A Double Blind Placebo Controlled Trial of Low Dose Clotrimazole in Rheumatoid Arthritis

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Abstract. Seventy-three patients with rheumatoid arthritis were randomized in a double blind study to receive either clotrimazole (20 mg/kg/day) 2 days a week for 12 weeks or matching placebo. Patients receiving clotrimazole had significant improvements (p < 0.05) from baseline in measurements of grip strength, joint count, and patient assessment of pain, but did not show significant improvement over patients treated with placebo. More adverse experiences, predominantly gastrointestinal complaints, occurred in patients taking clotrimazole resulting in 9 patients discontinuing therapy. (J Rheumatol 1990;17:1003-7)

Key Indexing Terms:
RHEUMATOID ARTHRITIS CLOTRIMAZOLE CONTROLLED TRIAL

Clotrimazole [1-(chloro-α-diphenylbenzyl]imidazole] is an imidazole derivative which is utilized primarily for its antifungal and oral candidiasis. Clotrimazole and other imidazoles have also been shown to have immunomodulating properties such as a dose dependent inhibition of polymorphonuclear (PMN) chemotaxis and inhibition of lymphocyte stimulation by phytohemagglutinins, concanavalin A and pokeweed mitogen. Imidazoles such as cimetidine, phenytoin, metronidazole, levamisole, fenfluramine, imidazole-2-hydroxybenzoate, tiflamizole, and clotrimazole have been studied in the treatment of rheumatoid arthritis (RA) with mixed results. After the report of an encouraging but uncontrolled study, clotrimazole was compared to ketoprofen in a controlled study by Wotjulewski, et al. "Up to 80 mg/kg/day of clotrimazole" was given orally for 8 weeks, and although there was a trend in favor of the clotrimazole group during the second month, only one variable reached statistical significance. Adverse effects were more common in the clotrimazole group and 7/24 patients in that group withdrew.

Our study was designed to assess the efficacy and safety of a lower dose of clotrimazole in the treatment of RA. The dosage was selected because of an unacceptably high incidence of adverse effects in trials using a higher dose of clotrimazole, the effectiveness of levamisole at lower and weekly doses, and a report from an uncontrolled trial of possible efficacy at lower doses.

MATERIALS AND METHODS

A total of 73 adult patients from the rheumatology clinics at North Carolina Baptist Hospital were entered into the study. Eligibility required either definite or classical RA by the 1985 American Rheumatism Association criteria. Active disease was defined by the presence of 3 of the following: number of tender or painful joints ≥ 6, number of swollen joints ≥ 3, duration of morning stiffness ≥ 30 min, and Westergren erythrocyte sedimentation rate (ESR) > 28 mm/h.

All patients signed informed consent documents as approved by the local Internal Review Board. Patients were excluded if signs or symptoms of other rheumatic diseases were present, as were patients with active peptic ulcer disease, gastritis, or other important gastrointestinal (GI) diseases (based primarily upon clinical criteria), cirrhosis, liver enzyme abnormalities > 20% above the upper limits of normal, or any active systemic disease not well controlled by medications or potentially causing a problem to the patient. Pregnant or lactating females and premenopausal females not following acceptable birth control methods were excluded. Patients were also excluded who were treated with corticosteroids within 2 months of beginning the study and patients treated with other second line agents such as gold, penicillamine, antimalarias, or cytotoxic drugs within 3 months of beginning the study. Stable NSAID therapy for at least one month was required and maintained throughout the trial.

Eligible patients were randomized to one of 2 double blinded treatment groups. They were scheduled to receive either clotrimazole in 250 mg compressed/tablet (provided by Miles Pharmaceuticals, West Haven, CT) in a dose of 20 mg/kg/day or identical placebo tablets in 4 divided doses on 2 consecutive days/week for 12 weeks. For inclusion in the efficacy analysis, a patient had to complete at least 4 weeks of therapy; all patients were included in the adverse experiences analysis.

