Chloroquine and sulphadoxine-pyrimethamine efficacy for uncomplicated malaria treatment and haematological recovery in children in Bobo-Dioulasso, Burkina Faso during a 3-year period 1998–2000

H. Tinto1,2, E. B. Zoungrana1, S. O. Coulibaly1, J. B. Ouedraogo1,2, M. Traoré1,2, T. R. Guiguemde1, E. Van Marck3 and U. D’Alessandro4

1 Centre Muraz, Bobo-Dioulasso, Burkina Faso, Africa
2 Institut de Recherche en Sciences de la Santé, Bobo-Dioulasso, Burkina Faso, Africa
3 University of Antwerp, Antwerp, Belgium
4 Prince Leopold Institute of Tropical Medicine, Antwerp, Belgium

Summary

We determined the parasitological resistance and the clinical failure to chloroquine (CQ) and sulphadoxine-pyrimethamine (SP) by the WHO 14-day in vivo test over three consecutive years in 948 children aged 6–59 months with uncomplicated malaria attending four health centres in the province of Houet, Burkina Faso. Children were alternatively allocated to either CQ or SP. Packed cell volume (PCV) was measured at days 0 and 14. Parasitological resistance (RI, RII and RIII) to CQ was 18% (83 of 455) and to SP <1% (two of 308). Clinical failure with CQ was 12% (53 of 455) with no evidence of increase over time. Only one case of clinical failure was detected among the children treated with SP. The prevalence of anaemia (PCV <25%) was about 40% at day 0 and had decreased substantially by day 14 in both groups. However, in children treated with SP the prevalence of anaemia at day 14 was significantly lower than in those treated with CQ:RR = 3.15 (95% CI: 1.33–7.42, P = 0.008). CQ and SP are still efficacious for the treatment of uncomplicated malaria in children, at least in this area of Burkina Faso. However, the prevalences of CQ resistance reported from other areas of the country are worrying because of its potential spread. Regular surveillance of resistance to commonly used antimalarial drugs should continue.

Keywords malaria, chloroquine, sulphadoxine-pyremethamine, resistance, children, Burkina Faso

Correspondence Dr Halidou Tinto, IRSS/Centre Muraz, 01 BP 153, Bobo-Dioulasso, Burkina Faso, Africa. Tel: +226 974868; Fax: +226 972824; E-mail: tintoh@hotmail.com

Introduction

Chloroquine (CQ) resistance is a major obstacle for malaria control in endemic countries as prompt and effective treatment is a fundamental component of the global strategy for malaria control (WHO 1993). CQ resistance seems to have spread more rapidly in Eastern than in Western Africa (Bloland et al. 1993; Bakyaita 2000). In Burkina Faso the national malaria control programme still recommends CQ as the first and sulphadoxine-pyrimethamine (SP) as the second-line drug. However, high parasitological resistance to CQ has been observed in 2000 in Côte d’Ivoire, a neighbouring country (M. C. Henry, personal communication). Therefore, in Burkina Faso there is a need to monitor the levels of CQ and SP resistance to start the process of changing the current drug policy when needed (Keita 1994). We investigated the efficacy of CQ and SP and the haematological recovery in children aged 6–59 months with uncomplicated Plasmodium falciparum malaria and we report here the results collected during three consecutive years (1998–2000).

Patients and methods

Study area

The study was conducted in four health centres (one urban and three rural) in Houet Province (Region of Bobo-Dioulasso) situated at 365 km from Ouagadougou, the
capital city, on the main road linking Burkina Faso to Côte d'Ivoire. The rainy season occurs from June to October (average rainfall: 1000 mm/year; mean temperature >25 °C) and it is followed by a cold dry season from November to February (minimum temperature 15 °C) and a hot dry season from March to May. Malaria transmission is seasonal from June to December (Robert et al. 1988) although around rice field areas it can be perennial with seasonal peaks. In 1999–2000, the number of infected bites/man/year (entomological inoculation rate, EIR) was estimated to be about 60 in the town of Bobo Dioulasso, 20 in dry areas such as Toussiana and 200–500 in marshy areas or rice fields (Léna and Bama) (T. Baldet, personal communication). The commonest vectors are *Anopheles gambiae*, *A. funestus* and *A. arabiensis* and *P. falciparum* is the predominant malaria parasite. Malaria is the primary reason for visiting health centres and the first for hospital admission (Ministère de la Santé, DEP 1995) where the case-fatality rate varies from 5% to 20%.

