Equivalent Therapeutic Efficacy and Safety of Ivermectin and Lindane in the Treatment of Human Scabies

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Objective: To compare the therapeutic efficacy and safety of ivermectin and lindane for the treatment of human scabies.

Design: Randomized, prospective, controlled, double-blind, “double-dummy,” and parallel clinical study.

Setting: A single department of dermatology at a hospital in Buenos Aires, Argentina.

Patients: Patients were outpatients, hospitalized patients, and those referred to our hospital from nursing homes and asylums. Fifty-three patients had clinical signs and symptoms compatible with scabies.

Intervention: Patients received either a single oral dose of ivermectin (150-200 µg/kg of body weight) or a topical application of 1% lindane solution. Treatment was repeated after 15 days if clinical cure had not occurred.

Main Outcome Measures: Clinical healing and adverse effects.

Results: Of 53 patients, 43 (81%) completed the study, 19 in the group treated with ivermectin and 24 in the group treated with lindane. At day 15, 14 patients (74%; 95% confidence interval, 48.8%-90.8%) in the group receiving ivermectin showed healing of their scabies and 13 patients (54%; 95% confidence interval, 32.8%-74.4%) in the group treated with lindane were healed. At 29 days, both treatments resulted in statistically equivalent therapeutic efficacy: 18 patients (95%; 95% confidence interval, 74.0%-99.9%) were healed with ivermectin and 23 patients (96%; 95% confidence interval, 78.9%, 99.9%) were healed with lindane (P<.02). Adverse effects from the treatments were few, mild, and transient. Results from laboratory tests showed no major abnormalities and no difference between treatments.

Conclusions: Ivermectin is as effective as lindane for the treatment of scabies. Ivermectin is simpler to use and, therefore, is a promising tool to improve compliance and to control infestations.

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CABIES IS a contagious pruriginous parasitosis of polymorphous clinical aspect affecting many millions worldwide. It is caused by an infestation with the mite Sarcoptes scabiei var hominis and transmitted by direct contact, especially under crowded living conditions. Lesions consist of tiny gray specks, burrows, or both. Nonspecific lesions consist of prurigolike or urticarial papules and itchy excoriations and crusts. The lesions are usually found in interdigital folds of the hands, the flexor aspects of the forearms, axillary folds, nipple areola, the periumbilical area, and around the male external genitalia. Affected persons have moderate to severe pruritus, usually with nocturnal exacerbation. Epidemics may affect all residents in enclosed areas, such as asylums, nursing homes, and military barracks.

The standard treatment of scabies is based on the application of acaricides (eg, lindane, permethrin, benzyl benzoate, crotamiton, or other agents) that must remain on the affected area for a certain period and later be removed with soap and water. This type of treatment may need to be repeated several times according to different schedules. With topical treatments, care should be taken to treat the entire body.1,2

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The ideal treatment would be an inexpensive and safe drug involving a single administration. Topical applications may require skilled nursing in an institution. Furthermore, in some parts of the world, the water supply is poor, justifying the
PATIENTS AND METHODS

PATIENTS

From April 6, 1996, to February 3, 1997, men and women older than 18 years with clinical or parasitologic signs and symptoms compatible with scabies (described earlier) were eligible for this study. Patients were outpatients, hospitalized patients, or those referred to our hospital from asylums and nursing homes. All patients were asked to sign a written consent form.

Pregnant or breast-feeding women; patients who had been under treatment of scabies during the 4 weeks before entry into the study; those who showed renal dysfunction (serum creatinine level, $>150 \mu mol/L$ [$>1.8 \text{mg/dL}$]) or hepatic dysfunction (total bilirubin, aspartate and alanine aminotransferase, and $\gamma$-glutamyltranspeptidase levels 3-fold greater than higher reference values); patients who were taking antidepressive drugs or drugs prescribed for pruritus or anxiety that could affect the sensorium; those suffering from severe immunodeficiency, according to clinical variables; patients who were seropositive for the human immunodeficiency virus (HIV) and/or had clinical indicators of high risk for HIV; patients with neoplasias (such as leukemia and lymphoma) that could affect the immune system; those receiving or likely to receive immunosuppressive therapy or radiotherapy; patients with gastrointestinal dysfunction; and those with a history of convulsions were excluded from the study.

