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Short Report

Clinical efficacy of chloroquine or sulfadoxine–pyrimethamine in children under five from south-western Uganda with uncomplicated falciparum malaria

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Abstract

We conducted a 14-day study (during March–May 1998) to assess the efficacy of chloroquine and sulfadoxine–pyrimethamine (SP) for treating uncomplicated *Plasmodium falciparum* malaria in Uganda. Overall treatment failure rates were 43 (81·1%) of 53 chloroquine recipients and 16 (25·0%) of 64 SP patients. Strategies to improve the life-span of standard and affordable antimalarial drugs are needed.

Keywords: malaria, *Plasmodium falciparum*, chemotherapy, chloroquine, sulfadoxine–pyrimethamine, children, efficacy, Uganda

Introduction

Most African countries still rely on chloroquine (CQ) and sulfadoxine–pyrimethamine (SP) to treat uncomplicated falciparum malaria. However, resistance of *Plasmodium falciparum* to CQ is widespread and resistance to SP is increasing in Africa (KROGSTAD, 1996; WHO, 1997).

In Uganda, published data and data from the Ministry of Health have documented a decrease of the clinical efficacy of CQ and SP in different parts of the country (KAMUGISHA *et al.*, 1994; NEVILL *et al.*, 1995; MINISTRY OF HEALTH, 1997; NDYOMUGYENYI & MAGNUSSEN, 1997, 2000). No data exist for Mbarara, an area of mesoendemic transmission of predominantly *P. falciparum* in the south-western part of the country. However, local clinicians report high treatment failure rates with CQ necessitating the frequent use of SP. We

report the results of a 14-day clinical efficacy study assessing CQ and SP (first- and second-line drugs in Uganda at the time of the study) for treating acute uncomplicated *P. falciparum* malaria in children aged <5 years from Mbarara.

Materials and Methods

Children were recruited from the outpatient department of the Mbarara Regional Hospital. Eligible subjects were febrile (axillary temperature ≥37·5°C) children, aged 6–59 months, with uncomplicated *P. falciparum* malaria and an asexual parasitaemia ranging from 500 to 100 000/µL. Written informed consent was obtained from all parents or guardians.

Enrolled children were initially assigned to receive 25 mg/kg bodyweight of CQ base (chloroquine phosphate, IDA, Holland), administered over 48 h. The following group received SP (Fansidar®, Roche) at the dose of 1·25 mg/kg bodyweight of pyrimethamine, given once. All drug administration was supervised. Follow-up was for 14 days. Parasitological examinations were made on Days 0, 3, 7 and 14. All blood slides were read twice in a blinded fashion by experienced microscopists. Discrepant results were resolved by a third blinded read. Urine Saker–Solomon test was performed on Day 0 for the detection of CQ and its metabolites (MOUNT *et al.*, 1989). The haematocrit (Hct) was measured on Days 0 and 14 (for children followed on Day 14 with Hct <25% on Day 0).

End points were those defined by the WHO 1996 protocol for assessing therapeutic response (WHO, 1996).

Early treatment failure (ETF):

(i) development of danger signs or severe malaria on Days 1–3 in the presence of parasitaemia,

(ii) Day 2, axillary temperature ≥37·5°C and a parasitaemia > pre-treatment level (Day 0),

(iii) Day 3, axillary temperature ≥37·5°C and parasitaemia,

(iv) Day 3, parasitaemia ≥25% of the Day 0 parasitaemia;

late treatment failure (LTF):

(i) development of danger signs or severe malaria on Day 4–14 in the presence of parasitaemia without previously meeting the criteria of ETF,

(ii) axillary temperature ≥37·5°C and parasitaemia on Day 4–14 without previously meeting the criteria of ETF;

adequate clinical response (ACR):

(i) absence of parasitaemia on Day 14 irrespective of axillary temperature, without previously meeting the criteria of ETF,

(ii) axillary temperature <37·5°C irrespective of the presence of parasitaemia, without previously meeting the criteria of ETF.

Only patients who completed the study were included in the efficacy analyses. Five of the SP recipients were failures from the CQ group. They were included

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Table. Baseline characteristics at enrolment and study outcomes of children aged <5 years with acute uncomplicated falciparum malaria treated with chloroquine (CQ) or sulfadoxine–pyrimethamine (SP) in Mbarara, south-western Uganda, March–May 1998

	CQ group	SP group
Baseline characteristics	$N = 57$	$N = 61$[a]
Mean age (SD) in months	27·9 (14·5)	23·2 (11·7)
Male:female ratio	0·73	1·44
Prestudy self medication[b]	24 (42·9)	42 (68·9)
Mean temperature (SD) in °C	38·1 (0·51)	38·1 (0·62)
Asexual parasitaemia/μL[c]	16 770 (519–86 937)	14 908 (528–96 281)
Outcomes[b]	$N = 57$	$N = 66$
Lost to follow-up	4 (7·0)	2 (3·0)
Therapeutic response[d]		
Early treatment failure	26 (49·1)	10 (15·6)
Late treatment failure	17 (32·1)	6 (9·4)
Days 4–7	13 (24·5)	0 (0·0)
Recurrent parasitaemia	4 (7·5)	6 (9·4)
Adequate clinical response	10 (18·9)	48 (75·0)

[a]5 CQ recipients not included.
[b]n (%).
[c]Median (range).
[d]Proportions based on denominators of 53 for CQ, and 64 for SP.

in all of the analyses for the CQ group, but only in the efficacy analysis for SP.

