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CYCLOGUANIL PAMOATE IN THE TREATMENT OF CUTANEOUS LEISHMANIASIS

INITIAL TRIALS IN PANAMÁ

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Cutaneous leishmaniasis in Panamá occurs for the most part in rural populations. The infected persons, because of economic status and distance from medical services, are all too frequently unable to obtain effective medical care, since the time-proved treatment with antimonials requires multiple injections over an extended period.

In the summer of 1966, a study of the effectiveness of cycloguanil pamoate for a small series of patients infected with *Leishmania braziliensis* was undertaken at the Gorgas Memorial Laboratory. Two groups of investigators, one from Costa Rica[1] and one from México,[2] have reported good results with this drug in the treatment of the infection in their respective countries and indicated that the particular advantage of its use was that only one injection was usually necessary.

Cycloguanil pamoate has been used primarily as a repository antimalarial drug in man and animals with an attributed effective action up to 6 months.[3, 4]

MATERIALS AND METHODS

The requirements of the case for inclusion in the study were a definitive diagnosis of leishmaniasis established by demonstration of leishmania in stained smears of scrapings from lesions, in sections of tissue taken at biopsy, or by culture of material from biopsies of the lesion; the absence of tuberculosis or other chronic illnesses; and no treatment for leishmaniasis within 30 days before use of cycloguanil pamoate. If these conditions were met and the patient consented to participate, he was made a part of the investigation. For children, the consent of the parents was obtained.

The cycloguanil pamoate was formulated as a suspension in an oleaginous vehicle of 40% benzyl benzoate and 60% castor oil. Each milliliter contained an amount of the drug equivalent to 140 mg of base.

The drug was administered as a single intramuscular injection in the buttock in the following dosages: 6 months to 4 years, 140 mg; 5 years to 10 years, 280 mg; and 11 years and older, 350 mg.

Whenever possible the patient was hospitalized during the first 2 weeks after administration of the drug for the purpose of making daily observations to detect adverse local or general reactions.

The course of therapy was followed by examination of blood, urine, and the lesions at scheduled intervals. A pretreatment blood count and urine examination were compared with similar examinations performed, as nearly as possible, at 7, 14, 28, 42, and 56 days. The presence or absence of parasites was also determined at these intervals.

The preferred procedure for showing the presence of parasites was culture of tissue removed from the lesion. The specimen was obtained with a 5 mm dermal biopsy punch from the border of the lesion just outside the ulcerated area and cultured according to the technique of Herrer *et al.*[5] The defect at the biopsy site was packed with Gelfoam® to control bleeding and to promote healing. Although, in our experience, this is the most sensitive and reliable procedure, it is generally the least acceptable to the patient. Therefore, when patients refused biopsy, scrapings at different points along the border of the ulcer were depended upon to detect the presence or absence of parasites.

The criteria for cure were complete epithelization of the lesion with disappearance of edema, induration or other signs of inflammation, and absence of parasites.

RESULTS

The series of patients comprised 26 individuals ranging in age from 10 months to 67 years (Table 1).

The results obtained in the 26 cases are shown in Table 2. There were 15 cases of a single lesion

TABLE 1

Age and sex distribution in treated cases

Age (*years*)	Number	
	Male	Female
10/12	1	0
1–9	1	0
10–19	3	2
20–29	4	1
30–39	3	1
40–49	4	0
50–69	4	2
All ages	20	6

TABLE 2

Efficacy of a single injection of cycloguanil pamoate as related to location and number of lesions

Location of lesions	Single lesion		Multiple lesions	
	Success	Failure	Success	Failure
Upper portion of the body	7	3	5	2
Lower portion of the body	4	1	1	0
Both portions	0	0	2	1
Total	11	4	8	3

only; 11 of these responded to treatment and healed completely, while four were considered failures. Eleven cases presented multiple lesions and of these, eight healed completely and three failed to heal. Neither the location of lesions nor the presence of more than one lesion appeared to affect the cure rate.

One case of mucocutaneous leishmaniasis failed to respond to treatment. During a 60-day observation period, the lesions became more extensive, and supplementary therapy was instituted.

With a single injection of cycloguanil pamoate an over-all cure rate of 73% (19 cases) was obtained while 27% (seven cases) were judged failures.

In the cases successfully treated the time for complete healing varied considerably.

