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CONTRIBUTION TO THE THERAPY OF MALARIA WITH PALUDRINE IN EXPERIMENTAL INFECTION BY INOCULATION OF INFECTED BLOOD

Preliminary Note

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(This article, with the original illustrations, will appear in the Bulletin of the World Health Organization).

We have recently tried out paludrine in the therapy of malaria transmitted by the inoculation of infected blood. These experiments were carried out in malarial therapy centres, with the special aim of providing information on the effect of the medicament in relation to various strains of parasites, local endemic conditions and degrees of immunity that arise from the latter. We have further endeavoured to use the minimum effective doses, which is of very special importance for malarious countries whose economic resources are limited.

A. Infection with P.vivax. Our own strain was used (of "spontaneous infection" origin). This is now going through its 279th passage (1683 patients), maintained since June 1941 only by means of inoculations of infected blood; the virulence of the parasite appears to remain intact. Out of 350 patients infected with malaria during 1946, 94.1 per cent contracted the infection; 91.3 per cent clinically (febrile attacks and parasites); only 2.8 per cent developed temporary parasitaemia while 5.9 remained immune altogether (A-P-).

Experiments in treatment with paludrine. Forty patients inoculated with this strain of P. vivax were treated as follows:

(1) eight patients received one dose of 100 mgms.
(2) twenty-four were given a course of treatment lasting 7 days during which they received 200 mgms. daily.
(3) eight received 300 mgms. for seven days.

(1) Out of eight patients who received one single dose of 100 mgms. seven were treated between the fourth and eighth day, while in the eighth case the paroxysms had been going on for a fortnight.

In 7 cases out of 8, fever disappeared within twenty-four hours of the administration of the drug; in the eighth case the temperature reverted to normal three days after the administration of paludrine.

In two cases, the absence of parasites (test on thick drop) was observed on the third day, in four on the fourth, and in two on the fifth day following the administration of the single dose.

During a fairly brief period in hospital neither renewed fever, nor reappearance of the parasite was reported.

Prior to the patients' leaving the hospital a seven-day schizontocide treatment is generally given, followed by a five-day gametocide treatment.

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(2) Twenty-four patients, inoculated in the same circumstances, were treated with 200 mgms. of paludrine for seven days. Out of these twenty-four, (a) four had reached the 4th-5th day of fever; (b) eleven the 10th-11th, (c) nine the 11th-17th day.

The disappearance of fever occurred as follows:

2.5 days for group (a), 1.5 days for group (b); 1.22 days for group (c).

All three groups were clear of parasites in the thick drop, after 4.25, 3.5 and 3.22 days respectively.

Briefly, the fever abated, on an average, after 1.65 days; the disappearance of the parasites occurred after an average of 3.65 days.

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(3) Eight patients infected with malaria received 300 mgms. of paludrine daily for seven days in succession; the treatment was begun between the 5th and the 14th attacks.

No variation in the result has been observed in relation to the point during the febrile attack at which the treatment was begun.

On an average the fever dropped after 1.75 days, parasites were found to have disappeared from the bloodstream after an average period of 3.5 days.

Conclusions. (1) In experimental infection by intra-venous inoculation of infected blood (P.vivax) one single dose of 100 mgms. of paludrine is amply sufficient to arrest the attacks, the parasites do not disappear from the bloodstream until an average of 4 days after the administration of the drug.

(2) During the treatment with 200 mgms. of paludrine daily for 7 days, the fever abates after an average period of 1.65 days, the parasites disappear after an average period of 3.65 days.

(3) Similar results have been observed after treatment with 300 mgms. of paludrine for 7 days, the fever ceases after an average of 1.75 days, and the parasites disappear after 3.5 days.

Two control cases of natural spontaneous infection with P.Vivax behaved in a similar fashion in regard to the direct action of the drug upon temperature and parasites.

Infection with P. malariae. Strain "$Q^{W.A.}$" (of African origin) was used. This is now in its 137th passage (640 patients), and has retained its virulence since 1938. During 1946, 112 patients were inoculated, of whom 90.4 per cent developed a parasitic infection, 82.4 per cent contracted the clinical disease (A+P+), while 9.6 per cent remained immune (A-P-).

Previous tests to ascertain the relative sensitiveness of P. malariae to various schizontocide substances showed that this species have a more marked resistance than P. vivax and P. falciparum; and for this reason we decided also to apply large doses of paludrine.

In view of the special development of quartan infection and the longer fever period required for the purposes of malariotherapy, we have frequently refrained from beginning the treatment until after the patients had had several paroxysms.

(a) Nine patients inoculated intra-venously with infected blood received 200 mgms. of paludrine for seven days; four of them from the 4th and the 10th day of fever, four from the 12th to the 15th, one on the 24th day.

On an average the fever dropped after 1.88 days and the parasite disappeared after 8.8 days (extremes ranging between 3 and 14 days) irrespective of the stage the attack had reached, when the treatment began.

The parasites disappeared in the course of a seven-day treatment in only 3 patients out of 9; in the other six, the presence of the parasite was still observed after the treatment was at an end; and for this reason we decided to follow it up with a gametocidal treatment with 0.02 grammes of plasmoquine for a period of five days.

(b) A second group of 4 patients at varying stages between the 11th and 32nd days of the attack were given 600 mgms of paludrine for 7 days. Despite the triple dosage no considerable difference was observed, on an average the fever abated after 1.7 days, the parasites did not disappear from the thick drop before an average period of 10 days; the extremes ranged between the 9th and the 11th day.

