

Comparative antirelapse efficacy of CDRI compound 80/53 (Bulaquine) vs primaquine in double blind clinical trial

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One-year follow-up of malaria patients was undertaken to monitor the antirelapse efficacy of CDRI compound 80/53 (Bulaquine). A total of 697 patients of *Plasmodium vivax* malaria were included in three arm double blind randomized study comparing CDRI 80/53 with placebo and primaquine. Drugs were given once a day for 5 days and the dose for CDRI 80/53 and primaquine was 25 mg and 15 mg, respectively. Thirty-four patients were lost to follow-up and 663 patients completed one year trial. Two hundred and fourteen patients came back with second episode during the one-year followup period. A detailed analysis revealed that the relapse rate during non-transmission period with placebo in 16 (10.6%) patients was higher than both in primaquine (3.0%) and CDRI 80/53 (4.9%) groups.

PLASMODIUM vivax malaria constitutes about 60–65% of total malaria cases in India. Mortality in this infection is low, but involves high morbidity¹. Due to persistence of the hepatic or hypnozoite forms of the parasite, relapses occur in *P. vivax* infections at intervals from 6 weeks to 2 years^{2,3}. Primaquine, an 8-aminoquinoline is the only available drug active against hypnozoites of relapsing malarial parasites and gametocytes of all human malaria species. Although toxic symptoms with primaquine are rare when used in usual doses, higher doses may be accompanied by gastro-intestinal side effects, leucopenia, anaemia and sometimes suppression of myeloid activity². Individuals deficient in enzyme glucose-6-phosphate dehydrogenase may suffer severe haemolysis with this drug, even at therapeutic doses. It is usually self-limiting, but blood transfusion may be required in severe cases⁴. Further, primaquine is contraindicated in pregnant women and infants⁵. Efforts have thus continued to develop safer 8-aminoquinolines for prophylactic and antirelapse efficacy against *P. vivax* malaria, viz. WR 238605 and CDRI 80/53 (WHO assigned INN: Bulaquine)^{6–8}. In the quest for newer and safer antimalarial drugs, Central Drug Research Institute (CDRI), Lucknow has developed activated enamine of primaquine, which

is chemically *N*-(3-acetyl-4-5-dihydro-2-furanyl)-*N*-(6-methoxy-8-quinlinyl)1,4-pentadiamine. This compound has shown antirelapse activity in preclinical model of *P. cynomolgi* B infection in monkeys⁸. Toxicological and haematological studies in beagle dogs have established its safety⁹. In normal volunteer studies the compound, in single dose in the range of 5–75 mg and in multiple doses of 25 mg administered for 7 days daily, is safe and well tolerated¹⁰. The present communication reports the results of comparative clinical efficacy of CDRI 80/53 vs primaquine in preventing relapse in *vivax* malaria.

Two clinics (at 2, Nanak Enclave and 22-Sham Nath Marg) of Malaria Research Centre (MRC) at Delhi were selected for the study. The clinics attract patients from 8 to 9 periurban villages within 4 to 5 km area. The inhabitants belong mainly to low socio-economic status. The study area has low endemicity for malaria, the predominant species being *P. vivax*¹¹. This area is under the influence of two malaria vectors, *An. culicifacies* and *An. stephensi*. *An. culicifacies* is a monsoon-associated species and is predominantly involved in transmission from July to mid-November, whereas *An. stephensi* is an intradomestic species that is found nearly throughout the year, but it attains epidemiological significance only during the monsoon and post-monsoon periods when climatic factors are favourable³. Sporadic transmission by *An. culicifacies* may occur during April–May³.

The study was approved by the ethical committee of CDRI. A total of 697 adults (males and females) with *vivax* malaria aged between 15 and 65 years were recruited in the study. Patients with history of *vivax* infection in the previous year or treatment with antimalarials within the past previous 15 days, concomitant severe anaemia (Hb < 5 gm%), clinical evidence of renal impairment, cardiac insufficiency, glucose-6-phosphate dehydrogenase deficiency, lactating and pregnant women were excluded from the study. Written informed consent was obtained from all patients before formal enrolment in the study.

Assuming a 30% relapse rate in *vivax* malaria without antirelapse treatment and reduction of relapse rate to 10% with the test drug, 206 patients will be needed in each arm using $\alpha = 0.01$ and $\beta = 0.99$.

Patients were given 1500 mg chloroquine base in divided doses over 3 days. On day-4 patients were allocated to one of the three drug groups according to serial numbers. The three drugs, viz. CDRI 80/53, primaquine and placebo were labelled serially at CDRI by using random tables and numbered from 1 to 700. The drugs were administered strictly under supervision in the clinic to ensure compliance and if vomiting occurred within half an hour of administration, the dose was repeated.