ASSESSMENT

During the initial visit, a medical history was taken following a thorough physical examination. Previous concomitant medication use was recorded. A detailed dermatologic examination was then carried out and recorded, including a description of the lesions, their distribution on a body diagram, and the assessment of severity of the scabies lesions on a scale of 0 to 4, as follows: 0 indicates free of lesions (no scabies); 1, 10 or fewer lesions (mild); 2, 11 to 49 lesions (moderate); 3, 50 or more lesions (severe); and 4, crusty (very severe). Pruritus was graded as follows: 0 indicates no pruritus; 1, mild; 2, moderate; 3, intense; and 4, very intense.

Compatible lesions were scarified only at the initial visit, and the resulting specimens were examined microscopically for evidence of $S$ scabiei (adult forms), their eggs, or their fecal pellets. Results were considered positive if any of these were identified.$^{15}$ A positive result of the scarification was considered an ancillary indicator for the diagnosis. A negative result had to be evaluated together with the presence of other signs and symptoms to determine infestation and cure.

Laboratory tests included a pre-entry pregnancy test on all women of child-bearing age and standard blood tests. These tests were repeated on day 8 and, for those who were re-treated (second dose on day 15), on day 22. Any laboratory test that showed an abnormal result during the treatment was repeated at appropriate intervals until the abnormal result resolved, proved stable, or its cause was determined.

search for an easily administered treatment involving a single dose and with minimal adverse effects.

Ivermectin is an antihelminthic agent used to control onchocerciasis and other parasitosis and ectoparasitosis.

TREATMENT

Patients were randomly assigned to receive either a single oral dose of ivermectin, 150 to 200 $\mu$g/kg in 6-mg tablets, and a placebo topical solution, 60 mL (20 patients), or a single dose of 1% lindane topical solution, 60 mL, and placebo tablets (27 patients). Patients who did not fulfill the criteria for a clinical cure—defined as the absence of both pruritus and clinical lesions or a reduction of signs and symptoms to a mild degree—in 15 days repeated the initial treatment. The final evaluation was on day 29.

Patients received explicit written instructions about lotion application. It had to cover the body (from neck to toe) and be kept there for 8 hours. Bed clothes and personal clothes had to be washed with warm water or kept in polyethylene bags for 48 hours and then washed.

Members of the same household who were infested but could not be enrolled in the study received a commercially available product containing 1% lindane or (for infants) a 6% precipitated sulfur cream. Household members who did not show any clinical evidence of scabies were given the same drugs according to their age. For those who did not attend the appointment, it was suggested that they have a follow-up examination in the nearest hospital, and the study patients were encouraged to avoid contact with them during the study period.

Tablets were taken in the presence of the attending physician, and the lotion was applied by the patient. Patients were examined on days 8, 15, 22, and 29. No topical symptomatic treatment was added after the initial therapy.

Clinical cure was defined as the absence of pruritus and clinical lesions or a reduction of signs and symptoms to a score of 1 (mild pruritus and mild lesions) 15 days after the initial treatment or, if applicable, 15 days after the second dose.

STATISTICAL METHODS

Patients were randomly assigned to receive 1 of the 2 treatments on a 1:1 basis. Randomization was performed using a random numbers table and allocating 30 random numbers to each treatment.

The study sample size was calculated using expectations based on previous observational studies and the authors’ experience in similar trials. Calculations assumed that ivermectin and lindane might have a common 80% healing rate at 15 days, with an equivalence margin of 0.2 and a Bonferroni adjustment made for multiple comparisons, with a global significance of $0.05$, a 10% dropout rate, and an 80% statistical power by the Blackwelder test.$^{16}$ Under the preceding constraints, the minimum sample size required for the trial to be successful was 18 patients per treatment, or a total of 36 patients.

Statistical analysis of efficacy was based on the Students $t$ test and the Fisher exact test. For low-frequency events, the exact Blyth and Smith formula$^{17}$ was used to calculate the 95% confidence intervals (CIs).

A statistical analysis of the equivalence of therapeutic efficacy was performed using the Blackwelder test under the alternative hypothesis that ivermectin is, within a margin of equivalence, as effective as lindane. Results were considered significant if $P < 0.05$.

