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Mechanisms of enhanced pruritogenicity of chloroquine among patients with malaria: a review

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Summary

The mechanisms whereby the intrinsic pruritogenic effect of chloroquine (a property also encountered among some other 4-amino-quinolines including amodiaquine) becomes aggravated during paroxysmal malarial suppressive chemotherapy with the drug form the basis of this paper. Physiological itching has been linked to the concept of 'spontaneous itch', as compared to pathological itching which has been associated with another concept of 'itching hyperexcitability', and the pathophysiology of pruritus, including the involvement of peripheral and central (neuropeptide) mediators of itch, were considered. The modulating function of spinal and supraspinal 'gateway control' mechanisms, which have been used to explain the overriding effect of pain-over-itch sensation, were also considered and related to itching hyperexcitability.

From current data and the records of previously-published reactions to chloroquine, during fever or malarial chemotherapy in man and some mammals, the possible involvement of racial and skin pigment factors, histamine factor, other peripheral mediators of itch, tissue pharmacokinetic factors, central mediators of itch, pyrogenic haemodynamics, and 'gateway' modulation in producing enhanced pruritic reaction during chloroquine antimalarial chemotherapy, were examined in relation to the aggravating role of ischaemia on itch excitability.

A trilateral approach to the clinical management of chloroquine-induced pruritus among patients with malaria has been used. In line with the principles of clinical treatment of severe generalized pruritus of uncertain aetiology, this approach has been adapted to reflect the epidemiological, clinical and pathophysiological variables that appear to influence chloroquine-induced pruritus.

Résumé

Les mécanismes par lesquels l'effet de démangeaison intrinsèque de la chloroquine (une propriété présente aussi parmi quelques autres 4-aminoquinolines, y compris l'amodiaquine) s'aggrave pendant la chimiothérapie répressive d'un paroxysme paludéen avec ce médicament, constituent le centre d'intérêt de ce rapport. Commençant par la démangeaison physiologique liée au concept de la 'démangeaison spontanée' en comparaison de la démangeaison pathologique qui a été liée à un autre concept d'hyperexcitabilité de démangeaison, la pathophysiologie de prurit, y compris le rôle des médiateurs périphériques et centraux ('neuropeptides') de démangeaison, a été considérée. Le rôle modificatif des mécanismes de 'portail de contrôle' spinaux et supraspinaux avec lesquels on a expliqué l'éffet prépondérant de la douleur sur la démangeaison a été considéré et lié à l'hyper-excitabilité de démangeaison.

A partir des données courantes et des rapports déjà publiés sur les réactions à la chloroquine chez l'homme et quelques mammifères atteints de la fièvre pyrogénique, ou pendant la chimiothérapie paludéenne chez l'homme et quelques mammifères, les roles possibles de la race et de facteurs de pigmentation de la peau, du facteur de l'histaminémie, d'autres médiateurs périphériques de démangéaison, de pharmacocinétique en tissu, des médiateurs centraux de démangeaison, de l'hémodynamique pyrogénique, du 'portail de contrôle', dans la provocation de l'accroissement de réaction prurigineuse à la chloroquine au cours

de la chimiothérapie paludéenne, ont été considérés par rapport au rôle aggravant de l'ischémie sur l'excitabilité de démangeaison.

Un traitement clinique tridimensionnel pour le prurit provoqué par la chloroquine chez les malades paludéens, conformant aux principes de traitement des graves démangeaisons généralisées, dont la causalité est inconnue, a été adapté pour refléter les variables épidémiologiques, cliniques et pathophysiologiques qui paraissent influencer le prurit provoqué par la chloroquine.

Introduction

Pruritus (itching) has been defined as an unpleasant cutaneous sensation which provokes the desire to scratch or rub the skin [1]. Itch has emerged as one of the most enigmatic of the subjective sensations of nociception, and the development of drugs which control pruritus remains one of the challenges of medical research [2].

Casual physiological itching has been associated with the concept of 'spontaneous itch' [3] which can be distinguished from pathological itching which often accompanies skin diseases and has become associated with another concept called 'itching hyperexcitability' [4]. Physiological itch has been described further as an immediate, evanescent, well-localized pricking sensation arising from stimulation of an itch spot. The impulse is conveyed via fast-conducting A (delta) cutaneous sensory nerve fibres to the spinal cord, followed by a diffuse, poorly-localized sensation of itch which persists beyond termination of the initiating stimulus, hence it has been called 'spontaneous itch' [5, 6]. The impulse of 'spontaneous itch' is also carried via C-fibres, in addition to A-fibre pathways that conduct physiological itch.

