Novel Treatment of Meningitis Caused by Multidrug-Resistant Mycobacterium tuberculosis with Intrathecal Levofoxacin and Amikacin: Case Report

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We report the case of a 25-year-old HIV-negative man with disseminated multidrug-resistant tuberculosis (MDRTB), who—on a retreatment regimen—experienced total resolution of TB miliary disease, but progressive TB meningitis. Therefore, intrathecal treatment with amikacin and levofoxacin was instituted, with successful clinical and microbiological results.

Isoniazid, rifampin, and pyrazinamide are usually effective in the treatment of meningitis caused by susceptible strains of Mycobacterium tuberculosis. However, there is little experience treating meningitis caused by M. tuberculosis resistant to the major first-line agents isoniazid and rifampin. Two major concerns with alternative agents are that their bactericidal activity is less and their penetration of the blood-brain barrier is uncertain. We report a case of meningitis caused by multidrug-resistant (MDR) M. tuberculosis that is highly informative for the following reasons. During a retreatment regimen, the patient had dramatic resolution of his pulmonary and miliary disease but had profound simultaneous progression of M. tuberculosis meningitis. Deterioration in his condition occurred despite the use of high doses of pyrazinamide, to which the isolated strain was susceptible in vitro; this case raises important questions regarding the activity of this drug within the CNS.

The patient’s condition was successfully managed with use of intrathecal administration of a novel regimen.

Case report. A 25-year-old HIV-negative man from Vietnam presented in December 1997 to Columbia/Wesley Hospital (Wichita, KS), with a 2-month history of fevers and nausea and a 9-kg weight loss (to 54 kg). No signs or symptoms of meningeal involvement were noted. A chest radiograph showed a classic miliary pattern; the diagnosis of tuberculosis was confirmed by sputum culture results that were positive for M. tuberculosis. Bone marrow biopsy was performed; analysis of the biopsy specimen revealed caseating granulomas, but smear and culture of the specimen were negative for mycobacteria. Treatment with isoniazid (200 mg daily), rifampin (450 mg daily), ethambutol (600 mg daily), and pyrazinamide (750 mg daily) was started at that time.

While this regimen was being administered, the patient continued to have fever and other constitutional symptoms for the subsequent month. During that time, analysis of CSF obtained from lumbar puncture revealed a normal protein concentration, and smear and culture of CSF were negative for mycobacteria (table 1; specimen 1). Sputum culture revealed M. tuberculosis resistant to both isoniazid and rifampin. Cycloserine and capreomycin were therefore added to his therapeutic regimen; dosages of isoniazid, ethambutol, and pyrazinamide were increased to 900 mg twice weekly, 1200 mg daily, and 1250 mg daily, respectively. During this new regimen, he had defervescence, and chest radiography revealed clearing. However, in this period, he began to have worsening headache and stiffness of the neck. Analysis of CSF obtained from lumbar punctures performed just before and 4 weeks into the new regimen showed increasing protein concentrations, and results of CSF cultures were positive for M. tuberculosis (table 1; specimens 2 and 3). Progressive enhancement at the basilar meninges was noted by MRI.

The patient was therefore transferred to the National Jewish Medical and Research Center in Denver in May 1998 for management of MDR tuberculosis with escalating symptoms mainly related to CNS involvement. There a revised therapeutic regimen was chosen on the basis of results of in vitro susceptibility testing of isolates from his sputum and CSF. The regimen included intravenous levofoxacin (500 mg/d) and amikacin (1500 mg/d), oral cycloserine (250 mg b.i.d.), ethambutol (1200 mg/d), and pyrazinamide (1250 mg/d). Treatment with isoniazid and rifampin was discontinued. Despite these revisions, his clinical status declined and CSF parameters worsened over the next 3 weeks. Because of apparently inadequate antimycobacterial cov-
oral (pyrazinamide only) doses were administered (table 2).

formed on serum and CSF samples after intrathecal, iv, and
studies of levo−oxacin, amikacin, and pyrazinamide were per-
maya reservoir and lumbar epidural drain. Pharmacokinetic
negative. Minimal complications occurred with use of the Om-
MRI. Results of cultures of all subsequent CSF specimens were
into therapy showed marked improvement (table 1), as did
effects were minor, including insomnia, myalgias, and
arthralgias during the first 1–2 months of therapy. All effects
were ascribed to levo−oxacin and later subsided. Minor hearing
loss was noted after 4 months of treatment with intrathecal
and iv amikacin. The patient returned to Kansas 1 month after
intrathecal therapy was started, receiving intrathecal and iv
therapy and treatment with low doses of prednisone for a total
of 6 months. He continued to receive treatment with oral lev-
ofloxacin, cycloserine, ethambutol, and pyrazinamide and re-
ained clinically well 12 months later.

