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Enteral Ciprofloxacin or Levofloxacin for Ventilator-Associated Tracheobronchitis in Children

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Abstract

Introduction Pseudomonas aeruginosa is the most commonly isolated organism in children with ventilator-associated tracheobronchitis (VAT). Enteral treatment with ciprofloxacin or levofloxacin is sometimes employed, but supportive data are limited. The purpose of this study was to evaluate the effectiveness and safety of enteral ciprofloxacin and levofloxacin administration for VAT in children. Methods This was a retrospective review of electronic medical records for children less than 18 years of age who received enteral ciprofloxacin or levofloxacin for the treatment of VAT from January 2013 through January 2020 at an academic children's hospital. Results Seventy-six children (median age 9.5, IQR 3.6-13.1 years), received ciprofloxacin or levofloxacin for VAT treatment during the study period. Median treatment duration was 8 (range 7-10) days. Most tracheostomy cultures (n=70/82, 85%) were polymicrobial, with P. aeruginosa most commonly isolated (n=67/224 organisms, 30%). Sixty-five children (86%) were successfully treated with an enteral fluoroquinolone. Antibiotics were changed or extended for two (3%) children. Ten (13%) children were prescribed antibiotics and eight (11%) required hospitalization for a lower respiratory tract infection within 30 days of completion of their fluoroquinolone course. Six (8%) patients received a seizure rescue medication, seven (9%) experienced emesis, and one (1%) had elevated transaminases. Tendonitis, tendon rupture and QTc prolongation were not observed. Conclusions The results of this study suggest enteral fluoroquinolones may be effective for the treatment of VAT in children. Further study is warranted to clarify the role of these agents in pediatric VAT.

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Conflicts of Interest

The authors report no conflicts of interest.

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Abstract

Introduction

Pseudomonas aeruginosa is the most commonly isolated organism in children with ventilator-associated tracheobronchitis (VAT). Enteral treatment with ciprofloxacin or levofloxacin is sometimes employed, but supportive data are limited. The purpose of this study was to evaluate the effectiveness and safety of enteral ciprofloxacin and levofloxacin administration for VAT in children.

Methods

This was a retrospective review of electronic medical records for children less than 18 years of age who received enteral ciprofloxacin or levofloxacin for the treatment of VAT from January 2013 through January 2020 at an academic children's hospital.

Results

Seventy-six children (median age 9.5, IQR 3.6-13.1 years), received ciprofloxacin or levofloxacin for VAT treatment during the study period. Median treatment duration was 8 (range 7-10) days. Most tracheostomy cultures (n=70/82, 85%) were polymicrobial, with *P. aeruginosa*most commonly isolated (n=67/224 organisms, 30%). Sixty-five children (86%) were successfully treated with an enteral fluoroquinolone. Antibiotics were changed or extended for two (3%) children. Ten (13%) children were prescribed antibiotics and eight (11%) required hospitalization for a lower respiratory tract infection within 30 days of completion of their

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fluoroquinolone course. Six (8%) patients received a seizure rescue medication, seven (9%) experienced emesis, and one (1%) had elevated transaminases. Tendonitis, tendon rupture and QTc prolongation were not observed.

Conclusions

The results of this study suggest enteral fluoroquinolones may be effective for the treatment of VAT in children. Further study is warranted to clarify the role of these agents in pediatric VAT.

Introduction

Ventilator-associated tracheobronchitis (VAT) is an infection in tracheostomy-dependent patients and those who are temporarily intubated secondary to acute illness. Although no formal definition exists, VAT is generally considered to lie on the continuum between bacterial colonization of the trachea and ventilator-associated pneumonia (VAP)[1]. Ventilator-associated tracheobronchitis is typically signified by the presence of an artificial airway for at least 48 hours along with new or increased sputum production, elevated or depressed temperature or white blood cell count, and a tracheal gram stain with the presence of moderate to heavy white blood cells and bacterial growth. Additionally, a lack of chest radiograph findings indicating pneumonia is usually required for diagnosis of VAT[1-3]. Development of VAT in children increases days of mechanical ventilation and pediatric intensive care unit (ICU) length of stay[4,5], while treatment of VAT with appropriate antibiotics is associated with a decrease in mechanical ventilation days and incidence of VAP[6,7].

