High Direct Bilirubin Associated With Levofloxacin Use in a Neonate

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Limited data exist regarding the use of fluoroquinolones in the neonatal population. Levofloxacin has some utility in this population because it is one of a very limited number of antibiotics with activity against *Stenotrophomonas maltophilia*. We describe the successful treatment of *S maltophilia* tracheitis in a premature neonate using levofloxacin 10 mg/kg every 24 hours and the subsequent unexpected sharp rise in the direct bilirubin. This case illustrates a previously unrecognized adverse drug effect associated with levofloxacin use in neonates.

ABBREVIATIONS IVFE, intravenous fat emulsions; SMZ-TMP, sulfamethoxazole-trimethoprim

KEYWORDS adverse drug event; hyper-direct bilirubinemia; levofloxacin; neonate; *Stenotrophomonas maltophilia*

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Introduction

Stenotrophomonas maltophilia is a Gram-negative bacillus implicated increasingly in nosocomial infections. It is an environmental bacterium found in plant, food, and water sources.¹ Although *S maltophilia* is not considered a highly virulent pathogen, mortality rates have been estimated at 37.5% in adults.² This relatively high mortality rate may be due to inherent multidrug resistance that is associated with this organism. *Stenotrophomonas maltophilia* is commonly resistant to many broad-spectrum β -lactams, including cefepime, piperacillin/tazobactam, and carbapenems.¹ Furthermore, *in vitro* susceptibility data may not correlate well with clinical outcomes, possibly because of further resistance development during treatment.

Recognized clinical manifestations of *S maltophilia* infection continue to evolve. Although early evidence focused on disease only in immunocompromised patients, subsequent reports have proven it a true pathogen, particularly in nosocomial infections.³ Bacteremia, endocarditis, as well as infections of the central nervous system, eye, respiratory, or urinary tracts, have been reported due to *S maltophilia*. The respiratory tract is the most common site of *S maltophilia* isolation in hospitalized patients, accounting for 56% to 69% of *S maltophilia* cultured.³ Because *S maltophilia* is a common colonizer of mechanically ventilated patients, it may be difficult to differentiate colonization from true infection. However, *S maltophilia* nosocomial pneumonia has been linked to significant increases in mortality.

Evidence of *S maltophilia* infection in neonates is sparse; however, reports detail bacteremia, pneumonia, and infections of the urinary tract and central nervous

system. A single-center case-control study showed 82% of *S maltophilia* infections in neonates to be respiratory, 9% bacteremia, and 9% conjunctivitis, with a mortality rate of 17%.⁴ They found that the neonatal risk factors for *S maltophilia* infection were gestational age <37 weeks, low birth weight (<2500 g), invasive procedures (e.g., intubation, mechanical ventilation, urinary catheter), duration of hospitalization, and broad-spectrum antimicrobial exposure.

Management of *S maltophilia* infections in neonates poses a particular challenge because of inherent antibiotic resistance combined with limited alternative therapies available in this population. Sulfamethoxazole-trimethoprim (SMZ-TMP) has the greatest *in vitro* and *in vivo* evidence; unfortunately, the drug is contraindicated in infants younger than 2 months because of the risk of hyperbilirubinemia and kernicterus.⁴ Levofloxacin is the second most active agent against *S maltophilia*, and there is extensive evidence of its use in adults with both pneumonia and urinary tract infections.⁵ Although case reports and case series document the use of both agents in neonatal *S maltophilia* infections, there is minimal information to support the efficacy of levofloxacin in the treatment of *S maltophilia* infections in these neonates.^{6,7} This lack of information leaves a gap in knowledge regarding safety, including adverse reactions that may occur in neonates receiving levofloxacin, such as elevation in direct bilirubin, as described in this paper.

Case

The male infant is a dichorionic, diamniotic twin who was born via spontaneous vaginal delivery at 24 and

Figure. Direct bilirubin trends associated with levofloxacin use.

5/7 weeks' gestation (641 g) to a 34-year-old gravida 5 para 4 Hispanic mother. As the "B" twin, he was born 28 minutes after his sister. He required positive pressure ventilation and intubation in the delivery room. Although his amniotic fluid was clear, his sister was delivered in a pocket of pus. Because of this birth history and hyperglycemia requiring insulin, he received an initial 7-day course of ampicillin and gentamicin for presumed sepsis. In addition to respiratory failure, sepsis, and hyperglycemia, his initial course was also complicated by severe intraventricular hemorrhage, including hydrocephalus and periventricular leukomalacia. On day of life 4, he was switched from conventional ventilation to the high-frequency jet ventilator due to evidence of pulmonary interstitial emphysema on chest radiograph.

On the 11th day of life, the endotracheal tube was occluded by secretions and required replacement. Upon reintubation, a tracheal aspirate collected via the new tube was reported as heavy growth of *S maltophilia*. Sensitivities were reported as resistant to ceftazidime but susceptible to levofloxacin and SMZ-TMP. A blood culture collected 2 days prior to the tracheal aspirate was eventually reported as negative. No other cultures were available. At the time of the culture, he was receiving antimicrobial coverage with vancomycin and gentamicin for presumed sepsis and amphotericin B for a disseminated fungal rash and possible fungal sepsis. His failure to completely respond to a week of antimicrobial therapy accompanied by thick yellow secretions and persistent ventilator dependence led to the decision to treat the tracheitis secondary to *S maltophilia*.

