We treated a 23-year-old aboriginal woman with drug-resistant pulmonary tuberculosis (TB). She experienced intolerance to her oral anti-TB medications, had subtherapeutic drug levels, and failed to respond to treatment. She then was effectively treated with percutaneous gastrojejunostomy tube (PGJT) administration of drugs. We present our data on the serum drug levels of rifampin, para-aminosalicylic acid, and levofloxacin after PGJT administration, and compare these values to published levels for oral administration of these drugs. In our patient, serum drug levels peaked and began to decline earlier than in the published data for oral administration of the same drugs.

(CHEST 2002; 121:281–284)

Key words: levofloxacin; para-aminosalicylic acid; percutaneous gastrojejunostomy tube; pharmacokinetics; rifampin; tuberculosis

We describe a female patient with drug-resistant pulmonary tuberculosis (TB) whose treatment failed while receiving directly observed therapy (DOT). This resulted from covert vomiting of a large percentage of drug doses, resulting in subtherapeutic serum drug levels. Percutaneous gastrojejunostomy tube (PGJT) drug delivery achieved therapeutic serum drug levels and was associated with a clinical success. To our knowledge, this is the first published report of TB drug treatment administered via a PGJT.

Case Report

In 1990, a 65-kg aboriginal woman received a diagnosis of fully drug-susceptible, culture-positive pulmonary TB. In spite of DOT at home in a remote northern community, drug-resistant TB developed with resistance to isoniazid, streptomycin, and pyrazinamide. After treatment failure with medication, she responded to surgical resection. She relapsed in 1995 and again had treatment failure with DOT. Because of persistent treatment failure with DOT, she was admitted to the hospital for investigation of treatment failure.

Blood was collected in plain red-top vacuum tubes for the determination of serum drug levels. After centrifugation, the serum was harvested and frozen, and then shipped on dry ice to the Infectious Disease Pharmacokinetics Laboratory at National Jewish Medical and Research Center, Denver, CO. Ethionamide, ofloxacin, para-aminosalicylic acid (PAS), and rifampin levels were determined using validated high-performance liquid chromatography assays; ethambutol levels were determined using a validated gas chromatography-mass spectrometry assay. All assays complied with the guidelines of the College of American Pathologists. The assay results revealed subtherapeutic serum drug levels with the patient receiving oral medications (Table 1). Normal serum carotene, vitamin B₁₂, and folate levels, and a normal xylose absorption test result indicated that her GI absorption was normal. The nursing staff reported that the patient predictably vomited up the medication within 30 min of DOT. A trial of IV rifampin and amikacin was briefly attempted, but was discontinued because of the development of ototoxicity. After 30 doses of amikacin, 11 mg/kg, hearing loss developed. The audiogram showed a hearing threshold of 70 decibels consistent with amikacin-induced toxicity.

A PGJT then was placed (under fluoroscopic visualization) to bypass the stomach and thereby avoid the problem of vomiting. Rifampin, 600 mg, suspended in simple syrup; ethambutol, 1,200 mg, comprised of crushed 400-mg tablets; levofloxacin, 750 mg, comprised of crushed 500-mg tablets; and PAS, 8.7 g, comprised of crushed 500-mg tablets, were administered via the PGJT. The desired serum drug levels were achieved via this route. Furthermore, serum levels had peaked and were already in decline by 2 h after administration.

After 10 weeks of PGJT-administered treatment, sputum smear and culture findings were negative. She was discharged from the hospital, and therapy was continued at home via the PGJT. Treatment was completed successfully, and she remains well. Culture findings were negative 18 months later.

Table 1—Serum Drug Levels

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Therapeutic Range,* µg/mL</th>
<th>Levels 2 h After Oral Administration, µg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifampin</td>
<td>8–24</td>
<td>6.25</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>2–6</td>
<td>0.84</td>
</tr>
<tr>
<td>Ethionamide</td>
<td>1.0–5.0</td>
<td>0.77</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>8.0–12.0</td>
<td>Trace</td>
</tr>
</tbody>
</table>

*Normal ranges are from the National Jewish Medical and Research Center, Denver, CO.
Our patient developed drug-resistant pulmonary TB and failed treatment while receiving DOT. This resulted from covert vomiting of a large percentage of drug doses, resulting in subtherapeutic serum drug levels. PGJT drug delivery achieved therapeutic serum drug levels and was associated with a clinical success.

