A CHAULMOOGRA PREPARATION FOR INTRAVENOUS USE, AND ITS THERAPEUTIC EFFECT

By Drs. Masao Ota and Saburo Sato

From the Dermatological Clinic, Tohoku Imperial University,

and

Tatsuro Masuzawa

From the Dispensary of the University Hospital, Sendai, Japan.

INTRODUCTION

Chaulmoogra oil has been used from ancient times as a specific drug for leprosy. It is chiefly administered orally or injected subcutaneously or intramuscularly, but these methods not infrequently induce gastro-intestinal disturbances, or give rise to local pains, or cause delayed absorption. To avoid these defects intravenous injection has been attempted by a large number of workers: Vahram (1916), Rogers (1916-1919), Stévenel (1917-1920), Muir (1921), Hooper (1921), Harper (1922), Hasseltine (1922-1924), Lamoureux (1923), Aoki, Kawamura, Kamakiwa and Fukamachi (1924), and Lara, de Vera and Eubanas (1928). These workers used the oil itself, or sodium compounds of its fatty acids, or a suspension of the ethyl esters of the fatty acids. Although some of them reported success in arresting leprosy to a certain extent, the amount of effective substance injected was in every case exceedingly small. For instance, in the case of sodium gynocardate used by Rogers the amount so given at one time was not in excess of 2.5 grains (0.162 gram). Of five preparations used by Aoki and his collaborators only two, "leprol" and "antileptin," had any therapeutic effect. Leprol is a sodium sulphonate compound of chaulmoogra oil (a Sankyo product), and antileptin is a 1 per cent solution of leprol with 0.25 per cent of mercuric iodide and sodium iodide, mixed in equal amounts. Of the former preparation the amount used at one time was 4 to 6.6 cc., and of the latter, 1.7 to 8.5 cc. Even if intravenous injection is much superior to other methods of administration, not much could be expected from such small doses.

Since 1933 we have attempted to obtain a chaulmoogra preparation suitable for intravenous injection. Utilizing the experiences of the afore-mentioned workers, we started our experiments with (1) the oil itself, (2) the sodium compound of its fatty acids, and (3) the ethyl esters. With the sodium compound there was comparatively little untoward reaction, but not infrequently venous thrombosis was induced at the site of the injection. Moreover, the aqueous solution contained not more than 3 per cent of the substance, and it was impossible to preserve it for a long time; it loses its effectiveness if not used immediately after preparation. Next, an emulsion of the whole oil was given trial, but this proved too difficult and had to be abandoned. With the remaining preparation, the ethyl esters, success was obtained with comparative ease, hence the study was confined mainly to this field. Success was ultimately achieved by the preparation of an effective emulsion which could be used without any undesirable reaction.

METHOD OF PREPARATION

The particles of an emulsion which is to be injected intravenously must be far smaller than the red corpuscles. Means of preparing such an emulsion used at the present time are: (a) a supersound-wave producing device, and (b) mechanical pressure which forces the substance through minute holes. As for the emulsifier used to stabilize the preparation, gum arabic, gelatine, lecithin, protalbin-acid-soda, etc., are the materials most appropriate. We find two or three of these substances to be suitable.

With the use of the supersound-wave device an emulsion having a maximum ethyl-ester content of 30 per cent can be prepared in a comparatively short time. The minimum diameter of the particles thus prepared is approximately 0.3 micron, and the emulsion is very stable. Moreover, micro-organisms which are occasionally contained in the mixture are annihilated by the supersound-wave. This makes subsequent sterilization by heat unnecessary, and conveniently establishes the stability of the emulsion. The only defect in this method lies in the fact that the emulsion cannot be produced in large quantities at one time. As for the second method, many devices can be used but the best results were obtained by the employment of special apparatus.