Pathological itching, on the other hand, is a highly unpleasant, poorly-localized, and intractable form of itch which occurs within partially-injured skin where itch nerve and receptor mechanisms are still functional. Proteases, their substrate breakdown products, and humoral factors released into the injured skin either trigger off 'spontaneous itch' attacks or make the skin itch hyperexcitable to many kinds of mild, non-specific or casual physical or chemical stimuli. The type of itch impulse produced is conveyed via the slower conducting C-fibres [5]. This forms the basis of the concept of 'itching hyperexcitability'. Whereas physiological itching may evoke mild scratching responses, pathological itching may compel the sufferer to scratch the skin down to the epidermodermal junction to obtain some relief, analogous to the effect of stripping the epidermis from the corium with adhesive tape, which can cause itch sensibility to disappear, leaving pain [6].

Conscious perception of itch is subjected to psychic modulation, and, while mental distraction may depress itch perception, alertness and boredom may intensify itch with the same amount of pruritogenic stimulus [7]. Unconscious itch perception, evoking spinal reflex activity such as scratching during sleep, can also be modulated by psychic influences such as hypnotic suggestion [8], hypnosedative drugs [9,10], anxiolytics and antidepressants [11].

Progress on the evaluation of the pathophysiology of pruritus has been very slow when compared to pain, another distinct sensation of nociception which employs the same neural mechanisms as itch. This is probably because there has been no synthetic or naturally-occurring palliative with specificity for severe itch such as morphine for pain relief. Thus, there has been no specific lead to follow for development of new antipruritic agents. Also, empirical screening for antipruritic agents has been difficult because of the absence of any reliable and widely-accepted subhuman model of pruritus.

The complexity of the problem of pruritus, lack of remarkable progress, and imprecision in defining the pathophysiology of itch can be well appreciated by consulting two reviews [5,6] on the physiology of itch. While no remarkably new knowledge has emerged about the peripheral mediators of itch, there is now a greater understanding of the possible involvement of some active neuropeptides as putative central nervous system mediators of itch perception. These include endogenous opioids [12] and bombesin [13]. However, a possibility that remains largely unexplored, is that other neuropeptides found in the cortex, such as cholecystokinin, vasoactive intestinal peptide, and somatostatin, could also be involved in the conscious perception of itch.

The occurrence of a moderately severe type

of generalized pruritus, among patients with malaria treated with chloroquine, has provided a continuing basis for varied epidemiological and clinical reports on chloroquine-induced pruritus from Nigeria [14–16], with increasing interest in its phenomenology.

Epidemiology of chloroquine-induced pruritus

During initial clinical trials among healthy volunteers

Chloroquine produced moderately-severe pruritus in one out of 32 healthy volunteers during the 4th week of a 5 week administration schedule, at a daily dosage of 400 mg of chloroquine, but there was no associated dermatosis [17]. In another study, one of 30 healthy volunteers, a 21-year old negro male, receiving 0.5 g chloroquine weekly for one year developed lichenoid eruptions at 8 months, and with progression of the dermatosis had mild pruritus and scaling lesions by the 11th month [18]. These reports revealed the pruritogenic potential of chloroquine with and without any associated dermatosis.

During clinical trials for malarial suppression

Early reports on the chemotherapeutic suppression of malaria with chloroquine apparently did not encounter severe pruritus as an adverse reaction to the drug. Pullman *et al.* [19] did not report any pruritic reaction among eight patients with vivax malaria treated with 2 g chloroquine base divided into oral doses over 7 days. Scott [20] evaluated the toxic and antimalarial suppressive effects of chloroquine administered intravenously to 110 patients with falciparum malaria in Honduras and did not report any pruritic adverse reaction. Ekpechi and Okoro [14] in a letter of reply to a previous review publication [21], listing only pruritus ani as an itchy reaction to chloroquine, described the pruritic reaction to chloroquine among Nigerian patients with malaria. They estimated an 8–15% incidence of the reaction among all patients presenting for chloroquine treatment for acute malarial fever. Further reports [15,16] have confirmed the prevalence rates of the reaction and have also characterized it.

