

## Causal prophylactic activity of a new 8-aminoquinoline derivative against *Plasmodium cynomolgi* B in rhesus monkeys

S.K. Puri & G.P. Dutta

Division of Microbiology, Central Drug Research Institute, Lucknow

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A new 8-aminoquinoline derivative, N<sup>1</sup>-(3-acetyl-4-5-dihydro-2 furanyl)-N<sup>4</sup>-(6-methoxy-8-quinoliny)1,4-pentanediamine, synthesized at CDRI, Lucknow, showed causal prophylactic activity at 3.16mg/kg × 3 doses (on day -1, 0 and +1) against sporozoite induced *P.cynomolgi* B infection in rhesus monkeys. Single dose of 10mg/kg of this compound on day 0 also prevented establishment of patent infection. Activity of the compound was comparable to that of primaquine (with causal prophylactic activity at 1.78mg/kg in three day test and at 10.0mg/kg in single dose test).

The number of antimalarial drugs currently available for clinical use as causal prophylactic or anti-relapse agents against exoerythrocytic forms of *Plasmodium vivax* and *P.ovale* is limited<sup>1</sup>. Primaquine introduced nearly 40 yr ago is the only drug in clinical use, known to have such activity. However, its utility is limited because of its toxicity and associated side effects<sup>2</sup>. Evaluation of several synthetic compounds of 8-aminoquinoline class at the Central Drug Research Institute (CDRI), Lucknow against *P.cynomolgi* B in rhesus monkeys has resulted in identification of a new anti-relapse compound (CDRI 80/53) whose activity is comparable to that of primaquine<sup>3</sup>. This compound is a potential drug undergoing Phase I clinical evaluation. The present communication reports the causal prophylactic activity of this new compound in comparison to primaquine, against simian malaria parasite *P.cynomolgi* B.

### Material & Methods

*P.cynomolgi* B infection in rhesus monkeys is

being maintained in our Institute by cyclic transmission through *Anopheles stephensi* mosquitoes for the last 6 yr. The detailed procedures for the maintenance and infection of mosquitoes and harvesting of sporozoites have been described elsewhere<sup>4</sup>. For evaluation of causal prophylactic activity, monkeys were inoculated with  $1 \times 10^5$  to  $1 \times 10^6$  sporozoites intravenously. Treatment with primaquine or compound 80/53 was administered orally either in three doses *i.e.*, on day -1, 0 and +1 of sporozoite inoculation or in a single dose *i.e.*, 2 h before sporozoite inoculation on day 0. Blood smears from infected/treated monkeys were checked daily from day 8 onwards till day 70 post-sporozoite inoculation. Animals which remained negative throughout this observation period were recorded as cured. Pure sample of primaquine diphosphate was obtained from SIGMA Chemicals. Compound 80/53, N<sup>1</sup>-(3-acetyl-4-5-dihydro-2-furanyl) N<sup>4</sup>-(6-methoxy-8-quinoliny) 1, 4-pentanediamine, was synthesized at CDRI, Lucknow.

**Table I.** Causal prophylactic activity of new compound CDRI 80/53 and primaquine against *P.cynomolgi* B in 3-day treatment regimen

Daily dose mg(base)/kg	No. of monkeys	Response to treatment		
		Protected*	Not protected	
			No. of monkeys	Patency on day
<i>Compound CDRI 80/53</i> :				
10.00	3	3	0	—
3.16	3	3	0	—
1.78	2	1	1	25
1.00	3	0	3	15,17,19
<i>Primaquine</i> :				
10.00	3	3	0	—
3.16	3	3	0	—
1.78	3	3	0	—
1.00	3	0	3	17,25,30
<i>Control</i> :				
	4	0	4	8,8,9,9

\* Remained negative during the observation period of 70 days post sporozoite inoculation

**Table II.** Causal prophylactic activity of compound CDRI 80/53 and primaquine against *P.cynomolgi* B after single dose treatment

Dose mg(base)/kg	No. of monkeys	Response to treatment		
		Protected*	Not protected	
			No. of monkeys	Patency on day
<i>Compound CDRI 80/53</i> :				
10.00	3	3	0	—
3.16	3	0	3	20,25,29
<i>Primaquine</i> :				
10.00	3	3	0	—
3.16	3	0	3	25,29,36
<i>Control</i> :				
	4	0	4	9,9,9,10

\* Remained negative during the observation period of 70 days post sporozoite inoculation

## Results

Three monkeys treated with reference drug primaquine at 1 mg (base)/kg  $\times$  3 doses became patent on day 17, 25 and 30 respectively while monkeys treated with 1.78, 3.16 and 10.0 mg/kg  $\times$  3 days remained negative during the observation period of 70 days post-sporozoite inoculation.

Similarly, three monkeys treated with compound 80/53 at 1.00 mg/kg also developed patency on day 15, 17 and 19 respectively and one of the two monkeys at 1.78 mg/kg became patent on day 25. The other monkey at 1.78 mg/kg and three monkeys each at 3.16 and 10.0 mg/kg dose were completely protected (Table I).

Results on single dose prophylactic activity show that three monkeys each treated with primaquine and compound 80/53 at 3.16 mg/kg dose became patent while treatment at 10.0 mg/kg dose prevented the appearance of patent infection during observation period of 70 days post-sporozoite inoculation (Table II).

## Discussion

There is no safe drug available for prophylaxis of vivax malaria excepting primaquine which produces several adverse effects including methaemoglobinaemia, haemolytic anaemia in G-6-PD deficient subjects, gastrointestinal disorders etc.<sup>1,2</sup>. Carson<sup>1</sup> in a recent review has focussed attention to the need to develop a safe causal prophylactic agent. The present study describes the causal prophylactic efficacy of compound 80/53 in the 3 day as well as single dose schedule. Detailed toxicological and haematological studies with this compound in beagle dogs at our institute have established the safety of this new compound. Methaemoglobin toxicity induced by the compound is much less, (3-4 times), as compared to primaquine<sup>5</sup>. Acute toxicity studies in Swiss mice have shown that the LD<sub>50</sub> of compound 80/53 is 681 mg/kg, as compared to 80 mg/kg for primaquine<sup>6</sup>. Sub-acute toxicity studies in two hosts (rats and monkeys) have also shown that the compound is safe and does not produce any toxic manifestations even after administration for 90 consecutive days<sup>7</sup>. The compound which is currently undergoing Phase-I clinical trials is considered a potential candidate as an anti-relapse and causal prophylactic agent.

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Reprint requests : Dr. G.P. Dutta, Deputy Director, Division of Microbiology, Central Drug Research Institute, Lucknow 226001