Patients and inclusion criteria

This is part of a larger study that investigated CQ and SP efficacy in children between 6 months and 15 years of age. However, in the following analysis, 6–59-month-old children were only considered. Children with fever (auxillary temperature ≥37.5 °C) and a presumptive diagnosis of ‘clinical malaria’ were screened for malarial infection. Children weighing 5 kg or more with a *P. falciparum* monoinfection and a parasite density between 2000 and 100 000/µl were recruited if a parent or guardian gave informed consent. Children were excluded if they had (i) danger signs (unable to drink or breast-feed; vomiting more than twice in 24 h; recent history of convulsions; were unconscious or unable to sit or stand), (ii) signs of severe malaria (WHO 1996), (iii) a clear history of adequate malaria treatment in the preceding 72 h, (iv) any evidence of chronic disease or of a concurrent non-malarial febrile illness and (v) history of allergic reactions to CQ or SP.

Treatment and follow-up

The WHO 14-day in vivo test was carried out (WHO 1996). The patient’s address, symptoms, signs and laboratory results were recorded on standard forms. Children were alternately allocated to either CQ (25 mg/kg in 3 days) or SP (25 mg/kg of sulphadoxine stat). All doses were given under direct supervision. Children were observed for at least 30 min for vomiting and a replacement dose was given when needed or they were withdrawn from the study. Auxillary temperature and clinical information were collected at days 0, 1, 2, 3, 7 and 14 after treatment. Thick and thin blood films were collected at days 0, 3, 7 and 14. Packed cell volume (PCV) was measured at days 0 and 14.

Definitions of outcomes

Outcomes were defined according to the clinical or parasitological response. Clinical response was classified in three groups: early treatment failure (ETF), late treatment failure (LTF) and adequate clinical response (ACR) as defined previously (WHO/CTD 1996).

Parasitological response was classified according to four categories: sensitive (clearance of parasites after treatment without subsequent recrudescence), RI (initial clearance followed by recrudescence, early before and late after day 7), RII (reduction of parasitaemia to less than 25% of initial parasitaemia but no clearance) and RIII (no reduction of parasitaemia or reduction to a level equal to or greater than 25% of the initial parasitaemia).

Each clinical failure received alternative treatment: SP for those treated with CQ and quinine for those treated with SP. Children presenting with or evolving to severe malaria were referred to the National Hospital where they were treated with quinine (15 mg/kg followed by 8 mg/kg every 8 h). This study was reviewed and approved by the Centre Muraz’s Ethical Committee.

Laboratory methods

Thick and thin blood films were stained with Field stain. Parasite density was determined on the basis of the number of parasitized red blood cells (PRBC) assuming 4 000 000 RBC/µl.

Statistical methods

Data were entered and analysed using Excel version 97 and Epi-Info 6.04 (Center for Disease Control and Prevention, Atlanta, GA, USA). Anaemia was defined as a PCV <25%. Differences in proportions were tested with the chi-square test and a value of *P* < 0.05 was considered statistically significant.

Results

We screened 2895 children during the 3-year study period; 70% (2037) had a microscopically confirmed malaria infection and of these, 948 were recruited for the study (Figure 1). A total of 388 children were assigned to CQ and 360 to SP, 455 children in the CQ group and 308 in...
the SP group completed the follow-up. CQ parasitological resistance (RI, RII and RIII) was 18% (83 of 455), most being late RI (Table 1). SP parasitological resistance was less than 1% (Table 1). Resistance did not vary significantly between years. Clinical treatment failure to CQ was 12% (53 of 455), the highest value being found in the first
### Table 1
*Plasmodium falciparum* parasitological resistance to CQ and SP by year

<table>
<thead>
<tr>
<th>Years</th>
<th>CQ</th>
<th></th>
<th></th>
<th>SP</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 108 (%)</td>
<td>n = 147 (%)</td>
<td>n = 200 (%)</td>
<td>n = 455 (%)</td>
<td>n = 73 (%)</td>
<td>n = 124 (%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitive</td>
<td>87 (80)</td>
<td>127 (86)</td>
<td>158 (79)</td>
<td>372 (81)</td>
<td>72 (99)</td>
<td>123 (99)</td>
</tr>
<tr>
<td>RI</td>
<td>15 (14)</td>
<td>11 (8)</td>
<td>35 (17.5)</td>
<td>61 (13)</td>
<td>1 (1)</td>
<td>0</td>
</tr>
<tr>
<td>RII</td>
<td>5 (5)</td>
<td>7 (5)</td>
<td>6 (3)</td>
<td>18 (4)</td>
<td>0</td>
<td>1 (1)</td>
</tr>
<tr>
<td>RIII</td>
<td>1 (1)</td>
<td>2 (1)</td>
<td>1 (0.5)</td>
<td>4 (1)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

