Chloroquine diphosphate

Chemical name: N^4-(7-chloro-4-quinolinyl)-N^1, N^1-dimethyl-1,4-pentanediamine diphosphate salt
Synonym: chloroquine phosphate
CAS: 50-63-5
MF: $C_{18}H_{26}ClN_3 \cdot 2H_3PO_4$
MW: 515.9
pKa=8.4
Solubility: soluble in water; soluble in chloroform, ether and dilute acids.

Major uses
Chloroquine diphosphate (further **chloroquine**) is an antimalarial agent first synthesized in 1934. It has also been used to treat rheumatoid arthritis, systemic lupus erythematosus, and in the systemic therapy of the liver diseases caused by protozoa (e.g. amebic liver abscesses).

Human toxicity
Chloroquine is a potentially fatal poisoning, often characterized by rapid deterioration. Features of toxicity may develop within 1 to 2 h, and death may occur abruptly, generally from myocardial depression and dysrhythmia.

Symptoms at an acute overdose are as following: hyperexcitability, agitation, seizures, cerebral edema, ventricular dysrhythmia, hypotension, shock, cardiac arrest, respiratory arrest, coma, and death. Among gastrointestinal symptoms, nausea, vomiting, diarrhea, and hemorrhagic gastritis have been reported with therapeutic use or overdose [1].

Therapeutic oral dose of chloroquine for malaria is 500 mg in once weekly dose, for 3 to 4 weeks, or in daily doses of 250 mg for rheumatoid disease [2].

As little as 2-3 g of the chloroquine may be fatal in an adult. The most commonly reported lethal dose for adults is 3 to 4 g. A minimum lethal dose in man is estimated at 30 to 50 mg/kg.

Therapeutic plasma levels for chloroquine are in the range from 0.02 to 0.04 mg/l to 0.15 to 0.25 mg/l [1].

Chloroquine toxicity is dose dependent. When doses less than 2 g were ingested, no clinical symptoms were registered, and serum chloroquine level was less than 2.5 mg/l. At higher doses ingested, from 2 to 4 g, serum chloroquine level was in the range of 2.5 to 5.0 mg/l; when ingested dose was greater than 4 g, serum chloroquine level was greater than 5 mg/l [1]. The average plasma chloroquine concentrations in 5 persons who ingested 3-20 g of the drug was 10 mg/l (range 3-16 mg/l; post-mortem specimens){reviewed in [2]}. The mean clinically measured acute lethal serum concentration of chloroquine, based on data from several handbooks, was 11 mg/l [3].

Carcinogenicity: group 3 (IARC, 1987) [1]. No data are available in humans.

Kinetic data
Absorption: chloroquine is rapidly and almost completely absorbed from the small intestine [1].

Kinetic is triphasic [3]. See below: *Blood plasma half life*.

Bioavailability is 89% for tablets [1].

Volume of distribution: from 116 to 285 l/kg (mean 204 l/kg) [1]. 94 l/kg [3].

Distribution: there is a large amount of tissue storage; chloroquine accumulates especially in kidney, liver, pancreas, lung and spleen, and is strongly bound in melanin containing cells (eye and skin). Chloroquine can be accumulated in heart, liver, kidney, and lung [3]. It is early accumulated in erythrocytes [3], as well in lymphocytes, macrophages and granulocytes [4]. The drug can still be found in plasma, erythrocytes and urine of patients 5 years after their last dose [1].

Passage of blood-brain barrier: free [2].

Time to peak blood concentration: 1-3 h [2].

Elimination blood plasma half-life: 3-6 h at a therapeutic dose [4]. Following this first phase, the second phase takes place, when plasma half-life varied from 2 to 7 days, at a therapeutic dose, following by the third phase with a half-life about 6-7 days [4]. The third phase may be prolonged up to 20 to 45 days at an overdose [3].

Blood protein binding: 55-61% [3].

Passage of blood brain barrier: free [3].

Metabolism and excretion

Chloroquine is a derivatives of 4-aminoquinoline. It is biotransformed in the liver, where it undergoes oxidative N-dealkylation and oxidative deamination. Main metabolite is desethylchloroquine (13%-23%). Among minor metabolites are listed didesethylchloroquine and 4-amino-7-chloroquinoline.

Desethylchloroquine has also therapeutic activity, but lower than chloroquine itself [1, 2].

Excretion: by the kidney in the urine. Unabsorbed drug is excreted via feces. Excretion is slow, but it increases by acidification of the urine. About 50% is excreted in urine and about 10% in feces by 77 days following therapy with 310 mg/day, for 14 days [1]. In persons on chronic therapy about 8% of a dose is eliminated in the daily feces and about 33% in the urine [2].

Toxicological mechanisms

The mechanisms are not well understood. Several hypothetical mechanisms were proposed: a) chloroquine can stabilize cell membranes leading to reduction of excitation and conduction in heart, and, consequently to cardiotoxicity [3]; b) chloroquine has a high affinity to melanin and accumulates in the pigmented epithelium; high concentrations of the drug in melanin lead to retinopathy (retinotoxic lesions in the eye) [5]; c) inhibition of functions of mitochondria [1]; d) inhibition of the synthesis of DNA and RNA [1]; e) inhibition of protein synthesis, and, particularly, inhibition amino acid incorporation in protein [5].

Target organs: heart, vascular system, CNS [3].

References

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Written by Ada Kolman, January 2006; revised March 2007
ada.kolman@telia.com