

CASE REPORT

Intravenous Streptomycin for Treatment of *Mycobacterium tuberculosis* Meningitis in an Infant

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Although tuberculous meningitis is rarely encountered in the United States, clinicians need to have a high index of suspicion for this disease. Intramuscular streptomycin is usually administered as part of a four-drug antituberculous regimen. However, we describe an 8-month-old girl who was diagnosed with *Mycobacterium tuberculosis* meningitis and received streptomycin intravenously. This route was chosen to avoid daily intramuscular injections because the infant had poor lean muscle mass. The patient's regimen consisted of isoniazid 15 mg/kg/day, rifampin 20 mg/kg/day, and pyrazinamide 40 mg/kg/day by nasogastric tube, and intravenous streptomycin 15 mg/kg twice/day administered using a controlled-rate infusion pump. The *M. tuberculosis* strain was subsequently found to be susceptible to all four antituberculous drugs. Her condition improved, and no drug toxicities were observed during her treatment course; isoniazid and rifampin were continued after discharge. The patient was readmitted 1 month later for mental status changes and right-sided weakness. Magnetic resonance scan of the brain revealed numerous solid and ring-enhancing hypointense tuberculomas in the suprasellar cistern, left medial temporal lobe, and brainstem, with significant secondary vasogenic edema as the cause of her symptoms. Although treatment failure was not suspected, cerebrospinal fluid and gastric cultures were tested; all were negative for *M. tuberculosis*. Dexamethasone was started for treatment of the focalized cerebral edema, presumably occurring from the breakdown of existing tuberculomas, and the patient rapidly improved. She was discharged and continued to receive oral antituberculous therapy for a total of 12 months. At her 1-year follow-up visit, the patient had recovered fully and had no apparent neurologic, otologic, or developmental deficits. The safe and effective use of intravenous streptomycin in this infant suggests that this route of administration may be an alternative to intramuscular streptomycin.

Key Words: tuberculosis, *Mycobacterium tuberculosis*, pediatric, tuberculous meningitis, streptomycin, intravenous.

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Tuberculosis is a serious public health problem in the United States and abroad. Although tuberculous meningitis is now rare in the United States, clinicians need to have a high index of suspicion for this disease. Prompt and adequate treatment is critical to avoid

complications. For several decades, intramuscular streptomycin has been an important component of the initial quadruple-drug regimen for this serious complication of tuberculosis. We describe an 8-month-old infant who was diagnosed with tuberculous meningitis

and successfully treated with a four-drug antituberculous regimen, including streptomycin; however, streptomycin was administered intravenously instead of intramuscularly.

Case Report

An 8-month-old girl of Southeast Asian heritage born in the United States was brought to our tertiary care pediatric hospital with fever, irritability, and cervical lymphadenopathy. She had a history of weight loss and failure to thrive over the previous 4 months. Three weeks earlier, she had decreased activity, increased irritability, a low-grade fever, and an enlarged right cervical lymph node. Her symptoms persisted despite a 2-week course of oral amoxicillin for presumed bacterial lymphadenitis.

Physical examination revealed a bulging anterior fontanel and bilateral nontender cervical adenopathy, but otherwise without focal findings. The patient had an elevated peripheral white blood cell count of $21.2 \times 10^3/\text{mm}^3$ and thrombocytosis (platelet count $534 \times 10^3/\text{mm}^3$). A chest radiograph showed diffuse consolidation of the right middle and lower lobes and rounded areas of low density within the right midlung zone. Computed tomography (CT) scans of her head revealed dilation of the third ventricle and temporal horns, consistent with hydrocephalus, which is a common complication of tuberculous meningitis. A CT scan of her neck, chest, and abdomen uncovered an 18-mm subcarinal lymph node with characteristic central necrosis, hypodense lesions in the spleen, and free fluid in the abdomen—findings that are all suggestive of systemic mycobacterial dissemination. Analysis of the patient's cerebral spinal fluid (CSF) revealed a glucose level less than 20 mg/dl, protein 562 mg/dl (normal < 20 mg/dl), 34 red blood cells/mm³, and 465 white blood cells/mm³

(normal < 20 white blood cells/mm³). Both CSF and blood were obtained for aerobic bacterial cultures; results were ultimately reported as negative.

