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HYDROXYCHLOROQUINE INDUCED AQUAGENIC PRURITIS: A RARELY REPORTED CLINICAL ENTITY

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ABSTRACT

Hydroxychloroquine (HCQ) belongs to quinolone group of antimalarial drugs which has both anti-malarial and anti-inflammatory actions. Pruritis is a major adverse effect of quinolone group of anti-malarials and is an important cause of noncompliance to the drug. Here we present a unique case of HCQ induced pruritis in a 43 yr old male which was aquagenic in nature. Aquagenic pruritis (AP) is a skin condition characterized by the development of severe itching on contact with water without observable skin lesions.[1] The aquagenic pruritis develops within 5 to 10 mins of contact with water and within the next few mins it increases in intensity and spreads to assume a generalised form. Though the severity decreases within 30 mins to an hour, the pruritis lasts for several hours with its intensity decreasing gradually. After thorough research of the available literature in related journals and the database of references and abstracts found online in various search engines related to medical literature, we believe this to be the first case of "Hydroxychloroquine induced Aquagenic Pruritis" from India to be documented as a case report. As the sensory neural pathway for HCQ induced itch sensation differs from the histaminergic pathway of itch sensation[2], anti-histaminics usually exhibit poor efficacy to control AP and different modalities of treatment must be explored for the treatment of HCQ induced aquagenic pruritis.

KEYWORDS: Hydroxychloroquine, Pruritis, Pharmacokinetics.

CASE DESCRIPTION

In November 2021, a 43-year-old male from Mumbai travelled to the city of Nashik, to his relatives' place which is an endemic area for the viral disease of Chikungunya caused by the Chikungunya virus and transmitted by the vector mosquito; Aedes Aegypti.[3] After about 3 days he returned back to Mumbai but experienced chills along with fever on the day of his return. Within 3-4 days after contracting fever, he experienced severe joint pain in his shoulder and knee joints. The arthralgia spread to involve the elbow joint, the wrist joint and the ankle joint in the next couple of days. Upon relevant investigations, patient's serum IgM and IgG titre was indicative of Chikungunya infection but negative for Dengue viral fever. All other reasons of viral fever with polyarthritis were also ruled out with relevant investigations. Patients CBC showed lymphocytosis, with normal C-reactive protein (CRP) value. All other investigations like liver and renal function tests, lipid profile, fasting blood sugar and glycosylated haemoglobin were normal except for serum Homocysteine levels which were measured as 41 micromol/L with 16.2 micromol/L being the highest acceptable value of normal range. Investigations for Rheumatoid factor and p-ANCA, c-ANCA antibodies were done which came out to be negative. Symptomatic treatment was started with Paracetamol and Ibuprofen for the fever and short-term Methyl-prednisolone treatment along with Hydroxychloroquine (HCQ) was started for severe painful reactive arthritis.

Methyl-prednisolone was started with an initial dose of 8mg BD for the first 15 days which was then reduced to 8mg OD for the next 15 days. After this, it was gradually tapered and eventually stopped in the next 15 days.

HCQ was started as an initial dose of 200mg twice a day, for the first 30 days. The arthralgia improved. After that the dose was reduced to 200mg once a day for the next 30 days but there was no improvement in the symptoms of arthritis with this daily dose. So, the dose of HCQ was then increased to 300mg once a day and it was prescribed for the next 3 months. Within 8 to 10 days of this increased dose which was by end of February 2022,