Details of procedure.—The proper amount of one of the colloidal materials used as the emulsifier is mixed with distilled water, the ethyl esters are added

in proportions of 10 to 50 per cent, and the whole is thoroughly mixed by stirring. The mixture is emulsified by means of the apparatus for a definite time. The finished emulsion is poured into a long glass tube and left for a time in an upright position. The middle layer, which contains the largest portion of the emulsion, is then separated and drawn off into ampules. Finally, sterilization is accomplished by subjecting the material to a temperature of 65° to 70°C. for 30 minutes, thrice in three days. The particles of this emulsion, which are more or less uniform in size, are about 1 micron in diameter; rarely we find some measuring 2 to 5 microns.

A more or less acid reaction will be manifested in the course of preparing this emulsion. This is due to its lecithin content, as well as to an increase in acidity brought about by the sterilization. To neutralize it caustic soda solution is used. In filling the ampules care is taken to prevent formation of an air space, in order to prevent Ramsden's phenomenon by which dissociation of the emulsion results.

As for the concentration of the emulsion, for practical convenience we are inclined to use 40 per cent and 10 per cent preparations as the standards for preservation, even though a stable emulsion can be made with as much as 50 per cent of the esters.[1] For intravenous injection, although the solution can be used in its original state it is preferred to make a 1 : 5 or 1 : 10 dilution with the addition of a 4.5 per cent solution of glucose, or physiologic saline, or distilled water. The diluted emulsion usually induces much less untoward reaction.

In preparing the emulsion the following conditions should be met: (1) The particles of ethyl esters should be uniform in size and as minute as possible. (2) The emulsifier should: (a) be colloidal in its physico-chemical nature, (b) lower as much as possible the surface tension between the water and the esters, and (c) have no reaction of its own. (3) The emulsion should have a certain amount of viscosity. (4) It should not contain any electrolyte. Our emulsion satisfies these conditions, and contains nothing that is harmful even after sterilization. Hemolysis, if caused at all, is negligible. The stability of an emulsion may be affected by temperature, time and ethyl-ester content. By our process the temperature used and time spent in sterilization in no way affects emulsion, and the desired stability is secured by the use of 10 to 40 per cent of the esters.

[1] The 10 per cent, 15 per cent and 20 per cent emulsions have been prepared by the Sankyo Company, which owns the sales rights. This product is named "Esperol," and is produced in quantities large enough to meet a universal demand.

ANIMAL EXPERIMENTS

For these experiments rabbits were used. At first intravenous injections of the undiluted 40 per cent emulsion were given. The results indicated that the fatal dose for a single injection of an emulsion made with undistilled esters is 3 to 4 cc. per kgm. The animals that died did so immediately after injection, showing a state of uneasiness and distress. Postmortem examination disclosed congestion and hemorrhage in the lungs. Coagulation of blood was found in the large vessels of the lungs and in the ventricles of the heart. In no case was pulmonary embolism demonstrated.

When the emulsion was injected repeatedly at intervals of 4 to 6 days the critical dose ranged from 2 to 3 cc. per kgm. Some of the animals were able to endure more than 10 injections, but a great number of them died soon after the 3rd or 4th injection. Generally speaking, the concentration of the emulsion rather than the amount given determines the ability of animals to stand the injections. Thus, for animal No. 8 concentrated doses were used up to the 4th injection, but in the subsequent 10 injections the emulsion was diluted 5 times with saline and these the animal was able to withstand. On dissecting the dead animals we found that pathological changes had occurred mainly in the lungs, where inflammation and congestion were seen, often accompanied by adhesive pleurisy. Nevertheless, in no instance were we able to find embolism due to the fatty substance. On examining the tissues of the organs stained with Sudan III there were found particles of the ethyl esters the size of red corpuscles, but not larger, and these did not appear in groups.

