A large number of piperidyl quinolinemethanols were investigated for antimalarial activity in avian infections because of close chemical similarity to quinine, as part of the wartime search for new and more effective antimalarial agents. In preliminary observations, SN-10,275,\(^2\) or 6,8-dichloro-2-phenyl-α-2-piperidyl-4-quinolinemethanol (Figure 1), gave greatest indication of promise. It is a compound of the Ainley-King series, which has a high degree of antimalarial activity in catemhemerium and lofphurae malaria in the duck and moderate activity in gallinaceum and lophurae malaria in the chick (1).

**PROCEDURES AND METHODS**

*General.* Details of the general procedure and the plan of observations are reported elsewhere (2). Healthy Caucasian volunteers\(^4\) at Stateville Penitentiary were infected with Southwest Pacific vivax malaria (Chesson strain) (3) by the bites of infected *Anopheles quadrimaculatus* mosquitoes. This strain is characterized by a high relapse rate when treated with non-curative drugs such as quinine and quinacrine (atabrine), by a short period of latency between successive attacks, and by almost complete absence of delayed primary attacks. In the tests for prophylaxis, three test subjects and three controls were inoculated by bites from the same group of mosquitoes. In the tests for therapeutic activity, five similarly inoculated volunteers undergoing primary attacks or second relapses were treated soon after the appearance of parasitemia.

\[\text{FIG. 1. STRUCTURAL FORMULA OF SN-10,275}\]

*Selection of patients.* When a series of attacks of (Chesson) malaria, as observed under these standardized conditions, was divided (4) into two groups according to the length of the prepatent and preceding latent periods, there was a significant difference in relapse rate between the groups after treatment with suppressive drugs. The group with short intervals showed a relapse rate of 98 per cent, whereas the group with the longer intervals had a rate of 67 per cent.

In the therapeutic tests, SN-10,275 was administered to two individuals whose attacks belonged to the first group and, therefore, constituted a severe therapeutic

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\(^1\) 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 Antimalaria1s 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.

The authors express their thanks to the Malaria Study Section of the National Institute of Health for editorial assistance and for arrangements in regard to the publication of this paper. They are also grateful to the Abbott Laboratories, E. I. du Pont de Nemours and Company, Inc., E. R. Squibb and Sons, Eli Lilly and Company, Sharp and Dohme, Inc., and Wyeth, Inc., for contributing toward the publication costs.

\(^2\) Formerly Captain, M.C., A.U.S.

\(^3\) Developed by Buchman and Koepfli and collaborators at the California Institute of Technology.

\(^4\) The observations reported in this paper would not have been possible except for the enthusiastic cooperation of the inmates and administrative officers at Stateville Penitentiary.
challenge. It was also tested against three attacks which fell into the group offering a milder challenge.

Drug administration. One gram of SN-10,275 mono-
hydrochloride (equivalent to 0.859 gram of base) per day was administered in four to six divided doses. The sub-
jects in the prophylactic test received drug on the day
before, the day of, and for six days after inoculation. The therapeutic trial was conducted at the same daily
dosage but consisted of a 14-day course of treatment.

Determination of drug in the plasma. Whole oxalated
blood was centrifuged for 15 minutes at 2,000 r.p.m.; the plasma was separated and re-centrifuged for 60 minutes
at the same speed to insure complete removal of the
components of the buffy coat.

SN-10,275 was analyzed by the method of Butler (5)
modified as follows: Five ml. of 0.2 M Na2HPO4 and 1
ml. of non-fluorescent absolute alcohol were placed in a
50-ml. glass stoppered centrifuge tube. Two or 3 ml. of plasma were added to the mixture followed by 15 ml. of
purified non-fluorescent benzene. The mixture was shaken
for 15 minutes, centrifuged and the water layer aspirated.
The benzene phase was decanted into 8 ml. of 10 per cent
NaOH and shaken for five minutes. After centrifugation
and aspiration of the alkali layer, exactly 10 ml. of the
benzene layer were transferred to a 50-ml. glass stoppered
centrifuge tube containing 10 ml. of 10 N H2SO4. After
the mixture was shaken for 15 minutes, centrifuged, and the benzene layer aspirated, the acid layer was transferred
to cuvettes. The fluorescence was read in a Coleman
12 A photofluorometer with B-1-S and PC-1 filters.

Recoveries and standards were run simultaneously with
the unknown.