### Table 2
*Plasmodium falciparum* clinical resistance to CQ and SP by year

<table>
<thead>
<tr>
<th>Year</th>
<th>CQ</th>
<th></th>
<th></th>
<th>SP</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 108 (%)</td>
<td>n = 147 (%)</td>
<td>n = 200 (%)</td>
<td>n = 455 (%)</td>
<td>n = 73 (%)</td>
<td>n = 124 (%)</td>
</tr>
<tr>
<td>Adequate clinical response (ACR)</td>
<td>88 (81)</td>
<td>138 (94)</td>
<td>177 (88.5)</td>
<td>402 (88)</td>
<td>73 (100)</td>
<td>123 (99)</td>
</tr>
<tr>
<td>Early treatment failure (ETF)</td>
<td>3 (3)</td>
<td>6 (4)</td>
<td>4 (2.0)</td>
<td>14 (3)</td>
<td>0</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Late treatment failure (LTF)</td>
<td>17 (16)</td>
<td>3 (2)</td>
<td>19 (9.5)</td>
<td>39 (9)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
We found only few cases of SP resistance. The first two cases of in vivo SP parasitological resistance in Burkina Faso were reported in 1990 and 1991 from Bobo Dioulasso (Guiguemde et al. 1994) giving a prevalence of resistance of 7%. A third case was reported in 1997. SP resistance has not changed in the last few years. We observed one case of parasitological resistance in 1998 and one in 1999. However, in 1999, we also observed one ETF, the first to SP reported from Burkina Faso. SP resistance remains low in Burkina Faso and in the neighbouring countries probably because its use is still extremely low. In 1999, SP resistance was lower than 1% in Mali (Diourte et al. 1999) and 3.1% in The Gambia (Von Seidlein et al. 2000). A longer follow-up, at least until day 28 after treatment, might have identified more late recrudescences. This would have required more resources. In addition, it would have been necessary to genotype the parasites in order to distinguish between new infections and late recrudescences. Therefore, when monitoring the efficacy of commonly used antimalarial drugs over a long period, extending the follow-up beyond 14 days might not be required. Nevertheless, when comparing new drugs or new drug combinations likely to be almost 100% efficacious at day 14, an extended follow-up at least until day 28 may be necessary for choosing the best option.

The study design used, non-randomized with alternate allocation to treatment, is not optimal and could result in major bias. Although the two treatment groups differ by size we think that a major bias in the estimation of CQ and SP resistance is unlikely. The imbalance between the groups can be explained by the fact that we originally recruited children aged 6 months to 15 years who were alternately allocated to CQ or SP while the results presented here refer only to children 6–59 months old. In endemic countries malaria is a major cause of anaemia. The variation of haematological parameters such as the haemoglobin (Hb) or the PCV after treatment can be used as an additional indicator of the efficacy of the drug. Unfortunately, we were unable to measure the PCV on all children as one site lacked this capacity. Nevertheless, it is unlikely that this resulted in a major bias as the PCV was measured in most of the children.

### Table 3: Haematological recovery at day 14 by treatment and year

<table>
<thead>
<tr>
<th></th>
<th>CQ</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1999</td>
<td>2000</td>
<td>Total</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n = 127 (%)</td>
<td>n = 178 (%)</td>
<td>n = 305 (%)</td>
<td></td>
</tr>
<tr>
<td>Anaemia at day 0</td>
<td>54 (42)</td>
<td>77 (43)</td>
<td>131 (43)</td>
<td></td>
</tr>
<tr>
<td>Anaemia at day 14</td>
<td>12 (9)</td>
<td>18 (10)</td>
<td>30 (10)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1999</td>
<td>2000</td>
<td>Total</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n = 93 (%)</td>
<td>n = 99 (%)</td>
<td>n = 192 (%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>37 (40)</td>
<td>35 (35)</td>
<td>72 (37)</td>
<td></td>
</tr>
</tbody>
</table>

year of the study (Table 2). Only one case of clinical failure was detected among the children treated with SP.

In 1999 and 2000, PCV was measured (in three of the four sites) at days 0 and 14 in 305 children treated with CQ and in 192 of those treated with SP. At day 0, 131 (43%) children treated with CQ and 72 (37%) treated with SP were anaemic. By day 14, 30 (10%) children in the CQ group and six (3%) in the SP group were still anaemic. Haematological recovery was significantly different between the two drugs [RR = 3.15 (95% CI: 1.33–7.42, P = 0.008), Table 3].

