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REVIEW

Antimalarials in Dermatology: Mechanism of Action, Indications, and Side Effects☆

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Abstract Antimalarial drugs have been in common use in dermatology since the 1950s. Their mechanism of action is complex, and it is now known that they act through various pathways. We review the indications for antimalarials in dermatology, their adverse effects, and some less well-known effects, such as their antithrombotic and hypolipidemic action. The most recent recommendations concerning ophthalmological screening in patients on antimalarials are also reviewed.

PALABRAS CLAVE
Antipalúdicos;
Cloroquina;
Hidroxicloroquina;
Lupus eritematoso

Antipalúdicos en dermatología: mecanismo de acción, indicaciones y efectos secundarios

Resumen Los antipalúdicos (AP) son fármacos de uso habitual en dermatología desde la década de los 50. Su mecanismo de acción es complejo, y actualmente se sabe que actúan por diversas vías. En este artículo se revisan las indicaciones de los antimaláricos en dermatología, sus efectos secundarios y algunos efectos menos conocidos, como el antitrombótico o el hipolipidemiante. Se recogen también las recomendaciones más recientes acerca del seguimiento oftalmológico de estos pacientes.

Antimalarial drugs have been known for more than 300 years. The antipyretic properties of bark from cinchona, a tree native to South America, were already known in the 17th century. The first natural antimalarial agent, quinine, was obtained from this tree and was used by European colonists in tropical countries as protection against malaria. The beneficial effects of quinine in patients with lupus erythematosus (LE) were published in 1894 by Payne, who reported the successful treatment of discoid LE with this drug.[1] The

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first synthetic antimalarial, quinacrine (QC), was made in 1930. Chloroquine (CQ) and hydroxychloroquine (HCQ) followed (CQ was first synthesized in 1934 and HCQ in 1955).[2] The use of antimalarials as a treatment for LE became widespread in 1951, with the publication of an article by Page,[3] which described good response to QC treatment in 18 patients with LE.

The antimalarials used in dermatology are CQ, HCQ, and QC. The latter of these is not commercially available in Spain and can only be used by making an application for a foreign medicine.

Pharmacokinetics

CQ and HCQ are 4-aminoquinoleins which differ from each other in that HCQ has a hydroxylated side chain. CQ is formulated as a diphosphate for oral administration. Between 90% and 100% is absorbed in the gastrointestinal tract. Stable plasma concentrations are reached after 4 to 6 weeks, and so most cases require drug administration for at least this duration to obtain therapeutic response. CQ binds strongly to plasma proteins which are deposited in tissues such as the liver, spleen, kidneys, and lungs, and in blood cells.[4,5] Avidity is particularly high for skin and melanin-containing retinal cells, where concentrations are between 100 and 200 times the plasma concentration. Between 45% and 50% of these plasma proteins are eliminated in urine. CQ has a long half-life, which can vary between 74 hours and 50 days depending on the cumulative dose. The drug can remain in the skin for 6 to 7 months after discontinuation of therapy.[6] Both drugs cross the placenta and are excreted in small amounts in breast milk.[7]

QC is a 9-aminocridin and its pharmacokinetics are similar to those of the 4-aminoquinoleins. It is also quickly absorbed after oral administration and steady-state concentrations are reached after 4 weeks.

Mechanism of Action

The mechanism of action has not been fully elucidated, but they are known to act on a range of pathways and have immunomodulatory, anti-inflammatory, antiproliferative, and photoprotective effects. Antimalarials are weak bases that can readily cross cell membranes and accumulate in acidic cytoplasmic vesicles (lysosomes or endosomes), where they remain trapped in a protonated state.[8] This mechanism of action places antimalarials in the therapeutic group known as lysosomotropic drugs.[9] The pH in lysosomes increases as antimalarials accumulate there, subsequently interfering in binding of antigenic peptides with class II molecules of the major histocompatibility complex. Presentation to $CD4^+$ T lymphocytes is thus avoided, leading to inhibition of the production of cytokines that participate in the generation of inflammatory response.[10,11] A mechanism has been proposed whereby antimalarials can act as immunomodulators without causing immunosuppression. According to this proposed mechanism, inhibition of binding with the major histocompatibility complex only occurs for autoantigens and not for exogenous peptides. Autoantigens are low affinity peptides. Thus, they do not bind to the alpha and beta chains of the major histocompatibility complex molecules when the pH of the vesicle increases. Exogenous peptides, in contrast, have a high affinity, and so binding does occur and they are presented to the T lymphocytes.[12,13]

Table 1 Mechanisms of Action of Antimalarial Agents.

Inhibition of antigen processing and presentation
Inhibition of cytokine release: interleukin (IL) 1, IL-2, IL-6, IL-18, tumor necrosis factor α, interferon γ
Inhibition of stimulation of toll-like receptors (TLR) 9 that participate in immune response
Decreased activity of natural killer cells
Inhibition of the activity of cytotoxic T lymphocytes and self-reactive CD4+ lymphocytes
Regulation of apoptosis
DNA binding: competitive inhibition of anti-DNA antibodies
Inhibition of phospholipase A2: decrease in prostaglandin and leukotriene levels
Inhibition of lysosome protease activity
Decrease in membrane receptor concentrations: decreased response to mitogenic stimuli
Inhibition of polymorphonuclear chemotaxis
Interaction with protein synthesis
Superoxide radical block

In addition, antimalarials act through other immunomodulatory, anti-inflammatory, and antiproliferative mechanisms (Table 1).[10,14–18]

Finally, a photoprotective effect has been attributed to these drugs, although the mechanism is not yet understood. One possibility is that these drugs may have a certain screen effect, absorbing certain wavelengths of sunlight.[17] Another is that antimalarials inhibit the inflammatory response of keratinocytes which is triggered by exposure to sunlight through induction of apoptosis and subsequent exposure to keratinocyte antigens.[11] Moreover, the drug may enhance natural photoprotection of the epidermis through induction of *c-jun* transcription.[19]

Other Antimalarial Actions

Other actions have also been attributed to antimalarials. These include antithrombotic, lipid-lowering, and glucose-lowering effects and effects on bone metabolism. The studies cited below have been conducted mainly in patients with systemic lupus erythematosus (SLE), and in most cases the agent used was HCQ.

Antithrombotic Action

The antithrombotic effect of antimalarials has been attributed to a range of mechanisms. First, a reduction in red blood cell aggregation has been observed.[20] Second, antimalarials inhibit platelet aggregation,[21,22] and might also reduce blood viscosity.[23] Antimalarials also hinder platelet aggregation induced by antiphospholipid antibody,[24] and inhibit the production of thromboxane A2 through deactivation of phospholipase A2 and prostaglandins in platelet membranes.[25] In addition, some authors have suggested that these drugs have a synergistic antiatherosclerotic effect