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A Quinoline Methanol (WR 30090) for Treatment of Acute Malaria

D. C. MARTIN, J. D. ARNOLD, D. F. CLYDE, M. AL IBRAHIM, P. E. CARSON, K. H. RIECKMANN, AND D. WILLERSON, JR.

Harry S. Truman Research Laboratory, Kansas City, Missouri 64108, University of Maryland School of Medicine, Baltimore, Maryland 20201, and Laboratory for Tropical Diseases, Rush-Presbyterian-St. Luke's Medical Center, Chicago, Illinois 60612

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WR 30090 at a dose of 230 mg every 8 hr for 6 days has proven to be a safe, well-tolerated compound with photosensitivity proving to be a minor consideration. WR 30090 was found to be an effective medication for the treatment of acute malaria caused by several strains of *Plasmodium falciparum*. At the dose of 230 mg every 8 hr for 6 days, all of six men infected with a chloroquine-susceptible strain (Uganda I) were cured, all of 13 subjects infected with moderately chloroquine-resistant strains (Malayan Camp, Malayan Taylor, and Philippine Per) were cured, and 19 of 23 subjects infected with strains highly resistant to chloroquine (Vietnam Smith and Vietnam Crocker) were cured. All of five subjects infected with the chloroquine-resistant Vietnam Marks strain were cured with only 3 days of therapy. Blood-induced *P. vivax* (Chesson strain) infection showed a mixed response. Six out of seven volunteers were cured when treated for 3 days with WR 30090. The one recrudescence responded to a repeated course of therapy for 3 days. However, recrudescence occurred in one volunteer treated for 6 days. Treatment with WR 30090 failed to cure sporozoite-induced *P. vivax* (Chesson strain) infection in any of four subjects. In all subjects treated, there was good suppression of parasitemia and relief of symptoms. The susceptibility of the strains of malaria to WR 30090 to some degree parallels their susceptibility to chloroquine.

A group of quinoline methanols was studied extensively as antimalarial compounds during World War II (2). Compounds of this type were found to have strong schizontocidal action in animal malaria and human vivax malaria, but none of them appears to have been used to treat falciparum malaria.

These compounds possess other pharmacological features in addition to their action against malaria. The most unique is the capacity to induce photosensitivity in animals and man. In addition, this group of compounds has antiarrhythmic (6), antihypertensive (4), antiserotonin (5), and antibacterial action (8).

WR 30090 (Fig. 1) was not studied in man after its synthesis by Lutz (7). In the re-examination of this compound by the Walter Reed animal screening system, it was determined that WR 30090 had promising activity in mammalian malaria and a minimal capacity to produce photosensitivity (9). Its action in avian mlaria had been noted previously (G. R. Coatney et al., unpublished report NIH 2066).

In this study, WR 30090 was examined for its effect against a panel of strains of *Plasmodium falciparum* and *P. vivax* in human volunteers. It was necessary to use a number of strains of malaria because the therapeutic response to standard drugs such as chloroquine and pyrimethamine now varies widely throughout the world. The strains included in the panel were chosen because they seemed to represent the important variations in drug response at the time of this study.

Drug tolerance and safety were determined in a group of 39 normal volunteers. A total of 84 volunteers with experimental malaria and one patient with naturally acquired malaria were treated with WR 30090 to determine efficacy.

The chemical synthesis, drug formulation, animal therapeutic screening, animal toxicology, and pharmacology were carried out as part of the U.S. Army Malaria Research Program. These data were compiled and the drug was approved for human use by the Office of the Surgeon General and by the U.S. Food and Drug Administration.

MATERIALS AND METHODS

The methods employed have been previously described (1). In the phase I study of tolerance and toxicity, the graded increases in drug dosage

shown in Table 1 were tested in 39 subjects. The therapeutic effect of WR 30090 was assessed in 83 volunteers with induced malaria. The parasites employed were the Uganda I, Malayan Camp, Malayan Taylor, Philippine Per, Vietnam Smith, Vietnam Crocker, and Vietnam Marks strains of *P. falciparum*, and the Chesson strain of *P. vivax*. The anticipated responses of the *P. falciparum* strains to standard antimalarial agents are shown in Table 2.

