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 chemoprophylaxis, mefloquine is not well tolerated at prophylactic dosages” [2], and the guidelines state that “mefloquine is the drug of choice for chemoprophylaxis 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 trial involving heterogeneous, nonimmune travelers has provided good evidence that mefloquine prophylaxis has the potential to cause harm.

Second, the article by Overbosch and colleagues [1] shows that, although earlier studies of atovaquone-proguanil therapy given to lifelong residents of areas where malaria is endemic may indeed have demonstrated that, in those populations, this drug combination has a safety profile that is “similar to placebo” [3, 4], the same is not true of atovaquone-proguanil therapy for nonimmune Western travelers. Of the Overbosch study participants randomized to receive atovaquone-proguanil, 64.5% reported ≥1 adverse event [1]. If one categorizes headache as a neuropsychiatric adverse event, then neuropsychiatric effects are again the most common category of unwanted effects in users of atovaquone-proguanil, as they are in users of mefloquine.

On a point of detail, Overbosch and colleagues refer to trial “subjects” and to “compliance” with appropriate chemoprophylaxis. These terms are obsolete. In modern scientific terminology, those who consent to take part in trials are “participants,” and those consumers who are offered therapy may or may not choose to “adhere” to it. If the therapy involves use of a new or relatively untried drug, they may be wise not to do so [5].

Ashley M. Croft* and Andrew Herxheimer
*Surgeon General’s Department, Ministry of Defense, and United Kingdom Cochrane Center, London, United Kingdom

References