the patient started experiencing severe generalised (migratory) itching which showed all the properties of aquagenic pruritis. The pruritis used to begin immediately after a bath (within 5-10 mins) typically on the thorax. It used to then spread to the abdomen, followed by upper and lower back and finally to the thighs and upper arms. Within 8-10 mins of onset, the pruritis used to be generalised, as described above. There were no visible skin eruptions or abnormalities apart from redness of skin areas exhibiting pruritis. The severity of pruritis for the first 25 to 30 mins was severe enough to render the patient incapable of performing any personal, interactive or professional activities. The severity used to slowly decrease after that but the pruritis persisted for the next 7 to 8 hours with its intensity decreasing gradually. Anti-histaminics like Levocetrizine (10mg), Fexofenadine (30mg) and Ebastine (20mg) had been used with no significant improvements or relief in symptom of pruritis. As the symptoms of arthritis improved gradually, the dose of HCQ was also tapered by mid of May 2022 to 300 mg on every alternate day but the pruritis persisted which was triggered by bathing. By 1st week of June the dose was tapered to 300 mg twice a week which brought about decrease in the severity of pruritis but it was still present. Owing to further improvement in his arthritis symptoms, HCQ was discontinued in the 3rd week of June 2022**.** Within 7 to 8 days of complete discontinuation of HCQ, frequency of pruritis episodes started to decrease and by the end of June 2022 the patient experienced about 1 episode of pruritis per week post bathing. This continued for a month with each subsequent episode of pruritis being lesser in intensity and lasting for a lesser time as compared to the previous episodes. It has now been just over 2 months since HCQ has been completely discontinued and the patient has not experienced a single episode of pruritis since end of July 2022**,** i.e., for a period of 1 whole month.

In view of the improvement of symptoms on dechallenge with HCQ, we conclude that the severe symptoms of pruritis experienced by the patient were attributable to treatment with HCQ. This appears to be a rare side-effect, but one that can be severe in those affected. Common features with the pruritis associated with chloroquine include the poor response to systemic anti-histamine preparations[6,7] and absence of scratch marks. In view of the condition's severity, rarity and lack of literature, further investigation is warranted in this matter so as to find ways to prevent or effectively treat the troublesome and debilitating symptom of severe pruritis, in the process improving patient compliance as well.

DISCUSSION

HYDROXYCHOLOROQUINE

Hydroxychloroquine (HCQ) belongs to quinolone group of antimalarial antibiotics which shares a bicyclic core structure. It is a derivative of Chloroquine (CQ) in which one of the N-ethyl groups is hydroxylated at position 2 (Beta-hydroxylation).[4] It has both anti-malarial and anti-inflammatory activities and is a commonly prescribed medication in the treatment of uncomplicated malaria, chronic discoid lupus erythematosus, systemic lupus erythematosus and various conditions of reactive, inflammatory arthritis secondary to rheumatism, psoriasis, gout, ankylosing spondylosis, acute viral infections etc. HCQ is metabolised mainly in the liver by de-alkylation and has a half-life of elimination of approximately 40 days.[5] However, slow release from sequestered stores of the drugs means that after discontinuation, they continue to be released into the plasma for years.[5] Some of the common side effects encountered with HCQ are headache, dizziness, loss of appetite, nausea, diarrhoea, epigastric pain, vomiting and rash.[6] Although pruritis is a very common side effect encountered in patients taking its parent molecule Chloroquine, it is fairly uncommon with the use of Hydroxychloroquine. The prevalence of CQ-induced pruritis has been estimated up to 50% of patients taking CQ in several studies[7], while recently the prevalence of HCQ-induced pruritis has been estimated to be less than 10%.[7] The above presented case is a unique case of HCQ induced aquagenic pruritis in a 43yr old male which was triggered post contact with water. Aquagenic pruritis is a skin condition characterized by the development of severe itching on contact with water without observable skin lesions.[1] It has been shown that Hydroxychloroquine stimulates the itch nerves by activating the G protein-coupled receptor "Mrgpr"(Mas-Related G-Protein coupled Receptor), expressed exclusively in peripheral sensory neurons.[2] As antimalarial drug induced aqaugenic pruritis is relayed to the sensory cortex via non histaminergic pathway[2], conventional anti-histaminics often fail to provide any meaningful symptomatic relief from the HCQ induced AP.[8,9] Pruritis in such cases can be of debilitating severity so as to even interfere with the patient's quality of life.

