A clinical trial of ‘AM’, a Ugandan herbal remedy for malaria*

Merlin L. Willcox

Abstract

Background Mortality and morbidity from malaria is still high in Africa, and may further increase as resistance to antimalarial drugs spreads. Many people rely on herbal medicines as the first line of treatment. Yet there has been very little clinical research into their effectiveness.

Methods Patients being treated for malaria at a herbalists’ clinic in South-West Uganda were followed up and their response to a particular herb, ‘AM’, was monitored. Eighty-eight patients were enrolled; 72 were followed up for at least 2 days, and were questioned about side-effects. Nineteen patients infected with *Plasmodium falciparum* had initial parasite counts sufficiently high for parasite clearance to be assessed.

Results No severe adverse reactions were observed, although about 50 per cent experienced minor side-effects. Although complete parasite clearance was achieved in only one case, the geometric mean of parasite counts had declined significantly by day 7. There was also a marked symptomatic improvement in 17 of the 19 patients.

Conclusions AM appears safe, although it is not always well tolerated. Significant symptomatic improvement and a reduction of parasite counts were observed in patients taking AM. There is a need for further research, such as a randomized controlled trial, to assess the efficacy of this treatment.

Keywords: clinical trial, herbal medicine, malaria, Uganda

Introduction

The global prevalence of malaria infection is estimated to be 300–500 million, with 90 per cent of cases in Sub-Saharan Africa.¹ The incidence has increased recently in many African countries.² Mortality associated with malaria is estimated at 1.5–2.7 million per year,¹ and is rising as a result of increasing drug resistance.³

Malaria is perceived by many African communities as their most important problem.⁴ Patients with uncomplicated malaria are incapacitated for an average of 3.5 days (5 days in children), and take up the time of other family members who must look after them. In malarious areas, adults experience 1–2 attacks per year, and children 1–7 attacks.⁵ In Africa, the cost has been estimated at 21 days of output per case, or 1 per cent of GDP in 1995.⁶ Furthermore, about 3 million people (mostly in Africa) suffer from long-term neurological sequelae of malaria.⁷

Meanwhile, prevalence of resistance to conventional chemotherapy is increasing. Data for Uganda are presented in Fig. 1.⁷–⁹ Several countries have already abandoned chloroquine as the first line of therapy. Malawi, Kenya and South Africa have switched to sulphadoxine–pyrimethamine,¹⁰ and Cameroon to amodiaquine.¹¹

In a meeting in Dakar, Senegal, African and European scientists called for new approaches to the control of malaria.¹² Much research has focused on preventive measures such as medicated bednets or chemoprophylaxis. Yet in hyperendemic areas, such measures may interfere with the development of natural immunity. They may therefore fail to reduce mortality in the long term, or may even increase it.¹³–¹⁵ In practice, control of malaria in Africa relies almost entirely on early diagnosis and treatment of clinical cases.

Yet only 8–25 per cent of people with malaria visit health services.² The use of herbal antimalarials is widespread throughout the developing world. Kengeya-Kayondo et al.¹⁶ interviewed Ugandan women at their homes; they admitted to using herbs to treat malaria more often than going to health facilities. This is not surprising in view of the fact that one medical practitioner covers a population of about 20 000, whereas there is one traditional healer per 200–400 people.¹⁷ Eighty per cent of Uganda’s population rely on traditional healers for their health care.¹⁸ Annual government expenditure on health services is a mere US $2.82 per capita, whereas annual private spending on health care is estimated to be US $4.91 per capita.¹⁹ In the study site, all antimalarials cost more than $1 per treatment course, except for chloroquine and amodiaquine from the government clinic. Herbal medicines are free to those who know which herbs to use and how to prepare them; prices charged by traditional healers vary widely from place to place.

