THE TESTING OF SOME ANTIMALARIAL DRUGS FOR MUTAGENIC ACTIVITY

K.R. Middleton, David Wiseman, Postgraduate School of Studies in Pharmacy, University of Bradford, Bradford, West Yorkshire, BD7 1DP.

The antimalarial activity of quinacrine, chloroquine and some other drugs has been suggested to result from their ability to form intercalated complexes with DNA (Hahn et al 1966). As quinacrine has been shown to be a mutagen using the Ames test system it seemed desirable that chloroquine and other antimalarial drugs should also be screened for mutagenic activity.

The system developed by Ames uses histidine requiring mutants of Salmonella typhimurium to detect mutagens capable of causing base-pair substitutions (strains TA1535 and TA100) or frameshift mutations (strains TA1536, TA1537, TA1538 and TA90). The methods were essentially those of Ames et al (1975) and the tester strains were obtained from Dr. B. Ames, University of California.

Amodioquine, chloroquine, dapsone, hydroxychloroquine, primaquine, proguanil, pyrimethamine, quinacrine, quinine and sontoquine were all tested by the spot test method which involves placing a few mgm of drug on the surface of minimal salts agar plates carpeted with tester strains, incubating the plates and examining them for the presence of rings of revertant colonies around the applied spot.

Chloroquine and quinacrine were also tested by the plate incorporation assay method in which known amounts of the test compound are incorporated into the agar, the numbers of revertant colonies counted and dose response curves constructed. Both types of test were carried out with and without the addition of "S9 mix" (Ames et al 1975) a rat liver homogenate preparation capable of activating some compounds to mutagenic metabolites.

Of the drugs tested only quinacrine showed mutagenic activity, tester strains TA1536, 1537 and 90 giving rings of revertant colonies around samples of the drug in spot tests. Plate incorporation assays with these strains gave dose response curves showing up to 1,000 revertant colonies per plate in the presence of 1μ mole of quinacrine per plate compared to less than 60 revertants per plate in drug free controls. None of the other drugs gave any rings of revertant colonies with any of the tester strains in spot tests and plate incorporation assays using chloroquine and strains TA1536, 1537 and 90 gave no evidence of mutagenic activity even with 100μ moles of drug per plate. S9 mix caused no activation of the drugs to mutagenic activity.

Antimalarial drugs are often administered to humans for prolonged periods and it is therefore particularly important that such drugs are non-carcinogenic. McCann et al (1975) have shown that most carcinogens can be detected as mutagens with the Ames test system and the negative results reported here are encouraging from the toxicological point of view.

This work also has significance in terms of the mode of action of chloroquine. It was thought that chloroquine interacted with DNA in a similar manner to its acridine analogue quinacrine but the results reported here suggest that this is not so. This observation is in keeping with the increasingly held view that inhibition of DNA replication due to intercalation of chloroquine or quinacrine between the base pairs is not a totally satisfactory explanation for the antimalarial activity of both these drugs.

Ames, B.N., McCann, J. & Yamasaki, E. (1975). Mutat. Res., 31, 347-364.
Hahn, F.E., O'Brien, R.L. et al. (1966). Milit. Med., 131 (Suppl.), 1071-1089.
McCann, J., Choi, E. et al. (1975). Proc. Natl. Acad. Sci. USA, 72, 5135-5139.

0022-3573/81/120075P-01$02.50/0