Chloroquine in malaria chemotherapy

Although quinine first became available over 150 years ago the therapeutic properties of cinchona bark for the treatment of malaria were known as early as the beginning of the 17th century. Quinine is very effective in the treatment of malaria but disadvantages include tinnitus and the precipitation of blackwater fever and in the 1940's, the 4-aminoquinolone drug chloroquine virtually replaced it as the agent of first choice for malaria. Chloroquine, given in an initial dose of 4 tablets, each containing 150 mg of chloroquine base, followed 2 h later by a further 2 tablets and then 2 tablets daily for 2 days has until recently been the treatment of choice for all types of malaria. Chloroquine is relatively non-toxic, although when given rapidly by intravenous injection to young children fatal encephalopathy can result. Parenteral administration may, however, be required for patients who are vomiting or seriously ill and the dose for injection is 200-300 mg. Children must not be given more than 5 mg per kg body weight by slow intramuscular injection. The intravenous injection of chloroquine in adults must take at least 10 min as faster administration may cause peripheral circulatory failure with hypotension and collapse.

During the past 15 years malaria caused by chloroquine-resistant Plasmodium falciparum strains has become increasingly recognized in Asia east of Burma and also in South America (Leading Article, British Medical Journal, 1974). To date, chloroquine-resistance has not been seen in Africa although there have been reports (Ansdell, Boosey, Geddes & Morgan, 1974) of several patients from Africa suffering from malaria which has not responded particularly well to chloroquine and has only been cured by quinine.

A number of alternative drugs are available for the treatment of malaria when chloroquine-resistance is suspected. Quinine may be given by intravenous infusion over a period of 2-4 h in a dose of from 10-20 mg per kg body weight per day, the size of the dose depending on the severity of the infection. At least four doses should be given at intervals of from 8-12 h. The serum half-life of quinine is prolonged in patients with hepatic or renal failure in whom the lower dose regime should be employed. Colonel A. P. Hall of the SEATO Medical Research Laboratory in Bangkok reporting on his extensive experience of chloroquine-resistant falciparum malaria in South-East Asia, recommends that quinine therapy should be followed by a single dose of pyrimethamine combined with sulphadoxine (Hall, Doberstyn, Mettapraking & Sonkom, 1975). This combination contains 1 or 1.5 g of sulphadoxine and 50 or 75 mg of pyrimethamine. A combination of quinine with tetracycline has been shown to be of some value in falciparum malaria (Colwell, Hickman & Kosakal, 1972). Clindamycin is probably the most potent anti-malarial antibiotic although it is only partially effective and thus has only a limited role in the therapy of malaria. Hall, Doberstyn, Nanakorn & Sonkom (1975) reported that multi-dose clindamycin therapy produced a cure rate of only 50% in falciparum malaria as compared with one of 85% with a single dose of pyrimethamine and sulphadoxine. Trimethoprim, like pyrimethamine, is an anti-folate pyrimidine and has anti-malarial as well as anti-bacterial properties. Co-trimoxazole, the combination of trimethoprim with sulphamethoxazole, has been successfully employed for the treatment of acute attacks of falciparum malaria (Fowle, 1970) although trimethoprim has been mainly studied in combination with the long-acting sulphonamopyrazine as a single-dose treatment for malaria (Martin & Arnold, 1968). Unfortunately, the combination of trimethoprim with a sulphonamide does not appear to be of much value in the treatment of certain of the South-East Asian multi-resistant Plasmodium falciparum strains (Rollo, 1975). Mefloquine, a quinoline
methanol compound also shows some promise in chloroquine-resistant falciparum malaria and is under investigation for this purpose (Hall, 1975).

Chloroquine remains the drug of first choice for the treatment of benign tertian malaria. However, following the three day course of chloroquine for benign tertian malaria an 8-aminoquinoline compound such as primaquine must be given for 14 days in order to eradicate extra-erythrocytic plasmodia from the liver and thus effect a cure. The dose of primaquine is 15 mg daily. Before prescribing primaquine it is important to ensure that the patient does not suffer from glucose-6-phosphate dehydrogenase (G 6-P D) deficiency as haemolysis can occur if patients with this condition are given primaquine. Even in the absence of G 6-P D deficiency haemolysis may occur and patients receiving primaquine should be supervised during the 14 day course.

A. M. GEDDES
Department of Communicable and Tropical Diseases,
East Birmingham Hospital

Additional text is present in the image, which includes references and a section on extra-vascular injections of antibiotics. The text discusses the frequency with which extra-vascular injections of drugs are given to patients both in and out of hospital, and the general factors governing the absorption of drugs so given. The injection of a drug into a site outside the blood circulation is widely assumed to result in rapid and complete absorption and to give superior bioavailability to that of an orally-administered drug. Recently these views have been challenged for drugs acting on the central nervous system (Dam & Olesen, 1966; Greenblatt, Shader & Koch-Weser, 1974). Furthermore there appears to be differences in the rates of absorption between the various anatomical sites commonly used for intramuscular injections. The choice of intramuscular injection site is usually governed by nursing considerations rather than by medical prescription but for at least one drug, lidocaine, the desired therapeutic effect may well require injection into the correct site. Following a previous report (Cohen et al., 1972) of differences in plasma levels of lidocaine injected intramuscularly into the deltoid, buttoc'k and lateral thigh regions, Schwartz et al. (1974) found both anti-arrhythmic activity and blood levels to be superior for deltoid muscle injection over the lateral thigh site. These differences may well be related to the vascularity of the muscles concerned as 113Xenon washout studies show the resting muscle blood flow is higher for the deltoid muscle than for thigh muscle, which in turn was higher than for buttock muscle (Evans, Proctor, Fratkin, Velandia & Wasserman, 1975). Perhaps more surprising is the suggestion that similar differences in absorption rates also apply to subcutaneous injections. The clearance of 111I-labelled lente insulin has been noted to be more rapid from the upper part of the thigh (Joiner, 1959). Nora, Smith & Cameron (1964) found that 111I-labelled lente insulin was cleared more rapidly from deltoid region injections than those into the thigh, there being no significant differences between intramuscular or subcutaneous injections for any one anatomical region. Similar differences for insulin were described by Binder (1969), and the uptake of another large molecule, gammaglobulin, may also be similarly affected (Smith, Griffiths, Mallison & Mallison, 1972).

The effect of injection site on absorption has been studied by us for 3 antibiotics in healthy volunteers (Reeves, Bywater, Wise &