Pan American Health Organization

ADVISORY COMMITTEE ON MEDICAL RESEARCH

Seventh Meeting

Washington, D.C., 24-28 June 1968

Item 22 of the Agenda

PROGRESS REPORT ON FIELD STUDIES WITH A LONG-ACTING ANTIMALARIAL DRUG, CYCLOGUANIL PAMOATE (CAMOLAR®)

Ref: RES 7/17
10 June 1968

PAN AMERICAN HEALTH ORGANIZATION
Pan American Sanitary Bureau, Regional Office of the WORLD HEALTH ORGANIZATION

Washington, D.C.
In recent years attention has been directed towards the greater utilization of antimalarial drugs in eradication and pre-eradication programs (24, 25). Drugs used at present must be taken every week or every two weeks to provide an acceptable degree of protection, particularly in areas with a high transmission of malaria. The administration of drugs to population groups, although carried out at less frequent intervals, may be of value in reducing the parasite reservoir in certain areas. Nevertheless, the synthesis of a repository antimalarial drug, having the capacity to prevent or inhibit the growth of plasmodia for several months, would be a very significant advance towards the goal of world-wide eradication of malaria.

Sustained research in this area by Thompson and his coworkers (22) led to the development of cycloguanil pamoate (CI-501; Camolar), a repository preparation of the dihydrotriazine metabolite of chlorguanide. Due to the poor solubility of the dihydrotriazine pamoate salt, absorption occurs very slowly from intramuscular sites into which it has been injected; this results in very low but persistent concentrations of the drug in body fluids. A single dose of the triazine protected mice for many weeks against repeated challenges with Plasmodium berghei trophozoites (22) and protected rhesus monkeys for many months against repeated challenges with P. cynomolgi trophozoites (22) or sporozoites (21).
In clinical trials in the United States of America, an intramuscular dose of cycloguanil pamoate (5 mg base per kg) prevented patent infections in all adult volunteers who were given the drug and subsequently bitten by heavily infected mosquitoes on one or more occasions over the ensuing 6 months. Although mosquitoes were heavily infected with the Chesson strain of \textit{P. vivax}, they were unable to induce patent infections over a period of 20 months, in about one-half of the 28 treated volunteers (5, 6, 18). In addition, the drug also exerted a marked therapeutic effect in men with well-established vivax infections (5). Camolar protected two volunteers against trophozoite-induced infections with the McLendon strain of \textit{P. falciparum} (7). Protection was not conferred upon four other volunteers inoculated with erythrocytic parasites of a Southern Rhodesian strain of \textit{P. falciparum} but protection against sporozoite-induced infections of this strain was observed in all of the 14 volunteers for a minimum period of 10 months after medication (7). It was subsequently shown that asexual erythrocytic forms of the strain from Southern Rhodesia were partially resistant to chlorguanide (7), and that Camolar exerted a true causal prophylactic effect against this strain of \textit{P. falciparum} (11). In studies with three strains of chloroquine-resistant (and chlorguanide-resistant) \textit{P. falciparum} from Southeast Asia, Camolar did not confer long-lasting protection against sporozoite-induced infections, it did not effect radical
cure of established infections, and it did not seem to have any sporontocidal effects (17, 18). Subsequently, it was shown that Camolar, as early as 12 days after its administration to a volunteer, exerted no causal prophylactic effect against the multi-drug resistant Malayan (Camp.) strain of P. falciparum (13). No observations were made in the clinical studies to determine whether Camolar had a sporontocidal effect against drug-sensitive strains of malaria.

**Human tolerance to the drug**

Although 128 volunteers in the United States were involved in studies to ascertain human tolerance to the drug, 337 additional volunteers, participated in six tolerance trials that were conducted in South Korea, Thailand and Pakistan (16). A total of 257 subjects received Camolar in an oleaginous suspension (each ml containing cycloguanil pamoate equivalent to 140 mg of the dihydrotriazine base). Adults received Camolar at a dose of 350 mg and children were given the drug at a dosage range of 5 to 10 mg per kg of body weight. Of the 257 subjects, 109 received one injection, 101 received two injections, and 47 received three injections of Camolar; there was an interval of at least 3 to 4 months between injections. In addition to data obtained from specific tolerance studies in the field, a substantial body of data was obtained from field studies which had, as their primary objective, a determination of the antimalarial effects of the
drug. Observations in the latter studies were limited to an assessment of systemic and localized (injection site) side-effects, but some studies included an evaluation of teratogenic effects and hemoglobin or hematocrit levels.

1. **Systemic side-effects**

They were reported in only one tolerance study, and included headache, anorexia, joint pains, nausea or dizziness, all of which were mild and transient in nature. Although allergic-like reactions, such as urticaria, rashes, wheals, and itching, were observed in one out of 10 U.S. penitentiary volunteers after a second or a third injection, they were not seen in any of the subjects participating in the field studies.

