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Antimalarial aminoalcohol alternatives to mefloquine

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Introduction

Mefloquine is a new antimalarial drug presently undergoing extended field trials under the auspices of the World Health Organization. Developed by the U.S. Army, it has been shown to be remarkably effective against strains of *Plasmodium falciparum* malaria resistant to all known drugs, including quinine (Trenholme et al., 1975; Doberstyn et al., 1979). Structurally it is similar to quinine – it is a substituted 4-quinolinemethanol with an α -piperidyl side chain instead of a quinuclidine side chain. Unlike quinine the drug does not intercalate with bacterial DNA (Davidson et al., 1975).

The continued usefulness of any new antimalarial drug is a function of many factors. Two important biologic factors are lack of development of parasite resistance to the drug and lack of serious side effects. Thus far, there has been no evidence of resistance to the drug in human infections and no serious side effects have occurred. However, extensive studies in animals have shown that prolonged drug administration in certain species at high dose levels can be associated with toxicity (Rozman and Canfield, 1979). Whether this, or some rare form of toxicity not predicted by animal studies, will limit the usefulness of this drug in the future can only be conjectured. But, if this does occur, alternative drugs should be available. The purpose of this report is to review the status of development of several alternative drugs.

Materials and methods

The methods employed in the selection of antimalarial drugs for development have been recently reviewed (Canfield and Heiffer, 1978). Briefly, they involve the sequential testing of candidate drugs in a series of in vivo and in vitro test systems. In this manner a large number of active compounds has been effectively reduced and the most active compounds selected for safety testing in animals. This communication will present data for the best 2 candidate drugs in each of 3 classes of aminoalcohols: 4-quinolinemethanols, 9-phenanthrenemethanols, and 4-pyridinemethanols. The data on antimalarial activity are from 3 test systems: the *P. berghei*/mouse system (Osdene et

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al., 1967), the *P. falciparum*/Aotus monkey system of Schmidt (1978) and the *P. falciparum*/in vitro system (Desjardins et al., 1979). For the first 2 test systems CD₅₀'s were calculated from probit transformation of dose response curative data.

Tests for cross resistance with mefloquine were conducted in mice infected with a strain of *P. berghei* made resistant to mefloquine by serial passage in the presence of drug pressure, as previously described for chloroquine (Thompson et al., 1967). Doses of drug required to suppress parasitemia in these mice were compared with doses required to suppress parasitemia in mice infected with the parent strain and the results expressed as a ratio of the 2 doses.

The methods employed to determine estimates of the relative toxicity of the candidate drugs have also been recently reviewed (Canfield and Heiffer, 1978). Briefly, acute toxicity and 4-week subacute toxicity studies in animals were performed to predict safe doses in man and target organ toxicity. LD₅₀'s were calculated from probit transformed 7-day survival data. In the subacute studies toxic doses were defined as the lowest dose administered that produced any laboratory or clinical evidence of intolerance, including simple failure to gain weight normally. The safe dose was the next lower dose tested.

Results

Table 1 identifies the 6 aminoalcohols considered as alternatives to mefloquine. In the primary mouse test 4 of the drugs showed more activity than mefloquine, with WR 171,669 appearing to be the most active of these drugs against *P. berghei*. However, it was the least active in the Aotus monkey test system where WR 226,253 appeared to be not only the most active but also the

Table 1. Antimalarial efficacy of several aminoalcohols

Drug*	Primary mouse CD ₅₀ (mg/kg)	Aotus monkey CD ₅₀ (mg/kg)	In vitro ID ₅₀ ng/ml	Human curative dose (g/man)
WR 142,490	54.5	7.3	7.8	1.5
WR 122,455	30.4	16.7	1.8	1.4
WR 171,669	15.0	58.2	4.0	1.0
WR 184,806	298	38	7.7	—**
WR 226,253	167.0	5.3	1.0	—
WR 172,435	28.5	22.0	3.2	—
WR 180,409	50.0	18.6	48.5	—

* WR 142,490 (mefloquine) = dl-Erythro- α -(2-piperidyl)-2,8-bis(trifluoromethyl)-4-quinoline-methanol hydrochloride; WR 122,455 = 3,6-Bis(trifluoromethyl)- α -(2-piperidyl)-9-phenanthrenemethanol hydrochloride; WR 171,669 (halofantrine) = 1-(1,3-Dichloro-6-trifluoromethyl-9-phenanthryl)-3-di(*n*-butyl)aminopropanol hydrochloride; WR 184,806 = dl-2,8-Bis(trifluoromethyl)-4-[1-hydroxy-3-(*N*-*t*-butylamino)propyl]quinoline phosphate; WR 226,253 = Erythro- α -(2-piperidyl)-6,8-dichloro-2-trifluoromethyl-4-quinolinemethanol methanesulfonate hemihydrate; WR 172,435 = 3-Di-*n*-butylamino-1-[2,6-bis(4-trifluoromethylphenyl)-4-pyridyl]-propanol methanesulfonate; WR 180,409 = dl-Threo- α -(2-piperidyl)-2-trifluoromethyl-6-(4-trifluoromethylphenyl)-4-pyridinemethanol phosphate

** Studies not yet performed

Table 2. Relative toxicities of several aminoalcohols

Drug	Rat LD ₅₀ (mg/kg)		Subacute 28-day toxicity			
	Oral	IP	Rats (mg/kg/day)		Dogs (mg/kg/day)	
			Safe*	Toxic	Safe	Toxic
WR 142,490	880	130	12.5	30	5	30
WR 122,455	780	192	–**	2.5	–	20
WR 171,669	3400	2050	25	100	5	15
WR 184,806	2090	384	100	250	5	20
WR 226,253	1134	57.4	–	–	–	–
WR 172,435	2754	254	20	30	15	30
WR 180,409	518	–	20	30	30	45

* Safe – no toxicity of any kind noted; Toxic – minimal toxicity noted (e.g., vomiting, ↓ weight gain, etc.)

