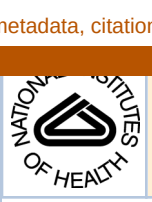

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Pharmacokinetics of Moxifloxacin in an Infant with *Mycoplasma hominis* Meningitis

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Abstract

Treatment of *Mycoplasma hominis* meningitis in infants is limited by a lack of consensus regarding therapy and limited pharmacokinetic data for agents to which *M. hominis* is susceptible. We report the successful treatment of a premature infant with *M. hominis* meningitis with doxycycline and moxifloxacin and provide a pharmacokinetic profile of moxifloxacin.

Keywords

meningitis; moxifloxacin; *Mycoplasma hominis*; infant; pharmacokinetic

Mycoplasma hominis meningitis is an uncommon but life-threatening infection among infants.[1] Survivors frequently have long-term morbidity including severe neurodevelopmental impairment. *Mycoplasma* species lack a cell wall, rendering them resistant to agents such as penicillins and cephalosporins that are often used for empirical therapy. *In vitro* testing has demonstrated susceptibility of *M. hominis* to chloramphenicol, tetracyclines, lincosamides, and fluoroquinolones.[2] Tetracyclines are often considered "first-line" therapies, but are bacteriostatic and contraindicated in children because of their effect on bones and teeth. Fluoroquinolones display marked intracellular accumulation and are bactericidal against *Mycoplasma* species. Use of fluoroquinolones in infants and children has been limited due to concern about cartilage damage.[3] Moxifloxacin[1] and ciprofloxacin[1, 4] are used to treat *M. hominis* meningitis in infants, but little is known about their pharmacokinetics (PK) in this population.

We present the successful treatment of a case of *M. hominis* meningitis with doxycycline and moxifloxacin in a preterm infant. Determination of moxifloxacin PK in our patient may help inform future studies of the dosing and effects of moxifloxacin in infants.

CLINICAL CASE REPORT

An 813 g male infant was born at a regional hospital at 26 weeks gestation. Maternal pregnancy history was otherwise unremarkable. The patient was intubated in the delivery

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room, and he received ampicillin, gentamicin, and ceftazidime for presumed sepsis. Ceftazidime was stopped after 5 days of therapy, but ampicillin and gentamicin were continued. He was successfully extubated on day of life 6, but the following day became hypotonic, had a prolonged apneic episode, and displayed generalized tonic-clonic activity concerning for a seizure. The patient was re-intubated, and on subsequent examination, was noted to have a full fontanelle. A head ultrasound was obtained that demonstrated hydrocephalus with blood in the ventricles consistent with a previous grade III intraventricular hemorrhage. Cerebrospinal fluid (CSF) obtained via lumbar puncture demonstrated 1920 white blood cells (WBC)/mm^3 (86% polymorphonuclear cells and 14% mononuclear cells); 6720 red blood cells (RBC)/mm^3; and > 460 mg/dL of protein. CSF glucose was not obtained. The patient was diagnosed with presumed meningitis, and amphotericin B deoxycholate was added to the ampicillin and gentamicin therapy. The ampicillin and gentamicin were discontinued on day of life 8 when the infant's regimen was changed to vancomycin and acyclovir, followed by fluconazole on day of life 10, and tobramycin and meropenem on day of life 12. These six antimicrobials were continued until day of life 19 when he was transferred to our hospital for neurosurgical evaluation due to worsening hydrocephalus. The initial CSF culture from day 6 of life was negative for bacteria, and subsequent attempts at lumbar puncture were unsuccessful.

CSF obtained via ventricular tap at our institution on day of life 20 demonstrated 23,750 WBCs/mm^3 (80% neutrophils, 7% lymphocytes, 6% monocytes). On day of life 24, the infant had another ventricular tap which demonstrated 13,733 WBCs/mm^3 (90% neutrophils, 4% lymphocytes, and 6% monocytes), protein of 1960 mg/dL and glucose of < 20 mg/dL in the CSF. CSF from day of life 24 and 26 yielded *M. hominis* by 16s rRNA sequencing. As a result of these findings, doxycycline (2 mg/kg IV Q 6 hours) and moxifloxacin (5 mg/kg IV Q 24 hours) were started to complete a six week course. Moxifloxacin dosing was recommended by our pediatric infectious disease consultants using linear, weight-based extrapolation from adult dosing and based on the infant's current weight of 1164g. The other antimicrobials were discontinued. A repeat ventricular tap after two weeks of therapy demonstrated 6 WBC/mm^3 (4% neutrophils, 20% lymphocytes, and 15% monocytes), protein of 1309 mg/dL, glucose of 27 mg/dL, and no identification of *M. hominis* in the CSF.

