In-vivo parasitological response to sulfadoxine-pyrimethamine in pregnant women in southern Malawi

K. Msyamboza[1], A. Amanor[1], P. Kazembe[1,3], B.J. Brabin[2,4,5], S. Meshnick[6,7], V. Mwapasa[7]

1. Malaria Alert Centre, College of Medicine, University of Malawi, Blantyre, Malawi
2. Child and Reproductive Health Group, Liverpool School of Tropical Medicine, England
3. Department of Paediatrics, Lilongwe Central Hospital Lilongwe, Malawi
4. EmmaKinderziekenhuis, Academic Medical Centre, University of Amsterdam, The Netherlands
5. Department of Community Paediatrics, Royal Liverpool Children's Hospital NHS Trust, Alder Hey, England
6. University of North Carolina, USA
7. Department of Community Health, College of Medicine, University of Malawi, Blantyre,

Correspondence: Kelias Msyamboza: kmsyamboza@mac.medcol.mw

Abstract

Background: Malaria in pregnancy is a significant cause of maternal and infant morbidity and mortality. Malawi adopted intermittent preventive treatment with sulfadoxine-pyrimethamine (SP) for the control of malaria in pregnancy in 1993. However there is little information on the in-vivo SP efficacy in pregnant women. This study was conducted to determine: prevalence of malaria and anaemia at the first antenatal visit and rate of parasitological failure to SP in pregnancy.

Methods: A cross-sectional followed by a prospective cohort study was conducted in women attending antenatal care clinic at Montfort Hospital in Lower Shire Valley from June 2004 to February 2005. Women were screened for malaria and anaemia at the first antenatal visit. After taking SP under direct observation, women with malaria parasitaemia were followed up to day 14 to determine parasitological response.

Results: Of 961 women screened, 9% had malaria, 77% had anaemia (HB<11.0g/dl), 24% had moderate anaemia (HB 7.0-8.9g/dl) and 6% had severe anaemia (HB<7.0g/dl). Malaria was significantly more frequent in primigravidae, the second trimester and in the post- rainy season (all p <0.05). Moderate anaemia (Hb < 9.0g/dl) was significantly more common in adolescents and primigravidae (both p <0.05). In the14-day follow up study, loss to follow up was 13%. Of the 74 women who completed the follow up, 89% cleared malaria parasites successfully and 11% had parasitological failure. Parasitological failures were all of the R1 type except for one with R2 failure.

Conclusion: Anaemia prevalence was high at first antenatal visit in this population. Rate of parasitological failure to SP in pregnancy increased from 5% in 1996 to 11% in 2004.

Introduction

In Malawi, anti-malarial chemoprophylaxis during pregnancy has been the primary strategy for malaria control in pregnancy for many years with chloroquine initially introduced in 1987. In 1993 sulfadoxine- pyrimethamine (SP) replaced chloroquine with a change from weekly chloroquine prophylaxis to intermittent preventive treatment.[3,12] Since that time surveillance data in children with uncomplicated clinical malaria indicate changing prevalence of malaria resistance to SP, from less than 5% in 1993 [8] to 14-20% in 2000. [2,6,9,10,15,16] It is uncertain whether treatment failure estimates in children indicate comparable risk of parasitological failure in pregnant women and information on the rate of SP treatment failure in pregnant women with peripheral parasitaemia is currently not available. The primary aim of the present study was to determine the rate of parasitological failure after SP treatment in pregnant women.

Materials and Methods

Study location

The study was conducted at Montfort Hospital in Chikwawa District in the lower Shire Valley-southern Malawi. This is a hot, dry, rural area whose population is mainly engaged in subsistence farming of maize, sorghum, sugar cane and cotton. This area lies between 100 and 300m above sea level and the rainy season extends from December to March. Anopheles gambiae, Anopheles funestus and Anopheles arabiensis are the main malaria vectors.[13]

Enrolment

Women attending antenatal clinic at Montfort Hospital from June, 2004 to February, 2005 were enrolled at their first antenatal visit after written informed consent was obtained. After receiving routine antenatal care, consenting women were interviewed for information on age, gravida, parity, history of fever, headache and use of antimalarials in the preceding two weeks. Gestation was estimated by abdominal palpation. A sub-sample of women with P.falciparum infection were included in the in vivo follow-up study if more than 14 weeks and less than 37 weeks gestation, had a haemoglobin concentration over 8.0 g/dl, single infection and no history of taking antimalarials in the previous 2 weeks. All women received SP by directly observed therapy (sulfadoxine 500 mg, pyrimethamine 25 mg) and haematinics supplements (200 mg ferrous sulphate, 250μg folic acid) according to Malawi Government malaria and anaemia control policies.

