

Treatment of cutaneous leishmaniasis with aminosidine (paramomycin) ointment: double-blind, randomized trial in the Islamic Republic of Iran

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Objective To compare the parasitological and clinical efficacy of four weeks versus two weeks of treatment with aminosidine (paramomycin) ointment in patients with cutaneous leishmaniasis caused by *Leishmania major* in the Islamic Republic of Iran.

Methods Double-blind, randomized trial of four weeks of aminosidine ointment ($n=108$) vs two weeks of aminosidine ointment and two weeks of placebo ($n=108$). Patients were assessed on days 15, 29, 45, and 105 for clinical cures and clinical and parasitological cures.

Findings Four weeks' treatment gave significantly better cure rates than two weeks' treatment: on day 29, there were 80/108 (74%) vs 64/108 (59%) clinical cures ($P=0.05$) and 47 (44%) vs 26 (24%) clinical and parasitological cures ($P=0.005$). By day 45, fewer patients who received four weeks' treatment had required rescue treatment with antimonials than those who received two weeks' treatment: 20 (19%) vs 36 (33%) ($P=0.02$). On day 105, the results still favoured those who had been allocated four weeks of active treatment, but the differences were no longer as clearly significant. No side-effects were observed or reported.

Conclusion Approximately two-thirds of patients given ointment for four weeks were cured clinically. Although about half of those cured might have recovered spontaneously even without treatment, four weeks of aminosidine ointment could become the first-line treatment for uncomplicated cutaneous leishmaniasis due to *L. major*, with antimonials needed in only the one-third of patients not cured by the end of treatment with aminosidine. This would considerably reduce the costs and side-effects associated with antimonial drugs.

Keywords Leishmaniasis, Cutaneous/drug therapy; Paramomycin/therapeutic use/administration and dosage; Ointments/administration and dosage; Administration, Cutaneous; Treatment outcome; Comparative study; Double-blind method; Randomized controlled trials; Iran (source: MeSH, NLM).

Mots clés Leishmaniose cutanée/chimiothérapie; Paramomycine/usage thérapeutique/administration et posologie; Pomade/administration et posologie; Voie cutanée; Evaluation résultats traitement; Etude comparative; Méthode double aveugle; Essai clinique randomisé; Iran (source: MeSH, INSERM).

Palabras clave Leishmaniasis cutánea/quimioterapia; Paramomicina/uso terapéutico/administración y dosificación; Pomadas/administración y dosificación; Administración cutánea; Resultado del tratamiento; Método doble ciego; Ensayos controlados aleatorios; Irán (fuente: DeCS, BIREME).

الكلمات المفتاحية: داء الليشمانيات، داء الليشمانيات الجلدي، المعالجة الدوائية لداء الليشمانيات الجلدي، الباروموميسين، الاستخدام العلاجي والجرعات للباروموميسين، مراهم، إعطاء المعالجة والجرعات بالمراهم، المعالجة الجلدية، نتيجة المعالجة، دراسة مقارنة، طريقة مزدوجة التعمية، اختبارات معشاة مضبوطة بالشواهد، إيران (المصدر: رؤوس الموضوعات الطبية، المكتب الإقليمي لإقليم شرق المتوسط).

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يمكن الاطلاع على الملخص بالعربية على الصفحة ٣٥٨.

Introduction

Cutaneous leishmaniasis due to *Leishmania major* is a common skin disorder in many parts of south-west Asia (1, 2). At present, the first-line treatment involves antimonials, which require multiple injections, are expensive, and can be toxic. Hence, WHO recommends no treatment for uncomplicated cutaneous leishmaniasis (defined as fewer than five lesions, with no lesion >5 cm in diameter or near a vital organ). Compliance with this recommendation is poor, however, as patients know that untreated lesions may take several months to heal and leave substantial scars. A safe, convenient, and affordable treatment is needed, but few viable options exist today (1).

