Randomized controlled trial of a traditional preparation of Artemisia annua L. (Annual Wormwood) in the treatment of malaria

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Summary The Chinese medicinal plant Artemisia annua L. (Annual Wormwood) contains the antimalarial compound artemisinin. The locally grown herb may offer an additional tool for the control of malaria, especially in poor countries where modern antimalarial drugs are often unavailable. In an open, randomized, controlled pilot trial, we investigated the efficacy and safety of traditional tea preparations of Artemisia annua in the treatment of uncomplicated malaria. Treatment resulted in a quick resolution of parasitaemia and of clinical symptoms. After 7 days of medication, cure rates were on average 74% for the Artemisia preparations compared with 91% for quinine. However, recrudescence rates were high in the Artemisia groups. Therefore, monotherapy with Artemisia annua L. cannot be recommended as alternative to modern antimalarials, but may deserve further investigation.

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1. Introduction

Despite efforts to control of malaria, global morbidity and mortality has not principally changed over the last 50 years. The key problem is the failure to get the existing, effective tools against malaria to be applied in those areas where they can be of most benefit (Guerin et al., 2002). The herb Artemisia annua L. (Annual Wormwood) has been used in traditional Chinese medicine for the treatment of febrile diseases and malaria for many centuries and is included in the current pharmacopoeia of China. It can be cultivated with relative ease in poor countries (Mueller et al., 2000). Its...
Artemisia annua with parasitaemia of >2000/μl, age ≥18 years, permanent residence in South Kivu Province for ≥5 years, and at least one of the following clinical symptoms of malaria: fever, chills, fatigue, vertigo, nausea, joint pain, vomiting, headache, abdominal pain, or diarrhoea. Exclusion criteria included pregnancy or lactation, treatment for other diseases, and known chronic and progressive life-threatening diseases. In the Artemisia annua groups, urine samples were examined by thin layer chromatography (TLC) for current medication with chloroquine or quinine, and positive patients were treated.

Eligible patients were randomly assigned to one of the following treatment groups: (i) A5 group, Artemisia annua tea (5 g herb/l); 1 l per day for 7 d; (ii) A9 group, Artemisia annua tea (9 g herb/l); 1 l per day for 7 d; (iii) QN group, quinine sulphate tablets (500 mg quinine sulphate, three times daily) for 7 d.

Artemisia annua L. cv. Artemis was cultivated, harvested and dried at Tübingen University, Germany, and leaves were prepackaged in sealed plastic bags in doses of 5 and 9 g. The artemisinin content of the dried plant material was 1.4%. One litre of tea prepared from 5 and 9 g herb contained 47 and 94 mg of artemisinin, respectively (Räth et al., in press). For each patient, 1 l of tea was freshly prepared each morning by the medical staff following standardized procedures. Patients took the first dose (250 ml) each morning under direct supervision of the medical staff, and were instructed to take three further doses of 250 ml each at noon, 16:00 and 20:00. In the QN group, patients took the first dose (500 mg) on day 0 and day 3 under direct supervision, and were instructed to take the further doses independently.

In the original protocol, an additional study arm was planned with chloroquine. However, local health officials raised concerns about chloroquine resistance in the area, and the assessment of the response rate in the chloroquine arm but not in the other treatment arms had to be modified. According to this modification all patients in the chloroquine group who had persistent parasitaemia on day 3 were withdrawn from the study, classified as treatment failures and received rescue treatment. This resulted in the initiation of quinine therapy in >60% of the chloroquine patients, and data of the chloroquine group were therefore excluded from the final analysis due to the lack of comparability between the chloroquine and the other treatment arms.

On days 3 and 7, pulse, blood pressure and body temperature (auxillary, mercury thermometer) were recorded, and patients were interviewed with a standardized questionnaire for clinical symptoms and adverse events. The level of parasitaemia was determined from a finger-prick using Giemsa-stained thick blood films. The number of asexual parasites was determined by light microscopy as described elsewhere (WHO, 1996). We have not attempted to genotype the pairs of parasite strains from admission and parasite reappearance to distinguish between true recrudescence and new infections. In the absence of such data, we have considered all patient parasitaemia on day 7 to be recrudescence and therefore treatment failures.

The primary end point was the cure rate on day 7, i.e. the proportion of patients with negative blood films on day 7. Secondary end points included the cure rates on days 14, 28, and 35, and the change of clinical symptoms recorded by the standardized questionnaire. The criteria for treatment failure were: development of severe malaria or danger signs; parasitaemia on day 3 equal or higher than the parasite count on day 0; parasitaemia on day 7; and initial parasite clearance by day 7 followed by recurrence up to day 35. Treatment failures were appropriately treated.

2. Materials and methods

The study was performed as a pilot trial in a rural primary health care scheme, involving a district hospital and three health centres, in the eastern Democratic Republic of the Congo from February to December 2001. The study protocol was approved by the Ethics Committee of Tübingen University Hospital, Germany, and by the Ministry of Health of South Kivu Province, DR Congo, and all patients gave verbal informed consent.

