Population and Public Health Sciences Faculty Publications

Population and Public Health Sciences

4-1998

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ALLOPURINOL AS AN ADDITIVE TO QUININE IN THE TREATMENT OF ACUTE COMPLICATED FALCIPARUM MALARIA

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Abstract. The emergence of chloroquine resistance, and a world-wide scarcity of quinine, have resulted in a search for newer antimalarial drugs directed against falciparum malaria. Allopurinol causes virtually complete inhibition of purine biosynthesis of malaria parasites, which may prove lethal to the parasites. This study was designed to examine if allopurinol is additive to quinine in the treatment of acute falciparum malaria. Forty-seven Asian-Indian adults with acute complicated falciparum malaria were assigned to a treatment period of five days. They were randomly assigned to receive either oral allopurinol (12 mg/kg in three divided doses for five days) plus quinine (600 mg intravenously every 8 hr for two days, followed by 600 mg orally every 8 hr for three days) (n = 24), or quinine alone (600 mg intravenously every 8 hr for two days, followed by 600 mg orally every 8 hr for three days) (n = 23). The responses were assessed by parasite clearance time, defervescence time, splenomegaly disappearance time, and cure rate. In the allopurinol-quinine (ALLQUIN)–treated group, all the durations were significantly shorter than those in the quinine alone (QUIN)–treated group. They were ALLQUIN versus QUIN (mean ± SD = 65.33 ± 11.47 hr versus 76.78 ± 18.20 hr; $P = 0.0214$; 57.66 ± 13.01 hr versus 82.52 ± 23.55 hr, $P = 0.0002$; 10 ± 1.64 days versus 14.65 ± 2.4 days; $P = 0.0002$), respectively. The cure rate was higher in the ALLQUIN group (91.7%) than in the QUIN group (87%). However, this difference was not statistically significant. Therefore, this study indicates that allopurinol can be an additive to quinine to bring about both faster eradication of *Plasmodium falciparum* and clinical remission than with quinine alone.

With the emergence of *Plasmodium falciparum* strains resistant to chloroquine and/or to sulfadoxine/pyrimethamine in almost all endemic areas,[1] quinine has remained one of the few drugs for treatment of falciparum malaria[2] and has caused a resurgence of its use.[3] Quinine administered daily for three days clears parasitemia within a few days; but after two to four weeks, parasitemia recrudesces.[4] Although, during successful antimalarial treatment, parasite clearance time in African children with severe *P. falciparum* infection did not usually exceed 60 hr, some parasites remained alive despite exposure to extremely high concentrations of quinine for up to 96 hr.[2]

Allopurinol has a broad antiprotozoal activity.[5] Due to a lack of a de novo purine biosynthesis pathway,[6] and malaria parasite's nonspecific hypoxanthine guanine phosphoribosyl transferase, malaria parasites use allopurinol as a hypoxanthine analog.[7] Consequently, 4-aminopyrazolopyrimidine ribonucleotide triphosphate, a highly toxic analog of adenosine triphosphate is formed and incorporated into protozoal ribonucleic acid.[8] Allopurinol thus brings about virtually complete cessation of intraerythrocytic (IE) plasmodial purine biosynthesis and protein metabolism, which prove lethal to the parasites. Allopurinol (11–36 mg/kg/day) is rapidly absorbed after ingestion, and has a half-life of 2–3 hr (its primary active metabolite oxypurinol has a half-life of 18–30 hr). This drug is usually given daily in three divided doses.[8, 9]

This study was designed to compare the effectiveness of a combined regimen of allopurinol plus quinine (ALLQUIN) with that of standard regimen of quinine (QUIN) in the treatment of acute complicated falciparum malaria. The objectives were to determine whether ALLQUIN therapy would shorten the overall course of the infection and produce a higher cure rate in falciparum malaria.

