

y to Amodiaquine alone or in combination with  
plicated *P. falciparum* malaria in Ghanaian Children:

The effect of CYP450 2C8 Mutations

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**Background:** Amodiaquine-artesunate (AQ-AS) is a widely adopted artemisinin combination therapy (ACT) regimen for the treatment of uncomplicated falciparum malaria in many sub Saharan African countries including Ghana. Amodiaquine (AQ) is almost exclusively metabolised into *N*-desethylamodiaquine by cytochrome P450 2C8 (CYP2C8) isoform. CYP2C8 variant alleles have been associated with defective metabolism of the anticancer drug paclitaxel. This raises the suspicion of impaired AQ metabolism which could in turn affect both efficacy and the frequency of adverse events (AEs). A high prevalence of the CYP2C8\*2 mutation has been found in Ghana. Though ACTs are thought to be widely safe and well tolerated, evidence about safety is largely lacking in relation to this mutation. Here, an assessment of AEs in relation to AQ-based therapies and the influence of CYP2C8 mutations in their occurrence is described, analysed and interpreted using data from a clinical trial carried out in Ghana in 2005.

**Objectives:** This study is focussed on assessing and comparing the incidence and severity of AEs among participants receiving either AQ alone or AQ-AS. Specifically, the effect of CYP2C8 mutations on the incidence and severity of AEs in the two treatment arms is analysed.

**Methods:** Data utilised in the study was collected during a randomised controlled, double blind trial carried out according to WHO, 2003 guidelines in Ghana to assess the efficacy and safety of AQ-AS in comparison to AQ alone. The study recruited 400 children, 6 to 59 months old who were randomised to receive either AQ-AS (10 mg/kg body weight and 4 mg/kg bodyweight, respectively) or AQ-placebo (10 mg/kg body weight) on days 0, 1 and 2. AEs were assessed from the day of enrolment and on days 1, 2, 3, 7, 14, 21 and 28 and any other day the child reported sick during the 28 days follow up period. A standardized checklist was applied during the assessment to maintain consistency. Alanine aminotransferase (ALT) and absolute neutrophil count (ANC) were regularly measured to assess potential hepatic and haematological AEs, respectively.



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p=0.05) was found to significantly higher in the AQ-  
occurred significantly more frequently in the AQ-AS arm.

The proportion of children experiencing AEs was largely independent from the CYP2C8 genotype as were ALT and ANC. However, abdominal pain (p=0.04) and anxiety (p=0.008) was less frequently reported among children with the CYP2C8\*2 mutation (heterozygote + homozygote) as compared with the wild type.

**Conclusion:** The evidence of increased risk of AEs occurring among those harbouring the CYP2C8 mutation is not convincing from this study. Therefore AQ- based therapies can be considered safe for those with both the mutant and wild type genotype. However, further research that is larger and more refined is required in order to draw more definite conclusions.