Aminosidine (paramomycin) is effective in experimental leishmaniasis (4–6), and various topical formulations have

been developed for clinical study (7–12). Some caused local irritation (9, 11), but encouraging results have been reported with an ointment containing 15% aminosidine plus 10% urea in white paraffin (12–13). In randomized, double-blind, placebo-controlled studies in Tunisia and the Islamic Republic of Iran, a two-week course of aminosidine ointment improved the short-term parasitological cure rates (14, 15), so more prolonged treatment might be more efficacious. We compared the parasitological and clinical efficacy of four weeks versus two weeks of such treatment. An untreated control group was not included, because two weeks of treatment was already known to be of some value, and if four weeks could be shown to be superior to two weeks of treatment, it must a fortiori be superior to no treatment.

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Methods

Participants

The study involved screening the catchment area of three primary health centres around Borkhar district north of Isfahan, Islamic Republic of Iran, which includes approximately 38 000 people. Visiting each house only once, teams of health workers identified and referred all possible cases of cutaneous leishmaniasis to the health centre for clinical and parasitological examination. Those patients with a single parasitologically confirmed lesion <5 cm in diameter were invited to participate unless they had had lesions for over four months, were aged <2 years, were pregnant or nursing mothers, had been treated previously, or had any intercurrent illness or history of allergy to aminoglycosides. All invitees or their parents were given information about the trial before they gave written consent. Of some 500 individuals assessed for eligibility, 233 met the inclusion criteria and were enrolled into the study between October and December, during the peak appearance of cases.

Interventions

The study was a randomized, double-blind trial, with follow-up visits scheduled at days 15, 29, 45, and 105. Patients were assigned randomly to receive four or two weeks of active treatment. Each patient ultimately received two tubes of ointment, which each contained 15 g of ointment — enough for two applications per day for 14 days. The first tube was given to all patients and contained active ointment. The second tube contained either active ointment or placebo (white paraffin oil) and was given to patients in accordance with a computer-generated randomization list after patients returned their first used tube after two weeks. They were examined clinically and parasitologically when they collected the second tube. The placebo and active ointments looked and smelled identical. In contrast to an earlier trial (15), treatment was unsupervised; however, patients were instructed carefully on the first day about how to apply the ointment twice daily (morning and bedtime) as a cross over the lesion and then to spread it with a plastic spatula to cover the entire lesion as well as the edges.

Different members of the research team were each tasked with verifying diagnosis, inclusion criteria, and subsequent assignment of participants to treatment groups. The clinical and parasitological evaluators were blinded to each other's assessment. All efforts were made to reduce the introduction of bias into this study; however, duration of the lesion, which was self-reported by the patients or their guardians, could introduce bias if the durations were significantly different in the two arms by chance.

Outcomes

Patients were re-examined clinically and parasitologically on days 15, 29, 45, and 105 after the start of treatment by researchers blind to their treatment. No smear was taken for parasitological examination from completely healed lesions (those with complete re-epithelialization), as this might have re-opened the scar. All smears were assessed by an experienced parasitologist (TJ), with Giemsa stain and direct microscopic examination. As in the earlier study (15), haematology and liver enzymes were monitored routinely for safety — no evidence of hazard was found. At each visit, any patients whose lesion had worsened and showed no sign of re-epithelialization received systemic or intra-lesional antimonial drugs as rescue treatment, and treatment with the ointment was considered to have failed.

“Clinical cure” was defined as >50% re-epithelialization of the original lesion, and “clinical and parasitological cure” as either complete re-epithelialization or clinical cure plus a parasitologically negative smear. The primary study endpoints were clinical cure and clinical and parasitological cure at day 29, when the four weeks of active treatment ended.

Statistical methods

EpiInfo software was used to calculate sample size and generate random numbers and for form design, double data entry, and calculations of statistical significance (which involved standard analyses of 2×2 tables). Sample size calculation was determined on the basis of a two-week cure rate of 50% (15) at day 45 and an expected four-week cure rate of 70%. When 10% attrition was allowed for, 233 eligible participants were randomized into two groups: 117 were allocated to receive four weeks of active treatment and 116 to receive two weeks of active treatment. Allocations were concealed by the use of opaque, sealed envelope and blinding of the investigators.