Follow up

The WHO 2001 guidelines for in vivo studies of malaria drug resistance were followed with follow-up at days 3, 7 and 14. At each visit information was collected on history of fever, headache or use of other antimalarial drugs. A finger prick blood sample was collected for a malaria thick smear and haemoglobin estimation (HemoCue®, Angelholm, Sweden). Quinine was prescribed to women who became symptomatic during follow up, with parasite recrudescence.

Laboratory tests

Thick films were stained with Field's stain. Parasite density was estimated by parasite counts per 200 white blood cells (WBC) [17] and geometric mean parasite densities (GMPD)

assuming a white cell count of 8000/μL blood. Ten percent of the slides were re-checked at the Illovo Clinic Laboratory for quality control.

Definitions

Anaemia was defined as a haemoglobin concentration <11.0 g/dl, moderate anaemia as 7.0-8.9 g/dl, and severe anaemia as < 7.0 g/dl. [14] Parasitological response was classified as a success with parasite clearance by day 7. Parasitological failure was defined as parasitaemia on or after day 7. Parasitological failure was sub-classified as R1, R2 or R3 (WHO, 2001): R1: Clearance then re-appearance of parasites as indicated by negative then positive thick smears on or after day 7; R2: No clearance of parasites from day 0 to day 14 with reduction in parasitaemia on day 3 to < 25% of day 0; R3: No clearance of parasites from day 0 to day 14 with no reduction or reduction on day 3 to >25% of the day 0 parasite density.

Analysis

Data were analysed using SPSS for Windows release 11.0.0 (SPSS, Chicago, IL) and Epi- info 2002 (Centres for Disease Control and Prevention, Atlanta). Chi-square or Fisher's exact tests were used to evaluate differences in proportions and the student's t-test or Mann-Whitney for differences in means.

Ethical Approval

Ethical approval was granted by the College of Medicine Research Committee (COMREC) and the Liverpool School of Tropical Medicine.

Results

Maternal characteristics

A total of 961 women were screened for malaria and anaemia at first ANC visit. Mean age, and gestation were 24.1 years (SD 5.6), and 24.9 weeks (4.4 weeks). One in five women were adolescent (<20 years) and 27.7% were primigravidae. One third commenced antenatal care in the third trimester and only 1.0% in the first trimester.

Malaria and anaemia at first ANC visit

Malaria prevalence was 9.3 % (95% CI 7.5-11.1%) at first antenatal visit. Anaemia was present in 76.5% of women, 23.8% had moderate anaemia and 5.7% had severe anaemia. All women with parasitaemia were asymptomatic. Malaria was commoner in first than later pregnancies (14.7%versus 7.4% p<0.05, odds ratio 2.2). Prevalence was highest in the second trimester (70/634 11.0%, compared to either the first (0/10, 0%) or last (19/316 6.0%), and in the post-rainy season (26/208, 12.5%), compared to the dry (35/375, 9.3%) or rainy season (28/378, 7.4%). Geometric mean parasite density at enrolment was 401 parasites per μl. Moderate anaemia was more common in adolescents than adults (35.2% versus 28.0%, p<0.05), in primigravidae than multigravidae (35.3% versus 27.2% %, p<0.05) and in the post-rainy season (34.1% versus 28.0% in other periods, p>0.05).

In vivo parasitological response

All women with malaria parasitaemia at the first antenatal visit (day 0) (n = 89) were eligible for the 14-day follow up study. Four women (4.5%) refused to participate because of the distance to travel to the hospital. Of 85 consenting women, 11 did not complete the 14 day follow up (12.9%). Women who failed to complete the follow-up did not differ at the first antenatal visit from women with known outcomes with respect to geometric mean parasite density, haemoglobin concentration, maternal age or gravida. At day 14, 8 of the 74 women who completed the follow (10.8%) had parasitological failure (table 1).