The ethical aspects of these studies were supervised by independent institutional review committees. A careful medical history and physical examination for all volunteers preceded admission to the malaria research units. In addition, a careful explanation of the character and risks of WR 30090 and malaria was presented orally and in writing to each volunteer; all volunteers gave an informed consent. Routine medical laboratory work included the following determinations: hematocrit value, total white blood cell (WBC) count, differential white cell count, platelet count, blood glucose, blood urea nitrogen (BUN), alkaline phosphatase, serum glutamic oxaloacetic transaminase levels (SGOT), and urinalysis. Additional studies at admission included chest X rays, serology, blood typing, tuberculin skin test, and Australia antigen determinations.

RESULTS

Phase I: tolerance and toxicity. In our trials of WR 30090 in 39 normal subjects at the dosages shown in Table 1, phototoxicity, determined by the method of Ison and Blank (3), was observed in only four subjects at doses of 0.02, 0.03, 0.46, and 0.79 g. The phototoxicity was ephemeral and was not present when retested 24 hr after cessation of drug. There were no other subjective complaints or laboratory abnormalities attributable to the drug.

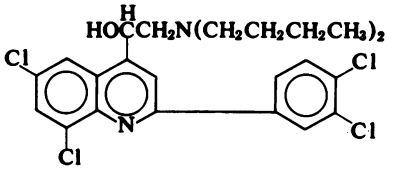

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FIG. 1. *Structural formula of WR 30090, 6,8-dichloro-2-(3', 4'-dichlorophenyl)-α-(di-n-butylaminoethyl)-4-quinolinemethanol hydrochloride.*

TABLE 1. *Phase I studies with WR 30090 in normal subjects*

No. of subjects	Total daily dose (g)	Divided dose (times/day)	No. of days
3	.005	1	3
2	.02	1	3
3	.03	1	3
3	.04	1	3
3	.08	1	3
3	.16	1	3
3	.26	1	3
3	.36	1	3
3	.46	1	3
3	.67	1	3
3	.80	1	3
1	.79	1	6
6	.69	3	6

TABLE 2. *Response[a] of various strains of P. falciparum malaria to standard antimalarial chemotherapy[b]*

Strain	Chloroquine	Pyrimethamine	Quinine
African			
Uganda I.	S	S	S
Philippine			
Per.....	R I	R I	S
Malayan			
Camp.....	R I–R II	R II	S
Taylor....	R I	R I	S–R I
Vietnam			
Marks....	R II	R III	R I
Smith.....	R III	R III	S–R III
Crocker...	R I	?	?

[a] Response: S, susceptible, radical cure; R I, resistant, asexual parasitemia is cleared but recrudesces; R II, resistant, parasite density is reduced but not cleared; R III, resistant, parasitemia not affected.

[b] The results were obtained with the following dosage schedules for the three drugs (all expressed as grams of base): chloroquine, 1.5 g over 3 days; pyrimethamine, 0.15 g over 3 days; quinine, 11.3 g over 7 days.

Phase II: therapeutics. Results of therapy with WR 30090 are shown in Tables 3 and 4. The best cure rate in our series occurred at a dose of 230 mg every 8 hr for 6 days. Treatment for 6 days was uniformly curative in six subjects infected with the Uganda I strain of *P. falciparum*, in six subjects infected with the Malayan Camp strain, in six subjects with the Malayan Taylor strain, and in one volunteer with the Philippine Per strain. The Smith and Crocker strains were not always susceptible, although 19 of 23 subjects were cured on the 6-day regimen.