RESULTS

Prophylactic effect. The results are sum-
marized in Table I. All three patients developed
parasitemia and fever. However, the prepatent
periods in the test group were six to nine times
as long as those in the control group. The plasma
concentrations at approximately the time of ap-
pearance of parasitemia ranged from 66 gamma
per liter to 110 gamma per liter.

Therapeutic effect. The results are summarized
in Table II. The two cases that presented a severe
therapeutic challenge relapsed. Of the three cases
that offered only a moderate challenge, one re-
lapsed. The others have been followed for over a
year. Drug disappeared from their blood plasma
108 and 135 days after end of therapy.

Following treatment with SN-10,275, the latent
periods of those individuals who relapsed were
296, 107 and 99 days. The median latent period
observed with quinine and quinacrine in the
Chesson strain of malaria under the conditions of
this investigation, is 15 and 34 days, respectively
(6). The plasma concentration of SN-10,275 at
approximately the time of appearance of para-
sitemia ranged from 59 to 80 gamma per liter.

Concentration of SN-10,275 in the plasma.
SN-10,275 remained in the plasma for long peri-
dods after medication had been discontinued. The
falling curves of plasma concentration are shown
for eight subjects in Figure 2. There was a wide
variation in rate of fall from individual to indi-
vidual. One subject differed markedly from the
remainder of the group in that the drug persisted

TABLE I

<table>
<thead>
<tr>
<th>Patient</th>
<th>Dose (base)</th>
<th>Mean plasma concentration during therapy</th>
<th>Prepatent period (parasitemia)</th>
<th>Plasma concentration at time of clinical attack</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Daily</td>
<td>Total</td>
<td></td>
<td></td>
</tr>
<tr>
<td>grams</td>
<td>grams</td>
<td>gamma per liter</td>
<td>days</td>
<td>gamma per liter</td>
</tr>
<tr>
<td>1</td>
<td>0.859</td>
<td>7.0</td>
<td>680</td>
<td>66</td>
</tr>
<tr>
<td>2</td>
<td>0.859</td>
<td>7.0</td>
<td>860</td>
<td>97</td>
</tr>
<tr>
<td>3</td>
<td>0.859</td>
<td>7.0</td>
<td>530</td>
<td>74</td>
</tr>
</tbody>
</table>

Three controls 12,13,12

TABLE II

<table>
<thead>
<tr>
<th>Patient</th>
<th>Dose (base)</th>
<th>Mean plasma concentration during therapy</th>
<th>Type of therapeutic challenge</th>
<th>Latent period (parasitemia)</th>
<th>Plasma concentration at time of relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Daily</td>
<td>Total</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>grams</td>
<td>grams</td>
<td>gamma per liter</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.859</td>
<td>12.0</td>
<td>1,200</td>
<td>Moderate</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>0.859</td>
<td>12.0</td>
<td>550</td>
<td>Moderate</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>0.859</td>
<td>12.0</td>
<td>1,500</td>
<td>Moderate</td>
<td>296</td>
</tr>
<tr>
<td>4</td>
<td>0.859</td>
<td>12.0</td>
<td>1,400</td>
<td>Severe</td>
<td>99</td>
</tr>
<tr>
<td>5</td>
<td>0.859</td>
<td>12.0</td>
<td>1,200</td>
<td>Severe</td>
<td>107</td>
</tr>
</tbody>
</table>

Length of observation since end of therapy in negative cases
FIG. 2. Concentration of SN-10,275 in the Plasma of Eight Individuals after Oral Administration was Discontinued

FIG. 3. Rate of Disappearance from the Plasma of Quinine, Chloroquine, Quinacrine (Atabrine), and SN-10,275

Schematic representation in terms of per cent of initial plasma concentration. Curve for SN-10,275 plotted on basis of loss of 20 per cent per week as derived from curves presented in Figure 1. Curves for quinacrine and chloroquine plotted on basis of losses of 50 per cent per week (7) and 60 per cent per week (8), respectively.
in his plasma more than twice the average time. The concentration of the drug in plasma decreased with time in approximately exponential fashion, the mean loss for the majority of the group being approximately 20 per cent per week. This is a much lower rate of disappearance than that shown by quinine and quinacrine (atabrine). Figure 3 illustrates schematically the comparative rates of decrease of plasma concentration of quinine, quinacrine, SN-10,275 and also that of the recently developed antimalarial, chloroquine (6, 8).

Toxicity. Eight patients received SN-10,275 at a dosage of 1.0 gram of the salt per day. One patient experienced mild gastrointestinal symptoms consisting of cramps, nausea and mild diarrhea during treatment. Another individual had fever of 102° F., headache, and backache towards the end of the 14-day course of therapy. Physical examination and laboratory studies gave negative results or normal values. The fever persisted for about 12 hours. Three doses of the drug were omitted, but since the entire episode appeared innocuous, therapy was resumed with no untoward effects.

