

# The Benefits of Chloroquine Multi-Mechanisms of Action on the Nervous System



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## Abstract

Chloroquine, primarily ant malarial drug, has other applications in treatment of inflammatory conditions, viruses and cancer chemotherapy. These conditions required long-term administration with associated side effects. Chloroquine neurotoxicity in form of psychosis and other symptoms is one of the side effects associated with chloroquine administration. However, the benefits of chloroquine in protecting the brain against ischemia proven it a vital drug. In this regard, chloroquine application in different medical conditions requires correct dosing and caution to minimize unwanted side effects. In this review, evidences confirm that chloroquine benefits outweigh its harm.

**Keywords:** Chloroquine; Neurotoxicity; Cancer; Chemotherapy

## Introduction

Chloroquine is a 4-aminoquinoline derived from the bark of cinchona tree, and is primarily used in the treatment and prophylaxis of malaria infection [1]. However, chloroquine had since found applications in the treatment of inflammatory conditions such as rheumatoid arthritis and systemic lupus erythematosus [2]. Use of chloroquine in viral treatment [3] and cancer chemotherapy [4] received wide attention and is currently under investigation due to the versatile mechanisms of chloroquine action. These mechanisms of chloroquine action arise mainly from its lysosomotropic ability, because chloroquine is a weak base, it easily accumulates in the lysosomes of cells, thereby causing its effects [5]. In malaria, chloroquine accumulates in the lysosomes and inhibit heme polymerase leading to accumulation of toxic by-product heme within the malaria parasite and subsequent cell death [6]. In inflammatory conditions, chloroquine exert anti-inflammatory effects by accumulating in the T-lymphocytes causing inhibition of antigen presenting cells and production of cytokines such IL-1, IL-6 and TNF [7]. In the viruses, chloroquine inhibit virus entry into host cells and in some viruses, it inhibits viral replication by pH modification [8]. In cancer cells, it causes the cell more sensitive to chemotherapy and radiotherapy by causing release of cellular degradation enzymes and inhibition of transmembrane protein known to extrude chemotherapeutic drugs from the target cancer cells [5]. The wide applications of chloroquine in diseases other than malaria required long duration of treatment with adverse side effects. Some of the organ toxicities of chloroquine include nephrotoxicity [9], cardiotoxicity [10], retinopathy [11] and neurotoxicity [12]. Special discussion on peripheral neuropathy

and central nervous system toxicity and benefits of chloroquine is important, considering the varying applications of chloroquine worldwide; especially Africa where malaria is endemic, poverty is commonplace, with rampant and profound chloroquine abuse taking place.

## Chloroquine Mechanism and its Harms to the Nervous System

Chloroquine is reported to accumulate in the brain, and is associated with psychosis, delirium, depression [13], lack of coordination, inability to concentrate and severe anxiety [12]. In a case report, recurrent psychosis characterized by disturbance of sleep and loss of appetite, delusions, auditory hallucinations, agitation and hostility had been associated with chloroquine treatment. Despite the patient reported had no previous history of psychiatric illness, the authors recommend caution when prescribing chloroquine to patients psychiatric history [14]. In addition, another case of chloroquine-associated psychosis was reported in a 7 year old child [15].

In another case report, myasthenia syndrome characterized by drooping of the eyelids, occurring concurrently with retinopathy was caused by chloroquine in a patient receiving treatment for psoriatic arthritis over ten years duration [16]. In addition, chloroquine is also reported to cause seizures in a patient with epilepsy [17]. Animal studies reveal that chloroquine causes degeneration, vacuolation and reduced cell population in the inferior colliculus, a part of the brain associated with the auditory pathway [18] and this could contribute significantly to chloroquine

ototoxicity [19]. Chloroquine neurotoxicity is an important adverse side effect to consider when prescribing chloroquine and screening for early signs of toxicity is highly recommended.

### Chloroquine Mechanism and its Benefits to the Nervous System

Current reports suggested that despite the neurotoxic problems of chloroquine, its neuroprotective effects are more profound. In a rat model study, chloroquine through its inflammatory action is reported to protect against experimental encephalomyelitis, which is a model for study of multiple sclerosis, thereby suggesting that chloroquine can be a candidate drug for treatment of multiple sclerosis [20]. In addition, chloroquine protect against traumatic brain injury in rats via its inhibition of autophagy and reduced synthesis of inflammatory mediators [21]. In another study using mice, the fetus were protected against microcephaly by administration of chloroquine in experimental pregnant mice, showing reduction Zika viral load in the fetal brain [22]. *In vitro* studies suggest chloroquine can protect the brain from ischemia and neurodegenerative diseases such as Alzheimer's disease, Parkinson's and stroke, by reducing glutamate-induced oxidative stress [23]. Furthermore, chloroquine is shown to suppress glioma cells in the brain by inducing cell death through different pathways including inhibition of tumor growth factor  $\beta$  (TGF- $\beta$ ) [24] and induction of autophagic vacuole accumulation, in addition to the other mechanisms mentioned above [25]. This suggested that chloroquine is useful in treatment of glioblastoma and might even cure the cancer cells as monotherapy or in combination.

### Discussion

Chloroquine is a very cheap and available drug, hence the reason for its excessive abuse in the malaria endemic countries of Africa. The use of chloroquine in malaria has since declined due to widespread chloroquine-resistant malaria and is replaced with more efficacious anti-malaria drugs. However, the application of chloroquine in other medical conditions provides another significant role for chloroquine. The neuroprotection of chloroquine is a vital drug to consider and ways to reduce the neurotoxicity should be investigated, appropriate dosing to minimize unwanted side effects on the nervous system should be established. In this regard weighing the benefits of chloroquine over its harm in the nervous system is paramount especially in the third world countries, where drugs that are more expensive are not always affordable.

### Conclusion

Chloroquine unequivocal efficacy in other disease conditions has proven it a vital drug for wide range of applications; however, caution is recommended during administration.

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