Treatment of Louse-borne Relapsing Fever with Low Dose Penicillin or Tetracycline: A Clinical Trial

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A clinical trial was conducted in order to evaluate the efficacy of procaine penicillin and tetracycline, respectively, in the treatment of louse-borne relapsing fever. 184 patients (160 men, 24 women) admitted to the Gondar hospital during the rainy season 1992 were assigned to 1 of 4 treatment groups: procaine penicillin 100,000 (PP100), 200,000 (PP200) or 400,000 (PP400) international units (IU) intramuscularly (i.m.), or tetracycline 250 mg per os (TTC, p.o.). All drugs were given as single doses. The overall case fatality rate was 3.3%. Frequency of relapses, Jarisch-Herxheimer-like reactions (JHR) and deaths were significantly different between patients treated with TTC and those treated with PP100. Relapses occurred most often in the group receiving the lowest dose of penicillin (46%), and decreased with increasing dosage of penicillin; none of the patients treated with TTC had a relapse. Occurrence of JHR showed the opposite pattern: whilst 2 (5%) patients treated with PP100 developed a JHR, 16 (29%) in the PP200 group, 10 (31%) in the PP400 group, and 27 (47%) in the TTC group developed a JHR. As mortality is linked to severe JHR, and most relapses are clinically mild and easily treated, these results speak in favor of using low-dose penicillin to initiate the treatment of relapsing fever.

INTRODUCTION
Louse-borne relapsing fever (LBRF) is an acute febrile disease caused by an infection with Borrelia recurrentis, a spirochetal organism that is transmitted to humans by the infected human body louse, Pedunculus humanus. Outbreaks of the disease are related to poor hygiene and crowding, and occur mainly during wars and periods of famine. The disease is endemic in Northeast Africa, South America and East Asia (1-7). In Ethiopia, more than 10,000 cases occur each year (4). If untreated, the case-fatality rate ranges from 30 to 70% (1). Antibiotic treatment has reduced mortality to 2-6% (3, 8, 9).

A variety of antibiotic drugs have been used in the treatment and have been proved to be efficient in removing spirochetes, for example tetracyclines including doxycycline, erythromycin, chloramphenicol, and penicillin. Clinicians favour a single dose or multiple doses of tetracyclines (8-11), low dose penicillins (3), or a combination of both (7) for treatment of adults. The clearance of borreliae is often accompanied by a Jarisch-Herxheimer-like reaction (JHR), characterized by a sudden rise in fever, blood pressure, and respiratory rate, being followed by a severe hypotonic phase. It has been shown that highly efficient drugs such as tetracyclines are associated with the highest rate of JHR. Drugs that are more slowly combatting the infection, for example slow-release penicillins, induce JHRS not only at a lower rate, but also less severely (1). Deaths during the shock phase of a JHR have been reported, with a case-fatality rate of up to 4% in patients treated with penicillins (5), and up to 6% in those receiving tetracyclines (1, 2, 7).

Clinical trials so far conducted have not resulted in a consensus as to the optimal drug, dose, and route of administration for the treatment of LBRF. Often, the trials included only low numbers of patients (5, 9, 11, 12), had a high percentage of lost-to-follow-ups (1, 8), and/or were not conducted as controlled clinical trials (8, 10).

The purpose of our study was to conduct a controlled clinical trial comparing single doses of the most commonly recommended drugs, tetracycline and penicillin, the latter one at different dose levels.

PATIENTS AND METHODS
During the rainy season (June-September) 1992, 255 patients with LBRF were admitted to the medical wards of the Gondar College of Medical Sciences in Gondar, Ethiopia. The diagnosis was verified microscopically by identifying the spirochetes in the patients peripheral blood smears. Patients in serious condition on admission (systolic blood pressure below 75 mmHg, coma, anuria, severe jaundice and/or acute heart failure with pulmonary edema), children below age 15 years, and those with a history of allergy to penicillin or tetracycline were not included in the study. All others were eligible for the study and consent was obtained from 184 patients, 160 men and 24 women. These were assigned to one of the following 4 treatment groups:

- procaine penicillin, 100,000 IU i.m. (PP100): 39 patients;
- procaine penicillin, 200,000 IU i.m. (PP200): 55 patients;
- procaine penicillin, 400,000 IU i.m. (PP400): 32 patients;
- tetracycline, 250 mg, p.o. (TTC): 38 patients.

The assignment of a patient’s drug regimen was chosen by drawing a card labeled with the drug and dose to be given. Out of 300 cards prepared, 30% were labeled PP200, 30% TTC, and 20% each were prepared for PP100 and PP400. PP200 and TTC were the treatments of choice at the clinic, and were therefore overrepresented. All drugs were given as a single dose after i.v. Ruid.

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as an increase in body temperature (>1°C) combined with tachycardia (pulse rate >100 min⁻¹), occurring within 4 h after treatment, followed by a drop in systolic and diastolic blood pressure greater than 10 mmHg. A relapse was recorded for those patients who suffered a further fever attack with positive blood smear at least 2 days after the first attack. The study was approved by the Ethics Committee in Gondar, Ethiopia.

Differences in the proportion of JHR and relapse among groups were tested using the Cochran-Mantel-Haenszel statistics, controlling for gender and age group. Age groups were set up as follows: 15–19, 20–29, 30–39, ≥ 40 years. Because of the low number of patients, all those above 30 years (n = 37) were included in 1 group when analyzing age as a risk factor for the development of JHRs and relapses. Logistic regression analysis was used to study the effect of clinical parameters on mortality, relapse and JHR incidence. Independent variables included in these models were: age, sex, drug, jaundice, cardiac gallop rhythm, blood pressure, and duration of symptoms before admission. All data analyses were performed using the SAS statistical analysis software (SAS Institute, Cary, NC).