MATERIAL AND METHODS

The infant was enrolled in an off-label therapeutic study that was approved by The University of North Carolina at Chapel Hill's Institutional Review Board. If an infant was receiving an off-label therapeutic as part of clinical care, we collected PK samples during times of routine blood draws and clinical information from the medical chart. The study did not prescribe the therapeutic agent or the dose. We obtained written informed consent from the patients' parents.

Moxifloxacin was infused over 1 hour, and blood samples were collected around the 7^{th} and 14^{th} doses of moxifloxacin at the following time points: 0.7, 1.9, 17.5, and 22.1 hours after end of infusion. Within 10 minutes of collection, 400 μL of whole blood was spun at 4000g for 10 minutes and the plasma (~200 μL) was frozen at -80 °C until shipping. The samples were shipped on dry ice to NorthEast BioAnalytical Laboratories (Hamden, CT) and analyzed using a validated liquid chromatography-tandem mass spectrometry method for simultaneous determination of moxifloxacin and its metabolites (M1 and M2) in plasma. Drug extraction was performed by protein precipitation. The calibration range of the Moxifloxacin ranged from 10 - 5000 ng/mL and for metabolites M1 and M2 ranged from 10 - 2500 ng/mL. Samples were analyzed in a single batch and the accuracy of all quality

control (QC) samples ranged from 95 - 107%, and coefficient of variation (CV) ranged from 0.3 - 7.9%.

PK indices were calculated using non-compartmental methods[5] with WinNonLin 6.1 (Pharsight, Cary, NC), assuming steady state and applying the superposition principle.

RESULTS

The concentration time profile for this infant compared with healthy adult volunteers is presented in Figure 1.[6] The maximum concentration (C_{max}), area under the curve (AUC_{0-24}), and systemic clearance (CL) were 1.7 mg/L, 16.5 mg*h/L, and 0.3 L/h/kg, respectively. The moxifloxacin concentration after 22 hours of drug administration was 0.18 mg/L. The C_{max} and $AUC_{0–24}$ for metabolites M1 and M2 were 1.2 mg/L, 17.8 mg*h/L and 1.5 mg/L, 22.2 mg*h/L, respectively.

DISCUSSION

This is the first report of moxifloxacin use in an infant where serial moxifloxacin concentrations were obtained. In this case, moxifloxacin therapy was successful against *M. hominis* meningitis. However, moxifloxacin PK parameters in our infant differed substantially from those reported in healthy adult volunteers.[7] Substantial PK differences frequently exist between infants, children, and adults, often leading to treatment failure or serious toxicity.[8] With increased antibiotic pressure in neonatal and pediatric intensive care units and the rise of resistant organisms, more agents considered “second-line” are used in infants and children without PK studies to guide dosing.

Moxifloxacin, like other fluoroquinolones, exhibits concentration-dependent killing of Gram-negative bacteria, and unlike some of the early-generation fluoroquinolones (e.g. ciprofloxaxin), moxifloxacin also displays concentration-dependent killing of Gram-positive organisms.[9] Various pharmacodynamics (PD) endpoints have been studied in vitro and clinically, and AUC_{24}:minimum inhibitory concentration (MIC) and C_{max}:MIC ratios are the primary predictors of bacteriological eradication and clinical efficacy.[10]

The appropriate PD endpoint for atypical organisms such as *M. hominis* is unknown. However, a full term infant with *M. hominis* meningitis was successfully treated with 13 mg/kg daily of oral moxifloxacin, in addition to ampicillin, cefotaxime, minocycline, ciprofloxacin, chloramphenicol, and acyclovir.[1] In that infant, the MIC of *M. hominis* for moxifloxacin was 0.063 mg/L and after 3 days of moxifloxacin therapy, concentrations in the serum and CSF were 0.30 mg/L and 0.16 mg/L, respectively.