During chronic antirheumatoid therapy

Although chloroquine is used worldwide principally for malarial suppression, it is also used in the treatment of several chronic rheumatoid diseases on a prolonged basis, with cumulative doses approaching 75 g over 10 months [21–23]. Such chronic use of chloroquine does not appear to lead to any pruritic reaction, even though the patients may develop oculocutaneous toxicity including retinopathy, cataract, bleached hair, and aberrant melanin pigmentation of skin and mucous membranes, often associated with accumulated storage of chloroquine in the affected tissues [22–24].

Factors possibly contributing to enhanced pruritogenicity of chloroquine

Racial and skin pigment factors

A relative absence of white patients with malaria experiencing chloroquine-induced pruritus in earlier reports of the reaction from Nigeria, had led to speculation that the exaggerated pruritic reaction to chloroquine was almost exclusively confined to blacks [14,15]. In another study recently, Osifo [16] reported historical experiences of chloroquine-induced pruritus from one white and two Asian patients. We have now performed a study to determine the occurrence of the pruritic reaction to chloroquine among patients from different racial backgrounds with malaria, and who have been long-term (over 10 years) residents in Nigeria and, like the indigenous population, are considered partially immune (Table 1).

The analysis of the figures in Table 1 indicate that race and skin melanin content are not overly significant epidemiological variables that predispose to chloroquine-induced pruritus among patients being treated with the drug for acute malarial fever in Nigeria.

Effect of chloroquine on peripheral mediators of itch

Histamine. Chloroquine does not appear to induce pruritus via release of histamine during malarial fever paroxysms. Although Maegraith and Onabanjo [25] detected measurable amounts of histamine in the blood of rhesus

Table 1. Prospective incidence of generalized pruritus among patients receiving chloroquine treatment for acute malarial fever in Nigeria

Racial groups with pruritus	Total number of patients	Historical reactors	Current reactors	Current reactors (%)
Negroids, including African albinos and Afro-caucasoids	166	101	17*	10.2
Caucasoids, including Indians	76	6	2*	2.6

*Comparison of current reactors by chi-square analysis: $\chi^2 = 31.19$, d.f. = 1, $P > 0.05$, hence the differences are not statistically significant.

monkeys infected with *Plasmodium knowlesi*, chloroquine has antagonized histamine-mediated responses, even bronchial asthma, under experimental and clinical conditions [26–29]. The lack of visible skin reactions, more commonly associated with histamine-mediated itching [30], and the lack of significant palliation or prophylaxis of chloroquine-induced pruritus by H_1 histamine receptor blockers [14,15], also argues against a specific histamine-mediated mechanism for chloroquine-induced pruritus.

Other peripheral mediators of itch. Several peptidases, papain, mucunain, and kallikrein (without causing histamine skin reactions), and mast cell chymase, trypsin and chymotrypsin (accompanied by weal-and-flare reactions) can induce itching [30–32]. Several peptides, including substance-P, vasoactive intestinal peptide, neurotensin, secretin, bradykinin, anaphylatoxins, and corticotrophin-derived peptide, as well as prostaglandins, acetylcholine, serotonin, bile salts, leucocyte proteases, and leukotrienes can also induce or potentiate itch by direct or indirect actions on the sensory nerves and receptors in the skin [6]. The effect, if any, of chloroquine on these other peripheral mediators of itch mechanism has not yet been elucidated.

Disposition of chloroquine in mammalian skin in relation to the temporal profile of its pruritic reaction among patients, and during its use for chronic rheumatoid diseases. In the recent pathophysiological model of the mechanism of itch induction, it is assumed that excess bile salts mediate or precipitate some drug-induced pruritus [6]. Whether chloroquine acts directly on sensory nerves and receptors in the skin, or indirectly by modulating the action of some neurohumoral factors at low concentrations (below 5 μg/ml) [33] in the skin, or via release of bile salts, remains to be determined. However, comparatively low concentrations of chloroquine (3.4 and 7.7 μg/g) were reported in corium samples of patients who had received a total of 8.75 g chloroquine in divided doses over 4 weeks, at average daily doses below that employed (0.5 g daily) for malarial chemosuppression [34]. We have also found a strong temporal correlation between the kinetic profile of chloroquine concentration in the skin of pigmented 'hooded' Long Island rats following bacterial pyrogen challenge [35], and the temporal profile of intensity of chloroquine-induced pruritus among malarial patients [16] (Fig. 1). This suggests, from reasonable extrapolation, that chloroquine kinetics in human skin during malarial fever could follow a similar pattern. At high concentrations, chloroquine exerts an anaesthetic effect and non-specific depression of excitable tissues [33]. Therefore, while the accumulation of chloroquine in the body during chronic anti-rheumatoid therapy [24], to levels exceeding the maximum that specifically augments some neurohumoral mechanisms [33], could possibly evoke the release of bile salts and organ toxicity in the liver at such high concentrations, its direct pruritogenic action, if any exists, could be offset by its anaesthetic and depressant effects [33]. On the other hand, the comparatively low concentrations of chloroquine found in human corium samples [34] and in the mammalian skin, after a single dose of chloroquine sufficient for antimalarial use [35], could augment neurohumoral mediators in the skin [33]; and, in a concentration-dependent manner, appear to directly evoke pruritus in the skin.

