Pulmonary Disposition of Moxalactam*

A. C. Braude, M.D., F.C.C.P.;† R. D. Cohen, M.D.;‡
J. L. Penner, Ph.D.;§ M. A. Preston, M.Sc.;‖ and
A. S. Rebuck, M.D., F.C.C.P.¶

Moxalactam is a new synthetic oxa-beta-lactam antibiotic with a broad spectrum of activity against Gram-positive and Gram-negative aerobic and anaerobic bacteria. It has proven clinical efficacy in pneumonia caused by a variety of infecting organisms. Therapeutic concentrations of moxalactam are achieved in most body tissues and fluids, including pleural fluid and sputum. However, assessment of the adequacy of lung tissue levels in pneumonia requires the sampling of material at an alveolar level. We performed bronchoalveolar lavage (BAL) in 13 patients one hour after they had been given moxalactam intravenously in doses ranging from 250 mg to 2 g. Absolute alveolar drug levels ranged from <1 to 6 mg/l, and serum levels from 5 to 50 μg/ml. When expressed per micromole of creatinine, there was a significant relationship (r = 0.85; p<0.01) between serum and alveolar moxalactam levels in those patients in whom the drug concentration could be quantified accurately in BAL fluid.

Moxalactam is a synthetic third generation cephalosporin with a broad spectrum of activity against Gram-positive and Gram-negative aerobic and anaerobic bacteria. It has proven clinical efficacy in lower respiratory tract infections caused by a variety of infecting organisms and has been used successfully in the treatment of patients with infections caused by susceptible strains of Pseudomonas aeruginosa and Serratia marcescens.¹

Therapeutic concentrations of moxalactam are achieved in most body tissues and fluids including pleural fluid and sputum.²,³ However, evaluation of the adequacy of lung tissue levels in lower respiratory infections necessitates the sampling of material at an alveolar level. With the advent of the technique of bronchoalveolar lavage (BAL), it has become possible to sample fluid and cells lining the alveolar acini.⁴ Previous workers have used bronchoalveolar lavage (BAL) to compare the lung and serum levels of such endogenous proteins as alpha-1-macroglobulin and alpha-antitrypsin, finding that a one-to-one correlation between lung and serum does not necessarily exist.⁵ Consequently, the pulmonary concentration of chemicals cannot be assumed from their serum concentrations.

To quantify the penetration of moxalactam into the lung at an alveolar level, we obtained both bronchoalveolar lavage fluid and blood from patients following an intravenous dose of moxalactam.

METHODS

Bronchoalveolar lavage was performed in 13 patients one hour after they had received moxalactam intravenously in doses ranging from 250 mg to 2 g. The drug was reconstituted, diluted in 50 ml of normal saline solution and infused immediately over ten minutes.

Procedure

After the potential hazards of bronchoscopy and topical anesthesia were explained, signed informed consent was obtained from all patients. They were given 10 mg diazepam as premedication and were administered oxygen throughout the bronchoscopy procedure. The ECG was monitored continuously. After routine inspection of the respiratory tract and aspiration of tracheobronchial secretions, the bronchoscope tip was wedged into a subsegmental bronchus of the lingula or right middle lobe. Lavage was performed with 100 ml of sterile normal saline solution, divided into five equal aliquots. After injection of the saline solution, the fluid was suctioned with a negative pressure of 50 to 100 mm Hg. The pooled sample was collected in a sterile sputum trap. Blood was drawn simultaneously for moxalactam and creatinine assay.

