

Chloroquine induced pruritus - questionnaire based epidemiological study

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SUMMARY

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 in blacks is chloroquine induced pruritus (CP). A descriptive cross sectional questionnaire based epidemiological study of medical and nursing students, medical doctors and other workers with historic CP in a Nigerian tertiary (teaching) hospital was carried out to determine factors and features related to the development of CP. From the study the intensity of CP was not reduced by taking less CQ. About 92% of the subjects had close relations who suffered from CP. 84.5% of responders itched for 1-3 days. The longest duration for CP was 7 days. The sites of itching in descending order were generalized (49.2%) hands (46%), legs and feet (46%), perineum/genitalia (28.5%). Relieving factor/drug was identified in 66.6% of responders. Itching with oral CQ occurred in 100%. Intramuscular injection of CQ caused 49% of itching. 19% had pre-chloroquine itch. 28.5% had CP with other antimalarials notably Amodiaquine (23.8%). 50.7% took other antimalarials when down with malaria. There is a need for the identification of a cheap and readily available antidote for CP to enable CQ remain useful/relevant in Nigeria and in the West African sub -region.

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Introduction

Chloroquine (CQ) is a very useful drug with a broad spectrum of activity. It is best known however as an antimalarial drug. It is also useful for other microbial diseases like Amoebiasis. Non microbial entities like rheumatoid arthritis, sarcoidosis, Lupus erythematosus and scleroderma also respond to CQ. It is readily available in developing countries of Africa and is relatively cheap. A major side effect first highlighted in 1948 and mentioned further (in Nigeria) around 1968 [1] is chloroquine induced pruritus (CP). It is found predominantly in blacks. The itching which has certain peculiarities (episodic, fleeting, without residual scratch marks) has caused many in the

developing countries of Africa to progressively shun this useful drug. The mechanism for the itching remains a mystery. There are however various hypotheses [2, 3,]. The reasons for these hypotheses stem from a need to look for a way or a drug to reduce, or abolish the itching. Considering the morbidity and mortality from malaria in Africa and the need to provide quality health at an affordable cost, a prospective epidemiological study was conducted. The study was undertaken to highlight features/peculiarities of chloroquine pruritus, hoping that these would help plan

trials of drugs that can help reduce or abolish the pruritus. This is not an original thought, but it is hoped that it shed some light on this enigma. There are differences in findings from epidemiological studies in different parts of Africa, and even in the same countries. CP, for example was found to occur with and without parasitaemia in one [4] study, while another study documented rarity of CP in the absence of parasitaemia [5].

Methods

This was a descriptive cross sectional questionnaire based epidemiological study. It was conducted between July 2002 and March 2004.in South Western Nigeria in Black volunteers. Subjects aged 15 years and above were studied. They were educated and had experienced CP. This decision was taken to ensure adequate recall and to assure reliability of data obtained (since historical CP is the focus). Nursing and medical students, medical doctors and other health workers and non-health workers such as secretaries working within the University College Hospital (UCH), Ibadan, Nigeria formed the study population. These chosen subjects would no doubt have tried a wider range of antimalarials than individuals in the rural areas or the uneducated since they work or studied in a health institution. Structured questionnaires (see appendix) were served on the subjects to help obtain the required information. Since there was no documentation of a gender or socio economic relationship to predisposition to CP questionnaires were serve at random to all who have had itching CP in the past and who were willing to participate in the study. Severe CP was regarded for the study as CP which was bad enough to significantly disturb sleep. Moderate CP disturbed daily activity significantly but did not prevent sleep. It was discovered before the study commenced by verbal questioning during formal student lectures that 78% of medical students on their clinical posting in UCH had suffered CP at one time or the other.