Results

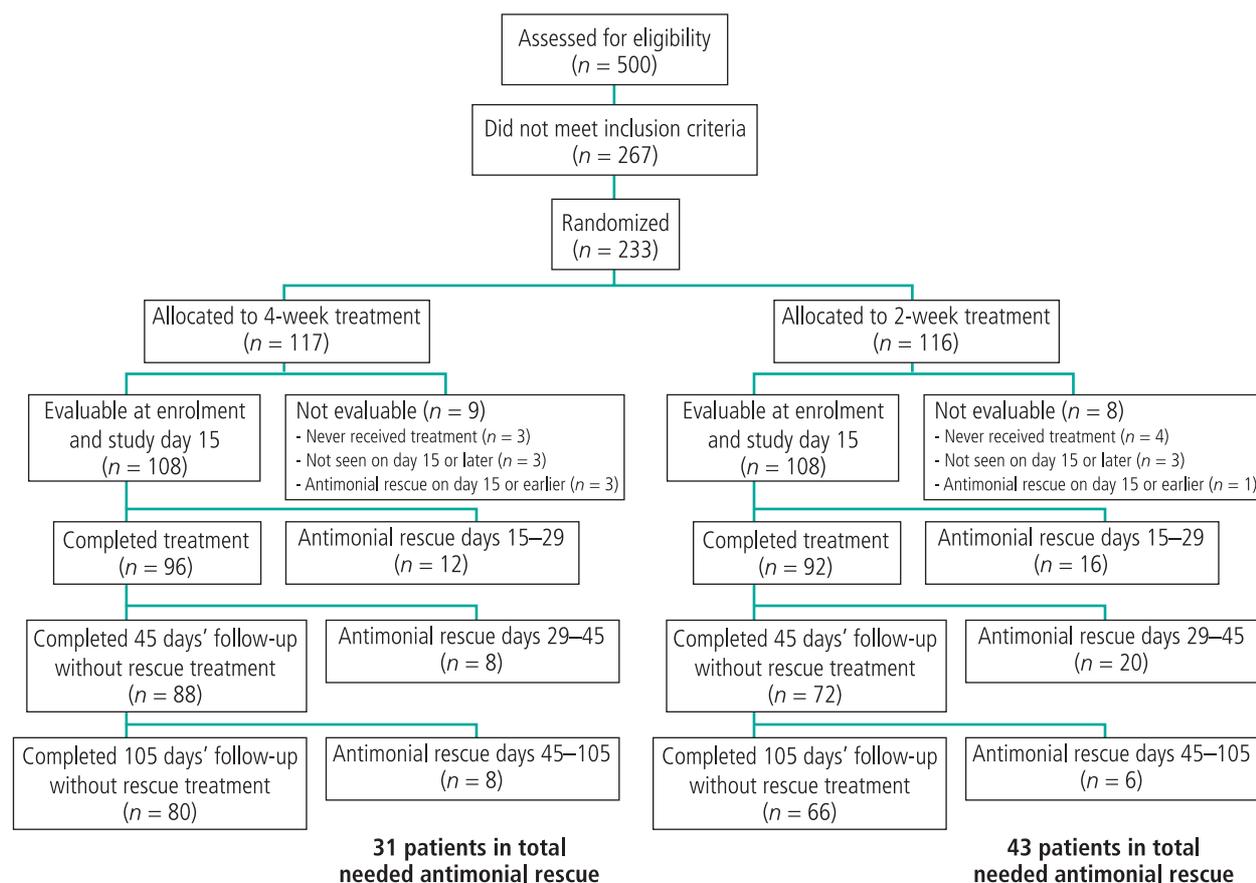
Analyses were restricted to those patients who, at two weeks, had not lapsed from the study (four vs three never started and three vs three never attended after day 15 in the two- and four-week treatment groups, respectively) and had not had antimonial rescue (one vs three), which left 108 patients in each treatment group for analysis.