It was estimated that more than 6 million people in more than 30 countries were treated with ivermectin at a dose of 150 to 200 $\mu$g/kg of body weight to control endemic onchocerciasis in Africa, South America, and Mexico. Ad-
verses—such as headache, hypotension, tachycardia, nausea and vomiting, abdominal pain, rash, pruritus, myalgia, and arthralgia—were transient and mild.\(^{3-6}\) Ivermectin has been used successfully in animals for the treatment of scabies and other parasitosis.\(^{7,8}\)

Since 1992, several clinical trials\(^{9-14}\) have been carried out to test the use of ivermectin (100-200 μg/kg) for the treatment of human scabies. These trials revealed high cure rates—70% to 100%—for both the classic form and the crusted Norwegian scabies variety.

Based on those results, we conducted a clinical trial to study whether ivermectin is effective for the treatment of human scabies and to compare its effectiveness with that of 1% lindane by topical application.

**RESULTS**

Fifty-three patients were eligible for the study. Their mean age was 40.8 years; 19 (36%) were men and 34 (64%) were women.

The Figure shows a flow diagram illustrating the progress of patients throughout the trial. Randomization resulted in 2 patient groups similar in demographic and clinical variables and in the severity of scabies. All statistical comparisons between these 2 groups at baseline were nonsignificant.

Slightly more patients dropped out of the group receiving ivermectin (7 of 26) than of the group receiving lindane (3 of 27).\(^{3}\) A subgroup analysis of dropouts vs completers did not show any significant difference at baseline, although the statistical power to detect any difference was impaired by the reduced sample size of the subgroups involved. Thus, with the information at hand, we could not ascertain if these patients dropped out because they perceived the treatment as ineffectual or because they healed and did not return for further examination. Among those who did return, the group treated with ivermectin showed a slightly more favorable healing of their scabies condition after 15 days from the administration of treatment (\(P = .22\)) (14/19 [74%; 95% CI, 48.8%-90.8%]) than the group treated with lindane (13/24 [54%; 95% CI, 32.8%-74.4%]). This tendency, if smaller, still holds if all patients who received medication are taken into account.

Five patients in the group treated with ivermectin and 11 in the group treated with lindane required a second dose. We did not detect any baseline demographic difference between these patients. The patients who required a second dose within each treatment, however, had more severe forms of scabies. Of 35 patients whose scabies healed after a single treatment dose, 6 (17%) had lesions scored as severe. The mean scores for these 35 patients were 1.9 for severity of scabies and 2.4 for pruritus. Of the 16 patients who required a second dose, 8 (50.0%) had lesions scored as severe (\(P = .02\)), with mean scores of 2.4 for the severity of scabies (\(P = .01\)) and 3.3 for pruritus (\(P = .001\)). This difference remains valid even if the intervening treatment is taken into consideration.

As the Figure shows, results from the second application were similar. The overall assessment of treatment efficacy at day 29 indicates that 18 (95%; 95% CI, 74.0%-99.9%) of 19 patients in the group treated with ivermectin and 23 (96%; 95% CI, 78.9%-99.9%) of 24 patients in the group given lindane had healing of their scabies. This difference is not significant (\(P > .99\)). Furthermore, the results of the formal Blackwelder test for the significance of the equivalence of therapeutic efficacy shows that ivermectin is statistically no less efficacious than lindane (\(z = -2.13, P < .02\)).

Adverse effects were mild and transient for both treatments. The group treated with lindane, however, had a higher rate of headaches (6 patients vs 1 patient treated with ivermectin) whereas the group treated with ivermectin had hypotension (1 patient), abdominal pain (1 patient), and vomiting (1 patient). Laboratory test results revealed no significant difference between the 2 treatments.

