Research Journal of Parasitology

ISSN 1816-4943

Academic Journals Inc.

www.academicjournals.com

Research Journal of Parasitology 4 (1): 28-32, 2009
ISSN 1816-4943

Efficacy of Cotrimoxazole-Chloroquine in the Treatment of Chloroquine or Sulphadoxine-pyrimethamine Treatment Failure: A Short Communication

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Abstract: We evaluated the efficacy of cotrimoxazole plus chloroquine in the treatment of chloroquine or sulphadoxine pyrimethamine treatment failure in an area of malaria hyperendemicity. Thirty-two consecutive children who had earlier been treated with either chloroquine or pyrimethamine-sulphadoxine but failed to achieve cure were enrolled into the study. Each child was treated with oral medication of chloroquine using the standard regimen of 10 mg kg^{-1} body weight each on days 0, 1 and 5 mg kg^{-1} body weight on day 2 plus cotrimoxazole at an equivalent dose of 40 mg kg^{-1} body weight in 2 divided doses daily for three days, that is, days 0-2. All were followed up for a period of 14 days both clinically and parasitologically. All children were asymptomatic and aparasitaemic by day 3 and remained free of malaria parasite till day 14. We concluded that cotrimoxazole in combination with chloroquine is efficacious in the treatment of chloroquine or sulphadoxine treatment failure and inadvertent use of this combination might have been responsible for delay in the advent of chloroquine resistant malaria in South-West Nigeria.

Key words: Combination, therapy, cotrimoxazole, malaria, antifolates, resistance

INTRODUCTION

Malaria is the most important parasitic disease of humans and it is estimated to cause at least 1 million deaths annually most of these deaths occurring in sub Saharan Africa (World Health Organization, 2005). The discovery and eventual introduction of chloroquine, a 4-aminoquinoline immediate post Second World War II was thought to present an opportunity for eliminating the disease but advent of strains of *Plasmodium falciparum* that exhibit resistance to chloroquine and many other antimalarial drugs has since changed that view (Spencer, 1985; Wernsdorfer, 1991). In Nigeria, chloroquine was first-line antimalarial drug while sulphadoxine-pyrimethamine was second-line until 2004 when the country changed to artemisinin based combination chemotherapy, reflecting the WHO recommendation (World Health Organization, 2001; Federal Ministry of Health, 2004).

In sub Saharan Africa, malaria and respiratory tract infections account for considerable childhood mortality and both do occur together. (World Health Organization, 1999) Cotrimoxazole, a combination of sulphamethoxazole and trimethoprim has antimicrobial spectrum including bacterial and protozoan infections like malaria (Bloland *et al*., 1991; Fehintola *et al*., 2002, 2004). Chloroquine and cotrimoxazole were sometimes prescribed together once there was suspicion of respiratory tract infection co-existing with malaria (Fehintola *et al*., 2006). There is yet a dearth of information on the activities of such inadvertent combination therapy on the relative slowness of evolution of chloroquine resistant malaria in Nigeria compared to East African countries like Kenya (Fogh *et al*., 1979; Lege-Oguntoye *et al*., 1989).

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The aim of the present study is to evaluate the efficacy of cotrimoxazole plus chloroquine in such instances when chloroquine or sulphadoxine have failed to treat acute uncomplicated falciparum malaria.

MATERIALS AND METHODS

Patients and Drug Treatment

Patients involved in the study were drawn from those attending the General Outpatient Department of University College Hospital, Ibadan, Southwest Nigeria between July 2001 and March 2002. Thirty-two consecutive children aged between 1 and 14 years presenting with clinical and parasitological features of malaria who had failed treatment with either chloroquine or sulphadoxine-pyrimethamine were enrolled into the study. Prior to enrolment, a careful history was obtained from an accompanying parent or guardian and physical examination was performed. Body weight and axillary temperature were recorded and thick and thin blood films prepared for parasite identification and quantification. Nineteen of the children had earlier been treated with standard dosing regimen of chloroquine while the remaining 13 were treated with sulphadoxine-pyrimethamine 10-14 days earlier (Table 1).

