PROPHYLACTIC ACTIVITY OF MEFLOQUINE HYDROCHLORIDE (WR 142490) IN DRUG-RESISTANT MALARIA

by

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1. INTRODUCTION

Protection of persons against falciparum malaria may be difficult in areas where chloroquine-resistant strains are prevalent. Currently available drugs are often ineffective in preventing or suppressing malaria infections. Undesirable side-effects, the possible selection of resistant bacteria, and awkward medication schedules further limit the utilization and value of some drugs or drug combinations. During recent investigations with mefloquine (WR 142490), it was found that a single dose of the drug had a prolonged suppressive activity against a strain of Plasmodium falciparum with a pronounced resistance to chloroquine and pyrimethamine. Preliminary results obtained with this 4-quinolinemethanol compound are described in the present report.

2. METHODS

These studies involved the participation of 17 non-immune adult male volunteers according to previously established procedures (Rieckmann et al., 1972; Canfield & Rozman, 1974). They were divided into five groups. In each group one or two men received a single dose of

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7 Ethical and medical aspects of the study were performed according to established procedures of the Committee on Human Investigation. The purpose and procedures of the study were explained in detail to each volunteer and special emphasis was placed on the voluntary nature of his involvement. The volunteers were told that they could terminate their participation at any time during the course of the study.

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1 g of mefloquine hydrochloride \( \text{MR} 142490; \times(2\text{-piperidyl})\cdot 2, 8\text{-bis(trifluoromethyl)}\cdot 4\text{-quinolinemethanol} \)\(^1\) and one or two men served as control subjects and received no medication at that time.

Between two and 21 days after drug administration, participants were exposed to Anopheles stephensi mosquitoes infected with the drug-resistant Viet-Nam (Marks) strain of P. falciparum (Rieckmann, 1971). Although persons in different groups were bitten by a variable number of infected mosquitoes (five to 35), all individuals within a group were exposed to the same batch of mosquitoes and received a comparable inoculum of sporozoites.

Thick blood films from each individual were examined for at least 60 days after exposure to mosquitoes or until the onset of patent parasitaemia. Those who became infected either participated in other studies or were cured by administration of amodiaquine and tetracycline (Rieckmann et al., 1972).

3. RESULTS

Table 1 presents pertinent information concerning eight volunteers who received a single dose of mefloquine and nine volunteers who were given no medication at that time. The control subjects first showed parasites between nine and 14 days (mean = 11 days) after exposure to infected mosquitoes.

**TABLE 1. PROPHYLACTIC ACTIVITY OF A SINGLE DOSE OF 1 G OF MEFLOQUINE HYDROCHLORIDE AGAINST THE VIET-NAM (MARKS) STRAIN OF P. FALCIPARUM**

<table>
<thead>
<tr>
<th>Group</th>
<th>Volunteer</th>
<th>Weight (kg)</th>
<th>Interval between drug administration and sporozoite inoculation (days)</th>
<th>Day of patent after sporozoite inoculation</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>1 Control</td>
<td>56</td>
<td>-</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>62</td>
<td>14</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>78</td>
<td>14</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>66</td>
<td>-</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>74</td>
<td>-</td>
<td>11</td>
</tr>
<tr>
<td>II</td>
<td>4</td>
<td>79</td>
<td>14, 16</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>69</td>
<td>14, 16</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>86</td>
<td>-</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>92</td>
<td>-</td>
<td>14</td>
</tr>
<tr>
<td>III</td>
<td>6</td>
<td>73</td>
<td>21</td>
<td>34 (55)(^a)</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>86</td>
<td>21</td>
<td>17 (38)(^a)</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>65</td>
<td>-</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>59</td>
<td>-</td>
<td>12</td>
</tr>
<tr>
<td>IV</td>
<td>8</td>
<td>73</td>
<td>21</td>
<td>37 (58)(^a)</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>63</td>
<td>-</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>74</td>
<td>-</td>
<td>9</td>
</tr>
</tbody>
</table>

\(^a\) ( ) = Number of days between drug administration and onset of patent parasitaemia.

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\(^1\) 250 mg tablets of mefloquine hydrochloride were supplied by the Walter Reed Army Institute of Research, Washington, D.C., United States of America.
Volunteer 1, bitten two days after medication, did not develop patent parasitaemia. Volunteers 2, 3, 4 and 5, bitten 14 to 16 days after drug administration, were also protected.

In studies with volunteers 6, 7 and 8, bitten 21 days after medication, the drug suppressed parasitaemia in at least two, possibly three, of the individuals, but it did not prevent the development of patent infections. The interval between drug administration and appearance of parasites was 55, 38 and 58 days, respectively. Pre-patent periods in the three volunteers ranged from 17 to 37 days (mean = 29 days) and, in the four control volunteers, they ranged from nine to 12 days (mean = 10 days). After onset of patency, all three persons developed signs and symptoms of an acute attack of malaria.

