

Editorial



Addressing the Gaps in Malaria Treatment in Korea

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► See the article “Suboptimal Doses of Antimalarials Relative to Increasing Body Weight and the Risk of *Plasmodium vivax* Recurrence in the Republic of Korea Armed Forces, 2012–2021” in volume 39, number 49, e314.



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Malaria is believed to have been endemic in Korea for many years.¹ The first documented case of malaria in the country dates back to 1913, and a significant rise in cases occurred during the Korean War. With the collaborative efforts of the Korean government and the World Health Organization in the 1960s and 70s, malaria was successfully controlled, and no local cases were reported between 1985 and 1992. However, the re-emergence of malaria in 1993 led to the peak of 4,141 annual cases in 2000. Since then, the number of cases has gradually declined, with an annual incidence of 300–600 cases over the past decade.² While the incidence of malaria has been stable and its occurrence confined in high-risk regions, climate change poses a potential risk of altering the epidemiology of malaria transmission in Korea in the future. Thus, awareness of physicians on malaria is critical for rapid diagnosis and effective treatment, which are in turn cornerstones for the eradication of malaria.

In the current issue of the *Journal of Korean Medical Science*, Hwang et al.³ investigated the trends in weight-based dosages of antimalarial drugs (hydroxychloroquine [HCQ] and primaquine [PQ]) and the risk of recurrence among the Korean Armed Forces service members over a 10-year period. There was a small but significant increase in mean body weight over the study period, accompanied by a corresponding increase in dosage. Despite this, a large proportion of the patients (90.2% for HCQ and 70.9% for PQ) received doses that fell below the WHO recommended dosages (chloroquine [CQ] base 25 mg/kg body weight and PQ 3.5 mg/kg body weight). Recurrence occurred in 4.4% of the patients; the risk of recurrence was associated with not administering or underdosing PQ, but not with HCQ dosage.

The primary objectives of malaria treatment are rapid parasitological cure and the prevention of recurrence.⁴ To achieve these goals, appropriate weight-based dosing is recommended to maximize the chances of rapid reduction in parasite burden and to maintain effective drug concentrations for a sufficient time to eliminate *Plasmodium* parasites. Furthermore, *Plasmodium vivax* can remain dormant in the liver as hypnozoites, which may cause relapse months or even years later. Standard antimalarial therapy does not eliminate these liver forms, and primaquine is necessary to eradicate hypnozoites and prevent relapse.

The study's key finding – that underdosing of antimalarial drugs is common – is not surprising. Several factors complicate appropriate weight-based dosing of antimalarial drugs.

HCQ and PQ are formulated as fixed-dose tablets, and not all dose formulations are readily available in pharmacy. Physicians caring adults are often unfamiliar with weight-based dosing; calculation of dosage and rounding to the nearest combination of available formulations are cumbersome, which is further complicated by the different units of HCQ (salt v. base). Also, some old literature suggested fixed doses of 2,000 mg HCQ salt (1,500 mg CQ base) over 3 days and 15 mg PQ for 14 days, which is appropriate for patients ≤ 60 kg but may be insufficient for those ≥ 70 kg. As the body sizes of younger generations increase, these fixed-dose recommendations are becoming suboptimal. However, there is an example of weight-based dosing as a standard treatment regimen for a well-known infectious disease: tuberculosis. The dosage of first-line antituberculosis agents is recommended to be adjusted by weight, and the drugs are formulated accordingly. Tuberculosis guidelines usually provide tables of dosages by weight range and available formulations, instead of giving just dose per body weight. Physician education, provider-friendly guidance, and wider availability of differently dosed formulations may enhance the appropriateness of malaria treatment.

Interestingly, the study found no significant correlation between HCQ dosage and recurrence, even though the median time to recurrence was 5 weeks, suggesting that many of the recurrences were likely due to recrudescence (treatment failure). The proportion of the patients who received adequate HCQ dose was too small (~10%), which may have limited statistical power of the analysis. On the contrary, failure to receive an adequate dose of PQ was shown to be associated with recurrence. An increase in the total dose of PQ can be accomplished by doubling the doses, which was shown to be more effective in preventing relapse without increasing the risk of adverse events.⁵ The current WHO guidelines recommend a higher total dose (7 mg/kg body weight) of primaquine for “the tropical, frequent-relapsing *P. vivax* prevalent in East Asia and Oceania.” The recent Korean guidelines also suggest a daily dose of 30 mg PQ for those weighing > 70 kg.⁶

Another noteworthy finding of this study is the low rate of follow-up blood smears, performed in less than 50% of patients. This is consistent with previous reports from Korea.^{7,8} Due to the relatively mild nature of vivax malaria, many patients do not need hospitalization for long enough to confirm parasite clearance. Nevertheless, adherence to testing guidelines could be improved with intervention from public health authorities.⁸

The authors conducted the study in the military setting. Demographic characteristics of the military, mostly composed of young and healthy men, are usually disadvantageous for medical research. The incidences of most diseases are very low and the results from research have limited generalizability to the general population. However, there also exist several advantages, such as homogenous population, controlled environment, and standardized healthcare system. Medical research in the military has greatly contributed to our understanding of various infectious diseases, including malaria, human adenoviral infection, and vector-borne diseases. The work by Hwang et al.³ is a welcome addition to this tradition, which I wait for more to come.

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