PATIENTS, MATERIALS, AND METHODS

Adult patients with acute, complicated, falciparum malaria admitted to Jawaharal Nehru Hospital and Research Center (Bhilainagar, India) during a two-year period (1993–1994) were included in this study. The diagnosis was confirmed in all patients by finding asexual forms of *P. falciparum* in the peripheral blood. Written informed consent for investigation, treatment, and follow-up were obtained from all patients or their family members. The study was reviewed and approved by Hospital Ethical Committee. Patients who had a known or suspected history of allergy to allopurinol or quinine, a history of recent antimalarial drug treatment, and female patients who were pregnant or nursing babies were excluded from the study. Parasite identification was done on thin and thick Leishman-stained peripheral blood smears.

On thick blood smears, parasites per 200 white blood cells (WBCs) were counted and converted to parasites/μl by using the WBC count. On thin blood smears, parasites for 1,000 red blood cells were counted and converted to percent of parasitized erythrocytes. Parasites were counted in this manner every 8 hr for 72 hr, then every 12 hr until none could be detected, and finally, once a week for eight weeks. The body temperature was recorded every 4 hr until the patient was afebrile for 24 hr, then once a day until discharge, and once a week thereafter for eight weeks (56 days).

The eight weeks follow-up for patients given ALLQUIN was necessary because of the long half-life of its active metabolite oxypurinol, and recrudescences of malaria that occur after 35 days of treatment with nonquinine drugs.[1] With antimalarial drugs that have shorter half life, such as quinine, most recrudescences occur within four weeks of treatment. Patients with severe complicated falciparum malaria were diagnosed according to the World Health Organization (Geneva, Switzerland).[10] Thus, severe complicated malaria was

TABLE 1
Admission clinical and laboratory data of patients with complicated falciparum malaria*

	Allopurinol† plus quinine‡	Quinine‡
No. of patients	24	23
Males	14	15
Females	10	8
Age (years)	32.3 (13–66)	34.04 (15–56)
Weight (kg)	53.6 (32–86)	52.3 (37–85)
Temperature (°C)	38.3 (37.5–41.8)	38.4 (37.6–41.6)
Parasitemia (%)	6.4 (5.2–10)	5.6 (5.4–20)
Hemoglobin (g/dl)	8.4 (5.6–14.2)	8.5 (6.2–14)
Unconjugated bilirubin (mg/dl)	1.9 (1.4–2.5)	2 (1.8–2.2)
ALT (U/liter)	110 (80–140)	113 (105–120)
Serum creatinine (mg/dl)	4.3 (3.4–4)	4.7 (3.2–8)
Blood urea nitrogen (mg/dl)	32 (26–40)	50 (26–40)

* Values in parentheses are ranges. ALT = alanine aminotransferase.
† See Materials and Methods for dosage details.
‡ See Materials and Methods for dosage details given alone/along with allopurinol.

diagnosed in our study if patients had more than 5% parasitized erythrocytes with or without hyperpyrexia (temperature ≥ 40°C), and who were diagnosed to have cerebral malaria (after exclusion of other causes of encephalopathy by clinical examination and laboratory investigations), and had in addition jaundice (total bilirubin > 2 mg/dL) or oliguric acute renal failure.

All hematologic, hepatic, and renal functions tests were done upon admission to hospital and during follow-up examinations. An electrocardiogram was recorded before initiation of treatment, and during and after the completion of treatment. Evaluation of spleen size was done by palpation before, during and after the completion of treatment. Patients were randomly assigned (open randomization) into two treatment groups: 1) ALLQUIN: allopurinol (12 mg/kg in three equally divided doses orally or through a nasogastric tube daily for five days) plus quinine (600 mg intravenously every 8 hr for two days followed by 600 mg orally every 8 hr for three days; and 2) QUIN: quinine (600 mg intravenously every 8 hr for two days followed by 600 mg orally every 8 hr for three days). Patients were kept in the hospital for a minimum period of seven days. The parameters used in outcome determinations included 1) defervescence time, 2) parasite clearance time, 3) spleen size, and 4) cure rate. After discharge from the hospital, patients were followed up at weekly intervals for eight weeks. They were considered to be cured if there was no recrudescence of malaria within 28 days after the last treatment for QUIN group and 56 days for ALLQUIN group.

