Early bactericidal activity of a moxifloxacin and isoniazid combination in smear-positive pulmonary tuberculosis

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Background: In vitro and animal studies have shown that moxifloxacin-containing combinations may improve the bactericidal efficacy of antituberculosis regimens.

Patients and methods: We measured the decline in the sputum viable count of 13 patients who were given a combination of moxifloxacin 400 mg daily and isoniazid 300 mg daily.

Results: The time required to reduce the viable count by 50% (vt50) was 0.38 days (95% CI –0.03–0.78 days, SEM 0.13) and the mean early bactericidal activity (EBA) was 0.60 log10 cfu/day (95% CI 0.23–0.97, SEM 0.14). This compares with the vt50 calculated for isoniazid and moxifloxacin alone in the same population of 0.48 and 0.88 days, respectively. The EBA values for isoniazid and moxifloxacin alone were 0.77 and 0.53 log10 cfu/day, respectively.

Conclusions: The combination of moxifloxacin and isoniazid is not antagonistic, but the combination does not significantly enhance bactericidal activity above that of isoniazid alone.

Keywords: Mycobacterium tuberculosis, clinical trials, drug effects, quinolones

Introduction

While we await novel antituberculosis agents, the fluoroquinolones have been identified as agents whose activity might permit the duration of therapy to be shortened. Moxifloxacin is highly active in vitro and in mouse studies. Combination therapy studies in mice suggest that a rifampicin, moxifloxacin and pyrazinamide regimen reduces the time to culture conversion compared with the other regimens, including rifampicin, isoniazid and pyrazinamide. Moreover a recent study suggests that the rifampicin, moxifloxacin and pyrazinamide regimen substantially shortens the duration of therapy required to cure tuberculosis in mice. There is thought to be antagonism between isoniazid and rifampicin in the mouse model and it is not clear whether this also occurs in patients. We and others have shown previously that moxifloxacin has bactericidal activity in patients with smear-positive pulmonary tuberculosis comparable to that of rifampicin. It is important, therefore to investigate the activity of moxifloxacin combinations in patients with sputum smear-positive tuberculosis. Early bactericidal response to therapy is one of the rapid ways of evaluating the activity of new agents, alone or in combination, using group sizes of between 4 and 15 subjects. We report that the combination of moxifloxacin and isoniazid is not antagonistic, but the combination does not significantly enhance bactericidal activity above that of isoniazid alone.

Patients and methods

Ethics

Our study was approved by the ethical committee of Kilimanjaro Christian Medical College, the National Institute of Medical Research and the National AIDS Control Programme of Tanzania, and each patient gave witnessed oral consent.

Patients and treatment

Patients were recruited from those presenting to the Kibong’oto National Tuberculosis Hospital, Sanya Juu, Tanzania with sputum smear-positive pulmonary tuberculosis. Inclusion criteria for the study were (i) presence of acid fast organisms found in a Ziehl-Neelsen stained smear of sputum, (ii) mild to moderate disease on clinical grounds, (iii) age over 18 years, (iv) no prior chemotherapy,
(v) production of an adequate volume of sputum, (vi) weight between 40 and 60 kg and (vii) consent to HIV serology. Patients were excluded from the study if they had severe, rapidly progressive disease or had any serious concomitant condition, renal or hepatic failure, as judged by the admitting physician or if there was a history of hypersensitivity to the trial agents. A total of 13 patients received the 400 mg moxifloxacin and 300 mg isoniazid combination daily for 5 days.

Bacteriology and data analysis

Sputum was collected over 16 h and serial colony counts by culture on 7H11 Middlebrook agar made selective by the addition of polymyxin B sulphate (200 units/mL), carbenicillin (100 mg/L), trimethoprim lactate (20 mg/L) and amphotericin B (10 mg/L) using Selectatabs (Mast, UK) were performed as described previously.6 The results of sputum viable count were recorded and the time taken to reduce the viable count by 50% (vt50) and the 48 h early bactericidal activity (EBA) were calculated using methods published previously.8–10 Additional data from Jindani et al.9 for other combinations was recalculated by the vt50 method for comparison as described previously.8–10

Results

It was possible to calculate the vt50 for five subjects and the EBA for seven due to contaminated cultures. The combination of moxifloxacin and isoniazid was highly bactericidal and these data are compared with single agents and other combinations given in Figure 1. The mean vt50 for moxifloxacin/isoniazid was 0.38 days (95% CI –0.03–0.78, SEM 0.13) and the mean EBA was 0.60 log10 cfu/day (95% CI 0.23–0.97, SEM 0.14). This compares with the vt50 calculated for isoniazid and moxifloxacin alone in the same population of 0.48 and 0.88 days, respectively. The EBA values for isoniazid and moxifloxacin alone were 0.77 and 0.53 log10/day, respectively. None of these differences was statistically significant using the Mann–Whitney U-test.

Discussion

It was hoped that the combination of these drugs might enhance the bactericidal activity. We were able to compare the results obtained in this study with the data collected from patients receiving moxifloxacin or isoniazid alone in a similar group of patients at the same site within the previous 6 months. Although there is a trend that suggests that the addition of isoniazid to moxifloxacin increases the bactericidal activity, the numbers studied were too small to confirm this. On the other hand it implies that, even if the combined drugs are beneficial, the size of the advantage is very small. Isoniazid is considered to be the most bactericidal of the antituberculosis agents and previous early bactericidal response studies showed that the addition of other drugs to isoniazid did not increase the bactericidal activity of the combined regimen over isoniazid alone.9,11

It has been suggested that moxifloxacin might antagonize the effect of isoniazid.1 Our data demonstrates that at worst this combination makes no difference to the activity of isoniazid and there is a suggestion that it may augment it. Our study did not demonstrate a significant difference between isoniazid, moxifloxacin or the combination as the numbers were too small; the same inability of other drug combinations to enhance the bactericidal activity of isoniazid alone has been shown by other groups.9,11 Further studies with larger numbers of patients concentrating on finding the most potent combination of antituberculous drugs and moxifloxacin are required. These should initially focus on the first 2 months of therapy as this agent has been shown to be safe in extended therapy in patients with tuberculosis.12

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Transparency declarations

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References

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