When doses as small as 0.5 cc. per kgm. of 40 per cent emulsion were given no response was obtained on the whole. The animals seemed able to endure any number of such injections. Owing to the fact that the technique of preparing the drug had not been fully mastered at that time, animals 11 and 12 died soon after the 6th and the 11th injection, respectively. Animals which had received more than 10 injections were killed to ascertain whether any changes had occurred in their viscera. In some rare instances slight pneumonia or pleurisy had developed, but in the majority no noticeable changes were found. If doses of 0.5 or 0.25 gm. per kgm. of the 40 per cent emulsion be diluted 10 to 20 times with distilled water, or physiologic saline, or 4.5 per cent glucose, the animals show no evidence of injury

and are able to bear 10 or more injections. Such animals when examined after being killed occasionally showed slight congestion of the lung, but in the remaining organs there were scarcely any morbid findings. We have never, in our experiments, encountered cerebral embolism.

A dose of 2.5 cc. of 40 per cent emulsion contains 1 cc. of ethyl esters. This amount is sufficient for one injection in man. For people whose weight is 40 kgm. the amount injected should not be in excess of 0.0652 cc. per kgm. In animals such as the rabbits used, weighing 2 kgm., not more than 0.1250 cc. is used. Taking into account the results of the animal experiments, we undertook an experiment using 2.5 to 5 cc. doses for intravenous injection in man, with the assumption that there would be no possibility of danger. This assumption was confirmed. Danger in the use of this emulsion will be still lessened by dilution.

Generally speaking, if a 40 per cent emulsion is used in intravenous injection there is greater chance of its remaining in the lesser circulation than of getting into the greater circulation, the lungs being a favorable spot for harboring the drug. On the other hand, if it is diluted 20 times it passes into the systemic circulation and is distributed throughout the entire body. This was distinctly evidenced both in animal and human experimentation.

It is interesting to note that preparations made with undistilled esters induced less untoward reaction than the one made with esters purified by distillation. In the animal experiments the latter induces various irritative symptoms and consequently the fatal dose is smaller than the 3 to 4 cc. indicated above; in experiments made under otherwise similar condition it was 1.2 to 1.6 cc. This preparation, introduced into the human body, tends to irritate the respiratory tract, besides causing other undesirable symptoms. Therefore, in the preparation of our drug undistilled ethyl esters are used.

Comparing the accumulated data obtained from the foregoing animal experiments with past records, we find that use of the drug which we have prepared enhanced the capacity of animals to endure injections. This capacity is wholly dependant on the minuteness of the particles of the esters.

APPLICATION TO PATIENTS

Experiments in the treatment of leprosy were carried out from the end of April, 1933, to April of the following year, employing the