Clinical research on herbal treatments is sadly lacking.²⁰ At least 11 different plants are used in Uganda for the treatment of malaria.
malaria, but there is no evidence on which, if any, are effective. Bitahwa et al. reported a series of four cases responding to a herbal remedy, three of which had failed to respond to standard chemotherapy. Although the case records were not very detailed, and the number was too small for any firm conclusions to be drawn, these results justify a more substantial investigation. That was the purpose of this project.

Methods

Study site

This research was conducted at the Rukararwe Partnership Workshop for Rural Development (RPWRD), 3 km from Bushenyi town, Western Uganda. Bushenyi District is a hilly, fertile area approximately 200 km southwest of Kampala. Rainfall reaches up to 1375 mm per year. The population numbers about 525,000, Banyankole by tribe; most are subsistence farmers cultivating bananas, beans and groundnuts, and rearing cattle.

RPWRD is a non-governmental organization established in 1979, aiming to improve the standard of living of the rural community through the more efficient use of local resources. One facet of this integrated development project is ‘Meditrad’, the Medical–Traditional Healers’ Association. A group of traditional healers holds clinics twice a week in conjunction with scientifically trained medical laboratory technicians. The healers briefly interview patients, request basic investigations (blood films for malaria, stool and urine microscopy), and then prescribe appropriate herbal remedies. The preparation and packing of the herbs has been standardized. Patients pay a fee similar to the charges for out-patient diagnosis and treatment at private medical clinics in Bushenyi town. Up to 12,000 patients a year have been treated at the Meditrad clinic.

This is an area of unstable malaria transmission. There was an epidemic of malaria in 1998, peaking in January–March, just before the present study began. Cases in Bushenyi district rose by 34 per cent, and many people died. At the local Nyamiko primary school, two children had died; in one class of 26, selected at random, a show of hands revealed that 23 had had malaria this year, and six had lost a relative to the disease. In this region, WHO estimates that malaria is responsible for 60–70 per cent of out-patient consultations, 25–50 per cent of patient admissions and 25–30 per cent of patient deaths. The commonest species is Plasmodium falciparum.

Furthermore, local health practitioners and people believed that malaria was often resistant to drugs. A study conducted in the nearest large town, Mbarara, in March–May 1998 found that 80 per cent of infections were resistant to chloroquine, and about 25–30 per cent were resistant to sulphadoxine–pyrimethamine.

Subjects

Patients were recruited at the twice-weekly clinics at Rukararwe, from March to May 1998. Those with a history of non-specific febrile illness were tested for malaria. Initial thin blood films for rapid assessment of positivity were stained with Leishman’s, and examined for 3–5 min by an experienced laboratory technician (J.W.B. Mujinya). For patients who had not previously taken antimalarials, an immunochromatographic test (ICT) was also performed.

Patients positive for malaria were asked for their consent, and about their ability to return for follow-up visits. If they agreed to participate, a full history was taken, a full physical examination was performed, temperature was measured with an electronic thermometer, and urine was tested with a dipstick (Bayer N-Multistix). Urinary tract infection was diagnosed if either leucocytes or nitrites were detected; this method has a good sensitivity and specificity. Stool samples were also examined by microscopy if there was a history of diarrhoea. Patients were excluded if a specific cause was found for the febrile illness (such as urinary or respiratory tract infections, or amoebic trophozoites in the stool), if they were concurrently taking other herbs or Western medicines, if they were pregnant, or if there were signs of severe malaria (such as coma, shock, severe anaemia, or pulmonary oedema). For those patients who met the inclusion criteria, thick blood films were made for parasites to be counted. Travel expenses were paid in advance for return to follow-up.

Interventions

The herbal remedy under investigation is known by the code name of ‘AM’, to protect the intellectual property rights of the traditional healers. AM consists of the leaves of a particular tree, which are dried and ground. Patients are sold sachets, containing a standard amount of the herb, and instructed to boil each sachet in three mugs of water, to produce a tea. They should then drink half a glass of this three times a day. Smaller doses are prescribed for children according to their age and body mass. The first set of doses is provided in a bottle of ready-prepared tea, which is made not only with the tree leaves but also with the leaves of three other plants. Although it is believed
that the antimalarial effect comes from the AM tea, patients are also instructed to take ‘rema’ powder. This is thought to act as an antiemetic, to counteract the nausea and vomiting caused both by malaria itself and as a side-effect of AM. Rema is a sawdust-like powder, produced by grinding the bark of a local tree. Patients are instructed to put a teaspoonful of the powder in their tea after every meal.

