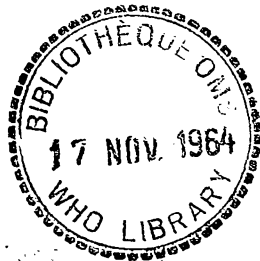


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THE EFFECT OF 6-METHOXY-8-(5'-PROPYLAMINOAMYLAMINO)
QUINOLINE PHOSPHATE AGAINST THE ASEXUAL ERYTHROCYTIC
FORMS OF A STRAIN OF CHLOROQUINE-RESISTANT PLASMODIUM
FALCIPARUM FROM THAILAND¹

by

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The chief current value of the effective 8-aminoquinoline antimalarial drugs, of which primaquine is now the most widely used, stems from their capacity to destroy exoerythrocytic forms of Plasmodium vivax and P. malariae. The relative ineffectiveness of primaquine and other extensively studied 8-aminoquinoline antimalarial agents against asexual erythrocytic parasites, especially those of P. falciparum, has limited the usefulness of those compounds (WHO, 1961). Berberian et al. (1962) studied a relatively new 8-aminoquinoline drug, 6-methoxy-8-(5'-propylaminoamylamino) quinoline phosphate (Win 5037), and they reported that this compound, in comparison with primaquine, was 10 times more active against schizonts of P. lophurae and two to three times more active against schizonts of P. cynomolgi. Hoekenga (1962) presented the results of investigations in which this relatively new 8-aminoquinoline drug was administered to patients infected with P. vivax or P. falciparum in Panama.

¹ From the Army Medical Research Project of the Department of Medicine, Division of Biological Sciences, University of Chicago, Chicago, Illinois, United States of America. These studies were supported in major part by the Medical Research and Development Command, Office of the Surgeon General, Department of the Army, under Contract DA-49-007-566 with the University of Chicago and Winthrop Laboratories, New York, New York. The studies were made possible through the co-operation of the inmates and the administrative staff of the Illinois State Penitentiary, Stateville Branch, Joliet, Illinois, United States of America.

He reported that this compound administered in the particular dosage schedule he employed, was not as rapidly effective as single doses of 4-aminoquinolines but that it was "generally effective" (more so against P. vivax than against P. falciparum) in the treatment of acute attacks of malaria. Some studies, however, have not substantiated early suggestions or expectations that this compound may prove useful for suppression or for treatment of acute attacks of malaria (WHO, 1961). Evidence obtained in Turkey by Gökberk (1960) who administered this drug to three patients, indicated that the drug, used alone, was not rapidly effective against acute attacks caused by P. vivax; the patients he treated developed short-term "relapses", or recrudescences, suggesting that the drug had not completely eliminated asexual erythrocytic forms of P. vivax.

This report presents the results of studies in which 6-methoxy-8-(5'-propylamino-amylamino) quinoline phosphate was administered to two healthy, adult, Caucasian volunteers infected with a strain of chloroquine-resistant P. falciparum from Thailand (Young et al., 1963; Jeffery et al., 1963; Powell et al., 1964). The two volunteers were not immune to malaria and they did not have glucose-6-phosphate dehydrogenase deficiency. The study was conducted in a non-endemic area and under conditions that precluded reinfection. Methods employed have been described in detail previously (Alving et al., 1948; Powell et al., 1964). The drug was administered orally in the form of tablets; each tablet contained 10 mg of the salt (7.5 mg of base). Each volunteer received two courses of therapy with this drug. The initial courses of therapy corresponded in dosage to that used to treat adults infected with malaria in Panama (Hoekenga, 1962), i.e. 60 mg of the salt, equivalent to 45 mg of base, in divided doses on the first day of treatment; 30 mg of the salt, equivalent to 22.5 mg of base, in divided doses on the second day; and 10 mg of the salt, equivalent to 7.5 mg of base, daily for the next 11 days. Initial courses of therapy with this 8-aminoquinoline drug failed in both volunteers to control acute attacks caused by this strain of chloroquine-resistant P. falciparum (Figs. 1 and 2). It was necessary to administer intermittent doses of quinine, concurrently with the 8-aminoquinoline compound, to both volunteers to prevent dangerously high levels of parasitaemia. Both volunteers subsequently received a second course of therapy with this 8-aminoquinoline drug consisting of 60 mg of salt

(45 mg of base) daily for 14 days and even this dosage of the medication (total dose: 840 mg of the salt, equivalent to 630 mg of base) failed to effect radical cure of the infections (Figs. 1 and 2).

