Tolerability of Antimalaria Drugs

Sir—The multicenter randomized trial reported by Overbosch and colleagues [1] is important for 2 reasons. First, the study shows that when taken as malaria prophylaxis, mefloquine is not well tolerated by many travelers. Of the study participants randomized to receive mefloquine, 67.1% reported ≥1 adverse event, and, in 6% of mefloquine users, these events were severe (defined as requiring medical advice). The most common category of unwanted effects in the mefloquine treatment arm were neuropsychiatric adverse effects, which were reported by one-third of all mefloquine users [1]. This disturbing finding contradicts the advice in the most recent guidelines on malaria prevention for US travelers issued by the Centers for Disease Control and Prevention (CDC; Atlanta, Georgia); the guidelines state that “mefloquine is the drug of choice for prophylaxis for most travelers [and] is well tolerated at prophylactic dosages” ([2], p. 1767). This assurance, which is plainly incorrect, was based on findings from uncontrolled studies of tourists and Peace Corps volunteers and from mefloquine trials that involved young, healthy soldiers. The CDC guidelines urgently need to be revised now that a randomized, double-blind study comparing atovaquone-proguanil with mefloquine as prophylaxis for malaria [2]. We would like to respond to the issues that specifically pertain to the study.

The primary study end point was the overall frequency of adverse events, regardless of whether they were attributable to one of the study drugs. There is a high rate of adverse events overall among travelers, so the adverse events that we considered to be related to treatment are of particular interest.

When only adverse events attributed to 1 of the study drugs were evaluated, 6 subjects (1%) who were receiving atovaquone-proguanil and 24 (5%) who were receiving mefloquine discontinued their drug therapy (P = .001). Further analysis revealed that subjects who received atovaquone-proguanil also experienced fewer treatment-related neuropsychiatric adverse events than did subjects who received mefloquine (69 [14%] vs. 139 [29%], respectively; P = .001). Croft and Herxheimer [1] correctly note that we did not include headache as a neuropsychiatric adverse event; however, subjects who received atovaquone-proguanil also reported fewer treatment-related headaches than did subjects who received mefloquine (19 [4%] vs. 34 [7%], respectively; P = .040).

To assess the efficacy of an antimalarial,