Encyclopedia of Inflammatory Diseases
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Antimalarial Drugs

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Synonyms

Aminoquinolones; Chloroquine; Hydroxychloroquine

Definition

Hydroxychloroquine and chloroquine are antimalarial drugs used in the treatment of rheumatoid arthritis, systemic lupus erythematosus (SLE), antiphospholipid syndrome, skin diseases, and in the treatment of chronic Q fever. Hydroxychloroquine is the more widely used.

Chemical Structures and Properties

See Fig. 1.

Metabolism and Pharmacokinetics

The metabolism and clearance of hydroxychloroquine and chloroquine are similar. Both are rapidly absorbed. During long term treatment, the excretion of unchanged chloroquine and hydroxychloroquine account for about 20 % and 8 % of daily doses, respectively (McChesney 1983). Lesser amounts are excreted as metabolites which have lost ethyl and hydroxyethyl side chains (McChesney 1983) (Fig. 2). Two metabolites of hydroxychloroquine are also produced from chloroquine (Fig. 2). A feature of the antimalarials is their long terminal half lives of about 40 days which indicate that steady state is achieved after treatment for 3–6 months (Tett et al. 1989). The therapeutic plasma concentrations of hydroxychloroquine and chloroquine are approximately 0.2 mg/L (0.6 μmol/L) (Miller et al. 1991). As about 50 % is not bound to plasma proteins, this corresponds to an unbound concentration of about 0.1 mg/L (0.3 μmol/L). The plasma concentrations of chloroquine are similar.

Pharmacological Activities

The mechanism of action of the antimalarials in the treatment of inflammatory diseases is unclear. Both antimalarials are lysosomotropic agents i.e. as weak bases they are taken up selectively into acidic cellular compartments such as lysosomes (de Duve et al. 1974). It is widely proposed that the antimalarials raise

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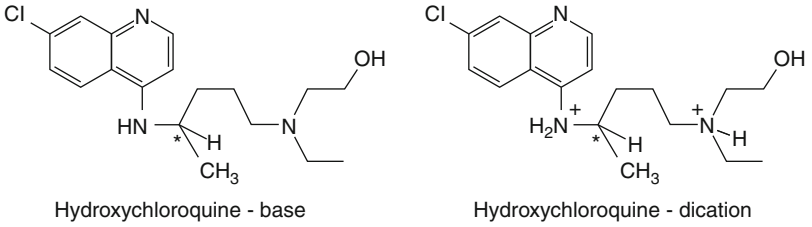

Fig. 1 Hydroxychloroquine showing the structures of the neutral base and the dication which is the major form at physiological pH values. The pKa values of the cation form are 8.11 and 10.11 at 37 °C (Ferrari and Cutler 1987). Hydroxychloroquine is an enantiomeric compound. The chiral centre is marked. It is available as the racemic mixture. Chloroquine does not have the hydroxyl on the side chain. Hydroxychloroquine is used as its sulfate salt (100 mg of sulfate is equivalent to 78 mg of base)

