Antimalarials and Other Second-Line Drugs

Antimalarials

History

The use of antimalarials in rheumatoid arthritis has had a chequered history since the publication of controlled studies in the 1950s.

Chemistry

Chloroquine (CQ) and hydroxychloroquine (HQ) are 4-aminoquinolines which are effective against the malarial parasite. Chloroquine phosphate is a white bitter powder which is soluble in water. The d-isomer is less toxic than the l-isomer. Hydroxychloroquine is formed by the hydroxylation of one of the N-ethyl substituents of chloroquine.

Pharmacology

Chloroquine and hydroxychloroquine are almost completely absorbed from the gastrointestinal tract and circulate in bound–free equilibrium with plasma proteins. At therapeutic concentrations approximately 55% is bound in the case of CQ. Excretion is mainly by the renal route, most of the drug appearing as desethylchloroquine or unchanged in urine. The renal excretory mechanism is enhanced by acidification and retarded by alkalinisation of the urine. Approximately 10% of the administered dose is excreted in the faeces and a substantial proportion of the remainder cannot be accounted for by either of these routes. It has been suggested that concentration and loss in hair and epidermal cells may be responsible for at least some of this discrepancy. Deposition in tissues rich in melanin and in parenchymatous organs is cumulative.
Rheumatological Indications

1. Rheumatoid Arthritis. Antimalarial enthusiasts advocate ready prescription of CQ and HCQ to patients with early rheumatoid arthritis, and continue this therapy indefinitely. At the other end of the spectrum are rheumatologists who refuse to use antimalarials at all. Discussion of the antimalarials should be placed in a “2nd line” context.

Much of the controversy centres on ocular toxicity, with contradictory reports in the literature. Certainly several studies have demonstrated that after a delay of several months both CQ and HCQ will produce symptomatic relief superior to placebo and lead to a fall in the erythrocyte sedimentation rate and in rheumatoid factor titres. While to date no radiological improvement has been documented, there is no doubt that these drugs produce significant benefit in many of the rheumatoid patients for whom they are prescribed. This benefit falls short of that seen in patients who respond to gold. The problem of toxicity is discussed in more detail below. Therapy should not be commenced without the cooperation of an ophthalmologist who will monitor the patient at least three times per year and, as always, with the informed consent of the patient. Blinding is an emotive topic and discussion of possible ocular toxicity needs careful handling. Many patients who remain unconcerned when bone marrow, skin or renal toxicity is discussed in relation to gold or penicillamine react dramatically and immediately to any mention of the possible visual adverse effects of chloroquine. Our policy is to explain that the drugs are safe in the first year if they are taken in the prescribed dose with appropriate ophthalmological monitoring. This should be undertaken before therapy is commenced and at 4-monthly intervals thereafter.

We insist on a formal rheumatological review after 1 year to assess the advisability of further therapy. At this stage we emphasise that there may be a small risk of ocular toxicity and that regular monitoring remains mandatory. Patients who have shown significant improvement may elect to continue therapy. Alternatively treatment is discontinued for 3–6 months and if disease activity increases CQ or HCQ is reintroduced. As in other fields, the patient needs to understand the facts insofar as they are known since compliance is essential.

Both CQ and HCQ are effective and toxicity is reported with each. The recommended dose of chloroquine phosphate (Avloclor) is 250 mg daily and of hydroxychloroquine (Plaquenil) 200 mg b.d. Some authors have suggested a daily dose of 4 mg/kg CQ and 6 mg/kg HCQ, but the difficulty in dividing the tablets currently available makes calculating individual doses an unrewarding exercise. This is, however, of more importance if antimalarials are used in children (Laaksonen et al. 1974) since appropriate dose calculation is essential in paediatric practice. There is no evidence that monitoring serum concentrations is of value in predicting efficacy or toxicity.

2. Systemic Lupus Erythematosus. Antimalarials are thought to be of value in SLE, particularly for skin and joint manifestations, although there are no adequately controlled studies in this disease. In several small studies placebo was substituted for active antimalarial in SLE patients who had responded and almost all patients relapsed.