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Ralph Jones Jr., ... , Alf S. Alving, Lillian Eichelberger

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THE THERAPEUTIC EFFECTIVENESS OF LARGE DOSES OF PALUDRINE IN ACUTE ATTACKS OF SPOROZOITE-INDUCED *VIVAX* MALARIA (CHESSON STRAIN)¹

BY RALPH JONES, JR.,² THEODORE N. PULLMAN,² C. MERRILL WHORTON,²
BRANCH CRAIGE, JR.,² ALF S. ALVING, AND LILLIAN EICHELBERGER

(From the Malarial Research Unit, Department of Medicine, University of Chicago)

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INTRODUCTION

Paludrine is a new antimalarial agent which was developed in England during World War II. In an extensive investigation of the antimalarial activity of pyrimidine derivatives, Curd, Davey, and Rose (1, 2) synthesized the drug, N₁-p-chlorophenyl-N₆-isopropylbiguanide, in 1945 and demonstrated that it exhibited a high degree of activity in avian malaria. Maegraith, Adams and their co-workers (3, 4, 5) tested this compound in human infections and found that it was a highly effective agent in the treatment of both *vivax* and *falciparum* malaria in man. Paludrine has been studied extensively by English (5) and Australian investigators (6) and its activity and usefulness have been confirmed. Maegraith *et al.* (5) have reported that a single dose of 50 to 400 mgm. will

produce clinical cure of relapses and delayed primary attacks of naturally acquired *vivax* malaria. The drug is well tolerated in doses as high as 1.5 grams a day for 14 to 28 days. In 157 cases of *vivax* malaria treated with paludrine in doses of 20 to 1,500 mgm. per day for 14 to 28 days, however, the effect on the relapse rate was no greater than that of quinacrine.

We have studied the effect of paludrine against a standardized infection of a Southwest Pacific strain of *vivax* malaria in order to compare it with suppressive agents, and have attempted to determine whether or not it exhibits synergistic action with quinine or pentaquine.

PROCEDURE AND METHODS

General

¹ This investigation was carried out under contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Chicago. The studies were planned in cooperation with the Panel on Clinical Testing of Antimalarials of the Board for the Coordination of Malarial Studies. This work was further aided by the participation of Army Medical Officers assigned to the project by the Surgeon General, U. S. Army.

Through a cooperative arrangement between Professor Clay G. Huff and Dr. Frederick Coulston, Department of Bacteriology and Parasitology, and the Malarial Research Unit, Department of Medicine, the former group bred *Anopheles quadrimaculatus* mosquitoes, supervised their infection and the inoculation of volunteers, and determined the intensity of infection in the salivary glands of the mosquitoes. The latter group assumed the responsibility for clinical care of patients studied by both groups.

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² Captain, M.C., A.U.S.

The subjects for the tests were presumably susceptible healthy, white, inmate volunteers in the Stateville Prison, which is located in a non-endemic area.³ All subjects were infected with Southwest Pacific *vivax* malaria (Chesson strain) (8) by the bites of ten infected mosquitoes, or by injection of their infected salivary glands.¹ To minimize the factor of acquired immunity, only primary attacks and early relapses were treated. Treatment with paludrine was started promptly after the demonstration of fever and parasitemia. A detailed report of the procedures used has been published (7).

The Chesson strain was chosen because it is characterized by a high relapse rate, a short latent interval between relapses, and a low incidence of delayed primary attacks (9, 10, 11). This strain has been used extensively in testing new antimalarial agents. It is possible under the conditions of these investigations to differentiate between subjects with severe infections and those with moderate infections, on the basis of the length of the prepatent period or the preceding parasitic latent period. In subjects with short preceding prepatent or latent periods the relapse rate of Chesson infections was 98 per cent after treatment with suppressive drugs,

³ The investigations reported in this paper would not have been possible except for the enthusiastic cooperation of the inmates and the administrative staff of Stateville Penitentiary.

whereas when these periods were long, the relapse rate was only 67 per cent (11).

Drug dosage and administration

In this report, the dosage of all drugs is given in terms of the weight of free base. All drugs were administered orally.

Paludrine. The daily dose of paludrine was 0.97 gram of base (equivalent to 1.11 grams of the monohydrochloride). The drug was administered to ten subjects in equally divided doses given at four-hour intervals throughout the 14 days of treatment. This dosage was chosen because earlier work of British investigators had demonstrated that 0.97 gram of the base per day produced minimal symptoms of toxicity. This dosage was the largest that had been used in man at the time our studies were begun, and was many times greater than the dosage which has been found effective in other strains of malaria (5, 6).

Throughout these studies the dosage and schedule of administration of paludrine have been the same whether it was administered alone or concurrently with other drugs.

