WHITE BLOOD CELL COUNTS AND MALARIA


White blood cells (WBCs) were counted in 4697 individuals who presented to outpatient malaria clinics in Maesod, Tak Province, Thailand, and Iquitos, Peru, between 28 May and 28 August 1998 and between 17 May and 9 July 1999. At each site and in each year, WBC counts in the Plasmodium falciparum-infected patients were lower than those in the Plasmodium vivax-infected patients, which, in turn, were lower than those in the uninfected patients. In Thailand, one-sixth of the P. falciparum-infected patients had WBC counts of <4000 cells/µL. Leukopenia may confound population studies that estimate parasite densities on the basis of an assumed WBC count of 8000 cells/µL. For instance, in the present study, use of this conventional approach would have overestimated average asexual parasite densities in the P. falciparum-infected patients in Thailand by nearly one-third.


ANTIMALarial ACTIVITIES AND THERAPEUTIC PROPERTIES OF FEBRIFUGINE ANALOGS


Febrifugine is the active principal isolated 50 years ago from the Chinese herb chang shan (Dichroa febrifuga Lour), which has been used as an antimalarial in Chinese traditional medicine for more than 2,000 years. However, intensive study of the properties of febrifugine has been hindered for decades due to its side effects. We report new findings on the effects of febrifugine analogs compared with those of febrifugine extracted from the dry roots of D. febrifuga. The properties of the extracted febrifugine were comparable to those obtained from the standard febrifugine provided by our collaborators. A febrifugine structure-based computer search of the Walter Reed Chemical Information System identified 10 analogs that inhibited parasite growth in vitro, with 50% inhibitory concentrations ranging from 0.141 to 290 ng/ml. The host macrophages (J744 cells) were 50 to 100 times less sensitive to the febrifugine analogs than the parasites. Neuronal (NG108) cells were even more insensitive to these drugs (selectivity indices, > 1,000), indicating that a feasible therapeutic index for humans could be established. The analogs, particularly halofuginone, notably reduced parasitemias to undetectable levels and displayed curative effects in Plasmodium berghei-infected mice. Recrudescence of the parasites after treatment with the febrifugine analogs was the key factor that caused the death of most of the mice in groups receiving an effective dose. Subcutaneous treatments with the analogs did not cause irritation of the gastrointestinal tract when the animals were treated with doses within the antimalarial dose range. In summary, these analogs appear to be promising lead antimalarial compounds that require intensive study for optimization for further down-selection and development.