Original Articles

MALARCAN IN THE TREATMENT OF INDIAN STRAINS OF MALARIA

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UNTIL recently quinine was the only drug employed in the treatment of all forms of malaria, but Acton (1920) showed that, while it cured 90 per cent of malignant tertian infections if properly given, in benign tertian infections the primary cures were not more than 25 to 30 per cent even after a two months' course. Cinchona febrifuge which contains all the alkaloids of cinchona bark gave a cure rate of about 50 per cent (Acton *et al.*, 1921) so that it could be reasonably concluded that there must be alkaloids other than quinine which are responsible for this enhanced rate of cure. These other alkaloids were tested by him individually. Cinchonine and quinidine in 10-grain doses twice daily gave a cure rate of 60 per cent of benign tertian infection after a short course. Fletcher (1923) tested the action of different cinchona alkaloids individually in the treatment of malaria and testified to their having well-marked anti-malarial properties. The anti-malarial action of these alkaloids, however, varied in potency; quinine and quinidine, for instance, were more powerful than cinchonine and cinchonidine. It would appear from this that not only do the different cinchona alkaloids vary in their anti-malarial activity generally but that their action on different species of the plasmodium also varies. Attempts have, therefore, been made by workers to develop compounds of these alkaloids by altering the side chains round the main nucleus and by combining them with other substances, such as aniline, acridine or other suitable compounds. In this way it is hoped that compounds with enhanced anti-plasmodial activity against one or other species may possibly be produced which will act on both the sexual and the asexual cycle, or that perhaps such compounds will even have a destructive action on the sporozoites injected by the mosquito bite and in this way act as true prophylactics.

'Malarcan' appears to be a product which has been prepared with this end in view. It was supplied to us through the courtesy of Dr. P. Rezak of Vienna in order that we might test its therapeutic efficacy against malaria in India.

The drug is sold in the form of tablets which have a bright yellow colour. The makers recommend two tablets to be given every four hours day and night, *i.e.*, 12 tablets within 24 hours, till the patient no longer shows any signs of fever. This is often not feasible and in our trials we gave the requisite amount of the drug in 3 or 4 divided doses daily. They recommend that tablets should be swallowed after a meal or light refreshment, with water. After the fever has subsided it is advised that two tablets be taken three times daily. The total dose necessary varies according to the severity of the attack from 80 to 120 tablets. In children smaller doses are recommended according to age.

The makers also recommend the drug as a protective against malarial fever, two tablets being taken daily after any meals during the period the patient is exposed to infection and two tablets every other day for three weeks after leaving the malarial zone. The method of administration advised in itself shows that the drug is not claimed to be a true prophylactic, inasmuch as it is not expected to destroy the sporozoites injected by the mosquitoes, but to act as a curative in the same way as quinine does. The drug, it is said, produces no toxic or untoward symptoms and does not precipitate blackwater fever, like quinine does in susceptible patients.

'Malarcan' is said to be a compound of a stereo-isomeric base of methyl-cupreine with methyl-acridinium-chloride and hydrocholic acid. It is thus probably a derivative of quinine or quinidine and, in high dilutions, it shows fluorescence under ultra-violet light.

The anti-malarial properties of Malarcan on the Indian strains of malaria were tested by us in a series of 29 patients in the Carmichael Hospital for Tropical Diseases. Patients were admitted under the senior author and soon after admission thick and thin films from the peripheral blood were examined. In some cases a parasite count was also made. Except in urgent cases the anti-malarial treatment was withheld for a few days in order to identify correctly the species of the infecting parasite as well as to make sure that there was no chance of spontaneous recovery. The patients were then put on Malarcan, and no other drugs except purgatives were given. After the completion of treatment the patients were kept under observation in the hospital for a fortnight, daily examinations of the blood were made for 15 consecutive days, and a blood culture for malarial parasites was taken in many patients before discharge. It would undoubtedly have been advantageous if the patients could have been kept under observation for a longer period after treatment, but as soon as the temperature settled down they wanted to leave the hospital and it was with great difficulty that they could be persuaded to stay for a fortnight. Besides, in an endemic

area like Calcutta it is very difficult to distinguish between a relapse and a reinfection, but by this procedure it was hoped that an idea could be formed regarding the efficacy of the drug. During these trials regard was paid to the effect of the drug :

(*a*) on the temperature and other symptoms met with in the disease,

(*b*) on the sexual and asexual forms of the parasites and the time taken for their disappearance from the peripheral blood, and

(*c*) on the splenic enlargement and relapse;

(*d*) on the relapse rate;

note was also taken of any untoward effects produced.

In the table opposite details of 29 patients on which this drug was tried are given.