Laboratory determinations included hemoglobin and hematocrit levels, white cell, differential, platelet and reticulocyte counts, erythrocyte sedimentation rates, bilirubin determinations, serum transaminase assays, blood urea nitrogen levels, thymol turbidity estimations, and urinalyses. As in the United States trials, variations in these parameters were usually isolated and transient. Elevated white blood counts or erythrocyte sedimentation rates and altered hemoglobin or hematocrit values were usually related to localized reactions at the injection site. In one study, mild eosinophilia was noted and attributed to intestinal parasitic infections.
2. Localized side-effects at the site of injection

Local tissue reaction at the site of injection was common after the administration of Camolar. Affected individuals had one or more of the following symptoms or signs: pain, a limping gait, tenderness, induration, swelling, heat, formation of an abscess which often discharges through a sinus. Fortunately, most reactions were mild in nature and consisted only of slight pain which subsided in one or two days. An early field trial showed that reactions were more common when the drug was injected into the upper arm than when it was injected into the buttock (15). Consequently, in all other field trials, Camolar was given as a deep intra-gluteal injection. It was noted by McGregor (12), and confirmed by other investigators, that the incidence of abscess formation with a draining sinus could be reduced to almost nil by injecting the drug into a site which was relatively free from adipose tissue. The technique used to achieve this was to place the left index finger on the right anterior superior iliac spine, to abduct the middle finger and, placing it just below the iliac crest, to inject the drug into muscle tissue located beneath the triangular area formed by the two fingers and the iliac crest. Some investigators reported a lower incidence of local reactions following second or third injections of Camolar; this may have been due mainly to an improvement in the technique of injection.
In spite of a good technique of drug administration at the preferred site of injection, a very small proportion of individuals developed moderate or severe local reactions following the administration of Camolar. The more severe reactions commenced either within a few days of drug administration or within 1 to 4 weeks after medication. One of the investigators felt that there might be a relationship between strenuous physical exercise following the injection and the occurrence of the more severe reactions (20). The incidence and severity of local reactions in the different studies cannot be readily compared because such reactions, determined in different population groups by different investigators, were probably not subject to uniform interpretation. Nevertheless, using the preferred injection technique, it is unlikely that more than one in 10 subjects experienced sustained discomfort in any of the studies and undoubtedly, a much smaller proportion of subjects were prevented from pursuing their normal activities. Some of the more severe reactions persisted for 1 to 2 weeks, but usually subsided either with or without salicylate treatment. In the Guatemalan field trial (23), antihistamines, muscle relaxants and prednisolone were used; in some subjects prednisolone was especially effective in reducing pain.

Two investigators reported that many people requested a second injection, or accepted a second injection more readily than the first one.
(12, 19, 20). In some instances, this included subjects who had experienced severe local reactions following the first drug administration. Wherever attitudes like these prevailed, it is obvious that people, either individually or collectively, had decided that the favorable effects of Camolar outweighed the unfavorable effects at the injection site.

3. **Teratogenic effects**

In a study in Pakistan which included 651 women in the child-bearing age group, 278 women were treated with Camolar, 207 received a placebo and 166 were not treated (16). Over a period of 18 months, 98 pregnancies were observed with the following results: 87 live births, eight abortions, three stillbirths, nine neonatal deaths, four congenital anomalies and three maternal deaths. Among the group that had received Camolar, 34 pregnancies terminated in 30 live births, three abortions and one stillbirth; three neonatal deaths, but no congenital anomalies were observed.

During the course of field studies in the Gambia, New Guinea and Senegal, the outcome of 41 pregnancies was observed in women who had received Camolar. No congenital anomalies were seen in 38 babies born to these women and all the babies gained weight during the first month after delivery. The three other pregnancies terminated in abortions, each one occurring in a different geographic area; one abortion was
associated with severe lobar pneumonia and another one was self-induced.

**Antimalarial effects of the drug**

Table I summarizes some pertinent data concerning the antimalarial effects of Camolar in 15 field studies. In nine of the areas studied, *P. falciparum* accounted for all, or most, of the malaria infections (3, 4, 8, 10, 12, 16, 19, 20) and in five other areas it was about as prevalent as *P. vivax* (16, 19, 20). The latter species was responsible for all infections in the New Guinea 1 study (1). Available data indicate that *P. malariae* was present in at least five of the areas studied (4, 10, 12, 16, 20) and *P. ovale* was present to a very minor extent in the Gambia 1 and Tanzania 2 studies (4, 12).

No organized antimalarial measures had been undertaken in any of the areas just prior to the administration of Camolar. With the exception of half the adults in the Gambia 2 study (16), Camolar was administered to adults at a dose of 350 mg dihydrotriazine base. The dosage of the drug in children ranged from 4 to 15 mg/kg; in later field studies the mean dosage was approximately 10 mg/kg, almost double the dosage used in the earlier studies. Along with Camolar, subjects in four studies

---

Some results from studies which have not been published (investigators not named in Table I) were kindly made available by the Research Division, Parke, Davis and Company. The data were contained in reports forwarded to the Company by field investigators and have been incorporated in a Parke, Davis Company Monograph on Camolar (1968)
received a single oral dose of a 4-aminoquinoline (600 mg base for adults and proportionately less for children). In the Nigerian study (16) a weekly dose of a 4-aminoquinoline (300 mg base) was given to 32 adults during a period of 6 months; these subjects served as a control group for 32 adults administered a single dose of Camolar. Subjects who formed part of control groups in other trials were given an oleaginous placebo vehicle, a saline placebo, or nothing. In some of the field studies (Gambia 1, New Guinea 2, New Guinea 4, Senegal 1, Tanzania 2, West Pakistan 2), a number of subjects received a second injection of Camolar and the response of subjects with patent infections is included in Table II.