The clinical examination of patients was done daily during drug administration while peripheral smear was

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prepared on day-0, day-6, fortnightly for 6 months, followed by monthly intervals for 1 year. During each visit, blood smear was prepared and history of any illness was taken. In case the peripheral smear was positive for *P. vivax* after being negative on day-6, the patient was labelled as a case of relapse and grouped accordingly. A slide was considered negative only after 200 fields had been examined without finding a parasite. Patients were advised to take personal protection measures to avoid reinfection during this period. They were also instructed to report to the malaria clinic in case of fever any time during the follow-up period.

Between July 1993 and August 1994, 697 patients satisfying inclusion criteria were enrolled. Thirty four patients were lost to follow-up. Therefore, 663 patients were considered evaluable. Two hundred and twenty-four received placebo, 220 primaquine and 219 were given CDRI 80/53. The demographic data of each group are shown in Table 1. All treatment regimens were well tolerated. All the patients had fever clearance within 72 h after chloroquine treatment. On day-6, post therapy peripheral smears of all the patients were negative.

In the placebo group 40.1% patients came back with second episode, while only 26.8% and 29.6% of patients, respectively, in primaquine and CDRI 80/53 groups had second episode during follow-up period of one year. However, since differentiation between reinfection and relapse in endemic area during transmission is difficult, the results were further analysed on the basis of relapse rates during non-transmission period in the study area. During this period (mid-November–March) the relapse rates in the three groups, viz. placebo, primaquine and CDRI 80/53 were 10.6%, 3.0% and 4.9%, respectively. The categorization of this non-transmission period was based on the results of longitudinal vector incrimination studies carried out in the same geographical area, (vectors *An. culicifacies* and *An. stephensi*) and the likely non-transmission period is mid-November to March³.

In the present study, the incidence of relapse of *P. vivax* malaria in the three groups was analysed. There was no statistical difference in the relapse rate between two treatment groups during the one-year follow-up period, while CDRI 80/53 and Primaquine groups

showed significantly less number of relapses than the placebo group ($P < 0.05$).

Similar to the observation of one-year follow-up study, during non-transmission period also, the relapse rate between placebo and the other two groups (primaquine and CDRI 80/53) was significantly different ($P < 0.05$), while there was no difference between primaquine and CDRI 80/53 groups.

Primaquine is the only drug available for use as anti-relapse antimalarial in *P. vivax* malaria. At recommended doses adverse effects like anorexia, nausea, abdominal pain are minimal. However, higher doses, viz. 30 mg/day can produce methaemoglobinemia in normal individuals^{3,12}. Individuals with congenital deficiency of methaemoglobin reductase are more prone to this side effect. The other more serious adverse effect is induction of haemolytic episodes in subjects with deficiency of glucose-6-phosphate-dehydrogenase¹³. The occurrence of such an effect has not been seen with CDRI 80/53 (ref. 14). Comparative data on primaquine and CDRI 80/53 after 7 days administration have shown that, with primaquine methaemoglobin levels rise from 3.97% to 16.32% whereas with CDRI 80/53 the rise from 2.29% to 3.02% was insignificant¹⁴. In another study, CDRI 80/53 did not damage normal as well as glucose-6-phosphate-dehydrogenase-deficient erythrocytes to the same extent as primaquine¹⁵.

In the present study, efficacy of this new 8-aminoquinoline was compared with known standard antirelapse drug primaquine. The dose schedule used in the study for both the drugs was according to the national drug policy, where 5-day treatment is given instead of international 14-day regimen, because of relative safety of the former¹¹. The results of the study show that 5-day treatment with both antirelapse drugs is not fully effective since a proportion of subjects still have relapses. Similar observations have been also reported earlier with primaquine^{16,17}.

Since there is no statistical difference in relapse rate between primaquine and CDRI 80/53 groups, the efficacy of both can be considered to be equivalent. Considering the lower incidence of haemolytic effects in animal model and *in vitro* studies, it offers a significant advantage over primaquine. However, further studies in glucose-6-phosphate-dehydrogenase-deficient individuals and efficacy of 14-day treatment regimen (followed internationally) are needed to confirm the safety and efficacy profile of CDRI 80/53.

Table 1. Demographic characteristics of patients

Drug treatment	Sex		Age (years)		Relapse rate over 1 year (%)
	Male	Female	Male	Female	
Primaquine	181	39	27.69 (16–50)	30.38 (17–45)	26.8
CDRI 80/53	181	38	29.84 (16–45)	29.84 (16–45)	29.6
Placebo	182	42	27.25 (15–52)	30.05 (17–46)	40.1

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- ACKNOWLEDGEMENT. We are grateful to V. P. Kamboj, Ex Director, CDRI, Lucknow for constant guidance, co-operation and encouragement during the study. We also thank the staff of MRC for technical assistance.
- Received 26 May 2000; revised accepted 6 December 2000
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