# Clinical Pharmacology & Toxicology Pearl of the Week

## ~Hydroxychloroquine~

- ✓ Hydroxychloroquine (HCQ) is classified as an aminoquinoline (Antimalarial) agent.
- ✓ It is a quinine derivative with an interesting history dating back to 1630 (Figure 1).
- ✓ HCQ is used in autoimmune disease, most commonly lupus and rheumatoid arthritis. It is rarely used as an antimalarial agent nowadays due to a high degree of Plasmodium resistance.

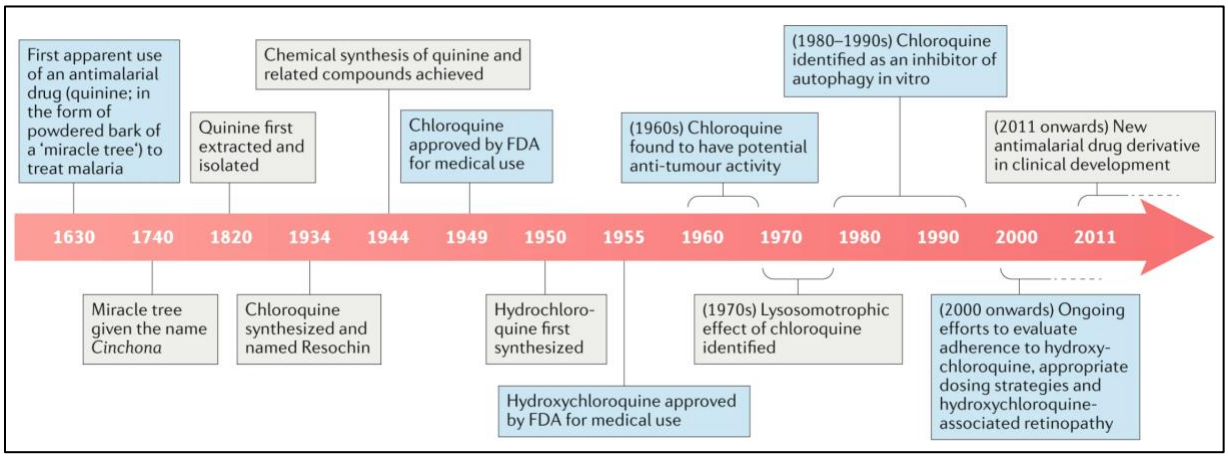


**Figure 1: Timeline of hydroxychloroquine's introduction into medical practice**. *Adapted from Nature Reviews Rheumatolgy (2020)*

**Mechanism of Action:**

- hydroxychloroquine is a weak base that accumulates in lysosomes and inflamed tissues due to their more acidic environments.
- When used for antimalarial prophylaxis, it interferes with digestive vacuole function in malarial parasites by increasing the pH and interfering with lysosomal degradation of hemoglobin, thereby depriving the parasites of sustenance.
- In autoimmune disease it has been found to interfere with lysosomal function, autophagy, membrane stability, cell signalling pathways and protein transcription. These molecular effects culminate in inhibition of immune activation via reduction of Toll-Like Receptor (TLR) signalling and cytokine production.

**Pharmacokinetics**

- Absorption: Incomplete and variable at ~70% on average.
- Protein binding: ~40%, mostly to albumin.
- Distribution: High volume of distribution (> 100 L/kg).
- Metabolism: HCQ is N-dealkylated by CYP3A4 into the active metabolite desethylhydroxychloroquine and inactive metabolites bidesethylchloroquine and desethylchloroquine; It is a minor substrate of CYP2D6.
- Elimination: Half-life elimination is 40 days on average. Routes of elimination are via urine, with 15% to 25% as metabolites and up to 60% as unchanged drug.

**HCQ Toxicity & management**

- Toxicity is as a result of sodium and potassium channel blockade, a sulfonylurea-like effect on beta islet cells, and intracellular potassium shift.
- Symptoms may appear as early as 1-3 hours post ingestion.
- Clinical features include nausea, vomiting, diarrhea, sedation, coma, seizures, psychosis, hallucinations, hypotension, prolonged QTc and dysrhythmias (bradycardia, ventricular tachycardia, ventricular fibrillation, torsades).

- Patients who vomit early post ingestion appear to have a lower risk of toxicity, whereas those with a QRS duration > 120 ms, systolic BP < 80 and hypokalemia all suggest a poor prognosis.
- Laboratory findings may include hypokalemia (which may be severe), hypoglycemia, methemoglobinemia and hemolytic anemia (in patients with G6PD deficiency).
- Chloroquine and hydroxychloroquine are substrates of CYP 2C8 and 3A4. Medications that inhibit these enzymes (e.g. clarithromycin, azole antifungals, grapefruit juice, and protease inhibitors) may cause or worsen toxicity.
- Management in suspected HCQ intoxication includes rapid assessment and management of ABC's, GCS and blood glucose, followed by stat ECG and bloodwork including CBC & electrolytes, venous or arterial blood gas, peripheral blood smear, haptoglobin and reticulocyte count (if hemolysis is suspected)
- Chloroquine and hydroxychloroquine levels are **not** clinically useful
- Urgent consultation with a Toxicologist is recommended for further guidance on management of multisystem effects of HCQ intoxication, including administration of activated charcoal (all patients should receive 1 g/kg of activated charcoal via PO/NG/OG unless contraindications are present (e.g. GCS < 15 without protected airway)).

**The Calgary Clinical Pharmacology physician consultation service is available Mon-Fri, 9am-5pm. The on-call physician is listed in ROCA. Click HERE for clinical issues the CP service can assist with.**

**The Poison and Drug Information Service (PADIS) is available 24/7 for questions related to poisonings. Please call 1-800-332-1414, and select option 1.**

**References**


1. Schrezenmeier, E., Dörner, T. Mechanisms of action of hydroxychloroquine and chloroquine: implications for rheumatology. Nat Rev Rheumatol 16, 155–166 (2020)
2. Wishart DS, Knox C, Guo AC, Shrivastava S, Hassanali M, Stothard P, Chang Z, Woolsey J. Hydroxychloroquine. Drugbank. Available at https://go.drugbank.com/drugs/DB01611. Accessed on September 19, 2020.
3. Hydroxychlorouine. Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. Available at: http://online.lexi.com Accessed September 20, 2020.
4. Browning DJ. Pharmacology of Chloroquine and Hydroxychloroquine. *Hydroxychloroquine and Chloroquine Retinopathy*. 2014;35-63.
5. Guidelines for management of chloroquine and hydroxychloroquine poisoning (2020). Poison and Drug Information Service (PADIS), Calgary, Alberta, Canada.