There are many reports regarding the pharmacokinetics of orally administered TB drugs. The usual recommended sampling time of serum drug levels for anti-TB medications is 2 h after administration, or 1 to 2 h for PAS tablets. The reason for these recommendations is that peak serum levels are usually achieved at 1 to 2 h after oral administration, after which time the levels drop off. We did not find any published reports of the pharmacokinetics of anti-TB medications delivered via a PGJT. When drugs are administered via a PGJT, they are crushed and delivered directly into the jejunum. It could be expected that peak serum levels might occur earlier via this method, when compared to oral administration. We therefore took serum levels earlier than the recommended times, as well as at the recommended times. We compared our pharmacokinetics data for rifampin, levofloxacin, and PAS tablets to published serum levels after oral absorption of these

**Figure 1.** Serum rifampin levels from 1 to 4 h after administration via a PGJT (circles) compared to published oral administration levels (squares). Serum levels after administration via a PGJT peaked at 1.5 h compared to 2 to 3 h with oral administration.

**Figure 2.** Serum PAS levels from 1 to 4 h after administration via PGJT (circles) compared to published oral administration levels (squares). Serum levels after administration via a PGJT peaked at 1 h compared to 2 h with oral administration of PAS tablets.
drugs (Figs 1–3). Because of the patient’s frequent vomiting, her serum levels after oral administration did not reflect the true oral absorption of the drugs and were therefore not useful for comparison. As Figure 1 shows, the peak serum level for rifampin was higher and occurred earlier than that published for oral administration of the same dose (600 mg).3,5 For PAS, the dose our patient received, 8.7 g in tablet form, was greater than that in the oral absorption study (4 to 6 g in tablet form) [W.W. Yew, MD; personal communication; January 2001],5 and we achieved higher serum levels (Fig 2). However, it is notable that serum level peaked and began to decline earlier than for oral absorption.

The altered pharmacokinetics of the TB medications following PGJT administration are important because of the clinical implications. If rifampin and PAS are delivered via a PGJT, and serum levels are desired, samples should be drawn earlier than the times recommended for oral dosing.1,2,6 Interestingly, our findings for levofloxacin were different than observed for the other TB drugs. We used a dose of 750 mg with our patient in order to achieve a higher peak concentration: the minimal inhibitory concentration ratio against Mycobacterium tuberculosis. This dose was higher than the 500 mg used in published data7 with which we compared our results, and explains our higher serum levels. However, the elimination slopes of the two curves were similar. Because levofloxacin is rapidly absorbed following oral administration (time to peak is generally 60 to 90 min), PGJT administration did not shorten the time to peak levels.8–10 These data indicate that if one wishes to determine the actual peak level of the TB drugs after PGJT administration, an earlier sampling time should be employed.

To our knowledge, this is the first published report of TB drug treatment administered via a PGJT. This method was successful in achieving adequate drug serum levels and was well tolerated by the patient for an extended period of time. It was associated with a bacteriological, radiographic, and clinical cure when oral intolerance due to persistent vomiting resulted in treatment failure of DOT.

**Conclusion**

PGJT administration of anti-TB medication was effective when DOT oral therapy was persistently unsuccessful. The desired serum levels of anti-TB medications were obtainable via PGJT administration. For rifampin and PAS, peak serum levels occurred earlier via PGJT administration than published levels for the oral route. This should be considered when measuring peak serum levels of drugs administered via a PGJT.

**References**

Management of Tension Pneumatocele With High-Frequency Oscillatory Ventilation*  

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We report the successful application of high-frequency oscillatory ventilation in a patient with tension pneumatocele (TP). The proposed check-valve mechanism for the development of pneumatoceles predicts that positive-pressure ventilation could lead to distension of these airspaces and formation of TPs. Therefore, high-frequency ventilation could be more applicable in conditions, such as massive air leak due to bronchopleural fistula, that are difficult to manage by conventional ventilator modes.

(CHEST 2002; 121:284–286)

Key words: bronchopleural fistula; high-frequency oscillatory ventilation; pneumatocele; Streptococcus pneumoniae

Abbreviations: BPF = bronchopleural fistula; CMV = conventional mechanical ventilation; CXR = chest radiograph; FIO2 = fraction of inspired oxygen; HFOV = high-frequency oscillatory ventilation; MAP = mean airway pressure; RR = respiratory rate; RUL = right upper lobe; TP = tension pneumatocele

We present a case of severe pneumonia, enlarging pneumatoceles, and pneumothorax in a patient receiving conventional mechanical ventilation (CMV). Pneumatoceles decreased after the application of high-frequency oscillatory ventilation (HFOV).