An additional promising finding for this drug has been the results of retreatment of those volunteers who had recrudescences after primary therapy with WR 30090. Six men were retreated with the same or slightly higher doses of WR 30090, and all were cured. This does not prove that eventual resistance to the drug is unlikely, but it does indicate that resistant strains will not occur as rapidly as with some drugs (pyrimethamine, for example). Two recrudescent subjects encountered in the treatment of *P.*

TABLE 3. *Treatment of acute P. falciparum malaria with WR 30090*

Malaria strain and patient[a]	Total daily dose (g)	Divided doses (times/day)	No. of days	Parasite count	Days to recrudescence	Cure (days of follow-up)
African Uganda I						
Ric(J)	0.8	1	3	430	9	—
	0.8	1	3	600	—	92
Bal(J)	0.46	2	3	29,770	—	64
Wil(J)	0.46	2	3	2,120	23	—
	0.46	2	3	360	—	65
Woo(J)	0.69	3	3	160	—	65
War(J)	0.69	3	3	1,380	24	—
Ben(J)	0.69	3	3	2,660	—	63
Pag(J)	0.69	3	6	280	—	60
Tay(J)	0.69	3	6	160	—	60
Han(J)	0.69	3	6	730	—	60
Gar(J)	0.69	3	6	320	—	75
Mcn(J)	0.69	3	6	3,420	—	63
Spo(J)	0.69	3	6	1,530	—	64
Malayan Camp						
And(J)	0.8	2	3	1,780	—	79
Gar(J)	0.46	2	3	2,780	—	98
Jac(J)	0.46	2	3	200	—	70
Twi(J)	0.46	2	3	10,280	—	62
Bus(J)	0.4	2	3	9,790	—	67
Tin(J)	0.46	2	3	230	—	62
Fle(J)	0.46	2	3	9,310	25	—
	0.46	2	3	420	—	64
Chr(J)	0.69	3	3	310	—	60
Hol(J)	0.69	3	6	90	—	60
Mcn(J)	0.69	3	6	8,100	—	60
Wil(J)	0.69	3	6	1,510	—	60
Wil(J)	0.69	3	6	1,150	—	60
Mcd(J)	0.69	3	6	840	—	60
Rig(J)	0.69	3	6	600	—	60
Malayan Taylor						
Hob(M)	0.69	3	6	5,430	—	60
May(M)	0.69	3	6	2,200	—	60
Shi(M)	0.69	3	6	3,700	—	60
Mar(M)	0.69	3	6	20,520	—	57
Fre(M)	0.69	3	6	4,080	—	60
Coo(M)	0.69	3	6	63	—	60
Philippine Per						
Gre(M)	0.69	3	6	240	—	60
Vietnam Crocker						
Cro(J)	0.69	3	6	30,560	21	—
Joh(J)	0.69	3	6	1,230	—	61
Nol(J)	0.69	3	6	1,200	—	72
Vietnam Marks						
Mcn(S)	0.69	3	3	18,570	—	60
Haw(S)	0.69	3	3	2,160	—	60
Cat(S)	0.69	3	3	190	—	60
Syn(S)	0.69	3	3	400	—	60
Erv(S)	0.69	3	3	560	—	60
Vietnam Smith						
Mor(J)	0.8	2	3	880	—	75
Cox(J)	0.67	2	3	3,860	—	73
Bat(J)	0.46	2	3	620	—	67
Joh(J)	0.46	2	3	5,880	—	61

[a] The letter in parentheses following the shortened form of the patient's name represents the institution where the test was performed.

