Adequate Primaquine for Vivax Malaria

Scott Kitchener, Peter Nasveld, Sonya Bennett, and Joseph Torresi

Background: Treatment of vivax malaria with primaquine prevents the relapse of infection from residual liver stages of the parasite. Inadequate dosage is related to a higher relapse risk.

Methods: A comparison was made of vivax malaria relapse–prevention treatments with primaquine 22.5 mg or 30 mg daily for 14 days on 146 reports to the Australian Army Central Malaria Register.

Results: The lower dose of primaquine was found to carry a relative risk of 6.63 for a relapse of vivax malaria compared with the higher dose.

Conclusions: The available data presented here suggest that vivax malaria in this region is increasingly tolerant of the 22.5 mg daily treatment regimen of primaquine and that the greater dose of at least 30 mg daily is more effective.
were included. From this group a series of relapsing vivax malaria cases were specifically reviewed.

Three hundred eighteen reports fulfilled the inclusion criteria. Nineteen records indicated deployment to others areas north of Australia known to be malarial in addition to East Timor, namely, Papua New Guinea and Solomon Islands. The total includes 241 initial cases (primary parasitemia) of vivax malaria and 77 clinical episodes of relapsing vivax malaria, of which 5 were considered recrudescent.9

Results

The 241 initial cases of vivax malaria had a mean time to onset after departure from the malarial area of 119 days (range 4–507 d after return to Australia). The median time to onset after repatriation to Australia was 89 days.

From approximately 7,000 ADF personnel serving on East Timor with InterFET for approximately 5 months (the operation continued for several years under the name of the United Nations Transitional Administration in East Timor), 230 primary vivax malaria cases were recorded. The primary vivax attack rate is approximately 3.3% or 8 cases per 100 person-years of exposure.

Of the 318 clinical episodes included, 77 clinical episodes of vivax malaria were second or subsequent episodes of parasitemia, classified as relapses. These included 55 primary relapses or second episodes of parasitemia found on clinical presentation. Forty-four of these relapses occurred within 180 days after the initial episode of parasitemia, a relapse rate of 18% at 6 months.

Multiple relapses have also been reported (not limited to within 6 months). Seventeen of the 55 patients with primary relapses have developed a second relapse, or third episode of parasitemia. Of these, 4 patients progressed to a third relapse (fourth parasitemia), and 1 has been treated for 4 relapses, or 5 clinical episodes with Plasmodium vivax parasitemia (Table 1).10

With all relapses included, the mean time to relapse was 137 days. Lag times to relapse were dispersed from 21 days after the previous episode to a maximum lag time to relapse of 484 days (SD 105 d). The median time to relapse was 94 days.

From the CMR, 146 cases of primary vivax malaria with complete, documented primaquine treatment data were identified and reviewed. Those treated with a total dose of 315 mg of primaquine were more likely to relapse (RR 6.63, CI 2.75–15.96) than were those treated with a total dose of 420 mg (Table 2).

Discussion

Other than recrudescence within the pharmacologically active period after chloroquine treatment, the rate of vivax relapse following treatment reflects responsiveness to primaquine. A rate of 20 to 30% failure is consistent with that reported from the early studies of primaquine against Chesson strain P. vivax.5 Also, the rate is close to that found more recently in Australia upon treating civilians for the infection following travel to Papua New Guinea and other parts of the southwest Pacific.8 However, the lack of observed compliance suggests these are underestimates of the true efficacy of primaquine.

It is possible that parasites presenting in relapse infections and multiple relapses are more recalcitrant to primaquine than in primary infections. This would suggest that relapse infections are more likely to relapse further; however, contrary to this is that with increasing age of the hypnozoites, relapses cease. These influences may be irrelevant or counteracting as lag times from the last primaquine dosage to the first clinical episode are notably similar to those between clinical episodes.

Conclusion

The available data presented here suggest that vivax malaria in this region is increasingly tolerant of the 22.5 mg daily treatment regimen of primaquine and that the greater dose of at least 30 mg daily is more effective.

Declaration of Interests

Drs. Kitchener, Nasveld, and Bennett were full-time employees of the Australian Defence Force when the research was conducted. The authors have no financial or other conflicts of interest to disclose.

| Table 1 | Vivax Malaria among Australian Soldiers after Service in East Timor |
|-------------|-------------------------|-----------------|
| Incidents of Parasitemia | No. of Cases | Rate (%) |
| Single malaria episode | 241 | — |
| One relapse | 55 | 23 |
| Two relapses | 17 | 31 |
| Three relapses | 4 | 24 |
| Four relapses | 1 | 25 |
| Total vivax malaria episodes | 318 | — |

| Table 2 | Relapse following 315 mg versus 420 mg Total Primaquine Treatment for Primary Vivax Malaria |
|-------------|----------------|----------------|----------------|
| Dose | Number Treated | Number Cured | Relapse Rate (%) |
| 315 mg | 75 | 40 | 47 |
| 420 mg | 71 | 66 | 7 |
ions expressed are those of the authors and do not necessarily reflect those of the Defence Health Service or any extant Australian Defence Force policy.

References
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