THE THERAPEUTIC EFFECTS OF PHTHALIC ACID SALTS

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The effect of intravenous injections of phthalic acid in leprosy has recently been discussed by the author in this Journal [**2** (1934) 139]. Further study has confirmed the impressions: (a) that phthalic acid has a definite and relatively rapid beneficial action in an ill-defined percentage of cases; (b) that the improvement, though rapid and apparently specific, is the result of the first eight or ten injections, and that as a rule improvement does not continue with further administration of the drug; (c) that in 40 per cent of patients—and possibly as much as 60 per cent—the drug appears to have no action whatever, or only a slight one; and (d) that a large number of the cases that are benefited tend to relapse.

Both phthalic acid and its derivative fluorescein, given in an optimum number of injections, may cause marked improvement in a limited number of cases for a limited period of time. In an attempt to overcome the defects that have been noted, different water soluble salts of phthalic acid were tried. An English firm[1] kindly undertook the experimental work of producing such salts. It was hoped at first that a soluble combination with iodine could be prepared, but this proved impracticable. Finally they succeeded in producing the following four salts: magnesium phthalate, calcium phthalate, potassium-hydrogen phthalate and cotarnine phthalate. Of these the cotarnine salt was by far the most expensive, costing nearly £15 per pound. Cotarnine itself has a vasoconstrictor action, so that it appeared at the start that its therapeutic effects might be somewhat involved.

After preliminary animal experiments 80 patients were chosen, 20 for each drug. It may be pertinent to describe here the type of patients who undergo experiments of this kind in this institution. Five factors are involved in their selection: (a) No patient is put on an untried drug except voluntarily; (b) the patient must be of

[1] Burroughs and Wellcome, Ltd., London.

sufficient intelligence to understand the nature of the experiment; (c) his lesions must be clearly defined, so that clinical alterations can be detected readily; and (d) he must be free from concomitant disease. In actual practice volunteers are mostly those whose lesions have proved obdurate to any other treatment.

The patients chosen for this experiment were all adults, and were all found by preliminary examination to be suitable for the experiment. No patient was chosen who had a history of lepra reaction within the last six months, and only cases with lesions of over a year's duration were taken. During the experiment they were all given the same food, and they received no other treatment. Each patient had his temperature taken twice a day. Twice a month the weight was taken, the sedimentation rate of the blood was determined, and clippings of the center and edge of a defined skin lesion were made. The patients were seen daily by two separate observers.

Intravenous injections of 20 cc. of a 1 per cent solution of the drug under test were given twice a week. This dose appeared to give no untoward effects. Solutions of these salts are colorless except for cotarnine phthalate, which is a faint yellow. The injections were continued for six months.

It may be said at once that injections of magnesium phthalate, calcium phthalate and potassium-hydrogen phthalate produced no significant effects on the weight, the sedimentation index, or the lesions. There was rapid improvement of the lesions in one patient receiving calcium phthalate, and two who were given potassium-hydrogen phthalate showed a fairly marked recession of lesions. In treating groups of twenty patients with a new drug, such results are to be expected as a normal feature of leprosy research. These salts, then, had no therapeutic effect, and the patients undergoing treatment with them actually served as controls for the fourth group.

One patient of the cotarnine phthalate group had to be dropped from the experiment, owing to concurrent disease, leaving nineteen patients. At the end of one month the dose was increased from 20 cc. of a 1 per cent solution to the same quantity of a two per cent solution. By the end of three months twelve of the patients had shown a marked drop (25 per cent or more) in the sedimentation rate. The body weights showed no significant change. Twelve out of the nineteen showed very marked improvement in condition of the lesions, four showed slight improvement, and three appeared unaltered.

CASE 1. Leong Sai, male, Chinese, age 32, type C2. Raised reddish infiltrations over face, arms and thighs. After three months these had entirely disappeared, but skin clippings still showed a few bacilli.

CASE 2. Vellain, male, Indian, age 22, type C2-N2. Large discrete nodules on face, arms and chest. Left ulnar and left auricular enlarged (++). After three months the nodules had almost completely flattened. During the second three months there was no further change.