In case 1 two tablets thrice daily up to 34 tablets were given, and, in case 2, six tablets in 24 hours. In these patients the effect of the drug was only observed on the sexual forms of *Plasmodium falciparum;* these patients had crescents in the blood and suffered from no other symptoms. It will be observed that no effect whatsoever was produced and the crescents persisted in the peripheral blood after administration of Malarcan.

The drug was then tried in smaller doses than those recommended by the makers in order to see what effects were produced on the malarial parasites circulating in the blood as well as on the symptoms produced. In cases 3 to 15, the patients were mostly given two tablets of Malarcan three times a day for 5 to 6 days. They were suffering from either *Plasmodium falciparum* or *Plasmodium vivax* infection and in one patient there was a mixed infection with these two species. A perusal of the table will show that in cases of *Plasmodium falciparum* infections the asexual forms generally disappeared within three days of the administration. The crescents were not touched in any case. As regards the infections with *Plasmodium vivax,* both the sexual and asexual forms disappeared from the peripheral blood within 3 to 4 days, that is to say, the parasites of this species took somewhat longer to disappear than those of *Plasmodium falciparum.* Further details of the treatment are given below :—

Case 3.—He had been given 6 tablets of Malarcan and 4 doses of plasmochin, 0.01 gm. each, a fortnight ago; this time 6 tablets a day for 6 days; left hospital on the eighth day.

Case 4.—Two tablets thrice daily for 5 days. No parasites found for 9 days.

Case 5.—One tablet b.d. up to 7 tablets; scanty crescents on the fourth day; rings and crescents on the eighth day.

Case 6.—Had been given 7 tablets 9 days before; 2 tablets b.d. up to 17 tablets and plasmochin for 2 days; crescents persisted and scanty rings found on the fifteenth day.

Case 7.—Half tablet b.d. for 5 days; parasites reappeared on the eleventh day.

Case 8.—Two tablets t.d.s., for 5 days, no parasites for 15 days, culture sterile.

Case 9.—Two tablets 4 times a day for 5 days; no parasites for 15 days; culture sterile.

Case 10.—Two tablets b.d. for 5 days; no parasites for a week.

Case 11.—Two tablets t.d.s. for 5 days; no parasites for a week; culture sterile.

Case 12.—Two tablets t.d.s. for 5 days; no parasites for 15 days; culture sterile.

Case 13.—Two tablets 4 times a day for 5 days; left hospital.

Case 14.—Two tablets 4 times a day for 5 days; had a course of atebrin 5 months ago.

Case 15.—Two tablets t.d.s. for one day then b.d. for 4 days; no asexual forms seen for 10 days; crescents disappeared after 4 days.

Out of this series of 13 patients, 4 (30 per cent) showed no signs of recrudescence of the attack while under observation for the fortnight following the treatment, while 3 (23 per cent) apparently relapsed and showed the same species of parasite which they originally carried. The remaining 6 unfortunately left the hospital before the period of observation expired, but all of them were parasite-free on the date of discharge.

Of the remaining, 10 patients received 12 tablets of Malarcan daily for 7 to 8 days, that is, the full dose advised by the makers. Of this series, 6 (60 per cent) were apparently cured, and three relapsed while still under observation in the hospital; one left hospital before the expiry of the period of observation. These patients suffered from either *Plasmodium falciparum* or *Plasmodium vivax* infection except two patients who had mixed infections.

Case 16.—Four tablets t.d.s. up to 80 tablets; no asexual forms for 15 days; crescents persisted.

Case 17.—Two tablets 4 times a day up to 40 tablets; again 16 tablets a day up to 64 tablets; no parasites for 17 days; culture sterile.

Case 18.—Four tablets t.d.s. up to 80 tablets; no asexual forms seen for 15 days; culture sterile; crescents persisted and were removed with plasmochin.

Case 19.—Four tablets 4 times a day till 80 tablets; no parasites for 5 days.

Case 20.—Twelve tablets a day till 80 tablets; parasites disappeared from the fifth day of treatment; parasites reappeared on the fifteenth day; then treated with atebrin.

Case 21.—Twelve tablets a day up to 80 tablets; parasites on the tenth day.

Case 22.—Two tablets 4 times a day up to 80 tablets; no parasites from the sixth day of treatment for 15 days.

Case 23.—Two tablets 6 times a day up to 80 tablets; parasites on the fourteenth day and treated with atebrin.

Case 24.—One tablet t.d.s. up to 15 tablets; parasites still present, then 2 tablets t.d.s. up to 30 tablets; no parasites for 12 days.

Case 25.—One tablet t.d.s. up to 15 tablets; parasites on the fourth day. Two tablets t.d.s. up to 30 tablets; parasites disappeared from the second day of treatment for 12 days; culture sterile.

