Is Chloroquine Making a Comeback?

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(See the articles by Ursing et al, on pages 109–116.)

Chloroquine began as a first-line antimalarial in 1946, the same year that the rock star Cher was born. Similar to Cher, chloroquine peaked in popularity in the early 1960s. Cher has famously made several major comebacks. Is it now chloroquine’s turn?

For decades, chloroquine was a remarkably effective, safe, and inexpensive antimalarial. Optimism about effectiveness of chloroquine led public health professionals to predict the eradication of malaria by 2000 [1]. By 1979, the equivalent of >500 million tablets of chloroquine were used each year [2]. Unfortunately, Plasmodium falciparum gradually became resistant to chloroquine. After first appearing in Southeast Asia and South America in the late 1950s, resistance spread throughout Africa by the 1980s [3]. Meanwhile, alternative antimalarials were more expensive, and many countries continued to use chloroquine despite evidence that it was not effective. Recognition of this led to accusations of malpractice against the World Health Organization and the World Bank and a vigorous drive to replace chloroquine with more-effective artemisinin combination therapies [4].

Can chloroquine make a comeback? Evidence from Malawi suggests that chloroquine resistance faded a decade after it was withdrawn from use, restoring the clinical efficacy of the drug [5]. In addition, evidence presented by Ursing et al [6] suggests that, even in the presence of chloroquine resistance, a change in the dosing regimen restores efficacy.

Ursing et al. [6] reported in this issue of The Journal of Infectious Diseases and in previous articles [7-8] that the in vivo chloroquine failure rate can be decreased by giving the drug twice per day instead of once per day. Doubling the frequently used dose of chloroquine in this way achieved a high cure rate (95%) despite preexisting chloroquine resistance and did not result in an increase in adverse events. Of interest, these authors also showed that use of this modified chloroquine dosing regimen in Guinea-Bissau has stabilized the spread of chloroquine resistance, as measured by the prevalence of pfcrT 76T [7, 9–10].

This increase in efficacy can be explained by the pharmacokinetics of chloroquine. Chloroquine can penetrate most tissues (eg, brain, eyes, heart, kidneys, leukocytes, liver, lungs, and spleen) and, therefore, has a large volume of distribution [11]. After oral administration, chloroquine is 85% absorbed in the plasma, with a time to peak plasma levels of 1–2 h, and then it is cleared in 2 phases. There is an initial brisk decrease in plasma concentration that is in accordance with first-order rate kinetics and occurs as the drug rapidly distributes throughout the body. This is followed by a second, slower phase, during which chloroquine moves from the body tissues to the plasma (Figure 1). This second phase results in the trough blood levels of chloroquine and may determine the efficacy of the dose given. By increasing the frequency of administration and dose of chloroquine, trough levels are progressively elevated.

Although chloroquine resistance is widespread, resistance is, in general, not very potent [12]. In vitro, parasites are considered to be chloroquine resistant the 50% inhibitory concentration (IC50) of the drug is >160 nmol/L (51 µg/L) [13]. Recent reports from areas where malaria is endemic documented that the majority of chloroquine-resistant isolates of P. falciparum have IC50 values <400 nmol/L (128 µg/L) [14–21]. In contrast, typical trough levels are 80–125 nmol/L (25–40 µg/L). Thus, the majority of chloroquine-resistant isolates have IC50 values that are only 3–5-fold higher than typical trough plasma concentrations. In accordance with these findings, increasing the dose and frequency of administration of chloroquine can increase plasma concentrations to levels higher than the IC50 values of chloroquine-resistant parasites.

A second reason why the new regimen may be more effective is that trough levels
of chloroquine vary substantially among individual patients, especially among those who have been previously infected with malaria [22]. The reason for the variability in these levels is not known but could depend on genetic factors, the nutritional status, or the amount of hemozoin (released during previous malaria infections) already present in tissues [23]. Thus, the double-dose chloroquine regimen might be especially effective, because it leads to increased plasma chloroquine trough levels in patients in whom trough levels might be subtherapeutic during the standard regimen.

Of course, doubling the dose of chloroquine might lead to increased adverse effects. Although none were seen in the study by Ursing et al [6], a larger study would be needed to rule out the possibility of low-frequency serious adverse events.

Similar to the artemisinin derivatives, prospects for long-term chloroquine efficacy will be enhanced if it can be used in combination, such as chloroquine-azithromycin [24]. With the right dosage and combined agent, the prospects for a chloroquine comeback are good.

References