Harvested lavage fluid was filtered to remove mucus, and the cells removed by centrifugation at 500 g for ten minutes. The supernate was again filtered to remove any residual cellular debris. Serum was separated by centrifugation and both the serum and BAL supernate frozen at −20°C. Prior to assay, the supernate was concentrated in a freeze dryer and the powder resuspended in distilled water to yield a 30 times concentration over the original volume. Moxalactam concentrations in serum and BAL were determined by a microbiologic agar diffusion assay.⁶ Standard solutions of moxalactam were prepared in phosphate buffer (pH 6.0). Plates (1.8×24.3×24.3 cm) were seeded with 100 ml of antibiotic medium 1 containing 0.1 ml of bacterial inoculum. The inoculum was prepared by combining 10 ml of overnight broth culture of Providencia stuartii ATCC 33770, with 40 ml of fresh broth (antibiotic medium 3). Thirty microliter aliquots of moxalactam standard solutions, serum samples, and BAL samples were added to wells (6 mm diameter) of the hardened agar. After overnight incubation at 30°C, the diameters of the zones of inhibition were measured to the nearest 0.1 mm with Vernier calipers. Standard curves were determined for each set of patient's samples and obtained by plotting the average zone sizes against the logs of standard concentrations. The coefficient of variation for the microbiological assay was 6.7 percent.

The concentrated BAL fluid creatinine level was measured by the automated Jaffe reaction, and serum creatinine by the automated SMA 12 assay system.

*From the Division of Respiratory Medicine, Toronto Western Hospital and Department of Microbiology, University of Toronto, Toronto, Canada.
†Staff Physician, Division of Respiratory Medicine.
‡Respiratory Research Fellow.
§Professor of Microbiology.
‖Doctoral Student in Microbiology.
¶Professor of Medicine.

Manuscript received February 1; revision accepted June 19.
Reprint requests: Dr. Rebuck, Suite 204, Edith Cavell Wing, Toronto Western Hospital, Toronto, Ontario, Canada M5T 2B8

CHEST / 86 / 6 / DECEMBER, 1984 881
Table 1—Patient Summary

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Moxalactam Dose</th>
<th>Serum Creatinine (µmol/L)</th>
<th>BAL Creatinine (µmol/L)</th>
<th>Moxalactam Levels (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>82</td>
<td>M</td>
<td>Aspiration pneumonia</td>
<td>250 mg</td>
<td>103</td>
<td>29</td>
<td>8</td>
</tr>
<tr>
<td>2</td>
<td>65</td>
<td>M</td>
<td>Bronchial carcinoma</td>
<td>500 mg</td>
<td>70</td>
<td>34</td>
<td>12</td>
</tr>
<tr>
<td>3</td>
<td>47</td>
<td>M</td>
<td>Pulmonary TB</td>
<td>750 mg</td>
<td>57</td>
<td>25</td>
<td>9</td>
</tr>
<tr>
<td>4</td>
<td>19</td>
<td>M</td>
<td>Sarcoaidosis</td>
<td>1.5 g</td>
<td>87</td>
<td>33</td>
<td>19</td>
</tr>
<tr>
<td>5</td>
<td>60</td>
<td>M</td>
<td>Idiopathic pulmonary fibrosis</td>
<td>1.5 g</td>
<td>91</td>
<td>27</td>
<td>40</td>
</tr>
<tr>
<td>6</td>
<td>63</td>
<td>M</td>
<td>Idiopathic pulmonary fibrosis</td>
<td>1.5 g</td>
<td>98</td>
<td>30</td>
<td>19</td>
</tr>
<tr>
<td>7</td>
<td>58</td>
<td>M</td>
<td>Bronchiectasis</td>
<td>2 g</td>
<td>89</td>
<td>31</td>
<td>33</td>
</tr>
<tr>
<td>8</td>
<td>57</td>
<td>F</td>
<td>Scleroderma</td>
<td>2 g</td>
<td>74</td>
<td>23</td>
<td>50</td>
</tr>
<tr>
<td>9</td>
<td>71</td>
<td>M</td>
<td>Pneumonia</td>
<td>750 mg</td>
<td>99</td>
<td>23</td>
<td>13</td>
</tr>
<tr>
<td>10</td>
<td>58</td>
<td>M</td>
<td>Bronchiectasis</td>
<td>1.5 g</td>
<td>108</td>
<td>38</td>
<td>11</td>
</tr>
<tr>
<td>11</td>
<td>35</td>
<td>F</td>
<td>Pneumonia</td>
<td>500 mg</td>
<td>70</td>
<td>30</td>
<td>11</td>
</tr>
<tr>
<td>12</td>
<td>64</td>
<td>M</td>
<td>Pneumonia</td>
<td>250 mg</td>
<td>79</td>
<td>47</td>
<td>8</td>
</tr>
<tr>
<td>13</td>
<td>19</td>
<td>F</td>
<td>Marfans syndrome cough</td>
<td>1 g</td>
<td>79</td>
<td>22</td>
<td>15</td>
</tr>
</tbody>
</table>