Outcome measures

Patients were asked to return after 2, 7, 14 and 28 days. On each occasion they were asked about their symptoms, and any side-effects experienced. Patients were asked directly about common symptoms of malaria and common side-effects: fever, rigor, tiredness, dizziness, headache, joint pains, nausea, vomiting, abdominal pain, diarrhoea and cough. The number of symptoms was counted at each visit.

Patients were also asked about their compliance with the herbal remedy, and any other medicines taken. Axillary temperature was measured with an electronic thermometer. Thick and thin blood films were made, and travel expenses were paid to go home and return to the subsequent follow-up clinic.

Thick and thin films were stained with 3 per cent Giemsa at pH 7.2 for 30 min. Parasites were counted per 200 leucocytes; if the count was lower than 10 parasites per 200 leucocytes, parasites were counted per 500 leucocytes. The reading was then converted to parasites per microlitre assuming a leucocyte count of 8000 per microlitre.27 Parasite counts were performed independently by two blinded observers (the author and Rosemarie Gutmann, MLSO, Neusäß, Germany), and the geometric mean taken of both counts. When the parasite counts differed by more than a factor of two, a third blinded observer was asked to check the parasite count (Professor David Warhurst, London School of Hygiene and Tropical Medicine). The parasite density was then taken as the geometric mean of this and the other count(s) agreeing with it within a factor of two. The overall geometric means were taken of the parasite densities for all patients on each day. Ninety-five per cent confidence intervals (CIs) were calculated according to the method described by Gardner and Altman.28

Results

Subjects

Eighty-eight people were enrolled in the study. Of these 16 were excluded: seven took other herbs, five did not return to follow-up, in three another diagnosis was later discovered, and one refused to take AM because of its bitter taste.

Seventy-two patients taking AM were followed to at least 2 days (see Table 1). There were 35 men and 37 women with a mean age of 22.2 years (range 11 months–50 years). On average, patients took AM for 8.4 days (range 1–35 days). All these patients were included in the analysis of the side-effects of AM.

Table 1 The number of patients followed up on each day

<table>
<thead>
<tr>
<th>Days of treatment</th>
<th>Followed up</th>
<th>Excluded</th>
<th>Lost to follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>19</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>17</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>7</td>
<td>13</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>14</td>
<td>7</td>
<td>8</td>
<td>4</td>
</tr>
</tbody>
</table>

Nineteen patients were included in the analysis of the response of falciparum malaria to AM. There were 53 exclusions. Forty-one had initial parasite counts insufficient for response to treatment to be assessed (<400 per microlitre); four patients’ blood slides were lost; three patients took antimalarial tablets or injections before the first follow-up, and three admitted to taking an insufficient dose of AM. Two patients were excluded because their malaria was not P. falciparum: one was infected with P. malariae, and one with P. vivax.

In the group of 19 patients there were 13 men and six women, with a mean age of 17.0 (range 11 months–50 years). Four were aged <10, eight were aged 11–15, and seven were aged >15. On average they had had three previous attacks of malaria (range 0–30), and 26 per cent had a palpable spleen. The geometric mean of the initial parasite counts was 5540 per microlitre (95 per cent CI 3342–9161).

Of those excluded during the course of the study, four had taken conventional antimalarials (because they felt they were not improving) and four had simply stopped taking AM (two stopped because of vomiting after the herb and not improving, one child refused to drink AM because of its bitter taste, and one patient simply ran out of AM). The two patients not followed up on day 2 did attend subsequent follow-ups. Of those lost to follow-up by day 14, two did not attend, and two were enrolled too late in the course of the study to be followed up at 14 days.