### Discussion

In West Africa, in vitro CQ resistance was first observed in Burkina Faso in 1983 (Baudon et al. 1984). Subsequently it was confirmed in vivo in 1988 (Guiguemde et al. 1994). During a 3-year period we estimated the parasitological resistance and the clinical failure to CQ at 18% and 12%, respectively. CQ clinical failure was higher in children 1–2 years old (40 of 53), showing the interaction between immunity and drug activity. In the same region, in 1991 in vivo CQ resistance was 25% (Guiguemde et al. 1994) and in 1995–96 around 20% (Ouedraogo et al. 1998). Similar values have been reported from Mali in 1997 where treatment failure to CQ in Mopti and Bandiagara was 16.9% and 12.8%, respectively (Doumbo 1999). Apparently, the prevalence of CQ resistance in this region is stable, despite its large use by the population. However, this does not apply to the whole country. Parasitological resistance to CQ as high as 74.4% has been reported in 1992 from Goundry, in the north-east of the country (Del Nero et al. 1994). Similarly, in 1999 a 43% parasitological resistance to CQ has been reported from Koudougou, in the centre of Burkina Faso (H. Tinto, E. B. Zoungrana, S. O. Coulibaly et al., unpublished observation). Such local differences could be explained by several factors, among others the drug pressure, the intensity of malaria transmission or the population immunity. In Bobo Dioulasso, CQ resistance might increase in the next few years as the result of its spreading from the centre of the country to the west.

We found only few cases of SP resistance. The first two cases of in vivo SP parasitological resistance in Burkina Faso were reported in 1990 and 1991 from Bobo Dioulasso (Guiguemde et al. 1994) giving a prevalence of resistance of 7%. A third case was reported in 1997. SP resistance has not changed in the last few years. We observed one case of parasitological resistance in 1998 and one in 1999. However, in 1999, we also observed one ETF, the first to SP reported from Burkina Faso. SP resistance remains low in Burkina Faso and in the neighbouring countries probably because its use is still extremely low. In 1999, SP resistance was lower than 1% in Mali (Diourte et al. 1999) and 3.1% in The Gambia (Von Seidlein et al. 2000). A longer follow-up, at least until day 28 after treatment, might have identified more late recrudescences. This would have required more resources. In addition, it would have been necessary to genotype the parasites in order to distinguish between new infections and late recrudescences. Therefore, when monitoring the efficacy of commonly used antimalarial drugs over a long period, extending the follow-up beyond 14 days might not be required. Nevertheless, when comparing new drugs or new drug combinations likely to be almost 100% efficacious at day 14, an extended follow-up at least until day 28 may be necessary for choosing the best option.

The study design used, non-randomized with alternate allocation to treatment, is not optimal and could result in major bias. Although the two treatment groups differ by size we think that a major bias in the estimation of CQ and SP resistance is unlikely. The imbalance between the groups can be explained by the fact that we originally recruited children aged 6 months to 15 years who were alternately allocated to CQ or SP while the results presented here refer only to children 6–59 months old.

In endemic countries malaria is a major cause of anaemia. The variation of haematological parameters such as the haemoglobin (Hb) or the PCV after treatment can be used as an additional indicator of the efficacy of the drug. Unfortunately, we were unable to measure the PCV on all children as one site lacked this capacity. Nevertheless, it is unlikely that this resulted in a major bias as the PCV was measured in most of the children.
recruited in the other three sites. Several diseases can cause anaemia. However, in malaria endemic areas, malaria is a major cause of anaemia. In African children the Hb can increase by 1.5–2 g/dl after efficacious antimalarial treatment (Le Bras et al. 1986). In our study the prevalence of anaemia decreased significantly between days 0 and 14. This decrease was more important in the SP group than in the CQ group, reflecting the higher efficacy of the drug. Similar results have been reported from Mali (Doumbo 1999).

In conclusion, CQ and SP are still efficacious for the treatment of uncomplicated malaria in children, at least in this part of Burkina Faso. The prevalence of CQ resistance reported from other parts of the country is worrying because it could spread to this area (Del Nero et al. 1994). Regular surveillance of resistance to commonly used antimalarial drugs should continue.

Acknowledgements

We thank the parents of the children included in this study for their participation. We would also like to thank the health staff of the health centres where the study was conducted for their collaboration. We thank the French Cooperation for its financial support.

References


