EVALUATION OF ANTIMALARIAL DRUG ACTIVITY AGAINST *P. FALCIPARUM* BY AN IN VITRO RADIOISOTOPIC METHOD

D.G. Sixsmith, W.M. Watkins and J.D. Chulay* (Pharmacy Department, University of Nairobi, &*Clinical Research Centre/USAMRU-Kenya).

An in vitro method (Desjardins et al 1979) was used to measure the antimalarial activity of five drugs: proguanil, its active metabolite cycloguanil, pyrimethamine, chloroquine, and an experimental compound M&B 35769.

P. falciparum in human erythrocytes was cultured in RPMI medium 1640 at 37°C. For testing, aliquots of culture were added to 96-well microculture plates containing doubling dilutions of drug and incubated for 42 hr. During the final 18 hr cultures were pulsed with ^{3}H-hypoxanthine. The contents of the wells were then harvested onto glass fibre filters which retained macromolecules, and radioisotope incorporation into nucleic acids was measured by liquid scintillation counting. Drug sensitivity was evaluated by determining the drug concentration causing 50% inhibition of radioisotope incorporation. A sensitive laboratory strain (JC1), two Kenyan (K34, K39), two Vietnamese (Smith, FVO), one Malaysian (Camp), and three Thai (CH81, CH84, T30) strains were tested.

P. falciparum strain	Mean ID_{50} ng.ml^{-1}				
	pyrimethamine	cycloguanil	proguanil	M&B 35769	chloroquine
JC1	21	8	5481	17	10
FVO	38	2139	5225	6	125
CAMP	212	22	1682	13	8
K34	638	183	1499	99	15
K39	1269	192	3570	100	11
SMITH	1447	1151	2363	139	59
CH81	1936	1695	2845	231	150
CH84	2170	2774	3383	307	115
T30	2554	1619	1970	221	100

These strains exhibited considerable differences in sensitivity to these drugs. Cross resistance between the dihydrofolate reductase inhibitors (DFRI) cycloguanil and pyrimethamine was usually observed, but the FVO strain was resistant to cycloguanil but sensitive to pyrimethamine, and the Camp strain was resistant to pyrimethamine but sensitive to cycloguanil. Proguanil, generally considered to be an inactive pro-drug, was less effective than its metabolite cycloguanil, yet was active at about the same level against both cycloguanil- and pyrimethamine-resistant parasites. This suggests that the site of action of proguanil may be separate from that of either of the other two DFRI compounds, and it may therefore play a role in the overall action of the drug.

Sensitivity to chloroquine, which is not a DFRI, was as expected not related to DFRI sensitivity. Strains resistant to both cycloguanil and pyrimethamine were resistant to M&B 35769, but strains resistant to only one of these two drugs were sensitive to M&B 35769. M&B 35769 activity correlated well with that of pyrimethamine (r^2=0.88), although it was, on average, nine times more active on in vitro testing, and thus shows good potential as an antimalarial drug.

Desjardins, R.E. et al (1979) Antimicrob. Agents Chemoth. 16: 710-718

0022-3573/82/120041 P-01$02.50/0