Side-effects

No major adverse reactions were observed. Thirty-five patients reported no side-effects at all from AM; 37 reported one or more minor side-effects. The commonest were vomiting after drinking the herbal tea (13 patients), abdominal pain (12 patients) and nausea (nine patients). The abdominal pain was especially severe in two patients with a past history of peptic ulcer disease, to the extent that they stopped taking AM. Although most patients noticed the bitter taste of the herbal tea, two children (3 and 6 years old) stopped taking it because of this. Two patients complained of pruritus, one of appetite loss, and one of dizziness. At least six patients stopped taking AM because of side-effects (two because of epigastric pain; two because of vomiting; two because of bitter taste).

Symptoms

Figure 2 illustrates the significant decline in number of symptoms recorded per patient as treatment progressed.
Temperature

Only six of the 19 patients were febrile (temperature >37.5°C) at the time of attending the initial assessment. Patients afebrile at the time of examination were not excluded if they had a convincing history of recent febrile illness and symptoms of malaria. Recent studies have found that only a third to half of children with malaria were pyrexial at the time of examination. The number of febrile patients declined as treatment progressed, with the exception of day 14, when two patients had a recurrence of fever. This is illustrated in Fig. 3.

Parasite counts

The geometric mean of the parasite count declined as illustrated in Fig. 4 and Table 2. Because of the wide variation in parasite counts between individuals, the CIs are very wide. They become narrower on day 7, when parasite counts had declined in 11 of the 13 patients followed up, and do not overlap with the 95 per cent CIs for day 0. However, in only one of these 13 patients were parasites cleared completely. In five others the count was less than 400 per microlitre. In the remaining seven patients, the parasite count on day 7 remained above 400 per microlitre.

Discussion

As treatment with AM progressed, some subjective (symptomatic) and objective (parasitological) improvement was observed, with only minor side-effects. However, there are a number of problems with this study: inconsistent dosage, natural immunity, and the poor reliability of parasite counts. These will be discussed in turn.

Inconsistent dosage

As implied in the description of the herbal remedy AM above, the recipe was different for the first few days, when a tea of several herbs was used, and for subsequent days, when patients themselves prepared a tea from one herb only. Doses were probably inconsistent: ‘mug’ and ‘glass’ sizes are variable. Duration of boiling probably varied, perhaps destroying different amounts of the active ingredients.

Vomiting and diarrhoea would decrease the absorption of active ingredients. Six of the 19 subjects mentioned vomiting as a side-effect, and in four cases this was after taking the herb. Two of these stopped taking AM after 3 days because they were not improving (and their parasite counts also increased). One persevered with AM for 7 days, then switched to amodiaquine.

Table 2 Parasite counts in patients taking AM

<table>
<thead>
<tr>
<th>Days of treatment</th>
<th>Geometric mean of parasite counts</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>5540</td>
<td>3342–9161</td>
</tr>
<tr>
<td>2</td>
<td>4243</td>
<td>1648–10941</td>
</tr>
<tr>
<td>7</td>
<td>511</td>
<td>105–2478</td>
</tr>
<tr>
<td>14</td>
<td>364</td>
<td>25–5330</td>
</tr>
</tbody>
</table>
The fourth persisted with AM for 2 weeks, but did not improve. Even in those not vomiting, malaria itself may cause malabsorption, and diarrhoea also occurs as a side-effect of AM. Nine of the 19 patients reported diarrhoea, five as a primary symptom, and four after commencing AM.

Furthermore, some patients may have taken less than the recommended dose because of the bitter taste or other side-effects. Although all patients were questioned about the dosage used, not all may have admitted incorrect dosages; some may have subconsciously underestimated the amount of ‘half a glass’. There was no objective measure of compliance, or of concurrent medication. However, there was no obvious motive for patients to lie about their use of other drugs when questioned – a number did indeed admit to this, and were thence excluded from analysis. However, another similar study found that about one-quarter of patients had taken chloroquine without admitting it.

