THE USE OF HYDERGINE IN THE TREATMENT OF TROPHIC ULCERS IN LEPROSY

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Trophic ulcers in leprosy have long been believed to be connected with a disturbance of the blood supply to the extremity.

Fite ([6]), studying a series of 77 lepromatous cases, found that 30 out of 41 "severe" cases showed granulomatous changes in the small vessels, but only 2 out of 36 of the "less severe" group showed such changes. All of his cases were lepromatous, and in these only the severe ones (i.e., those with a high bacteriologic index) showed involvement. It is, however, a matter of general observation that trophic ulcers more commonly affect nonlepromatous cases.

Barnetson ([1, 2]) studied the blood flow in the extremities by means of oscillometry, and made skin temperature studies of reflex vasodilation. In the skin temperature studies he was not able to demonstrate the presence of the reflex response. He therefore concluded that the ability of the blood vessels to alter the supply in accordance with the demands of stress is impaired.

Dharmendra *et al.* ([5]) and Chatterjee ([4]) both hold that diminution in blood supply is a fundamental cause of persistent ulceration.

Paterson ([8]) concluded, from a study of angiographs in leprosy, that there is dilation of the arteriovenous shunts, and hence sometimes defective filling of the digital arteries due to short-circuit of blood.

Gokale ([7]) studied the effect of Hydergine given intraarterially twice or thrice weekly in doses of 0.3 mgm. and obtained good results.

Following the publication of Gokale's results, it was decided in this institution to conduct a controlled trial of the effect of Hydergine, using, however, the more simple and practical method of administering it in the form of sublingual tablets.

Perfect control in a trial series of foot ulcers in leprosy is impossible, due to the following reasons:

(*a*) The variety and range of severity of the ulcers.

(*b*) The degree of deformity of the foot, the reduction in the weight bearing area, and the extent of scarring.

(*c*) The difficulty of obtaining the cooperation of patients who, having lost their sensation of pain, have no incentive other than the instructions of the doctors to persuade them not to walk.

These factors are probably to a large extent responsible for the erratic and contradictory results of different workers in the treatment of such ulcers. In the present series, random selection was used in order to render the first two factors as little effective as possible. It was believed that in this way the type of ulcer would be fairly evenly distributed between the two groups set up, one for treatment and the other for control. If the total sample had been larger, this would probably have been more true than it was in the actual series.

The effect of factor (*c*), namely, the cooperation of the patients, was reduced to a minimum by including in the series only those patients who were admitted to a special "Ulcer Block" for the entire duration of the trial. This block is reserved for cases with very chronic and severe ulcers which have defied ambulatory treatment. Hence the time required for healing of the ulcers is considerable, which accounts for the few which healed during the trial.

METHOD

Selection of patients.—The patients included in this trial comprised only those who were admitted to the special "Ulcer Block." In this block patients are not permitted to walk, a wheel chair being provided for their use to go to the bathroom and to the treatment room for dressings. Food is served in the room. There is, however, supervision only during certain hours of the day, and hence the extent to which the patients make use of available facilities is not known.

A list was drawn up of all the patients in the ward taken in the random order in which they presented themselves in the treatment room for dressings. The 19 patients listed were then divided into two groups by taking alternate names from the list. The selection of patients for the groups was, therefore, unconnected even subconsciously with the type or severity of the ulcer. Lots were drawn to determine which group should receive the drug and which the placebo. The patients were aware that a trial was on; but neither they, nor the nurse administering the tablets, nor the house surgeon taking the blood pressures, were aware which group was taking the drug. Assessment of results and progress notes were made by the author who saw the patients once a week and carefully avoided asking their names and finding their group distribution. Thus, a double-blind technique was adopted throughout.

Drug used.—The drug used was Hydergine (Sandoz), in the form of sublingual tablets each containing equal parts of the three alkaloids dihydroerogocornine, dihydroergocristine, and dihydroergocryptine, with a total of 0.25 mgm. of alkaloids.

The placebo used consisted of citric acid gr. ¼, lactose, and excipient q.s.

