Tropical Medicine and International Health

VOLUME 4 NO 1 PP 72–73 JANUARY 1999

Letters to the Editors

Acute intravascular haemolysis (blackwater fever) after antimalarial treatment

Sirs, Van den Ende *et al*. (1998) describe 5 recurrences of blackwater fever (BWF) and warn that increasing frequency of this syndrome is to be expected in imported malaria due to more frequent use of quinine and related drugs. We had a similar experience with 5 cases of BWF during the last three and-a-half years: in one case BWF was triggered by halofantrine, in another by mefloquine, in two cases by quinine and in one case by quinine and/or halofantrine. In our ward, the centre with the highest number of malaria cases in Italy, no similar case had been seen before. We give a brief history:

Case 1 (**May 1994**)

A 49-years-old Italian nun who had lived in the Central African Republic for the previous 5 years was repatriated and admitted to our ward 4 days after developing high fever with jaundice and black urine apparently triggered by presumptive antimalarial treatment with quinine. On admission she was apyretic, weak, pale but not icteric, with hepatomegaly and gross splenomegaly. The laboratory findings were compatible with recent haemolysis (Hb 7.5 g/dl, LDH 960 U/l (N < 430)) and haemoglobinuria. The titre of antimalarial antibodies (IFAT) was 1 : 5120, blood films and a QBC® test were negative for malaria parasites. The patient improved slowly but constantly; however, 18 days after repatriation, she presented high fever again, this time with positive blood films for low-level *P. falciparum* infection (< 1000/μl). She received 1500 mg of halofantrine divided into three doses without complications and was apyretic, QBC® and blood film-negative three days later. One week later she was retreated with halofantrine. Three hours after the second dose she had a sudden fever with shivering, passed red and later black urine, and developed jaundice. Laboratory analysis revealed frank haemolysis with a drop in haemoglobin from 8.7 to 4.1 g/dl within a few hours, LDH 4092 U/l, bilirubin 70.4 mol/l (N < 17.1) and haemoglobinuria. Shortly thereafter, disseminated intravascular coagulation occurred (FDP 12800 ng/ml, N < 200) with massive vaginal bleeding. Intravenous heparin, plasma and packed RBC transfusions were given. Several hours later the patient became frankly dyspnoeic and an X-ray showed ARDS. Mechanical ventilation achieved favourable evolution of the DIC and resolution of the pulmonary picture in 24 h. Systematic screening for other possible causes of haemolysis gave negative results. The Coombs antiglobulin test was negative.

Case 2 (**April 1995**)

A 59-year-old Italian nun coming from Ivory Coast, where she had lived for 15 years, was admitted for low-parasitaemia *P. falciparum* malaria (< 1000/μl). She was treated with mefloquine, 750 mg plus 500 mg, and 24 h after the the second dose presented fever, jaundice and black urine. Haemoglobin dropped from 10.5 to 4.8 g/dl in 72 h, and she received corticosteroids and an RBC transfusion. The Coombs test (both direct and indirect) was positive. G6 PD deficit as well as other major causes of haemolysis were excluded.

Case 3 (**November 1996**)

An Italian priest aged 44 living in Congo developed high fever and black urine a few hours after self-administration of quinine tablets for presumed malaria. He was repatriated and admitted to our ward 48 h later, apyretic but jaundiced, with HB 7.5 g/dl, LDH 3465, FDP 6400 ng/ml and haemoglobinuria. Blood films and QBC® test were negative for malaria parasites. The course was relatively mild and he recovered spontaneously without transfusion. Three weeks later, as his anaemia failed to improve, a thick film showed scanty *P. falciparum* trophozoites. He was treated with pyremethamine-sulphametoxazole and recovered without further problems.

Case 4 (**December 1997**)

A 74-year-old Italian missionary and medical doctor resident in the Central African Republic consulted us more than one month after the acute phase. He reported a history similar to the other cases, but complicated by transient anuria. The episode followed administration of both quinine and halofantrine and therefore it was impossible to determine which drug was directly involved in this case. Haemoglobin was still only 7.5 g/dl; thick film and QBC® were negative.

