Original Articles

NOVARSENOBILLON AND MAPHARSIDE IN THE TREATMENT OF THE ATTACK OF MALARIA

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ARSENIC in various forms has for many years been given in malaria, sometimes to patients suffering from malarial fever, but more often to those convalescing from malaria.

The use of arsenic after an attack of malaria is traditional. We have however traced no definite statement regarding the rationale of such a use of arsenic; it is apparently intended to combat the anæmia and to reduce the tendency to relapse, although there is no proof that it does so. This use of arsenic is not discussed any further here. The writer has had no opportunity of studying this matter or of assessing the value of arsenic used in this way. We are here concerned with the use of arsenic in the control of an attack of malaria.

The history of the use of arsenic in the attack of malaria really dates from the introduction of the arsphenamines. The earliest available reference to the subject in the literature is that of Werner (1910); and there are several other early contributions on the subject; altogether over twenty publications on the subject have been traced. Most of these publications appeared shortly before, during, and after the last war, when the subject raised considerable interest. Certain limitations of the treatment of malaria with these preparations then became apparent, and the subject was left there.

What brought the matter to life again was the introduction of malaria therapy for neuro-syphilis. Here one was dealing with a known species of the parasite, usually *P. vivax*, and the efficacy of the neoarsphenamines in the control of *P. vivax* infection was clearly indicated. Moreover the use of the neoarsphenamines was obviously not contra-indicated in persons suffering from neuro-syphilis. Therefore several publications appeared on this matter, and the neoarsphenamines came to hold a definite place in the control of therapeutic malaria, but no one suggested their use in naturally acquired malaria until Goldman (1938) described the cure of a case of naturally-acquired malaria with numerous relapses with the new trivalent arsenical preparation produced by Parke, Davis & Co., and known as mapharside*. This preparation in syphilis is of high potency and low toxicity. Niven (1940) tested this preparation in naturally acquired malaria in Malaya against *P. falciparum*, *P. vivax* and *P. malariæ*. Niven's two tables summarizing the effect of the drug on the peripheral blood findings are here reproduced.

* Actually mapharside is not an arsphenamine but an arsenoxide.

TABLE I

Disappearance of asexual parasites in acute falciparum malaria treated with mapharside or quinine

	Number of cases showing asexual parasites each day following commencement of treatment						
	1	2	3	4	5	6	7
Mapharside	18	17	18	18	18	18	18
Quinine ..	20	20	18	6	2	1	0

TABLE II

Disappearance of asexual parasites in acute vivax malaria treated with mapharside or quinine

	Number of cases showing asexual parasites each day following commencement of treatment						
	1	2	3	4	5	6	7
Mapharside	20	8	0	0	0	0	0
Quinine ..	20	20	13	5	1	0	0

His conclusions were as follows :—

Mapharside is found to have dramatically rapid effect on the sexual and asexual forms of *P. vivax*.

Mapharside is shown to be relatively inert against *P. falciparum* and *P. malariæ* and to have little effect on either the production or the viability of 'crescents'.

It is concluded that the place of mapharside in the treatment of malaria is limited and will probably be mainly confined to therapeutic vivax malaria. The drug may possibly be of value also in chronic relapsing vivax malaria but on this point further evidence is desirable.

These findings are quite definite and clear-cut, and in normal times with adequate quinine available, no one would think of recommending these preparations for the treatment of naturally acquired malaria in general. In fact such a procedure will be fraught with danger and might cause many preventable deaths, for the dangerous form of malaria, namely *P. falciparum* infection, is little influenced by this treatment.

In times of quinine shortage, however, other considerations come into play, and it might be justifiable in suitable cases to make use of the anti-malarial properties of these arsenical preparations.

The work briefly reported in this paper was undertaken with the following objects : (1) To find out whether in patients in hospital in whom blood examination and the identification of the parasite were possible, the treatment with neo-arsphenamines might reasonably be adopted. (2) To find out whether the new preparation mapharside was more effective in controlling malarial fever than the older preparations such as novarsenobillon.

Patients were admitted to hospital showing malarial fever and malarial parasites in considerable number in the blood. They were

kept without any treatment, if possible for two or three days, to make sure that the infection was not a naturally subsiding one. (This fact made it impossible to study heavy infections of malignant malaria, because it was considered dangerous to keep them without any treatment.) Treatment was then instituted, and the effect of the treatment on the fever and on the peripheral blood findings was carefully recorded by the keeping of 4-hourly temperature charts and by careful examination of blood films twice daily morning and evening. In some cases, parasite counts were also done, and in all cases the rough estimation of the number of parasites was made.

