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EFFECT OF SINGLE DOSES OF A COMBINATION
OF CHLOROQUINE AND PYRIMETHAMINE

by

Professor G. Raffaele and Dr P. Carrescia
Istituto di Malariologia "E. Marchiafava", Rome

Preliminary Note¹

Some of the new synthetic antimalarials are so effective that they bring about the disappearance of the parasites from the blood after the administration of only one dose of the drug. This makes it possible rapidly to overcome the disease symptoms and to render non-infective the parasites in human carriers so that the latter no longer act as a reservoir of infection for anophelines.

Investigations of the effect of a single dose have been carried out with several drugs, including chloroquine, amodiaquine, proguanil and pyrimethamine. In India, numerous observations have been made on Plasmodium vivax and P. falciparum infections. J. Singh et al. (1953) used single 400 and 600 mg doses of amodiaquine, chloroquine biphosphate (Resochin) and chloroquine sulfate (Nivaquine) in 169 cases of P. vivax and P. falciparum infections. They found that all these drugs brought about disappearance of the parasites from the blood in 48-72 hours. In general, the chloroquine salts acted more rapidly than amodiaquine.

Srivastava et al. (1953) brought about the disappearance of P. vivax from the blood in 48-72 hours with a single 25 or 50 mg dose of pyrimethamine (7 patients). They found that the same doses took 24 hours (16 patients), 48 hours (10 patients), 72 hours (7 patients) or more than 96 hours (4 patients) to eliminate P. falciparum from the blood.

¹ A full report will appear in the "Rivista di Malariologia"

Gupta (1954) carried out experiments with single doses of various drugs (proguanil, chloroquine, amodiaquine and pyrimethamine). He obtained the best results with a single 600 mg dose of chloroquine; a larger dose, namely 1500 mg, administered all at the same time, sometimes caused serious toxic side-effects. Single 20-25 mg doses of pyrimethamine gave variable results; larger doses (75-100 mg) had toxic effects. 600 mg of amodiaquine gave good results, whereas a 100 mg dose of proguanil did not eliminate the parasites from the blood. Larger doses (300 mg) gave better results but these were only temporary.

J. Singh (1955) carried out several trials in India with single 50, 100, 200 and 300 mg doses of pyrimethamine. He found in the case of both P. vivax and P. falciparum infection that single doses did not always succeed in freeing the blood of parasites. In some cases the febrile symptoms even persisted for more than 5 days. The dose which gave the best results was 300 mg, administered in two separate doses, but even with this amount the parasites persisted in the blood for more than 10 days in two cases. The same persistence was observed when the drug was administered in a single 300 mg dose. In P. falciparum infections the parasites were immediately eliminated from the blood in 15 cases out of 42 and in P. vivax infections, in 28 cases out of 86. In the remaining cases the parasites persisted for 2-10 days, or even longer.

On the other hand, in 30 cases of P. vivax infection, J. Singh et al. (1953) succeeded in halting the fever within 72 hours and eliminating the parasites in 96 hours with a single dose of pyrimethamine.

These trials have been repeated by different authors in different countries with varying single doses. We have mentioned only a few of these investigations in the foregoing. In general, opinions agree concerning the effectiveness of a single 600 mg dose of chloroquine, whereas they vary as regards the action of a single dose of pyrimethamine ranging from 25 to 300 mg.

The synthetic antimalarials whose use is most advocated in malaria treatment clinics are chloroquine and amodiaquine, both in a single 600 mg dose.

