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Received 13 October 2000; revised 5 April 2001; accepted for publication 9 May 2001

TRANSACTIONS OF THE ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE (2001) 95, 517–518

Short Report

Acute asymptomatic hepatitis in a healthy normal volunteer exposed to 2 oral doses of amodiaquine and artesunate

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Abstract

Combination antimalarial therapy is being explored to delay development of resistance to falciparum malaria. This report describes an unexpected drug-induced hepatitis in a previously healthy young woman exposed to 2 doses of amodiaquine and artesunate. Use of these combinations should be closely monitored.

Keywords: antimalarial agents, amodiaquine, artesunate, adverse events, volunteer, liver function, hepatitis, South Africa

Multidrug-resistant *Plasmodium falciparum* is a global problem (WERNSDORFER & PAYNE, 1991). The use of antimalarial drug combinations with independent mechanisms of action is a rational approach to delay the onset of drug resistance and safeguard existing drugs (WHITE & OLLIARO, 1996). Current field research is assessing oral artesunate combined with standard antimalarials, e.g., sulfadoxine–pyrimethamine, amodiaquine, for treating acute uncomplicated falciparum malaria. Artesunate has a short half-life and produces a rapid and substantial reduction of malaria parasites; those that remain are then killed by the combinant drug acting over a longer time period. To complement the field studies, an interactive pharmacokinetic study of artesunate and amodiaquine was conducted in normal healthy volunteers at the University of Cape Town. We report the occurrence of asymptomatic hepatitis in a woman during this study.

This single-dose 3-phase cross-over study was conducted in 15 volunteers, 10 male and 5 female, aged 19–42 years. All volunteers received 1 dose of oral artesunate (4 mg/kg) on day 0, followed, on day 7, by either 1 dose of oral amodiaquine (10 mg/kg) alone or combined with a single dose of artesunate (4 mg/kg). Subjects were given the alternative regimen on day 28. Blood for routine haematology and biochemistry was taken on days 0, 6, 27 and 48.

Our subject was a healthy 20-year-old South African woman of African–Caucasian descent, with no previous significant illnesses. During the study she did not take any prescribed or over-the-counter drugs, including paracetamol, and had no reported drug allergies. She did not drink alcohol and had no risk factors for hepatitis B. Her family history was unremarkable. Clinically, there were no abnormal physical signs and her baseline blood tests were all normal. She received artesunate (day 0), amodiaquine (day 7), followed by the combination (day 28). Six days after taking artesunate alone, her aspartate aminotransferase (AST) and total bilirubin were normal but she had a slight increase in alanine aminotransferase (ALT) of 31 IU/L (normal 1–25 IU/L) that was not considered clinically significant (Figure). On day 27, all blood tests were normal. On day 48, her transaminases were elevated, rising to peak values (AST 236 IU/L, ALT 483 IU/L) on day 69, decreasing thereafter to normal values over 45 days (day 124). Lactic dehydrogenase (LDH) and gamma glutamyl transpeptidase (γGT) were also elevated. She remained asymptomatic and afebrile throughout her illness. She did not develop any physical signs of either liver dysfunction or the possible aetiology of her hepatitis: in particular no rash, lymphadenopathy, splenomegaly, enlarged tonsils. Pertinent investigations were non-contributory and included a normal urea, creatinine, CPK, total white cell, neutrophil, lymphocyte and eosinophil counts, and prothrombin time. There were no atypical lymphocytes. Serologies for hepatitis A, B and C, and autoantibodies [anti-nuclear factor (ANF), anti-mitochondrial and smooth-muscle antibodies] were negative. A liver ultrasound on day 72 was normal. A liver biopsy was postponed after the first improved transaminase results.

This normal, healthy female volunteer developed an asymptomatic rise in liver enzymes following the sequential administration of artesunate and amodiaquine which we believe was most probably caused by the amodiaquine alone. Other causes of asymptomatic hepatitis, e.g., Epstein–Barr virus, cytomegalovirus, toxoplasmosis were considered unlikely in the absence of other physical signs, the lack of lymphocytosis, her immune competent state (HSU *et al.*, 1995). Furthermore toxoplasmosis is rare in Cape Town (Liver Unit, University of Cape Town, personal communication).