Initial findings were suggestive of disseminated *Mycobacterium tuberculosis* infection. Gastric aspirates, bronchopulmonary lavage, and a lymph node biopsy were obtained for acid-fast bacilli (AFB) culture, and quadruple antituberculous therapy was begun. Acid-fast bacilli were seen on all smears and were later confirmed as *M. tuberculosis* by DNA probe from smear and culture. Consistent with this finding, lymph node biopsy revealed necrotizing granulomas. A tuberculin skin test revealed a 12-mm induration. Testing for human immunodeficiency virus was negative.

Treatment was started with isoniazid 15 mg/kg/day, rifampin 20 mg/kg/day, and pyrazinamide 40 mg/kg/day by nasogastric tube. Streptomycin was chosen as the fourth drug over ethambutol in accordance with the current recommendations of the American Academy of Pediatrics.¹ This preference for streptomycin is based on ethambutol's bacteriostatic activity against *M. tuberculosis*; in addition, the patient was too young to participate in vision assessments for monitoring of ethambutol-related ocular toxicity. Due to her poor lean muscle mass, to avoid daily intramuscular injections, streptomycin 15 mg/kg was administered intravenously as a 1-hour infusion twice/day for 5 weeks. The *M. tuberculosis* isolate was subsequently found to be susceptible to pyrazinamide, streptomycin, isoniazid, rifampin, and ethambutol.

Steady-state 30-minute, random, and trough streptomycin levels were determined by using high-performance liquid chromatography. The peak concentration, measured 30 minutes after a 1-hour infusion, was 20.3 µg/ml. A random level measured 4.5 hours after the end of the infusion was 1.4 µg/ml, and a trough level measured 1 hour before the next dose was less than 1 µg/ml was. We extrapolated the patient's elimination rate constant to be 0.669 hour⁻¹, elimination half-life 1.04 hour, volume of distribution 0.38 L/kg, peak concentration 28.4 µg/ml, and trough concentration 0 µg/ml using a first-order single-compartment pharmacokinetic model.

To monitor for nephrotoxicity, blood urea nitrogen and serum creatinine concentrations were measured twice/week, which remained within their normal ranges throughout the 5-week streptomycin course. To monitor for possible ototoxicity, a brain auditory evoked-

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response examination was performed; results were normal at the conclusion of streptomycin therapy. The patient's condition improved, and results of gastric and stool cultures were negative for AFB after 9 days. Her treatment was deemed successful, and she was discharged home 2 months after admission, still receiving rifampin and isoniazid by gastric tube.

One month after discharge, the infant was brought back to the hospital with marked irritability and weakness of her right arm and leg. Magnetic resonance scan of the brain revealed numerous solid and ring-enhancing hypointense tuberculomas in the suprasellar cistern, left medial temporal lobe, and brainstem associated with significant vasogenic edema. Repeat gastric and CSF AFB stains and cultures were negative. Pyrazinamide 40 mg/kg/day by gastric tube was restarted, and both isoniazid and rifampin were continued as treatment failure was not suspected. Given that her new symptoms were most consistent with focalized cerebral edema from the breakdown of existing tuberculomas, intravenous dexamethasone 0.2 mg/kg twice/day was begun.² The patient rapidly improved, regaining mobility and strength in her left arm and leg and was discharged home within 1 week. Oral dexamethasone was weaned slowly over several weeks. The patient completed 12 months of therapy that included 5 weeks of streptomycin, 10 months of pyrazinamide, and 12 months of isoniazid and rifampin. Her clinical condition remained stable, with no apparent neurologic or developmental deficits.