(c) A third group of twelve patients (between the 5th and 21st days of the attack) were given 600 mgms. of paludrine for 10 days. Despite the administration of a total quantity of 6 mgms. of paludrine, the results were the same.

On an average, the fever has abated after 2.6 days and the parasites have disappeared from the blood stream after 8.8 days.

The persistence of fever for 3 - 5 days in four cases (out of 10 patients treated) suggests a faulty application of the method; the tablets were administered without being previously dissolved in liquid.

By the use of this method of treatment (600 mgms. of paludrine for 10 days) only one advantage is obtained; the parasites disappear more rapidly from the bloodstream.

Sub-inoculations were carried out on new patients in the course of the treatment of two patients; the results were as follows:

(a) After the third day of treatment, the blood of a donor transmitted the infection to a new subject. The latter's incubation period lasted 11 days. The blood of that same donor no longer transmitted the infection to other subjects after the seventh day of treatment despite the fact that on that day the parasite (degenerate forms) was still present in the donor's blood stream.

(b) The blood of another donor on the tenth day of treatment no longer transmitted the infection to a new subject despite the presence of the parasite in the donor's blood. A positive result on a thick drop during a course of paludrine is not, therefore, an absolutely certain means of controlling the efficacy of the drug, it should be supplemented by sub-inoculation into new patients, especially after the seventh day of treatment.

Finally, P. malariae shows a degree of resistance to paludrine which recalls that previously observed towards other schizontocidal preparations. While in eight cases, its effect upon the attacks was obvious within 48 hours, there were four others in which the fever did not abate before four or five days of treatment.

The duration of the treatment in infections with P. malariae should not, therefore, be less than ten days. In the circumstances in which our tests were carried out, a longer period of treatment with an average daily dose appears preferable to a high dosage of paludrine; the 600 mgms. daily dosage does not appear to yield very much better results than that of 200 mgms. daily. Only a vast amount of experience could finally lead to a definite ruling, if 200 or 300 patients suffering from quartan malaria were available.

Special cases (under direct laboratory observation)

Spontaneous P. falciparum infection.

First case. Has suffered for four months from a spontaneous P. falciparum infection, admitted to hospital during his fourth relapse;

daily attacks, temperature 104°, presence of trophozoites and gametocytes of both sexes in the blood (25/17). After two days' treatment with 200 mgms. of paludrine, the temperature reverted to nomal ; the trophozoites did not disappear until after the fourth day. The gametocytes disappeared after a five-day treatment with 20 mgms. of plasmoquine.

A daily blood test shows that after the administration of 600 mgms. of paludrine (200 mgms. daily for three days), the macro-gametocytes show a marked degenerescence, the micro-gametocytes do not appear to be affected to the same degree.(1)

Two days after then nd of the 5-day course of paludrine the morphological aspect of the gametocytes is practically normal.

Second case (Dr. E. Radocovici) Relapse with P. falciparum; trophozoites and gametocytes, temperature 103°-104°, liver congested, spleen palpable. Treatment with paludrine; 200 mgms. for three days and 300 mgms. for four days; a progressive decrease in temperature occurs during the first four days of the treatmant; a very few gametocytes are still found, which disappear after administration of 20 mgms. of plasmoquine. No relapse during the three months that followed.

Third case (Dr. E. Radocovici) Relapse with P. falciparum: presence of trophozoites, a few gametocytes appearing two days later, red corpuscles, 3,140,000; haemoglobin 70 per cent; temperature 104°; spleen palpable.

Treatment with paludrine was given as follows; 300 mgms. for ten days, followed by a weekly dose of 300 mgms. for seven weeks.

Temperature dropped to normal after the first days of treatment; the gametocytes remained in the blood stream for 13 days. Throughout an observation period lasting 47 days no temperature was registered, nor were there parasites in the blood.(1)

Fourth case Early stage of P.vivax infection; temperature 112.2, daily attacks , 25/20 parasites of all forms in the blood, dizziness, nausea, splenomegaly.

Paludrine treatment, 300 mgms. for seven days followed by a weekly dose of 300 mgms. for three weeks.

Temperature reverts to nommal 24 hours after the first dose of paludrine; the parasites do not disappear until after the fourth dosel

No parasitic or clinical relapse during the following five months.

Fifth case Relapse of P. vivax infection, tertian attacks, spleen palpable, temperature 104°.

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(1) The original includes figures showing morphological changes of the gametocytes. (Editor's note).

The temperature dropped three days after the beginning of the treatment; the parasites (all forms) disappeared after the fifth day. No further relapses were reported during the three months that followed.

Sixth case Primary attack of P. vivax; temperature 106.7°, violent shivering fits, vomiting, 25/75 parasites in the blood.

Treatment. 300 mgms. for 13 days, followed by a weekly treatment of 300 mgms. for five weeks.

The fever abated 48 hours after the beginning of the treatment; disappearance of trophozoites and schizonts after the second dose; remains of gametocytes observed for another two days.

80 days after the end of the treatment, relapse with high temperature, numerous parasites in the blood, labial herpes.

Treatment: 300 mgms. for ten days followed by a weekly dose of 300 mgms.

Temperature dropped 24 hours after the beginning of the treatment; schizonts disappeared after 48 hours; a large number of gametocytes did not disappear before the first five days of treatment.