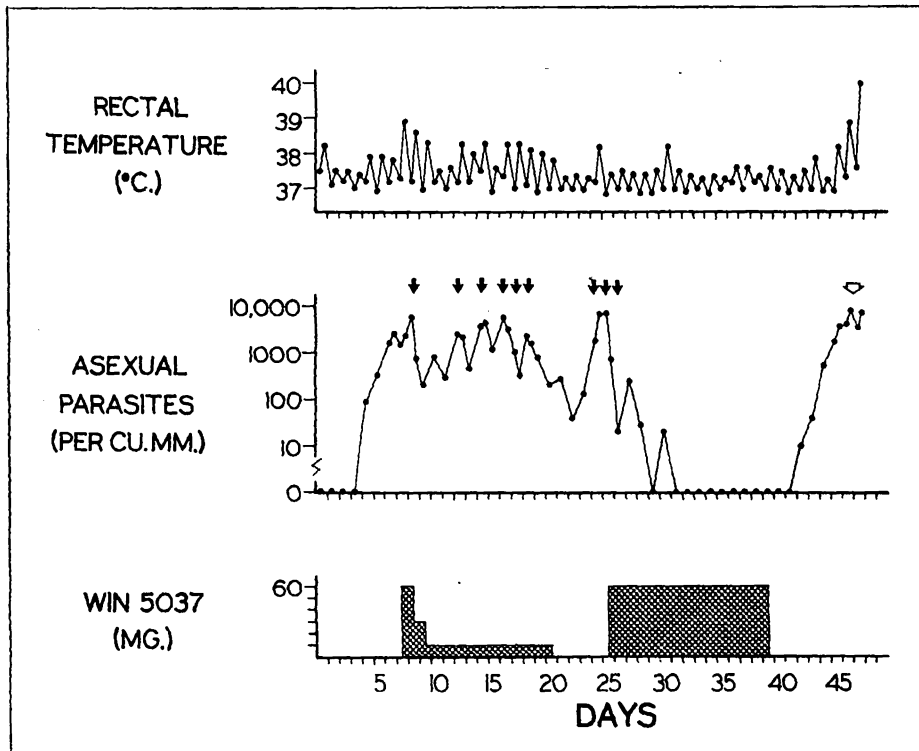
These studies were conducted as a part of a continuing effort to evaluate or to develop compounds that may be effective against chloroquine-resistant P. falciparum (Bruce-Chwatt, 1964). The 8-aminoquinoline compound studied, 6-methoxy-8-(5'-propylaminoamylamino) quinoline phosphate, did not display marked blood schizontocidal activity against a strain of chloroquine-resistant P. falciparum from Thailand.

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FIG. 1

COURSE OF TEMPERATURE AND PARASITAEMIA IN A VOLUNTEER HAVING A BLOOD-INDUCED INFECTION WITH A STRAIN OF CHLOROQUINE-RESISTANT *P. falciparum* FROM THAILAND.^a