TABLE 1.—*Details of cases treated, amount of treatment given, and results.*

Case	Sex and age	Type of case, and degree [a]	Duration, years	Injections		Side-effects	Results
				No.[b]	Cc.[c]		
1. T.K.	M. 27	Nerv. N2	13	50[d]	148	First 5: headache, chill and rigor.	Gain in weight.
2. K.T.	M. 22	Mac. C2	1½	50	132	None.	Improvement.
3. T.Y.	M. 28	Tub. C3-N1	7	44	131	First 6: headache, chill and rigor.	Improvement; gain in weight.
4. M.F.	M. 26	Tub. C2	3	43	115	First 6: headache; rigor once.	Nodules absorbed; flushed face cleared.
5. S.K.	M. 58	Mac. C1-N1	3 mo.	43[d]	112	Headache sometimes.	No change.
6. M.H.	F. 25	Tub. C2	2	39[d]	113	None.	Improvement.
7. M.T.	M. 55	Tub. C3-N2	15	34	111	Early: headache.	Nodules absorbed; ulcers healed.
8. T.S.	M. 43	Mac. C2	1	31	80	None.	Improvement.
9. S.T.	M. 39	Tub. C2	13	30	82	None.	At 25th; nodules absorbed; reaction.
10. T.T.	M. 26	Mac. C2-N1	2 mo.	30	80	None.	No change.
11. Z.N.	M. 31	Tub. C2	6	29	83	None.	Nodules absorbed; improvement.
12. Y.I.	M. 66	Mac. C1-N2	3	28	70	Early: headache.	Ulcers healed.
13. S.S.	M. 56	Mac. C1-N2	1½	27[d]	74	None.	Macules disappeared.
14. S.K.	M. 19	Mac. C2	3	27	72	First 4: slight chest oppression.	Macules decreased.
15. S.O.	M. 29	Tub. C1	2	26	80	None.	Improvement; gain in weight.
16. K.S.	M. 28	Mac. C2	6 mo.	24	60	None.	Macules decreased.
17. S.H.	F. 51	Mac. C1	3 mo.	24	62	None.	Improvement.
18. S.T.	M. 13	Nerv. N1	3 mo.	22	22	None.	Improvement.
19. K.T.	M. 38	Tub. C2	1	21[d]	63	None.	Ulcers healed.
20. K.H.	M. 12	Tub. C2	1	20	20	None.	Nodules absorbed.
21. K.K.	M. 25	Mac. C3	3	17	45	None.	No change.
22. I.G.	M. 24	Mac. C1-N2	4	13	30	None.	No change.
23. N.U.	F. 17	Mac. C2	1½	12	22	First 3: chest oppression.	Macules disappeared.
24. E.S.	M. 62	Mac. C2	3	12	30	None.	Improvement.
25. M.K.	M. 35	Tub. C2	5	12	27	In 4th: chest oppression, cough.	No change.
26. W.N.	M. 40	Tub. C2	2	12	31	None.	Nodules absorbed; improvement.
27. M.S.	M. 34	Tub. C2	1½	12	32	None.	Improvement.
28. K.W.	M. 46	Mac. C2	2	11	29	None.	No change.
29. I.A.	M. 32	Mac. C2	1	10	26	None.	Flushing of face decreased.
30. M.O.	M. 23	Nerv. N2	3	10	25	None.	No change.
31. Y.A.	M. 29	Tub. C3	10 mo.	8	24	None.	Nodules absorbed.
32. I.Y.	M. 29	Nerv. C2	14	7	17	None.	Improvement; ulcers healed.
33. K.M.	F. 17	Tub. C3	7	6	2	Lumbar pain; treatment discontinued.	No change.
34. Z.M.	M. 32	Mac. C2	1 mo.	6	15	None.	Macules of face decreased.
35. S.S.	M. 18	Mac. C1-N1	1	6	11	Flushing of face, chest oppression.	No change.
36. K.K.	M. 20	Tub. C2	5	5	10	Chest oppression.	No change.
37. K.M.	F. 17	Tub. C3	5	5	7	Chest oppression.	No change.

[a] The type designations used are those of the classification official in Japan, namely, neural, macular and tubercular; the symbols are those adopted by the Leonard Wood Memorial Conference.

[b] For patients given intramuscular injections the numbers of injections so given are double these figures, which apply only to the intravenous injections.

[c] Showing the total amount of the standard 40 per cent emulsion given, regardless of dilution for injection.

[d] Not given intramuscular injections.

emulsion of ethyl esters intravenously. The cases treated were 48 in number, 39 males and 9 females. Their classification according to type was: nodular, 16; macular, 16; and neural, 5. The ages ranged from 12 to 61 years. The largest age group, 13 cases, was from 21 to 30 years old; next were 8 in the 11 to 20 group, and 7 in the 31 to 40 group; 3 were between 41 and 50, 4 between 51 and 60, and 2 beyond 60. In the course of the experiment, aside from the two periods of rest in August, 1933, and January, 1934, injections were given once every week. Since it was not our primary object to compare the effect of these intravenous injections with chaulmoogra oil given intramuscularly, a large proportion of the patients were given chaulmoogra oil into the gluteal muscles simultaneously with the intravenous injections. The intra-muscular injections were given twice a week.

