td>
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<tr>
<td>Serum nickel levels</td>
<td>0.9</td>
<td>0.5</td>
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<tr>
<td>Self-assessed global change</td>
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<td>1.0</td>
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<tr>
<td>Clinician's assessment of global change</td>
<td>0.6</td>
<td>0</td>
</tr>
<tr>
<td>Independent physician's assessment of global change</td>
<td>3.5</td>
<td>3.0</td>
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</tbody>
</table>

*All data are presented as α values.
Nickel absorption varied, as was expected, among patients receiving the active intervention (steady state serum nickel levels of 20.5-426 nmol/L; mean±SD, 211.3±42.6 nmol/L). Patients taking the placebo had significantly lower serum nickel levels (mean±SD, 15.3±5.1 nmol/L). The effect of nickel absorption on psoriatic improvement was evaluated by grouping the patients receiving active treatment into high (mean serum nickel levels ≥211.3 nmol/L; n=10) and low (mean serum nickel levels <211.3 nmol/L; n=12) subgroups. During the 12 weeks of active treatment, patients in the high serum nickel subgroup improved significantly more than those in the low subgroup (self-assessment, P=.02; clinical assessment, P=.02; and independent photographic assessment, P=.01). When compared with the patients taking the placebo, the high serum nickel subgroup improved significantly while the low serum nickel subgroup did not.

Two patients taking the active medication had minor cutaneous eruptions that resolved spontaneously in 1 to 3 weeks. Systemic nickel reaction is a possible explanation. No cutaneous eruptions occurred while patients were taking the placebo medication. Other adverse events that occurred in both the active intervention and placebo groups were mild and no patient found it necessary to discontinue participation in the study. Results of routine laboratory studies revealed no identifiable problems.

Comment. Nickel and psoriasis are ubiquitous subjects in dermatology, yet their juxtaposition has been exceedingly rare.1 2 We believe the administration of nickel and bromide addresses an unexplored genetic biochemical defect. We hypothesize that genetically susceptible individuals require and retain excess nickel in an attempt to compensate for a defective nickel-dependent enzymatic process.1 We do not have a hypothesis for the role of bromide in the pathogenesis of psoriasis; however, antiproliferative effects of bromide have been reported in vitro.3

To test our hypothesis we administered oral nickel dibromide to 22 patients in a designed crossover study. We found that patients receiving active treatment improved more than those taking the placebo to a statistically significant degree (P<.05). A blood level–response relationship for nickel was also established (P<.05), further confirming pharmacological action. The beneficial effects were modest on average; however, this may have been due to the low doses administered. The low doses combined with the low level of nickel absorbed by some patients appear to be substantial factors in lowering the overall performance of the active intervention medication.

We present this information suggesting a link of nickel and bromide pharmacological characteristics (and possibly pathophysiological features) with the psoriatic process. Further studies are needed to investigate not only the independent effects of treatment with nickel and bro-
mide, but also the dose-response relationship of multiple-dose groups and the underlying mechanism of action.

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Dr Smith holds US patents 5 171 581 and 5 433 954 covering the use of nickel and bromide compounds for the treatment of psoriasis. These patents are licensed to Plymouth Pharmaceuticals Inc, Tulsa. Dr Smith is the majority shareholder in Plymouth Pharmaceuticals Inc.

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