Statistical analysis. To compare the outcome variables, mean parasite clearance time, mean defervescence time, and mean splenomegaly disappearance time between the two study groups (QUIN and ALLQUIN), a multivariate analysis of covariance was conducted. In this analysis, the effect of the treatment is adjusted for the effects of the covariates, age, weight, and sex. A chi-square analysis was done to compare the cure rate between the two study groups.

RESULTS

The clinical data are presented in Table 1. Twenty-four patients (14 males and 10 females) were treated with the ALLQUIN combination. All patients completed the treatment. The mean age was 32.3 years (range = 13–66 years) and the mean parasitemia was 6.4% (5.2–10%) (range = 0.011–10%). All patients had fever at the time of admission with a mean ± SD temperature of 38.3 ± 1.05°C. Twenty-three patients (15 males and 8 females) were treated with QUIN alone. All patients completed the treatment. The mean age in the QUIN group was 34.04 years (range = 15–56 years) and the mean parasitemia was 5.6% (5.4–20%) (range = 0.01–20%). All patients had fever at the time of admission with a mean ± SD temperature of 38.4 ± 1.05°C.

Patients in both treatment groups were anemic. The mean serum bilirubin and transaminase levels were mildly elevated. These levels returned to normal within seven days. Many patients had acute oliguric renal failure in each group at the time of admission. Mean serum creatinine and blood urea nitrogen levels were elevated in both groups. These levels returned to normal in 10 days with conservative management. In three cases of cerebral malaria, consciousness was regained within 48 hr of initiation of therapy without neurologic sequelae. Two patients had severe falciparum malaria with uneventful recovery and were discharged on the tenth hospital day.

The treatment responses in both groups are presented in Table 2. The multivariate analysis of covariance resulted in a P value = 0.0001 for the group effect, indicating that the means for defervescence time, parasite clearance time, and splenomegaly disappearance time differ significantly between the two groups after adjusting for the effects of age, weight, and sex. The P values for each individual outcome variable are given in Table 2. In the ALLQUIN group, there was rapid remission of fever in all patients. The mean ± SD defervescence time was 57.6 ± 13.01 hr (range = 30–96 hr). The mean ± SD parasite clearance time in this group was 65.33 ± 11.48 hr (range = 48–96 hr). The mean ± SD splenomegaly disappearance time was 10 ± 1.64 days (range = 7–13 days). In the QUIN group there was slow remission of fever. The mean ± SD defervescence time was 82.52 ± 23.55 hr (range = 48–144 hr). The mean ± SD parasite clearance time was 76.78 ± 8.21 days (range = 48–120 days). Disappearance of splenomegaly was observed in 56.5% of patients by 14 days and 100% of patients by 18 days. Mean ± SD splenomegaly disappearance time was 14.65 ± 2.40 days (range = 8–18 days). Thus, mean defer-

TABLE 2
Comparison of treatment responses between two groups in patients with falciparum malaria*

	Allopurinol plus quinine (n = 24)	Quinine (n = 23)	P
Mean defervescence time (hr)	57.67 ± 13.01	82.52 ± 23.55	0.0002
Mean parasite clearance time (hr)	65.33 ± 11.48	76.78 ± 18.21	0.0214
Splenomegaly disappearance time (days)	10 ± 1.64	14.65 ± 2.4	0.0002
Cure rate at 28 days (%)	91.7	87	0.666

* n = number of patients. Values are the mean ± SD.

vescence time, parasite clearance time and splenomegaly disappearance were significantly longer in the QUIN group than in the ALLQUIN group (Table 2).

The overall cure rate for ALLQUIN group was 91.7% at the end of both 28 and 56 days. The overall cure rate for QUIN group was 87% at the end of 28 days (Table 2). The difference in cure rate between the two groups was not significant (P = 0.666, by chi-square test).

Adverse reactions in both treatment groups are presented in Table 3. The incidence and severity of adverse reactions were not significantly different between the two treatment groups.