TABLE 3.—*Continued*

Malaria strain and patient[a]	Total daily dose (g)	Divided doses (times/day)	No. of days	Parasite count	Days to recrudescence	Cure (days of follow-up)
Cla(J)	0.46	2	3	220	—	60
Rai(J)	0.46	2	3	330	—	60
Bow(J)	0.46	2	3	19,440	25	—
	0.46	2	3	25,160	—	63
Har(J)	0.46	2	3	1,260	35	—
	0.46	2	3	17,520	—	62
Str(J)	0.46	2	3	3,250	10	—
	0.69	3	3	670	—	60
Fle(J)	0.69	3	3	1,860	—	61
Cru(J)	0.69	3	3	860	15	—
Tho(J)	0.69	3	3	1,780	—	64
Phi(J)	0.69	3	6	1,280	—	60
But(J)	0.69	3	6	520	—	60
Lov(J)	0.69	3	6	760	—	60
She(J)	0.69	3	6	650	—	60
Mos(J)	0.69	3	6	740	—	68
Cow(J)	0.69	3	6	390	—	61
Flo(J)	0.69	3	6	5,590	—	71
Bal(J)	0.69	3	6	14,620	—	71
Fri(J)	0.69	3	6	4,980	—	70
Kno(J)	0.69	3	6	11,710	21	—
Hec(J)	0.69	3	6	4,600	35	—
Kat(M)	0.69	3	6	1,120	—	60
How(M)	0.69	3	6	860	13	—
	0.69	3	6	1,018	—	60
Haw(M)	0.69	3	6	3,120	—	60
Shi(M)	0.69	3	6	2,060	—	60
Hep(M)	0.69	3	6	9	—	60
Mcr(M)	0.69	3	6	2,160	—	61
Bel(M)	0.69	3	6	180	—	61
Hag(M)	0.69	3	6	220	—	61
Joh(M)	0.69	3	6	320	—	61

TABLE 4. *Treatment of acute P. vivax malaria (South Pacific Chesson strain) with WR 30090*

Patient	Total daily dose (g)	Divided doses (times/day)	No. of days	Parasite count	Days to recrudescence	Clinical cure (days of follow-up)
Swe(J)	0.46	2	3	50	—	68
Cok(J)	0.46	2	3	160	—	60
Wri(J)	0.46	2	3	3,100	—	66
Lor(J)	0.46	2	3	290	19	—
	0.46	2	3	140	—	64
Nug(J)	0.8	2	3	1,140	—	91
Swe(J)	0.69	3	3	4,370	—	60
Lam(J)	0.69	3	3	480	—	65
Den(J)	0.69	3	6	990	28	—
	0.69	3	6	80	—	60
Gif(M)[a]	0.69	3	6	280	31	—
Gen(M)[a]	0.69	3	6	8,220	24	—
She(M)[a]	0.69	3	6	560	23	—
Jon(M)[a]	0.69	3	6	8,940	71	—

[a] Sporozoite-induced infections (all others were blood-induced).

falciparum (Smith strain) at the dosage of 230 mg every 8 hr for 6 days were given the same dose of WR 30090 plus sulfalene (1.0 g) every other day for 3 days. Both were cured.

The *P. falciparum* strain in the patient from Vietnam (termed the Crocker strain) seems to fall in the same category. The patient was treated with WR 30090 after treatment with chloroquine, quinine, pyrimethamine, and the sulfonamides had failed to suppress his parasitemia. WR 30090 quickly suppressed his parasitemia and he was asymptomatic for 2 weeks before a recrudescence occurred. His blood was used to infect two volunteers. Both of these men were cured by the 6-day course of WR 30090. In view of these findings, it seems that these variations may reflect either differences in drug metabolism or differences in host-parasite relationship rather than the development of a strain of resistant organisms.

For all strains except Smith, parasitemia cleared by the fourth day of therapy. With the Smith strain, parasitemia cleared by the fifth day in all except four patients who cleared between 6 and 9 days after initiation of therapy. However, in two of these four subjects, recrudescence subsequently occurred.

The Chesson strain of *P. vivax* was quite susceptible to WR 30090 (Table 4). Remission of acute attacks occurred in all volunteers receiving 3- or 6-day courses in blood-induced infections, and radical cures were probably obtained in six of the eight first attacks and in both of the recrudescences; however, in the four mosquito-induced infections, parasitemia recurred.