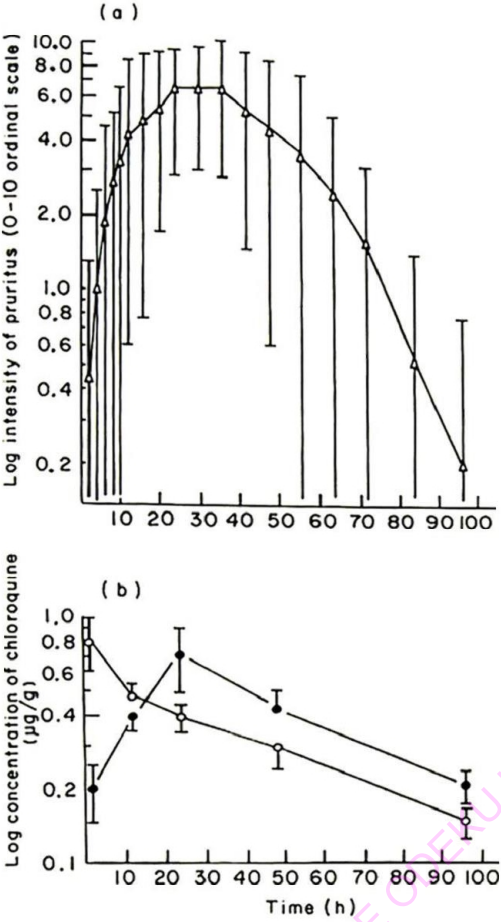

Fig. 1. Semilogarithmic plot of the mean ordinal scale scores of (a) the temporal intensity (△) of chloroquine-induced pruritus among 15 malarial patients, each receiving a maximum of 3.5 mg/kg body weight, in divided doses orally, of chloroquine diphosphate, and, (b) the mean concentration of chloroquine in four pigmented skin samples of control (○) and pyrogen-treated (●) rats, dosed with 14 mg/kg body weight i.p., of chloroquine disphosphate. Vertical bars indicate 1 standard deviation above or below the means.

Chloroquine and central mediators of itch

The central mediator role of opioid neuropeptides for itch perception has been shown by the reduction of morphine itch in normal persons pretreated with naloxone [12]. Naloxone also abolishes the placebo response to itch and pain presumably by suppressing endogenous opioid peptide release [36,37]. Another neuropeptide, bombesin is not antagonized by naloxone, and is believed to mediate the stimulation of central itch receptors and perception of itch in the presence of certain tumours, e.g. oat cell lung carcinoma, in the body [13]. It still remains to be determined, through mapping studies, whether any of the other active neuropeptides, especially those found in significant amounts in the cortex, mediate conscious perception or integration of sensory mechanisms. In this direction, the recent announcement of the discovery of asperlicin, a non-peptide cholecystokinin antagonist holds out great expectations that other analogous antagonists or agonists of neuropeptides will be discovered in the future, and will help to improve the understanding of the functions that modulate the neuropeptides in normal and disordered central nervous systems [38]. Such a development will hopefully improve the therapeutic equipment available to combat the agonizing effects of conscious perceptions of bodily dysfunction.

Chloroquine, at ordinary therapeutic doses for malarial suppression, has produced adverse central nervous system effects such as transient dyskinesias and dystonias [39,40]. During chronic anti-rheumatoid therapy, it has produced aberrant melanin pigmentation in nail bed and palate [24] possibly through central interference with endocrine control of patterns of melanocytic pigmentation [41]. Therefore, chloroquine is potentially capable of interfering with other specific neurohumoral or neuroendocrine mechanisms in the central nervous system, and it ought to be investigated for a possible direct or indirect mediating role on central itch receptors.