DISCUSSION

Over the past 30 years there has been a gradual realization that malaria cannot be completely eradicated and most of the studies have emphasized the need for reliance on antimalarial drugs.[11] The emergence of *P. falciparum* resistant to existing antimalarial drugs has warranted a search for new therapeutic endeavors for falciparum malaria. A rational approach to the selection of new drugs requires a detailed knowledge of enzymology and metabolism of both the parasite and the host and to find the differences that can be exploited for selective destruction of the parasites.[6] In view of the prohibitive cost of developing and licensing new antimalarial formulations,[3] the demonstration of useful antimalarial activity in a drug already licensed for another purpose will be an important advance. Both in vitro and in vivo studies have shown that certain inosine analogs have broad antiprotozoal activity.[5] One such inosine analog is allopurinol, which has been shown to bring about virtually complete cessation of IE plasmodial purine biosynthesis and protein metabolism in in vitro studies and models.[6, 7, 12] The selective

TABLE 3
Adverse reactions

	Allopurinol plus quinine (n = 24)	Quinine (n = 23)
Cinchonism	2	4
Nausea	2	3
Abdominal pain	1	3
Vomiting	1	3
Diarrhea	4	3
Loss of appetite	4	6
Myalgia	2	0
Bradycardia	0	2
Depressed white blood cell count	1	0
Skin rashes	3	0
Eosinophilia	3	0

antiparasitic action of allopurinol is believed to be due to its incorporation into the protozoal but not the mammalian purine salvage pathway.[8] However, the lack of in vivo effect, and the report on the enhancement of parasite multiplication in rodent malaria by *P. berghei* can be explained by the fact that smaller animals may metabolize the drug more quickly, and in a different way and with subgenera of *Plasmodium* that less closely resemble those affecting humans.[13, 14]

The disappointing results of clinical trial by Phillips and others[14] strengthen the evidence that laboratory-derived, highly chloroquine-resistant strains of *P. berghei* in mice are not always an adequate model for *P. falciparum* in humans,[13] and that the human malarias are different from the rodent malaria.

Work on the response of *P. falciparum* in vitro to various 4-aminoquinolines has led other workers to doubt the relevance of chloroquine-uptake studies in *P. berghei* to the mechanism of resistance in *P. berghei* to the mechanism of resistance in *P. falciparum*.[15] However, a distinct possibility remains that allopurinol would block the metabolism of quinine leading to higher effective in vivo dosage of quinine. In this way, these two drugs may appear additive.

Vivax malaria occurred during follow-up of patients with falciparum malaria in whom initially mixed malarial infection was missed or not identified as a result of treatment with pyrimethamine-sulfadoxine, qinghaosu derivatives, and mefloquine.[1, 16, 17] With ALLQUIN treatment, none of the patients had *P. vivax* in peripheral blood during follow-up. It has been reported that *P. vivax* infection is not detectable until *P. falciparum* has been eradicated by treatment with quinine,[1, 16, 17] suggesting that a mixed infection may occur. Allopurinol has a parasiticidal effect on *P. vivax*. We have observed a curative effect of allopurinol when combined with quinine (ALLQUIN) in the treatment of mixed malarial infections caused by *P. falciparum* and *P. vivax* (Sarma PSA, Mandal AK, unpublished data).

Use of quinine for seven days resulted in higher recrudescence rate and higher incidence of cinchonism.[1] Quinine used for 14 days to prevent delayed recrudescences still results in 33.3% recrudescence.[18] The established second-line drug regimen for treatment of severe complicated falciparum malaria (excluding pregnant women and children) is quinine plus tetracycline for seven days.[1] The cure rate for quinine/tetracycline is 93%, but the long-term treatment decreases compliance.[1, 4]

We have investigated the effectiveness and safety of allopurinol in acute severe and complicated falciparum malaria. The combination therapy is well tolerated and reduces parasitemia more rapidly than by quinine alone. The defervescence time is significantly shorter and the adverse effects

are rather mild. The splenomegaly disappearance time is shorter than in patients treated with quinine alone. However, the cure rate was comparable between the two groups.

In conclusion, this study suggests that allopurinol is an additive to quinine, and that the combination therapy effectively cures acute, complicated, falciparum malaria. This combination therapy is worthy of further trials in falciparum malaria.