Inclusion criteria were P. falciparum malaria with parasitaemia of ≥2000/μl, age ≥18 years, permanent residence in South Kivu Province for ≥5 years, and at least one of the following clinical symptoms of malaria: fever, chills, fatigue, vertigo, nausea, joint pain, vomiting, headache, abdominal pain, or diarrhoea. Exclusion criteria included pregnancy or lactation, treatment for other diseases, and known chronic and progressive life-threatening diseases. In the Artemisia annua groups, urine samples were examined by thin layer chromatography (TLC) for current medication with chloroquine or quinine, and positive patients were treated.

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3. Results

The disposition of patients is shown in Figure 1. At enrolment, the treatment groups were similar with respect to gender, age, weight, and clinical features (data not shown). Clinical efficacy data are summarized in Table 1. On day 7, cure rates were 30/39 (77%, 95% CI 61–89) and 23/33 (70%, 95% CI 51–84) in the A5 and A9 group, respectively, compared with 39/43 (91%, 95% CI 78–97) in the QN group. During follow-up, cure rates in the Artemisia groups dropped, indicating a higher rate of recrudescence (Table 1). Most of the reported malaria symptoms improved or resolved within three days after initiation of therapy, as expected for an artemisinin or quinine treatment (Table 1). Adverse events were similar in all treatment groups and indistinguishable from malaria-related complaints, except for reports of tinnitus in the quinine group (27% of patients). The Artemisia preparations were well tolerated.

4. Discussion

Our pilot study showed that treatment with traditional Artemisia annua preparation results in a rapid improvement of malaria symptoms as well as resolution of parasitaemia in most patients. Both Artemisia dosages were within the range specified by the pharmacopoeia of China (i.e. 4.5–9 g/d) and were equally effective. The minimum dose or plasma concentration of artemisinin required for clinical efficacy is unknown, but the minimum concentration required for growth inhibition of \textit{P. falciparum} (9 ng/ml; de Vries and Dier, 1996) can clearly be exceeded with the Artemisia preparations. On the other hand, the traditional Artemisia preparations contained at best 94 mg artemisinin/l (Rath et al., in press), i.e. 19% of the usual clinical dose of pure artemisinin (500 mg/d), and resulted in unacceptable recrudescence rates. The much lower recurrence rates in the parallel quinine group confirmed that the observed recurrence in the...
Artemisia annua in malaria treatment

Table 1  Efficacy of a seven day treatment with Artemisia annua preparations in uncomplicated Plasmodium falciparum malaria compared with quinine

<table>
<thead>
<tr>
<th></th>
<th>Artemisia annua tea (5 g herb/d)</th>
<th>Artemisia annua tea (9 g herb/d)</th>
<th>Quinine (1500 mg/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cure rate day 7</td>
<td>30/39 (77%)</td>
<td>23/33 (70%)</td>
<td>39/43 (91%)</td>
</tr>
<tr>
<td>Cure rate day 14</td>
<td>20/35 (57%)</td>
<td>18/31 (58%)</td>
<td>35/39 (90%)</td>
</tr>
<tr>
<td>Cure rate day 28</td>
<td>12/32 (38%)</td>
<td>11/30 (37%)</td>
<td>31/36 (86%)</td>
</tr>
<tr>
<td>Cure rate day 35</td>
<td>11/32 (34%)</td>
<td>9/30 (30%)</td>
<td>27/34 (79%)</td>
</tr>
<tr>
<td>Symptomsa</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>31/34 (91%)</td>
<td>26/32 (81%)</td>
<td>34/37 (92%)</td>
</tr>
<tr>
<td>Chills</td>
<td>23/25 (92%)</td>
<td>18/18 (100%)</td>
<td>24/24 (100%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>29/33 (88%)</td>
<td>19/26 (73%)</td>
<td>23/33 (70%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>17/21 (81%)</td>
<td>10/20 (50%)</td>
<td>21/27 (78%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>11/12 (92%)</td>
<td>5/6 (83%)</td>
<td>7/11 (64%)</td>
</tr>
<tr>
<td>Headache</td>
<td>22/24 (92%)</td>
<td>19/22 (86%)</td>
<td>18/19 (95%)</td>
</tr>
<tr>
<td>Joint pain</td>
<td>6/7 (86%)</td>
<td>4/4 (100%)</td>
<td>13/17 (76%)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>8/8 (100%)</td>
<td>10/12 (83%)</td>
<td>12/14 (86%)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>1/1 (100%)</td>
<td>1/1 (100%)</td>
<td>0/0</td>
</tr>
</tbody>
</table>

* No. of patients with symptom improved or resolved on day 3/no. of patients with symptom on day 0.

Artemisia groups are indeed due to recrudescence, not to reinfection. Monotherapy with tea preparations from Artemisia annua can therefore not be recommended as a treatment option for malaria because of recrudescence, as well as concerns about possible resistance development against artemisinin. Further research will have to evaluate whether modifications of this therapy, for example combination with other antimalarials, may result in effective, safe and affordable treatment options for combating malaria, especially in poor countries.

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