** Studies not performed

only compound more active than mefloquine. WR 226,253 was also the most active in vitro, but there were 4 other drugs that appeared more active than mefloquine. The 3 drugs listed that have had clinical trials against chloroquine-resistant *P. falciparum* in man show remarkably little difference in their minimum effective dose.

Tests for cross resistance in strains of *P. berghei* with induced resistance to mefloquine showed that all 6 compounds were strongly cross-resistant. Doses greater than 256 times the normally curative dose in non-resistant strains failed to cure infections in mice.

The toxicity data for the 6 potential drugs are shown in Table 2. In acute oral toxicity studies 4 drugs were less toxic than mefloquine. Three of these 4 also appeared to be less toxic than mefloquine when administered parenterally. Comparisons among the drugs in the subacute studies were more difficult because dose levels tested were frequently different. However, WR 122,455 appeared to be more toxic in both rats and dogs. The type of toxicity observed with all drugs varied in severity from simple failure to gain weight properly to lesions of the lymphoid tissues, lungs or liver at the highest doses.

Discussion

Since its development in the 1940's chloroquine has been successfully used by millions of human beings for prevention or treatment of all species of malaria. The remarkable success of this drug, however, has been somewhat marred by 2 factors, the first of which has been development of parasite resistance to chloroquine.

The requirement for larger doses of chloroquine for some strains of *P. falciparum* was recognized shortly after the introduction of the drug and this was considered to be a degree of drug resistance (Peters, 1970). In 1956 chloroquine resistance was produced against *P. gallinaceum* in chicks (Ray and Sharma, 1956) and 4 years later chloroquine resistance in *P. falciparum* was documented from South America. Since then it has been reported from many other areas and finally in 1979 it was reported from Africa (Kean, 1979).

Mefloquine is effective against all known strains of human plasmodia, including those resistant to chloroquine and/or quinine. However, as was reported for chloroquine, some strains of *P. falciparum* require a larger dose to cure than others. In addition, mefloquine resistance has already been produced in *P. berghei*-infected mice (Peters et al., 1977). It is therefore imperative to consider the possibility of mefloquine-resistant *P. falciparum* occurring in nature and limiting the usefulness of the drug.

Six aminoalcohols of diverse structure are presented in this report as potential alternatives to mefloquine. They exhibit variable degrees of activity against *P. berghei* and *P. falciparum* in animals. The 2 that have been tested against *P. falciparum* in man have curative doses similar to mefloquine. Based on available antimalarial activity data any of these 6 could be considered a suitable candidate replacement for mefloquine. However, tests against mefloquine-resistant *P. berghei* show that there is a large degree of cross resistance with mefloquine. Whether this model can be considered predictive for falciparum malaria or not can be debated. But, there is no evidence at present to suggest that the alternative drugs would have any advantage against naturally occurring mefloquine-resistant *P. falciparum* and thus the search for new drugs effective against such potential strains must continue.

The second factor that has somewhat marred the success of chloroquine has been the occurrence of serious side effects at high doses. These were not predicted by human tolerance studies. Short term studies of the tolerance of chloroquine in volunteers showed dizziness, pruritis, and blurred vision (Berliner et al., 1948). Longer term studies for one year showed headache, bleaching of the hair, electrocardiographic changes, weight loss, skin eruptions, and visual disturbances (Alving et al., 1948). The visual disturbances were characterized as difficulty in changing focus from near to a far object and subsequently have been reported as a reversible disturbance of the accommodative power of the eye (Bernstein, 1968). These tolerance studies did not predict the severe retinal damage seen with larger doses of chloroquine or the unusual occurrence of ototoxicity, psychosis, or seizures (Torrey, 1968).

The side effects found with single large doses of mefloquine were dizziness and nausea (Trenholme et al., 1975). These symptoms were minimal at the lower doses used for treatment of acute infections. Repeated administration in a 6-month suppressive prophylactic field study was not associated with any reported untoward effects (Pearlman et al., 1980), but more rigorously con-

trolled studies have not been reported. Whether mefloquine will or will not produce serious adverse effects similar to those seen with chloroquine cannot be predicted from the experience with the drug thus far.

Six drugs are discussed in the present report that might be suitable candidates for an alternative to mefloquine if serious toxicity is encountered. They are all aminoalcohols, but with significant ring and side chain differences. Mefloquine itself was developed by molecular modification of a phototoxic precursor, SN 10275. In this case trifluoromethyl substitution for phenyl on the quinoline ring eliminated this serious side effect and resulted in a compound devoid of phototoxicity. The 6 aminoalcohols represent a diversity of structures, all very active antimalarials. It is hoped that at least one of these could be rapidly produced and used if toxicity limited the use of mefloquine. It is unlikely any could be used if parasite resistance to mefloquine was the limiting factor.

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