Pathophysiological factors

Pyrogen-induced haemodynamic changes. Some remarkable haemodynamic changes occur during febrile conditions in mammals, including man, especially in warm climates. The essential changes consist of peripheral vasoconstriction and increased visceral haemoperfusion which appear to be independent of the febrile response to pyrogens, because antipyretics blunt the fever but do not abolish these haemodynamic responses [42]. A neurohumoral mechanism has been implicated in pyrogenic

haemodynamics. Thus, individuals with a high spinal transection injury [43] did not develop the peripheral vasoconstrictory chill and shivering responses to pyrogen below the level of the transection. Injection of pyrogen into the cerebrospinal fluid, from where little, if any, could escape into the systemic circulation [44] also evokes the generalized haemodynamic changes. The relationship of pyrogens, including malarial pyrogen [45] to fever and hyperthermia has previously been reviewed [46,47].

During the febrile paroxysms of malaria, the frequency, intensity and duration of the peripheral vasoconstriction associated with chills and rigors provide an avenue for a partial ischaemic injury to the skin, leading to itching hyperexcitability. Such itching hyperexcitability is inducible in human limbs by completely obliterating the blood flow with an inflated sphymomanometer cuff for about 30 min (occlusion anaesthesia), within which time hypoalgesia develops progressively with ischaemia, but itching hyperexcitability supervenes [5]. In dogs, a moderate ischaemic stress, arterial hypoperfusion, reversibly applied for 8 h to one hind limb, enhances chloroquine-induced itching in the sham-operated contralateral hind limb, and also leads to more amplified itching activity in the ischaemically-stressed hind limb itself [48]. Therefore, total or partial ischaemia of sufficient duration can induce itching hyperexcitability in mammalian skin.

In both the human and animal models for producing itching hyperexcitability via ischaemia, a selective lesioning of nerves and receptors in the skin is believed to occur, but with relative sparing of itch sensibility. The concomitantly-released epidermal proteases, their substrate breakdown products, peptides and other peripheral mediators of itch in the injured skin, generate or sensitize itch mechanisms with varied physical and chemical stimuli. In the dog model [48], systemic absorption of the products of ischaemic injury from the affected hind limb occurs via the uninterrupted venous circulation and can sensitize other normally-perfused skin, such as in the sham-operated hind limb. This leads to enhanced itching sensitivity, probably of the physiological 'spontaneous itch' type rather than of the pathological 'itching hyperexcitability' type, because there has not been any ischaemic lesioning of the skin of the sham-operated hind limb.

Gateway control theory and pathological itching hyperexcitability. The modulating role of supraspinal and spinal (substantia gelatinosa and dorsal horn transmitting cells) mechanisms in inhibiting or facilitating pain impulse traffic to higher levels of perception in the central nervous system, via the spinal cord, forms the so-called gateway control mechanism of pain [49]. It has been adapted to explain the overriding effect of some other cutaneous sensory stimuli, principally resulting in pain, e.g. severe scratching to overcome itch for as long as it is applied [6]. The itching hyperexcitability induced by ischaemia and other conditions of partial and selective damage to sensory nerve and receptor structures, with relative sparing of itch mechanism in the skin, e.g. in eczematous dermatitis, in lichenified skin, and in cutaneous areas of meralgia paraesthetica [5], can also be explained on the basis of the gateway control phenomenon. Thus, reduction or abolition of the preferentially-transmitted pain impulses that override itch mechanisms in the gateway, could cause a fortuitous enhancement of uninhibited itch impulses through the gateway. Such enhanced itch mechanisms would need to be blocked at the sites of action of central mediators of itch, and therefore will prove more intractable than physiological and spontaneous itch mechanisms which are not only subjected to gateway modulation but are presumably well palliated by antagonists of peripheral mediators of itch.

Clinical implications for the management of chloroquine-induced pruritus among patients with malaria

Olatunde [50] suggested a trilateral approach to the management of chloroquine-induced pruritus among patients with malaria.