Discussion

This infant was diagnosed with *M. tuberculosis* meningitis and was successfully and safely treated with a regimen that included intravenous streptomycin. Although the use of intravenous streptomycin was reported as early as 1946, since that time very few published reports have documented this route of administration in either children or adults requiring antituberculous therapy,³ and the intramuscular route became preferred.⁴⁻⁶ As controlled-rate infusion pumps are now routinely used, streptomycin can be administered intravenously, mimicking the pharmacokinetic profile of intramuscular injections while avoiding the unnecessary pain of this route.⁷

We could not identify any infant-specific intravenous streptomycin dosing studies for *M. tuberculosis* treatment; thus, we used an online

pediatric dosing recommendation: streptomycin 15 mg/kg administered over 30–60 minutes twice/day.⁸ Of note, intramuscular streptomycin dosing recommendations for children and adults with tuberculosis are 20–40 mg/kg/day and 15 mg/kg/day, respectively.^{1,8}

Recent pharmacokinetic modeling data estimate that 30-minute intravenous infusions produce peak concentrations (36.58 µg/ml) similar to those with intramuscular administration (37.08 µg/ml), although intravenous peak levels occur sooner (0.5 hr) than those with intramuscular administration (1.76 hrs).⁷ In a study of 16 adults, 30-minute intravenous infusions of streptomycin 15 mg/kg/day resulted in a median peak concentration of 44 µg/ml.⁹ In our patient, a 1-hour infusion resulted in a peak concentration of 28.4 µg/ml. The longer infusion was acceptable as streptomycin demonstrates CSF penetration ranging from 7–21% at steady state and exhibits slow diffusion into the CSF.^{10,11}

Our 8-month-old patient's elimination half-life was one fourth that of an adult patient (1.04 vs 4.3 hrs).⁸ Her streptomycin levels were expected to remain above 1 µg/ml—the minimum inhibitory concentration for *M. tuberculosis*—for approximately 5 hours after the completion of the infusion. The postantibiotic effect of streptomycin is highly variable, with a mean of 32.2 hours (range 0.7–60.2 hrs) with monotherapy, or a mean of 167.9 hours (range 72.6–286.9 hrs) with our patient's four-drug regimen, leading to our choice of twice-daily dosing.¹²

During the patient's hospitalization, the Connecticut Department of Public Health began an investigation to determine the potential initial source of the infection. The infant was cared for in a household consisting of two parents, a young sibling, and two cousins. One parent was born in Southeast Asia but came to the United States as a toddler. Household members all had negative tuberculin skin tests at baseline and 15 weeks after the child's initial *M. tuberculosis* diagnosis. One grandparent, also born in Southeast Asia, who had frequent interaction with the infant, had a positive tuberculin test but a normal chest radiograph and two negative sputum cultures for *M. tuberculosis*. No contacts receiving care for *M. tuberculosis* were identified.

Traditional source investigations of children with tuberculosis do not always find the source case.¹³ One new approach incorporates molecular genotyping data to help define possible transmission from unsuspected sources. Our patient's

M. tuberculosis isolate was genotyped using both spoligotyping and mycobacterial interspersed repetitive unit typing.¹⁴ The strain did not match that of any known case of *M. tuberculosis* in Connecticut. Almost all (> 92%) of Connecticut's culture-positive specimens are genotyped. A review of national genotyping data, which are available from the Centers for Disease Control and Prevention National Tuberculosis Genotyping Service, determined that nine cases of *M. tuberculosis* strains matched the infant's genotype.¹⁴ Seven were isolated from individuals born in three different Southeast Asian countries, and four of the strains were from the same country of origin as our patient's family. None of these patients had lived in Connecticut, and all were diagnosed and treated before our patient's birth. No source case was found.

Conclusion

The safe and effective use of intravenous streptomycin was demonstrated in an 8-month-old patient with disseminated *M. tuberculosis*, including tuberculous meningitis. This case suggests that intravenous streptomycin, in combination with other antituberculous drugs, may be a safe and less painful alternative to intramuscular streptomycin for infants.

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