The most common causative organisms isolated in infants and children with VAT are *Pseudomonas aeruginosa* , *Haemophilus influenzae* , *Klebsiella* species, *Staphylococcus aureus* , and *Enterobacteriaceae* species. Initial treatment typically includes obtaining a tracheal culture and initiating either broad-spectrum antibiotics or antibiotics based on previous culture results[8], with the majority of hospitalized patients initiated on intravenous antibiotics at diagnosis. Targeted therapy is based on susceptibilities of organisms isolated from the tracheal culture. Optimal treatment duration has not been determined; however, data favors shorter ([?]7 days) versus longer courses[8]. Once symptomatic improvement occurs and justification no longer exists for hospitalization, patients are often transitioned to enteral antibiotics to complete the treatment course at home.

Enteral treatment options for *P. aeruginosa* , the most commonly isolated organism, are limited to the fluoroquinolones ciprofloxacin and levofloxacin. Both treat the most commonly isolated pathogens in VAT, with the exception of *S. aureus* for ciprofloxacin and methicillin-resistant *S. aureus* for levofloxacin. The absolute oral bioavailability of ciprofloxacin and levofloxacin is excellent (70% and 99%, respectively) and the area under the curve of the oral and intravenous formulations are equivalent for both medications[9,10], resulting in comparable tissue exposure between formulations. Because of these factors, either ciprofloxacin or levofloxacin is often used for treating VAT when an enteral medication is desired. Enteral fluoroquinolones have favorable efficacy and safety in treatment of pulmonary exacerbations in the pediatric cystic fibrosis population[11,12] (11, 12). Enteral treatment with ciprofloxacin or levofloxacin is sometimes employed in VAT, despite not being labeled for this indication and limited supportive data. The purpose of this study was to evaluate the effectiveness and safety of the use of enteral ciprofloxacin or levofloxacin for VAT in children.

Methods

This retrospective cohort study was approved by the Institutional Review Board at Loma Linda University Children's Health. Pediatric patients less than 18 years of age with an artificial airway who received at least five days of enteral ciprofloxacin or levofloxacin for treatment of VAT between January 2013 and January 2020 were included.

Data collected through medical record review included patient demographics, length of hospital admission, primary diagnosis, comorbidities, and presence and duration of tracheostomy and/or intubation. Antibiotic dosing, culture data including susceptibility results, inflammatory markers, respiratory viral panel results, chest radiography, and secretion description were also collected. For the purpose of analysis, antibiotic susceptibility results reported as "intermediate" were considered to not provide appropriate antimicrobial

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coverage. The following pathogens were considered nonpathogenic: Group B *Streptococcus* , *Neisseria saprophyticus* , *Streptococcus viridans* , coagulase-negative*Staphylococcus.* Data was also collected in relation to adverse events including gastrointestinal upset, QT prolongation and QT-prolonging medications, liver function tests and medications that may affect liver function tests, tendonitis and/or tendon rupture, use of seizure rescue medication, and death within 30 days of enteral fluoroquinolone administration. Follow-up provider visits within the healthcare system, rehospitalization for pulmonary infection, and extension of or change in antibiotic course within 30 days of antibiotic course completion were recorded.

The primary endpoint was infection resolution with the use of enteral ciprofloxacin or levofloxacin, as measured by those who did not require a change or extension of antibiotic regimen, initiation of new antibiotic course, or rehospitalization for pulmonary infection within 30 days of completion of antibiotics for VAT. Secondary endpoints included the type and frequency of adverse events. Descriptive statistics were used to describe continuous data. All statistical analyses were performed using Microsoft Excel.

Results

Patient Characteristics and Medication Administration

Seventy-six patients were included in the study with a median age of 9.5 years (IQR 3.6, 13.1; range 3 months - 17.9 years) (Table 1). Most patients were in the step-down ICU at time of enteral fluoroquinolone initiation (n=54, 71%). The median hospital length of stay was 5 days (IQR 3, 10). The most common admitting diagnoses were respiratory distress or failure (n=38, 50%) and lower respiratory tract infection (n=14, 18%). All patients had respiratory comorbidities and almost all patients (n=75, 99%) had tracheostomies in place prior to admission. Ciprofloxacin was used more frequently (n=72, 95%) than levofloxacin (n=4, 5%) for treatment of VAT (Table 2). Median treatment duration was 8 days (IQR 7, 10). Twenty patients (26%) received additional antibiotics simultaneously, with sulfamethoxazole/trimethoprim accounting for over half of these (n=12, 52%). Diagnostic information is provided in Table 3.

