

Tafenoquine for children: a step towards implementation

Robert J Commons*, Ric N Price

Global Health Division, Menzies School of Health Research and Charles Darwin University,
Darwin, Northern Territory, Australia (RJC, RNP), WorldWide Antimalarial Resistance
Network (WWARN) (RJC, RNP), Internal Medicine Services, Ballarat Health Services,
Ballarat, Victoria, Australia (RJC), Centre for Tropical Medicine, Nuffield Department of
Clinical Medicine, University of Oxford, Oxford, UK (RNP),

***Corresponding author:**

Dr Robert J Commons
Global and Tropical Health Division
Menzies School of Health Research
Charles Darwin University
PO Box 41096
Casuarina, NT 0811
Australia
Ph: +61889468600
Email: robert.common@gmail.com

After several decades under development, tafenoquine, an 8-aminoquinoline compound, was finally registered by the United States Food and Drug Administration in 2018 as a single dose regimen for the prevention of *Plasmodium vivax* malaria relapse and weekly regimen for the chemoprophylaxis of malaria. The drug is a welcome addition to the antimalarial pharmacopoeia, although several challenges remain before it can be used widely in malaria-endemic countries.

Relapses of vivax malaria are caused by hypnozoites, dormant liver stages that reactivate weeks to months after the initial infection, leading to recurrent episodes of malaria. Young children are particularly vulnerable to multiple relapses that can lead to a cumulative risk of anaemia, school absenteeism and reduced school performance.^{1,2} Relapses are estimated to cause 60-90% of all vivax malaria episodes,³ highlighting the vital role of anti-relapse antimalarials, such as tafenoquine and the widely used antimalarial primaquine, in the control and elimination of this parasite.

Although recommended in most national antimalarial guidelines, in practice, implementation of primaquine and tafenoquine is confounded by the risk of haemolysis in patients with glucose-6-phosphate dehydrogenase deficiency (G6PDd). The lack of affordable point-of-care tests for G6PDd has resulted in most patients in malaria endemic countries being treated without prior G6PDd testing. Primaquine is prescribed as a daily dose and can be ceased if signs of haemolysis occur, however, this is not possible with single dose tafenoquine which is eliminated slowly (half-life ~12 days). To prevent severe drug-induced haemolysis, tafenoquine is only recommended in individuals with >70% G6PD activity, compared to a 30% threshold used for primaquine. In addition, tafenoquine is not currently recommended for

children, and its use is restricted to combination therapy with chloroquine to kill the *P. vivax* blood stages.

The dosing regimens of most antimalarial drugs are based on allometric scaling of doses optimised for adults. However, the pharmacokinetics of antimicrobials can differ significantly between adults and children. This has resulted in suboptimal paediatric dosing of several antimalarials, including sulphadoxine-pyrimethamine and dihydroartemisinin-piperaquine.^{4,5} Recent studies suggest that the current recommended paediatric doses for primaquine and chloroquine may also be too low.^{6,7} In *The Lancet Child & Adolescent Health* this week, Vélez and colleagues present a clinical study to determine the correct dose of tafenoquine in children.⁸ They enrolled 60 children aged between 2 and 12 years, to define the pharmacokinetics of the 150mg tablet and a new 50mg dispersible paediatric formulation. Four weight-based tafenoquine dosing bands were selected using a population pharmacokinetic model of patients ≥ 16 years old, that were refined after a pre-planned interim analysis. Their results demonstrate that tafenoquine drug exposure was consistent with exposures following administration of 300mg (the recommended adult dose) in a 60kg adult.

Although the study was primarily designed to optimise the paediatric dose, it provides the first evidence of the safety and efficacy of tafenoquine in children. Haemoglobin concentrations fell to a nadir at day 3, with a maximum drop of 2.9g/dL, but recovered rapidly with no patients developing significant anaemia. Febrile children with malaria are prone to vomit their medication, and this can be exacerbated by certain antimalarials and formulations. In the initial phase of the study, high rates of vomiting were observed in children administered multiple dispersible tablets, but this was mitigated subsequently, in part by providing two standard 150mg tablets to children weighing 35-62kg and reducing the dose from 3 to 2 dispersible

tablets in children weighing 12-20kg. Unfortunately, no data were available for children aged <2 years or weighing <12kg.

Whilst the study was not powered to determine anti-relapse efficacy, patients were followed for 4 months and only three had recurrent *P. vivax* parasitaemia, suggesting an efficacy of >90%. However, the study sites were in two low endemic settings, in Vietnam and Colombia, and larger studies with longer follow up will be needed to determine whether the proposed dosing regimen provides reliable efficacy in children in higher transmission settings. The efficacy of tafenoquine will also need to be compared with the widely used low dose primaquine regimen (total dose 3.5mg/kg) and the higher dose regimen (total dose 7mg/kg) recommended for South-East Asia and Oceania.

Vélez and colleagues' important study provides a framework from which future single dose strategies can be explored for preventing *P. vivax* relapses in children. If additional barriers to implementing safe and effective radical cure of vivax malaria can be overcome, including implementation of point-of-care testing to identify patients with G6PDd, the simplified management of vivax malaria treatment has the potential to substantially benefit individuals in vivax malaria endemic countries and facilitate the ultimate control and elimination of this terrible disease.

Conflict of interest

The authors declared no conflicts of interest

References

- 98 1. Douglas NM, Lampah DA, Kenangalem E, et al. Major burden of severe anemia from
99 non-falciparum malaria species in Southern Papua: a hospital-based surveillance study. *PLoS*
100 *Med* 2013; **10**(12): e1001575; discussion e.
- 101 2. Fernando D, de Silva D, Carter R, Mendis KN, Wickremasinghe R. A randomized,
102 double-blind, placebo-controlled, clinical trial of the impact of malaria prevention on the
103 educational attainment of school children. *Am J Trop Med Hyg* 2006; **74**(3): 386-93.
- 104 3. Commons RJ, Simpson JA, Watson J, White NJ, Price RN. Estimating the Proportion
105 of *Plasmodium vivax* Recurrences Caused by Relapse: A Systematic Review and Meta-
106 Analysis. *Am J Trop Med Hyg* 2020; **103**(3): 1094-9.
- 107 4. Hoglund RM, Workman L, Edstein MD, et al. Population Pharmacokinetic Properties
108 of Piperaquine in Falciparum Malaria: An Individual Participant Data Meta-Analysis. *PLoS*
109 *Med* 2017; **14**(1): e1002212.
- 110 5. Barnes KI, Little F, Smith PJ, Evans A, Watkins WM, White NJ. Sulfadoxine-
111 pyrimethamine pharmacokinetics in malaria: pediatric dosing implications. *Clin Pharmacol*
112 *Ther* 2006; **80**(6): 582-96.
- 113 6. Chu CS, Watson JA, Phyo AP, et al. Determinants of Primaquine and
114 Carboxyprimaquine Exposures in Children and Adults with *Plasmodium vivax* Malaria.
115 *Antimicrob Agents Chemother* 2021; **65**(11): e0130221.
- 116 7. Commons RJ, Simpson JA, Thriemer K, et al. The effect of chloroquine dose and
117 primaquine on *Plasmodium vivax* recurrence: a WorldWide Antimalarial Resistance Network
118 systematic review and individual patient pooled meta-analysis. *Lancet Infect Dis* 2018.
- 119 8. Vélez I, Hien T, Green J, et al. Tafenoquine exposure assessment, safety and relapse
120 prevention efficacy in children with *Plasmodium vivax* malaria. *Lancet Child Adolesc Health*
121 2021.

122