CASE 3. Choon Lam, male, Chinese, age 38, type C3-N2. Covered with raised, serpiginous lesions showing central anesthesia. *Main en griffe* of both hands. Early in the treatment exfoliation of lesions occurred, but no essential change. After six months the lesions had become decidedly paler and subsided. However, I felt that this result was fortuitous, and marked him as "no change."

CASE 4. Palanisamy, Indian, male, age 30, type C2. Raised depigmented macules with heaped-up margins. These showed fine exfoliation at first, and had receded slightly after three months, but they relapsed to their original condition before the sixth month was up. No change.

CASE 5. Chon Sang, Chinese, male, age 30, type C2. Chronic raised lesions on face and exterior surfaces of limbs. After the first few injections a whitish areola appeared around the lesions (cotarnine vasoconstrictor effect?). After three months the face lesions had almost disappeared, and the arm and leg lesions had definitely receded. The improvement was held, but did not progress in the next three months. Definite improvement, but not progressive.

CASE 6. Yong Oi, Chinese, male, age 19, type C3. Whole face covered with a slightly thickened lesion, trunk and limbs with a fine infiltration. Improvement continued for four months, by which time the face lesions had almost entirely disappeared and one or two ill-defined clear areas appeared on the body. No further improvement after that; the lesions remained slightly positive. Definite improvement, but not progressive.

CASE 7. Seah Thoh, Chinese, male, age 32, type C1. Slight thickening of both ear lobes; one or two pigmented macules on legs. After six months of treatment there was no change.

CASE 8. Ty Sin, Chinese, male, age 56, type C3. Whole face and exterior surfaces of arms infiltrated. Large macule with raised edge covered right side of upper trunk. After three months there was heavy exfoliation of the trunk lesion. Other lesions had become more wrinkled and softer. After six months no further improvement. Slight improvement.

CASE 9. Ahmad bin Sahat, Malay, male, age 25, type C2-N1. Large raised nodular plaque over one side of face and neck. Infiltrated areas over both shoulders. After six months no alteration of lesions.

CASE 10. Teh Ooi, Chinese, female, age 22, type C2. Slight thickening of both ear lobes. Dark, thickened macule on right cheek. Raised, discrete macules on arms and feet. After three months there was very marked improvement, and after four months the lesions had disappeared. Sensation was returning at the end of the six months period. Now no signs of leprosy. Definite improvement.

CASE 11. Kiew Moi, Chinese, female, age 50, type C2. Raised thickened macules on both cheeks. Thickening and infiltration of fingers of left hand. After three months the lesions had definitely faded and flattened. Improvement in sensation after six months. Definite improvement, but not progressive.

CASE 12. Moi Moi, Chinese, female, age 15, type C3. Face generally infiltrated and covered with hard pea-sized nodules. Infiltration of arms, hands and legs. After three months the nodules were much softer, and the ear lobes had somewhat subsided. Lesions continued to recede until after the fourth month, when no further improvement was observed. Improvement, but not progressive.

CASE 13. Kwoi Kee, Chinese, female, age 16, type C3. Leonine face, with large indurated nodules. After three months the lesions became softer, paler and flatter, and the ear lobes had shrunk to half their original size. No further improvement was obtained after the fourth month. Marked improvement, but not progressive.

CASE 14. Les Lee, Chinese, male, age 15, type C2. Cheeks, forehead and ear lobes thickly infiltrated. A thickened nodule below each nipple. After three months the lesions had faded, flattened and became darker. No further change in next three months. Slight improvement.

CASE 15. Tuck Soon, Chinese, male, age 33, type C2. Slight thickening of both ear lobes, faint red infiltration of right side of face, chronic infiltration of outer surface of right forearm. After four injections a white areola appeared around the lesions. After three months the lesions were practically invisible. However, a faint erythematous tinge is beginning to appear at the site of the old lesions after seven months. Very marked (if temporary) improvement.

CASE 16. Chong Kim, Chinese, male, age 17, type C2. Raised, thickened infiltration over both arms and shoulders. Two isolated thickened macules on back, each about 2 inches in diameter. After four injections a faint white areola appeared around the lesions. After three months the lesions were flat and much paler. Improvement continued for another month, after which no further change was observed. Definite improvement, so far as it goes.