Case 26.—Two tablets t.d.s.; treatment stopped on the third day on account of a reeling sensation which continued for 5 days.

Case 27.—Had been given 8 tablets a day for 5 days three weeks ago; this time 12 tablets a day; treatment stopped in the middle of the course on account of a reeling sensation.

Case 28.—Two tablets thrice daily till 7 doses.

Case 29.—Two tablets in 24 hours.

TABLE

No.	Race, sex and age	Recent treatment	Findings before treatment				Findings during and after treatment								Days of fever	Resultant effect on plasmodial infection
							2nd day		3rd day		4th day		5th day			
			Species of parasite	Asexual	Sexual	Temp.	Asexual	Sexual	Asexual	Sexual	Asexual	Sexual	Asexual	Sexual		
1	M., M., 28	No	M.T.	0	Sc.	98.2°	0	Sc.	0	Sc.	0	Sc.	0	Sc.	..	Persisted.
2	H., M., 37	..	M.T.	0	Sc.	98°	0	Sc.	0	Sc.	0	Sc.	0	Sc.	..	Do.
3	H., M., 37	Yes	M.T.	Sc.	0	99.6°	Sc.	0	0	0	0	0	0	0	2	Undetermined.
4	I. Ch., M., 20	No	M.T.	+	0	100°	+ (rings)	0	Less than 40	0	0	0	0	0	2	Cleared.
5	M., M., 8	..	M.T.	Sc.	0	101°	Less than 40	0	0	0	0	0	0	0	2	Persisted.
6	M., M., 8	Yes	M.T.	Sc.	Sc.	99°	Sc.	Sc.	Sc.	Sc.	0	Sc.	0	v. sc.	1	Do.
7	A.-I., F., 2½	..	B. T.	2,000		104°	Sc.		0	0	0	0	0	0	3	Do.
8	A.-I., F., 11	Yes	B. T.	7,720		99°			Sc.	0	0	0	0	0	1	Cleared.
9	E., M., 47	..	B. T.	+	0	98°	Sc.	0	0	0	0	0	0	0	..	Do.
10	A.-I., F., 13	Yes	B. T.	++	Sc.	103.6°	+	Sc.	Sc.	0	Sc.	0	0	0	3	Undetermined.
11	H., M., 16	Yes	M.T.	+	0	103°	+	0	Sc.	0	0	0	0	0	2	Do.
12	M., F., 35	..	B. T.	600		102°	0	0	0	0	0	0	0	0	1	Cleared.
13	H., M., 25	..	B. T. M.T.	+	0	103°	+	Sc. (B.T.)	Sc.	Sc. (B.T.)	Sc.	0	0	0	4	Undetermined.
14	M., M., 35	No	B. T.	3,600	0	102.6°	+	Sc.	0	0	0	0	0	0	2	Do.
15	H., M., 54	..	M.T.	Sc.	0	99.8°	Sc.	0	Sc.	0	0	0	0	Sc.	3	Undetermined (crescents cleared).
16	H., M., 38	..	M.T.	3,600	0	102°	2,300	0	240	640	Sc.	+	0	1,000	2	Cleared (crescents persisted).
17	M., M., 35	..	B. T.	++	Sc.	103°	+	v. sc.	Sc.	0	0	0	0	0	1	Cleared.
18	H., M., 38	..	M.T.	3,600	0	102.8°	2,300	0	240	640	Sc.	1,200	0	1,000	2	Cleared (crescents persisted).
19	M., M., 25	..	Q. T.	800		101°	400		Sc.	v. sc.	0	0	0	0	2	Undetermined.
20	H., M., 25	..	B. T., M.T. & Q. T.	2,000 (no crescents)		103.4°	1,600 (no crescents)		800 (no crescents)		Sc. (no crescents)		0	0	3	Persisted.
21	H., M., 22	..	B. T. M.T.	5,200	0	103°	1,500	0	600	0	0 (no gametocytes of B. T.)	Sc.	0	Sc. (crescents)	3	Do.
22	A.-I., F., 15	..	B. T.	++		104°	++		+				Sc.	0	4	Cleared.
23	M., M., 30	..	B. T.	+		102.8°	+		Sc.		Sc.		0	0	3	Persisted.
24	H., M., 6	..	M.T.	+	0	99.4°	+	0	Sc.	0	Sc.	0	Sc.	0	slow fever persisted	Cleared.
25	A.-I., F., 7	..	B. T.	+		102°	Sc.	0	Sc.	0	0	0	0	0	3	Do.
26	H., M., 20	..	B. T.	4,200			+	+	Sc.	0	v. sc.	0	0	0	..	
27	H., M., 25	Yes	M.T.	Sc.	Sc.	100.8°	Sc.	Sc.	0	Sc.	0	Sc.	0	Sc.	..	
28	H., M., 35	..	B. T.	Sc.	0	100°	Sc.	0	0	0	0	0	0	0	1	
29	H., M., 22	..	B. T.	5,600		102°	Sc.		Sc.		Sc.		0	0	2	