All eight patients manifested photosensitivity of the skin. This varied from a slight tingling of the facial skin to severe burning sensations in the same area accompanied by erythema. One individual had some desquamation of the skin of the nose, and another had mild labial edema. These symptoms appeared only after exposure to sunlight for periods of 15 minutes or more. With the exception of one individual who still had symptoms and detectable concentration of drug in the plasma ten months after he received SN-10,275, this sensitivity to sunlight persisted for one-half to four months, gradually diminishing in intensity. Two subjects manifested increased irritability of the skin when subjected to mild mechanical trauma such as shaving or rubbing. Another patient noted smarting and burning of the eyes after exposure to sunlight. As shown in Table III, the severity and duration of these symptoms are roughly correlated with the mean concentration of SN-10,275 in the plasma during therapy. Abnormal amounts of porphyrins could not be detected in the urine of three patients.

**SUMMARY AND CONCLUSION**

In the prophylactic tests, SN-10,275 did not prevent the development of malaria. Parasitemia appeared when the plasma concentrations had fallen to 66–110 gamma per liter. This required 66 to 97 days, a period six to nine times as long as the usual prepatent interval in controls.

In the therapeutic tests against attacks presenting a mild therapeutic challenge, one out of three patients underwent further relapse. This occurred when the plasma concentration had fallen to 64 gamma per liter, 296 days after termination of treatment with SN-10,275. In the tests against the two attacks offering a severe therapeutic challenge, both patients suffered further relapse. Parasitemia appeared when the plasma drug levels fell to 59 and 80 gamma per liter, requiring 99 and 107 days, respectively.

The observed prolongation of the prepatent and latent periods may be attributed to the persistence

### TABLE III

<table>
<thead>
<tr>
<th>Patient</th>
<th>Mean plasma concentration (gamma per liter)</th>
<th>Facial tingling</th>
<th>Facial erythema</th>
<th>Facial edema</th>
<th>Duration (months)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1,500</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
<td>10</td>
<td>Hyperirritability of skin on mechanical trauma.</td>
</tr>
<tr>
<td>2</td>
<td>1,400</td>
<td>+++</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>Slight hyperirritability of skin on mechanical trauma. Mild photophobia.</td>
</tr>
<tr>
<td>3</td>
<td>1,200</td>
<td>+++</td>
<td>+++</td>
<td>0</td>
<td>2</td>
<td>Desquamation of nasal skin following sun burn on one occasion.</td>
</tr>
<tr>
<td>4</td>
<td>1,200</td>
<td>++</td>
<td>+</td>
<td>0</td>
<td>§</td>
<td>Headache, backache, and fever during drug administration.</td>
</tr>
<tr>
<td>5</td>
<td>860</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>1½</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>680</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>1½</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>550</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>1½</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>530</td>
<td>+++</td>
<td>+++</td>
<td>0</td>
<td>1½</td>
<td>Fair complexion.</td>
</tr>
</tbody>
</table>

**Clinical toxicity of SN-10,275 in eight volunteers**
in the body fluids of SN–10,275 for long periods of time. Butler (9) has shown that the drug is almost entirely in undegraded form. The concentration of drug in the plasma at the time that parasitemia became patent was of the same order of magnitude in all patients studied. One individual showed a latent period after treatment three times that of the others. However, in this individual the rate of loss of drug was much lower, so that at the time of relapse, his plasma concentration was within the range observed in the other patients.

Similarly, the same individual showed persistence of photosensitivity far longer than the remainder of the group. The degree of tingling of the skin showed a positive correlation with the initial plasma concentration achieved, and the duration of this symptom was roughly proportional to the rate of loss of drug from the plasma.

The toxic manifestations and the variation in rate of disappearance from the body of SN–10,275 limit the value of the drug as a suppressive agent. However, further investigation of constitutionally related compounds is indicated because a non-toxic drug which retained the antimalarial activity of SN–10,275 and remained in the body for long periods of time, would have great value in the chronic suppression of malaria.

BIBLIOGRAPHY


\footnote{It is of interest to note that quinine (10 to 12) and other cinchona alkaloids (13, 14) are degraded in the body by oxidation on the 2-position of the quinoline ring to form carboxystyrs. SN-10,275 has a phenyl group on the 2-position and this substitution may account for the apparent absence of degradation products in the plasma.}