CASE REPORT

A 3-year-old girl had a temperature of up to 40°C, cough, and rhinorrhea. She had had no history of specific medical illnesses. Four days after initial symptoms appeared, poor appetite, hyperpnea, and dyspnea developed. She was then admitted to a hospital. A chest radiograph (CXR) on the first day disclosed right upper lobe (RUL) pneumonia and pleural effusion (Fig 1, top left). A normal WBC count (5,900/μL) with severe left shift (39% band form) was noted. Empirical antibiotics were administered, but the symptoms still progressed. Disseminated intravascular coagulation was suspected by thrombocytopenia and coagulopathy. Hypotension and hypoxemia developed soon after. She was intubated, and treatment with inotropic medications was initiated, along with ventilatory support with time-cycled pressure control. A throat swab culture, blood culture, and pleural fluid studies were performed. Results of these microbiological studies showed positive pneumococcal antigen in the pleural effusion. Culture findings from all other sites were negative. A chest tube was inserted due to the clinical diagnosis of complicated parapneumonic effusion; pleural effusion data included WBC, 1,512/μL; and lactate dehydrogenase, 1,779 U/L. Antibiotics were switched to ceftriaxone, erythromycin, and vancomycin on the next day.

In the days that followed, hemodynamics and oxygenation became stabilized, yet fever and leukocytosis persisted. Serial CXRs revealed RUL consolidation with multiple, progressively enlarging pneumatoceles. One week later, the chest tube was removed, but pneumothorax on the same side developed thereafter (Fig 1, top right). After reinsertion of a new chest tube, massive air leak was noted. Low-pressure suction (10 cm H2O) through the chest tube was applied. On the next day (day 9 of hospitalization), she was transferred to our hospital. On hospital admission, she appeared lethargic and confused. Her body weight was 12 kg. Vital signs were as follows: body temperature, 38°C; heart rate, 160 beats/min; BP, 94/76 mm Hg; and respiratory rate (RR), 30 breaths/min. The patient received time-cycled pressure control ventilation, with settings of peak inspiratory pressure control. A throat swab culture, blood culture, and pleural fluid studies were performed. Results of these microbiological studies showed positive pneumococcal antigen in the pleural fluid. Culture findings from all other sites were negative. A chest tube was inserted due to the clinical diagnosis of complicated parapneumonic effusion; pleural effusion data included WBC, 1,512/μL; and lactate dehydrogenase, 1,779 U/L. Antibiotics were switched to ceftriaxone, erythromycin, and vancomycin on the next day.

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On day 10, because of massive air leak and persistence of poor oxygenation with CMV, HFOV (model 3100A; SensorMedics; Yorba Linda, CA) was applied. Initial settings were as follows: peak end-expiratory pressure, 47 cm H2O; RR, 30 breaths/min; and fraction of inspired oxygen (FiO2), 100%. Mean airway pressure (MAP) was lowered from 25 cm H2O on day 11 (day 2 of HFOV) to 14 cm H2O on day 14 (day 5 of HFOV), the size of RUL pneumatocele decreased on serial CXRs (Fig 1, bottom left and bottom right). However, fever, leukocytosis, and mild air leak persisted. Nevertheless, weaning of HFOV proceeded without difficulty. After the patient was withdrawn from sedation and paralysis, spontaneous breathing during HFOV was allowed, but the symptoms still progressed. Disseminated intravascular coagulation was suspected by thrombocytopenia and coagulopathy. Hypotension and hypoxemia developed soon after. She was intubated, and treatment with inotropic medications was initiated, along with ventilatory support with time-cycled pressure control. A throat swab culture, blood culture, and pleural fluid studies were performed. Results of these microbiological studies showed positive pneumococcal antigen in the pleural fluid. Culture findings from all other sites were negative. A chest tube was inserted due to the clinical diagnosis of complicated parapneumonic effusion; pleural effusion data included WBC, 1,512/μL; and lactate dehydrogenase, 1,779 U/L. Antibiotics were switched to ceftriaxone, erythromycin, and vancomycin on the next day.

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