Mini review

Chloroquine has not disappeared

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Summary
Chloroquine (CHQ), an antimalarial, is also used as an anti-inflammatory drug for systemic lupus erythematosus and rheumatoid arthritis (RA). Hydroxychloroquine (HCQ) reduces the frequency of organ involvement and disease flares, and relieves skin and joint symptoms. CHQ reduces the immunologically-mediated inflammation of the joints. HCQ and combination therapies have a significant benefit on synovitis, pain and physical disability on RA. We advocate the investment of resistance *Plasmodium* prevalence determinations in countries beset by malaria, and to match thereafter the quantity of persons administered CHQ. Follow-up investigations are essential to diagnose and prevent visual damage.
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Chloroquine (CHQ) is an antimalarial drug taken for the prophylaxis and treatment of malaria, and is also widely used as an anti-inflammatory drug in treating systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). Antimalarial drugs (CHQ or hydroxychloroquine, HCQ) assist with mild skin disease, fatigue and arthralgias that cannot effectively be controlled with non-steroidal anti-inflammatory drugs. CHQ and HCQ are used in the third world to reduce joint swelling, the antirheumatic properties of these compounds interfering with "antigen processing" in macrophages and other antigen-presenting cells to reduced auto-digestion[1]. After several decades of declining CHQ sensitivity in malaria parasites worldwide, recent reports in the literature suggest that CHQ could regain its usefulness after a prolonged absence associated with a disappearance of the drug resistance genotype in falciparum malaria[2]. Based on these findings, we propose a strategy that could see CHQ coming back to reclaim its position as the mainstay of malaria chemotherapy. The downside of antimalarial use has always been the inadvertent appearance of potentially serious side-effects such as irreversible loss of vision, uncomfortable skin symptoms (rashes), gastrointestinal disturbances, alopecia, and neuropathy. These adverse effects are usually associated with chronic administration of the drug or high doses such as those administered in the treatment of SLE and RA. The rationale for this mini-review is therefore to advocate the importance of restoration of CHQ to the antimalarial armamentarium, and to highlight the benefits associated with continued use of the drug elsewhere, notably in SLE and RA. We are simply suggesting CHQ's comeback, and not arguing the point that it has already successfully being re-adopted, as that will be in the future.

The criteria used in this mini-review for selecting articles to be included were both theoretically and practically motivated and adopted from proposed criteria including:

- Articles with internationally recognised impact factors.
- Criteria for selection of literature used included the relevance of the data and methodology for CHQ use; the adequacy of subject numbers; and statistically significant variables and pharmacological parameters.
- The time frame used was limited to 1990-2007 inclusive.
- Compilation of materials for the review started with published literature or easily accessible academic research.
- The articles were accessible from on line sources including PubMEd and Medline.

Despite widespread CHQ resistance in *Plasmodium* species, cost and availability continue to favour CHQ as the drug of choice in most poor third world countries. In these malaria-endemic regions, we contend that the two major factors that contribute to the emergence of CHQ-resistance parasites are CHQ self-medication and the continued use of CHQ as a prophylactic agent against

malaria. In these two scenarios, prolonged exposure of parasites to sub-therapeutic drug levels creates selective pressure for the evolution of drug tolerant (resistant) parasites. We therefore propose the withdrawal of CHQ as an over-the-counter medication and cessation of its use as a prophylactic in all malaria endemic regions based on previous findings[2]. CHQ use should only be re-introduced following a rigorous revaluation of parasite sensitivity to the drug and, if necessary, in combination with quinoline-resistance reversing agents[3]. In the meanwhile alternative drugs such as the artemisinin derivatives, fixed-dose combinations of Malarone (atovaquone/proguanil), coartemether (artemether/lumefantrine), and Lapdap (chlorproguanil/dapsone) could be used. These have the added advantage that they do not have any cross-resistance with the quinoline-based antimalarials. Artemisone is also another drug that represents an important addition to the repertoire of artemisinin combination therapies currently used due to its enhanced antimalarial activity, improved bioavailability and stability over current endoperoxides[4].

Two inherent caveats of our proposition are that multi-drug combinations are usually too expensive for most third world countries, and the mechanisms for monitoring CHQ sensitivity of parasites are often not available or too costly to implement. However, for most developing countries we think that the long term benefits associated with a return of CHQ sensitivity in malaria parasites will by far out-weigh the high costs associated with employing the alternative drugs in the interim. For monitoring antimalarial drug resistance in parasites, it is important to use cheap *in vitro* standardised therapeutic efficacy tests. Although *in vitro* tests are considered inferior to the more costly genotyping methods, they have the overall advantage that they are cheaper and can be employed for monitoring resistance to several chemotherapeutic agents whereas the use of molecular markers are confined to a few drugs for whose resistance they have been identified.

CHQ is known to reduce the frequency of flares in SLE and is recommended for all but the mildest of cases unless contraindicated. Although some patients present with hypersensitivity rashes in response to hydroxychloroquine (HCQ) treatment, these are rare and the drug has the advantage of reducing new organ involvement and disease flares, and relieves skin and joint symptoms[5]. HCQ is well tolerated in SLE and is of equal efficacy with acitretin, although adverse effects are more frequent and severe with the latter[6] – hence the advantage of HCQ medication.

RA is a particularly uncomfortable condition, commonly afflicting the limbs of geriatric patients. Recently there has been a number of combination therapies proposed to alleviate the symptoms of RA. The advantage of CHQ is that it reduces the immunological-mediated inflammation of the joints. Additionally, HCQ has a significant benefit on synovitis, pain and physical disability on RA. Patients are mostly willing to put up with the psychological dysfunction of the antimalarial in exchange for a relief of their RA symptoms. More enhanced treatment responses are observed in CHQ-treated patients following initiation of leflunomide or HCQ-entanercept combinations[7]. The role of CHQ in RA treatment is therefore unquestionable.

In conclusion we advocate the withdrawal of CHQ as an over-the-counter medication and cessation of its use as a prophylactic in all malaria endemic regions in order to circumvent the emergence of drug resistant parasites; and the investment of resistance *Plasmodium* prevalence determinations in countries beset by malaria. It is vital thereafter to match resistance with the quantity of persons administered CHQ. Additionally, in order to prevent the deleterious effect of chronic CHQ or high dose therapies, regular follow-up investigations should be made to diagnose and prevent visual damage.

References

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