

Sustained clinical efficacy of sulfadoxine-pyrimethamine for uncomplicated falciparum malaria in Malawi after 10 years as first line treatment: five year prospective study

Christopher V Plowe, James G Kublin, Fraction K Dzinjalama, Deborah S Kamwendo, Rabia A G Mukadam, Phillips Chimpeni, Malcolm E Molyneux, Terrie E Taylor

Abstract

Objective To measure the efficacy of sulfadoxine-pyrimethamine treatment of falciparum malaria in Malawi from 1998 to 2002, after a change from chloroquine to sulfadoxine-pyrimethamine as first line treatment in that country in 1993.

Design Prospective open label drug efficacy study.

Setting Health centre in large peri-urban township adjacent to Blantyre, Malawi.

Participants People presenting to a health centre with uncomplicated *Plasmodium falciparum* malaria.

Main outcome measures Therapeutic efficacy and parasitological resistance to standard sulfadoxine-pyrimethamine treatment at 14 days and 28 days of follow up.

Results Therapeutic efficacy remained stable, with adequate clinical response rates of 80% or higher throughout the five years of the study. Analysis of follow up to 28 days showed modest but significant trends towards diminishing clinical and parasitological efficacy over time within the study period.

Conclusion Contrary to expectations, sulfadoxine-pyrimethamine has retained good efficacy after 10 years as the first line antimalarial drug in Malawi. African countries with very low chloroquine efficacy, high sulfadoxine-pyrimethamine efficacy, and no other immediately available alternatives may benefit from interim use of sulfadoxine-pyrimethamine while awaiting implementation of combination antimalarial treatments.

Introduction

In 1993 Malawi became the first African country to change its first line antimalarial drug from chloroquine to sulfadoxine-pyrimethamine on a nationwide basis in the face of rising rates of resistance to chloroquine.¹ At the time, this was a controversial decision. Rapid resistance to these antifolate drugs and the precipitous decline in their efficacy after introduction in South America and South East Asia meant that experts predicted that sulfadoxine-pyrimethamine would have a useful therapeutic life of five years or less in Africa

because of higher rates of transmission of malaria and of use of the drug.² Because other countries in Africa continue to rely on chloroquine and only a few have begun to change their policies within the past few years, Malawi serves as a sentinel site for failure of sulfadoxine-pyrimethamine for the rest of the continent.

We began monitoring the efficacy of sulfadoxine-pyrimethamine at one site in Malawi in 1998. We treated patients with uncomplicated falciparum malaria and measured their parasitological and therapeutic responses to the drug.

Methods

Study site and participants

We monitored the efficacy of sulfadoxine-pyrimethamine from February 1998 to June 2002 at the government health centre in Ndirande, a township in Blantyre, Malawi. Sulfadoxine-pyrimethamine has been the standard treatment for uncomplicated malaria and the presumptive treatment for most fevers since 1993 at all health facilities and in many shops. Alternative oral antimalarial drugs are seldom used, and chloroquine has been almost unobtainable locally for the past 10 years.

Patients were eligible for the study if they were aged 3 months or over and presented to the health centre with signs or symptoms consistent with malaria, had positive smears for *Plasmodium falciparum* mono-infection, and had none of the following exclusion criteria: history of allergy or adverse reaction to sulfadoxine-pyrimethamine or sulfa drugs; known pregnancy; haematocrit < 15%; parasitaemia > 10%; prostration; respiratory distress; bleeding; recent seizures, coma, or obtundation; inability to drink; or persistent vomiting. Documented fever was not a requirement for eligibility.

Treatment

We gave standard treatment doses of sulfadoxine-pyrimethamine under direct observation, and observed participants for at least 60 minutes. If vomit-

Editorial by
Greenwood

Malaria Section,
Center for Vaccine
Development,
University of
Maryland School of
Medicine, 685 West
Baltimore Street,
HSF1-480,
Baltimore, MD
21044, USA

Christopher V
Plowe
associate professor
James G Kublin
clinical instructor

Blantyre Malaria
Project, College of
Medicine,
University of
Malawi, Blantyre,
Malawi

Fraction K
Dzinjalama
research associate
Deborah S
Kamwendo
research associate

Rabia A G
Mukadam
research associate
Phillips Chimpeni
clinical officer

Malawi-Liverpool-
Wellcome Trust
Clinical Research
Programme,
Blantyre, Malawi
Malcolm E
Molyneux
professor