None of those included in the study missed more than one of the three follow-up visits on days 29, 45, and 105, so the status (with respect to clinical cure without antimonial rescue) at the missed visit could be inferred without bias from the other visits. Only 2% of the first two visits were missed: one vs one were taken as clinical cures because the visits before and after involved apparently complete healing, and five vs two as not clinical cure (because the visits before or after involved antimonial rescue for four patients and clinical worsening for the other three) in the four- and two-week treatment groups, respectively). At the final visits, 15 (7%) patients were missing, and for these, the previous status was assumed to persist (five vs four clinically cured without antimonials, and three vs three not clinically cured, in the four- and two-week treatment groups, respectively). Full placebo control, and hence blindness of assessment, was maintained throughout. Fig. 1 shows participant flow through the study.

Treatment was well tolerated, and no adverse reactions to the ointment were observed or reported in either group. Of those given a tube of active or placebo ointment at day 15, 216 (98%) returned at day 29, and all reported that they had used the ointment. Table 1 gives the characteristics of the 216 patients seen on or after day 29, who contribute to the main analyses: no marked imbalances were seen. Table 2 gives the main results at days 29 (when treatment was completed for those allocated four weeks of active ointment), 45, and 105.

At day 29, few of the lesions were bad enough to require antimonial rescue, and no significant difference was seen between the groups in the numbers that did (four weeks vs two weeks: 12 (11%) vs 16 (15%). A significant improvement was seen, however, in the numbers achieving clinical cure (80 (74%) vs 64 (59%); $P = 0.05$) and clinical and parasitological cure (47 (44%) vs 26 (24%); $P = 0.005$) by day 29, with four weeks of active treatment significantly better than two weeks of active treatment plus two weeks of placebo

Fig. 1. Participant flow



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Table 1. Initial characteristics of 216 patients included in statistical analyses after treatment with two or four weeks of treatment with aminosidine ointment

Characteristic	Allocated treatment duration		
	4 weeks (n = 108)	2 weeks (n = 108)	P-value
Age (years) ^a	9.2 (8.9)	9.0 (8.8)	0.8
Haemoglobin (g/l)	132 (14)	133 (13)	0.6
Serum glutamic oxaloacetic transaminase (U/l)	9.9 (2.4)	9.7 (2.2)	0.5
Sex ratio (male:female)	47:53	44:56	0.7
Ulcerated lesion ^{b,c}	85 (79)	95 (88)	0.1

^a Values in parentheses are standard deviations.

^b Values in parentheses are percentages.

^c Status at day 0; subsequent comparisons between the two treatment arms are standardized for the status of the lesion at day 15.

treatment. The absolute improvement in clinical and parasitological cure was 20% (95% confidence interval 7–32%).

After active treatment stopped, some of the lesions in both treatment groups deteriorated, and at day 45, the numbers given antimonial rescue then or earlier were 20 (19%) vs 36 (33%) ($P = 0.02$). The numbers who had achieved clinical cure at day 45 without antimonial rescue were correspondingly greater for those who had received four weeks of treatment than two weeks (77 (71%) vs 59 (55%) clinical cures, $P = 0.03$), but in terms of clinical and parasitological cure at day 45, the advantage of longer treatment was no longer significant (40 (37%) vs 31 (29%)). By day 105 — 11 weeks after treatment ended — the results still

favoured those who had originally had four weeks of treatment, but the differences were less significant.

Table 3 subdivides the results by the status of the lesion at day 15 — after two weeks of active treatment for both groups (i.e. before there was any difference in management). The numbers are too small to be stable statistically, but they do suggest that the advantage of an additional two weeks of ointment was seen chiefly in those who had not already achieved clinical cure with the first two weeks of ointment (upper half of Table 3). It was notable, however, that a substantial minority of those who had achieved clinical cure (i.e. partial, or even complete, re-epithelialization) by day

Table 2. Results at days 29 (when trial treatment ended), 45, and 105 in patients who received aminosidine ointment for four weeks ($n = 108$) or two weeks ($n = 108$)^a