Patients were assessed on a weekly basis after an initial history, examination, disease assessments, and laboratory analyses. Hours of morning stiffness, grip strength, joint count, 10 point patient and observer visual analogue scales, and weekly stool hemocult cards were obtained at each visit. Automated serum chemistries (SMAC), urinalysis, and complete blood counts (CBC) were obtained every other week; a rheumatoid factor (RA latex) and ESR were scheduled for the initial and 12th or early termination visits. In the case of dropouts before 4 weeks, RA latex and ESR were not repeated. A modified rheumatoid activity index (MRAI) was calculated before treatment and at completion of the study. The MRAI was a slight modification of the described MRAI which is based upon the sum of par-
tial scores for 6 measures. That MRAI was developed from McCarty's rheumatoid activity index which has been partially validated for some of the components. The relative weights assigned to each variable were grip strength (0–30), joint count (0–40), patient and observer assessments of pain (0–50 each), ESR (0–45) and RA latex (0–30). The joint count relative score is based upon a total joint count of 0–60 rather than the 0–200 value in the prior indices. The 6 subscores are summed and multiplied by 5/6 to obtain the MRAI. A clinical rheumatoid activity index (CRAI) based on the scores for grip strength, joint count, and patient and observer assessment of pain, was also calculated in order to include patients in an intent to treat analysis which did not have a final ESR and RA latex. The CRAI was multiplied by 6/4 in an effort to make it comparable in magnitude to the MRAI. The MRAI and CRAI gave similar results for those patients for whom both could be calculated.

Adverse experiences were defined as untoward signs and symptoms which could in any way be related to drug administration. A question was posed to the patient “How do you feel?” on each visit and the answer recorded. These were later reviewed and categorized by the investigator before unblinding. If a patient withdrew before study completion, an effort was made to determine the reason for dropout. A history, examination and laboratory assessments were performed at dropout or at study completion by the same observer (out of 3) when possible. All patients who returned for at least one followup evaluation were included in the adverse experiences analysis.

Statistical considerations. The MRAI was considered the primary response variable. Estimation of the required sample size was made using data on variability from a recent 6-month protocol comparing 500 mg/day penicillamine with up to 100 mg/day azathioprine. Based on this study a difference of 11 in an initial to final MRAI change was chosen as a clinically significant improvement. Therefore, for a Type I error equal to 0.05 (2 tailed t test) with a power of 0.80, 32 patients/group would be needed to detect a true difference of 11 in an initial to final MRAI change.

Measurements in Table 1 were used to evaluate efficacy. Paired t statistics were calculated to test average changes within treatment groups. Differences between average changes for treatment groups were tested with a 2 sample t test. \( \chi^2 \) analyses were performed on adverse experience data. No adjustment in probability levels was made for tests involving multiple secondary response variables. For secondary variables relative p values based upon the t tests are shown but these are presented as a basis for hypothesis development.

RESULTS
A total of 73 patients were enrolled in this study, 37 in the placebo group and 36 in the clotrimazole group. The patients in each group were well matched with respect to disease duration (mean of each group = 112 months), age (mean of each group = 51 years) and the male/female ratio. The distribution of NSAID therapies for the 2 groups was also well balanced. About 50% of patients in both groups reported previous use of second line therapy. Average duration of previous second line treatment was similar in both groups as well as type of agent used; gold compounds and prednisone were the most prevalent forms of therapy. The average length of time since discontinuation of second line therapy was 55 months for placebo and 52 months for clotrimazole patients. When considering initial clinical measurements (Table 1) there was a higher initial ESR (51 vs 35 mm/h) (p < 0.025) for the clotrimazole patients. No other entry variables had notable differences.

Three patients, (2 clotrimazole, 1 placebo) never returned after they were randomized. For 6 other patients, 4 taking clotrimazole and 2 taking placebo, final ESR and RA latex measures were not obtained as specified in the protocol for withdrawal before the end of the 4th week. The efficacy analysis completed on 64 patients, 34 placebo and 30 clotrimazole, is summarized in Table 1. An intent to treat analysis based upon the 36 placebo and 34 clotrimazole patients who returned for at least one followup was performed on the clinical index (CRAI-last line Table 1). The ratio of final to initial level of the measures shown in Table 1 were

Table 1. Changes in clinical measurements in patients completing 4–12 weeks of treatment with clotrimazole or placebo