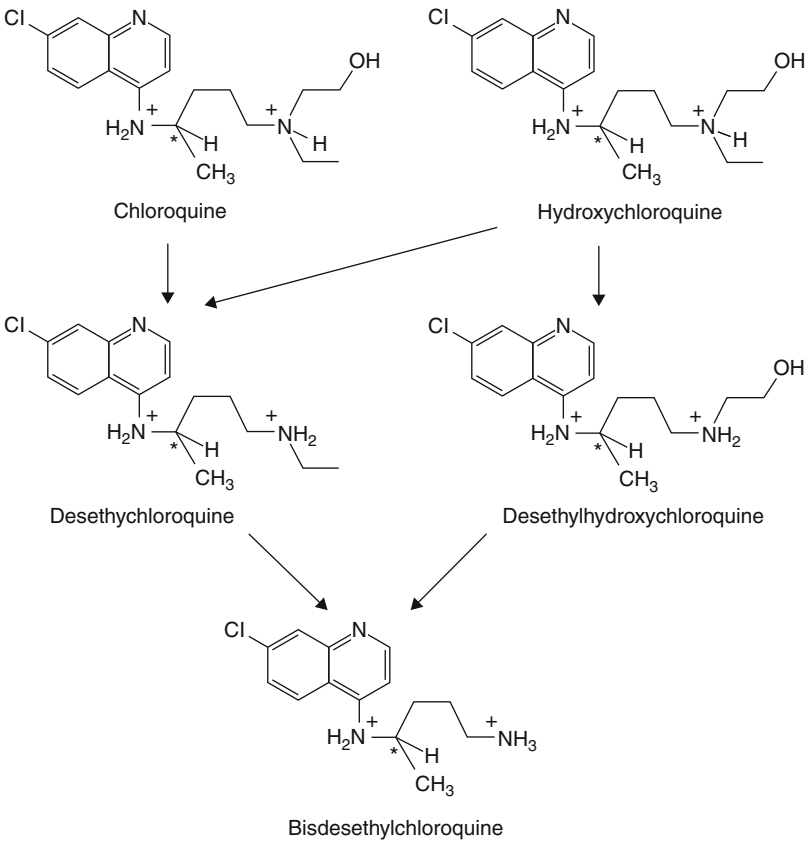

Fig. 2 Metabolism of chloroquine and hydroxychloroquine

the pH of lysosomes leading to inhibition of their constituent enzymes and inhibition of proteolysis, chemotaxis, phagocytosis, and antigen presentation. Although the antimalarials are localized within lysosomes, there is surprisingly little data at therapeutic concentrations to support this hypothesis of inhibition of lysosomal enzymes at extracellular therapeutic concentrations. The plasma concentrations of macrophage derived pro-inflammatory cytokines Il-1, Il-6 IL-18 and TNF are decreased during treatment, particularly in patients with high levels before treatment (Tang et al. 2012; Wozniacka et al. 2006). Inhibition of matrix metalloproteinases, and T and B-cell receptor calcium signaling may also occur. Antimalarials may also modify innate immunity via their inhibition of toll-like receptor 3, 7 and

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9 signalling (Dorner 2010). The beneficial effect of antimalarials in cutaneous lupus may relate to the absorption and blocking of UV light cutaneous reactions and binding and stabilization of DNA.

Therapy with the antimalarials is also associated with a variety of little known but potentially clinically significant effects. These include decreases in atherogenic lipids, blood glucose, platelet aggregation and hazard rates for cancer (Tang et al. 2012). These effects are also shown by non-steroidal anti-inflammatory drugs and paracetamol (Graham et al. 2013) and are consistent with a generalized anti-inflammatory effect of the antimalarials.

Clinical Use

In addition to their use in acute malaria, the antimalarials are most commonly used in the treatment of rheumatoid arthritis, SLE, palindromic rheumatism and antiphospholipid syndrome. Less common indications include eosinophilic fasciitis, dermatomyositis, Sjogren's syndrome, porphyria cutanea tarda, polymorphous light eruption, granuloma annulare, sarcoidosis and lichen planus.

The maximum daily doses should be based on lean body mass – up to 4 mg/kg/day chloroquine (200–300 mg daily) and up to 6.5 mg/kg/day hydroxychloroquine (200–400 mg daily). An initial higher daily dosage of 1,200 mg hydroxychlororquine day has been used for the first 6 weeks; this accelerates the clinical response in rheumatoid arthritis but with higher gastrointestinal side effects (Tett et al. 1989). Caution is advised in the use of antimalarials in severe hepatic and renal impairment.

Rheumatoid Arthritis

Hydroxychloroquine and chloroquine are mild anti-rheumatic drugs with low toxicity. These properties make them useful for the treatment of early rheumatoid arthritis. Unlike other slow acting slow acting drugs, they do not appear to retard the ongoing joint damage of rheumatoid arthritis. They appear most useful in rheumatoid patients with mild disease activity. They are also useful in combination with other anti-rheumatic drugs.

SLE

Hydroxychloroquine decreases disease activity, and may reduce the frequency and severity of acute exacerbations (flares). Its withdrawal in clinically stable SLE patients leads to more frequent flares of disease in the subsequent 6 months (Tang et al. 2012). Hydroxychloroquine also appears to reduce the frequency of class IV glomerulonephritis, and retards the occurrence of renal damage. Thrombovascular events are reduced in SLE by up to two-thirds. Also, hydroxychloroquine is protective against thrombosis in patients with antiphospholipid syndrome with and without lupus. At least two prospective studies have shown significant reductions in mortality which appear to be dependent on the length of treatment. Amongst mothers with SLE who were anti-Ro/La positive, hydroxychloroquine taken during pregnancy decreases the development of cardiac neonatal lupus (Tang et al. 2012).