The 40 per cent emulsion was used as the standard, and doses appearing in Table 1 and in this discussion are based on this concentration. At first the original 40 per cent concentration was used; but later, finding that patients usually tolerated the diluted ones more easily, we diluted it 10 to 20 times with one of the diluents mentioned, giving the injections very slowly. With these injections the occurrence of untoward reactions was most uncommon. Though glucose solution is considered best for purpose of dilution, distilled water causes no ill effect.

Patients receiving more than 5 injections each totalled 37 (32 males and 5 females); 20 received 20 injections in succession, 5 received 30 to 39 injections, 3 were given 43 or 44 injections, and 2 had 50 or more. The maximum amount given to any patient was equivalent to 148 cc. of the 40 per cent emulsion. At first, 0.5 to 1 cc. of that concentration was injected, and as the patients were able to stand this the amount was gradually increased. Later, after discovering the advantage of using a diluted solution, the dose was increased to 2.5 to 3 cc., and this dose was generally used thereafter except in some cases where larger amounts had to be used, when 5 cc. was given per injection.

From the results of our present experiment there is no fear of the occurrence of side effects. Much concern was felt before the technique of preparation was perfected because of continuous occurrence of such effects. The characteristic effects were flushing of the face, a feeling of oppression in the chest, and coughing, but at times head-

ache, chills or rigors followed injection. There were 7 or 8 patients who showed such symptoms, and with one of them it became necessary to stop treatment. This patient was a 17-year old girl who had nodular leprosy with "facies leontina" and marked loss of weight. Immediately after injection she complained of lumbar pain, consequently the diluted emulsion in very small amounts was given, but the injections had to be discontinued after the sixth dose. With chaulmoogra oil given intramuscularly she showed no untoward reaction whatever.

There is little relation of side action to the constitution of the patients; it depends chiefly on the preparation of the drug. Such reactions were seen in almost all cases in which our earlier preparation was used. With the improved emulsion hardly any side action can be noticed, and either the concentrated solution or the dilution can be employed with safety.

RESULTS OF TREATMENT

The problem of judging the relative merits of the intravenous injection of the ethyl esters and intramuscular injection of chaulmoogra oil is one difficult of decision, because both are chaulmoogra preparations. It can hardly be expected that there will be any well-defined differences of effect between subcutaneous, intramuscular and intravenous injections. The differences, if any, will be in the degree of effectiveness, distinction of which is difficult to make.

Since our foremost objective was to prepare a suitable preparation of chaulmoogra oil for intravenous injection, we did not lay stress on other drugs or on other modes of injection. In the majority of the cases treated the oil was injected into the muscle simultaneously with the intravenous injections, as has been said. Details of the treatment given and results obtained are shown in Table 1; the numbers of intramuscular injections given are not shown but in each case it was double the number of intravenous injections.

In five cases only the ethyl ester emulsion was used; these are Nos. 1, 5, 6, 13, 19 of the table. One of them, a neural case to whom 43 injections were given, revealed no change whatever in his symptoms. If we consider the clinical features of this type of the disease we cannot expect more than this. In the other four cases there was gain in weight or disappearance of macules, which fact goes to show that this treatment has a certain therapeutic effect.

The remaining 32 cases were treated by both methods. Of these, 25 received more than 10 intravenous and 20 intragluteal injections; 7 showed no improvement in the clinical picture, but the rest showed more or less evidence of amelioration. This was indicated by fading or disappearance of macules or of flushing of the face, partial or complete disappearance of nodules, or the healing of ulcers.

So far as can be told from our small-scale experiment it appears that, at least for patients in the early stage of leprosy with erythema, numbness, formication, etc., the intravenous injections combined with intramuscular injections produce speedier therapeutic results than intramuscular injections alone. Outstanding examples of this are Cases 20 and 31. The former was a lad 12 years old who had developed the nodular type of leprosy in the previous year; the nodules were localized on both thighs. The latter was a man 29 years old who had started receiving treatment 10 months after the onset. His case was a rather severe one; the face, in particular, was thickly covered with nodules of various sizes. Both patients had not previously received any special treatment, but nodules were seen to disappear in Case 20 at about the 15th intravenous injection, and in Case 31 at the 6th.