Drug treatment following enrolment was a combination of chloroquine 10 mg kg^{-1} body weight on days 0, 1 and 5 mg kg^{-1} body weight on day 2, that is, a total of 25 mg kg^{-1} body weight in 3 days and cotrimoxazole at an equivalent dose of 20 mg of sulphamethoxazole kg^{-1} body weight twice daily for 3 days. All drugs were in tablet form and only the first doses of the drugs were directly

Table 1: Presenting symptoms in patients with acute uncomplicated falciparum malaria

Sex	Age (years)	Previous treatment	Temp. D0 (°C)	Parasite den. D0	SCT
M	3.00	CQ	36.7	21073	2
M	4.00	CQ	37.2	18900	1
F	14.00	CQ	38.1	21492	3
F	14.00	SP	36.6	9552	2
F	4.42	SP	37.7	4760	2
F	4.67	SP	37.3	137799	2
F	6.25	SP	40.6	9505	2
M	1.50	CQ	37.7	3015	2
F	6.00	CQ	37.3	9058	2
M	1.00	CQ	39.2	2290	2
F	4.67	SP	38.5	5940	2
M	12.00	CQ	36.5	3000	3
F	5.00	CQ	36.6	2376	3
M	2.50	CQ	36.3	14910	1
F	6.00	SP	36.8	8276	1
F	4.58	SP	37.0	11822	1
M	2.10	CQ	39.3	29876	2
F	4.00	SP	37.9	5289	3
M	1.50	CQ	38.6	6090	2
F	7.00	SP	37.3	11885	2
M	5.00	CQ	40.0	126000	3
M	3.00	CQ	8.8	15600	3
M	4.83	CQ	36.2	35644	3
M	10.00	CQ	37.1	11084	3
M	1.00	CQ	38.5	3610	2
M	1.25	CQ	39.0	6090	2
M	3.30	CQ	39.3	1050	1
F	6.50	SP	38.8	1370	2
M	9.00	SP	38.6	16500	3
F	4.50	SP	38.1	3628	2
M	7.00	SP	36.7	6314	1
M	4.00	CQ	37.6	2929	2

SCT: Symptom Clearance Time; CQ: Chloroquine; SP: Sulphadoxine-pyrimethamine, M: Male; F: Female

observed rest of the medication were given to parents/guardians with clear instructions to be administered at home. The foregoing was an attempt to simulate what operates in real practice and propriety of administration of the subsequent doses was verified at the clinic on day 3. In all, patients were seen on days 0, 3, 7 and 14 and at each visit history and physical examination as well as blood film was carried out.

Parasitological Assessment

Giemsa stained blood films were examined by light microscopy under an oil immersion objective at x1000. Asexual parasitaemia in thick films was estimated by counting asexual forms relative to leucocytes, 500 asexual forms of *P. falciparum*, or the number of such parasites corresponding to 200 leucocytes, were counted, whichever occurred first. The parasite density was subsequently calculated by assuming a leukocyte count of 6000 μL^{-1} of blood:

$$\text{Parasite density} = \frac{\text{No. of parasite}}{\text{No. of leukocyte}} \times 6000$$

The parasite clearance time was defined as the time from drug administration until there was no patent asexual parasitaemia. The fever clearance time was defined as the time from drug administration until the axillary temperature fell to 37.4°C or below. The symptom clearance time was defined as the time between drug administration and the disappearance of all presenting symptoms.

All symptoms and signs emerging after commencement of treatment and/or presenting symptoms and signs that became worse following commencement of treatment were classified as adverse events. Treatment was considered a failure if (asexual) parasitaemia on day 3 was greater than 25% of the day 0 value, if parasitaemia did not clear by day 7 or if Parasitaemia cleared before day 7 but reappeared before day 14. The cure rate was defined as the proportion of patients who remained asymptomatic and free of parasitaemia on day 14 of follow-up, that is, adequate clinical and parasitological response (ACPR).

Data obtained were entered into EPI INFO version 6 to obtain descriptive statistics which were compared using chi square or students t test and p-value was set at 0.05.