In every case the parasites, except the crescents, disappeared from the blood within four days. Of the three patients who relapsed one suffered from benign tertian and two were cases of mixed infections. That the drug had no action on the sexual forms of *Plasmodium falciparum* (crescents) is shown by the fact that in case 1 they were only scanty crescents, no asexual forms being present before treatment; 34 tablets produced no effect on these parasites. In case 2 six tablets were given without any decrease in the number of crescents. Case 15 was peculiar in that the crescents could not be found four days after the treatment. As the patient had only scanty crescents before the treatment was begun, their disappearance was probably spontaneous and not the result of the treatment. In case 16, the drug appears to have stimulated the growth of gametocytes and stopped that of the asexual forms.

A careful study of these cases shows that the action of Malarcan closely resembles that of quinine in that it is equally effective against the asexual and sexual stages of *Plasmodium vivax* and *Plasmodium malariæ* and has no action on the sexual forms of *Plasmodium falciparum*. Its action is also somewhat stronger on the asexual forms of malignant tertian than on those of benign tertian. The effect of the drug on the splenic enlargement is practically the same as that of quinine. After treatment with Malarcan, there was a great reduction in the size of the spleen where this organ was soft. The drug produced no appreciable effects on the blood pressure, pulse or respiration.

Certain untoward symptoms were met with during the treatment with Malarcan which, however, were not serious. Cases 26 and 28 had a reeling sensation which gradually disappeared when the drug was stopped. In two patients flatulence, abdominal discomfort and insomnia developed, but they were temporary and were got rid of with a dose of carminative or a bromide mixture.

Summary and conclusion

(1) Malarcan is said to be a compound of a stereo-isomeric base of methyl-cupreine combined with methyl-acridinium-chloride and hydrocholic acid. It is probably a derivative of quinine or quinidine.

(2) The effect of Malarcan on Indian strains of malaria closely resembles that of quinine. Its action on the asexual forms of malignant tertian is rapid, while on the crescents it has no action whatsoever. On the sexual and asexual forms of benign tertian and quartan the drug has an action similar to that of quinine.

(3) The action of the drug on relapses is also very similar to that of quinine.

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GLABELLAR PRESENTATION, ITS INCIDENCE AND TERMINATION

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Variations in the degree of flexion in cephalic presentations have been noted for a long time by obstetricians and different names have been given to various presentations depending upon the degree of flexion of the head. Thus we have vertex, brow and face presentations; and among vertex presentations, we have the sub-classifications, posterior fontanelle and anterior fontanelle presentations, depending upon whether the head is fully flexed, hyper-flexed, flexed to the normal extent, or slightly under-flexed. That such variations in the degree of extension might also occur cannot be denied. So far, however, the literature has got but few references to any definite types that have occurred, and no nomenclature has been suggested to these variations. It will be seen from a description of cases given below that variations in the degree of extension occur with sufficient frequency to justify this nomenclature.

My attention was first drawn to this abnormality about a couple of years ago, and since then there have occurred ten other cases which seem to me to justify the suggestion that a definite nomenclature should be introduced for these abnormal presentations. They deserve a separate description in the literature and hence the new nomenclature suggested.

Glabellar presentation.—This is a presentation wherein the head lies in a position of extension

(Continued from previous column)

(4) Malarcan is not a toxic drug and in the doses recommended by the makers it produced no serious untoward symptoms.

(5) The drug is about 4 to 5 times more expensive than quinine and appears to have no advantage over that drug.

References

Acton, H. W. (1920). Treatment of Benign Tertian Fever. *Lancet*, Vol. I, p. 1257.

Acton, H. W., Curjel, D. F., and Dewey, J. O. (1921). The Diagnosis and Treatment of Benign Tertian and Malignant Tertian Fevers. Sections II and VI. *Indian Journ. Med. Res.*, Vol. VIII, pp. 762 and 853.

Fletcher, W. (1923). *Notes on the Treatment of Malaria with the Alkaloids of Cinchona.* John Bale, Sons and Danielsson Ltd., London.

Kingsbury, A. N. (1931). *The Annual Report of the Institute for Medical Research, Federated Malay States.* The Federated Malay States Government Printing Office, Kuala Lumpur.

Rennie, P. M., Acton, H. W., Curjel, D. F., and Dewey, J. O. (1921). The Diagnosis and Treatment of Benign Tertian and Malignant Tertian Fevers. Section V. *Indian Journ. Med. Res.*, Vol. VIII, p. 787.