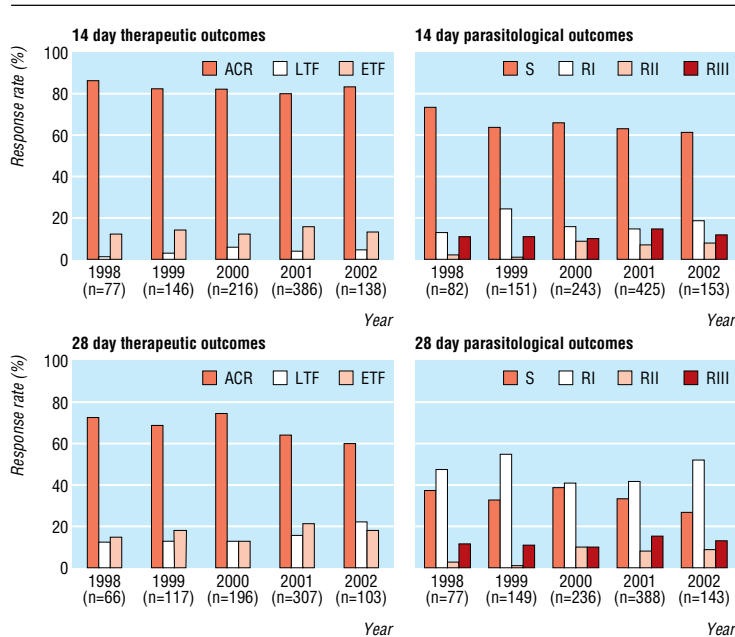
College of
Osteopathic
Medicine, Michigan
State University,
Lansing, MI, USA
Terrie E Taylor
professor

Correspondence to:
C V Plowe
cplowe@medicine.
umaryland.edu

BMJ 2004;328:545-8



This is the abridged version of an article that was posted on
bmj.com on 2 February 2004: <http://bmj.com/cgi/doi/10.1136/bmj.37977.653750.EE>



Sulfadoxine-pyrimethamine treatment outcomes, 1998-2002. Top left: therapeutic efficacy at 14 days; bottom left: therapeutic efficacy at 28 days; top right: parasitological resistance at 14 days; bottom right: parasitological resistance at 28 days. ACR=adequate clinical response; LTF=late treatment failure; ETF=early treatment failure; S=sensitive; RI-RIII=parasitological resistance at the RI-RIII levels

ing occurred within 30 minutes, we repeated the full dose; if it occurred within 60 minutes we repeated half of the dose. We treated treatment failures with halofantrine. The box shows the definitions we used for resistance and treatment failure.

Definitions of resistance and treatment failure

Therapeutic efficacy

Early treatment failure—Danger signs (not able to drink or breast feed, vomiting everything, recent history of convulsions, lethargic or unconscious state, unable to sit or stand up) or severe malaria on days 1, 2, or 3, with parasitaemia; axillary temperature $\geq 37.5^{\circ}\text{C}$ on day 3 in the presence of parasitaemia; or parasitaemia on day 3 $\geq 25\%$ of day 0 level

Late treatment failure—Development of danger signs or severe malaria in the presence of parasitaemia during days 4-14, or axillary temperature $\geq 37.5^{\circ}\text{C}$ in the presence of parasitaemia during days 4-14, and no criteria for early treatment failure

Adequate clinical response—absence of parasitaemia on day 14 irrespective of temperature, or axillary temperature $< 37.5^{\circ}\text{C}$ irrespective of parasitaemia, without previously having met any of the criteria for early or late treatment failure

Parasitological resistance

RIII—No reduction in parasitaemia, or reduction to $\geq 25\%$ of day 0 level, by day 3

RII—Reduction in parasitaemia to $< 25\%$ of day 0 level, without clearance leading to retreatment or followed by persistent parasitaemia

RI—Initial clearance of parasites indicated by negative thick smear after day 0, with subsequent positive thick smear by day 14

Sensitive—Clearance of parasites by day 14 with no recurrence of parasitaemia

Statistical analysis

We assessed trends over time in rates of adequate clinical response versus early or late treatment failure and rates of sensitive or RI parasitological response versus RII or RIII resistance by using logistic regression, with odds ratios calculated to represent the average odds of treatment success in successive years. We used univariate analyses and multiple logistic regression to test for associations with post-treatment anaemia.

