

of the government's ambitious agenda for modernisation are likely.³

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Evidence of *Plasmodium falciparum* malaria resistant to atovaquone and proguanil hydrochloride: case reports

Anna Färnert, Johan Lindberg, Pedro Gil, Göte Swedberg, Yngve Berqvist, Mita M Thapar, Niklas Lindegårdh, Sándor Berezcky, A Björkman

Department of Medicine, Division of Infectious Diseases, Karolinska Institute, Karolinska Hospital, S-171 76 Stockholm, Sweden

Anna Färnert
medical doctor
Mita M Thapar
PhD student
Anders Björkman
professor
Sándor Berezcky
PhD student

Department of Infectious Diseases, Sahlgrenska University Hospital, Östra, Gothenburg, Sweden
Johan Lindberg
associate professor

Department of Pharmaceutical Biosciences, Division of Microbiology, Uppsala University, Uppsala, Sweden
Göte Swedberg
associate professor

Centro de Malária e outras Doenças Tropicais, Instituto de Higiene e Medicina Tropical, Universidade Nova de Lisboa, Lisboa, Portugal

Pedro Gil
post doctoral researcher

Department of Clinical Chemistry, Falun Central Hospital, Falun and Dalarna University College, Borlänge, Sweden

Yngve Berqvist
associate professor
Niklas Lindegårdh
PhD student

Correspondence to: A Färnert
anna.farnert@medks.ki.se

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The increased spread of drug resistant malaria highlights the need for alternatives for treatment and chemoprophylaxis. The combination of atovaquone and proguanil hydrochloride (Malarone, GlaxoSmithKline, NC) has shown high efficacy against *Plasmodium falciparum* with only mild side effects and has been registered for use in several countries, including Denmark, Germany, Sweden, the United Kingdom, and the United States.¹ Treatment failures have been attributed to suboptimal dosage, reinfections, or to a point mutation in the cytochrome b gene.^{1,2} Bioavailability of atovaquone depends on the concomitant intake of a fatty diet, yet drug concentrations were not analysed in these reports. We provide evidence of resistance in two

patients treated with atovaquone and proguanil hydrochloride for *P falciparum* infection.

Methods and results

In September 2000, two boys and their mother were diagnosed as having *P falciparum* malaria at the university hospital in Gothenburg, after returning from an eight week visit to the Ivory Coast. They had taken chloroquine weekly and proguanil daily for chemoprophylaxis against malaria. Case 1, the youngest boy (18 months), had fever, convulsions, and 1% infected erythrocytes. He was treated with atovaquone and proguanil hydrochloride (table). His fever continued, and

Details of three patients treated with atovaquone and proguanil hydrochloride (Malarone; GlaxoSmithKline) for *Plasmodium falciparum* malaria

Patients' details	Infected erythrocytes (%)	No of tablets	Gene mutations*	
			Cytochrome b	Dihydrofolate reductase
Case 1 (11 kg)				
Day of presentation	1	2	Wild type	Wild type
Days after presentation:				
1	5	1		
2	4	Mefloquine†		
4	Gametocytes only			
7	Gametocytes only		Wild type	Wild type
28	0			
Case 2 (19 kg)				
Day of presentation	0.5	1	Mutant type 1	Wild type
Days after presentation:				
1		1		
2	0.2	1		
4	Gametocytes only		Negative	Negative
7	Gametocytes only		Negative	Negative
28	1.6	Mefloquine†	Mutant type 1	Mutant type 2
Case 3 (101 kg)				
Day of presentation	Few rings	4	Mutant type 1	Wild type
Days after presentation:				
1		4		
2	0	4		
3	Gametocytes only		Mutant type 1	Negative
7	Gametocytes only		Mutant type 1	Negative
28	0		Negative	Negative

Mutant type 1=locus 268-Ser. Mutant type 2=loci 51-Ile, 59-Arg, and 108-Asn.

*Detected by polymerase chain reaction.