AQUAGENIC PRURITIS

Until today, the pathophysiology of Aquagenic Pruritis (AP) is not completely explored and therefore not fully understood. It was only until 1981 that AP was defined to be a separate clinical entity clearly distinguished from aquagenic urticarial.[10] It is characterised by a widespread intense itching evoked by a brief contact with water at any temperature, in the absence of visible skin signs.[10] Bathing evoked pruritus is reported as common among young adult Nigerians.[11] A population-based cross-sectional study showed a prevalence of 23.8%. A subtype of ‘aquagenic pruritus of the elderly’ has also been reported. It occurs characteristically in aged occupants of residential homes for the elderly who are exposed continually to warm dry ambient temperatures[12] and, unlike classical AP, it responds well to emollients.[12] Drug-induced AP has been reported in patients treated with clomipramine, a tricyclic antidepressant[13], bupropion, prescribed for smoking cessation[14] and antimalarials: chloroquine and hydroxycholoroquine.[15] A high intensity pruritis is

triggered by contact with water, onset of which is within few mins and it typically lasts for 15-20 mins. The pruritis then subsides to a lower intensity which then persists for several hours. Drug induced AP is typically unresponsive to anti-histaminics, thereby suggesting a different mechanism of neuronal transmission other than the histaminergic pathway.

MRGPR (MAS-RELATED G-PROTEIN COUPLED RECEPTOR) AS RECEPTORS OF ITCH SENSATION

In 2009, Liu et al.[2] published a landmark study showcasing Mrgpr as receptors whose activation resulted in itch sensation. In their study, the antimalarial drug chloroquine was determined to be a ligand of Mrgpra3 in mice and MRGPRX1 in humans. Chloroquine-mediated itch is nonhistaminergic. It does not result in skin eruptions, wheal, flare, or other symptoms of mast cell degranulation. Additionally, antihistamine treatment fails to alleviate pruritus.[16]

To test the role of Mrgprs in chloroquine-mediated pruritus, Liu et al.[2] generated an Mrgpr cluster knockout (Cluster−/−) mouse in which 12 intact coding open reading frames which coded for the Mrgpr A-C subfamilies were identified on the DNA and deleted. The acute injection of chloroquine caused pruritus in wild-type mice, but failed to do so in Cluster−/− mice. Dorsal root ganglion isolated from Cluster−/− animals failed to respond to chloroquine, as determined by either calcium imaging or electrophysiological recording.[2] Since Liu et al.'s study, several Mrgprs have been identified as receptors for different pruritogens, which, in turn, have informed models of peripheral itch sensation.[17] Even if more research is still required regarding these receptors, sufficient literature now exist to suggest that Mrgpr are present on the peripheral sensory neurons. Their interaction with different pruritogens results in neuronal changes that lead to depolarisation of these neurons, thereby brining about generation and propagation of sensation of itch.

CONCLUSION

Quinolone group of anti-malarials viz., Chloroquine and Hydroxychloroquine are commonly used for their anti-malarial, anti-inflammatory and immunosuppressant actions.

Pruritis is a major adverse effect of quinolone group of anti-malarials like Cloroquine and Hydroxychloroquine, and is an important reason of noncompliance.

Aquagenic pruritis is a subset of and a severe form of Hydroxychloroquine induced pruritis characterised by widespread intense itching evoked by a brief contact with water at any temperature, in the absence of visible skin signs.

Hydroxychloroquine induced aquagenic pruritis is not initiated and mediated by the histaminergic pathway and therefore resistant to treatment with anti-histaminics.

Although sufficient pharmacokinetic data is available on HCQ[5,18,19,20], further pharmacodynamic studies need to be conducted as far as active metabolites of HCQ are concerned and their role in triggering aquagenic pruritis needs to be thoroughly investigated.

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