1. Clearance of parasites 7 to 15 days after treatment

Camolar exerted a marked effect on the asexual erythrocytic forms of all four species of malaria within 48 to 72 hours after treatment. Excluding subjects who were given concurrent treatment with a 4-aminoquinoline, 768 subjects had patent infections just before treatment with Camolar. By 7 to 15 days after medication, no asexual parasites were seen in blood films from any of the subjects with the exception of films from four individuals who showed 4-5 trophozoites per mm$^3$ (one vivax and three falciparum infections). These low grade parasitemias were found in subjects of the Tanzania 3 and the New Guinea 2 studies (9; personal observation); in the former study, chloroguanide and pyrimethamine
resistant strains were common and, in the latter study, parasites resistant to chlorguanide were prevalent 3 to 4 months after medication with Camolar.

Gametocytes of *P. vivax* and *P. malariae* were not found 7 to 15 days after treatment, whereas gametocytes of *P. falciparum* were evident at 7, 15 and 30 days after treatment and usually occurred in subjects showing trophozoites, gametocytes, or both, before treatment.

2. Duration of protection

The duration of protection against malaria in field studies was generally shorter than that observed in clinical studies with chlorguanide-sensitive strains of malaria. Although strains of malaria with an increased tolerance to chlorguanide were found in many field studies, the Gambia 1 study showed that an early reappearance of parasitemia after treatment was not necessarily related to the emergence of such strains (12). Parasitemias generally reappeared in adults a few weeks later than they did in children, yet, with the exception of the Tanzania 1 study (3), a marked difference in the duration of protection was apparent between adults in clinical trials and those in field trials. McGregor (12) advanced the possibility that the sustained muscular activity of subjects in his study could have resulted in hyperemia and a faster rate of absorption of the drug from the injection site. Subjects in most of the field trials continued
their normal activities after medication and, in these predominantly agriculture communities, such activities undoubtedly entailed a degree of muscular activity greater than that engaged in by volunteers in American penitentiaries. Another field investigator (20) felt that moderate or severe reactions at the injection site occurred to a greater extent in subjects who had engaged in very strenuous physical activity following drug administration. In this connection, it has been reported that an increased local tissue reaction may at times be associated with an accelerated release and excretion of the cycloguanil (6). Although some investigators were unable to establish a relationship between the severity of local reactions and the duration of protection (1, 12; personal observation), other investigators have suggested that a relationship might exist (6, 23).

It was mentioned earlier that the duration of protection against malaria was shorter in children than it was in adults. As most of the studies were conducted in localities with a perennially high transmission of malaria, the longer periods of protection in older subjects may have been largely due to the greater degree of immunity against malaria in these subjects. Nevertheless, it was felt that higher doses of Camolar might extend the duration of protection in children. In the Tanzania 1 study, *P. falciparum* reappeared between 4 and 5 months in six out of 23 children receiving less than 9 mg/kg of the drug and in one out of 17 children receiving more than that amount (3). On the other hand, the
Gambia 1 study showed that children receiving Camolar at a dosage range of 5-10 mg/kg were protected as long as those receiving 10-15 mg/kg (12). In the Gambia 2 study (15), 65 of the children under 7 years old were divided into two equal groups: Group A received 4-6 mg/kg of the drug and Group B received 10-12 mg/kg. Three months after medication, eight children in Group A and seven children in Group B had patent parasitemia; 4 months after medication, an additional eight children in Group A and seven children in Group B showed patent infections. The administration of higher doses of Camolar to children in some other field studies did not prevent the early reappearance of parasitemia. However, no firm conclusions can be drawn from findings in the last-mentioned studies because they were conducted either in different geographic locations or in areas where strains of parasites had an increased tolerance to chlorguanide or pyrimethamine.

2a. *P. falciparum*

The effects of Camolar against falciparum malaria were assessed in 14 different studies. The duration of protection conferred by the drug upon all subjects in a study group varied from one study to another. In areas where no drug resistant parasites were demonstrated the period of protection varied between 2 and 5 months, whereas in areas where drug resistant parasites were found the period of protection was only 1 or 2 months. Furthermore, half the individuals in a study group, relative to
the number of subjects with parasitemia before treatment, were protected for longer than 2 to 3 months in all studies; in areas where no drug resistant parasites were apparent they were protected for at least 4 months and, in a number of studies, for much lengthier periods of time. In general, adults were protected a few weeks longer than children.

2b. P. vivax

The effects of Camolar against vivax malaria originating in New Guinea and West Pakistan were assessed in six different studies. The New Guinea 1 study (1) was the only one which was not conducted in an endemic area. It involved 24 Government officers who had spent an average of about three and one-half years in New Guinea and were given Camolar shortly after their return to malaria-free Australia. The relapse pattern of vivax infections had been studied in similar groups of men during previous years and, on this basis, it was concluded that Camolar had delayed the appearance of patent parasitemia in this group of men for about three months. In studies conducted in endemic areas of New Guinea, the occasional patent vivax infection was noted during the second or third month after medication but a larger number of patent infections did not occur until the fourth month. In the studies in West Pakistan, patent vivax infections were not found until four or five months after the administration of Camolar.
2c. *P. malariae*

With the exception of three patent infection in the New Guinea 2 study and the limited observations of the Tanzania 2 study, the duration of protection against malariae infections was in excess of 6 months.

2d. *P. ovale*

The prevalence of ovale infections in two studies was so low that findings following medication were not reported in detail.