The tablets were administered thrice daily. The blood pressures of the patients were taken daily. The ulcers were classified according to type and severity, as shown in Table 1.

TABLE 1.—*Types and numbers of ulcers.*

Type	Number of ulcerated feet	
	Hydergine	Control
Superficial, clean granulations [a]	5	3
Superficial, granulation with slough	4	4
Deep, no bone involved	3	0
Deep, with rough bone felt	1	4
Extensive, with deep multiple sinuses	1	1
Total	14	12

[a] By "superficial" is meant an ulcer with a soft base which is visible and without any contact with bone, tendon or any deep sinus.

The ulcers in which bone was felt were treated in the routine way, with removal of the dead bone. All the ulcers were dressed thrice weekly with the same dressing, which consisted of equal parts of 50 per cent magnesium sulfate and pure glycerine.

Duration of trial.—Two batches of patients were included in the trial. One was continued for 8 weeks and the other was started a fortnight later and continued for 6 weeks. In 2 cases treatment was discontinued because the ulcers had healed (Table 2).

TABLE 2.—*Duration of treatment.*

Duration	Hydergine	Controls
8 weeks	7	5
6 weeks	7	5
4 weeks	0	1
3 weeks	0	1

RESULTS

Side effects.—Hydergine group: Four of the patients complained of slight giddiness after taking the tablets. Three complained of increased appetite, and 2 of diminished appetite. One had a feeling of heat in the body, and 3 complained of burning of the eyes.

Control group: One complained of giddiness, 1 of light-headedness, and 2 of increased appetite.

None of the complaints was serious, and the patients were not inconvenienced by them.

Blood pressure.—Recordings were made in the morning after the patients had had their breakfast, with the patient lying on an examination couch in the ward. There was no significant alteration in the blood pressure (Table 3).

TABLE 3.—*Comparison of average blood pressures during the first and last weeks of treatment.*

	Hydergine	Control
First week average	113/71	107/66
Last week average	117/68	116/62

At the end of the study the results were assessed under four heads, healed, improved, unchanged, or worse (Table 4). They suggest that Hydergine taken by mouth in the dosage used in the trial has no effect on the course of the trophic ulcer of leprosy.

TABLE 4.—*Comparison of results in the two groups.*

	Hydergine	Control
Healed	1	3
Improved	4	2
Unchanged	6	7
Worse	3	0
Total	14	12

DISCUSSION

The negative results of this study are not unexpected on theoretic grounds, if the findings of Barnetson are accepted. The abolition of response to heating the opposite extremity suggests gross impairment of the normal vasomotor control of the circulation. Since the action of the alkaloids is said by the manufacturer to be largely mediated through the vasomotor nerves, destruction of the nerves would presumably render the drug ineffective.

It is, however, within the experience of every worker in the field of leprosy that most trophic ulcers do not readily bleed in the course of ordinary dressing. But if the edges of the ulcer are cut away, the bleeding is often marked and prolonged. This would suggest that while the blood supply to the extremity may be normal, or even increased, the blood may be prevented from access to the granulation tissue by an intervening thickness of relatively avascular fibrous tissue ([3]). This would account for the chronicity of the ulcer while the limb may even be warmer than a normal extremity, suggesting that there is a better blood supply than normal.

SUMMARY

A controlled study was made on a small series of 19 patients with 26 ulcerated feet between them. Ten patients (with 14 ulcerated feet) were given 0.25 mgm. Hydergine thrice daily in the form of sublingual tablets, and 9 patients (12 feet) were controls and were given a placebo. The results showed that there was no substantial difference in the progress of the ulcers in the two groups.

RESUMEN

Este estudio fiscalizado fué ejecutado en 19 enfermos que en conjunto tenían 26 pies ulcerados. Diez enfermos (con 14 pies ulcerados) recibieron 0.25 mgm. de Hidergina tres veces diarias en forma de tabletas sublinguales y 9 enfermos (12 pies afectados) fueron testigos, recibiendo un placebo. Los resultados demostraron que no hubo mayor diferencia en la evolución de las úlceras en los dos grupos.

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