**Immunity**

It could be argued that the reduction in parasite counts and symptoms would have occurred anyway, as a result of partial immunity. There are few data on the time course of untreated malaria, and in any case this would vary widely between different populations. *P. falciparum* parasitaemia has been seen to clear without treatment in as little as 6 days. McGregor observed that even the first infection in a child’s life may be mild or asymptomatic, with 80 per cent recovering without treatment, and parasitaemia lasting an average of 22 days. However, subsequent attacks lasted longer and became more severe. White stated that although the initial peak of parasitaemia usually subsides naturally, the duration of untreated infection averages 7 months and in many cases exceeds 1 year.

There are several potential influences on immunity to malaria in the study site. With unstable transmission, it is unlikely that all patients were semi-immune. Out of 38 children aged 2–9 examined in the course of the study, six (16 per cent) had a palpable spleen, compared with 26 per cent of patients in the final study group. This implies that malaria is mesoendemic. Sickle cell disease, which affords natural resistance to malaria, is said to be common in Uganda, although the prevalence in this area is unknown. Although HIV infection is common (prevalence unknown, but estimated at 10–30 per cent), this does not affect the response to treatment of malaria.

Spontaneous recovery cannot be ruled out in the absence of a control group. However, it would be unethical to have a no-treatment control group. A control with orthodox drugs (e.g. chloroquine) would also have been impractical in this setting. Most of the patients coming to the traditional healers’ clinic did not wish to take Western medicines, as they had already tried them, and believed that they were ineffective or caused too many side-effects. To include a comparison group, further research should be located in a different institution, where patients have no particular expectations. For example, children could be recruited at school when they first develop signs and symptoms of malaria. In this setting, dosage could be standardized and patients observed taking the medication.

This study is a first step towards a randomized controlled trial. It is an observational ‘screening’ study of the sort advocated by Warrell. Further research could involve randomization to AM or to the local conventional treatment, chloroquine. Alternatively, AM could be compared with placebo for malaria prophylaxis. There is anecdotal evidence that drinking a small amount of AM every day helps to prevent malaria.

**Parasite count reliability**

The parasite counts are likely to be inaccurate, because they assume a white cell count of 8000 per microlitre. Leucocyte counts may be affected by many variables; even stress during blood taking, especially in children, can produce a mild neutropenia.

Leucocyte counts may also vary as the episode of malaria resolves. In any case, parasite counts fluctuate widely in the course of untreated malaria infection. Paradoxically, low peripheral parasite counts may be associated with sequestration of parasites, and more severe disease. For this reason, WHO states that the clinical response of patients should be the main criterion for assessing effectiveness of antimalarial drugs. It is therefore encouraging in this study that patients taking AM improved symptomatically, and none were observed to develop complications of malaria.

Total parasite clearance may be an unrealistic objective in endemic areas, and may indeed do more harm than good. Natural resistance to the malaria depends on continuous challenge and the continued presence of parasites, at a low level, in the body. At an appropriate dose, AM may be strong enough to cure symptoms and prevent complications of malaria, but gentle enough to allow a low level of parasitaemia, and thus natural immunity, to be maintained.

**Conclusions**

1. AM appears safe. No patient experienced life-threatening adverse reactions.
2. Minor side-effects are common, and affect compliance in a small proportion of cases.
3. Patients taking AM improved symptomatically over 1 week, and none were observed to develop serious complications.
4. Parasitaemia declined between day 1 and day 7 of treatment with AM, although total parasite clearance occurred in only one case.
5. Further research is needed to determine whether these effects were the result of AM treatment or of natural immunity to malaria. Patients should be randomized to a standard, optimal dose of AM or another treatment.
(6) Observational studies can be an important first step in evaluating the usefulness of herbal medicines for malaria.

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References


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