Early Bactericidal Activity of Paromomycin (Aminosidine) in Patients with Smear-Positive Pulmonary Tuberculosis

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The early bactericidal activity of the aminoglycoside paromomycin (aminosidine) in doses of 7.5 and 15 mg/kg of body weight was measured in 22 patients with previously untreated smear-positive pulmonary tuberculosis. It is determined by measuring the rate of decrease in viable CFU of Mycobacterium tuberculosis per milliliter of sputum during the first 2 days of treatment with the drug under investigation (10). It has been used to evaluate and compare both new (13, 14) and established (3, 15) antituberculosis drugs and to determine the lowest effective dose of a drug (3).

Paromomycin, also known as aminosidine, is a broad-spectrum aminoglycoside closely related structurally to neomycin and kanamycin and less closely related to streptomycin (5). Although its main use at present is for the management of visceral leishmaniasis (kala-azar) (6, 16), it has been shown, both in vitro (8) and in animal experiments (9), to have considerable activity against M. tuberculosis, including multidrug-resistant strains, and there are anecdotal reports of its use for the management of pulmonary tuberculosis (17). It lacks cross-resistance with streptomycin and other aminocyclitol antibiotics. The MIC of paromomycin for M. tuberculosis ranges from ≤0.09 to ≤1.5 μg/ml (8). In humans, peak concentrations of paromomycin of 11.6 to 25.6 μg/ml 1 h after a 500-mg intramuscular dose have been reported (4). In this pilot study, the EBA of paromomycin at dosages of 7.5 and 15 mg/kg of body weight was evaluated.

Materials and Methods

This study was undertaken in the Department of Internal Medicine of Tygerberg Hospital, the teaching hospital of the Faculty of Medicine of the University of Stellenbosch. Tygerberg Hospital serves a number of socioeconomically deprived communities in the Western Cape province of South Africa, a region with a notified tuberculosis incidence of >500 cases/100,000 people in 1998. The study was undertaken between November 1997 and June 1998.

Patients. Patients had newly diagnosed, previously untreated, pulmonary tuberculosis, were between 18 and 40 years of age, and weighed more than 40 kg. Patients in poor general condition or suffering from other serious medical complications, women who were pregnant or lactating, and patients unable to produce at least 10 ml of sputum overnight were excluded from the study, as were those in whom initial sputum or urine specimens traces of isoniazid or its metabolites could be detected. Also excluded were those with any known hypersensitivity to any aminoglycoside and those whose initial M. tuberculosis isolates were found to be resistant to isoniazid, rifampin, streptomycin, or paromomycin. Resistance to isoniazid, rifampin, or streptomycin, if found, would indicate that the patient might have received previous antituberculosis treatment. Thirty-two patients were randomized to receive either 15 mg of paromomycin per kg (18 patients) or 7.5 mg of paromomycin per kg (14 patients). The results from 10 patients, 7 from the 7.5-mg/kg group and 3 from the 15-mg/kg group, were excluded from the analysis. The reasons for exclusion were resistance to isoniazid in the isolates for five patients, resistance to isoniazid and inadequate homogenization of the sputum specimen for one patient, and no growth or only very poor growth for four patients.

Sputum collection and drug administration. Patients were actively encouraged to cough, and a 16-h collection of sputum was done from 0800 on the day of admission to 0800 the next day (S1 sputum sample). Soon after 0800, paromomycin was given by intramuscular injection, and the sputum collection procedure was repeated to obtain sputum specimens following the first and second doses of paromomycin (S2 and S3, respectively).

On completion of the study protocol after the S3 sputum collection, the patients were commenced on isoniazid, rifampin, pyrazinamide, and ethambutol as recommended by the South African National Tuberculosis Control Programme.

Microbiologic methods. Sputum in the S1, S2, and S3 collections was examined conventionally by direct smear, culture, and sensitivity testing. CFU counts on the sputum collections were carried out as described previously (13). Without preliminary centrifugation, 20 μl of the dilutions were set up on thirds of triplicate plates of selective 7H10 medium. Drug resistance was not developed during the 3 days of the study. Analysis of sputum and urine specimens for isoniazid and its metabolites was done by a previously described high-performance liquid chromatography method (12).

Statistical methods. The EBA for each patient was calculated by first obtaining the mean CFU count (X) at the most appropriate dilution, which was that permitting counting of between 20 and 200 colonies. Then, we used the equation

\[
Y = \log_{10}(Y/X),
\]

where \( f \) is the dilution factor and \( Y \) is \( \log_{10} \) CFU per milliliter of sputum. EBA were calculated, and 95% confidence limits from

\[
\text{log}_{10} (Y_{1}) \pm 1.96 \times \text{SD}.
\]

The means and standard deviations of \( Y_{1}, Y_{2}, Y_{3} \), and EBA were calculated.
Table 1. Viable counts of CFU of tubercle bacilli in sputum collections S1, S2, and S3 and in groups receiving no drug

<table>
<thead>
<tr>
<th>Dosage (mg/kg) or no-drug group (reference no.)</th>
<th>Number of patients</th>
<th>Log₁₀ CFU/ml of sputum (mean [SD]) for:</th>
<th>EBA</th>
<th>Mean (SD)</th>
<th>95% Confidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.5</td>
<td>7</td>
<td>S1 6.513 (0.898) S2 6.449 (0.715) S3 6.381 (0.774) Mean 0.066 (0.210)*</td>
<td>-0.134–0.266</td>
<td></td>
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<tr>
<td>15</td>
<td>15</td>
<td>A 6.961 (0.611) B 6.956 (0.761) C 6.777 (0.754) Mean 0.092 (0.140)*</td>
<td>-0.015–0.013</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A (13)</td>
<td>13</td>
<td>D 6.762 (0.461) E 6.770 (0.460) F 6.791 (0.464) Mean -0.015 (0.013)</td>
<td>-0.022–0.007</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B (14)</td>
<td>10</td>
<td>6.924 (0.326) 6.935 (0.320) 6.949 (0.361) Mean -0.011 (0.052)</td>
<td>-0.082–0.026</td>
<td></td>
<td></td>
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<tr>
<td>C (15)</td>
<td>8</td>
<td>6.236 (1.177) ND* 6.161 (1.206) Mean 0.038 (0.047)</td>
<td>-0.002–0.077</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>10</td>
<td>7.002 (0.757) 6.827 (0.757) 6.921 (0.753) Mean 0.041 (0.113)</td>
<td>-0.040–0.122</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* The difference between the means and zero was nonsignificant for the 7.5-mg/kg group but significant \( t = 2.55, P = 0.023 \) for the 15-mg/kg group.

DISCUSSION

In this study, paromomycin produced a small but statistically significant increase in EBA, as shown by both the nonparametric trend test \( P = 0.03 \) and the regression analysis on the group means \( P = 0.029 \). Streptomycin, given in a dosage of approximately 20 mg/kg of body weight to a group of four patients, had a similar EBA, 0.094 (7). The CL of both estimates are so wide that comparison is inconclusive. The finding that paromomycin at a dose of 7.5 mg/kg did not have a detectable effect compared to zero suggests that the antituberculosis activity may be limited.

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REFERENCES