In all, about 20 cases were treated. It is not proposed here to present details of all the 20 cases but merely to outline the main findings.

(*a*) *Results in benign tertian malaria*

Novarsenobillon was given intravenously to begin with in doses of 0.15 gramme and later in doses of 0.3 and 0.45 gramme. To begin with only one injection was given, but later the number of injections was increased to three at intervals of 4 or 5 days.

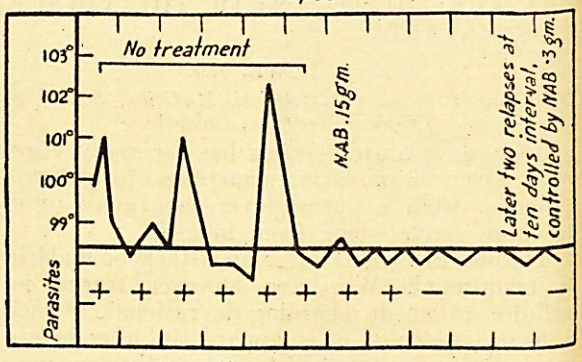
On the whole, the results of treatment were excellent. A single injection of novarsenobillon cut short the attack of malaria very promptly. The temperature fell to normal within 24 hours, and the peripheral blood became negative usually within 48 hours, sometimes within 24 hours. Our findings agree with those of Goldman, that the effect of arsenic in benign tertian malaria is more dramatic than that of quinine. The patients suffered none of the discomforts usually associated with quinine treatment.

The treatment, however, had certain disadvantages which became clear. After one injection only, relapse was common, sometimes within a few days, and after two or three injections also, relapse was not infrequent but at a later period. It cannot be said that after three injections the relapse rate was higher than it is after a one week's course of quinine, but the relapse rate was sufficiently high to indicate that even after three injections the treatment failed to eliminate the infection in a considerable number of cases.

Another disadvantage of the treatment lay in the fact that even though a patient on admission showed only benign tertian parasites in the blood, there was in some cases a latent malignant infection which revealed itself only after the tertian parasites had disappeared as the result of treatment. This is another indication of the fact that *P. falciparum* is not susceptible to the action of arsenic.

With *mapharside*, results were similar to those obtained with novarsenobillon. The dose of mapharside given was 0.04 gramme. The number of patients treated with mapharside was not large, so final conclusions are not justifiable, but there was no definite evidence that mapharside was any more effective in controlling the fever and making the peripheral blood negative than novarsenobillon; in fact the evidence was rather to the contrary; the results obtained with mapharside were not quite so dramatic as those obtained with novarsenobillon.

NAB. in P. vivax infection.
Fever controlled and blood made negative.
Relapse

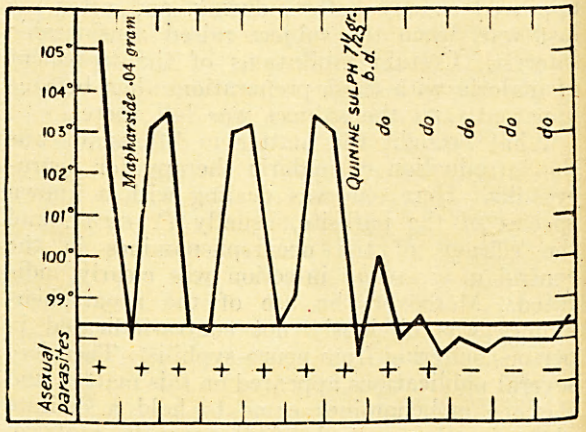


Results with MAPHARSIDE were similar.

(*b*) *Results in malignant tertian malaria*

In malignant malaria both mapharside and novarsenobillon had very little effect. The cases studied were all of low grade infection, with low fever, and *P. falciparum* constantly in the blood, but neither of the arsenical preparations used appeared to control the fever or to cause the disappearance of parasites from the blood. In all the cases, quinine treatment had to be instituted, and the response to treatment with quinine was excellent.

MAPHARSIDE in P. falciparum infection.
Failure: fever easily controlled by quinine.