Quinacrine (atabrine). The drug was administered in the form of the dihydrochloride. After an initial dose of 0.87 gram of the base (1 gram of the salt) given in four divided doses in the first 24 hours, the daily maintenance dose was 0.35 gram (0.4 gram of salt) given in four divided doses. Treatment was continued for seven days.

Pentaquine. Pentaquine was administered in the form of the monophosphate salt. The daily dose was 60 mgm. of the base given in single doses of 10 mgm. every four hours throughout the 14 days of therapy.

CHEMICAL METHODS

The concentration of paludrine in plasma was determined by the method of Spinks and Tottey (12); a modification (13) of the method of Brodie, Udenfriend, and Taggart (14) was used for pentaquine.

RESULTS

Comparison of paludrine with other suppressive agents. The efficacy of paludrine in terminating the acute attack of malaria was less than that of quinacrine, as evidenced by the number of days of parasitemia and the number of paroxysms with fever over 101° F. (rectal) after the start of treatment. Chloroquine (15) cleared the blood of parasites more rapidly than paludrine. Paludrine did not clear the peripheral blood of parasites in all patients until the seventh day of therapy whereas, in all patients treated with quinacrine, the thick film was negative in four days (Figure

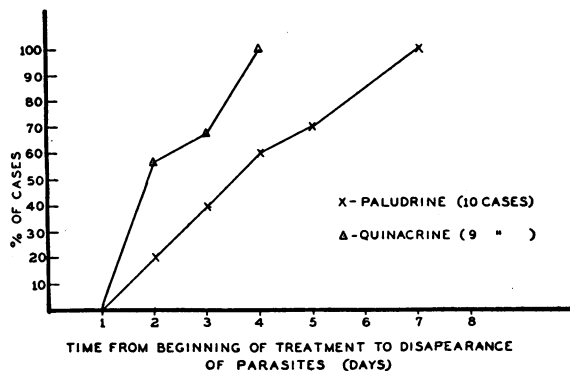


FIG. 1

1). All ten subjects treated with paludrine experienced one malarial paroxysm after treatment was started, and one subject had two paroxysms after the first day of treatment. No subjects treated with quinacrine had more than one paroxysm.

Seven of the ten subjects treated with paludrine relapsed after treatment; three subjects have shown no evidence of malaria during the 11 months which have elapsed since the end of therapy (Table I). Two of 22 subjects treated with quinine (15) failed to relapse, but all of the subjects treated with quinacrine or chloroquine (15) relapsed.

In no patients with severe infections was radical cure obtained when any one of these drugs was administered alone. The five subjects who failed to relapse after treatment with paludrine or quinine had infections of only moderate intensity (11).

The median period of parasitic latency following treatment with paludrine was slightly less than after quinacrine (Figure 2 and Table I). In four of the seven patients who relapsed after treatment with paludrine, parasitemia reappeared in 29 days or less. Parasitic relapse occurred within 34 days in half of the subjects who relapsed after treatment with quinacrine. After treatment with chloroquine (15) and after treatment with quinine (15), 60 days and 15 days, respectively, elapsed before parasitemia reappeared in half of the subjects.

The mean concentration of paludrine in the plasma during the period of therapy varied from 630 to 1,300 gamma per liter in individual subjects (Table II).

TABLE I

Therapeutic effect of paludrine administered alone and concurrently with other drugs

Drug	Dosage regime		Number of cases	Relapse ratio: Individuals relapsed Individuals treated		Duration of parasitic latent period in subjects who relapsed	Duration of follow-up in subjects who failed to relapse
	Total dose	Duration of therapy		Moderate infection	Severe infection		
	grams	days				days	months
Comparison of paludrine with quinacrine							
Paludrine	13.6	14	10	0/3	7/7	25, 28, 28, 29, 30, 34, 85	11, 11, 11
Quinacrine	3.0	7	9	2/2	7/7	29, 29, 31, 33, 35, 37, 37, 39, 43	
Effect of paludrine and quinine administered concurrently							
Paludrine and quinine	13.6 23	14	10	1/1	8/9	22, 25, 26, 34, 35, 36, 42, 62, 71	6
Effect of paludrine and pentaquine administered concurrently							
Paludrine and pentaquine	13.6 0.84	14	5		4/5	24, 29, 36, 120	6
Pentaquine	0.84	14	4		2/4	12, 128	11, 11

Paludrine was well tolerated at this dosage. Three subjects complained of mild transient abdominal discomfort during the first few days of therapy, and one subject complained of slight blurring of vision on occasions. No other subjective or objective evidence of toxicity was demonstrated by routine studies for drug toxicity (7).