Treatment day	Antimonial "rescue" treatment needed now (or given earlier)			Clinical cure without ever needing antimonial rescue			Clinical and parasitological cure without ever needing antimonial rescue		
	Treatment		<i>P</i> -value ^b	Treatment		<i>P</i> -value ^b	Treatment		<i>P</i> -value ^b
	4 weeks	2 weeks		4 weeks	2 weeks		4 weeks	2 weeks	
Day 29	12 (11)	16 (15)	0.51	80 (74)	64 (59)	0.05	47 (44)	26 (24)	0.005
Day 45	20 (19)	36 (33)	0.02	77 (71)	59 (55)	0.03	40 (37)	31 (29)	0.30
Day 105	28 (26)	42 (39)	0.07	72 (67)	61 (56)	0.18	62 (57)	46 (43)	0.04

^a All 216 patients were seen at day 15; no patient missed more than one subsequent visit; few missing values are interpolated (2% at days 29 and 45; 7% at day 105).

^b Stratified for the status of lesions on day 15.

Table 3. Percentage of patients who received aminosidine ointment for four weeks or two weeks with various outcomes, by status at day 15 (after two weeks of identical active treatment for both groups)

Treatment day	Antimonial "rescue" treatment ever given (%)		Clinical cure (without antimonial rescue) ^a		Clinical and parasitological cure without antimonial rescue ^b	
	Treatment		Treatment		Treatment	
	4 weeks	2 weeks	4 weeks	2 weeks	4 weeks	2 weeks
No clinical cure at day 15 ^{c,d}						
Day 29	11	22	64	35	43	11
Day 45	25	44	55	37	27	17
Day 105	30	50	59	48	52	35
Clinical cure (over 50% re-epithelialization) at day 15 ^{d,e}						
Day 29	11	7	81	83	44	37
Day 45	14	22	83	72	44	41
Day 105	23	28	72	65	61	50

^a $\geq 50\%$ re-epithelialization.

^b Clinical cure plus smear negative for parasites.

^c 44 vs 54 patients in 4- and 2-week treatment groups, respectively.

^d The non-significant imbalance in denominators at day 15 is only because of chance, as treatment was double blind and, before day 15, was identical in both groups.

^e 64 vs 54 patients in 4- and 2-week treatment groups, respectively.

15 subsequently deteriorated, irrespective of whether an additional two weeks of treatment were given.

Some differences in Table 3 are seen between the two treatment groups in the numbers who had already worsened by day 15 or who had already achieved partial re-epithelialization. These differences were not statistically significant ($P = 0.2$), however, and must have been entirely caused by chance, because the treatment of both groups before day 15 was identical and the study was double blind. Moreover, these chance imbalances did not contribute at all to the statistical significance in Table 2 of the results at later times, for the *P*-value calculations in Table 2 were conditional on the 15-day results in Table 3 (i.e. they showed whether, given the chance imbalances at day 15, the subsequent results significantly favoured longer treatment).

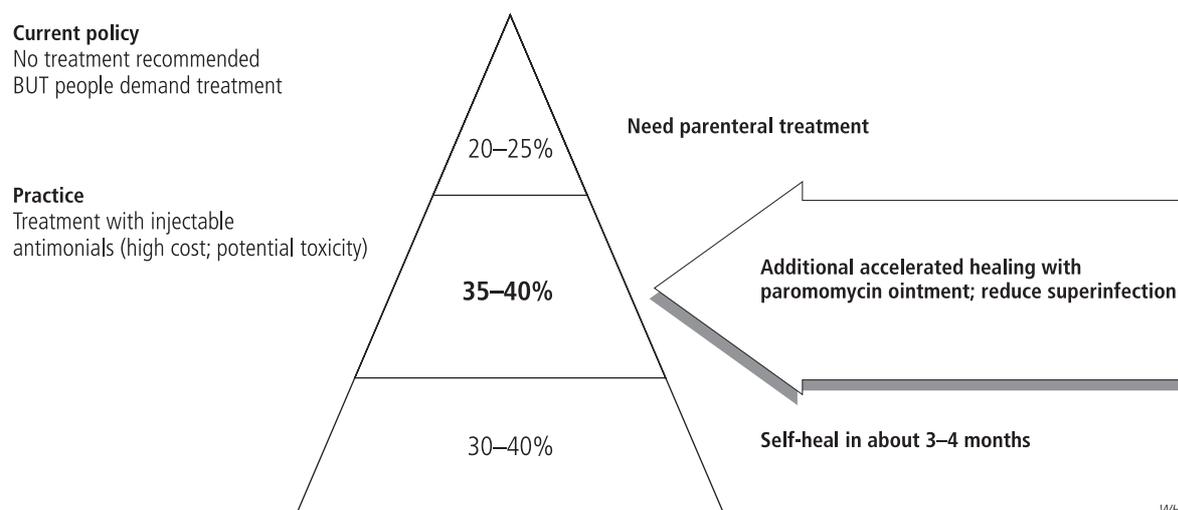
When the results on days 29, 45, and 105 were taken together, the average of the difference between the percentages cured within four weeks and within two weeks of treatment was 14% (irrespective of whether cure was defined as clinical cure or as clinical and parasitological cure). This can be converted into a number needed to treat of approximately seven — i.e. if seven patients were treated for four weeks rather than two weeks, then one more would be cured by ointment alone, without the use of antimonials.

