is rapid. The drug and its metabolite appear in the urine within one hour of its administration and little remains in the body after 48 hours (44-45). The decline of plasma quinine concentration with time after a single dose of the drug is monoexponential with an elimination half-life of 10-12 hours in normal persons. The main mechanism of quinine elimination is via hepatic metabolism, renal clearance of unchanged quinine accounting for only about 20% of the total clearance. There is some evidence that renal excretion of quinine is by both glomerular filtration and tubular secretion (45).

The recent studies of White et al. (45) show that the pharmacokinetics of quinine are altered significantly by malaria infection. Total clearance and the apparent volume of distribution are lower in falciparum malaria, the reduction being greater with increasing severity of the infection. Renal clearance is decreased in malaria but the reduction does not appear to have any relationship with the severity of the infection. Renal insufficiency does not alter the disposition of quinine significantly although it is customary to recommend reduction of dose of quinine in the presence of impaired renal function. Hepatic metabolism of quinine is reduced in hepatic insufficiency (46). Since there is reduced hepatic blood flow as well as histopathological evidence of liver damage in experimental malaria (47-48), the reduction in the total clearance of quinine and the prolongation of its half-life are probably related to impaired liver function in the acute phase of the infection.

PYRIMETHAMINE

Pyrimethamine is absorbed relatively rapidly from the intestine so that after an oral dose peak plasma level is reached between 2 and 6 hours. The absorption is almost complete. It is distributed throughout the body fluid and is moderately bound to tissues with an apparent volume of distribution of about 3 l/kg. It is about 80% bound to plasma protein. Salivary concentration is about 20% of that of plasma and reflects the unbound drug concentration in the plasma (49).

The drug persists in the plasma and continues to be excreted in the urine for as long as two weeks after the administration of a single oral dose of 25 mg. The elimination half-life in a number of studies has been of the order of 80 - 100 hours (49-50).

PROGUANIL

Proguanil is rapidly absorbed from the intestine peak concentration after a single oral dose being reached in about 4 hours. It is concentrated in the red blood cells where the concentration is 4-8 times greater than that of plasma. It is converted in the body to a triazine metabolite, cycloguanil, which is thought to be the active compound. Excretion is slow and takes place largely through the kidney. About 40% of a given dose is recoverable in the urine and faeces in the unchanged form, the rest as the metabolite. The plasma elimination half-life is about 24 hours.

SULPHADOXINE AND SULFALENE

These two compounds are long-acting sulphonamides. They are rapidly and well absorbed but slowly excreted. The elimination half-life of sulphadoxine is estimated to be between 100 and 200 hours while that of sulphalene is about 64 hours. They are highly bound to plasma protein. Only a small proportion is metabolised, about 5% to the acetyl derivative and 2-3% to the glucuronide. Acetylation of sulphonamides is now known to be genetically determined, there being slow and rapid acetylators. However, in view of the very small percentage of these sulphonamides subject to acetylation, differences in acetylator
phenotypes should not affect the activity of these drugs in man.

DAPSONE

Dapsone is well absorbed from the intestine peak plasma concentration being reached 3-6 hours after an oral dose. It is distributed widely in all tissues. It is about 75% bound to plasma protein. Salivary concentration which reflects the free plasma dapsone concentration is about 25% of the total plasma concentration but the concentration in red blood cells is practically the same as in plasma.

Dapsone is polymorphically acetylated in man initially to monoacetyldapsone (51) but the pharmacokinetics of dapsone are similar in both fast and slow acetylators. The half-life for the elimination of dapsone from the plasma is about 28 hours (49,51-52). Dapsone and its metabolites are excreted into the bile and reabsorbed from the intestine. Urinary excretion ultimately accounts for the elimination of about 90% of an administered dose of dapsone mainly in the form of metabolites, the remainder being excreted in the faeces.

FIXED-DOSAGE COMBINATIONS

Some of the most widely used antimalarials at the present time are fixed dosage combinations of two different antimalarial drugs. The advantages of such combinations are (1) the two drugs potentiate the actions of each other so that the combination is effective against strains resistant to each of the individual components and may act on stages of the parasites' life cycle not normally sensitive to either of the components; (2) there is possibility of administering reduced dose of each component with consequent reduction in dose-related adverse reactions; (3) there is a diminished liability of resistance developing to the component drugs. It is important that certain pharmacokinetic parameters, particularly absorption and elimination half-lives, of the individual drugs in a combination should be as close as possible. This is not always the case. Thus, although the elimination half-lives of pyrimethamine and sulphadoxine, the components of Fansidar, are similar (about 100 hours), those of dapsone (25 hours) and pyrimethamine, the components of Maloprim, are quite dissimilar.

There are only very few studies on the effects of one member of a combination on the pharmacokinetics of the other. One such study is that of Ahmad et al. (49) who investigated the interaction between dapsone and pyrimethamine. They found that the pharmacokinetics of pyrimethamine were not affected by dapsone. On the contrary, the peak concentration of dapsone was decreased and its apparent volume of distribution increased by pyrimethamine. Pyrimethamine also displaces dapsone from plasma protein binding sites thus increasing the free plasma dapsone concentration, but has no effect on its elimination half-life. It is therefore obvious that studies on the pharmacokinetic interaction between the individual drugs in a combined preparation should prove helpful in evaluating their optimal proportion in the combination.

MEFLOQUINE

Mefloquine is still largely in restricted use in the treatment of malaria. It has been extensively evaluated in different parts of the world and these studies have shown that it is a potent blood schizonticide active against both CQ-sensitive and multi-resistant falciparum malaria in a single dose of 500-1000 mg base.

Mefloquine is well and rapidly absorbed after an oral dose. Its pharmacokinetics has not been studied to any great extent, but it is known that
after a single dose, effective drug levels may persist for 30 days or longer. It has a long but variable half-life of 6-33 days with a mean of about 21 days. These pharmacokinetics properties account for the therapeutic and long term efficacy of a single dose of the drug.

Mefloquine appears to be as well tolerated as the more widely used antimalarial drugs. It is also well tolerated, while retaining its efficacy, in combination with sulphadoxine and pyrimethamine.

Conclusion

Recent studies on the pharmacokinetics of the commonly used antimalarial drugs have provided useful new data for the more rational use of these drugs in malaria. However there are still substantial gaps in our knowledge of the metabolism and pharmacokinetics of some of the drugs. Continued studies are therefore essential in these aspects of antimalarial drugs since data so collected would contribute to the safer and more effective use of the drugs, and could point to directions for the development of new and better drugs or better formulations of existing drugs to use as tools in the task of better malaria control world-wide.

REFERENCES