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Placebo (n=34)</th>
<th>Clotrimazole (n=30)</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Initial</td>
<td>Final</td>
<td></td>
</tr>
<tr>
<td>Grip strength (mm Hg)</td>
<td>120 ± 12.2</td>
<td>134 ± 12.7</td>
<td>14.9 ± 5.4**</td>
</tr>
<tr>
<td>Joint count (0–60)</td>
<td>30 ± 2.7</td>
<td>28 ± 3.1</td>
<td>-2.6 ± 2.5</td>
</tr>
<tr>
<td>Patient assessment of pain (0–10)</td>
<td>6 ± 0.3</td>
<td>6 ± 0.4</td>
<td>-0.2 ± 0.3</td>
</tr>
<tr>
<td>Observer assessment of pain (0–10)</td>
<td>5 ± 0.3</td>
<td>5 ± 0.4</td>
<td>-0.1 ± 0.3</td>
</tr>
<tr>
<td>ESR (mm/h)</td>
<td>35 ± 4.2</td>
<td>38 ± 4.5</td>
<td>2.8 ± 3.4</td>
</tr>
<tr>
<td>RA latex (tube dilutions)</td>
<td>6 ± 0.5</td>
<td>6 ± 0.4</td>
<td>0.1 ± 0.2</td>
</tr>
<tr>
<td>MRAI†</td>
<td>97 ± 5.9</td>
<td>93 ± 6.9</td>
<td>-4.2 ± 4.3</td>
</tr>
<tr>
<td>CRAI‡</td>
<td>111 ± 7.5</td>
<td>103 ± 9.4</td>
<td>-8.2 ± 5.8</td>
</tr>
</tbody>
</table>

† Values shown are mean ± SEM.
‡ Clotrimazole treated group versus placebo treated group by 2 sample t test.
* p < 0.05.
** p < 0.025.
§ Modified rheumatoid activity index.
† Clinical rheumatoid activity index.

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also calculated for these 70 patients. The percentages of patients who showed at least 25% improvement in the measures for placebo (P) and clotrimazole (C), respectively, are grip strength, 3(P), 0(C); joint count, 33(P), 38(C); patient assessment of pain, 19(P), 31(C); observer assessment of pain, 19(P), 18(C); ESR, 26(P), 23(C); RA latex, 0(P), 10(C); MRAI, 17(P), 23(C); and CRAI, 25(P), 26(C). It was noted that the joint count increased by more than 25% for 1/3 of the placebo but only 1/6 of the clotrimazole patients.

Both clotrimazole and the placebo groups had sizable improvements in grip strength (p < 0.05 and p < 0.025) (Table 1). The clotrimazole group also showed significant (p < 0.05) improvements in joint count and patient assessment of pain. Measurements of ESR, RA latex, and MRAI showed improvements for the clotrimazole group but these were not significant. There were no significant differences seen between changes within the clotrimazole group compared to changes within the placebo group for either primary or secondary response variables. The results of the intent to treat analysis were not in conflict with the results of the efficacy analysis and also revealed no significant differences between the groups. Additional analyses compared those clotrimazole patients who completed a 12 week course (n = 19), to those who completed 4-8 weeks (n = 9); also placebo patients completing 12 weeks (n = 26) were compared with the corresponding clotrimazole group (n = 19) and no significant differences were found. Compliance for patients included in the efficacy analysis was acceptable for both the placebo (> 99%) and clotrimazole arms (97.2%) whose lower compliance was affected primarily by adverse experiences.

Withdrawals. In the placebo group, 11 patients withdrew prior to the completion of the study, while 18 patients in the clotrimazole group withdrew (Table 2). Clotrimazole dropouts occurred somewhat earlier on average than placebo dropouts. Lack of effect as perceived by the patient was given as the reason for withdrawal in 5 patients in both groups. In the placebo group, one patient developed a rash and was withdrawn from the study, while 9 patients in the clotrimazole group were withdrawn because of adverse experiences.

Table 2. Summary of patients withdrawing before study completion

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Clotrimazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number enrolled</td>
<td>37</td>
<td>36</td>
</tr>
<tr>
<td>Number withdrawing &lt; 4 weeks*</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Total withdrawals</td>
<td>11</td>
<td>18</td>
</tr>
<tr>
<td>Reason for withdrawal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse experience</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>Lack of effect</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Unrelated†</td>
<td>5</td>
<td>4</td>
</tr>
</tbody>
</table>

* Excluded from efficacy analysis.
† Intercurrent illness: lost to followup.

No particular NSAID therapy was found to associate with withdrawal. Only 4 of 9 patients among the clotrimazole dropouts withdrew within the first 4 weeks. Reasons included burning upon urination, decreased mental alertness, upper GI tract symptoms, and elevated liver enzymes. Other adverse experiences occurred in the 9 patients and 19 of 89 total occurrences were in these patients. Five patients in the placebo group and 4 patients in the clotrimazole group were either lost to followup or withdrew from the study because of an intercurrent illness. In addition, there were more adverse experiences in the clotrimazole patients, both among those who withdrew before 12 weeks and those who completed the study.