Antimicrobial Activity

An unusual aspect of the antimalarials is that their treatment is associated with a substantially decreased incidence of infections with an odds ratio <0.1 although prospective studies are required to confirm these findings (Dorner 2010). Decreased infections is surprising as, in vitro, the antimalarials decrease the digestion of bacteria by macrophages (de Duve et al. 1974). Hydroxychloroquine is particularly recognized in the treatment of chronic *Coxiella burnetti* (Q fever) endocarditis in combination with doxycycline. The antimalarials have antiviral actions against and human corona virus human immunodeficiency

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virus (HIV) (Ben-Zvi et al. 2012). Presently available drugs for the treatment of HIV are very effective and it is unlikely that the antimalarials will gave great use for HIV.

Adverse Effects

Hydroxychloroquine and chloroquine are generally tolerated well although both have been associated with considerable number of adverse effects. The amount transferred during lactation is very low and is without toxicity to the child. Adverse effects of the antimalarials include:

Overdose
- Neurotoxicity:
  - Confusion, seizures, coma.
  - Cardiotoxicity:
    - Decreased contractility, arrhythmias, hypotension and cardiac arrest possible at doses above 30 mg/kg.

Therapeutic dosage
- Eye:
  - Bulls eye retinophathy. Retinopathy is the most significant adverse effect of the anntimalarials and, if it occurs, is an absolute reason for cessation of treatment. The risk increases with time, with 0.33 % retinal toxicity amongst SLE patients at 7 years, increasing tenfold to 3 % at 20 years of therapy with hydroxychloroquine. Cumulative dose relates to retinopathy better than the daily dosage previously used. New data have shown that the risk of toxicity increases sharply toward 1 % after 5–7 years of use. A maximum total cumulative dose of 1,000 g of hydroxychloroquine has been recommended by the American Academy of Ophthalmology, which approximates 7 years usage at 400 mg per day.
  - Corneal deposition of medication may cause visual halos or photosensitivity. The latter is rare in doses up to 400 mg/day and treatment may continue with resolution taking 2 months after stopping.
  - Diplopia may occur transiently on initiation of therapy.
  - Baseline macular review is recommended with annual screening after 5 years usage or earlier if renal or liver disease is present. Fundal examination must be supplemented with automated 10-2 visual fields and as indicated one of multifocal electroretinogram (mfERG), spectral domain optical coherence tomography (SD-OCT), or fundus autofluorescence (FAF),
- Current recommendations for ophthalmic screening:
  - At baseline:
    - If no “risk factors” present, begin annual monitoring from 5 years of use
    - If risk factors present, annual monitoring using one of the above sensitive tests recommended
    - Factors increasing risk of retinal toxicity with use of hydroxychloroquine:
    - Duration of use >5 years
    - Cumulative dose >1,000 g
    - Daily dose >400 mg/day

Older age
- Kidney, hepatic dysfunction

Obesity
- Ocular disease – retinal disease or maculopathy
- Cardiac:

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Hydroxychloroquine is unlikely to alter cardiac conduction greater than that seen in the underlying disease group, although chloroquine may alter conduction.

Central nervous system:

Headaches, nightmares and tinnitus.

Gastrointestinal:

Loss of appetite in 10 % patients on hydroxychloroquine with occasional vomiting and diarhoea.

Allergic:

Urticaria and erythroderma.

Skin and hair:

Up to 20 % develop blue-grey skin pigmentation of the face, forearm and shins. Bleaching of hair and nail bed discolouration is also reported. These may not reverse. Possible changes should be monitored.

Peripheral neuropathy is uncommon.

Foetus: Hydroxychloroquine and chloroquine cross the placenta but, unlike several slow acting antirheumatic drugs does not seem to cause foetal harm.

Drug Interactions

Very few interactions between the antimalarials have been reported although the antimalarials have been reported to increase the plasma concentrations of digoxin and beta blockers (Tang et al. 2012).

Cross-References

- ▶ Antiphospholipid Antibody Syndrome
- ▶ Disease Modifying Anti-Rheumatic Drugs
- ▶ Monocytes
- ▶ Rheumatoid Arthritis

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