Results

We enrolled 1377 patients into the study. Characteristics on enrolment were similar over the five years of study, although parasite density on presentation apparently increased in 2001 and 2002. One thousand and eighteen (73.9%) of the enrolled participants completed 14 days of follow up; 246 (17.9%) were lost to follow up before day 14, 30 (2.2%) withdrew consent to continue in the study, 40 (2.9%) were withdrawn owing to protocol violations, and 43 (3.1%) had incomplete follow up for unspecified reasons. We could not determine therapeutic efficacy for 95 (9%) of 1054 participants for whom parasitological outcomes could be determined. No trends towards increasing rates of withdrawals or loss to follow up occurred throughout the course of the study.

As shown in the figure, the 14 day efficacy remained stable over the five year study period, with adequate clinical response rates remaining above 80% (top left of figure: $P=0.44$, odds ratio 0.95, 95% confidence interval 0.82 to 1.09). Among participants followed for 28 days, the rate of adequate clinical response decreased from 73% in 1998 to 60% in 2002 (bottom left: $P=0.02$, odds ratio 0.86, 0.75 to 0.98). Rates of sensitive or RI parasitological responses at both 14 and 28 days also decreased significantly over the five year study period (top right: $P=0.015$, odds ratio 0.84, 0.73 to 0.97; bottom right: $P=0.004$, odds ratio 0.81, 0.71 to 0.94). Neither parasitological resistance nor therapeutic failure was associated with age in this population with a median age of 2.4 years.

In univariate analyses, anaemia (haemoglobin < 10 g/dl) at day 14 was associated with both treatment failure (odds ratio 2.05, 1.15 to 3.65, $P=0.009$) and RI-RIII resistance (odds ratio 1.46, 1.01 to 2.10, $P=0.034$). However, when we included treatment failure and parasitological resistance separately in a logistic regression model with parasite density at day 0 and age as covariates, only the association between age and anaemia at day 14 remained significant ($P<0.001$). Anaemia was more common at day 28 among patients with adequate clinical response and asymptomatic parasitaemia than in patients with adequate clinical response and no parasites (42.4% v 26.7%; relative risk 1.59, 1.23 to 2.05, $P<0.001$). This association remained significant after we controlled for age and initial parasitaemia in a regression model ($P=0.009$).

We found excellent agreement between measures of therapeutic efficacy and parasitological resistance. With adequate clinical response corresponding to sensitivity or RI resistance, late treatment failure corresponding to RII resistance, and early treatment failure corresponding to RIII resistance, we found only 10/959 (1%) cases of discordance among

cases for which both efficacy and resistance could be determined.

Discussion

Our data show that rates of adequate clinical response at 14 days, the standard measure of efficacy of antimalarial drugs, have remained stable at over 80% for five years, starting five years after sulfadoxine-pyrimethamine became the standard treatment for uncomplicated malaria in this country. Rates of early treatment failure also remained stable, at 13% in both 1998 and 2002. Although early treatment failure rates over 10% are of concern, most were so designated on the basis of the rate of parasite clearance and not of clinical deterioration of study participants. We have previously shown that the standard definition of therapeutic efficacy may be too sensitive,³ so treatment success rates are at least 80% and possibly higher.

Losses to follow up were relatively high at nearly 18%, and treatment failure rates may have been higher in this group. However, nearly all were attributable to migration from the study area, and they did not differ from those with known outcomes with respect to age, parasite density, or haemoglobin concentration at the time of treatment.

Why has loss of efficacy been slower than expected?

We hypothesise that a combination of epidemiological and molecular factors may explain the surprisingly durable efficacy of sulfadoxine-pyrimethamine in this setting. Mutations in parasite dihydrofolate reductase (DHFR) confer resistance to pyrimethamine, and mutations to dihydropteroate synthase (DHPS) confer resistance to sulfadoxine.⁴⁻⁵ Resistance to sulfadoxine-pyrimethamine in Africa is associated with three mutations in DHFR and two in DHPS that became highly prevalent in Malawi in 1998, just as these studies began.⁶⁻⁷ Despite the near ubiquity of these mutations, sulfadoxine-pyrimethamine resistance may have peaked and stabilised in Malawi.

The DHFR mutation from isoleucine to leucine at codon 164 is common in parts of South East Asia and South America where sulfadoxine-pyrimethamine resistance is high,⁸ but it has not been confirmed to be present in Africa. The DHPS ala-581-gly mutation is also common in areas with high rates of sulfadoxine-pyrimethamine resistance but is very rare in Africa.