3. Resistance of parasites to chlorguanide, pyrimethamine and second doses of cycloguanil pamoate

A number of studies were carried out in areas known to harbor parasites resistant to chlorguanide, pyrimethamine, or both: Senegal 2, Tanzania 3 and West Pakistan 2 (10, 14, 16). The prior use of pyrimethamine or chlorguanide was established in locations within 30 km of the Senegal 1 and New Guinea 1 study areas (14; personal observations); in the latter area, pyrimethamine had always been administered in the form of a chloroquine-pyrimethamine combination. As chlorguanide and pyrimethamine have been widely used in different areas of the world, it is conceivable that parasites in other field studies could have been exposed to these drugs.

In determining the susceptibility of parasites to chlorguanide,
pyrimethamine, or Camolar in eight different field studies, an increased tolerance to one or the other of these drugs was established in seven of the studies. Table II shows the susceptibility of asexual erythrocytic forms of *P. falciparum*, *P. vivax* and *P. malariae* to these drugs; the tests were carried out with a number of subjects either before or after the first administration of Camolar. Although some studies with Camolar were purposely conducted in areas where parasites were known to be resistant to chlorguanide or pyrimethamine, a decreased sensitivity of parasites to these drugs was discovered in many areas only after medication with Camolar. In two such areas, Tanzania 2 and New Guinea 4, tests to determine the susceptibility of parasites to chlorguanide, pyrimethamine, or both, prior to treatment with Camolar, failed to reveal the presence of any resistant strains (4, 20). However, these tests involved a relatively small proportion of all infected subjects and it is quite possible that strains with a decreased sensitivity to these drugs were missed during the preliminary investigations. In the New Guinea 2 study there can be little doubt that parasites were highly resistant to chlorguanide and cycloguanil pamoate. It is the only field study in which resistance of erythrocytic forms of *P. vivax* to a second injection of Camolar has been demonstrated. Although various drug regimens were used in the different field studies, it is readily apparent (Table II) that different strains of *P. falciparum* showed varying degrees
of sensitivity to these drugs. Unlike the 4-aminoquinolines (25) no uniform grading of the susceptibility of parasites to "antifolic" drugs has been widely accepted. However, in the opinion of different investigators (4, 8, 14, 20), the response of *P. falciparum* to chlorguanide or pyrimethamine in these susceptibility tests seemed to indicate a certain degree of resistance to these drugs.

4. **Administration of a 4-aminoquinoline in conjunction with Camolar**

In fully susceptible strains of *P. falciparum*, Fairley and his co-workers (9) showed that pre-erythrocytic forms of the parasite were susceptible to doses of chlorguanide which were ineffective against asexual erythrocytic forms. Furthermore, Contacos and co-workers (7) found that a standard dose of the dihydrotriazine metabolite of chlorguanide conferred protection against mosquito-induced infections but did not do so against blood-induced infections of the Southern Rhodesian strain of *P. falciparum*. When two volunteers, infected with this strain, were treated with chlorguanide 300 mg daily for 5 days, asexual erythrocytic parasites were not evident 3 days after treatment, but were evident 6 or 11 days after treatment. It was subsequently shown that volunteers given Camolar 6 days after bites by infective mosquitoes, did not develop *falciparum* infections but did develop subpatent or patent infections when Camolar was administered 7 or more days after being bitten by infective mosquitoes. Thus, Camolar exerted a satisfactory causal prophylactic,
but only a transitory blood schizontocidal, effect against the Southern Rhodesian strain of *P. falciparum*.

In view of the above findings, it was felt that the administration of an effective blood schizontocide, in conjunction with Camolar, might provide a longer period of protection than if Camolar was administered alone. Thus, a 4-aminoquinoline at an adult dose of 600 mg base (proportionately less for children) was administered concurrently with Camolar in four field studies. One of the studies was conducted in an area of Senegal where parasites were considered to have a decreased sensitivity to chlorguanide and pyrimethamine (14), and in two of the other three areas (Tanzania 2 and New Guinea 4) an increased tolerance of parasites to proguanil, pyrimethamine, Camolar, or all three, was demonstrated 2 to 4 months after medication with the cycloguanil and amodiaquine (4, 20). In the Tanzania and Senegal studies a comparison group of subjects were given Camolar but were not given a 4-aminoquinoline. The findings in these two studies were as follows: In Tanzania, six out of a sample of 189 subjects and 13 out of a sample of 67 subjects showed falciparum infections 1 and 2 months, respectively, after the medication with Camolar alone; one out of a sample of 193 subjects and three out of a sample of 63 subjects showed falciparum infections 1 and 2 months, respectively, after medication with Camolar and a 4-aminoquinoline. In Senegal, absenteeism at follow-up examinations was high (as in
Tanzania), and there seems to be some doubt as to whether all subjects received the specified doses of the cycloguanil or amodiaquine. The concurrent medication with a 4-aminoquinoline seemed to confer little additional protection to subjects in this field study. In the New Guinea 3 study, no falciparum infections were seen for 4 months after the combined administration of drugs and no patent vivax infections were seen for 2 months. The New Guinea 4 study showed the first patent falciparum and vivax infections during the second month after medication, but a marked increase in the number of patent infections was not seen until the fourth month.

**Large-scale field study with Camolar in Guatemala**

A large-scale field study with Camolar was commenced in Guatemala in May 1967, and results presented here have been compiled from interim reports forwarded by the investigators to the Malaria Division, Pan American Health Organization, Washington, D.C. (23).

The field study involved a population of over 12,000 persons living in two districts on the Pacific coast of the Republic of Guatemala. The study was enlarged to include a third district with a population of about 1400 but, at present, sparse data are available from this extension of the study. The project area was selected because it was typical of the problem areas in Central America where residual insecticide spraying and mass administration of chloroquine and primaquine had failed to
interrupt the transmission of malaria.