Results

Out of 100 questionnaires given out, 65 were returned; 63 were adequately completed or found to be suitable for evaluation. The male: female ratio was 1:1. The age range was 21 – 49 years, the average age being 24 years. The results obtained can be summarized as follows:

The intensity of CP is not reduced by taking less CQ.(69.8 % did not have a reduction in itching despite reducing dosage of CQ; 17. 5 % never tried a reduced dosage). About 92% had close relations who also suffered from CP. 84% of the responders itch for 1-3 days. Itching lasted more than three days in 11% of the study population. The longest duration for CP was 7 days.(in 11.0 %). The sites of itching in descending order were generalized (49.2%), Hands (46%), legs and feet (46%), perineum/genitalia (28.5%). Relieving factor/drug was identified in 66.6% of responders and these consisted of Antihistamines in 54%, corticosteroids in 7.9%, and Vitamin B Complex in 6.3%. Itching with oral CQ occurred in 100% of the responders and in 49% with intramuscular injection of CQ. The oral route was still the commonest route that was or had been used by the responders. 19% have “pre-chloroquine” itch, which is becomes worse after taking CQ. 28.5% of responders have CP with other antimalarials not due to chloroquine; notably Amodiaquine. (23.8 %). Sulphonamide containing antimalarials accounted for 3.2 %). To the question “*what do you do presently if you have malaria?*” The responses included:

- Use of alternative drugs to CQ ...32 (50.7 %)
- Reduced dosage of CQ.....5 (8.0 %)
- Adjuvant drugs7 (11.0 %)
- Avoid all antimalarials..... 4 (6.3 %)
- Others 15 (23.8 %)

Other responses included

- “ I take IM Chloroquine + Phernegan (an antihistamine) + prednesolone”
- “ I take CQ in the correct dose but spaced out over 5 days”
- “ I take IM CQ alone”
- I only itch when malaria is severe, therefore I take CQ before it (malaria) becomes severe”

“ I take normal doses of CQ and then face the consequences”

Discussion

CP is common among the black population of West Africa. It is, however, rare in Caucasians despite the frequent use of CQ in large doses for the treatment of connective tissue disorders particularly rheumatoid arthritis [6] and also for scleroderma [7] and sarcoidosis [8]. The reported incidence of CP in Nigeria appears to be on the increase, from 2-4% in 1958, [9], 8-15% in 1964, [10] and 28% in 1981 [11]. While it can be argued that these are figures from different geographical locations, it would appear that the trend is upwards. The prevalence among 250 medical students in the clinical years, in UCH in Ibadan, in the western region of the country was 78% in 1997 suggesting a continued trend upwards. It would appear that CP start to rise once CQ is introduced into a community. When Chloroquine phosphate was made available in May 1982 in Saradidi, Kenya, in each Village as part of a community based malarial control program, reports of chloroquine induced pruritus began to appear [4]. Until the sixties, in Nigeria, Quinine was the regular drug for malaria. Just before World II, Java (Indonesia) supplied over 90% of the world's consumption of Quinine, a most important drug for malaria. When the Japanese cut off this drug supply from the world, several synthetic antimalarials (Chloroquine, quinacrine and primaquine) were developed to replace Cinchona. It is thus not surprising that the first report of CP came up shortly after (Berliner et al, 1948) [12] and in Nigeria Ekpechi and Okoro documented same in 1964 [1]. CP prevalence thus seemed to be on an upward trend once introduced into a geographical area. In Nigeria, the commonly used antimalarial is still chloroquine, despite an increasing resistance to this medication. *Plasmodium falciparum* still accounts for up to 80% of the parasites encountered. Refusal to use CQ (because the pruritus can be as bad as or worse than the actual malaria itself), or the tendency to use a reduced amount (a practice that could encourage resistance) [5] are the problems facing this medication which is still a readily affordable

drug . CQ has the ability to treat many diseases of microbial and non-microbial origin. The result obtained in this study using questionnaire suggests that CP is not reduced by taking reduced dosage of CQ in 69.8% of responders. 93.6% of the study population had close relatives who itched after consumption of CQ. The latter finding can point to a genetic trait. The increasingly high figures however would suggest a pharmacologic reaction to a common agent used by family members rather than some form of inheritance. The high number of siblings having historical CP, 58.7% under the sub-heading “Relationship” to respondents, most likely reflects the marital status of the respondents in this study who were unmarried – nursing and medical students. 74.6% of the study population had CP lasting one to three days. One of the reasons for the increasing dislike for CQ is the fact that this side effect can be as bad as or worse than the malarial attack itself because of near exhaustion from lack of sleep. This is a clear justification for giving ‘sick leave’ to individuals who have CP [1].