4. DISCUSSION

In clinical studies conducted many years ago at the Malarial Research unit, University of Chicago, a 4-quinolinemethanol, SN 10275 \( \alpha-(2\text{-piperidyl})-6, 8\text{-dichloro}-2\text{-phenyl}4\text{-quinolinemethanol} \), was found to have a prolonged suppressive activity against asexual blood forms of P. vivax and a much slower rate of disappearance from plasma than chloroquine, mepracine or quinine. Unfortunately, phototoxic side-effects precluded its further use (Pullman et al., 1948).

Recently, as part of the present United States Army Malaria Research Programme, a related compound, WR 30090 \( \alpha-(\text{di-butyramino})\text{ methyl})-6,8\text{-dichloro}-2-(3', 4'-dichloro)\text{ phenyl}4\text{-quinolinemethanol} \), was studied at a number of different centres. No appreciable phototoxicity or other side-effects were observed and administration of this drug every eight hours for six days cured about 90\% of chloroquine-resistant infections (Martin et al., 1973; Canfield et al., 1973). Despite a rapid diminution in serum levels after administration of WR 30090 suppressive cures were recorded in 77\% of the volunteers who received the drug once a week for eight weeks (Clyde et al., 1973).

Pre-clinical investigations with other 4-quinolinemethanols indicated that mefloquine was more active than WR 30090 as an antimalarial agent. In our in vitro drug-screening system (Rieckmann, 1968), mefloquine was about 10 times more active than WR 30090 and equally effective against chloroquine-resistant and chloroquine-sensitive strains of P. falciparum (WHO Scientific Group, 1973). In the owl monkey system, Schmidt (1973; and in: WHO Scientific Group, 1973) found that this drug was far more active than WR 30090 and that a single dose cured infections with drug-resistant strains of P. falciparum.

On the basis of these findings, clinical studies were initiated to determine the safety and antimalarial efficacy of single doses of mefloquine. In non-immune patients infected with chloroquine-resistant strains of P. falciparum, administration of single, well-tolerated doses resulted in rapid clearance of fever and parasitaemia and in radical cure of their infections (Rieckmann et al., 1974). Serum samples obtained from these patients after drug administration were incubated with parasitized red cells from untreated individuals. Maturation of parasites was inhibited in cultures containing serum which had been collected up to 35 days after administration of mefloquine. These results suggested that, in addition to its therapeutic efficacy, the drug might have long-term suppressive activity against asexual blood forms of P. falciparum (Rieckmann, 1974).

5. CONCLUSION

The studies described in this report establish the prolonged suppressive activity of mefloquine against infections with the Viet-Nam (Marks) strain of P. falciparum. The results indicate that administration of the drug at relatively infrequent intervals, such as once a month, could protect individuals against drug-resistant malaria. The potential value of this drug as a prophylactic agent depends on the results of further studies to determine its effectiveness against other strains of P. falciparum and to establish its cumulative toxicity, if any, during repeated administration. Although no change in the drug-sensitivity of
parasites has been noted during clinical studies carried out so far, the possibility of the emergence of resistant strains should be borne in mind during further evaluation of this drug.

6. SUMMARY

Preliminary investigations with mefloquine (WR 142490) showed that a single dose exerted prolonged suppressive activity against a drug-resistant strain of *P. falciparum*. In the present studies development of patent parasitaemia was prevented when non-immune persons were exposed to infected mosquitoes two weeks after mefloquine medication and it was delayed when exposure occurred three weeks after drug administration.

RESUME

Les premières investigations concernant la méfloquine (WR 142490) ont montré qu'une dose unique de ce médicament exerçait une action suppressive prolongée contre une souche chimio-résistante de *Plasmodium falciparum*. Au cours des recherches décrites dans le présent rapport, on a observé qu'il n'apparaissait pas de parasitémie patente chez des sujets non-immuns exposés deux semaines après avoir pris de la méfloquine à des moustiques infectés par la souche Viet-Nam (Marks) de *P. falciparum* et que la parasitémie patente était retardée chez des sujets exposés trois semaines après administration du médicament. Ces résultats indiquent que l'administration de la méfloquine à intervalles relativement éloignés, par exemple une fois par mois, pourrait protéger contre le paludisme chimiorésistant. La valeur potentielle de la méfloquine comme agent prophylactique ne pourra être vraiment évaluée qu'après de nouvelles études visant à déterminer son efficacité contre d'autres souches de *P. falciparum* et à établir sa toxicité cumulative éventuelle à la suite de prises répétées. Bien qu'aucune modification de la sensibilité des parasites n'ait été notée lors des études cliniques faites jusqu'ici, il conviendra de garder toujours présente à l'esprit, au cours de l'évaluation de ce médicament, la possibilité de l'apparition de souches résistantes.
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