The ile-164-leu mutation in DHFR is deleterious to enzyme function, so in the absence of drug pressure parasites containing this mutation are at a disadvantage and would be selected against.⁹⁻¹⁰ In Africa, where transmission is usually intense, the proportion of parasites under drug pressure is much lower than in areas of low transmission such as South America and South East Asia, where sulfadoxine-pyrimethamine failed quickly. This is because where transmission is high, semi-immunity is common and most infections are asymptomatic and untreated. Where transmission and immunity are low, most infections are symptomatic and come under drug pressure. The amount of drug pressure relative to the total parasite population may be insufficient to permit DHFR ile-164-leu to arise or persist in Africa. Although no data are available on DHPS ala-581-gly affecting parasite fitness, it too

What is already known on this topic

Sulfadoxine-pyrimethamine has had a short useful therapeutic life where it has been used as the first line treatment for malaria in South America and South East Asia

Malawi was the first African country to use sulfadoxine-pyrimethamine on a national basis in 1993

Experts predicted that sulfadoxine-pyrimethamine would fail in Africa in as little as five years

What this study adds

The therapeutic efficacy of sulfadoxine-pyrimethamine was stable from 1998 through 2002, indicating a longer than predicted useful therapeutic life

Rates of parasite clearance declined during the study period, presaging a decline in efficacy and highlighting the need for new, effective treatments for malaria

Countries still using chloroquine despite high resistance but where sulfadoxine-pyrimethamine remains efficacious should consider using sulfadoxine-pyrimethamine as an interim measure

might be selected against in the absence of drug pressure. If this hypothesis is correct, the antifolate class of antimalarial drugs may have a longer useful life in high endemicity areas of Africa than elsewhere.

Ten years: approaching the limit?

Increases in both treatment failures and parasitological resistance over five years when follow up was extended to 28 days. These trends suggest that sulfadoxine-pyrimethamine efficacy may before long fall to unacceptable levels in Malawi, and the impact of increasing parasitological failure rates on anaemia is also of concern. Several antimalarial combination drug regimens are now being evaluated in Malawi.

On the basis of Malawi's experience, countries with similar levels of malaria endemicity could consider replacing chloroquine with sulfadoxine-pyrimethamine as an interim measure while awaiting more effective combination therapies designed to deter resistance. Regional studies of drug efficacy, and not predictions based on experiences in very different epidemiological settings, should form the basis of rational antimalarial drug policy.

We thank the clinical officers and district health officers of the Ndirande Health Centre for sharing their facilities and allowing us to recruit participants from their patient population; the clinical and laboratory staff of the Blantyre Malaria Project and Malawi-Liverpool Wellcome Trust Programme for assisting with the study; Steven Wasserman for statistical assistance; and Alasane Dicko for critical reading of the manuscript.

Contributors: See bmj.com

Funding: This study was supported by the National Institute of Allergy and Infectious Diseases, USA (grants no. R29 AI-40539 and R01-AI-44824).

Competing interests: None declared.

Ethical approval: The study protocol was reviewed and approved by institutional review boards at the College of Medicine, University of Malawi, and the University of Maryland, Baltimore.

- 1 Bloland PB, Lackritz EM, Kazembe PN, Were JB, Steketee R, Campbell CC. Beyond chloroquine: implications of drug resistance for evaluating malaria therapy efficacy and treatment policy in Africa. *J Infect Dis* 1993;167:932-7.
- 2 Nzila AM, Nduati E, Mberu EK, Hopkins SC, Monks SA, Winstanley PA, et al. Molecular evidence of greater selective pressure for drug resistance exerted by the long-acting antifolate pyrimethamine/sulfadoxine compared with the shorter-acting chlorproguanil/dapsone on Kenyan *Plasmodium falciparum*. *J Infect Dis* 2000;181:2023-8.
- 3 Plowe CV, Doumbo OK, Djimde A, Kayentao K, Diourte Y, Doumbo SN, et al. Chloroquine treatment of uncomplicated *Plasmodium falciparum* malaria in Mali: parasitologic resistance versus therapeutic efficacy. *Am J Trop Med Hyg* 2001;64:242-6.
- 4 Peterson DS, Milhous WK, Wellems TE. Molecular basis of differential resistance to cycloguanil and pyrimethamine in *Plasmodium falciparum* malaria. *Proc Natl Acad Sci USA* 1990;87:3018-22.
- 5 Triglia T, Menting JGT, Wilson C, Cowman AF. Mutations in dihydropteroate synthase are responsible for sulfone and sulfonamide resistance in *Plasmodium falciparum*. *Proc Natl Acad Sci USA* 1997;94:13944-9.
- 6 Kublin JG, Dzinjalimala FK, Kamwendo DD, Malkin EM, Cortese JF, Martino LM, et al. Molecular markers for failure of sulfadoxine-pyrimethamine and chlorproguanil-dapsone treatment of *Plasmodium falciparum* malaria. *J Infect Dis* 2002;185:380-8.
- 7 Kublin JG, Cortese JF, Njunju EM, Mukadam RAG, Wirima JJ, Kazembe PN, et al. Reemergence of chloroquine-sensitive *Plasmodium falciparum* malaria following cessation of chloroquine use in Malawi. *J Infect Dis* 2003;187:1870-5.
- 8 Plowe CV, Kublin JG, Doumbo OK. *P. falciparum* dihydrofolate reductase and dihydropteroate synthase mutations: epidemiology and role in clinical resistance to antifolates. *Drug Resist Update* 1998;1:389-96.
- 9 Cortese JF, Plowe CV. Antifolate resistance due to new and known *Plasmodium falciparum* dihydrofolate reductase mutants expressed in yeast. *Mol Biochem Parasitol* 1998;94:205-14.
- 10 Sirawaraporn W, Sathikul T, Sirawaraporn R, Yuthavong Y, Santi DV. Antifolate-resistant mutants of *Plasmodium falciparum* dihydrofolate reductase. *Proc Natl Acad Sci USA* 1997;94:1124-9. (Accepted 2 December 2003)