Discussion

In the previous randomized, placebo-controlled, double-blind trial with the same ointment (15), two weeks of treatment produced significant benefit by day 15, although many patients remained uncured or relapsed later. The present trial compared treatment with four and two weeks of ointment and found the longer treatment to be somewhat more effective. Even with four weeks of treatment, however, about one-third of all patients remained uncured — most of these eventually needed to be offered antimonials, and, of those who used the ointment and were cured, about half might have recovered spontaneously.

As four weeks of treatment is better than two weeks, and two weeks is better than no treatment (15), the four-week aminosidine regimen could become the first-line treatment for uncomplicated cutaneous leishmaniasis in *L. major* foci — at least until something better is found (e.g. an ointment with better bioavailability of aminosidine or some completely different active ingredients). Longer periods of treatment might increase the cure rate; as most cases heal spontaneously in 3–4 months (15), however, a more effective rather than longer treatment would be desirable. At the moment, the ointment can be produced in endemic countries, costs only

Fig. 2. Public health benefit of paromomycin ointment



about US\$ 1 per week, and reduces the need for medically administered injections of expensive antimonials — especially since the current WHO recommendation of withholding antimonial injections for several weeks (in hope of spontaneous cure) often is not complied with. Such topical treatment is practicable, even where specialist medical services are not available: as now formulated, the ointment has little or no toxicity, so it can be widely used; use of the ointment satisfies the demand from patients for some action to be taken; and simple clinical assessment at day 29 (without parasitological investigation) generally provides an adequate basis on which a decision about whether antimonial treatment will be needed can be made, because it correlates closely with the clinical assessment on day 45 and day 105 and is modified little by the parasitological assessment. Moreover, those who eventually will need antimonials (about one-quarter) and those who will not (about 75%) may benefit from four weeks of such ointment instead of four weeks of observation with no treatment. Although the trial did not study this, any treatment that helps control local infection may limit the depth and size of any eventual scar. Fig. 2 shows the current situation and potential public health benefits.

As cutaneous leishmaniasis is a self-healing disease, the duration the lesions had been active before treatment started would have a profound effect on cure rate. We had no way of determining the exact duration, so patients or their guardians were asked to give an estimate. This may have produced a bias

if the estimated duration was incorrectly uneven in the two treatment groups.

For patients with uncomplicated cutaneous leishmaniasis in *L. major* foci, four weeks of twice-daily use of this ointment (or of some variant of it with improved bioavailability) could be the first-line treatment, after which, if there is no sign of re-epithelialization, antimonial therapy may be considered. Although (to simplify matters) only patients with a single lesion were enrolled in the present study, other patients with uncomplicated cutaneous leishmaniasis also may qualify for such topical treatment. This strategy is, however, valid only for those areas where infection generally involves *L. major* infection, as the response to aminosidine varies for different species of *Leishmania* (6). ■

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Conflicts of interest: None declared.

