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PRIMAQUINE AND QUINOCIDE AS CURATIVE AGENTS
AGAINST SPOROZOITE-INDUCED CHESSON STRAIN VIVAX MALARIA

by

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INTRODUCTION

Primaquine, 8-(4-amino-1-methylbutylamino)-6-methoxyquinoline, was synthesized by Elderfield (1946) and its pronounced effectiveness as a curative agent against Chesson strain vivax malaria was demonstrated by Edgcomb et al., 1950. In military installations in the United States it was highly effective for the radical cure of Korean vivax malaria (Garrison et al., 1952, Alving et al., 1953, Coatney et al., 1953). It was first used on a large scale when the United States troops returned home from Korea by ship. Over 330 000 men each received a single 15-mg (base) dose, daily, during the 14-day Pacific crossing. The regimen was highly successful in preventing the introduction of this malaria into the United States (Archambeault, 1954). The total American experience resulted in a regimen which is generally accepted throughout the world for the radical cure of vivax malaria, i.e., a single 600-mg (base) dose of chloroquine or the standard 1500 mg (base) given over 3 days, to remove the circulating asexual parasites responsible for the illness, followed by primaquine, 15-mg (base), single dose, daily for 14 days. The 14-day regimen permitted a relapse rate of less than 1% against vivax malaria of Korean origin (Alving et al., loc. cit.). There is, however, a paucity of such data against the Chesson strain. The senior author carried out the first part of this study in 1956 with 24 white male volunteers infected by the bites of 10 heavily infected mosquitos. When an infection became patent, the subject was given a single 600-mg (base) dose of chloroquine followed by the standard 14-day primaquine treatment. Of the 24 subjects, nine (36%) exhibited an initial relapse, three (12-1/2%) had a second attack, and one (4%) had a third attack during an observation period of over two years.

In 1949, Elderfield (1955) synthesized another 8-aminoquinoline with the methyl group in the 4-position of the aliphatic side-chain, in contrast to primaquine where the methyl group is in the 1-position, and identified it as CN-1115. It did not receive an early trial in man because toxicity tests in rhesus monkeys showed its toxicity was approximately equal to that of pamaquine.

The Russian chemists, Braude & Stavrovskaya (1956) synthesized the same compound in 1952 and gave it the name, quinocide. In 1955, investigators in the USSR began publication of a series of papers dealing with the pharmacology and

general usefulness of quinocide as an antimalarial drug. The whole Russian experience with this compound was ably reviewed by Lysenko (1960) in which he stressed the curative properties of quinocide against vivax malaria and its lack of toxicity in adults at the recommended dosage of 15 mg (base) daily, for 14 days, or at 23 mg (base), daily, for 10 days.

Because the Russian experience did not include primaquine or any other 8-aminoquinoline controls, we considered it advisable to test it and quinocide simultaneously against Chesson strain vivax malaria. The following report presents the results of that investigation.

MATERIALS AND METHODS

All of the subjects included in this investigation were young, white, male volunteers, housed at the United States Penitentiary, Atlanta, Georgia; none had a history of previous malaria. Before being accepted as a participant in the study, each volunteer underwent the following procedures: complete medical history and physical examination, chest X-ray, electrocardiogram, complete blood count, including platelet estimation, and urine analysis.

Each of the volunteers was infected with the Chesson strain of Plasmodium vivax by the bites of 10 heavily infected Anopheles quadrimaculatus mosquitos. The biting technique, employing interrupted feeding, was the same as described by Coatney et al., 1947. Infection in the mosquitos was determined by post-prandial dissection of the salivary glands. In counting time, the day of an event is day zero, the next day is day one, the next day two, and so on.

When parasites were first demonstrated in Giemsa stained smears of the peripheral blood, the volunteer was assigned by lot to Group A or Group B. Treatment was started on the third day of patent parasitaemia, providing there had been an oral temperature of 101⁰ F. or more. Otherwise, treatment was deferred until day four. Each man in Group A received a single oral dose of chloroquine (600 mg, base). The next day he received a single oral dose of primaquine (15 mg, base) and this dose was repeated daily for a total of 14 doses. Each man in Group B received chloroquine, as above, and on the following day was given a single oral dose of

quinocide¹ (15 mg, base) and this dose was repeated daily for a total of 14 days.

Peripheral blood smears were made daily during therapy and weekly thereafter, for not less than 90 days. Thereafter, smears were made whenever there were clinical manifestations suggestive of malaria. When relapse was proved by two non-consecutive smears, the initial treatment was repeated and smears continued daily until the blood was parasite negative.

Because of the known haemolytic tendencies of all 8-aminoquinolines, haemoglobin determination, haematocrits, bleeding and clotting times were done every other day during therapy and the results compared with those obtained prior to the start of medication.

RESULTS

Primaquine Series. Among the 5 early primary attacks treated, one infection relapsed after 48 days. (See Table 1.) In the group of 5 volunteers with delayed primary attacks, one initial relapse occurred after 35 days and another after 504 days. The initial relapser had a second attack 250 days later. Total observation of the individuals in both groups ranged from 580 to 892 days.

Two volunteers among the ten complained of mild gastro-intestinal upset, gaseous distension and mild nervousness during therapy. In no case was the discomfort sufficient to warrant stopping the drug. No other toxic manifestations were observed.