Results

A total of 123 children were recruited from March to May 1998; 57 received CQ and 66 SP. All children had symptoms or signs consistent with malaria. Baseline characteristics were broadly similar between the 2 groups (Table). Children in the SP group were more likely to have taken antimalarial drugs prestudy ($P = 0·003$). Urine testing was done on 53 children of whom 34 (64·2%) were positive for CQ/metabolites: 19/31 (61·3%) in the CQ group, and 15/22 (68·2%) in the SP group ($P = 0·61$). Of the 34 children with positive urine tests, only 17 (50·0%) mothers remembered whether their child took antimalarial drugs prestudy. Six patients (4 CQ group, 2 SP group) did not complete the study and were excluded from the efficacy analyses. The overall treatment failure rate was 81·1% (43/53, 95% CI 67·6–90·1) for CQ recipients and 25·0% (16/64, 95% CI 15·4–37·7) for SP recipients (Table). The median Day 0 Hct, measured in 96 patients, was 27% (range 15–37). Among patients with Day 0 Hct <25% who were tested on Day 14 ($n = 16$; CQ = 4, SP = 12), 15 had ACR and 1 LTF. Their median Hct raised from 20·5% on Day 0 to 28·0% on Day 14 ($P < 0·001$).

Discussion

Our study has demonstrated a very limited clinical efficacy of CQ and a reduced clinical efficacy of SP when used for treating acute, paediatric falciparum malaria in Mbarara, Uganda. Of concern is the occurrence of early SP treatment failures, suggesting high-grade resistance to SP is present in Mbarara. A possible bias that limits the applicability of our results to other areas of Uganda is that children were recruited from the outpatient department of a referral hospital in an urban setting. For this reason, they may have been sicker or may have often received earlier treatment that had failed. Indeed, approximately half of them reported taking antimalarial drugs before the study. Compared to rural areas, urban areas are more likely to have higher levels of antimalarial drug resistance because of increased drug pressure that is due to easier access and increased consumption of antimalarial drugs (WHITE, 1992; WERNSDORFER, 1994). Even if the origin of our patients might have resulted in an over-estimation of

the true treatment failure rates, our results are consistent with data from other parts of Uganda, which show that the trend of drug resistance has been upwards in this country since the mid-late 1980s. Documented peak levels have been 77% for CQ and 12·5% for SP (NEVILL *et al.*, 1995; NDYOMUGYENYI & MAGNUSSEN, 1997; JELINEK *et al.*, 1999).

It is clear from our data that CQ monotherapy has no clinical utility for paediatric falciparum malaria in Mbarara. Local clinicians and, for example, shop keepers should, therefore, stop prescribing or selling CQ. The second choice, SP, currently has reasonable efficacy but this will decline in parallel with increasing use, as has been the case in Africa and other regions (WHITE, 1992; KROGSTAD, 1996). Thus, SP monotherapy may suffice as an interim measure until alternative, inexpensive, and efficacious drugs or combinations become available. In this regard, Uganda is in a similar position to other malaria-endemic countries that have high levels of CQ resistance and focal areas of increasing SP resistance. Combinations of an artemisinin derivative with standard antimalarial drugs may well represent the therapeutic and economically sound way forward for resource-strapped countries (WHITE *et al.*, 1999). However, this action has to be coupled with formulating sound drug policy and measures to reduce drug pressure through accurate diagnosis, rational prescribing, and appropriate patient education.

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Book Review

The Plato of Praed Street: the Life and Times of Almroth Wright. M. Dunnill. London: Royal Society of Medicine Press, 2000. xiii+269pp. Price £17.50. ISBN 1-85315-477-6.

Sir Almroth Edward Wright FRS (1861–1947)—frequently referred to as 'Almost Right'—was one of medicine's most colourful figures. He is best remembered as: Professor of Pathology at the great military hospital at Netley (a history of which has recently been published: Hoare, P. *Spike Island: the Memory of a Military Hospital*. London: Fourth Estate; 2001) in 1892–1902, a pioneer of typhoid vaccine(s) (during the Boer and Great Wars), as Sir Colenso Ridgeon in George Bernard Shaw's *Doctor's Dilemma* ('to stimulate the phagocytes'), and as a close colleague and mentor of Sir Alexander Fleming FRS (1881–1955) (and Leonard Colebrook) at St Mary's Hospital, London.

Wright was in a nutshell an idiosyncratic Irish genius who was in many ways ahead of his time; the title, 'Plato of Praed Street' was applied to him by the surgeon and (underrated) medical historian Zachary Cope, the author of *Almroth Wright: Founder of Modern Vaccine-Therapy* (London: Thomas Nelson; 1966).

At Netley he had been appointed in preference to Sir David Bruce FRS (1855–1931); he played an important role in the establishment of the Medical Research Committee (later, Council); and he attracted immense financial support for his laboratory from Parke Davis for his pioneering vaccine work. Throughout his life Wright was wholeheartedly opposed to women occupying important positions; he regarded them as intellectually inferior to men! He was also vehemently contemptuous of the Harley Street ethos of his time. Two biographies of Wright already exist (the most widely known being that by Colebrook: *Almroth Wright: Provocative Doctor and Thinker*. London: Heinemann; 1954). Do we really require a third? Having read, and greatly enjoyed Dr Dunnill's text I have no doubt that we do. Dunnill (a retired pathologist) has filled in numerous lacunae, as a result of his thorough and painstaking research, left out in the previous biographies. He has relied not only upon the 2 previous biographies but also on material at the Public Record Office, the Contemporary Medical Archive Centre at the Wellcome Institute, the archives of Trinity College, Dublin, and the manuscript collection at the British Library. The book is well produced, the illustrations satisfactory, and the (6-page) index is adequate. The Royal Society of Medicine's biographical series is somewhat inconsistent in its quality; this book is undoubtedly one of the best to have been included so far.

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