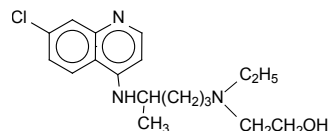


Hydroxychloroquine

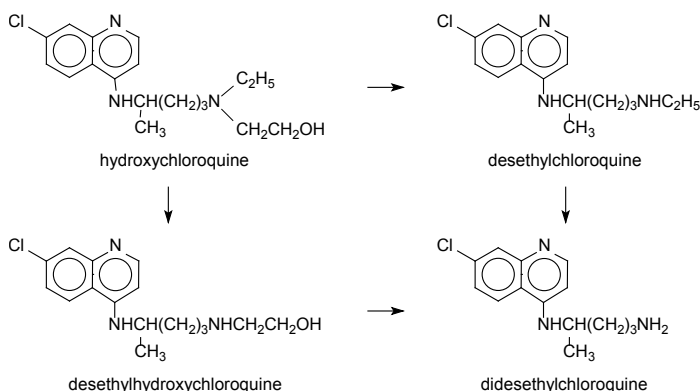
t_{1/2}: 16–36 days (plasma)
32–56 days (whole blood)
Vd: 580–815 L/kg
Fb: 0.40–0.45
pKa: 8.3 (base), 9.7 (base)
b/p: 1–21 (average, 7)
CAS: 118-42-3
MW: 335.87 (C₁₈H₂₆ClN₃O)



Occurrence and Usage. Hydroxychloroquine (Plaquenil) is an aminoquinoline derivative, closely related to chloroquine, that is used in the treatment of malaria, lupus erythematosus and rheumatoid arthritis. It is available as the sulfate salt in 200 mg tablets for oral administration. Adult doses range from as little as 400 mg per week for suppressive therapy to as much as 1200 mg in a single day for acute malarial attacks. Daily doses of 200–600 mg are used for lupus and rheumatoid diseases.

Blood Concentrations. A single oral 200 mg dose given to 27 healthy young Chinese men led to an average peak blood hydroxychloroquine concentration of 199 µg/L at 3.1 hours (Liu et al., 2012). Plasma hydroxychloroquine concentrations in healthy adults after single oral doses of 400 or 800 mg averaged 82 or 210 µg/L, respectively, at 3 hours, and 19 or 56 µg/L by 24 hours. In subjects receiving 400 mg oral doses once a week for several weeks, plasma concentrations averaged 121 µg/L (range, 106–140) at 3 hours after the dose, 62 µg/L (range, 45–77) at 24 hours and 15 µg/L (range, 11–24) at 96 hours. Plasma concentrations in excess of 10 µg/L were considered by the investigators to be effective in the suppressive treatment of malaria (McChesney et al., 1962). Healthy adults receiving daily oral 155 or 310 mg doses for 6 months attained average blood levels of 950 or 1900 µg/L, respectively, estimated to represent 96% of the eventual steady-state concentrations (Tett et al., 1989). Blood elimination half-lives exceeded those of plasma and averaged 48, 130 and 217 days for hydroxychloroquine, desethylhydroxychloroquine and desethylchloroquine, respectively (Tett et al., 1988). The oral bioavailability of hydroxychloroquine averages 79% (Tett et al., 1989). An average daily dose of 312 mg in 58 adult lupus patients led to average trough blood levels of 600 µg/L (range, 55–1935) for hydroxychloroquine and 353 µg/L (range, 118–1090) for desethylhydroxychloroquine (Sailler et al., 2007).

Metabolism and Excretion. In patients on daily therapy with hydroxychloroquine, only 13% of a dose is excreted in the daily urine as identifiable products. About 8% is eliminated as unchanged drug, 2% as desethylchloroquine, 2% as desethylhydroxychloroquine and 0.5% as didesethylchloroquine (McChesney et al., 1966). By the 4th week of once weekly oral dosing with 400 mg of the drug, 2 volunteers exhibited urine hydroxychloroquine concentrations of 2–10 mg/L during the first 24 hours post-dose; the concentrations of the 3 desethyl metabolites remained below 1 mg/L (Williams et al., 1988).



Toxicity. The adverse effects associated with hydroxychloroquine therapy include headache, dizziness, nausea and diarrhea. Acute hepatitis (Giner Galvan et al., 2007), cardiotoxicity (Chen et al., 2006) and retinopathy (Tripp and Maibach, 2006) may occur with therapeutic doses. Fatal toxic epidermal necrolysis has been reported to occur rarely (Murphy and Carmichael, 2001). The effects of overdosage with hydroxychloroquine include headache, drowsiness, visual disturbances, convulsions, cardiovascular collapse and respiratory arrest. An adult who ingested 36 tablets of the drug became moribund and vomited, but responded to supportive therapy; his plasma hydroxychloroquine level of 6.1 mg/L on admission declined to 2.7 mg/L after 2 days (Graham, 1960). An adult female ingested 12 g of the drug and survived; she exhibited cardiac arrhythmias and an admission plasma hydroxychloroquine level of 3.0 mg/L

(Villalobos, 1991). Another woman who survived the acute ingestion of 20 g had a plasma drug concentration of 9.9 mg/L at 2 hours post-ingestion; she was treated with intravenous epinephrine, potassium and diazepam for the first 24 hours (Jordan et al., 1999). Two other adults who survived ingestion of 20 g had serum hydroxychloroquine levels of 14 and 26 mg/L (Gunja et al., 2009).

A diabetic woman who believed she was pregnant attempted chemical abortion with the drug and died; her liver was found to contain 180 mg/kg hydroxychloroquine (Bonnichsen and Maehly, 1965). Heart blood, peripheral blood, liver and urine concentrations of 61 mg/L, 48 mg/L, 71 mg/kg and 970 mg/L, respectively, were observed postmortem in the case of a 16 year old boy who ingested an overdose of hydroxychloroquine and died within a short time thereafter (Dalley and Hainsworth, 1965). A 2.5 year old child accidentally ingested 12 g of drug and suffered seizures and cardiorespiratory arrest; postmortem blood and liver hydroxychloroquine concentrations of 104 mg/L and 500 mg/kg, respectively, were reported (Kemmenoe, 1990). A 17 year old girl, believed to have ingested an overdose of her mother's medication, was found comatose and died after several hours of resuscitative efforts; she had hydroxychloroquine concentrations of 7.5 mg/L in antemortem blood, 20 mg/L in postmortem heart blood and 220 mg/kg in liver (Treacy, 1999). Postmortem levels of 36–61 mg/L in blood and 211–724 mg/kg in liver were reported for 2 adults found dead following suspected acute overdose (Alha and Korte, 1977; Kristinsson, 2004).

Analysis. Hydroxychloroquine has been analyzed in biological specimens at therapeutic levels by fluorometry (McChesney et al., 1962) and at toxic levels by ultraviolet spectrophotometry (Bonnichsen and Maehly, 1965). Desalkyl metabolites of the drug are believed to interfere in both of these procedures. Liquid chromatography with ultraviolet (Morris, 1985; Brown et al., 1986), fluorescence (Tett, 1985; Williams et al., 1988) or mass spectrometric detection (Wang et al., 2012) is a more specific technique.

Hydroxychloroquine was stable in heparinized blood for 25 hours at room temperature (Wang et al., 2012). Hydroxychloroquine and its major metabolites were stable in heparinized blood for 8 months at 4 °C (Williams et al., 1988).

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