Measures to palliate the acute pruritic reaction when it occurs following chloroquine therapy. Specifically, he suggested antipyretic treatment with aspirin; parenteral administration of H_1 histamine receptor blockers; ammonium chloride mixture taken orally to facilitate rapid excretion of chloroquine in acidified urine; hypnosedative or anxiolytic treatment; and

topical application of a soothing skin lotion after a warm bath. These measures generally conform with the principles of itch management when the aetiology is uncertain, according to Winkelman and Muller [51]. Possible modifications of this antipruritic programme could be made by substituting cyproheptadine for ordinary H_1 histamine antagonists because of its equally specific antagonism of serotonin, and its usefulness in prostaglandin-potentiated itch induced by those amines [6]. Naloxone could also be tried, because, apart from opioid-induced itch which it palliates as a specific opioid antagonist, it has been found to be useful in cholestatic itch due to bile salts [12] which are also said to mediate some drug-induced itching [6].

Prophylactic antipruritic measures in anticipation of the reaction in patients with historical experience of the pruritus during previous malarial fever suppression with chloroquine. Specifically, avoidance of potential histamine-releasing analgesics, such as codeine and combinations containing it was suggested. Instead, other antipyretics like aspirin are recommended. Other prophylactic measures advocated are sedation with diazepam, and prophylactic H_1 histamine receptor blocker administration.

Although the hypnosedative and anxiolytic components of this anticipatory treatment programme are potentially beneficial non-specific mechanisms for elevating the itch perception threshold centrally [10], the prophylactic use of antihistamines has not appeared to modify the evolution of chloroquine-induced pruritus among patients with malaria in previous studies [15,16]. Since pyrogenic haemodynamics can potentially aggravate the pruritogenicity of chloroquine via ischaemic lesioning of the skin, the prophylaxis of chloroquine-induced pruritus among Nigerian patients may be greatly helped by promptly instituting suppressive treatment with rapid erythrocytic schizonticides, including chloroquine itself, at the slightest suspicion of malaria, to avoid paroxysms of fever. Such presumptive diagnosis does not necessarily have to await a febrile paroxysm before commencement of a full course of chloroquine for malarial chemosuppression in a zone of intense, perennially-transmitted (holoendemic) malaria in which Nigerians live. Some prodromal feelings that may herald malarial fever include an inexplicable mood of impending doom, bizarre dreams, neurasthenia, heaviness in the head or eyes, excessive tiredness unrelated to physical or mental exertion, lassitude, general debility, myalgias and arthralgias. These symptoms, occurring singly or in any combination, have become reliable warning symptoms of an impending malarial paroxysm which can be aborted without fear of developing pruritic reactions, on a full course of chloroquine (Osifo, personal observation). This advocacy of full treatment for presumptive malaria is consistent with the report by Fairley *et al.* [52] that malaria parasites can be shown to be present in the peripheral circulation of individuals exposed to infected mosquitoes even though the paroxysms of the disease have become suppressed by chemotherapeutic agents. Among the partially-immune population of holoendemic, falciparum malaria-infested Nigeria, *Plasmodium* species can be regarded, almost in a manner analogous to the situation investigated by Fairley *et al.* [52], as normal 'commensals' in the peripheral circulation.

Antimalarial chemoprophylaxis with dihydrofolate reductase inhibitors to prevent or reduce the frequency of malarial febrile paroxyxms. The rationale for this recommendation by Olatunde [50], was to ensure less frequent attacks of malaria and hence reduce the chances of taking chloroquine. This approach has not generally been effective, or widely practiced by medical personnel in Nigeria, except in special preventative health programmes for children under 5 years of age, and for pregnant women, probably because of 'breakthrough' attacks of malarial fever during regular chemoprophylaxis with the dihydrofolate reductase inhibitors like proguanil (daily) or pyrimethamine (weekly). Although combinations of sulphadiazine with proguanil or sulphadoxine with pyrimethamine were also advocated [50] from the standpoint of optimizing potential antipruritic effects, the combination of dapsone with pyrimethamine (Maloprim, Burroughs-Wellcome, U.K.) might be a better choice because dapsone is effective against the itch of dermatitis herpetiformis, by an action believed to be related to enzyme inhibition [6]. This could possibly reduce the mechanism whereby itching hyperexcitability is linked to peripheral itch mediators, including enzymes, whose release is in turn linked to peripheral ischaemia during pyrogenic

haemodynamics as proposed in the present report.