Drug distributors made house to house rounds every two weeks, but a relatively low percentage of the people had received the drug combination regularly; more recently, only about 60 percent of the population had received the medication in some areas.

1. Dose of drugs

Camolar was not given to children under 6 months of age, but older persons, after being weighed, received Camolar according to the following schedule (drug dose is expressed as dihydrotriazine base content):
<6 kg, 84 mg; 6 to 12 kg, 140 mg; 13 to 18 kg, 210 mg; 19 to 30 kg, 280 mg; >30 kg, 350 mg. A concurrent dose of chloroquine was given orally according to the following schedule (drug dose is expressed as base content):
6 to 11 months, 75 mg; 1 to 3 years, 150 mg; 4 to 6 years, 300 mg; 7 to 12 years, 450 mg; >13 years, 600 mg.

2. Acceptance of drugs

The first drug administration was given to 78.9, 74.1 and 84.5 percent of the population in Districts 1, 2 and 3 respectively. About 6000 subjects over 6 months of age lived in the first two districts. Some people reported to drug administration personnel about injection site reactions and all such individuals were examined by a physician. The number of such reactions classified as moderate or severe constituted 2.3 and 1.8
percent of the treated population in Districts 1 and 2, respectively.
Second injections of Camolar were offered to the same group of people about 6 months after the first injections. In District 1, 81.4 percent of the population received medication during the second round and in District 2, 79.8 percent of the population received medication. During the interval between first and second injections of Camolar, the attitude of the population towards the drug had improved and a slightly higher proportion of subjects accepted the drug during the latter round. Even persons who had previously experienced severe reactions at the injection site accepted another administration of Camolar. The response of the population to second injections was consistent with that seen in other field trials and many parents expressed their gratitude that their children had been relatively free of febrile episodes since receiving the first injections.

3. Work output by medicators

In the initial stages of the field study, people were given their medication at drug administration centers and individuals who did not attend were given the medication in their homes. Many of the people living in these districts had moved into the area as part of a land resettlement scheme and each family lived on its own land and not in a village community. Because the population lived in houses which were scattered
over a wide area, it was decided to concentrate exclusively on house to house drug administration. Using bicycles as means of transportation, the drugs were administered by seven teams of medicators, each team being composed of a male and a female medicator. Working only in daylight hours, averages of 13.8, 8.8, 12.5 and 10.1 persons medicated per man per day were obtained in different districts during the first and second drug administration rounds. In an effort to give the drugs to as many people as possible, medicators returned to a house if any of its occupants were absent during the first visit; this lowered the work output per medicator quite considerably.

4. Antimalarial effectiveness of the drugs

Table III presents parasitologic findings obtained before and after the administration of drugs. The effectiveness of Camolar was assessed by mass blood surveys (examination of all subjects, asymptomatic and symptomatic) and by surveillance (examination of subjects with symptoms or of those with a recent history of fever). The prevalence of patent infections as determined by these two different methods of assessment cannot be compared with each other because one method surveys the prevalence of parasitemia in an entire group of subjects at a given point in time whereas the other method involves a continuous search (usually an enquiry once a month) for subjects who are more
likely to have patent parasitemia than asymptomatic subjects.

In comparing the results of mass blood surveys in District 1, it is apparent that the prevalence of patent infections in the group (including 21 percent of subjects who remained untreated) 5 months after medication was about one-seventh of that prior to mass drug administration. This difference was not due to seasonal influences because the prevalence of patent infections was 30 times higher in untreated than in treated subjects. In the treated individuals, all three falciparum infections occurred more than 4 months after drug administration and the 13 patent vivax infections were detected 6 weeks to 5 months after drug administration (Table III), the mean and median time after medication being 4 months and 4 months and 9 days, respectively. Of the 16 subjects with patent infections, 14 had suffered a moderate or severe reaction at the injection site.

In District 2 relatively few falciparum infections were discovered prior to treatment and no falciparum infections were found among treated subjects up to 7 months after treatment. The first patent vivax infection in treated individuals was found 3 months and 7 days after treatment. Subjects who developed patent parasitemia after medication experienced no reactions at the site of injection.

Prior to mass drug administration, 26 subjects with patent parasitemia had been treated for 5 days with a daily dose of 300 mg of
chloroguanide in adults (proportionately less in children). In 23 subjects with vivax infections, 10 still showed an occasional trophozoite 5 days after commencement of treatment but trophozoites were not seen in any subjects 12 days after commencement of therapy. Three subjects with falciparum infections showed no trophozoites 5 or 12 days after commencement of treatment.

Brief review of findings

The value of the long-acting antimalarial drug, cycloguanil pamoate (Camolar) has been assessed in 21 field studies. Six studies were designed to determine the tolerance shown towards the drug by individuals of various ethnic groups whereas the primary objective of the 15 other studies was an evaluation of this drug as an antimalarial agent. In addition, a large-scale field project was commenced in 1967 in the Republic of Guatemala to evaluate the antimalarial potential of this drug in problem areas of some malaria eradication programs in Central America.

Tolerance studies in the field showed no significant systemic or teratogenic effects attributable to the drug. Local reactions at the site of injection were usually mild and transitory in nature. However, in most studies, a number of subjects (usually less than 2 percent), had severe reactions which, characteristically prevented them from pursuing
their normal activities for a few days. However, inspite of these local reactions, some investigators reported that the popularity of the drug did not wane but, on the contrary, that it improved.