RESULTS

Moxalactam concentrations in blood and BAL fluid are given in Table 1. In order to correct for variations in the quantity of lung fluid obtained by BAL, creatinine concentrations in blood and fluid were used to express the moxalactam levels; the range of serum creatinines was 57 to 108 µmol/L and the range of BAL fluid creatinines was 22 to 47 µmol/Liter. There was a significant correlation between blood and BAL fluid moxalactam concentrations (r = .85; p < 0.01), when each was expressed per micromole of creatinine, in the eight patients in whom the drug could be quantified accurately (Fig 1). In a further five patients, although the drug was detected in BAL fluid, it could not be quantified accurately because the levels were below the resolution of the assay method.

FIGURE 1. Serum and BAL moxalactam levels expressed as a function of creatinine concentration.

DISCUSSION

The measurement of serum levels is a fundamental principle of good antibiotic therapy, both to ensure that levels in excess of the MIC of the infecting organism had been achieved and that toxic levels are not reached. However, with the exception of infections causing septicemia, the serum level is only an indirect guide to the tissue concentration of antibiotic, and with few exceptions, such as the measurement of CSF antibiotic concentration in meningitis, at best, only an assumption can be made as to whether local tissue MIC has been achieved. The penetration of chemicals from the serum into tissues is variable, and may depend on local conditions such as the presence of inflammation and also on the intrinsic barrier properties of the organ or tissue concerned. It has been shown recently that the steroid methylprednisolone penetrates the alveolus significantly better than prednisone,7 so that even within a class of pharmacologic agents, assumptions of tissue penetration may be unreliable. Moxalactam has been shown to penetrate both pleural fluid and sputum,8,9 but levels within the alveolus have not been reported.

Bronchoalveolar lavage is a well-established technique allowing the sampling of cells and fluid lining the alveolar epithelium and distal bronchial tree. This technique has been used previously to study the concentrations of both endogenous and exogenous chemicals in the lung. Because saline solution is used as the lavage fluid, a dilution factor has to be accounted for when comparing BAL and serum concentrations.
In the present study, creatinine was used as a marker. It has a molecular weight of 113, of the same order of magnitude as moxalactam (564), can be measured readily by standard analytical techniques, and has been used previously in the comparison of lung and serum drug levels. However, in the clinical setting, collection of bronchial secretions alone for the monitoring of antibiotic penetration into the respiratory tract is difficult because of the pooling of respiratory secretions in the trachea. This pooling effect leads to an automatic averaging of antibiotic concentrations, which may be difficult to correlate with peak blood levels.

This study was undertaken to quantify the penetration of moxalactam into the alveoli, and to demonstrate a possible relationship between alveolar and serum levels. It was found that increasing levels of serum moxalactam were associated with increasing alveolar levels, when both were expressed per micromole of creatinine. However, as this study was performed one hour after patients had received a single dose, these levels do not represent steady-state pharmacokinetics. Although it is impossible to measure bactericidal effect at the site of pulmonary infection, the present study has demonstrated as well by virtue of its employing a microbiologic assay, that moxalactam retains its efficacy in alveolar secretions. In five patients studied, moxalactam was detectable in lavage fluid, but at a level below that of accurate resolution by the assay method. These results have been expressed as less than 1 µg/ml, and cannot be compared directly to specific serum levels. These data suggest that moxalactam, like tobramycin, penetrates the alveolus in a concentration proportional to the serum level.

REFERENCES