Fluoroquinolone Effectiveness

Sixty-five children (86%) were successfully treated with an enteral fluoroquinolone, without antibiotic duration extension, change in antibiotic regimen, or readmission or initiation of a new antibiotic for a LRTI within 30 days of fluoroquinolone completion (Table 4). Eight (11%) were readmitted for a respiratory-related condition within 30 days of enteral fluoroquinolone completion. One of these patients was treated with a fluoroquinolone that did not provide adequate coverage of an organism isolated in their culture. Fluoroquinolone duration was extended by seven days and changed to a different antibiotic for one patient each. A new antibiotic course was prescribed for pulmonary infection for 10 (13%) patients within 30 days of fluoroquinolone completion. Four of these antibiotic regimens included an enteral fluoroquinolone.

Tracheostomy Cultures

A total of 82 tracheostomy cultures were obtained for 76 patients (Table 5). Of these, 44 (54%) had many polymorphonuclear leukocytes (PMNs) on tracheostomy gram stain. Most bacterial growth was quantified as moderate or heavy growth (n=141/224, 63%). The majority of cultures were polymicrobial (n=70, 85%). From 82 cultures, 224 organisms were isolated, of which *P. aeruginosa* was most common (n=68, 30%), followed by *Serratia marcescens* (n=32, 14%) and*Staphylococcus aureus* (n=27, 12%). Eleven (41%) of isolated*S. aureus* organisms were methicillin-resistant.

Antimicrobial Coverage

Of 224 organisms isolated from 82 cultures, 131 (58%) were susceptible and 18 (8%) resistant to the fluoroquinolone used based on the patient-specific susceptibility report. Fluoroquinolone susceptibility of 75 (33%) organisms was not reported. Of these, 17 (23%) were presumed susceptible, 14 (19%) were not presumed susceptible but an additional antibiotic was used with appropriate coverage, and 20 (27%) organisms were not susceptible to the fluoroquinolone used, with no additional antibiotic utilized[13]. Of the 14 organisms resistant to the fluoroquinolone used but treated with an additional antibiotic that provided coverage of the

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resistant isolate, 10 (67%) were treated during or for at least 5 days immediately prior to the fluoroquinolone course. Twenty-four (32%) organisms without reported fluoroquinolone susceptibility were considered non-pathogenic.

In total, 172 (77%) bacterial isolates were treated with antibiotics with known or presumed appropriate activity; including organisms considered likely nonpathogenic (n=24, 32%), 196 (88%) of the 224 organisms were treated with agents with known or presumed antimicrobial activity. Twenty-eight (13%) isolates did not have appropriate antibiotic coverage provided.

Adverse Drug Events

Thirteen (17%) patients experienced at least one adverse drug event (Table 6). Seven (9%) patients experienced emesis, none of whom received an anti-emetic. A seizure rescue medication was used for six (8%) patients. No tendonitis nor tendon rupture was noted. Death occurred in two (3%) patients within 30 days of fluoroquinolone completion.

Discussion

The results of this study show that either enteral ciprofloxacin or levofloxacin is effective for treatment of VAT in children, with the majority of infections resolving with the first course of treatment. Fluoroquinolones were well tolerated with no documented QTc prolongation, tendonitis, or tendon rupture. Several patients did require use of seizure rescue mediation; it is challenging, however, to determine if use of these medications was tied to use of enteral fluoroquinolones, as 71% of patients in this study had a neuromuscular comorbidity on admission. Two patients died within 30 days of completion of the course of enteral fluoroquinolones, one of which was unrelated to respiratory infection. The second patient developed septic shock and multiorgan failure as a result of multi-drug resistant pneumonia or tracheitis. This patient was originally treated with enteral fluoroquinolones as initial cultures were susceptible, though later organisms developed resistance.