Although the average number of persons infected in one day by a medicator in the Guatemalan project is rather low, a preliminary assessment indicates that the use of Camolar is operationally feasible, it is more economical, and it is more popular among inhabitants of the area than the oral administration of drugs at intervals of two or three weeks. In geographic regions where people live in village communities it may be anticipated that the administration of a long-acting repository drug would be cheaper and present fewer problems.

Cycloguanil pamoate exerts an anti-plasmodial activity upon the asexual erythrocytic forms of all four species of human malaria and upon primary tissue schizonts of \textit{P. falciparum}. It does not seem to exert any effects against secondary tissue schizonts of \textit{P. vivax}. Although the drug seems to possess no gametocytocidal activity against \textit{P. falciparum}, observations regarding any sporontocidal effects in chlorguanide-sensitive strains of malaria have not been made.

After the first administration of Camolar, a marked blood schizontocidal activity was apparent within 48 hours of medication and, in 768 subjects with patent infections before treatment, only four subjects with low-grade asexual parasitemia were found 7 to 15 days after medication.
Some of these observations were conducted in areas where strains with a decreased sensitivity to chlorguanide-like drugs were prevalent.

In contrast, the duration of the antimalarial activity of the drug varied markedly from one study to another (Table I), and a relatively short duration of protection was not always associated with a decreased sensitivity of the parasites to chlorguanide-like drugs (Table II). In comparing the findings of the various field studies, the reappearance of asexual erythrocytic forms of *P. vivax* after drug administration seemed to follow a more consistent pattern than that observed with *P. falciparum* parasites. A marked degree of protection against patent infections of *P. vivax* was usually evident for 3 to 5 months, and many individuals were protected for 6 months or longer. Protection against patent infections with *P. falciparum* was more variable. In two studies, no patent infections were seen for 5 months after medication whereas in other studies, usually associated with a decreased sensitivity of parasites to chlorguanide-like drugs, protection conferred upon most subjects was limited to 2 or 3 months. The administration of a single oral dose of a 4-aminoquinoline, in conjunction with the cycloguanil, seemed to extend the duration of protection for a few weeks in some studies, but apparently did not achieve this to any extent in other studies. Protection of individuals against *P. malariae* infections seemed to be longer than that against the other two species.
Obviously, the value of cyloguanil pamoate in malaria eradication programs will be intimately related to the problem of resistance of malaria parasites to antimalarial drugs. Clinical studies with three chloroquine-resistant (and chlorguanide-resistant) strains of *P. falciparum* have shown that Camolar exerted no useful causal prophylactic, blood schizontocidal or sporontocidal effects against these strains. Therefore, it seems unlikely that Camolar would be of value if it were used in endemic areas where such strains are prevalent.

Many field studies with Camolar were conducted in areas where an increased tolerance to chlorguanide, but not to chloroquine, was established either before or after use of the cycloguanil. The origin of such strains found after the administration of Camolar is obscure at present. They may have emerged because of the sustained pressure of Camolar against more sensitive strains, but, whatever the mechanism may have been, parasites with a decreased sensitivity to chlorguanide-like drugs became apparent in a number of studies. On the other hand, Camolar had a marked and prolonged effect against parasites of all species of human malaria in a number of field studies and, employed judiciously, it may serve as a very useful adjunct in some malaria eradication programs.
BIBLIOGRAPHY


cycloguanil pamoate (CI-501) by falciparum malaria in West Pakistan.

an experimental investigation undertaken by the L.H.Q. Medical Research
Unit (A.I.F.), Cairns, Australia. _Trans. roy. Soc. trop. Med. Hyg._ 40:
105-162, 1946.

school children of the repository antimalarial properties of cycloguanil
pamoate, 4,4'-diacetyldiaminodiphenylsulfone, and a combination of

