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ROLE OF THE IODINE IN IODIZED OIL DERIVATIVES USED AS ANTILEPROTIC DRUGS

TRIAL OF PLAIN AND IODIZED OLIVE OIL ETHYL ESTERS *

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Iodine, chiefly as iodide, has long been employed in the treatment of leprosy, with varying results. Its use previous to 1911 was reviewed by Currie, Clegg, and Hollmann(1). The iodides had been largely abandoned as of no value or as apt to cause aggravation of the disease, but potassium iodide was reintroduced by Muir, partly for its supposed "lepromalytic" action and antigenic effect, partly for diagnostic and prognostic purposes and, used in conjunction with the erythrocyte sedimentation test, as a guide to the intensiveness with which special antileprosy treatment with the chaulmoogra group derivatives can be given (2).

Iodine in combination with the chaulmoogra ethyl esters was apparently first employed in Hawaii with the idea of enhancing the effect of the latter drug, but after several years experience with the iodized esters, both in the Philippines and in Hawaii, the conclusion was reached that the iodine apparently had no other effect than to reduce the irritant properties of the esters (3, 4).† For about nine years the continued use of iodine in the standard antileprotic drug in the Philippines (0.5 per cent iodized *Hydnocarpus wightiana* ethyl esters) has been solely on this account.

* This is a condensation of an article which appeared in the *Journal of the Philippine Islands Medical Association* 12 (1932) 485.

† This was based on results of treatment given by the older, intramuscular method.—Editor.

PRIMARY OBSERVATION

Nearly two years ago one of us (C.B.L.) carried out an experiment in which our standard antileprotic drug and a similarly iodized preparation of olive oil ethyl esters were injected intradermally into two comparable lepromatous lesions, both containing abundant bacilli. The olive oil preparation was expected to serve as a control on the effect of the chaulmoogra drug, for in a previous experiment the olive oil ethyl esters without iodine had been used similarly without remarkable effect, and had also been employed intramuscularly with similar results (5). The iodine was added with the expectation that it would lessen irritation as it does in the chaulmoogra drugs.

The immediate effect of the injections was marked local acute inflammation in the lesion treated with the iodized olive esters. When this had subsided it was observed, contrary to expectation, that this lesion had undergone a well-marked diminution in thickness, much more than had that treated with the standard drug. However, after several weeks the surfaces of the treated lesions were both practically level with the surrounding skin; the untreated parts of these lesions showed very slight change. Bacteriologically, one month after the injection the hydnocarpus lesion was found negative while the one treated with the olive esters still gave some bacilli. The same experiment was carried out simultaneously on three other patients, all of whom showed similar though less marked results.

These results cast doubt on our former conception of the rôle of the iodine in our standard drug. The inflammatory reaction had been especially marked. Since uniodized olive oil ethyl esters when previously used in a similar way had caused no such marked inflammation, the irritation must be attributed to the added iodine, an effect which is diametrically opposed to its known corrective action in the case of the chaulmoogra ethyl esters. But it has been shown that the degree of tissue irritation caused by the intradermal injection of oily preparations does not seem to be an important factor in the diminution of the bacilli and resolution of the lepromatous process (6). It seemed probable, therefore, that the marked improvement of the iodized olive esters lesion was due largely to the iodine. The degree of inflammatory reaction, in contrast to the usually slight irritation caused by the iodized wightiana esters, suggested a difference in the state of the iodine in the two preparations.

FURTHER EXPERIMENTS WITH IODINE

MATERIAL AND METHODS

Preparations employed.—Olive oil ethyl esters was selected as the vehicle for the iodine and the control preparation. The uniodized preparation is relatively little irritating and its injection can be tolerated by the patients over long periods of time. Since the addition of iodine increases its irritant properties, it was necessary to add another corrective in the form of benzocaine. The following preparations were adopted for trial:

(a) *Test preparation.*—Four grams of metallic iodine was ground in a mortar and olive oil ethyl esters gradually added up to 200 cc. The mixture was heated in an oven at 100°C. for 30 minutes. After it was cooled 600 cc. more of olive oil ethyl esters containing 16 grams of benzocaine were added. The whole mixture was again heated at 100°C. for 30 minutes, after which it was filtered and put in sterile bottles.

(b) *Control preparation.*—This had the same composition as the test preparation without the iodine.

For the sake of brevity the two preparations will further be referred to as the test and the control drugs, and the corresponding groups of patients as the test and the control groups.

Patients and lesions treated.—Two groups of 21 cases each were selected. All were apparently in good physical condition. During the experiment two patients of the test group had to be dropped. The groups were comparable as to type of disease and degree of involvement, the majority showing moderate to extensive active leprotic skin lesions, macules, and infiltrations. In the control group 46 macular areas were treated, 25 areas of infiltration, and two agglomerations of nodules; in the test group 64 macules, 8 infiltrations, and no nodules. All but two cases had multiple lesions.

Method of treatment.—Intradermal injections were employed, supplemented at times by intramuscular. They were given once a week, the cases with many or extensive lesions receiving in total fewer treatments per lesion or area than those with only a few small ones. The average weekly dose was about 5 cc. The local irritation produced by the two preparations was practically negligible. The period of trial was six months.