Table one: Follow up results of women with malaria parasitaemia enrolled in the in-vivo SP study (N= 85)

	Day of follow up		
Characteristic	3	7	14
Women followed up	82	78	74
Loss to follow up	3/85 (3.5%)	Old: 3 New: 5 Total: 8/85(9.4%)	Old: 8 New: 4 Total:11/85(12.9%)
Parasitological failure cases	1	Old:1 New: 5 Total: 6	Old: 6 New: 2 Total: 8

Discussion

Study Sample

This sample represents primarily second trimester attendances as few women attended early in pregnancy. Late attendance for antenatal care is an important reason for failing to complete the uptake of two SP doses during pregnancy. [1,18] Most women were anaemic with a characteristic pattern of higher prevalence in primigravidae which frequently occurs in malarious areas. [11] Malaria parasite prevalence at first antenatal visit was lower than in a previous prevalence study in this area during the mid-1990s [19] which may relate to changing malaria transmission patterns and increased use of impregnated bed nets. Parasite densities at enrolment were also low.

In-vivo parasitological response

A total of eleven women were lost to follow up in this 14-day followed up study. Failure rate may have been higher in this group. However, resolution of clinical symptoms was unlikely to explain for the loss to follow-up as women enrolled were asymptomatic and there were no differences at enrolment between women who complied with follow-up compared with those who missed visits. Pregnant women as a specific group may show reluctance to attend the several additional visits required for these studies in addition to their routine monthly antenatal care.

There are very few in vivo follow-up studies in pregnant women and in vivo follow-up studies in children with uncomplicated malaria have generally been used as a proxy to assess antimalarial drug efficacy in pregnancy. A recent comparison of in vivo results in children has shown a close correlation to in vivo results in pregnant women from the same study area. [5] The present study observed a

11% parasitological failure at day 14 which would indicate recrudescent infection. This SP parasitological failure rate in pregnant women is similar to the rates observed in children with clinical malaria from the recent published studies 1998-2002 undertaken in Malawi.[6, 9, 10, 15, 16] In the present study drug resistance was mainly of mild type (R1), whereas in children the resistance levels were moderate or severe (R2/R3). The parasite density was low in most women with geometric mean parasite densities below 1000 parasites per μl which is much lower than values usually seen in children with uncomplicated malaria. The low density of infection may partly explain the type of resistance pattern observed. A previous in vivo study of SP sensitivity amongst pregnant women attending this same hospital and completed in 1996 showed a 5% parasitological failure rate. [4] Eight years later this has increased to between 10-20% and paralleled changes in SP drug resistance in children. This supports the conclusion that changes in resistance patterns in pregnant women follow those observed in children, although the prevalence of resistance appears to be lower. The recent meta-analysis of African studies comparing chloroquine resistance in pregnant women and children, for studies conducted in the same location and at the same approximate time, would also support this conclusion. All of these studies were undertaken without PCR correction for identification of recrudescent infections. This is a limitation of the present and previous studies and future studies should include PCR corrected recrudescent rates with longer follow-up periods.

Although malaria prevalence at first antenatal visit was lower than in previous studies in this area ten years ago, anaemia at first antenatal visit remains a chronic problem. The low malaria prevalence could indirectly indicate acceptable levels of SP drug sensitivity within this population contributing to lower transmission, as well as increased use of bed nets by pregnant women. The prevalence of moderately severe and severe anaemia remains unacceptably high. Further efforts in this area are required to reduce this to more acceptable levels. The comparative prevalence of anaemia in this population of pregnant women has been described for the years 1992-1995 and 2002-2005.[7]

Acknowledgements

We are grateful to Management Committee and staff of Montfort Hospital for allowing this study to be done at Montfort, Mrs E. Ndasowa for her assistance in the recruitment and follow up of participants, Mr Elvis Kapinga and Charles Nyangulu for their support in laboratory work.