pamoate (CI-501) as a causal prophylactic against a Southern Rhodesian

guanil pamoate in the treatment and suppression of malaria in the

Carson, and R.D. Powell. Studi clinici sul _Plasmodium falciparum_

a la pyrimethamine, au proguanil et au CI-501 dans la région des Niayes


## TABLE 1.
Antimalarial effects of cycloguanil pamoate (Camolar®) in field studies

<table>
<thead>
<tr>
<th>Geographic Location</th>
<th>Investigators</th>
<th>No. of subjects</th>
<th>Dose of Camolar (base)</th>
<th>4-aminoquinoline treatment</th>
<th>Percent of subjects with asexual parasites before treatment ( f, v, o, m )</th>
<th>Percent of subjects showing first appearance of parasitemia after treatment ( f, v, o, m )</th>
<th>Percent of subjects showing first appearance of parasitemia after treatment ( f, v, o, m )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gambia (1)</td>
<td>McGregor et al.</td>
<td>79</td>
<td>45</td>
<td>124</td>
<td>4-15 mg/kg</td>
<td>CONTROL</td>
<td>No</td>
</tr>
<tr>
<td>Gambia (2)</td>
<td></td>
<td>76</td>
<td>45</td>
<td>121</td>
<td>CONTROL</td>
<td>No</td>
<td>61.1</td>
</tr>
<tr>
<td>New Guinea (1)</td>
<td>Black et al.</td>
<td>229</td>
<td>212</td>
<td>441</td>
<td>5-6 mg/kg</td>
<td>CONTROL</td>
<td>No</td>
</tr>
<tr>
<td>New Guinea (Tolotwa) (2)</td>
<td>Rieckmann</td>
<td>109</td>
<td>64</td>
<td>173</td>
<td>9-11 mg/kg</td>
<td>Yes</td>
<td>23.7</td>
</tr>
<tr>
<td>New Guinea (Utuan) (3)</td>
<td>Rieckmann</td>
<td>61</td>
<td>80</td>
<td>141</td>
<td>CONTROL</td>
<td>No</td>
<td>20.3</td>
</tr>
<tr>
<td>Nigeria (4)</td>
<td></td>
<td>0</td>
<td>32</td>
<td>32</td>
<td>CONTROL</td>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td>Senegal (1)</td>
<td></td>
<td>179</td>
<td>225</td>
<td>404</td>
<td>4-6 mg/kg</td>
<td>No</td>
<td>Mainly ( f )</td>
</tr>
<tr>
<td>Senegal (2)</td>
<td></td>
<td>48</td>
<td>40</td>
<td>88</td>
<td>9-12 mg/kg</td>
<td>No</td>
<td>Mainly ( f )</td>
</tr>
<tr>
<td>Tanzania (1)</td>
<td>Clyde</td>
<td>47</td>
<td>16</td>
<td>63</td>
<td>5-12 mg/kg</td>
<td>CONTROL</td>
<td>No</td>
</tr>
<tr>
<td>Tanzania (2)</td>
<td>Clyde and Avery Jones</td>
<td>159</td>
<td>103</td>
<td>262</td>
<td>9-14 mg/kg</td>
<td>No</td>
<td>48.5</td>
</tr>
<tr>
<td>Tanzania (3)</td>
<td>Laing et al.</td>
<td>60</td>
<td>0</td>
<td>60</td>
<td>8-15 mg/kg</td>
<td>No</td>
<td>55.3</td>
</tr>
<tr>
<td>West Pakistan (Kangahai) (1)</td>
<td>Contacos et al.</td>
<td>31</td>
<td>9</td>
<td>40</td>
<td>5 mg/kg approx.</td>
<td>No</td>
<td>40.0</td>
</tr>
<tr>
<td>West Pakistan (Kangahai) (2)</td>
<td></td>
<td>196</td>
<td>202</td>
<td>398</td>
<td>10 mg/kg approx.</td>
<td>CONTROL</td>
<td>No</td>
</tr>
<tr>
<td>West Pakistan (Khanayn) (3)</td>
<td></td>
<td>145</td>
<td>360</td>
<td>595</td>
<td>CONTROL</td>
<td>No</td>
<td>15.6</td>
</tr>
</tbody>
</table>

*Compiled from the published reports of authors (see References) and data supplied by the Research Division, Parke, Davis and Company.

\( f = P. falciparum; \) \( v = P. vivax; \) \( o = P. ovale; \) \( m = P. malariae \)

Parasitemia or parasitemia refer to asexual erythrocytic forms only. Percentages refer to percent of subjects with \( P. falciparum \) parasites only, except where another species is indicated. If the percentage comprises more than one species, the number of blood films positive for each species is shown below the percent of subjects with parasitemia.

Dose of Camolar in adults (A) = 350 mg base, unless indicated otherwise; dosage range in children as shown.

Whenever administered, dose of 4-aminoquinoline in adults = 660 mg base; proportionately less in children.
### TABLE II.

Response of asexual erythrocytic parasites to chlorguanide, pyrimethamine and second doses of Camolar

