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Clinical and parasitological response to oral chloroquine and primaquine in uncomplicated human *Plasmodium knowlesi* infections

Cyrus Daneshvar[1], Timothy ME Davis[2], Janet Cox-Singh[1], Mohammad Z Rafa'ee[3], Siti K Zakaria[1], Paul CS Divis[1], Balbir Singh[1*]

Abstract

Background: *Plasmodium knowlesi* is a cause of symptomatic and potentially fatal infections in humans. There are no studies assessing the detailed parasitological response to treatment of knowlesi malaria infections in man and whether antimalarial resistance occurs.

Methods: A prospective observational study of oral chloroquine and primaquine therapy was conducted in consecutive patients admitted to Kapit Hospital, Sarawak, Malaysian Borneo with PCR-confirmed single *P. knowlesi* infections. These patients were given oral chloroquine for three days, and at 24 hours oral primaquine was administered for two consecutive days, primarily as a gametocidal agent. Clinical and parasitological responses were recorded at 6-hourly intervals during the first 24 hours, daily until discharge and then weekly to day 28. Vivax malaria patients were studied as a comparator group.

Results: Of 96 knowlesi malaria patients who met the study criteria, 73 were recruited to an assessment of the acute response to treatment and 60 completed follow-up over 28 days. On admission, the mean parasite stage distributions were 49.5%, 41.5%, 4.0% and 5.6% for early trophozoites, late trophozoites, schizonts and gametocytes respectively. The median fever clearance time was 26.5 [inter-quartile range 16-34] hours. The mean times to 50% (PCT_{50}) and 90% (PCT_{90}) parasite clearance were 3.1 (95% confidence intervals [CI] 2.8-3.4) hours and 10.3 (9.4-11.4) hours. These were more rapid than in a group of 23 patients with vivax malaria 6.3 (5.3-7.8) hours and 20.9 (17.6-25.9) hours; $P = 0.02$). It was difficult to assess the effect of primaquine on *P. knowlesi* parasites, due to the rapid anti-malarial properties of chloroquine and since primaquine was administered 24 hours after chloroquine. No *P. knowlesi* recrudescences or re-infections were detected by PCR.

Conclusions: Chloroquine plus primaqine is an inexpensive and highly effective treatment for uncomplicated knowlesi malaria infections in humans and there is no evidence of drug resistance. Further studies using alternative anti-malarial drugs, including artemisinin derivatives, would be desirable to define optimal management strategies for *P. knowlesi*.

Background

The simian malaria parasite *Plasmodium knowlesi* causes symptomatic infections in humans throughout South-east Asia in areas inhabited by its natural macaque hosts (*Macaca fascicularis* and *M. nemestrina*) and mosquito vectors of the *Anopheles leucosphyrus* group [1-8]. Early trophozoites of *P. knowlesi* are morphologically similar to *Plasmodium falciparum* and all the other stages resemble those of *Plasmodium malariae* [9]. However, unlike *P. malariae* infections, knowlesi infections can be severe and even fatal. A recent observational study found complications in 10% of patients and a 2% mortality [10].

Previous reports have indicated that patients with uncomplicated knowlesi malaria respond well to chloroquine treatment [1]. In one recent study, the mean

* Correspondence: bskhaira55@gmail.com
[1]Malaria Research Centre, Faculty of Medicine & Health Sciences, Universiti Malaysia Sarawak, 93150 Kuching, Sarawak, Malaysia
Full list of author information is available at the end of the article