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Chloroguanide metabolism in relation to the efficacy in malaria prophylaxis and the S-mephenytoin oxidation in Tanzanians

Erik Skjelbo MD, Theonest K. Mutabingwa MD, Ib Bygbjerg MD, Karin K. Nielsen
PhD Lars F. Gram MD, Kim Brøsen MD.

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Abstract

S-Mephenytoin and chloroguanide (proguanil) oxidation was studied in 216 Tanzanians. The mephenytoin *S/R* ratio in urine ranged from <0.1 to 1.16. The distribution was skewed to the right, without evidence of a bimodal distribution. Ten subjects (4.6%, 2.2% to 8.3%, 95% CI) with an *S/R* mephenytoin ratio >0.9, were arbitrarily defined as poor metabolizers of mephenytoin. The chloroguanide/cycloguanil ratio ranged from 0.82 to 249. There was a significant correlation between the mephenytoin *S/R* ratio and the chloroguanide/cycloguanil ratios ($r_s = 0.73$; $p < 0.00001$). This indicates that cytochrome P450C19 or CYP2C19 is a major enzyme that catalyzes the bioactivation of chloroguanide to cycloguanil. Chloroguanide is a pro-drug, and hence a low CYP2C19 activity may lead to prophylactic failure caused by inadequate formation of cycloguanil. Fifty-eight women who previously took either 200 mg chloroguanide daily ($n = 26$) or 200 mg chloroguanide daily plus 300 mg chloroquine weekly ($n = 32$) in a malaria chemoprophylaxis study showed that there was a significant correlation between the number of earlier breakthrough parasitemia episodes and the chloroguanide/cycloguanil ratio ($r_s = 0.30$; $p = 0.02$). The breakthrough rate did not correlate with the *S/R* mephenytoin ratio. However, other factors, such as exposure to mosquitoes and sensitivity of the plasmodium to cycloguanil, are probably more important.