In the present study 57.1% often experienced severe itching. CP can disturb or prevent sleeping for days. The longest duration for CP in this study was seven days. CP has prevented the use of CQ for the treatment of connective tissue diseases in many Negroid. CP can be generalized or localized. It was generalized in 48.5% of individuals in the study. The common localized areas were the hands (46.0%), legs and feet (46.0%) and the perineum/genitalia (44.4%). It can be particularly embarrassing in the latter anatomical area. 66.6% claimed some relief with certain drugs.

The main group of drugs identified in the study were antihistamines (53.9%) followed by systemic corticosteroids (7.9%) and Vitamin B Complex. The role of lack or reduction of some essential factors (e.g. hypovitaminosis) in some population of CP, sufferers will need to be determined.

Some subjects appear to be relieved (to some extent) by Niacin , one of the B group of vitamins [5] and cycloheptadine [3]. Chloroquine pruritus has been considered by some as a form of paraesthesia. The B group

vitamins may thus be helping in a subset where these factors are lacking or deficient.

The relief by antihistamine is not supported by most of the current documented drug trials [2, 3]. The disparity may be partly explained by the severity of itching (may be the relief is for the mild cases of CP). The actual extent of bodily involvement (localized or generalized) may also contribute to the discrepancy. Antihistamines are also more widely prescribed and consumed than corticosteroids and would have featured more in the responses. 100% of responders itched with oral CQ. 48.5% did with parenteral CQ. It follows that 48.5% had CP whatever the route or Chloroquine. The oral route is the commonest. No one had itching by the parenteral route alone without itching when CQ is administered orally. In the past few years, it has become clear that there is a new trend of 'pre-chloroquine' itching [13]. 10% had such itching in this study. Documented evidence of parasitaemia accompanying this pre-drug itch is scanty. There is a need to organize a proper study to indicate the usefulness of this type of itch as a diagnostic or suggestive feature for malaria. 48.6% of the population studied had not tried other antimalarials. Camoquine (Amodiaquine) was the commonest alternative drug which caused chloroquine-like pruritus. It was the commonest choice since the switch from Quinine to the 4 Aminoquinolines. Halophantrine (Halfan) to which about 6% CQ has been documented is costly – about five times the cost CQ. It is not readily affordable by the majority of Nigerians. It is also being discouraged because of its adverse effect on the heart /conduction system. It is structurally different from the 4- Aminoquinolines.

The focus for the various studies on CP is the identification of an antidote that is relatively cheap, readily available, with minimal side effect that can be prescribed even at the primary health care level. This will enable chloroquine to remain useful in Nigeria and in the West African sub-region for the treatment of malaria, hepatic amoebiasis and other non-infectious entities like the collagen vascular diseases.

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Appendix 1

Highlights of questions in the questionnaire

- Is itching less by taking reduced dosage of Chloroquine?
- Is there a close relation who itches with Chloroquine? **
- Relationship of family members who itch to responders
- Average duration of chloroquine pruritus
- Average historical intensity of itching (mild, moderate, severe itching).
- Sites of itching
- Any relieving factors
- Relieving factors /drugs identified.
- Relationship of itching with route of CQ
- Do you itch when you have features of malaria /feel unwell even before taking antimalarial?
- Apart from Chloroquine, any itching with other antimalarials?
- What do you presently do if you have malaria?

**Close relation= parents, siblings, and offspring- member of the immediate family.