SHORT COMMUNICATION

Potent Inhibition of Cholesterol Biosynthesis as a Novel Mechanism for Chloroquine's Induced Pruritus

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Chloroquine (CQ) is a very useful drug with a broad spectrum of uses (as anti-malarial, anti-amoebiasis and for connective tissue diseases). A major side effect preventing or limiting its utilization is chloroquine induced pruritus (CP). A recent study done in Nigeria has shown that itching with oral CQ occurred in 100% and with intramuscular injection in 49% of patients [1]. 84.5% of responders itched for 1-3 days. The longest duration for CP was 7 days [1]. CP seriously affects the compliance of the patients, accentuating morbidity and mortality as well as promoting the onset of chloroquine resistance. In a study done in Kenya in 1987, it was detected that greater than 10% of pregnant women avoid malaria chemoprophylaxis with this agent, which is the safest and preferred drug for treatment of malaria during pregnancy, owing to the fear of pruritus [2]. CP is the commonest adverse drug reaction experienced by Black Africans [3].

CP is suggested to have multiple mechanisms, with pharmacogenetics, kinetics and blood parasite load as contributing factors. In human healthy volunteers chloroquine has been shown to release histamine, and in patients with malaria fever antihistaminic drugs attenuate CP in a subgroup of the study population, while prednisolone is highly efficacious as a prophylactic and palliative agent in CP. A strong positive correlation between the severity of pruritus and the antecedent malaria parasite density in blood was demonstrated. Thus, both histamine release and the malaria parasitemia or cytokines may contribute to chloroquine's pruritogenicity. [4] There is also pharmacokinetic evidence of slower chloroquine clearance in people who itch to chloroquine. Healthy volunteers who have a positive history of CP during malaria fever exhibited a slower metabolic conversion of single 600-mg oral doses of chloroquine to desethylchloroquine, leading to higher plasma chloroquine concentrations in historical chloroquine itching subjects[5]. Furthermore, it is suggested that the release of endogenous opioids by chloroquine may contribute to CP, as chloroquine is employed by drug addicts on the streets in conjunction with heroin (adulteration) and, more importantly, it is demonstrated that naltrexone exerts an antipruritic action in patients with CP in malaria fever [4].

Below, I would like to propose that the possible barrier defect induced by chloroquine's potent inhibition of cholesterol biosynthesis must be regarded as another contributor to the incompletely explained CP:

Cholesterol biosynthesis by keratinocytes is documented to be fundamental to the integrity of epidermal barrier function. It is shown that topical application of lovastatin to the skin of hairless mice leads to the development of epidermal hyperplasia, erythema, scaling and increased DNA synthesis. This effect, being secondary to the disruption of skin barrier as the result of decreased production of cholesterol by keratinocytes, was aborted with concomitant application of cholesterol [6]. An important point needing attention is that though topically applied statins induced epidermal barrier dysfunction, this effect is not seen with orally administered statins, most probably due to the low bioavailability of statins to keratinocytes [7].

Disturbance of barrier function results in increased transepidermal water loss and hence xerosis. Xerosis is supposed to induces itch by stimulating the release of various pruritogenic mediators from keratinocytes [8]. Moreover, microcracking of the stratum corneum could expose free intraepidermal terminals of C neurons, leading to local osmotic changes that could in turn cause depolarization [9].

Interestingly, chloroquine is reported to significantly decrease serum cholesterol levels, hence neutralizing the dyslipidemia seen in systemic lupus erythematosus patients taking steroids [10,11]. Chloroquine is shown to be a potent inhibitor of cholesterol biosynthesis by isolated rat hepatocytes. It does not affect fatty acid synthesis by isolated hepatocytes, suggesting that it acts on the cholesterol biosynthetic pathway beyond the cytosolic acetyl-coA branch-point of cholesterol and fatty acid synthesis [11].

In conclusion, putting all these facts together, it could be deducted that CP can be partly attributed to the possible epidermal barrier dysfunction induced by this agent's potent inhibition of cholesterol biosynthesis. This effect

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can also explain the aggravation of psoriasis by this agent [12].

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