References

1. Dorland's Illustrated Medical Dictionary (24th Edn). London: W.B. Saunders Company, 1965:1236.
2. Fitzpatrick TB, Johnson DP. Fundamentals of dermatologic diagnosis. In: Fitzpatrick TB, Arndt KA, Clark Jr, WH, Eisen AZ, Van-Scott EJ, Vaughan JH, eds. Dermatology in General Medicine. New York: McGraw Hill Company, 1971:33.
3. Rothman S. Physiology and Biochemistry of the skin. Chicago: University of Chicago Press, 1954.
4. Rothman S. Pathophysiology of itch sensation. In: Montagna W, ed. Cutaneous Innervation. New York: Pergamon Press, 1960:193.
5. Lorincz AL. Neurophysiologic reactions of the skin: Pathophysiology of pruritus. In: Fitzpatrick TB, Arndt KA, Clark Jr WH, Eisen AZ, Van-Scott EJ, Vaughan JH, eds. Dermatology in General Medicine. New York: McGraw Hill Company, 1971:212–16.
6. Alexander JO'D. The physiology of itch. Parasitology Today 1986;2:345–51.
7. Cormia FE. Experimental histamine pruritus. I. Influence of physical and psychological factors on threshold reactivity. J Invest Dermatol 1952;19:21–5.
8. Chapman LF, Goodell H, Wolff HG. Structures and processes involved in the sensation of itch. In: Montagna W, ed. Cutaneous Innervation. New York: Pergamon Press, 1960:Chapter 8.
9. Savin JA, Paterson WD, Oswald I, Adam K. Further studies of scratching during sleep. Br J Dermatol 1975;93:297–302.
10. Muston H, Felix R, Shuster S. Differential effects of hypnotics and anxiolytics on itch and scratch. J Invest Dermatol 1979;72:283.
11. Savin JA. Do systemic antipruritic agents work? Br J Dermatol 1980;103:113–18.
12. Bernstein JE, Swift RM, Soltani K, Lorincz AL. Antipruritic effect of an opiate antagonist, naloxone hydrochloride. J Invest Dermatol 1982;78:82–3.
13. Moody TW, O'Donohue TL, Jacobowitz DM. Biochemical localization and characterization of bombesin-like peptides in discrete regions of rat brain. Peptides 1981;2:75–9.
14. Ekpechi OL, Okoro AN. A pattern of pruritus due to chloroquine. Arch Dermatol 1964;89: 631–2.
15. Olatunde IA. Chloroquine-induced pruritus in Lagos, Nigeria. J Nigerian Med Assoc 1969;6: 23–33.
16. Osifo NG. Chloroquine-induced pruritus among patients with malaria. Arch Dermatol 1984;120: 80–2.
17. Berliner RW, Earle DP Jr, Taggart JV, Zubrod CG, Welch WJ, Conan N, Bauman E, Scudder SL, Shannon JA. Studies on the chemotherapy of the human malarias. VI. The physiological disposition, antimalarial activity and toxicity of several derivatives of 4-aminoquinoline. J Clin Invest 1948;27(suppl):98–107.
18. Craige B Jr, Whorton CM, Jones R Jr, Pullman TN, Alving AS, Eichelberger L, Rothman S. A lichen-planus-like eruption occurring during the course of chloroquine administration. J Clin Invest 1948;27(suppl):56–9.
19. Pullman TN, Craige B Jr, Alving AS, Whorton CM, Jones R Jr, Eichelberger L. Comparison of chloroquine, quinacrine (Atabrine), and quinine in the treatment of acute attacks of sporozoite-induced *vivax* malaria (Chesson strain). J Clin Invest 1948;27(suppl):46–50.
20. Scott V. Single intravenous injections of chloroquine in the treatment of *falciparum* malaria: toxic and immediate therapeutic effects in 110 cases. Am J Trop Med 1950;30:503–10.
21. Rees RB, Maibach HI. Chloroquine: a review of reactions and dermatologic indications. Arch Dermatol 1963;88:280–9.
22. Knox JM, Owens DW. The chloroquine mystery, including antimalarial agents in general. Arch Dermatol 1966;94:205–14.
23. Frisk-Holmberg M, Bergkvist Y, Domeij-Nyberg B, Hellstrom L, Jansson F. Chloroquine serum concentration and side effects: evidence for dose-dependent kinetics. Clin Pharmacol Ther 1979;25:345–50.
24. Tuffanelli D, Abraham RK, Dubois EI. Pigmentation from antimalarial therapy: its possible relationship to the ocular lesions. Arch Dermatol 1963;88:419–26.
25. Maegraith BG, Onabanjo AO. The involvement of histamine in malaria. Br J Pharmacol 1969;37: 535.
26. Agarwal SL, Deshmankar BS. The *in-vitro* antihistaminic and antianaphylactic actions of chloroquine. Arch Int Pharmacodyn 1963;143: 401–7.
27. Ciszek J, Walczak J. Treatment of bronchial asthma with chloroquine. Pol Med J 1971;10: 1125–30.
28. Voog R, Gavend M, Chouteau J. Le traitement de l'asthme par les antimalariques de synthèse: etude des dosages de l'histaminémie dans la démonstration de leur efficacité. Bronches 1972;22:220–9.
29. Ayitey-Smith EA, Boye GL. Effect of chloro-