doi 10.1136/bmj.37977.653750.EE

Prospective study of type 2 diabetes and cognitive decline in women aged 70-81 years

Giancarlo Logroscino, Jae Hee Kang, Francine Grodstein

Abstract

Objective To examine the association of type 2 diabetes with baseline cognitive function and cognitive decline over two years of follow up, focusing on women living in the community and on the effects of treatments for diabetes.

Design Nurses' health study in the United States. Two cognitive interviews were by carried out by telephone during 1995-2003.

Participants 18 999 women aged 70-81 years who had been registered nurses completed the baseline interview; to date, 16 596 participants have completed follow up interviews after two years.

Main outcome measures Cognitive assessments included telephone interview of cognitive status, immediate and delayed recalls of the East Boston memory test, test of verbal fluency, delayed recall of 10 word list, and digit span backwards. Global scores were calculated by averaging the results of all tests with z scores.

Results After multivariate adjustment, women with type 2 diabetes performed worse on all cognitive tests than women without diabetes at baseline. For example, women with diabetes were at 25-35% increased odds of poor baseline score (defined as bottom 10% of the distribution) compared with women without diabetes on the telephone interview of cognitive status and the global composite score (odds ratios 1.34, 95% confidence interval 1.14 to 1.57, and 1.26, 1.06 to 1.51, respectively). Odds of poor cognition were particularly high for women who had had diabetes for a long time (1.52, 1.15 to 1.99, and 1.49, 1.11 to 2.00, respectively, for ≥ 15 years' duration). In contrast, women with diabetes who were on oral hypoglycaemic agents performed similarly to women without diabetes (1.06 and 0.99), while women not using any medication had the greatest odds of

poor performance (1.71, 1.28 to 2.281, and 1.45, 1.04 to 2.02) compared with women without diabetes. There was also a modest increase in odds of poor cognition among women using insulin treatment. All findings were similar when cognitive decline was examined over time.

Conclusions Women with type 2 diabetes had increased odds of poor cognitive function and substantial cognitive decline. Use of oral hypoglycaemic therapy, however, may ameliorate risk.

Introduction

Many investigations have examined diabetes in relation to early cognitive decline, but only one large prospective study has focused on women.¹ Type 2 diabetes disproportionately affects older women and is a stronger risk factor for cardiovascular disease in women than in men.² Cardiovascular disease is also an independent risk factor for cognitive decline. Moreover, few studies have evaluated the influence of different treatments for diabetes on the association between type 2 diabetes and cognition.

We assessed the associations between type 2 diabetes, different treatments for diabetes, and cognitive function in more than 16 000 women.

Methods

The nurses' health study is a prospective cohort of 121 700 US female registered nurses who were aged 30-55 years in 1976, when the study began. From 1995-2001, participants aged 70 years and older who had not had a stroke were given baseline cognitive

Department of Epidemiology, Harvard School of Public Health, Boston, MA 02115, USA

Giancarlo Logroscino
associate professor of neuroepidemiology

Channing Lab, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02115

Francine Grodstein
associate professor of medicine

Jae Hee Kang
instructor of medicine

Correspondence to: G Logroscino
glogrosc@hsph.harvard.edu

BMJ 2004;328:548-51



This is the abridged version of an article that was posted on bmj.com on 23 February 2004: <http://bmj.com/cgi/doi/10.1136/bmj.37977.495729.EE>