RESULTS

Epidemiological characteristics

The patients' age ranged from 15 to 56 years with a mean of 23.4 years; 98 patients (53%) were in the age group from 20 to 30 years. The male:female ratio was 6.7:1. Of the male patients, 38 (23.8%) were soldiers or ex-soldiers, 30 (18.7%) students, 14 (8.8%) prisoners, 30 (18.7%) daily labourers or unemployed, and 12 (7.5%) farmers.

Clinical symptoms and signs

The average duration of symptoms before admission was 4.5 days (range 1–21 days). The most prominent symptoms reported were fever (100%), general malaise (82%), and headache (76%). Myalgia occurred in 104 patients (66%), arthralgia in 75 (41%), cough in 22 (12%), and diarrhoea in 21 patients (11%). On admission, all patients were febrile with a mean axillary temperature of 38.5°C. Jaundice was noticed in 45% of the patients, abdominal tenderness, hepatomegaly or splenomegaly or both were less common findings, occurring in 18.5%. The average blood pressure was 103/69 mmHg.

Fatalities

Out of the 184 patients 6 (3.3%) died after development of a JHR; no death occurred in the PP100 group, 1 in the PP200, 2 in the PP400, and 3 in the TTC group. The case fatality rate between PP100 and TTC was significantly different (p = 0.03). Mortality was significantly associated with the occurrence of a JHR (p = 0.009), but was unrelated to relapses, jaundice, cardiac gallop rhythm, age, gender, blood pressure, and length of symptoms prior to admission.

Relapses

Overall, 30 patients (16.3%) developed a relapse. Relapses occurred in nearly one-half (n = 18; 46.2%) of the patients in the PP100 group, and decreased in number with increas-

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Number</th>
<th>JHR</th>
<th>OR*</th>
<th>95% CI</th>
<th>Relapse</th>
<th>OR*</th>
</tr>
</thead>
<tbody>
<tr>
<td>15–19</td>
<td>49</td>
<td>1.00</td>
<td>0.32</td>
<td>0.11–0.95</td>
<td>0.23</td>
<td>0.04–1.34</td>
</tr>
<tr>
<td>20–29</td>
<td>98</td>
<td>0.56</td>
<td>0.25–1.24</td>
<td>0.82</td>
<td>0.31–2.14</td>
<td></td>
</tr>
<tr>
<td>≥ 30</td>
<td>37</td>
<td>0.32</td>
<td>0.11–0.95</td>
<td>0.23</td>
<td>0.04–1.34</td>
<td></td>
</tr>
</tbody>
</table>

*a adjusted for drug and gender

Table I. Adjusted odds ratios and 95% confidence intervals for the development of Jarisch-Herxheimer-like reactions and relapses in patients with louse-borne relapsing fever, Gondar, Ethiopia, 1992

Fig. 1. Frequency of relapses, Jarisch-Herxheimer-like reactions (JHR), and fatalities in patients with louse-borne relapsing fever treated with penicillin or tetracycline. June-September 1992. Gondar, Ethiopia.
DISCUSSION

We found an increasing rate of JHRs with increasing dose of penicillin, from 5.1% (PP100) to 31.1% (PP400). Penicillin clears the blood of spirochetes more slowly than do other relevant antibiotics, and accordingly induces JHRs later, at a lower rate and with less severity. Combined treatment using PP400, followed by 2 g of TTC a day later, has resulted in a JHR-rate of 13% (7). 47% of our patients receiving tetracycline developed a JHR. All but 1 (8) previous studies reported the development of JHR in all patients receiving tetracycline (1, 5, 9, 11, 12). These studies included severely ill patients - who in our study were excluded. Moreover, criteria for JHR were not clearly defined in those studies, so that a comparison with our results is hampered.

Low age was found to be a risk factor for the development of a JHR. A possible explanation is that younger individuals are likely to be of lower weight than older ones, thus receiving a higher drug dose per kg body mass. Unfortunately, the weight of patients was not recorded, and it can not be established if this association is spurious or real. More likely, the difference reflects a partial immunity to Borrelia and borrelia toxins in patients aged 30 years or more. When comparing our results to reports from other countries the high prevalence of malnutrition in our region has to be taken into consideration. Lack of data on body mass index enabled us to evaluate the effect that malnutrition could have on the incidence of JHR and/or relapses.

We noticed an overall case fatality rate of 3.3%. Deaths were significantly associated with the occurrence of JHRs. The different mortality rates between patients treated with PP100 and TTC are likely to reflect the different rates of JHRs.

The relapse rate in our study decreased with increasing dose of penicillin from 45.0% (PP100) over 16.7% (PP200) to 9.4% (PP400). Relapse rates of 1.2% have been reported for combined penicillin-tetracycline treatment (7), and 1.8% for PP400 administered twice (2). None of our patients treated with TTC showed a relapse, a finding consistent with previous reports (1, 5, 8, 11, 12).

In conclusion, it appears that treatment of LBRF should be initiated with low dose penicillin rather than the common use of tetracycline. A low dose of penicillin obviously reduces the rate of JHR, and thus mortality. Further clinical trials are needed to establish the optimal dose, or possibly combinations of doses or drugs for the treatment of this disease.

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REFERENCES


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