OBSERVATIONS

Changes in relation to amount of treatment.—Definite improvement was shown by 71 per cent of the treated lesions in the test

TABLE 1.—*Changes of lesions in relation to (a) number of injections, (b) total amount of drug given per lesion or area, and (c) the type of lesions treated.*[a]

Treatment	Test Lesions							Control Lesions						
	Number	Improved		Stationary		Worse		Number	Improved		Stationary		Worse	
		No.	per cent	No.	per cent	No.	per cent		No.	per cent	No.	per cent	No.	per cent
A. Number of injections														
1 to 10	65	48	74	17	26	0	—	64	6	9	54	84	4	6
11 or more	7	3	(43)	4	(57)	0	—	9	1	(11)	4	(44)	4	(44)
B. Amount of drug per lesion														
1 to 20 cc.	39	30	77	9	23	0	—	44	3	7	40	91	1	2
21 to 40 cc.	23	16	70	7	30	0	—	19	3	16	16	84	0	—
41 or more	10	5	(50)	5	(50)	0	—	10	1	(10)	2	(20)	7	(70)
C. Type of lesions treated														
Macule	64	49	76	15	23	0	—	46	6	13	34	4	6	13
Infiltration	8	2	25	6	75	0	—	25	1	4	24	96	0	—
Nodule	0	0	—	0	—	0	—	2	0	—	0	—	2	100
Total	82	51	71	21	29	0	1	73	7	10	58	79	8	10.9

[a] This table is a rearrangement and condensation of Tables 1 and 2 of the original article.

group, but by only 9.6 per cent of the controls. Eleven per cent of the latter became worse in spite of the treatment, but none of the test group. In Table 1 the changes observed in the cases are correlated to both (a) number of treatments and (b) amount of drug received.

(a) Of the test group that received only 1 to 10 injections, 74 per cent improved, though of the small group that received more only three out of seven (43 per cent) improved. No such difference was seen in the controls.

(b) In the control group there was, up to a certain point, a direct relation between the amount of drug and improvement. Of those receiving 20 cc. or less the improved were 7 per cent, of the smaller group receiving 21 to 40 cc. they were 16 per cent. However, of the ten that received more than 40 cc. only one improved, while seven became worse.

In the test group there was no relation between dose and improvement. Of those that received 20 cc. or less 77 per cent improved, and of the 21 to 40 cc. group 70 per cent. However, only five of the ten that received more than 41 cc. improved. This apparent relation or lack of relation is not explained by the data available. However, it is clear that the improvement was always greater in the test group than in the controls.

Changes in relation to type of lesion treated.—In both groups improvement was mostly in the macules (Table 1, C). Again, while 76.5 per cent of those in the test group improved, only 13 per cent improved with the control drug. The corresponding figures for the infiltrations were 25 and 4 per cent, respectively. The greater improvement in the macular lesions is in accord with experience with the chaulmoogra derivatives, or in the spontaneous improvement sometimes seen.

Change in general condition.—Estimations were made of the sum of changes in lesions treated locally, and of the progress of the other manifestations of leprosy. Of the control group 14 per cent of the cases had improved after six months of treatment. Of the test group 58 per cent improved, the number increasing as the total dose given increased. There was no such relation in the control group. In some cases the treated lesions improved while the untreated ones grew worse or fresh crops appeared, so that whatever improvement resulted from the local treatment was offset by the general progress of the disease. This occurred in both groups.

Lepra reaction.—Excluding the one that was dropped due to prolonged lepra reaction, eight cases, four in each group, developed mild reactions. In none was treatment discontinued. Two in the control group became worse, the other two remained stationary. In the test group two improved, one remained stationary, and one became worse after the reaction.

COMMENT

The results would indicate that the iodine was chiefly responsible for the improvement noted in the test group. In a few cases this was quite marked, especially in those with one or a few lesions. Despite the short trial and the relatively small numbers of patients, the marked disparity in the two groups indicates, in our opinion, that the apparent superiority of the iodized olive oil ethyl esters was not accidental.

The results with this preparation compare favorably with those obtained with the iodized chaulmoogra derivatives. This raises the question as to how much of the improvement following the use of the latter preparation is due to its iodine content and how much to the chaulmoogra group fatty acids. As stated, we had considered the iodine in our standard antileprotic preparation unimportant therapeutically, except indirectly by permitting more intensive treatment through its corrective effect on the irritant action of the esters. Is there any difference in the state of the iodine in these two iodized preparations that can explain the apparently paradoxical observations? If so, is the apparent therapeutic effect of the iodine in the iodized olive oil ethyl esters, or the apparent absence of such effect with the iodized chaulmoogra ethyl esters, due to the presence or absence of free iodine?

Clinically, the presence of free iodine in the iodized olive oil ethyl esters (without benzocaine) is indicated by the severe inflammation produced by its injection compared with that following the injection of uniodized olive ethyl esters.‡ We have not succeeded in preparing mixtures containing more than 0.5 per cent iodine and 2 per cent benzocaine without producing a murky precipitate. Since iodine and benzocaine in the proportions stated are, singly, readily soluble

‡ Mr. E. Paras, of the chemical section, Culion Leper Colony, using watery solutions of potassium iodide, was able to show qualitatively the presence of free iodine in both the iodized olive oil ethyl esters and the iodized wightiana ethyl esters. This finding should be verified.

in the olive oil ethyl esters, the formation of a precipitate on mixing the three also seems to indicate that not all of the iodine is bound by the unsaturated fatty acids in the olive oil ethyl esters, some remaining free to combine with the benzocaine.

It is noteworthy that the largest amount of iodine given in any case in the period of trial was less than one gram, of which one-half gram at most was given intradermally. Whether larger amounts of iodine, in preparations of higher concentration, would give better results remains to be determined.

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