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REFERENCES

1. Karbwang J, Na-Bangchang K, Thanavibul A, Dilla-in M, Harinasuta T, 1995. A comparative clinical trial of two different regimens of artemether plus mefloquine in multidrug resistant falciparum malaria. *Trans R Soc Trop Med Hyg 89:* 296–298.
2. Mapaba E, Heligren U, Landberg-Lindgren A, Rombo L, 1995. Susceptibility of *Plasmodium falciparum* to quinine in vitro: effects of drug concentrations and time of exposure. *Trans R Soc Trop Med Hyg 89:* 85–89.
3. White NJ, 1992. Antimicrobial drug resistance: the pace quickens. *J Antimicrob Chemother 30:* 571–585.
4. Kremsner PG, Zotter GM, Feldmeier H, Graninger W, Rocha, RM Weidermann G, 1988. A comparative trial of three regimens for treating uncomplicated falciparum malaria. *J Infect Dis 158:* 1368–1371.
5. Marr JJ, 1991. Purine analogs as chemotherapeutic agents in leishmaniasis and American trypanosomiasis. *J Lab Clin Med 188:* 111–119.
6. Daddona PE, Weismann WP, Milhouse W, Chern JW, Townsend LB, Hershfield MS, Webster HK, 1986. Expression of human malaria parasite purine nucleoside phosphorylase in host enzyme-deficient erythrocyte culture. *J Biol Chem 261:* 11667–11673.
7. Webster HK, Whaun JM, 1981. Purine metabolism during continuous erythrocyte culture of human malaria parasite (*P. falciparum*). *Proc Clin Biol Res 55:* 557–573.
8. Reynolds JEF, Parfit K, Parsons A, Sweetman SC, 1993. Antigout agents. Reynolds JEF, Parfit K, Parsons A, Sweetman SC, eds. *Martindale The Extra Pharmacopoeia.* 30th edition, London: The Pharmaceutical Press, 333–338.
9. Dellamonica P, Bernard E, Le Fichoux Y, Politano S, Carles M, Durand J, Mondain V, 1989. Allopurinol for treatment of visceral leishmaniasis in a patient with AIDS. *J Infect Dis 160:* 904–905.
10. Warrell DA, Molyneux ME, Beales PF, 1990. Severe and complicated falciparum malaria. *Trans R Soc Trop Med Hyg, 84 (suppl 2):* 1–65.
11. Phillips RE, Solomon T, 1990. Cerebral malaria in children. *Lancet 336:* 1355–1363.
12. Reyes P, Rathod PK, Sanchez DT, Mrema TEK, Rieckman KH, Heidrich HG, 1982. Enzymes of purine and pyrimidine metabolism from the human malaria parasite *Plasmodium falciparum. Mol Biochem Parasitol 5:* 275–290.
13. Anonymous, 1984. Chemotherapy of malaria in mouse and man. *Lancet i:* 318–320.
14. Phillips RE, Looareesuwan S, Karbwang J, Warrell DA, White NJ, Kasemsarn P, Warhurst DC, 1984. Failure of chloroquine-erythromycin and chloroquine-tetracycline combinations in the treatment of chloroquine resistant falciparum malaria in eastern Thailand. *Lancet i:* 300–302.
15. Geary TG, Jensen JR, 1983. Lack of cross-resistance to 4-aminoquinolines to chloroquine resistant *Plasmodium falciparum* in vitro. *J Parasitol: 69:* 97–105.
16. Li G, Arnold K, Guo X, Jian H, Fu L, 1984. Randomized comparative study of mefloquine, quinghaosu, and pyrimethamine-sulfadoxine in patients with falciparum malaria. *Lancet ii:* 1360–1361.
17. Mishra SK, Asthana OP, Mohanty S, Patnaik JK, Das BS, Srivastava JS, Satpathy SK, Dash S, Rath PK, Varghese K, 1995. Effectiveness of α, β-arteether in acute falciparum malaria. *Trans R Soc Trop Med Hyg 89:* 299–301.
18. Arnold K, Hein TT, Chinh NT, Phu NH, Phoung P, 1990. A randomized comparative study of artemisinin (qinghaosu) suppositories and oral quinine in acute falciparum malaria. *Trans R Soc Trop Med Hyg 84:* 499–502.