Patients treated with WR 30090 had an excellent clinical response. Lysis of fever was completed within 72 hr or less, and there was rapid suppression of parasitemia in all but a few patients treated with this drug. The drug was well tolerated.

DISCUSSION

The quinoline methanol WR 30090 demonstrated effective antimalarial action with low toxicity for the treatment of multi-drug-resistant *P. falciparum* strains. The drug showed a very useful broad spectrum of activity against all strains of *P. falciparum* and *P. vivax* tested. Adverse effects of the compound have been quite minimal. The drug appeared to be well tolerated by patients with malaria, as well as by normal volunteers. There were no significant complaints or physical changes which could be attributed to drug effect.

The potential of WR 30090 to induce photosensitivity was demonstrated to a very minor degree in 4 of the 124 men tested. In view of the dosage schedule required for therapy, WR 30090 is likely to be most useful for treatment of acute malaria. Photosensitization is unlikely to be of practical importance under these conditions. Those individuals who did demonstrate photosensitivity always had a negative response to ultraviolet light 24 hr after the drug was stopped; thus, it appears to be a very short-lived effect.

A major advantage of WR 30090 has been its rapid activity in suppressing parasitemia. In only four of the volunteers did the parasitemia persist for more than 5 days after medication was started. The relief of symptomatology was rapid (within 2 days) in most cases.

A review of the action of WR 30090 in our studies suggests that *P. vivax* responds better to chloroquine than to quinoline methanol, whereas *P. falciparum* (Smith strain) responds better to quinoline methanol than to chloroquine; it thus appears probable that quinoline methanol has a mechanism of action different from that of chloroquine.

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LITERATURE CITED

1. Arnold, J. D., D. C. Martin, P. E. Carson, K. H. Rieckmann, D. Willerson, Jr., D. F. Clyde, and R. M. Miller. 1973. A phenanthrene methanol (WR 33063) for treatment of acute malaria. Antimicrob. Ag. Chemother. **3**:207–213.
2. Buchman, E. R., H. Sargent, T. C. Myers, and D. R. Horton. 1946. Potential antimalarials (chloro-2-phenylquinolyl-4)-α-piperidyl-carbinols. J. Amer. Chem. Soc. **68**:2710–2723.
3. Ison, A. E., and H. Blank. 1967. Testing drug phototoxicity in mice. J. Invest. Dermatol. **49**:508.
4. Jandhyala, B. S., G. J. Grega, and J. P. Buckley. 1967. Hypotensive activity of several quinoline derivatives. Arch. Int. Pharmacodyn. Ther. **167**:217–226.
5. Kotler-Brajtburg, J. 1967. Poszukiwanie subsiancju o dzialaniu przeciwserotoninowym w grupie pochodnych chinoliny. Acta Pol. Pharma. (Transl.) **24**:127–131.

6. Luchi, R. J., H. L. Conn, and J. Helwig. 1962. Cardiovascular effects of a quinidine-related compound, 4 hydroxymethyl 6 methoxy quinoline. Amer. J. Cardiol. **10**:252–260.
7. Lutz, R. E., P. S. Bailey, M. T. Clark, J. F. Codinton, A. J. Deinet, J. A. Freek, G. H. Harnest, N. H. Leake, T. A. Martin, R. J. Rowlett, J. M. Salsbury, N. H. Shearer, J. D. Smith, and J. W. Wilson. 1946. Antimalarials, α-alkyl and dialkylaminomethyl-2-phenyl-4-quinolinemethanols. J. Amer. Chem. Soc. **68**:1813–1831.
8. Magarian, R. A., and W. L. Nobles. 1967. Potential anti-infective agents. I. Quinoline, phenolic, and β-aminoketone derivatives. J. Pharm. Sci. **56**:987–992.
9. Rothe, W. E., and D. P. Jacobus. 1968. Laboratory evaluation of the phototoxic potency of quinolinemethanols. J. Med. Chem. **11**:366–368.