Amodiaquine-induced hepatitis during malaria prophylaxis is well described and may be associated with neutropenia (LARREY *et al.*, 1986; NEFTEL *et al.*, 1986; WOODTLI *et al.*, 1986; CHARMOT & GOUJON, 1987; BERNUAU *et al.*, 1988; RAYMOND *et al.*, 1989). These side-effects are thought to be immune mediated but the pathogenesis remains unclear (CLARKE *et al.*, 1991). Hepatitis has occurred from as early as 3 weeks (exposure to 3 weekly doses) to as late as 10 months of prophylaxis (CHARMOT & GOUJON, 1987). Clinically, reported cases have ranged from a mild, transient elevation of liver enzymes with few symptoms (LARREY *et al.*, 1986; CHARMOT & GOUJON, 1987) to fulminant hepatitis with either slow recovery of function (LARREY

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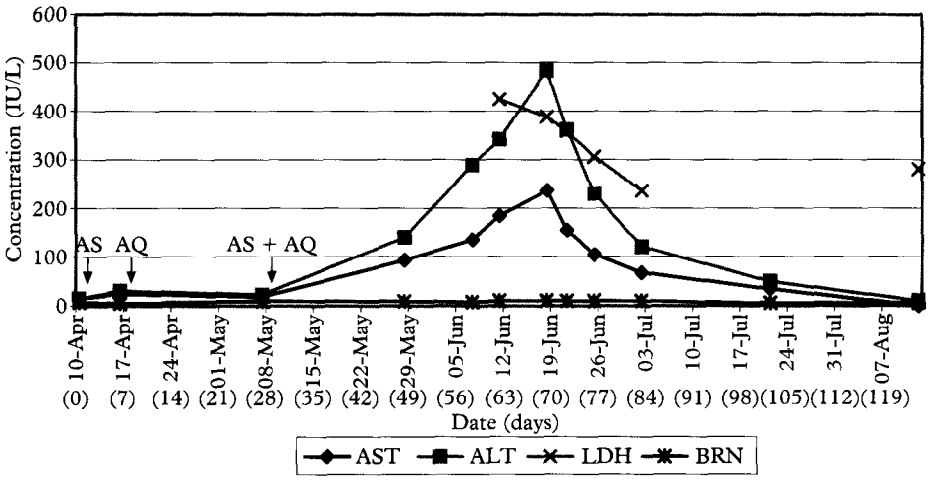

Figure. Liver enzyme profiles of a healthy female volunteer participating in an interactive cross-over pharmacokinetic study of oral artesunate and oral amodiaquine. (Normal ranges: aspartate aminotransferase (AST) 7–25 IU/L, alanine aminotransferase (ALT) 1–25 IU/L, total bilirubin (BRN) 1–17 μmol/L, lactic dehydrogenase (LDH) 175–350 IU/L, gamma glutamyl transpeptidase (γGT) 0–40 IU/L).
AS = dose of artesunate taken; AQ = dose of amodiaquine taken; AS + AQ = dose of both drugs taken.

et al., 1986; NEFTEL *et al.*, 1986), or death (NEFTEL *et al.*, 1986; BERNUAU *et al.*, 1988; RAYMOND *et al.*, 1989).

Data on hepatic toxicity and amodiaquine use in malaria-endemic areas are few. Amodiaquine appears to be safer as treatment rather than as prophylaxis. However, we are unable to identify studies examining delayed onset hepatitis following treatment, or longitudinal studies of repeated treatments (OLLIARO *et al.*, 1996). Artesunate has been widely used in South-East Asia and China and is well tolerated—there have been no reported cases of hepatitis (RIBEIRO & OLLIARO, 1998; PRICE *et al.*, 1999). Although we believe the amodiaquine alone was the probable cause of the hepatitis in our subject, we cannot exclude the possibility of an interaction between artesunate and amodiaquine. Close to 200 patients have received this combination in studies ongoing at the present time. Toxicity data from the field are awaited.

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Received 2 January 2001; revised 4 April 2001; accepted for publication 5 April 2001