Six, or 32%, of the lesions healed within 70 days; this was the provisional observation period set at the beginning of the study. However, in most patients, 69%, healing was considerably retarded. Eight lesions healed in a period of 80 to 100 days, while five required over 100 days.

In 10 of 19 patients successfully treated, parasites were not demonstrated after the initial examination. Five had no parasites within 28 days, and in the remaining four there were none after 30, 42, 49, and 70 days.

The cases of the seven patients for whom treatment was considered a failure are detailed in

TABLE 3

Failures with cycloguanil pamoate

Patient no.	Age (*years*)	Duration of lesion* (*months*)	Parasites last demonstrated† (*days*)	Location of lesions	Supplementary therapy	Time of healing (*days*)‡
2	60	36	14	Upper respiratory tract	Glucantime® §	50
8	10/12	1	28	Left cheek, right arm	Pyrimethamine	40
9	4	2	37	Tip of nose	Pyrimethamine	40
10	28	3	7	Right cheek	Glucantime	30
18	37	3	293	Right ankle	Glucantime	28
21	33	1	26	Left deltoid tuberosity, left big toe	Glucantime	104
32	31	1.5	70	Left portion of the neck, left arm	Glucantime	21

* Before treatment.

† After initiation of treatment with cycloguanil pamoate.

‡ With supplementary therapy.

§ N-methylglucamine antimonate.

Table 3. Auxiliary treatment of the two children, Nos. 8 and 9, was started on day 50 because there was a noticeable increase in the size of the lesions, and it was not considered justifiable to continue the observation period, since the lesions were located on the face.

The patient with mucocutaneous leishmaniasis (No. 2) was given supplementary treatment after 60 days' observation because of lack of clinical improvement and extension of the lesions.

Patient No. 18 showed marked clinical improvement during the 63 days after initiation of treatment; however, cultures of skin taken at biopsy remained positive. She failed to return after this period and was not seen again until day 293, when a residual lesion was present and positive for *L. braziliensis*.

Patient No. 10 had a large lesion on the right cheek that failed to improve during a 90-day period. Patient No. 21 was given supplementary treatment after 83 days because of an unimproved lesion on the left big toe that prevented him from working.

The final patient, No. 32, had lesions on the neck and on the left forearm. Both lesions were positive at 70 days. Because of his imminent departure from the area, he requested supplementary treatment, since he did not wish to leave with active lesions. His request was granted because he could be given no assurance that his lesions would heal with cycloguanil pamoate alone.

Adverse reactions to the drug, other than pain at the site of injection and limitation of motion for a short period of time, occurred in two patients. In both, a painful induration developed at the injection site, which subsided spontaneously. No significant changes were observed in the blood or urine of the patients.

COMMENTS

Based upon data obtained from this series of patients with cutaneous leishmaniasis, it appears that cycloguanil pamoate will prove to be a useful chemotherapeutic agent in this disease. With one injection of the drug a cure was effected in 73% of the patients. The instances of failure, with the exception of the one case that remained parasitologically positive after 293 days, might have healed if circumstances had justified a longer period of observation. All lesions that did not respond to the drug healed with supplementary therapy.

The time for complete healing in most cases was longer than 70 days, one being as long as 138 days. These findings are somewhat at variance with those reported by the groups from México[2] and Costa Rica.[1] The healing process in their cases was evident very soon after initiation of treatment and complete in a relatively shorter period of time than in the present series. In the series from México, healing was completed in from 2 to 4 weeks, while in our series, in many instances, signs of healing were just beginning at this time. Perhaps this reflects a condition due to parasite-species difference, which in México is *L. mexicana* and in Panamá *L. braziliensis*.

Cutaneous infections caused by *L. braziliensis* are characterized by extreme chronicity and long duration if untreated. Clinical observation in the Panamá area has shown that without specific therapy lesions may persist for as long as 9 to 10 years. The cures reported here appear to be the result of treatment with cycloguanil pamoate and do not represent spontaneous recovery.

SUMMARY

The effectiveness of cycloguanil pamoate in the treatment of a series of 26 cases of cutaneous leishmaniasis from Panamá was reported. Complete healing was accomplished in 19 cases; seven cases failed to respond. The time required for healing ranged from 38 to 138 days. More than half of the cases required more than 90 days.

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