References

1. Ashwood-Smith H, Coombs Y, Kaimira N, Bokosi M, Lungu, K. Availability and use of sulfadoxine-pyrimethamine (SP) in pregnancy in Blantyre District: a safe motherhood and Blantyre integrated malaria initiative (BIMI) joint survey. Malawi Medical Journal, 2002; Vol. 14, No. 1, pp 8-11.
2. Bloland PB, Lackritz EV, Kazembe P, Were JB, Steketee, Campbell CC. Beyond Chloroquine: Implications of Drug Resistance for evaluating Malaria Therapy and Treatment Policy in Africa. The Journal of Infectious Diseases 1993: 167:932-7
3. Brabin BJ, Verhoeff FH, Kazembe P, Chimsuku L, Broadhead R. Antimalarial drug policy in Malawi. Annals of Tropical Medicine and Parasitology, 1997; 91 (Supp 1): S113-S115
4. Howarth P. Haematological and parasitological parameters in a cohort of pregnant women in the Shire Valley, Malawi. Masters in Tropical Medicine Dissertation, Liverpool School of Tropical Medicine, Liverpool.
5. Kalanda GC, Hill J, Verhoeff FH, Brabin BJ. Comparative efficacy of chloroquine and sulphadoxine-pyrimethamine in pregnant women and children: a meta-analysis. Tropical Medicine and International Health, 2006; 11: 569-577
6. MacArthur JR, Stennies GM, Macheso A, Kolczak MS, Green MD, Ali D, Barat LM, Kazembe P, Ruebush TK. Efficacy of mefloquine and sulfadoxine-pyrimethamine for the treatment of uncomplicated Plasmodium falciparum infection in Machinga District, Malawi, 1998. American Journal of Tropical Medicine and Hygiene 2001; 65(6), pp. 679-684
7. Msyamboza K, Savage E, Kazembe P, Brabin BJ. Malaria and anaemia at first ante natal visit and delivery in southern Malawi 1993-1994 and 2004-2005 (in preparation)
8. Nwanyanwu OC, Ziba C, Kazembe P, Chitsulo L, Willima JJ, Kumwenda N, Redd SC. Efficacy of sulphadoxine/pyrimethamine for Plasmodium falciparum malaria in Malawian children under five years of age. Tropical Medicine and International Health 1996; Apr (2): 231-5
9. Nwanyanwu OC, Ziba C, MacHeso A, Kazembe P. Efficacy of sulphadoxine-pyrimethamine for acute uncomplicated malaria due to Plasmodium falciparum Malawi children under five years old. Tropical Medicine and International Health 2000 May, 5(5) 355-8
10. Plowe C, Kublin G, Dzinjalamala F, Kamwendo D, Mukadam R, Chimpeni P, Molyneux ME, Taylor T. Sustained clinical efficacy of sulfadoxine-pyrimethamine for uncomplicated falciparum malaria in Malawi after 10 years as first line treatment: five year prospective study. British Medical Journal 2004; 328: 545-8
11. Savage EM, Msyamboza K, Brabin BJ. The potential use of maternal anaemia as an indicator of malaria control in pregnancy (submitted publication).
12. Schultz LJ, Steketee RW, Macheso A, Kazembe P, Chitsulo L, Wirima JJ. The efficacy of antimalarial regimes containing sulfadoxine-pyrimethamine and/or Chloroquine in preventing peripheral and placental Plasmodium falciparum infection among pregnant women in Malawi. American Journal of Tropical Medicine and Hygiene, 1994; 51(5), pp 515-522
13. Spiers AA, Mzilahowa T, Altkinson D, McCall PJ. The malaria vectors of the Lower Shire Valley. Malawi Medical Journal 2002; 14, (1), 4-6.
14. Stoltzfus RJ. Re-thinking anaemia surveillance. Lancet 1997; 349: 1764-1766
15. Sulo J, Chimpeni P, et al. Chlorproguanil-dapsone versus sulfadoxine-pyrimethamine for sequential episodes of uncomplicated falciparum malaria in Kenya and Malawi: a randomised clinical trial. Lancet 2002; Vol. 360, pp1136-42
16. Takechi M, Matsuo M, Ziba C, Macheso A, Butao D, Zungu IL, Chakanika I, Bustos G. Therapeutic efficacy of sulfadoxine/pyrimethamine and susceptibility in vitro of P. falciparum isolates to sulfadoxine-pyrimethamine and other antimalarial drugs in Malawian children. Tropical Medicine and International Health June 2001; Volume 6, No.6, pp 429-434
17. Trape J.F. Rapid evaluation of malaria parasite density and standardisation of thick smear examination for epidemiological investigations. Transactions of Royal Society of Tropical Medicine and Hygiene, 1985; 79(2): 181-4
18. van Eijk AM, Ayisi JG, ter Kuile FO, Slutsker L, Otieno JA, Misore AO, Odondi JO, Rosen DH, Kager PA, Steketee RW, Nahlen BL. Implementation of intermittent preventive treatment with sulfadoxine-pyrimethamine for control of malaria in pregnancy in Kisumu, western Kenya. Tropical Medicine and International Health, 2004; 9(5): 630-637.
19. Verhoeff FH, Brabin BJ, Chimsuku L, Kazembe P, Broadhead RL. Malaria in pregnancy and its consequences for the infant in rural Malawi. Annals of Tropical Medicine and Parasitology, 1999; 93 (Suppl 1): S25-S33 World Health Organisation. Monitoring Antimalarial Drug resistance. Report of a WHO consultation Geneva, Switzerland 3-5 December 2001