Résumé

Traitement de la leishmaniose cutanée par une pommade à l'aminosidine (paromomycine) : essai randomisé en double aveugle en République islamique d'Iran

Objectif Comparer l'efficacité parasitologique et clinique d'un traitement de quatre semaines par une pommade à l'aminosidine (paromomycine) et d'un traitement de deux semaines chez des patients atteints de leishmaniose cutanée à *Leishmania major* en République islamique d'Iran.

Méthodes Un essai randomisé en double aveugle portant sur un traitement de quatre semaines par une pommade à l'aminosidine

($n = 108$) ou un traitement de deux semaines par l'aminosidine et deux semaines par placebo ($n = 108$) a été réalisé. Les patients ont été examinés les jours 15, 29, 45 et 105 afin de déterminer les taux de guérison clinique et les taux de guérison clinique et parasitologique.

Résultats Le traitement de quatre semaines donnait des taux de guérison significativement plus élevés que le traitement de deux

semanas : le jour 29, les taux de guérison clinique étaient de 80/108 (74 %) contre 64/108 (59 %) ($p = 0,05$) et les taux de guérison clinique et parasitologique de 47/108 (44 %) contre 26/108 (24 %) ($p = 0,005$). Le jour 45, un plus petit nombre de patients ayant reçu le traitement de quatre semaines avaient dû recevoir un traitement de secours par les antimoniés, par rapport à ceux qui avaient reçu le traitement de deux semaines : 20 (19 %) contre 36 (33 %) ($p = 0,02$). Le jour 105, les résultats étaient toujours meilleurs chez les patients ayant reçu quatre semaines de traitement mais les différences n'étaient plus aussi significatives. Aucun effet secondaire n'a été observé ni rapporté.

Conclusion Environ les deux tiers des patients ayant reçu la pommade pendant quatre semaines ont été cliniquement guéris. Même si chez près de la moitié des sujets guéris la guérison aurait pu survenir spontanément en l'absence de traitement, l'application pendant quatre semaines d'une pommade à l'aminosidine pourrait devenir le traitement de première intention chez les patients atteints de leishmaniose cutanée non compliquée due à *L. major*, les antimoniés n'étant nécessaires que chez le tiers de patients qui n'étaient pas guéris à la fin du traitement par l'aminosidine. Il serait ainsi possible de réduire considérablement les coûts ainsi que les effets secondaires associés aux antimoniés.

Resumen

Tratamiento de la leishmaniasis cutánea con pomada de aminosidina (paromomicina): ensayo aleatorizado en doble ciego en la República Islámica del Irán

Objetivo Comparar la eficacia parasitológica y clínica de cuatro semanas y dos semanas de tratamiento con pomada de aminosidina (paromomicina) en los pacientes con leishmaniasis cutánea causada por *Leishmania major* en la República Islámica del Irán.

Métodos Se llevó a cabo un ensayo aleatorizado en doble ciego de un régimen de tratamiento de cuatro semanas con pomada de aminosidina ($n = 108$) en comparación con dos semanas de aminosidina y dos semanas de placebo ($n = 108$). Los pacientes fueron evaluados a los 15, 29, 45 y 105 días para determinar la curación clínica y la curación clínica y parasitológica.

Resultados El tratamiento de cuatro semanas logró tasas de curación significativamente mejores que el de dos semanas: el día 29 se confirmaron 80/108 (74%) frente a 64/108 (59%) curaciones clínicas ($P = 0,05$) y 47 (44%) frente a 26 (24%) curaciones clínicas y parasitológicas ($P = 0,005$). El día 45, entre los tratados durante cuatro semanas había menos pacientes que hubiesen requerido tratamiento de rescate con

antimoniales que entre los tratados durante dos semanas: 20 (19%) frente a 36 (33%) ($P = 0,02$). El día 105, los resultados todavía favorecían a los asignados al régimen de cuatro semanas de tratamiento activo, pero las diferencias ya no eran claramente significativas. No se observó ni notificó ningún efecto secundario.

