Chloroquine: Consideration of Maximum Daily Dose (3.5 mg/kg Ideal Body Weight) Prevents Retinopathy

F.R.		Ochsendorf
U.		Runne

Department of Dermatology, University Hospital, Frankfurt, Germany

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Dr. F.R. Ochsendorf, Department of Dermatology, University Hospital, **Theodor-Stern-Kai 7**, D-60590 Frankfurt/M. (Germany)

In this journal, Lipsker et al. [1] emphasized the efficacy of the combination of chloroquine and quinacrine for the treatment of resistant cutaneous lupus erythematosus. 20% of their patients (3/15), however, developed abnormalities in the electroretinogram resulting in cessation of chloroquine therapy. The authors state that 'it seems very important that the daily dose of chloroquine and quinacrine should be as low as possible'.

The daily dose according to the ideal body weight is the most relevant factor for the development of chloroquine retinopathy. This report as well as a survey [2] published recently demonstrate that hitherto the latter findings have not been adequately considered by the dermatological community. We therefore want to highlight this practically important topic.

Chloroquine and hydroxychloroquine have been used in a restrictive manner only, which is due to the fear of development of irreversible chloroquine retinopathy. It is generally believed that chloroquine should not be given for longer than 1 year and the total cumulative dose should not exceed 100 g. A review of the literature published in this field, however, reveals that chloroquine therapy was considered too negatively in regard of the retinopathy. In the older studies, baseline examinations were often lacking. Furthermore up to now there are no reliable, generally accepted criteria for the diagnosis of chloroquine retinopathy. Therefore nearly each retinal deviation detected was suspected of being induced by chloroquine. In the meantime it was found that comparable changes (pigmentary changes, loss of the foveolar reflex and even the bull's eye, etc.) can occur also in patients never treated with chloroquine [see references in 3 and 4].

The important new finding is that neither the duration of therapy nor the total cumulative dose are decisive for the development of retinopathy but solely the level of the daily dose [3-5]. The higher the daily dose, the more probable is the development of a retinopathy. Most retinopathies occurred at daily doses of 500 mg or more. At 250 mg/day, a retinopathy is rare (0.5-2%) [3]. If the daily chloroquine dose is limited to 3.5-4 mg/kg ideal body weight (or 6-6.5 mg/kg for hydroxychloroquine), however, a retinopathy does not appear. This is also true for patients who received chloroquine for several years with total cumulative doses of 1,000-2,500 g [5].

Mackenzie [5] followed more than 900 patients with a mean treatment time of 6.8 years and a mean total cumulative dose of about 608 g chloroquine (calculated). If 4 mg/kg ideal body

weight for chloroquine (or 6.5 mg/kg for hydroxychloroquine) were not exceeded, no retinopathy occurred.

Table 1. Guide for maximum daily doses of chloroquine (3.5-4 mg/kg) with the example of Resochin® tablets of Resochin® syrup' (available in Germany)

In the weight classes given, the dose of chloroquine tends to be 4 mg/kg with lower weights and 3.5 mg/kg with higher weights. The dose should approach 3.5 mg/kg.

1 spoon supplied with the Resochin syrup (3.5 ml) contains 81 mg chloroquine; the maximum daily dose, 4 mg/kg ideal body weight, corresponds to 0.17 ml/kg.

The ideal body weight has to be taken into account due to the pharmacokinetics of chloroquine, as chloroquine is not stored in fat tissue. The ideal body weight can be calculated as follows: men = (height [in cm]-100)-10%; women = (height [in cm] - 100) - 15%. In the presence of kidney or liver insufficiency because of slower excretion, the chloroquine dosage has to be reduced further.

Consequently with 1 tablet of 250 mg chloroquine daily, patients with an ideal weight of more than 71 kg can be treated safely (3.5 mg/kg), patients with an ideal body weight between 63 and 71 kg receive doses between 3.5 and 4 mg/kg. Lighter persons, i.e. mainly women, however, must definitely receive lower daily doses (with 50 kg ideal body weight, for example, a maximum of 200 mg chloro-quine/day; table 1). In the report of Lipsker et al. [1], 14/15 patients were women. Unfortunately body weight and height were not given, so the maximum daily doses cannot be calculated.