CASE 17. Tock Foo, Chinese, male, age 18, type C2. Raised infiltrated area over face, and large nodular ears. Infiltration of lateral sides of thighs. After three months the thigh lesions were definitely paler and had receded and become wrinkled. The lesions on the face assumed a violet tinge, but did not change otherwise. No further change occurred. Slight improvement only.

CASE 18. Wah Kam, Chinese, male, age 15, type C3. Dark, raised, leathery areas on right cheek, over left mandible, and exterior surfaces of both arms and back of hands. Similar areas all over legs. After the first few injections a thin whitish areola appeared around the lesion edges, almost penciling out the affected areas. By the end of three months the lesions appeared to be softening and fading rapidly, but no further change occurred with subsequent treatment. Definite improvement, so far as it goes.

CASE 19. Govindan, Indian, male, age 30, type C1. Two large macules with erythematous edges, one on back and the other on right knee. These showed

a fine exfoliation after three injections. After three months they were definitely paler, and the erythematous edges had darkened and wrinkled. No further change occurred. Slight improvement.

Effect on bacillary content of lesions.—Even in cases showing marked improvement or disappearance of lesions, the areas affected still remained positive, although in some cases very few bacilli were found. On the whole, however, the gain was purely clinical. This fact, together with our general experience of the phthalate groups, leads me to assume that the results are impermanent in the absence of supporting treatment by other drugs. However, that the gain is more than a change in the local lesions is seen from the fact that twelve out of the nineteen cases showed more than a 25 per cent drop in the sedimentation rate.

Intravenous injections of 20 cc. of a 2 per cent solution of cotarnine phthalate appear to be well tolerated. In a few cases there were complaints of transient giddiness after the injection, or of a burning or itching sensation in the lesions. In a number of instances there was a feeling of numbness in the hands, and most of the patients declared that they felt drowsy for a few hours after the injection. It will be noted that in only one case on this drug was there any sign of improvement after the first three months. I have therefore assumed that this one case was benefited by some factor other than the drug.

Four control cases were given injections of cotarnine hydrochloride intravenously twice a week for three months. None of these showed the slightest alteration as a result of the injections. The number of this control series is not as large as one could have wished, but the available supply of cotarnine hydrochloride was limited at the time. On this basis, however, it seems likely that the cotarnine content of the drug is not the effective element.

It remains to attempt some explanation of why three of the four salts of phthalic acid appear to be completely inert, while phthalic acid itself and cotarnine phthalate have a marked if short-lived effect in a certain percentage of cases. It may be said that any new drug if striking enough will produce initial results. This cannot account for the results in the present series, as the results would have been more or less similar in all four groups. It may possibly be that cotarnine phthalate, because of its vasoconstrictor action, is retained in the body much longer than the other water-soluble salts, which are probably eliminated rapidly. Phthalic acid itself is only

slightly soluble in cold water; it is soluble in boiling water but tends to come out of solution if left for over twelve hours. The effect of the phthalate group is probably dependent, to some extent at any rate, on the length of time it is retained in the body.

The price of cotarnine phthalate renders it unlikely that its use can become widespread.

SUMMARY

(1) The magnesium, calcium, potassium-hydrogen and cotarnine salts of phthalic acid have been tried out, on twenty patients each, over a period of six months by intravenous injections twice a week.

(2) Intravenous injections of magnesium, calcium and potassium-hydrogen phthalate appear to have no therapeutic effect in leprosy in doses of 20 cc. of a 1 per cent solution.

(3) Out of nineteen cases treated with intravenous injections of cotarnine phthalate, in 20 cc. doses, first of a 1 per cent solution and later a 2 per cent solution, twice a week, twelve showed marked improvement, four slight improvement and three no change.

(4) The improvement in these cases occurred only during the first three months of treatment.

(5) The clinical improvement appears to be accompanied by a general increase in resistance as indicated by a drop of over 25 per cent in the sedimentation rate of twelve of the patients.

(6) It is suggested that the effect of the phthalate group in leprosy is dependent to some extent on the length of time the drug is retained in the body.