Role of Hydroxychloroquine within the framework of the Covid19 anaerobic hypothesis (SARS-Cov2 enables anaerobic bacteria colonization of lungs) in terms of its pH based mechanism of action in malaria

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Letter

The use of hydroxychloroquine (HCQ) and azithromycin to treat Covid19 patients with success [1–3] or failure [4, 5] is highly controversial - timing, protocol (usage of zinc [6] for example) and safety [7] being key considerations.

Based on evidence of colonization of the lungs by anaerobic bacteria, aided by SARS-Cov2, from sequencing data [8], a key question arises - is there basis to the fact the HCQ and azithromycin act synergistically on these bacteria?

HCQ is a lesser toxic [9] derivative of chloroquine used to prevent and treat malaria, rheumatoid arthritis [10], lupus [11], etc. HCQ is known to be involved in inhibition of cytokine production, lysosomal activity, interference with Toll-like receptor (TLR) signalling and autophagy [12]. HCQ is associated with an increased risk of retinopathy [12] and QT prolongation [7] - thus self-medication should be strictly avoided.

Hemozoin biocrystallization in malaria within acidic vacuoles

The antimalarial mechanism of action of HCQ is not fully known. The most widely accepted mechanism of action involves the aggregation of cytotoxic heme by inhibition of hemozoin biocrystallization [13]. Digestion of blood by Plasmodium releases high quantities of free heme (a pigment consisting of an iron atom), which is toxic to even the Plasmodium cells [14]. So, Plasmodium converts it into an insoluble crystalline form called hemozoin or malaria pigment [15]. These parasites degrade hemoglobin in an acidic food vacuole.

HCQ is basic - and increases pH - thus inhibiting hemozoin biocrystallization

HCQ (and chloroquine) increases pH within intracellular vacuoles and alter many processes [16]. In fact, resistance to chloroquine of malaria is due to a protein PfCRT [17], a mutation there reduces chloroquine accumulation in the digestive vacuole of the parasite [18].

Heme is toxic to bacteria also - the heme pigment is formed by lowering pH

Heme is toxic to bacteria at high concentrations [19]. The heme pigment of Porphyromonas gingivalis differs from that generated by Prevotella, though the pH for both is between 5.8 and 6 [20]. ‘The low pH encourages cell-surface deposition of insoluble Fe(III)PPIX.OH which would act as a barrier against oxygen and reactive oxygen species, and also protect against H₂O₂ through its inherent catalase activity’ [20].

Analogously HCQ stops heme pigment formation in anaerobic bacteria

Disseminated intravascular coagulation (DIC) is a serious disorder characterized by small blood clots developing throughout the bloodstream, blocking small blood vessels, depleting platelets and clotting factors leading to excessive bleeding. Lately, it is been reported that Covid19 is more of a vascular problem, than one of the lungs [21–25]. In this theory, the inception of the DIC happens through hemoglobin degrading proteins [26], heme-binding proteins sequestering heme after hemoglobin degradation [27], ‘plundering’ iron, and thereby sequestering oxygen [28]. And a very important enzyme - hemagglutinin, which causes thrombus formation, initially in venules and then in arterioles [29]. Thus, it is hypothesized the HCQ might be having an anti-bacterial effect by stopping heme pigment formation, which would form an abscess and then a clot.

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