The C_{max} for our infant was ~1/3 of that described in adults.[7] Based on existing MIC data for *M. hominis* this should provide a C_{max}:MIC ratio of 27; the concentration recorded 22 hours post dose (at the end of the dosing interval) was still 2.9 times greater than the organism MIC. However, moxifloxacin concentrations in our infant would be sub-therapeutic for many Gram positive and Gram negative organisms. This suggests higher moxifloxacin doses may be required in this population and should be further explored.

The C_{max} and AUC_{0-24} of metabolite M1 in our infant were 10 and 20 times greater, respectively, than that reported in healthy adults after a single dose of intravenous moxifloxacin.[7] The C_{max} and AUC_{0-24} of M2 were three times the levels measured in the same adult population. Moxifloxacin is metabolized via sulfate conjugation (M1) and glucuronidation (M2)[7] and developmental ontogeny of these pathways or differences in protein binding could account for the lower moxifloxacin concentrations observed. While

moxifloxacin metabolites are inactive, higher rates of metabolism for drugs in which the activity of metabolites is not known could make assessing the risk/benefit ratio difficult.

These PK data are limited by inclusion of only one infant and a limited number of PK data points collected to derive PK parameters. Sampling was limited to scheduled draws, and because our C_{max} was recorded 0.7h after the end of the infusion, we may have underestimated the C_{max} and consequently the AUC_{0-24}.

The PK of moxifloxacin in this infant differed substantially from that reported in healthy adults, which suggests that linear, weight-based extrapolation of adult dosing in this setting is inappropriate. This case also represents the successful collection and subsequent analysis of an off-label therapeutic agent in an infant using a novel study design, and may provide a model for the collection on PK data in these vulnerable children. In order to generalize these data, it should be incorporated into secondary analyses employing population and physiology-based PK analyses.

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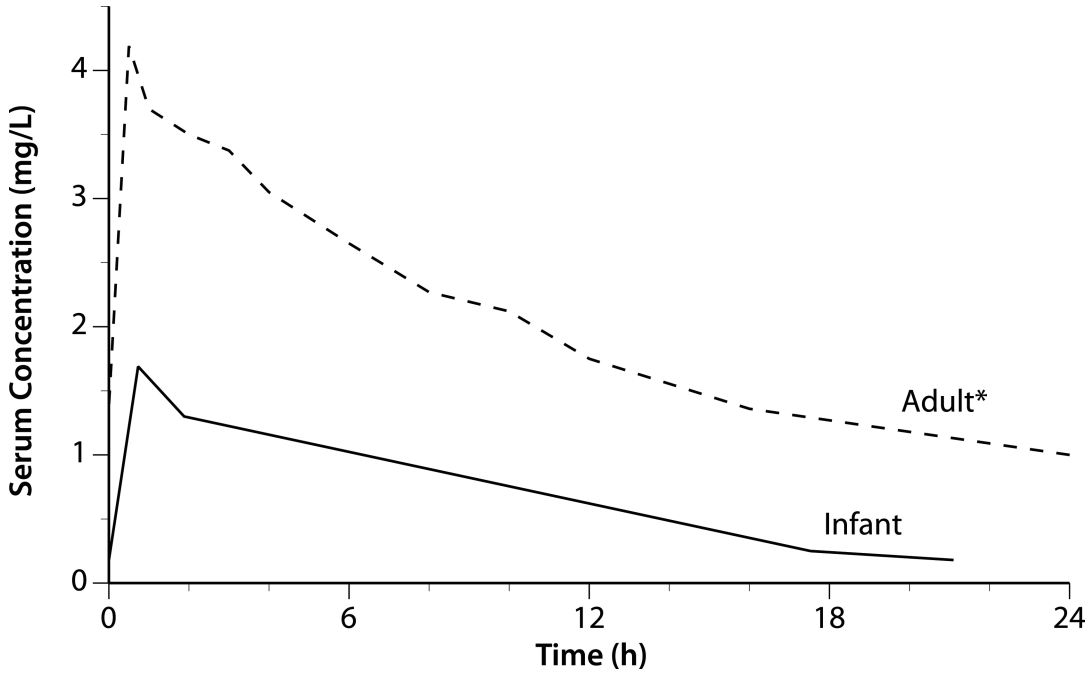

Figure 1.
Moxifloxacin serum concentrations in an infant compared with adults * Adult data adapted from Avelox® Label (Bayer Pharmaceuticals Corporation, Leverkusen, Germany).[6]