RESULTS

Thirty-two children aged between 1 year and 14 years were enrolled into and completed the study per protocol. In all, there were 18 males and 14 females (Table 1). The mean age of the children was 5.16±3.42 (range: 1-14 years) and mean weight was 16.65±9.01 kg (range: 7.1-46.8). Anorexia was the second commonest symptoms after fever and it was reported by 18 patients (56.3%), headache and vomiting were reported by 15 patients each. Also 5 children had cough two of whom had catarrh in addition. Mean temperature at presentation was 37.87±1.14°C and it ranged from 36.2 to 40.6°C. Mean parasite density was 17804+31101 asexual forms per microliter (range: 1050-137799).

Clinical and Parasitological Responses

Mean symptom clearance time was 2.09±0.69 (range: 1-3 days). All patients had cleared fever by the first follow up visit (day 3) as temperature has normalised and their blood films were also negative. Mean temperature (°C) on days 0, 3, 7 and 14 were, respectively; 37.87, 36.66±0.38, 36.40±0.43 and 36.55±0.38 (F: 32.96; $p<0.001$), indicating a significant difference.

The only untoward effect recorded was pruritus in a 3 year old boy who had presented with mild symptom which began on day 2 and lasted for about 1 day.

DISCUSSION

Malaria and respiratory tract infection are very common childhood conditions and may co-exist thus requiring the use of two or more antimicrobials. Both chloroquine and cotrimoxazole are easily available and inexpensive thus providing remedies for two very common conditions, malaria and respiratory tract infections (Fehintola *et al*., 2006). This inadvertent use of combination therapy might have contributed to the relative slowness in the establishment of drug resistant malaria in Nigeria (Fogh *et al*., 1979; Lege-Oguntoye *et al*., 1989). This study has in a limited way attempted to explore possible influence of cotrimoxazole on evolution of chloroquine-resistant malaria in Southwest Nigeria. The phenomenon of inadvertent combination therapy in malaria especially with reference to cotrimoxazole had probably never been examined prior to this study and report, it is therefore considered that this is the first time such study is been reported.

All of the children had symptoms compatible with acute uncomplicated falciparum malaria were treated on outpatient basis with fewer clinic visits in an attempt to simulate what obtains in real practice. The 14 day follow up was in recognition of the fact that beyond day 14 in areas of intense malaria transmission as ours, except with the use of molecular markers it may be difficult to differentiate between re-infection and recrudescence. However, sequel to our schedule clinic visits it was not possible to obtain the temperature readings on days 1 and 2 and therefore unable to calculate actual fever clearance time as well as parasite clearance time nonetheless the symptom clearance time apparent fever, and parasite clearance time were found to be similar with antimalarial drugs studies in the same area (Fehintola *et al*., 2007, 2008; Sowunmi *et al*., 2002; Sowunmi, 2005a). It may be premature to suggest any policy review based on our findings for a number of reasons including the fact that sample size was very small and follow up period short. In addition, relatively high level of treatment failures with chloroquine have been reported in most parts of Nigeria at the present. However, most of such reports have emanated from hospital based studies and therefore large community based epidemiological studies of cotrimoxazole containing antimalarial combinations should suffice to verify present findings. Amodiaquine, a congener of chloroquine possesses better activity than chloroquine and is currently favoured in the combination therapy for malaria but concerns do exist about its tolerance. On the other hand safety profile of chloroquine may almost be taken for granted thus giving chloroquine an edge with respect to tolerability. We considered that sulphadoxine-pyrimethamine and cotrimoxazole despite similar mechanism of action may not necessarily exhibit concordance with respect to treatment failure, perhaps because of the relatively short half-life of components of cotrimoxazole which may reduce selection pressure.

In view of the high childhood morbidity and mortality in sub Saharan-Africa ascribable to malaria and respiratory disease combination containing cotrimoxazole may even become more attractive Further, recent studies suggest cotrimoxazole alone or in combination negatively influence gametocyte generation when compared with sulphadoxine-pyrimethamine thus providing an added advantage over and above the latter (Fehintola *et al*., 2007, 2008; Sowunmi *et al*., 2005b). In conclusion cotrimoxazole-chloroquine combination possesses similar efficacy to other antimalarial drug combinations and large epidemiological and community based studies is hereby suggested for further evaluation.

ACKNOWLEDGMENT

We like thank Mr. Peter Nwachukwu for assisting in the screening of patients while the study lasted.

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