quine on histamine-induced bronchial asthma in the guinea pig. J Pharm Pharmacol 1974;26: 208–9.
30. Shelley WB, Arthur RP. Neurohistology and neurophysiology of the itch sensation in man. Arch Dermatol 1957;76:296–323.
31. Lagunoff D, Benditt EP. Proteolytic enzymes of mast cells. Ann NY Acad Sci 1963;103:185–98.
32. Hagermark O. Studies on experimental itch induced by kallikrein and bradykinin. Acta Dermat Venereol (Stock) 1974;54:397–400.
33. Jindal MN. Adrenergic neurone blockade with chloroquine and amodiaquine. Indian J Med Res 1973;58:1050–6.
34. Shaffer B, Cahn MM, Levy EJ. Absorption of antimalarial drugs in human skin: spectroscopic and chemical analysis in epidermis and corium. J Invest Dermatol 1958;30:341–5.
35. Osifo NG. Chloroquine pharmacokinetics in tissues of pyrogen-treated rats and implications for chloroquine-related pruritus. Res Commun Chem Pathol Pharmacol 1980;30:419–30.
36. Levine JD, Gordon NC, Fields HL. The mechanism of placebo analgesia. Lancet 1978;ii: 654–7.
37. Summerfield JA. Naloxone modulates perception of itch in man. Br J Clin Pharmacol 1980;10: 180–3.
38. Iversen SD. Neuropeptides in psychiatric disorders. In: Bearn AG, ed. Merck, Sharp and Dohme International News and Notes. New Jersey: Merck and Company Inc., 1987;March: 1–3.
39. Bhargava RK, Parakh KL, Hakim A, Gori MN, Bhandari NC. Extrapyramidal syndrome after antimalarials. J Assoc Physicians India 1973;21: 969–73.
40. Umez-Eronini EM, Eronini EA. Chloroquine-induced involuntary movements. Br Med J 1977;1:945–6.
41. Osifo NG. The regional uptake of chloroquine in the rat brain. Toxicol Appl Pharmacol 1979;50:109–14.
42. Bradley SE, Chasis H, Goldring W, Smith HW. Hemodynamic alterations in normotensive and hypertensive subjects during the pyrogenic reaction. J Clin Invest 1945;24:749–58.
43. Cooper KE, Johnson RH, Spalding JM. Thermo-regulatory reactions following intravenous pyrogen in a subject with complete transection of the cervical cord. J Physiol (Lond) 1964;171:55P–6P.
44. Cranston WI, Vial SU, Wheeler HO. The relationship between pyrogen-induced renal vasodilatation and circulating pyrogenic substances. Clin Sci 1959;18:570–85.
45. Cranston WI. Temperature regulation. Br Med J 1966;I(5505):69–75.
46. Pyrogens and Fever (Ciba Foundation Symposium, Wolstenholme GEW, Birch J, eds. London: Churchill Livingstone, 1971:8–11.
47. Fever and Hyperthermia (Symposium of the American Physiological Society). Fed Proc 1979;38:27–63.
48. Osifo NG, Kadiri AU. A possible ischaemic factor producing predisposition to chloroquine-induced pruritus in the hindlimb of dogs. IRCS Med Sci 1980;8:916–17.
49. Melczak R, Wall PD. Pain mechanisms: a new theory. Science 1965;150:971–9.
50. Olatunde A. The practical and therapeutic implications of chloroquine-induced pruritus in tropical Africa. Afr J Med med Sci 1977;6. 27–31.
51. Winkelman RK, Muller SA. Pruritus. Ann Rev Med 1964;15:53–64.
52. Fairley NH. Sidelights on malaria in man obtained by subinoculation experiments. Trans R Soc Trop Med Hyg 1947;40:621–76; and correction, 40:908.

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