Nseir and colleagues showed that appropriate antibiotic treatment reduced risk of transition from VAT to VAP (OR 0.12, NNT = 5)[7]. With only 58% of cultures in this study sensitive to fluoroquinolones, it is challenging to conclude that fluoroquinolones were appropriate in all these patients, though clinically only eight patients were readmitted with a lower respiratory tract infection. However, with 88% of patients receiving appropriate treatment based on patient-specific culture results, it was likely not treatment failure due to inadequate antimicrobial coverage that was responsible for breakthrough infections. The rate of progression from VAT to VAP in this study is also less than that shown in adult ICU patients, in which approximately one-third of patients experienced infection progression[14]. There is also evidence that other strategies, such as proper isolation techniques and infection control practices, significantly decrease VAT[15,16], which was not accounted for in the present study.

Citing a weak recommendation with low quality of evidence, guidelines from the Infectious Diseases Society of America and the American Thoracic Society suggest not providing antibiotic treatment for VAT in adults[2]. This guideline utilized Nsier et al.'s 2005 criteria for diagnosis[17], which were updated in 2015 (18); the guidelines have not yet been updated accordingly. This guideline was developed using one randomized controlled trial that included 58 patients and four observational studies, all conducted in adults. In the included randomized controlled trial, those that received antibiotic therapy had lower ICU mortality, less subsequent VAP, and more mechanical ventilation-free days than those who did not receive antibiotics, with no difference in duration of mechanical ventilation or length of ICU stay. The guidelines state concern regarding multidrug resistant organisms (MDROs) with antimicrobial treatment, since the aforementioned five studies showed that 61% of isolates were MDROs. While this present study did not assess organism resistance to other antibiotics, only 15 (7%) isolates were reported to be resistant to the fluoroquinolone used, with only one known patient proceeding to develop a clinically-relevant fluoroquinolone-resistant infection. The most commonly isolated organism in this study was *P. aeruginosa* , which is similar to the results of other studies in both pediatric[8] and adult critically ill patients[7,19,20]. *S. aureus* was also commonly isolated, again corroborated by pediatric and adult evidence[7,8,19].

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While eight days has been shown be comparable to 15 days of therapy for the treatment of VAP in adults, little is known regarding the appropriate duration of therapy for VAT in either adults or children[21]. Eight days of therapy was noted to be effective in multiple studies[15,22], though this has not been compared to other therapy durations. Patients in this study received treatment for a median of eight days and showed low rates of readmission due to respiratory infection, potentially indicating this duration is adequate in pediatric patients. Of note, Tamma et al. showed that treatment of VAT with antibiotics for at least seven days led to an increase of MDROs[8], so weighing the risks of under-treatment and the development of MDROs, a shorter duration may be more appropriate. Tamma et al.'s study, however, was conducted in pediatric ICU patients, whereas only 9% of the patients in this study were treated in the ICU.

There is question about how to distinguish VAT from VAP[23] (Keane 2018). A 2014 survey of providers in 16 countries reported diagnosing VAT based on both microbiological and clinical criteria (79.2%), and over half (50.3%) believe antibiotics should be utilized for treatment of VAT[24]. One of the challenges with treatment of VAT continues to be the variation in criteria for diagnosis, and there is no consensus on reference values or quantitative data that should be used[23,25]. Depending on the diagnostic criteria utilized[1,3,18,20,26], 26% to 74% of patients in this study would have been diagnosed with VAT. This diagnostic challenge continues to complicate the clinical picture of appropriate treatment for these patients, and many times treatment is initiated based on provider judgment due to the lack of robust evidence or consensus on the appropriate diagnostic criteria to use. This study supports the need for clear diagnostic criteria for VAT.

Since this study is retrospective, it is challenging to determine association between fluoroquinolone use and recurrence of respiratory infection, as many factors weigh into infection development. Similarly, it is difficult to parse out if use of fluoroquinolones was responsible for the documented adverse events without a sufficiently matched control group. This study also did not collect outpatient data, including medication adherence, medication administration in relation to other medications and enteral feeds, and follow-up in the outpatient setting. Therefore, it is challenging to determine if patients were adherent with their medication therapy, if it was appropriately administered, or if, once discharged, they received alternate antimicrobial therapy or were treated elsewhere for infection recurrence.

Conclusion

Fluoroquinolones are effective in treating ventilator-associated tracheobronchitis with minimal adverse events in the pediatric population. Further study is necessary to prospectively validate the results of this study and to determine appropriate diagnostic criteria for ventilator-associated tracheobronchitis.

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