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TREATMENT OF MALARIA WITH SMALL DAILY DOSES OF
CHLOROQUINE HYDROXYNAPHTHOATE OR TANNATE

by

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In medicated salt schemes the use of chloroquine diphosphate or sulfate has not been altogether satisfactory because of two problems: these soluble compounds tend to leach out of the mixture when it is stored under humid conditions, and their bitter taste becomes objectionable when their concentration exceeds 0.4% of the base.

On the other hand, chloroquine methylene-bis- β -hydroxynaphthoate does not tend to leach, and is tasteless, as is another compound, chloroquine tannate. Should these drugs prove as effective against malarial parasitaemia as are the diphosphate and the sulfate, they might be used to advantage in medicated salt.

Chloroquine hydroxynaphthoate, unfortunately, has been found to have a capricious antimalarial activity. Bruce-Chwatt & Charles (1957) reported from Nigeria that the compound was only one-quarter to one-fifth as active as chloroquine sulfate when compared as weight of base, and Clyde & Shute (1958), in the course of single-dose treatment of symptom-free trophozoite carriers, semi-immune African schoolchildren treated the previous year in Tanganyika, found that whereas a dose of 75 mg base of the diphosphate invariably cleared trophozoites of all species, as much as 450 mg base of the hydroxynaphthoate sometimes failed: no failure of absorption was observed in the initial trials of Fuhrmann & Koenig (1955). The failure among Africans seemed to be attributable to malabsorption related to hypochlorhydria. This matter was examined again by Clyde (1960) who concluded, from his finding of diminished chloroquine excretion in urine when gastric acidity had been neutralized, that absorption of chloroquine hydroxynaphthoate was proportional to the secretion of hydrochloric acid.

Chloroquine tannate, almost tasteless and therefore also of potential value for mixing with common salt, was tested among semi-immune trophozoite carriers in Tanganyika (Clyde, 1960). The results were more encouraging than with the hydroxynaphthoate: single doses of 75 mg base tannate were not always successful in clearing asexual parasitaemia (in contrast to the diphosphate), but a dose of 150 mg sufficed in all but one case out of 83 tested. It appeared that the absorption of chloroquine tannate did not depend to any marked extent on gastric acidity. Paulini & Pereira (1961) found that when daily doses of the naphthoate equivalent to 20 mg of chloroquine base-content were given to children for 21 consecutive days the average daily amounts of chloroquine excreted in urine were only slightly less than those observed with an equivalent dose of the diphosphate.

In view of these findings, it was thought that people with a low gastric acidity, unable to absorb large single doses of chloroquine hydroxynaphthoate, might nevertheless be able to absorb small amounts of the compound each day, and thus over several days accumulate enough of the drug for it to exert an anti-malarial effect. Although this would obviously have no place in the routine direct treatment of malaria, it might serve a useful purpose if administered in the form of medicated salt which is eaten in small quantities each day.

The suggestion has been assessed in semi-immune children aged 6-12 years, asymptomatic carriers of malaria attending schools in a district of malarial holoendemicity near Morogoro, Tanganyika. Chloroquine tannate has been tested similarly.

Chloroquine hydroxynaphthoate

Chloroquine hydroxynaphthoate was administered in tablet form under direct supervision in a dose each day of 19 or 38 mg base. One series was continued for five consecutive days, and another for seven treatment days (six consecutive, then a Sunday missed, then a final dose). No other treatment was given, nor were the children's diet or habits interfered with in any way. The results, shown in the table, were obtained from examination of thick blood films taken seven days after the final dose of chloroquine, this period having been found optimal in many previous drug trials in Tanganyika.

Chloroquine tannate

Chloroquine tannate was administered in tablet form under direct supervision in a dose each day of 19 or 38 mg base, the same regimen being followed as for the hydroxynaphthoate. The results are shown in the table.

TABLE
RESULTS OF DAILY ADMINISTRATION OF
CHLOROQUINE HYDROXYNAPHTHOATE AND TANNATE

Daily dose (mg)	Number of days dose was given	Number of infected cases treated	Number of asexual infections cleared	Percentage of cases cleared
<u>Hydroxynaphthoate</u>				
19	5	25	14	56.0
38	5	30	26	86.7
38	7	27	27	100.0
<u>Tannate</u>				
19	5	14	12	85.7
38	5	15	14	93.3
38	7	32	30	93.7

With both hydroxynaphthoate and tannate at the higher dosage the average densities of parasites in the surviving asexual infections were lower than before treatment. In all surviving infections the predominant parasite was Plasmodium falciparum, although two of the lower dosage hydroxynaphthoate films contained sparse P. vivax, as mixed infections. The few other cases of P. malariae and vivax were cleared.

DISCUSSION

For the medication of salt a concentration of at least 0.3% of chloroquine base in the form of easily soluble chloroquine compound, such as the diphosphate or sulfate, is generally recommended. Where the daily intake of salt is less than 10 grams (containing 30 mg base chloroquine if prepared in accordance with the recommendation), the proportion of drug must be increased in order to maintain a weekly consumption of at least 200 mg base. This is six times the suppressive dose given to semi-immunes in Tanganyika (75 mg once every two weeks), so that in East Africa at any rate there would seem to be an ample margin of effectiveness in the recommended dose.

Chloroquine hydroxynaphthoate, when given in this trial at approximately the recommended dose of 38 mg base daily for seven days, cleared asexual parasites in all the 27 cases treated. The cumulative quantity of 266 mg (38 mg x 7 days), effective in every case, is in striking contrast to the failure of massive single doses of up to 450 mg. It thus appears that the suggestion, that small daily doses of hydroxynaphthoate might be effective where large single doses have failed, is supported by the results of this trial.

Chloroquine tannate, on the contrary, proved less effective when given in small divided doses than in a single large dose. Of course, if the small doses were to be continued daily for two or more weeks (as they would in a medicated salt scheme), it is probable that enough drug would accumulate in the body to become effective.

SUMMARY

1. Large single doses of chloroquine hydroxynaphthoate equivalent to 450 mg of the base failed to clear asexual malarial parasitaemia in cases where 75 mg of chloroquine base, given in the form of the diphosphate or the sulfate, are generally successful. However small daily doses of the hydroxynaphthoate, corresponding to 38 mg of the base given for seven days (a total of 266 mg) were shown to be effective.
2. Similar small daily doses of chloroquine tannate proved less satisfactory.
3. This activity of small quantities of the tasteless chloroquine hydroxynaphthoate lends support to its use for the medication of common salt, which is eaten regularly in small amounts in the daily diet.

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