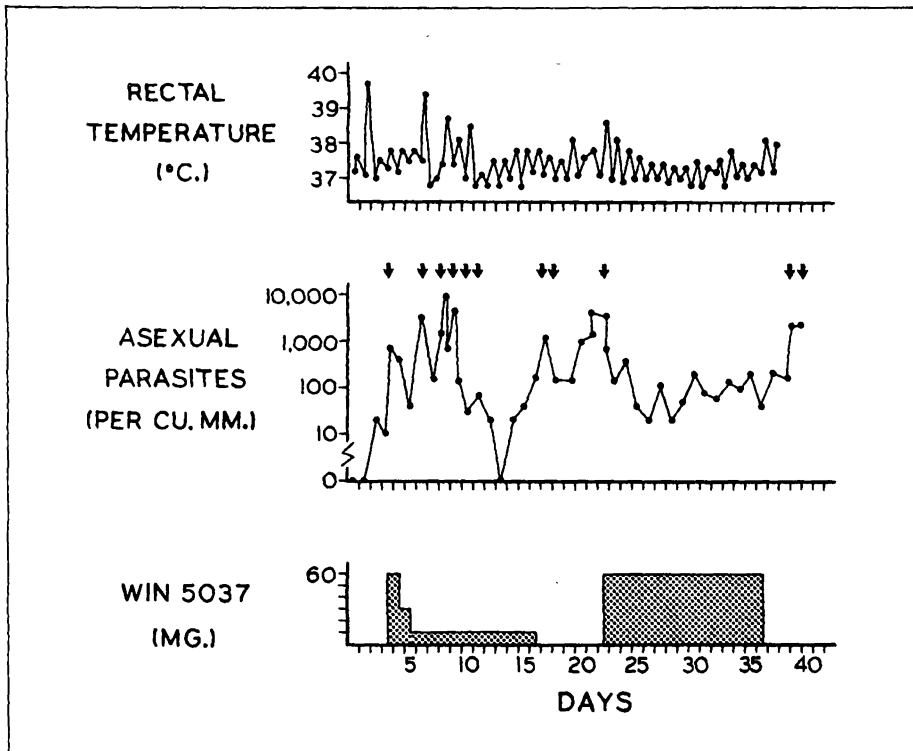


WHO 41284

^a The volunteer (31 years old) weighed 170 pounds. An infection with this strain of *P. falciparum* was obtained by intravenous inoculation of a small sample of infected blood 4 days prior to day 1 of this study. Each black arrow designates the administration of 540 mg. of quinine base orally. The effects observed, especially those during the second course of administration of 8-aminoquinoline medication, are attributable, in part, to the concurrent administration of quinine. The open arrow, at the right, indicates administration of a blood schizontocidal medication other than quinine

FIG. 2

COURSE OF TEMPERATURE AND PARASITAEMIA IN A SECOND VOLUNTEER HAVING A BLOOD-INDUCED INFECTION WITH A STRAIN OF CHLOROQUINE-RESISTANT *P. falciparum* FROM THAILAND.^a



WHO 41285

^a The volunteer (32 years old) weighed 200 pounds. An infection with this strain of *P. falciparum* had been obtained by intravenous inoculation of a small sample of infected blood 20 days prior to day 1 of this study. A patent infection had been present for 16 days prior to day 1 of this study; the volunteer had received quinine intermittently during this time. Each black arrow designates the administration of 540 mg. of quinine base orally

ACTION DU PHOSPHATE DE LA 6-METHOXY-8-(5'-PROPYLAMINOAMYLAMINO)
QUINOLINE SUR LES FORMES ERYTHROCYTAIRES ASEXUEES DE LA SOUCHE
DE P. FALCIPARUM DE THAILANDE RESISTANTE A LA CHLOROQUINE

Ce rapport présente les résultats d'études concernant deux volontaires caucasiens adultes infectés par une souche de P. falciparum de Thaïlande résistante à la chloroquine, qui ont été traités avec le phosphate de 6-methoxy-8-(5'-propylaminoamylamino) quinoline. Le médicament a été administré par la bouche sous forme de comprimés; chaque comprimé contenait 10 mg de sel (7,5 mg de base). Les deux volontaires furent soumis chacun à deux traitements avec ce médicament. Le composé étudié, connu également sous son nom de code (Win 5037) ne présenta aucune action schizontocide sanguine marquée contre la souche de P. falciparum de Thaïlande résistante à la chloroquine.

Ces études furent effectuées afin d'évaluer ou de développer des médicaments efficaces contre P. falciparum résistant à la chloroquine.

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