<table>
<thead>
<tr>
<th>Field Trial</th>
<th>Time of tests in relation to treatment with Camolar</th>
<th>Species of malaria</th>
<th>No. of subjects with infection</th>
<th>Drug administered</th>
<th>Dose of drug (adult equivalent)</th>
<th>Duration of treatment (days)</th>
<th>Parasitemia following onset of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gambia (1)</strong></td>
<td>After: 1-4 mo.</td>
<td>f</td>
<td>28</td>
<td>Chlorguanide</td>
<td>300 mg</td>
<td>1</td>
<td>0/28</td>
</tr>
<tr>
<td></td>
<td>After: &gt;4 mo.</td>
<td>f</td>
<td>42</td>
<td>Pyrimethamine</td>
<td>25 mg</td>
<td>1</td>
<td>0/42</td>
</tr>
<tr>
<td></td>
<td></td>
<td>f</td>
<td>72</td>
<td>Camolar</td>
<td>350 mg</td>
<td>1</td>
<td>0/72</td>
</tr>
<tr>
<td><strong>New Guinea (1)</strong></td>
<td>After: 1-4 mo.</td>
<td>v</td>
<td>1</td>
<td>Chlorguanide</td>
<td>150 mg</td>
<td>2</td>
<td>1/1</td>
</tr>
<tr>
<td></td>
<td>After: &gt;4 mo.</td>
<td>f</td>
<td>8</td>
<td>Chlorguanide</td>
<td>600 mg</td>
<td>5</td>
<td>8/8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>f</td>
<td>49</td>
<td>Camolar</td>
<td>350 mg</td>
<td>1</td>
<td>39/49</td>
</tr>
<tr>
<td></td>
<td></td>
<td>f</td>
<td>55</td>
<td>Camolar</td>
<td>350 mg</td>
<td>1</td>
<td>34/55</td>
</tr>
<tr>
<td><strong>New Guinea (2)</strong></td>
<td>Before</td>
<td>f</td>
<td>19</td>
<td>Chlorguanide</td>
<td>300 mg</td>
<td>1</td>
<td>0/19</td>
</tr>
<tr>
<td></td>
<td>After: 2-5 mo.</td>
<td>v</td>
<td>5</td>
<td>Chlorguanide</td>
<td>300 mg</td>
<td>1</td>
<td>0/5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>f</td>
<td>10</td>
<td>Chlorguanide</td>
<td>600 mg</td>
<td>1</td>
<td>0/10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>f</td>
<td>9</td>
<td>Chlorguanide</td>
<td>600 mg</td>
<td>1</td>
<td>0/9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>f</td>
<td>5</td>
<td>Chlorguanide</td>
<td>300 mg</td>
<td>7</td>
<td>1/5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>v</td>
<td>1</td>
<td>Chlorguanide</td>
<td>600 mg</td>
<td>7</td>
<td>0/1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>f</td>
<td>2</td>
<td>Pyrimethamine</td>
<td>75 mg</td>
<td>1</td>
<td>1/2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>f</td>
<td>11</td>
<td>Camolar</td>
<td>350 mg</td>
<td>1</td>
<td>0/11</td>
</tr>
<tr>
<td><strong>Senegal (1)</strong></td>
<td>After: 2 mo.</td>
<td>f</td>
<td>11</td>
<td>Chlorguanide</td>
<td>100 mg</td>
<td>7</td>
<td>5/10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>m</td>
<td>5</td>
<td>Chlorguanide</td>
<td>100 mg</td>
<td>7</td>
<td>2/5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>f</td>
<td>7</td>
<td>Pyrimethamine</td>
<td>50 mg</td>
<td>1</td>
<td>1/6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>f</td>
<td>11</td>
<td>Pyrimethamine</td>
<td>50 mg</td>
<td>2</td>
<td>8/9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>f</td>
<td>7</td>
<td>Camolar</td>
<td>350 mg</td>
<td>1</td>
<td>6/7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>m</td>
<td>1</td>
<td>Camolar</td>
<td>350 mg</td>
<td>1</td>
<td>1/1</td>
</tr>
<tr>
<td><strong>Tanzania (2)</strong></td>
<td>Before</td>
<td>f</td>
<td>12</td>
<td>Chlorguanide</td>
<td>600 mg</td>
<td>1</td>
<td>8/12</td>
</tr>
<tr>
<td></td>
<td>After: 2 mo.</td>
<td>f</td>
<td>5</td>
<td>Camolar</td>
<td>350 mg</td>
<td>1</td>
<td>3/5</td>
</tr>
<tr>
<td><strong>West Pakistan (1)</strong></td>
<td>After: 6 weeks</td>
<td>f</td>
<td>2</td>
<td>Chlorguanide</td>
<td>300 mg</td>
<td>5</td>
<td>0/2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>f</td>
<td>1</td>
<td>Pyrimethamine</td>
<td>50 mg</td>
<td>1</td>
<td>1/1</td>
</tr>
<tr>
<td><strong>West Pakistan (2 &amp; 3)</strong></td>
<td>After: 1-4 mo.</td>
<td>f</td>
<td>3</td>
<td>Chlorguanide</td>
<td>75 mg</td>
<td>10</td>
<td>Clearance of parasitemia was achieved</td>
</tr>
<tr>
<td></td>
<td>After: 10 mo.</td>
<td>v</td>
<td>3</td>
<td>Camolar</td>
<td>350 mg</td>
<td>1</td>
<td>0/1</td>
</tr>
</tbody>
</table>

f = P. falciparum; v = P. vivax; m = P. malariae

* A number of tests showed no resistance of parasites to chlorguanide or pyrimethamine.
TABLE III.
Parasitologic findings before and after a single administration of Camolar and a 4-aminoquinoline in the Guatemalan field study

<table>
<thead>
<tr>
<th>District number</th>
<th>Collection of blood films</th>
<th>Time of survey</th>
<th>No. exam.</th>
<th>Percent subjects with asexual parasites</th>
<th>No. of subjects with asexual parasites</th>
<th>No. of treated subjects with asexual parasites</th>
<th>Epidemiologic investigation of positive cases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>P. falc.</td>
<td>P. vivax</td>
<td>P. falc.</td>
</tr>
<tr>
<td>1</td>
<td>Mass survey</td>
<td>Pre-therapy (May - June)</td>
<td>4900</td>
<td>4.5</td>
<td>86</td>
<td>139</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Post-therapy July</td>
<td></td>
<td>2</td>
<td>7</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>August</td>
<td></td>
<td>0</td>
<td>8</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>September</td>
<td></td>
<td>1</td>
<td>18</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>October</td>
<td></td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>Mass survey</td>
<td>(July - Oct.)</td>
<td></td>
<td>476</td>
<td>8.0</td>
<td>3</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Post-therapy (Oct. - Nov.)</td>
<td>3299</td>
<td>0.6</td>
<td>9</td>
<td>12</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>Surveillance</td>
<td>Pre-therapy (July - Aug.)</td>
<td>1022</td>
<td>12.8</td>
<td>18</td>
<td>113</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Post-therapy (Sept. - Jan.)</td>
<td>565</td>
<td>3.9</td>
<td>3</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Post-therapy (Jan. - Mar.)</td>
<td>236</td>
<td>3.8</td>
<td>0</td>
<td>9</td>
<td>0</td>
</tr>
</tbody>
</table>