Results with NAB. were similar

Conclusions

Though the number of cases treated was not great, it was not considered justifiable to continue this line of investigation further. The experiment indicated clearly that the use of these two arsenical preparations in the treatment of malaria had severe limitations. They could only be used with safety in cases in which one was quite sure that one was dealing with a pure *P. vivax* infection. Our experience in

(*Concluded on opposite page*)

ORGANIC ARSENICALS IN THE TREATMENT OF SIMIAN MALARIA

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IT appears from the literature that organic arsenical compounds, such as the salvarsans, have not given results which justify their employment in the general treatment of malaria: a certain measure of success has been reported only in tertian malaria (*P. vivax*). Recently, however, Goldman (1938) has claimed striking results with 'mapharsen' in the same type of malaria: among 24 cases treated with this drug only 2 relapsed, and these were among the group of 14 cases who received but one injection of 0.04 to 0.06 gm. of the drug. On the other hand, Young and McLendon (1939) found that mapharsen failed to eradicate the parasites in

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Calcutta is that one can very rarely be sure of this. Even if one could feel sure, and applied the treatment with either of these preparations, the relapse rate would still be considerable. It is therefore clear that neither of these preparations can be recommended for wide use in the treatment of malarial fever.

It is, however, not impossible that a combined treatment of one of these preparations with quinine might be a very effective treatment for malaria, and that the relapse rate might be considerably reduced. We have no definite evidence on this point and are not at present in a position to study the matter. Nevertheless in *P. vivax* infection, the results of a single injection are usually so dramatic and the fever is so quickly controlled that the writer feels that if he himself developed an attack of malaria due to this parasite, he would feel strongly tempted to start his treatment with one injection of neoarsphenamine, and then to take quinine.

At the same time as the work was being done on human subjects mapharside was supplied to Dr. B. M. Das Gupta for trial in monkey malaria. His findings (reported elsewhere in this journal) are that in *P. knowlesi* infection in monkeys, mapharside has little therapeutic effect.

Acknowledgment

I wish to acknowledge the free gift of the supply of mapharside for use in this work by Messrs. Parke, Davis & Co., Bombay.

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any one of 10 cases of induced quartan malaria (*P. malariæ*), though the symptoms were relieved; the viability of the parasites was not affected. Recently Lowe at the School of Tropical Medicine has been experimenting with arsenicals in the treatment of human malaria, and, as an extension of this work, trials have been made with mapharside (the British name for mapharsen) and novarsenobillon ('N.A.B.') against *P. knowlesi*.

Material and methods

The methods of inducing *P. knowlesi* infection in rhesus monkeys (*S. rhesus*) and of estimating the intensity of the infections have been described elsewhere (Das Gupta and Siddons, 1943). The strain of *P. knowlesi* maintained in this laboratory almost invariably produces typical infections of a progressive and fatal character in monkeys, but the infection can be controlled by an efficient anti-malarial drug. These facts, together with considerations of economy under the present abnormal war-time conditions, have led to the minimum use of control animals in investigations on anti-malarial drugs being conducted in the department.

'N.A.B.' and mapharside were given daily by intravenous injections. The quantity of 'N.A.B.' in an injection varied from 0.0075 gm., or one-twentieth of the human dose of 0.15 gm., for a monkey weighing 1¼ kilos, to 0.1 gm., or one-third of the human dose of 0.30 gm., for a monkey weighing 2 kilos. The dosage of mapharside was 0.004 to 0.01 gm., from one-tenth to one-fourth of the human dose of 0.04 gm., for monkeys weighing 1½ to 3 kilos.

Observations with 'N.A.B.'

The essential data are given under experiments numbered 1 to 6 in the table.

In experiments nos. 1 to 3, quantities of 0.0075 to 0.045 gm. of the drug gave little or no evidence of parasiticidal action, and the infections increased to fatal intensities. The dosage of 0.0045 gm. (experiment no. 3) had some effect on the parasites, for the infection rate of the red cells remained stationary at roughly 6.2 per cent from the fourth to the sixth day of treatment. The parasites then appeared to recover their vitality, and the infection rate rose to 16 per cent, after which the animal was treated with a more efficient anti-malarial drug and the infection was controlled.

With higher doses of 0.06 to 0.09 gm. (experiments nos. 4 and 5), the infections were incompletely controlled and the animals survived; parasites could be found in the peripheral blood for at least eleven days after commencement of treatment. In experiment no. 6, treatment with 0.1 gm. of the drug gave the kind of results expected of an effective anti-malarial agent, with appreciable evidence of direct action on the parasites, but it was not surprising that such a large dose could not be tolerated.