Concurrent administration of paludrine and quinine. In order to determine whether or not there is a synergistic effect when paludrine and quinine are administered concurrently, ten subjects were treated during their primary attacks of Chesson *vivax* malaria with 0.97 gram of paludrine base and 1.6 grams of quinine base (2 grams of the

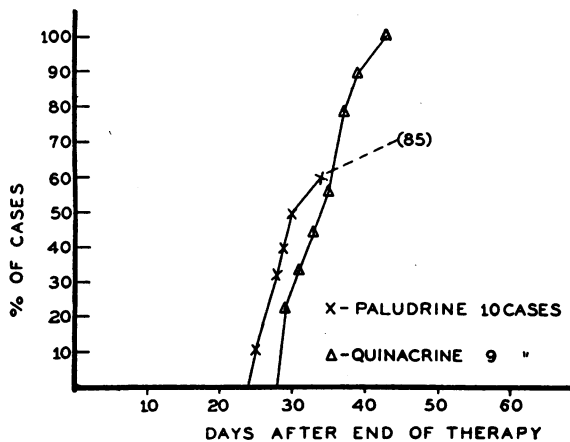


FIG. 2

TABLE II

Plasma concentrations of paludrine and concurrently administered drugs

Drug regime*	Range of mean concentration of paludrine in plasma	Range of mean concentration of concurrent drug in plasma
Paludrine alone	gamma/L. 630-1300	mgm./L.
Paludrine and quinine	770-1200	6-13
Quinine alone		3-10
Paludrine and pentaquine	650-1400	gamma/L. 140-450
Pentaquine alone		29-49

* All drugs were administered for 14 days in the following total dosage of base: paludrine 13.6 grams, quinine 23 grams, and pentaquine 0.84 gram.

sulfate) daily for 14 days (Table I). All patients experienced one paroxysm after therapy was instituted, and five to six days were required to clear the peripheral blood of parasites. The efficacy of this regime in terminating the acute attack of malaria was no greater than that of the same dose of quinine given alone (Table I). Nine of the ten subjects relapsed after therapy and one subject has shown no evidence of malaria for six months. In the nine subjects who relapsed, the parasitic latent period was no greater than that which followed treatment with the same dose of paludrine alone. The toxicity occasioned by this regime was mild, consisting of moderate abdominal pain, occasional vomiting, and diarrhea, plus mild cinchonism. The toxicity of the combined regime was therefore slightly greater than that produced by either drug when administered alone. There was no evidence of enhancement of the antimalarial effect of either drug by the concurrent administration of paludrine and quinine.

Concurrent administration of paludrine and pentaquine. Pentaquine (SN-13,276), a chemical analogue of pamaquin (plasmochin), has been shown to be superior to the latter as a curative agent in *vivax* malaria. The curative effect of pentaquine is enhanced by the concurrent administration of quinine (16). To determine whether concurrent administration of paludrine would also enhance the curative activity of pentaquine, a group of five subjects, whose previous history indicated that their infection presented a severe therapeutic challenge in tests for curative effect, were treated with paludrine and pentaquine concurrently.

The 14-day mean concentration of paludrine in the plasma, ranged from 650 to 1,400 gamma per liter. This was not different from the plasma concentration produced by the same dose of paludrine alone (Table II), or in combination with quinine. The 14-day mean concentration of pentaquine ranged from 140 to 450 gamma per liter in the subjects treated with pentaquine and paludrine, while in the control subjects treated with pentaquine alone, the plasma concentration varied from 29 to 49 gamma per liter. It is apparent that concurrent administration of paludrine increased the plasma concentration of pentaquine to a very marked degree. The mechanism responsible for this effect is unknown. It is of interest to note

that quinacrine has a similar effect on the concentration of pamaquin in plasma (17).

The effectiveness of the combined regime of paludrine and pentaquine in terminating the acute attack of malaria was not greater than that of pentaquine alone. Four of the five subjects treated concurrently with pentaquine and paludrine relapsed after treatment as did also two of four subjects treated with pentaquine (Table I). Only three of 17 patients presenting a severe challenge to the drug have relapsed following concurrent administration of pentaquine and quinine (16).

Despite the fact that concurrent administration of paludrine greatly increased the concentration of pentaquine in the plasma, it did not enhance the curative effect of pentaquine. Paludrine apparently does not manifest the synergistic effect on pentaquine which is exhibited by quinine.

CONCLUSIONS

Although paludrine fails to prevent relapse in the severely infected individual, it is a valuable drug for the treatment of the acute attack of *vivax* malaria (Chesson). It has little or no toxicity at doses much higher than the minimum necessary to suppress an attack; it does not stain the skin; and it is followed by a latent period longer than that after quinine and only slightly shorter than that after quinacrine (atabrine). Its prolongation of the subsequent latent period, however, is considerably less than that of chloroquine.

Concurrent administration of paludrine and quinine does not enhance the value of either in the treatment of malaria.

There is a marked increase in the plasma concentration of pentaquine when it is administered concurrently with paludrine, but there is no evidence of synergistic activity.

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