
***Plasmodium falciparum* outwits Malarone, protector of travellers**

Doctors in Sweden have reported resistance to Malarone, one of the newest and increasingly relied on products for preventing and treating malaria (*BMJ* 2003;326: 628-9). A study last year (*Malaria Journal* 2002;1:1) indicated that *Plasmodium falciparum*, the parasite that causes most malaria, was resistant to Malarone in vitro. The current finding confirms it: two patients treated at a Gothenburg hospital had ample amounts of the drug in their blood to

wipe out the parasite, yet the infection persisted.

The newfound resistance will affect travellers more than people living in malaria-endemic areas, however. The pink Malarone tablets have become a staple for visitors to climates in which the *Anopheles* mosquito, carrier of malaria-causing parasites, thrives. In trials leading to the drug's registration, its overall efficacy was found to be 98.7%. But the price of the drug severely limits its use in poor regions, including Africa where about 90% of all malaria infections occur.

Malarone is a combination of atovaquone and proguanil, two compounds that interfere with *P. falciparum* metabolism in different ways. Both have been used separately before (proguanil was approved in the US in 1948), but together they have a synergistic effect, and efficiently kill the malaria-causing parasite in red blood cells. Since 1996, more than 35 countries have approved the use of Malarone. Along with prescribing it as a prophylaxis, to prevent *P. falciparum* infection, doctors also administer the drug to treat malaria in travellers who have returned home.

However, resistance to both atovaquone and proguanil has been seen when the compounds are used individually. So it is not surprising that a strain of *P. falciparum* resistant to both could evolve, says David Ubben, a scientific advisor for the Geneva-based Medicines for Malaria Venture. "The malaria parasites are extremely agile at making themselves resistant to antimalarial agents," he says. "It's easy to imagine that *Plasmodium* strains that already carry a certain resistance can develop resistance to a second component."

The two young brothers treated in Sweden became infected with Malarone-resistant parasites during a two-month visit to the Ivory Coast. They had taken chloroquine and proguanil to ward off infection, but after returning north both boys developed a fever. The younger child failed to respond to Malarone, despite having therapeutic levels of atovaquone, proguanil and cycloguanil (the active metabolite of proguanil) in his blood. He recovered when treatment was switched to mefloquine. His four-year-old brother cleared the parasites after three days of Malarone treatment, in which therapeutic drug levels were reached, but the organisms reappeared within a month. The boy also recovered with mefloquine treatment.

To investigate further, researchers led by Anna Färnert of the Division of Infectious Diseases at the Karolinska Institute in Stockholm analysed the parasites in each boy's blood. The scientists found that the older child harboured a strain of *P. falciparum* carrying a genetic mutation that has been implicated in atovaquone resistance, as well as the case of Malarone resistance reported last year. However, the parasite in the younger brother did not have the changed gene, suggesting that "there might be other mechanisms involved," says Färnert.

While finding resistance to Malarone is not setting off alarm bells, it does sound a cautionary note. Physicians using it need to keep a close eye on the possibility of drug failure. "Malarone is a good drug, but it may not always be 100% effective," says Färnert. "But, that is the message for all malaria drugs." ■

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