Discussion. Isoniazid has been the keystone of treatment of
M. tuberculosis meningitis. This agent is highly bactericidal,
and because of its low molecular weight, lack of protein bind-
ing, and lack of charge, it passes readily into the CNS. Survival
rates for patients with M. tuberculosis meningitis reached the
plateau of roughly 70% with the introduction of isoniazid and
have not increased with the addition of newer agents, including
rifampin and pyrazinamide [3]. Agents such as rifampin, strep-
tomycin, and ethambutol have high molecular weights and
complex structures and have been shown to cross the blood-
brain barrier only poorly, resulting in suboptimal concentra-
tions in CSF [1, 3]. Pyrazinamide has a low molecular weight
and is structurally similar to isoniazid; it has been shown to
readily penetrate the CNS and has been theorized to be useful
for treatment of M. tuberculosis meningitis [4, 5]. However, the
therapeutic efficacy of pyrazinamide for meningeal tuberculosis
has not been demonstrated. Mitchison [6] proposed a theory,
which seems to be supported by findings from clinical trials,
that pyrazinamide is active only in the acidic debris in pul-
monary cavitary lesions. Thus, it is plausible that pyrazinamide,
which has minimal activity against M. tuberculosis at neutral
pH, would not be active within the CNS [6, 7].

Hence, CNS disease caused by strains of M. tuberculosis re-
sistant to isoniazid might be anticipated to be difficult to man-

<table>
<thead>
<tr>
<th>Specimen no.</th>
<th>Date (mo/dy)</th>
<th>Drug regimen</th>
<th>Protein level, g/dL</th>
<th>WBC count, cells/mm³</th>
<th>Segmented neutrophils, %</th>
<th>Lymphocytes, %</th>
<th>Results of:</th>
<th>PCR assay for DNA</th>
<th>AFB smear</th>
<th>AFB culture</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1/23/98</td>
<td>INH, Rif, Eth, PZA</td>
<td>77</td>
<td>68</td>
<td>65</td>
<td>22</td>
<td>NA</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>2</td>
<td>3/15/98</td>
<td>INH, Rif, Eth, PZA</td>
<td>192</td>
<td>293</td>
<td>64</td>
<td>33</td>
<td>NA</td>
<td>Negative</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>4/9/98</td>
<td>INH, Eth, PZA, Cyse, Cpm</td>
<td>208</td>
<td>330</td>
<td>71</td>
<td>16</td>
<td>NA</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>5/8/98</td>
<td>INH, Eth, PZA, Cyse, Cpm</td>
<td>278</td>
<td>420</td>
<td>66</td>
<td>31</td>
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<td>Negative</td>
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<tr>
<td>5</td>
<td>5/26/98</td>
<td>−a</td>
<td>87</td>
<td>123</td>
<td>41</td>
<td>48</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

NOTE. Despite revised treatment that resulted in clearing on the chest radiogram and resolution of constitutional symptoms, CSF markers showed progressive deterioration for specimens 2, 3, and 4. However, within 8 days of initiation of intrathecal therapy with amikacin and levo−oxacin, there was significant improvement. AFB, acid-fast bacilli; Cpm, capreomycin; Cyse, cycloserine; Eth, ethambutol; INH, isoniazid; NA, not available; PZA, pyrazinamide; Rif, rifampin.

*a Intrathecal treatment.
Table 2. Pharmacokinetic data and serum and CSF concentrations for amikacin, levofloxacin, and pyrazinamide used as treatment of meningitis caused by multidrug-resistant *Mycobacterium tuberculosis*.

<table>
<thead>
<tr>
<th>Drug (dose), time after administration</th>
<th>Drug concentration, μg/mL, in:</th>
<th>CSF-to-serum concentration ratio, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CSF</td>
<td>Serum</td>
</tr>
<tr>
<td>Levofloxacin (1 mg intrathecally)</td>
<td></td>
<td>NA</td>
</tr>
<tr>
<td>2 h</td>
<td>Mean, 0.38^a</td>
<td>NA</td>
</tr>
<tr>
<td>6 h</td>
<td>Mean, 0.57^b</td>
<td>NA</td>
</tr>
<tr>
<td>Levofloxacin (1.5 mg intrathecally)</td>
<td>2 h</td>
<td>1.64^c</td>
</tr>
<tr>
<td>Levofloxacin (500 mg iv)</td>
<td>2 h</td>
<td>1.99</td>
</tr>
<tr>
<td></td>
<td>6 h</td>
<td>1.65</td>
</tr>
<tr>
<td>Levofloxacin (750 mg iv)</td>
<td>0.5 h</td>
<td>1.05</td>
</tr>
<tr>
<td></td>
<td>1.5 h</td>
<td>8.60</td>
</tr>
<tr>
<td></td>
<td>4.5 h</td>
<td>1.88</td>
</tr>
<tr>
<td></td>
<td>11.5 h</td>
<td>0.65</td>
</tr>
<tr>
<td>Amikacin (5 mg intrathecally)</td>
<td>2 h</td>
<td>Mean, 4.26^a</td>
</tr>
<tr>
<td></td>
<td>6 h</td>
<td>Mean, 13.25^f</td>
</tr>
<tr>
<td>Amikacin (1200 mg iv [22 mg/kg])</td>
<td>2 h</td>
<td>9.8</td>
</tr>
<tr>
<td></td>
<td>6 h</td>
<td>10.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrazinamide (1250 mg orally [24 mg/kg])</td>
<td>2 h</td>
<td>63.37</td>
</tr>
<tr>
<td></td>
<td>3 h</td>
<td>40.0</td>
</tr>
<tr>
<td></td>
<td>10 h</td>
<td>23.39</td>
</tr>
</tbody>
</table>

**NOTE.** NA, not available.

^a Seven measurements; range, 0.21–0.53 μg/mL.