The so-called erythema nodosum leprosum (''lepra reaction'') was seen only in Case 9. This was a man 39 years old having numerous nodules, mainly on the face. He had become ill with this disease more than 10 years ago and appeared to be difficult to cure, but after receiving 10 or more intravenous injections he made speedy improvement, far beyond our expectations, and a large proportion of the nodules disappeared. At about the 25th injection, however, he suddenly developed ''fever lumps,'' a fresh outburst of soft, walnut-sized nodules on the head and forehead. Notwithstanding this fact injections were continued, with the result that at the 30th injection this acute nodule-formation nearly disappeared and the patient showed improvement.

The making of a chaulmoogra preparation suitable for intravenous injection, which was our chief aim from the beginning, having nearly been perfected we feel that further endeavor should be directed to comparing the therapeutic effect of our preparation with that of chaulmoogra oil itself. For this purpose experiments on larger numbers of patients in the leprosaria and criticisms derived from these are needed. Because large quantities of the emulsion are

required for this, its production is left in charge of the Sankyo Co., Ltd. The 10 per cent emulsion is the standard for therapeutic use and the name "Esperol" is designated for this.

Apart from the above experiments, we may consider theoretically the results of the chaulmoogra oil treatment in leprosy to depend, as contended by some, on its bactericidal effect upon the leprosy bacillus, or, as others maintain, to be due only to a stimulation of the body tissues which enhances the formation of bactericidal or immune properties. However this may be, in order to have the drug distributed throughout the entire system intravenous injection is, we maintain, superior to either intramuscular or subcutaneous injection. If gradual absorption of the drug accumulated in a certain tissue of the human body is regarded as one of the essential factors contributing to improvement, intramuscular injection of the same substance may be adopted in combination with its intravenous injection.

CONCLUSIONS

1. To make a preparation of chaulmoogra oil suitable for intravenous injection has been attempted by many investigators, but the attempts have hitherto been fruitless of results, and at present that method of injection has been practically given up. From the ethyl esters of *Hydnocarpus anthelmintica* we have produced an emulsion which is suitable for such injection.

2. This emulsion contains particles of the ethyl esters which are about 1 micron in diameter and nearly uniform, and its colloidal condition is so stable that it can be preserved for a long time, whether it contains 10 per cent or 50 per cent of the esters. We have used one containing 40 per cent as the standard, though what we call "Esperol" is a 10 per cent emulsion.

3. Experiments with rabbits have shown that the dose of the 40 per cent emulsion given at one time should be less than 2 cc. per kgm. If the dose is 0.5 cc. per kgm., no unpleasant symptoms are caused.

4. In patients we injected single doses of 2.5 and 3.0 cc. of the 40 per cent emulsion (1 cc. of the esters), and with some patients 5 cc. at times. Intravenous injections of such large amounts of ethyl esters have never been made before, and not only did this large amount cause noticeable secondary reactions, but also flushing of the face, feeling of oppression in the chest, etc. These reactions, which were occasionally met with at the first stage of our investigation, have

nearly been gotten rid of through improvements in the preparation. It is much safer to use the emulsion diluted about 5 to 10 times with distilled water, physiologic saline or 4.5 per cent glucose solution. The largest number of injections given to any of the patients treated was 50, and the total amount of the emulsion injected reached 148 cc., this figure being calculated as of the standard 40 per cent preparation.

5. What is the effect of the intravenous injections? Is this method superior to the usual intramuscular or subcutaneous injections? These questions are difficult to solve, and our experience is as yet too limited to decide upon them. They must be reserved for the investigation of specialists, but we are convinced that the method of injection we use is not inferior to those used up to this time.

We are much indebted in this study to a subsidy for the study of natural sciences furnished by Hattori Hokokai.

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