**COMMENT**

Ivermectin has proved to be extremely useful in the treatment of a wide range of nematode and arthropod parasites. Few studies record its use in human scabies, although it has long been used for the treatment of this mite infestation in different animals. Medical experience is anecdotal and refers to the observation\(^{3}\) of some patients whose scabies condition lessened with ivermectin during a prevention program of onchocerciasis or other filariasis.
Macotela-Ruiz and Peña-González\textsuperscript{13} conducted a controlled, double-blind study of 55 patients with scabies treated with a single dose of ivermectin, 200 µg/kg, vs placebo. Those treated with ivermectin had a healing rate of 74% (37/50) vs 15% (4/26) for those who took placebo (P<.001). Safety indicators, including laboratory test results and reports of adverse effects, were normal, showing no record of adverse effects in either group. In our study group, the therapeutic results with ivermectin were similar, as 14 patients (74%) healed 15 days after the initial treatment and 18 patients (95%) by day 29. Our study, however, compared the use of ivermectin with that of conventional topical 1% lindane treatment of scabies. Ivermectin treatment yielded higher healing rates than the topical treatment 15 days after the initial treatment and was statistically equivalent in therapeutic efficacy at the end of the study. If further studies involving more patients confirm the healing rate difference obtained at day 15, then statistical analysis could establish that ivermectin cures faster than lindane. The present study also addressed treatment safety based on clinical and laboratory variables. At the end of the study, secondary manifestations recorded were few, mild, and similar for both treatments; no severe adverse effect that would require treatment suspension was recorded.

Marty et al\textsuperscript{10} used higher doses of ivermectin in 53 patients either living or working in nursing homes. These patients, regardless of weight, received two 6-mg tablets the first day, followed by 2 tablets a week later. Ivermectin treatment was 100% effective. This result persisted 2 months after treatment. These observations are useful concerning the safety of drugs in older people who are generally receiving polymedication and live together in enclosed groups. The oldest patient in our study was aged 94 years, and 7 patients (13%) were older than 65 years. Although the follow-up lasted no longer than the allowed clinical cure time (15 or 29 days), we did not receive any worrisome report about the safety of ivermectin in the elderly patients treated at nursing homes. Lower doses than those used by Marty et al may also be useful in the treatment of large groups of patients epidemiologically at risk for the contagious diseases typical of enclosed institutions, thus allowing the eradication of the focus of chronic infestations.

To our knowledge, the only published study with similar methods to ours is the one conducted by Glaziou et al.\textsuperscript{18} They carried out a single-blind, comparative, randomized clinical trial in 44 patients using a single dose of ivermectin of 100 µg/kg and compared the results with those of the use of 10% topical benzyl benzoate. Thirty days later, 16 (70%) of 23 patients in the ivermectin group healed vs 10 (48%) of 21 in the group treated with benzyl benzoate. These results show that ivermectin may cure patients with scabies as quickly as benzyl benzoate.\textsuperscript{18} The use of a lower dose of ivermectin than the one we used (100 vs 100-200 µg/kg) might explain the lower rate of cure attained by these authors after 30 days (70.4% vs 94.7% in our study).

Meinking et al\textsuperscript{19} conducted an open-label study in which ivermectin was administered in a single oral dose of 200 µg/kg to 11 otherwise healthy patients with scabies and to 11 patients with scabies who were also infected with HIV, 7 of whom had the acquired immunodeficiency syndrome. None of the 11 otherwise healthy patients had evidence of scabies 4 weeks after receiving a single dose of ivermectin. Of the 11 HIV-infected patients, 4 had severe scabies (50 lesions), and 2 had crusted scabies. In 8 of these patients, the scabies was cured after a single dose of ivermectin, and 2 patients received a second dose 2 weeks later. Ten of the 11 patients had no evidence of scabies 4 weeks after their first treatment with ivermectin. Because of the many reports about the safety of the use of ivermectin in humans suffering from diseases caused by parasites, laboratory tests were not carried out, except when an abnormality was evidenced in the physical examination.\textsuperscript{19} Although there seems to have been a good tolerance to the drug, not enough information can be inferred about the safety of this treatment through this study.

In our study, a group of patients still had the clinical signs and symptoms of the disease 15 days after they had received the first dose of ivermectin, so it was necessary to administer a second dose. The subgroups who received 2 treatments had significant differences regarding the number of nonspecific lesions, total number of lesions, severity of the scabies lesions, and severity of pruritus, the patients with the most severe scabies requiring 2 treatments to ensure therapeutic success. The laboratory profile was within reference ranges in all patients. The low incidence of adverse effects recorded allows this new therapeutic approach to be considered safe.

We found ivermectin as effective as lindane for the treatment of human scabies, allowing a fast and safe cure of this condition through a simple administration. The oral treatment of scabies then becomes an effective resource to control infestation in confined populations and, more generally, for medical plans to eradicate human scabies.

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REFERENCES


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