^b Three measurements; range, 0.51–0.6 μg/mL.

^c One measurement.

^d NA because of improper timing.

^e Five measurements; range, 2.1–8.3 μg/mL.

^f Four measurements; range, 3.0–20.9 μg/mL.

^g Peak calculated level, 49 μg/mL.

age. However, limited data on meningitis caused by *M. tuberculosis* resistant only to isoniazid suggest that cure may be achieved with regimens that include rifampin [3]. *M. tuberculosis* meningitis or tuberculosis caused by *M. tuberculosis* strains resistant to both isoniazid and rifampin, and often other drugs as well, were noted to be highly problematic and often lethal in the MDR tuberculosis epidemics in persons with AIDS in New York City [8].

The current case, however, offers some unique insight into the treatment of meningitis caused by MDR *M. tuberculosis*. The florid CNS deterioration during resolution of the pulmonary and miliary disease and constitutional symptoms is a dramatic demonstration that the CNS can be regarded as a unique therapeutic compartment. In addition, this deterioration during pyrazinamide treatment provides circumstantial evidence that this drug may not be active against meningitis, even with adequate dosing. Although the pyrazinamide dosages we administered were below standard recommendations, the maximum serum concentration of the drug was within the desired range of 20–60 μg/mL, as was the CSF concentration [1] (table 2). The tolerability and efficacy of intrathecal levofloxacin and amikacin also suggest the potential utility of this strategy in the management of other cases of drug-resistant tuberculosis involving the CNS.

We used therapeutic drug monitoring to guide therapy with intrathecal, iv, and oral routes of these medications. CSF concentrations following intrathecal administration of both amikacin and levofloxacin were lower than expected. This finding
may have been caused by inconsistencies in the diffusion of the drug from the Ommaya reservoir, improper timing of sample collection, or more rapid CSF turnover than anticipated. Diffusion inconsistencies may have also played a role in the wide range of amikacin concentrations achieved in the CSF after intrathecal administration.

It is important to note that although the CSF concentrations of amikacin and levofloxacin after intrathecal administration were lower than expected, they usually exceeded the MIC of each drug (amikacin MIC, 16 μg/mL; levofloxacin MIC, 0.25 μg/mL). These concentrations may have been sufficient to provide clinical improvement in our patient.

For our patient, the starting dose of intrathecal levofloxacin was 0.5 mg (approximately one-third to one-half of our target dose of 0.96–1.2 mg), which we had hoped would achieve CSF concentrations near 8–10 μg/mL. The initial dose was increased from 0.5 mg to 1 mg on the basis of patient’s tolerance. One milligram of intrathecal levofloxacin produced concentrations lower than our expected concentration range (table 2). This finding, and the patient’s continued tolerance of therapy, prompted us to increase the dose to 1.5 mg. A higher CSF concentration was achieved, which was still lower than the range we expected. Because only one CSF sample was obtained after this dose was administered and there are no previously reported data on intrathecally administered fluoroquinolones, we cannot speculate if higher concentrations were achieved at a later time. The dose was not increased further because the patient was beginning to show signs of improvement and was experiencing mild adverse effects that were attributed to levofloxacin.

CSF-to-serum concentration ratios of amikacin and levofloxacin following iv doses in our case were consistent with, or higher than, previously reported data (table 2) [1, 10]. One measurement of CSF amikacin concentration that was much higher than expected may have been caused in part by the relatively large dose of amikacin administered (22 mg/kg), which allowed more amikacin to penetrate the blood-brain barrier; meningeal inflammation; and residual amikacin from the intrathecal dose administered the day before. Meningeal inflammation and residual intrathecal drug may also account for the higher than expected CSF-to-serum concentration ratio following iv levofloxacin administration.

Although iv dosing of both levofloxacin and amikacin did provide adequate CSF concentrations, we were reluctant to discontinue intrathecal therapy (in particular, with levofloxacin) for a variety of reasons. First, the patient’s condition had deteriorated clinically, even though he had been treated with oral levofloxacin, which theoretically achieves the same serum and CSF concentrations as iv levofloxacin [10]. Second, although recent reports indicate that the fluoroquinolones should continue to penetrate the blood-brain barrier as meningeal inflammation decreases, we were concerned that this may not be the case with levofloxacin and did not want to risk exposing the organisms in the CSF to monotherapy with intrathecal amikacin [9, 10]. To our knowledge, this is the first reported case of meningitis due to MDR M. tuberculosis that was refractory to systemic therapy but was treated successfully with intrathecal levofloxacin and amikacin.

References