¹ Sufficient material for our work was not available from Elderfield's original synthesis of this compound (CN-1115) so we requested Dr C. M. Suter, Director of the Sterling-Winthrop Research Institute, Rensselaer, New York, to synthesize the material for us. Shortly before the drug was available, we received a quantity of quinocide tablets containing 7.22 mg of the base, and a sample of the dihydrochloride powder, through the kindness of Dr P. Sergiev, Director, Institute of Medical Parasitology and Tropical Diseases, Moscow, USSR. Upon comparison, the newly synthesized compound was found to agree in all respects with the USSR samples. The Sterling-Winthrop drug (Win 10 448 or Chinocide) was employed in our work. Our thanks are extended to Dr Suter.

Quinocide Series. In the early primary attack group of 4 patients, two first relapses occurred 7 and 36 days after treatment;¹ two second relapses occurred in two patients after 21 and 218 days; and two third relapses appeared after 46 and 68 days. The delayed primary group also contained 4 patients; two relapses occurred at 32 and 140 days followed by a single second relapse in one of them 161 days later. The total observation time in this series ranged from 705 to 745 days. (See Table 1.)

Five of the 8 volunteers who received quinocide had abdominal discomfort including cramps and nervousness, but none of the complaints was considered severe enough to warrant terminating the medication. No other toxic manifestations were evident.

DISCUSSION

In trials to assess the overall effectiveness of a given compound, we have always attempted to present a severe challenge in the belief that results of such a test represent the true worth of a drug. In other words, if a drug will produce radical cure of a large proportion of Chesson strain vivax infections, probably the most severe challenge to radical cure by an 8-aminoquinoline, it will result in cure when used against a vivax parasite from any part of the world. This is not to say that a drug with less potential might not be highly curative against certain malarias, but when one is concerned with true cure, it appears to us better to use a drug which is most effective against a hard-to-kill parasite providing, of course, toxicity and other factors are equal.

The data show that primaquine is effective as a curative agent against the highly cure-resistant Chesson strain of Plasmodium vivax. In this study there were 3 failures out of 10, initially; those 3 were treated again and only one had a subsequent attack which was treated. In the Coatney study, referred to earlier, there

¹ [The relapse after 7 days might be considered as a recrudescence in view of the short interval after the administration of chloroquine - Editor]

were 9 failures out of 24 following the initial treatment. The 9 were given primaquine again and 3 infections relapsed; those infections were treated and one had a subsequent attack, and that, too, was treated. In the two series, taken together, the proportion of treatment-failures was 11/34, 4/11, 1/4, 0/1, or an overall proportion of 16/50 (32%).

When one examines the quinocide data in the same light, one sees that, initially, there were 4 treatment-failures out of 8. The 4 were treated again and 3 infections relapsed; those were treated and 2 had subsequent attacks which were treated. The treatment-failures for each attack were 4/8, 3/4, 2/3, and 0/2, or an overall failure of 9/17 (53%).

Even though there was no great spread in the treatment-cure ratio between the two drugs in these limited trials, there were proportionately more relapses after quinocide therapy than after treatment with primaquine.

We encountered no appreciable toxicity with either of these drugs, which agrees with Lysenko's work (1960) on quinocide.

It would appear, except in unusual circumstances, that primaquine, because of the extended experience with it since 1950, would be the drug of choice when the goal is radical cure with low toxicity.

SUMMARY

This study was undertaken to evaluate the curative efficacy of primaquine and of quinocide (CN-1115, Win 10 448), on an equal dose basis, against sporozoite-induced Chesson strain Plasmodium vivax in human volunteers. There was no clear-cut superiority of one drug over the other although there were proportionately more relapses following quinocide than after treatment with primaquine. Neither drug produced appreciable toxicity. It is concluded, on the basis of the greater proportion of relapses, the extended experience since 1950, and the relative lack of toxicity, that primaquine would be the drug of choice when the goal is radical cure of infection.

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TABLE 1

INCIDENCE OF RELAPSES AFTER TREATMENT OF EARLY AND LATE PRIMARY ATTACKS OF CHESSON STRAIN VIVAX MALARIA WITH PRIMAQUINE OR WITH QUINOCIDE EACH GIVEN IN A SINGLE ORAL DOSE (15 mg BASE) DAILY FOR 14 DAYS FOLLOWING AN INITIAL ORAL DOSE OF CHLOROQUINE (600 mg BASE)

Type of attack	1st relapse (Days)	2nd relapse (Days)	3rd relapse (Days)	Days of observation
		PRIMAQUINE		
E. P. ^a	1/5 (48) ^b	-	-	580-745
D. P. ^c	2/5 (35-504)	1/5 (250)	-	700-892
		QUINOCIDE		
E. P.	2/4 (7-36)	2/4 (21-218)	2/4 (46-68)	705-745
D. P.	2/4 (32-140)	1/4 (161)	-	742-745

^a E. P. = early primary, i.e., initial parasitaemia in less than 20 days after infection.

^b () = days to relapse after last dose of drug.

^c D. P. = delayed primary, i.e., initial parasitaemia delayed by suppressive treatment. (Either with 300 mg chloroquine base weekly or 25 mg pyrimethamine weekly.)