The investigations of Foy & Kondi (1952) and of Shute & Maryon (1954) have shown that if anophelines bite P. falciparum and P. vivax gametocyte carriers who have been given pyrimethamine, the development of the oocysts in the wall of the stomach of the mosquito is arrested and does not lead to the production of sporozoites. At Nairobi, Foy & Kondi administered 20 mg of pyrimethamine to a P. falciparum gametocyte carrier and allowed anophelines (A. gambiae) to feed on this patient before administration of the drug and during the six following days. They found infected salivary glands only in anophelines which had bitten before the patient had taken the drug. These results are particularly interesting, since research on monkeys, with higher doses than those advocated for man, has shown that pyrimethamine does not normally accumulate in the plasma and becomes fixed in moderate amounts in the lungs, liver, kidneys and spleen. The maximum concentration in the plasma was observed two hours after administration; subsequently the plasma level becomes too low for accurate determination (Covell et al. 1955). Consequently, except during the first few hours after ingestion, the quantity of pyrimethamine reaching the stomach of the mosquito in the blood meal should be extremely low, and it appears surprising that the traces of the drug present in the blood several days after ingestion can prevent the development of oocysts. However, according to Schmidt (see WHO/Mal/185, page 3) only half the dose administered is metabolized during the first 72 hours, and the remaining half subsequently disappears from the blood stream at the rate of 3 per cent. per day.

Shute & Maryon (1954) found that oocyst development was arrested in mosquitoes feeding on P. vivax and P. falciparum gametocyte carriers up to 50 hours after administration of 50 mg of pyrimethamine. Doses of 2.5 mg and 5 mg were found to be too low to stop the development of the sporozoites. By administering 25 mg of pyrimethamine to P. falciparum gametocyte carriers, they succeeded in stopping the development of oocysts in the mosquito up to 144 hours after ingestion of the drug. Hawking (1953) considers that this phenomenon might be explained by lack of para-amino benzoic acid (P.A.B. acid); he assumes that the pyrimethamine acts as a P.A.B. acid antagonist and thus prevents nuclear division.

These observations seem to show that minute traces of drug in the plasma suffice to prevent oocyst development, since it seems certain that after six days (144 hours) the pyrimethamine concentration in the plasma is very low.

The favourable results obtained in malaria treatment with single doses of drug encouraged us to investigate the therapeutic effect of a single 600 mg dose of chloroquine combined with 50 mg of pyrimethamine in terminating malarial therapy used in the treatment of paralytics at the E. Marchiafava Institute, Rome.

Nine cases of P. vivax infection and two of P. malariae infection were treated in this way. Three of the P. vivax infections were brought about by inoculation of sporozoites and the others by inoculation of infected blood. Four patients infected with P. vivax (three by means of sporozoites and one by means of infected blood) were exposed to the bites of anophelines before and after administration of a single dose of the combined drugs. The results were as follows:

(1) P. vivax infections (Madagascar strain): Three patients were treated after a certain number of attacks (from 8-12; in one case after 6 attacks) and the febrile symptoms were found to end after 24 hours while the parasites disappeared after 36 hours. In one case the schizonts disappeared after about 6 hours and the blood was negative after 24 hours.

Three patients inoculated with sporozoites and treated with the dose mentioned showed no relapse during the 30-40 days following the treatment, during which period it was possible to keep them under observation. The taking of the drugs was supervised by one of the authors.

Four patients were exposed to the bites of anophelines (A. maculipennis var. atroparvus) before and after administration of the two drugs. Despite the rather small number of gametocytes observed in ordinary smears, the anophelines which had fed before administration of the drugs showed **varying degrees** of infection. Anophelines which had fed on three of the patients 24 hours after administration of the drugs did not become infected, whereas those feeding on the fourth patient became infected and showed the normal sporogonic cycle leading to the production of sporozoites. A further patient was inoculated with the infected salivary glands of two of these anophelines and symptoms developed after an incubation period of 17 days.

No degenerate oocysts were seen in the stomach of anophelines which had fed on the three other patients with a negative result.

(2) P. malariae infections: In the two cases of quartan fever treated in the same way, the disappearance both of the fever and of the parasites was just as rapid as in the P. vivax cases. No relapse was seen in either of the two cases during a period of observation lasting 60 days.

The number of patients treated with this single combined dose of chloroquine and pyrimethamine is too small for conclusions of a general nature to be drawn.

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