Adverse experiences. Adverse experiences were common in both groups with 89 separate occurrences in the clotrimazole group and 60 in the placebo group (Table 3). Upper GI symptoms were the most frequent adverse experience in both groups with a significantly greater (p < 0.05) number of occurrences in the clotrimazole group. About 64% of patients in that group complained of nausea, vomiting, epigastric burning, indigestion, anorexia or regurgitation. Complaints of burning upon urination (genitourinary) were more common (p = 0.053) in the clotrimazole group, as were central nervous system (CNS) adverse experiences (p < 0.025) including decreased mental alertness and taste abnormalities. Liver function test elevation (LFT) (i.e., SGOT, SGPT, GGT) were more frequent in the clotrimazole group but this was not significantly different. Elevation was considered as a > 10% rise above the normal range or > 10% upward change during treatment if levels were initially elevated. Only one patient in the clotrimazole group was withdrawn because of elevated LFT. A total of 5 patients in both groups had abnormal LFT which resolved while on treatment. Five patients in the clotrimazole group had sustained mild elevation in LFT which resolved after completion of the study compared to 3 patients in the placebo group. When side effects were examined by NSAID classes, the placebo group showed a fairly equal number of incidences between the classes. Within the clotrimazole group and compared to the placebo group, somewhat more side effects were found with the propionic acids or with piroxicam. These differences were seen in GI, genitourinary, and CNS symptoms. No patient in either group had serious longterm morbidity resulting from treatment. No significant changes were observed in white blood cell counts either within or between groups.

DISCUSSION

Wyburn-Mason reported dramatic and essentially curative results in an uncontrolled study using clotrimazole at the daily dose of 25-100 mg/kg body weight for less than one month. He also noted similar results with only 10-20 mg/kg. A controlled study attempted to confirm this using 40 mg/kg/day clotrimazole and increasing this to 80 mg/kg/day.
in divided doses. Clotrimazole in these doses compared to ketoprofen at 50 mg PO TID produced no significant differences in clinical measurements after 8 weeks of treatment in 47 patients. One measurement, grip strength, favored clotrimazole at 4 weeks. There was a trend in favor of the clotrimazole group after 4 weeks and the consumption of analgesics was significantly lower in this group during the second month. In our study we attempted to control type II error at the p < 0.2 level by increasing sample size and felt that by increasing the duration of clotrimazole administration to 12 weeks and comparing it to placebo, a difference could be found if it existed. Thus, there is a 1 in 5 chance that a real difference greater than 11 in the MRAI change (chosen as a clinically significant change) was missed.

There were statistically significant improvements in clinical measurements in both the placebo group and the clotrimazole group but the level of these changes was not statistically significant between the groups. The trend toward improvement in the clotrimazole group might have reached statistical significance had a larger number of patients been included in each group, larger doses of clotrimazole been employed or a longer treatment regimen been utilized.

Entry ESR were significantly higher in the clotrimazole group than the placebo group. However, when calculating the MRAI in which the ESR is used in part, no difference could be detected in disease activity.

Our study resulted in a greater occurrence of adverse experiences and withdrawals when using clotrimazole than was noted in previous studies. Differences in definition of adverse experiences and concomitant NSAID treatment could explain, in part, the comparatively large numbers of adverse experiences in our study. The predominance of upper GI symptoms confirms Wotjulewski's experience. An explanation of the complaint of burning upon urination was not found when examining the urine chemistry and sediment.

Our laboratory has recently published the effects of clotrimazole treatment on arachidonic acid metabolism in peripheral blood polymorphonuclear leukocytes (PMNL) from 4 of the patients reported in this study. In those patients, clotrimazole treatment did not result in statistically significant effects on whole cell PMNL arachidonic acid metabolism or in vitro PMNL phospholipase A activity when compared to 5 placebo treated patients. Those findings are consistent with the lack of significant clinical effect reported here.

In conclusion, our study revealed no significant difference in efficacy in patients treated for at least 4 weeks with either clotrimazole or placebo. Adverse experiences were significantly greater in the clotrimazole treated group. Our findings thus do not support a therapeutic role for clotrimazole at doses utilized in this study for the treatment of patients with RA.

REFERENCES