Conclusión Aproximadamente las dos terceras partes de los pacientes que recibieron la pomada durante cuatro semanas se curaron clínicamente. Aunque alrededor de la mitad de los que sanaron podrían haberse recuperado quizá espontáneamente aun sin tratamiento, la administración de pomada de aminosidina durante cuatro semanas podría ser el tratamiento de primera línea de la leishmaniasis cutánea sin complicaciones por *L. major*, reservándose los antimoniales sólo para el tercio de pacientes no curados al término del tratamiento con aminosidina. Ello reduciría considerablemente los costos y los efectos secundarios asociados a los medicamentos antimoniales.

ملخص

معالجة داء الليشمانيات الجلدي بمرهم الأمينوزيدين (باروموميسين)؛ دراسة مزدوجة التعمية ومعشاة في جمهورية إيران الإسلامية

عولج لمدة أسبوعين، وبهذا تكون قيمة الاحتمال ($P = 0,05$). أما بعد مرور خمسة وأربعين يوماً فقد نقص عدد المرضى الذين تلقوا المعالجة لمدة أربعة أسابيع واحتاجوا لمعالجة بمركبات الأنتيموان إلى 20 مريضاً (19%) مقارنة بأولئك الذين عولجوا لمدة أسبوعين واحتاجوا لمعالجة بمركبات الأنتيموان إذ لم ينقص عددهم إلا إلى 36 مريضاً (33%) وقيمة الاحتمال ($P = 0,02$). وبعد مرور 105 أيام استمرت النتائج لصالح أولئك الذين تلقوا العلاج الفعّال لمدة أربعة أسابيع، رغم أن الفروق لم تعد واضحة كما كانت من قبل. ولم تلاحظ ولم تسجل أية تأثيرات جانبية.

الاستنتاج: لقد تحقّق شفاء ما يقرب من ثلثي من عولج بالمرهم لمدة أربعة أسابيع، ورغم أن نصف هؤلاء تقريباً كانوا سيشفون تلقائياً حتى ولو لم يتلقوا أي معالجة كانت، فإن المعالجة بمرهم الأمينوزيدين لمدة أربعة أسابيع قد تكون الخط الأول للمعالجة في حالات داء الليشمانيات الجلدية غير المصحوبة بمضاعفات والناجمة عن الليشمانيات الكبيرة؛ وستقتصر الحاجة على إضافة المركبات الأنتيموانية على ثلث المرضى الذين لن يتحقق لهم الشفاء في نهاية فترة المعالجة بالأمينوزيدين. وهذا ما سيؤدي إلى إنقاص ملحوظ في كل من التكاليف والتأثيرات الجانبية التي ترافق المعالجة بمركبات الأنتيموان.

الغرض: موازنة الكفاءة السريرية والتأثيرات على الطفيليات التي تنجم عن المعالجة بمرهم الأمينوزيدين (الباروموميسين) لمدة أربعة أسابيع وتلك التي تنجم عن المعالجة لمدة أسبوعين لدى مرضى الليشمانيات الجلدية الناجم عن الليشمانية الكبيرة في جمهورية إيران الإسلامية.

الطريقة: دراسة مزدوجة التعمية ومعشاة للمعالجة لمدة أربعة أسابيع بمرهم الأمينوزيدين لدى 108 مريضاً ومقارنته بالمعالجة بنفس المرهم لمدة أسبوعين، وبإعطاء دواء غفل لمدة أسبوعين لـ 108 مريضاً. وقد تم تقييم المرضى بعد مضي 15، 29، 45، 105 يوماً لتحري الشفاء السريري والشفاء من الطفيليات.

الموجودات: لقد أدت المعالجة لمدة أربعة أسابيع إلى نتائج بالشفاء أفضل من المعالجة لمدة أسبوعين؛ فبعد مرور 29 يوماً أدت المعالجة لمدة أربعة أسابيع إلى شفاء سريري في 80 حالة من أصل 108 حالة (74%) وذلك مقابل حدوث الشفاء السريري لدى من عولج لمدة أسبوعين لدى 64 حالة من أصل 108 (59%) وبهذا تكون قيمة الاحتمال ($P = 0,05$)، أما الشفاء السريري وشفاء الطفيليات معاً فقد كان لدى من عولج لمدة أربعة أسابيع 47 من أصل 108 (44%) مقابل 26 من أصل 108 (24%) لدى من

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