Case 5 (**January 1998**)

A 44-years-old Brazilian missionary resident for many years in Angola was treated with oral quinine for 'mild' *P. falciparum* malaria. After a few hours he suddenly presented high fever with shivering, black urine followed by oliguria and then anuria. He was admitted to a hospital in Luanda with Hb 5.4

g/dl and creatinine 19 mg/dl, transfused and submitted to haemodialysis twice, then transferred to Italy. Further deterioration of the renal indices necessitated two more dialysis sessions and another transfusion. At presentation blood films were negative for malaria parasites. Several days after recovery from the acute phase, the anaemia still failed to improve and a new, thorough search revealed scanty *P. falciparum* trophozoites. He was finally treated with pyremethamine-sulphametoxazole and recovered fully.

Considering the total number of *P. falciparum* malaria infections diagnosed in semi-immune expatriate African residents during the last five years in our ward, BWF accounts for about 3%, which is frankly alarming. Two patients (cases 1 and 5) would almost certainly have died without intensive care facilities. Moreover, we are aware of at least three deaths of Italian nuns in African countries that according to clinical observations and the few laboratory data available were compatible only with BWF. All our cases gave a previous history of several treatments with quinine at inadequate dosage and length (often 3 days at insufficient dose, without an associated drug). Such therapeutic conduct, although probably sufficient to cure acute malaria in semi-immune subjects, appears to be a serious risk factor for BWF and should be discouraged.

Once BWF is apparent, artemisinin derivatives would probably be the best therapeutic choice, as halofantrine and mefloquine are incriminated as triggers themselves and resistance to pyremethamine-sulfametoxazole is increasing. Alas, so far no drug of this family has been registered in Italy.

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Incidence of substandard drugs in developing countries

Sirs, The reports by Shakoor *et al.* (1997) and Verduin-Muttiganzi and Verduin-Muttiganzi (1998) on the potency of therapeutic agents in developing countries would appear to represent the tip of an iceberg. Quantification of the active ingredients in field-retrieved samples of chloroquine, amoxycillin, tetracycline, cotrimoxazole, ampiclox and prednisolone revealed up to 36.5% substandard samples (Shakoor *et al.* 1997) in Nigeria and Thailand, while all tested lots of prednisolone in Tanzania were substandard (Verduin-Muttiganzi & Verduin-Muttiganzi 1998). These drugs should be stored at room temperature (max. 25–30 °C). Innumerable drugs must be refrigerated at 2–8 °C or kept in cold storage at 8–15 °C. Common drugs requiring refrigeration include insulin, interferon, ergometerine maleate, oxytocin, pepsin, thrombolytic agents and vitamin D; while cold storage of digitoxin, isosorbide dinitrate, Vitamin A and suppositories ensures their potency (Reynolds 1996). Appropriate assays could be employed to quantify the active ingredients of both these groups of medicines. Investigations of the quality of ergometerine injections imported to Zambia point to the poor quality in all three bands (Nazerali & Hogerzeil 1998). Even before their distribution to remote hospitals and health centres outside Harare and Bulawayo, 17 of 26 lots tested failed potency tests. Field samples exhibited serious instability causing a mean potency loss of 17% over 4.8 months. Investigations of the quality of other drugs resembled the dismal record of heat-sensitive vaccines during field use (Afu *et al.* 1996).

The best way to tackle the scourge of ineffective therapeutic agents in developing countries would be to stabilize medication against deterioration in adverse environments. Stabilization of vaccines by adding trehalose, pirodavir, deuterium oxine or compounds based on electrostatic intervention (Brown 1996) has been encouraging. Furthermore, standardized simple one or two-step assays for use in the field are vital as an alternative to HPLC to quantify active ingredients in drugs. A semiquantitative paracetamol-specific test for field use works well and does not require trained personnel or costly equipment (Roy *et al.* 1997). Similar tests would be immensely useful to monitor the quality of drugs in pharmacies and other drug distribution centres.

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