A decision was made to treat with intravenous levofloxacin 10 mg/kg every 24 hours. SMZ-TMP was not used because of age-related contraindications, incompatibilities with continuous infusions he was receiving, and the need for significant volume associated with

intravenous delivery. The levofloxacin dose was based on that used in older infants and children. However, because of developmental pharmacology issues associated with prematurity (e.g., impaired clearance), we gave the same mg/kg dose but extended the dosing frequency from 12 hours to 24 hours.^{8,9}

An elevation in direct bilirubin was noted on the day following initiation of levofloxacin. The Figure illustrates the direct bilirubin values correlated with the timing of levofloxacin therapy. The neonate was receiving nothing by mouth and relied solely on parenteral nutrition. Although parenteral nutrition can be associated with cholestasis, the sharp increase in direct bilirubin in our patients was associated with initiation of levofloxacin. With the exception of a slight elevation in γ -glutamyl transferase, liver function tests on the second day of levofloxacin were within normal limits. An abdominal ultrasound documented normal biliary and hepatic anatomy. The direct bilirubin decreased significantly once the levofloxacin was discontinued. The infant received 4 days of the planned 7-day course of levofloxacin. A pediatric infectious disease consultant recommended no further treatment of the tracheitis. The infant had a typical course for his gestational age and was eventually transferred to another facility for treatment of retinopathy of prematurity on day of life 59.

Discussion

There are limited data on levofloxacin pharmacokinetics or safety in the neonatal population. Pharmacokinetic studies indicate that infants 6 months and older should receive levofloxacin 10 mg/kg intravenously every 12 hours.⁹ Because of concerns for immature organ function related to his prematurity, we opted to use levofloxacin 10 mg/kg intravenously every 24 hours in this scenario. A case series published shortly after our case occurred reported use of levofloxacin

in 6 neonates.⁷ In these cases they were also treating *S maltophilia* infections; however, they used a dose of 10 mg/kg intravenously every 12 hours. The patients in this case series did not experience any adverse effects associated with hepatotoxicity.

The Naranjo algorithm,¹⁰ a tool used to estimate the probability of an adverse drug event, was applied to this case, resulting in an outcome of “probable.” Points were assigned for appearance after the suspected drug was administered; for adverse effect improving when the drug was discontinued; for ruling out alternative causes; and for being confirmed by objective evidence. The first high direct bilirubin obtained on the day after levofloxacin started was the first one measured in this infant; therefore, we do not have a baseline direct bilirubin. The infant did not receive other drugs that can cause high direct bilirubin. One possible alternative cause for high direct bilirubin in infants relates to parenteral nutrition use. This infant received parenteral nutrition for the first 43 days of life. He received intravenous fat emulsions (IVFE) every day except for one through the start of the levofloxacin. Once the high direct bilirubin was noted, the IVFE was reduced from 1 g/kg/day to 0.5 g/kg/day for 3 days. The IVFE continued at a dose of 0.5 to 1 g/kg/day for several days but were held from days of life 24 to 29. No cycling of IVFE occurred.

Although not usually considered a common pathogen of infection, *S maltophilia* can carry serious consequences for those affected, particularly for those with nosocomial pneumonia. Evidence regarding treatment of *S maltophilia* in the neonatal population is severely limited, and it is hoped that this case report will add to the current literature to serve as a reference for future cases to provide guidance for monitoring its use in neonates. SMZ-TMP was considered for use in this infant but considered relatively contraindicated because of a risk of hyperbilirubinemia and kernicterus due to the infant's age. Furthermore, patient-specific factors made SMZ-TMP a less attractive choice because of the required diluent fluid volume and concerns for coinfection incompatibilities. SMZ-TMP is generally avoided in neonates because it is known to displace bilirubin from protein-binding sites, increasing the risk for kernicterus. The rise in direct bilirubin after levofloxacin administration suggest a different mechanism is more likely related to hepatic damage. It is unknown whether dose affects this adverse reaction. Because the elevation in direct bilirubin was observed immediately following administration it is unlikely that duration of treatment is a factor.

Levofloxacin exhibits concentration-dependent bactericidal activity and is known to concentrate in lung tissue, making it an ideal agent to treat respiratory infections.^{8,9} We observed a rise in direct bilirubin following initiation of levofloxacin. Although there is not much literature to support this drug reaction as a direct effect

of levofloxacin in neonates, it is the probable cause of hyperbilirubinemia per the Naranjo algorithm. Of note, this patient did fit within the increased risk population described previously, because his gestational age was less than 37 weeks, he underwent invasive procedures, he had an extended hospital stay, and he was administered broad-spectrum antibiotics.

Conclusion

It is probable that levofloxacin was the culprit of this neonatal patient's hyperbilirubinemia, given the timing between the two and the resolution of the hyperbilirubinemia after discontinuation of levofloxacin. The risk of hyperbilirubinemia with both SMZ-TMP and levofloxacin poses a unique challenge in this population, specifically for the treatment of *S maltophilia*. Ultimately, more research and pharmacokinetic studies are needed to determine optimal dosing and provide an accurate safety assessment in this population. Additionally, more data are needed to determine whether hyperbilirubinemia from levofloxacin is a common occurrence in the neonatal population and what the best treatment option would be for these patients. Practitioners using levofloxacin in the neonatal population should consider close monitoring of both direct and indirect bilirubin during treatment.

ARTICLE INFORMATION

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