For safety reasons, an ophthalmologic baseline examination (funduscopy, perimetry and color vision) should further be done before the start of therapy [3]. Yearly controls (patients older than 65 twice yearly) are regarded as sufficient screening [see references in 3,4]. In addition to these tests, the patient himself can screen his foveal function by Amsler grid charts. Should any of these screening tests yield abnormal results, more refined techniques such as electro-oculography and electroretinography should be used.

If the maximum daily doses of 3.5(-4) mg/kg ideal body weight for chloroquine or 6(-6.5) mg/kg ideal body weight for hydroxychloroquine are observed, a therapy for months or years appears to be safe.

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- A Naturally Occurring Ring Seborrheic Keratosis
11 Meffert", K.C. Deering"
Departments of "Dermatology and bDermatopathology, Wilford Hall Medical Center',
Lackland AFB, Tex., USA

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Seborrheic keratoses (SKs) are among the most common benign cutaneous neoplasms. Despite this, knowledge of the pathophysiology underlying SKs is incomplete. Much of what is known about the growth and biology of SKs is obtained indirectly while investigating 'more important' tumors, and SKs are studied as 'control neoplasms'. Ho and McLean [1] note that a true understanding of what makes SKs grow the way they do would help explain much about keratinocytes in general and the biology of the skin. We present what may be the first reported case of a naturally occurring ring-shaped SK, an entity which raises provocative questions about the growth factor milieu responsible for SKs.

Case Report

A 35-year-old man presented with an asymptomatic brown ring on his left arm which he had first noticed about 1 year previously (fig. 1). He was unsure if the lesion appeared de novo as a 1 - cm ring or if it had started as a solid papule and spread with central clearing. He denied any prior trauma or treatment such as cryotherapy, curettage, intralesional injections or topical wart therapies of any kind. Epi-luminescent biomicroscopy revealed sharp borders to the ring, scattered tiny (< 1 mm) milia, a few small comedo-like openings and the absence of a melanocytic pigment pattern. A punch biopsy revealed acanthosis, papillomatosis and a rare keratin pearl. Although the epidermis was slightly effaced in the center of the ring, there was no fibrosis or other indication of a scar from prior trauma. The patient.

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Fig. 1. Ring SK (1 cm diameter).

weary of inquiries from friends and family about his 'ringworm', desired treatment and liquid nitrogen cryotherapy to the ring was performed. He presented several months later with a small residual arc-shaped ridge which was successfully treated with a second course of cryotherapy which eliminated the lesion.

Discussion

Many inflammatory conditions (e.g. granuloma annulare, gyrate erythemas, porokeratoses) are characterized by annular growth where the most histopathologically diagnostic areas of the

lesion are found at the periphery of the ring rather than the often regressed or histologically nonspecific center. While neoplasms may exhibit centrifugal growth, a perfect ring is a rarity. Ring SKs, along with ring warts, are usually created when a lesion is incompletely frozen, destroying the center of a papule while not achieving destructive temperatures at the periphery. The SK described above underwent no such therapy and grew in a ring from the onset. The exact mechanism for this growth pattern is unclear, but one may conjecture a balance or 'vector sum' of growth factors which are favorable for SK growth at the periphery but not centrally. Elias et al. [2], in a review of the cytokine network regulating pulmonary inflammation and fibrosis, discuss the concept of a three-dimensional model of cytokine interactions. Depending upon where one looks in the region of inflammation, cytokines and other growth factors interact in different combinations and with a varying gradient of concentrations of those factors. This ultimately leads to different manifestations of the inflammation (fibrosis vs. granuloma vs. abscess) from one area to another [2].

Most of what is known about the biology and growth factors affecting SK growth has come out of studies where the focus was on other neoplasms and SKs were used as controls. The association of eruptive SKs with underlying malignancy (sign of Leser-Trélat) is not considered as meaningful as it once was, but one report describes sheets of SKs and palmar-plantar hyperkeratosis associated with elevated levels of immunoreactive human growth hormone and various underlying malignancies [3]. In another report, linear SKs regressed with removal of malignancies, suggesting that some unidentified epi-