†Rescue treatment.

he had a few convulsions but no impaired consciousness or other signs of severe malaria. On day 2 the parasitaemia was 4%. Treatment was changed to mefloquine, which was successful. His 4 year old brother, case 2, was febrile with 0.5% infected erythrocytes. His symptoms resolved with atovaquone and proguanil hydrochloride, and the parasites were cleared after three days. On day 28 he was again febrile with *P falciparum* parasites and was successfully treated with mefloquine. The mother (case 3), although asymptomatic, had a few *P falciparum* rings. She was treated with atovaquone and proguanil hydrochloride, which cleared the parasites without recrudescence.

Drug concentrations were measured by high pressure liquid chromatography in repeated serum samples. The concentrations of atovaquone (7.6-13.9 μ M), proguanil (300-1200 nM), and cycloguanil (125-400 nM) were all above the levels considered therapeutic in children and adults.³ Treatment failure could therefore not be attributed to poor bioavailability of the drug.

Cases 1 and 3 were infected with single clones whereas case 2 had five genetically diverse parasite populations, detected by analysis of merozoite surface proteins 1 and 2. Mutation A803G (changing tyrosine to serine in 268) in cytochrome b, related to resistance to atovaquone, was detected in cases 2 and 3 by polymerase chain reaction and restriction fragment length polymorphism of loci 133, 268, 272, 275, 280, and 284, and confirmed by sequencing (table).⁴ However, only wild types were found in case 1. Analyses of loci 51, 59, 108, and 164 in the dihydrofolate reductase gene, related to resistance to proguanil and cycloguanil, revealed wild types in all samples except those from case 2, in which triple mutation were found at recrudescence.⁵

Comment

Treatment of three patients with atovaquone and proguanil hydrochloride for *P falciparum* malaria was unsuccessful in two non-immune children but successful in an adult with probable partial protective immunity. The patients had adequate blood concentrations of the drugs, indicating resistance by *P falciparum*. Mutation in cytochrome b may have contributed to treatment failure but cannot be the only mechanism for resistance to the drug combination because it was also detected in the patient who responded well and was not detected in the patient with early treatment failure. Atovaquone and proguanil hydrochloride represents one of the main new developments in malaria chemotherapy, but because of the resistance shown at this early stage there is a need for careful surveillance of drug efficacy.

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Media criticism of doctors: review of UK junior doctors' concerns raised in surveys

Michael J Goldacre, Julie Evans, Trevor W Lambert

We conduct regular surveys of junior doctors' career intentions and views on their training and work.^{1 2} At the end of the structured questionnaire we invite respondents to add comments on any aspect of their career choice, training, or work. The great majority of the comments we receive relate to topics raised by us, although some respondents raise other topics. In the replies to questionnaires sent to doctors who qualified in 1999 and 2000, a new theme (not raised by us) emerged among the comments: critical portrayal of doctors in the news media. We report on these comments here.

Method and results

We sent questionnaires to all doctors who qualified from any UK medical school in 1993, 1996, 1999, and 2000; we did this towards the end of their preregistration year. In all, 5547 (74%) of the 7466 qualifiers of 1993 and 1996 replied, as did 5702 (67%) of the 8494 qualifiers of

1999 and 2000. Forty per cent (2194) of the respondents of 1993 and 1996 added written comments on their questionnaires, as did 39% (2217) of those of 1999 and 2000. Comments were keyed and imported into software designed for coding and searching text.³ After reading the doctors' comments, we decided to search systematically for all comments that included the text strings "media," "press," "news," "newspapers," "doctor bashing," and "doctor-bashing." We read all comments extracted by this search and eliminated any that used the word(s) in a different context from concerns about the portrayal of doctors in the news media.

This yielded comments from three respondents from the combined 1993 and 1996 cohorts and 63 from the combined 1999 and 2000 cohorts. The box shows some of these comments (verbatim)—chosen to represent the main issues raised and to illustrate the wide geographical spread of those who raised them. They tended to make their comments about the media

UK Medical Careers Research Group, Unit of Health-Care Epidemiology, Department of Public Health, University of Oxford, Institute of Health Sciences, Oxford OX3 7LF
Michael J Goldacre
director
Julie Evans
social scientist
Trevor W Lambert
statistician

Correspondence to: M J Goldacre
michael.goldacre@dphpc.ox.ac.uk

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